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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Rezzayo (rezafungin acetate)
Treatment of invasive candidiasis
EU/3/20/2385

Sponsor: Mundipharma GmbH

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Product and administrative information

Product	
Designated active substance	Rezafungin acetate
Other name	--
International Non-Proprietary Name	Rezafungin
Tradename	Rezzayo
Orphan condition	Treatment of invasive candidiasis
Sponsor's details:	Mundipharma GmbH De-Saint-Exupery-Strasse 10 Flughafen 60549 Frankfurt Am Main Hassia Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Mundipharma Corporation (Ireland) Limited
COMP opinion	3 December 2020
EC decision	6 January 2021
EC registration number	EU/3/20/2385
Post-designation procedural history	
Transfer of sponsorship	Transfer from Mundipharma Corporation (Ireland) Limited, Ireland, to Mundipharma GmbH, Germany – EC decision of 29 June 2022
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Bruno Sepodes / Jayne Crowe
Applicant	Mundipharma GmbH
Application submission	1 August 2022
Procedure start	18 August 2022
Procedure number	EMA/H/C/005900
Invented name	Rezzayo
Therapeutic indication	Rezzayo is indicated for the treatment of invasive candidiasis in adults. Further information on Rezzayo can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/rezzayo
CHMP opinion	12 October 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Olimpia Neagu / Zsofia Gyulai
Sponsor's report submission	18 May 2023 and 20 September 2023
COMP discussion and adoption of list of questions	3-5 October 2023
Oral explanation cancellation	7 November 2023
COMP opinion (adoption via written procedure)	13 November 2023

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2020 was based on the following grounds:

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing rezafungin acetate was considered justified based on early clinical data showing clinically meaningful treatment success rate in patients who received the proposed product;
- the condition is life-threatening with 30-day mortality rates in intensive care units reported to be over 50%;
- the condition was estimated to be affecting approximately 1.2 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing rezafungin acetate will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that suggest that in one of tested doses a higher proportion of patients treated with the proposed product achieved treatment success as compared to patients treated with caspofungin. The advantage over azoles and amphotericin B could be also assumed due to inferior safety and efficacy profiles of these products compared to echinocandins. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing rezafungin acetate as an orphan medicinal product for the orphan condition: treatment of invasive candidiasis.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Invasive candidiasis (IC) is a serious infection due to *Candida* species.

IC is a serious and life-threatening infection due to *Candida* species, associated with high mortality rates of approximately 50% (Murphy & Bicanic, 2021). *Candida* is the most frequently detected yeast

in the human microbiome (Cortés & Corrales, 2018), and can cause invasive disease characterised by both widely disseminated and/or bloodstream infections (Arendrup & Patterson, 2017).

IC is an acute disease that may present in one of three ways: bloodstream infection without deep-seated or visceral involvement – frequently referred to as candidaemia; candidaemia with deep-seated/visceral infection; and deep-seated candidiasis without candidaemia (Kauffman, 2019). No clinical signs or symptoms are specific for IC; patients with IC are frequently unwell due to other medical conditions, and thus it can be difficult to determine which symptoms are a result of *Candida* infection, and which are due to the underlying illness.

Early diagnosis of IC is challenging but key to effective management of the disease. Whilst microbiologic cultures are considered the gold standard for diagnosis of invasive *Candida* infections (Clancy & Nguyen, 2018), it remains an insensitive tool. Investigative techniques based on antigen detection or DNA-based techniques have been developed to expedite diagnosis for seriously ill patients for whom more rapid and sensitive techniques are essential (Kauffman, 2019).

'Invasive candidiasis' is differentiated from the more general term, 'candidiasis', which covers a wide range of diseases including milder, superficial/topical infections such as those involving the epidermal and mucosal surfaces, for example the oral cavity, pharynx, oesophagus, intestines, urinary bladder, and vagina. Invasive candidiasis has specific characteristics which allows it to be considered a distinct medical entity for the purpose of orphan designation.

Intravenous rezafungin, a new echinocandin antifungal agent, is being developed specifically to treat patients with systemic infections caused by *Candida*. Rezafungin is a semisynthetic echinocandin that inhibits the synthesis of 1,3-β-D-glucan, an essential component of the fungal cell wall of yeast forms of *Candida* species and regions of active cell growth of *Aspergillus* hyphae.

The approved therapeutic indication "REZZAYO is indicated for the treatment of invasive candidiasis in adults. Consideration should be given to official guidance on the appropriate use of antifungal agents" falls within the scope of the designated orphan condition "Treatment of invasive candidiasis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Since the orphan medicinal product designation for rezafungin acetate was granted in 2021, there have been no significant changes in the chronically debilitating and/or life-threatening nature of the condition. The sponsor has not identified any new therapies approved which could have improved the morbidity or mortality.

Candida species are the leading cause of invasive fungal infections worldwide and are associated with high mortality rates (40-60%) leading to an estimated 400,000 death globally each year (Lausch et al., 2018; Mohr et al., 2020; Murphy & Bicanic, 2021). However, rates differ depending on the region/centre and patient population. Mortality rates increase with host immunosuppression and infection with drug-resistant *Candida* species (Murphy & Bicanic, 2021). Appropriate antifungal treatment i.e., the right treatment at the right time is critical for survival – delayed treatment of *Candida* bloodstream infection has been identified as an independent risk factor for hospital mortality (Morrell et al., 2005). This is further supported by the observation that consultation with an infectious

disease specialist was associated with a lower risk for mortality, as was a significantly higher rate of echinocandins administered as first-line therapy (Mohr et al., 2020).

A study by De Rosa et al. examined the mortality rate depending upon when candidaemia was diagnosed compared with time after admission. Patients with early-onset candidaemia (EOC; ≤10 days after admission) had a mortality rate of 38.8% (71/183), whereas those with late-onset candidaemia (LOC; >10 days after admission) had a mortality rate of 47.5% (283/596) (De Rosa et al., 2013). In both situations, inadequate initial antifungal therapy and older age were associated with an increased risk of mortality.

In the paediatric setting, candidaemia is the most frequent fungal infection (Lausch et al., 2019). A recently published 11-year retrospective, pan-European study (N=201) showed that all-cause mortality (ACM) at 30 days was 14.4%. Infections caused by *C. tropicalis* and *C. krusei* were associated with higher rates; in addition, mortality was significantly increased in paediatric/neonatal ICU versus general and other paediatric wards (Warris et al., 2020).

The COMP concluded that invasive candidiasis remains a life-threatening condition with 30-day mortality rates in intensive care units reported to be over 50%.

Number of people affected or at risk

At the time of designation in 2020, the prevalence of IC in the European Union (EU), was estimated to be approximately 1.2 per 10,000 persons. For the maintenance application the sponsor calculated the prevalence of candidaemia first to include candidaemia with and without deep-seated or visceral involvement since the majority of published literature incidence rates are for candidaemia rather than for all IC. The prevalence of IC without candidaemia was then estimated from this figure based on published ratios of the incidence of the two conditions. The two rates were summed and adjusted for temporal trend. Duration of IC was identified as less than one year therefore, in line with guidance EMA/COMP/436/01 Rev.1, annual incidence rather than point prevalence was used in the estimate.

The candidaemia incidence estimates were identified for 19 of the EU, Switzerland, Iceland, Liechtenstein and Norway states as well as the UK as 7.4 per 100,000 persons. Candidaemia is an acute condition, therefore, to convert incidence into prevalence, the incidence estimate of 7.4 per 100,000 is multiplied by a mean duration of 1 year. The prevalence of candidaemia was therefore estimated as 7.4 per 100,000 population.

It has been reported that approximately one-third of patients with IC fall into the deep-seated candidiasis without candidaemia category (Leroy et al., 2009). The study of 180 intensive care units in France between October 2005 and May 2006, reported that 87 (32.1%) of 300 adult patients with proven invasive *Candida* infection who received systemic antifungal therapy had no documented candidaemia. If the percentage of IC with candidaemia is 67.9% (100 - 32.1%), then the total IC prevalence is estimated as 10.9 per 100,000 population (7.4 *100/67.9).

The 2022 prevalence of IC was therefore estimated as 10.9 per 100,000 population.

The sponsor also looked at trends in incidence over time. There was no obvious trend in direction of change overall (candidaemia or non-candidaemia) identified, although possibly a plateauing in more recent years were recorded. A sensitivity analysis figure of 16.2 per 100,000 to allow for an increase of 7% per annum from 2015 was given by the sponsor, but as no changes in incidence have been reported more recently the figure of lower estimate was accepted by the COMP.

The COMP agreed with the methodology proposed by the sponsor and accepted the proposed prevalence estimate of 1.1 in 10,000 persons.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor listed the medicinal products which are authorised for the treatment of invasive candidiasis and also discussed which ones would be considered satisfactory methods for this application based on the therapeutic indication (Table 1).

Table 1. Currently authorised antifungal therapies as per the ESCMID 2012 guideline for the diagnosis and management of *Candida* diseases

Tradename	**Member States(s) where authorised**	**Holder of the authorisation**	**Authorised indication(s)***	**Significant benefit discussion required?**
Azoles				
Diflucan (fluconazole)	Approved widely across the EU as generic versions of Diflucan	Pfizer Limited and various generic MAH	Indicated in adults for the treatment of: IC. Indicated in term newborn infants, infants, toddlers, children, and adolescents aged from 0 to 17 years old: For the treatment of IC[1]	Yes, the method is satisfactory as there is a complete overlap with the proposed therapeutic indication for rezafungin
Noxafil (posaconazole)	Centralised approval	Merck Sharp & Dohme	Not indicated for IC[2]	No, because the method has no overlap with the proposed therapeutic indication for rezafungin and recommended against use in guideline.

Vfend (voriconazole)	Centralised approval	Pfizer Europe MA EEIG	Indicated in adults and children aged 2 years and above as follows: Treatment of candidaemia in non-neutropenic patients. Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*). VFEND should be administered primarily to patients with progressive, possibly life-threatening infections[3]	Yes, the method is satisfactory as there is an overlap with the proposed therapeutic indication for rezafungin
Sporanox (itraconazole)	Approved widely across the EU as generic	Various generic MAH	Oral solution: oral and/or oesophageal candidosis Capsules: Vulvovaginal candidosis/oral candidosis[4]	No, because the method has no overlap with the proposed therapeutic indication for rezafungin and recommended against use in guideline.
Echinocandins				
Cancidas (caspofungin)	Centralised approval	Merck Sharp & Dohme and various generic MAH	Treatment of IC in adult or paediatric patients. Empirical therapy for presumed fungal infections (such as *Candida*) in febrile, neutropenic adult or paediatric patients[5]	Yes, the method is satisfactory as there is a complete overlap with the proposed therapeutic indication for rezafungin
Mycamine (micafungin)	Centralised approval	Astellas Pharma Europe B.V.	Adults, adolescents ≥ 16 years of age and elderly: Treatment of IC. Children (including neonates) and adolescents < 16 years of age: Treatment of IC[6]	Yes, the method is satisfactory as there is a complete overlap with the proposed therapeutic indication for rezafungin

Ecalta (anidulafungin)	Centralised approval	Pfizer Europe MA EEIG	Treatment of invasive candidiasis in adults and paediatric patients aged 1 month to < 18 years[7]	Yes, the method is satisfactory as there is a complete overlap with the proposed therapeutic indication for rezafungin
Polyenes				
AmBisome (Liposomal Amphotericin B)	Approved widely across the EU	Gilead Sciences International Ltd	Indicated in adults and children aged 1 month to 18 years old for: The treatment of systemic mycotic infections due to organisms susceptible to this anti-infective such as disseminated candidiasis[8]	Yes, the method is satisfactory as there is an overlap with the proposed therapeutic indication for rezafungin
Abelcet (Amphotericin B Lipid Complex)	Approved in several European countries	Various generic MAH	Severe IC[9]	Yes, the method is satisfactory as there is an overlap with the proposed therapeutic indication for rezafungin
Fungizone (Amphotericin B)	Approved widely across the EU as generic	Various generic MAH	Treatment of the disseminated forms of candidosis[10]	Yes, the method is satisfactory as there is an overlap with the proposed therapeutic indication for rezafungin

Abbreviations: EU = European Union; IA= invasive Aspergillosis; IC = invasive candidiasis; IFI = invasive fungal infections; IV = intravenous; MAH = Marketing Authorisation Holder
* Only indications relevant to the treatment of IC are presented, indications for treatment of non-*Candida* invasive disease and prophylaxis of IFIs in at-risk populations have not been included
1: Diflucan SmPC 2022; 2: Noxafil SmPC 2023; 3: Vfend SmPC 2023; 4: Sporanox SmPC 2023; 5: Cancidas SmPC 2021; 6: Mycamine SmPC 2020; 7: Ecalta SmPC 2020; 8: AmBisome SmPC 2019; 9. Abelcet SmPC 2022; 1. Fungizone SmPC 2022.

Significant benefit

The sponsor did not seek any protocol assistance from EMA regarding the evidence needed to justify significant benefit of rezafungin over existing methods of treatment of adult patients with invasive candidiasis. However, scientific advice was sought on the clinical development before the orphan designation.

The efficacy and safety of rezafungin was assessed in two studies. Study STRIVE was a phase 2, multicenter, randomized, double-blind study of the safety, tolerability, and efficacy of intravenous rezafungin versus intravenous caspofungin followed by oral fluconazole step-down in the treatment of

subjects with candidemia and/or invasive candidiasis. The primary efficacy outcome was overall response at day 14 defined as mycological eradication and resolution of attributable systemic signs of candidemia and/or IC that were present at baseline, no change of antifungal therapy for the treatment of candidemia and/or IC, and the subject was not lost to follow-up on the day of assessment. In Part A, subjects were randomised 1:1:1 to the following groups: i) Group 1: rezafungin 400 mg on Day 1 and Day 8; an optional 400 mg dose on Day 15; and for subjects with IC, an optional 400 mg dose on Day 2; ii) Group 2: rezafungin 400 mg on Day 1, 200 mg on Day 8; an optional 200 mg dose on Day 15; and for subjects with IC, an optional 200 mg dose on Day 22. Referred to as rezafungin 400/200 mg iii) Caspofungin IV: 70 mg loading dose on Day 1 and then 50 mg/day up to a maximum of 21 days for subjects with candidemia only, or up to a maximum of 28 days for subjects with IC. Success rates were high in all treatment groups with rates of 76.1% in Group 2, 60.5% in Group 1, and 67.2% caspofungin. The failure rates were 17.4%, 26.3% and 27.9% for Group 2, Group 1, and caspofungin, respectively.

The second study was a phase 3, multicentre, prospective, randomised and double-blind study (ReSTORE). Subjects were randomised in a 1:1 ratio to receive rezafungin as a 400 mg loading dose on Day 1, followed by 200 mg on Day 8 and once weekly thereafter, for a total of 2 to 4 weeks or caspofungin as a single 70 mg intravenous loading dose on Day 1 followed by caspofungin 50 mg intravenous once daily for a total treatment of 14 days to 28 days.

The primary efficacy outcome was global response (confirmed by the Data Review Committee [DRC]) at day 14. Global response was determined from clinical response, mycological response, and radiologic response (for qualifying subjects with IC). Non-inferiority was to be concluded if the lower bound of the 95 % confidence interval (CI) for the difference in Day 14 cure rates (rezafungin-caspofungin) was > -20 %. Secondary efficacy outcomes were all-cause mortality at Day 30 [30-day ACM], mycological response, clinical response, and radiologic response (for subjects with IC).

Based on the results of the primary endpoint, the rate of subjects with cure was 59.1% and 60.6% in the rezafungin and caspofungin groups, respectively. The failure rate (not including indeterminate responses) was 30.1% and 30.9% in the rezafungin and caspofungin groups, respectively. The indeterminate rate was 10.8% and 8.5%, respectively. Non-inferiority of rezafungin was showed (weighted treatment difference of -1.1 [95% CI: -14.9 to 12.7]), with the lower limit of the 95% CI for the difference in the mITT population exceeding -20%.

Based on direct and indirect comparisons against the currently available antifungal therapies, the sponsor argues that rezafungin can offer significant benefit to patients in the following ways:

- Once-weekly dosing regimen, enabling echinocandin treatment to be administered in the outpatient setting.
- Faster time to negative blood culture, important for avoiding deep-organ involvement.
- Improved outcomes in antifungal-naïve patients.
- Reduced length of ICU stay.
- Lower potential for drug-drug interactions.
- Efficacy against echinocandin-resistant strains.

The sponsor refers to an article by Demir et al 2021 which investigated the efficacy of approved treatments for IC. Random effect Bayesian network meta-analysis (NMA) methods were used to compare treatment outcomes over azoles and amphotericin. The conclusion was that the results support the

current guideline recommendations, which encourage the use of echinocandins as the first-line therapy for treatment of patients with invasive candidiasis.

A detailed description of the sponsor's argumentation for the significant benefit is presented below:

A) Significant benefit of rezafungin versus all the authorised treatments

Table 2. Rezafungin offers significant benefit over existing methods

Tradename	**Significant benefit**
Azoles **Echinocandins, including rezafungin, provide significant benefit over currently available azoles.** • Network meta-analysis (comparisons by drug class) (Demir, 2021): – The echinocandins showed a higher rate of *successful treatment compared to the polyenes (OR 1.41, 95% CI 1.04–1.92) and the triazoles (OR 1.82, 95% CI 1.35–2.51) overall.* – Rank probability analysis suggested that the echinocandins were favoured as the most effective for treatment of invasive candid*iasis 98% of the time, followed by the polyenes at 2%.* – The sensitivity analysis of patients with candidemia also demonstrated that the echinocandins performed better than the polyenes (OR 1.33, 95% CI 0.89–1.93) and the triazoles (OR 1.67, 95% CI 1.15–2.41*).* • Resistance: In contrast to the late 1990s, there has been a rise in the occurrence of invasive candidiasis (IC) caused by non-albicans Candida species as opposed to IC caused by C. albicans. As a result of the growing prevalence of IC caused by non-albicans Candida species, there is a greater level of concern regarding the emergence of resistance (Hendrickson et al., 2019). Population-based surveillance studies have indicated a rising incidence of fluconazole resistance among non-albicans Candida species. Results for the SENTRY Antifungal Surveillance Program demonstrated fluconazole resistance rates of 0.1% in C. albicans, 5.6% in C. glabrata, 5.5% in C. parapsilosis, and 3.3% in C. tropicalis during 2015-2016 (Pfaller et al., 2019). In addition, cross-resistance between fluconazole and voriconazole was common in fluconazole-resistant C. albicans (35.0% susceptible to voriconazole) and C. parapsilosis (32.7% susceptible to voriconazole) strains and virtually complete for fluconazole-resistant strains of C. glabrata (0.0% susceptible [MIC, ≤0.5 mg/L] to voriconazole) and C. tropicalis (3.6% susceptible to voriconazole) (Pfaller et al., 2019).
Diflucan (fluconazole)	ESCMID 2012 Guideline recommendation: C (Marginally supports a recommendation for use) Network meta-analysis (comparisons of individual antifungals) (Demir et al., 2021): • Rezafungin was associated wit*h a more favourable outcome (i.e., treatment success) than fluconazole (OR 2.506, 95% CI 0.809-7.64) (an odds ratio >1 represents a relatively favourable outcome).* • Rank probability analysis suggested that rezafungin was the preferred choice for successfull*y treating invasive candidiasis (26.2%), followed closely by micafungin (25.8%) and anidulafungin (21.9%). [this applies to all other antifungals]* Network meta-analysis (comparisons of individual antifungals; incl. 13 trials (n = 3632 patients) that *were published between 1996 and 2020) (Domingos et al., 2022)* • Fluconazole (400 mg) was rated worst for *overall response (17% in SUCRA), whereas isavuconazole (200 mg) had the worst microbiological response (8%).* • SUCRA demonstrated that [amphotericin B and] *fluconazole (400 mg) had the highest probabilities of causing abnormal liver function ([87% and] 68%, respectively), whereas caspofungin 150 mg was the safest alternative*

	• [Amphotericin B and] fluconazole (400 mg) were highly associated with discontinuation *([88% and] 65%, respectively)* Reboli, 2007: A randomised, double-blind, multicenter trial comparing anidulafungin with fluconazole for the treatment of candidemia and other forms of invasive candidiasis: • At the end of IV therapy, treatment was successful *in 75.6% of patients treated with anidulafungin, as compared with 60.2% of those treated with fluconazole (difference, 15.4 percentage points; 95% CI, 3.9 to 27.0).* Safety: For Diflucan, dose adjustment is required in patients with renal impairment. No *dose adjustment is required for rezafungin treatment. Fluconazole has been associated with QT prolongation and patients with hypokalaemia and advanced cardiac failure are at an increased risk for the occurrence of life-threatening ventricular arrhythmias and torsades de pointes. Patients treated with Diflucan® have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported. Rezafungin is not known to cause QT prolongation nor exfoliative cutaneous reactions.* DDIs: Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzymes 2C9 and 3A4. Fluconazole is also a strong inhibitor of *the isozyme CYP2C19. For these reasons, fluconazole interacts with a number of other products. Diflucan is contraindicated for use in patients receiving terfenadine or other medicinal products known to prolong the QT interval and which are metabolised via CYP3A4 such as cisapride, astemizole, pimozide, quinidine, and erythromycin due to the risk of QT prolongation and cardiac arrhythmias. Diflucan is not recommended for use with halofantrine and Diflucan should be used with caution in patients receiving amiodarone due to the risk of QT prolongation. Caution and dose adjustment may be required for the following products due to the effect of Diflucan on their metabolism: rifampicin, hydrochlorothiazide, abrocitinib, alfentanil, amitriptyline, nortriptyline, amphotericin B, anticoagulants, short acting benzodiazepines, carbamazepine, calcium channel blockers, celecoxib, cyclophosphamide, fentanyl, HMG-CoA reductase inhibitors, ibrutinib, ivacaftor, Olaparib, immunosuppressors (e.g. ciclosporin, everolimus, sirolimus, tacrolimus), losartan, lurasidone, methadone, non-steroidal anti-inflammatory drugs, phenytoin, prednisone, rifabutin, saquinavir, sulfonylureas, theophylline, tofacitinib, tolvaptan, vinca alkaloids, vitamin A, voriconazole, zidovudine, azithromycin, oral contraceptives. Rezafungin has not been found to have any clinically significant drug-drug interactions.* C. krusei is intrinsically resistant to fluconazole with MIC values usually >32 mg/L. C. glabrata, C. inconspicua, C. lipolytica, C. norvegensis, C. rugosa, C. pelliculosa and C. guilliermondii also have intrinsically elevated fluconazole MIC values (Castanheira et al., 2020).
Vfend (voriconazole)	ESCMID 2012 Guideline recommendation*: B (Moderately supports a recommendation for use)* A *network meta-analysis to compare the efficacy of individual antifungals showed that rezafungin was associated with a more favourable outcome (i.e., treatment success) than voriconazole (OR 1.766, 95% CI 0.497-6.123) (an odds ratio >1 represents a relatively favourable outcome) (Demir et al., 2021).*

	Safety: The Vfend SmPC has warnings regarding QT prolongation, squamous cell carcinoma of skin associated with phototoxicity, severe cutaneous adverse reactions such as SJS, TEN, and DRESS, adrenal insufficiency*, visual adverse reactions such as blurred vision, optic neuritis, and papilloedema, acute renal failure, and monitoring of pancreatic function in patients with risk factors for acute pancreatitis, whereas the proposed Rezzayo SmPC does not include any such warnings.* DDIs: Co-administration of voriconazole with products known to prolong the QT interval and which are metabolised via the cytochrome P4503A4 such as terfenadine, cisapride, astemizole, pimozide, quinidine, and ivabradine are contraindicated. C*oadministration of voriconazole with rifampicin, carbamazepine, phenobarbital, St John's Wort, higher doses or efavirenz, and higher doses of ritonavir since these medicinal products are likely to decrease plasma voriconazole concentrations significantly.* C*oadministration of voriconazole with ergot alkaloids, sirolimus, naloxegol, tolvaptan, lurasidone, and venetoclax is contraindicated since voriconazole increases the plasma concentrations of these medicinal products.* In addition, there are multiple medicinal products for which dose adjustment or clinical monitoring is required with concomitant use of voriconazole. Rezafungin has not been found to have any clinically significant drug-drug interactions.
Echinocandins **Echinocandins are recommended as the fir*st-line treatment option for invasive candidiasis – ESCMID 2012 Guideline recommendation: A (Strongly supports a recommendation for use)*** • As a class, the echinocandins show excellent antifungal activity against Candida species, including those that are less susceptible or resistant to other classes of antifungals such as amphotericin B and azoles (Patil, 2017). • The in vivo activity of *echinocandins on Candida biofilms, which azoles are lacking, may also contribute to their efficacy in treating invasive candidiasis (Boisvert et al., 2016).* • Echinocandin resistance rates are low for most Candida spp. Results for the SENTRY Antifungal Surveillance Program demonstrated echinocandin resistance rates of 0-0.2% in C. albicans, 1.3-1.5% in C. glabrata, 0% in C. parapsilosis, 1.3-2.0% in C. tropicalis, and 0% in C. krusei during 2015-2016 (across all three licensed echinocandins: anidulafungin, caspofungin, and micafungin) (Pfaller et al., 2019).	
Cancidas (caspofungin)	Dose adjustment is required in patients: weighing >80 kg; with moderate hepatic impairment; and should be considered when co-administering caspofungin in adult patients with certain indu*cers of metabolic enzymes. Rezafungin does not require dose adjustment in any patients.* Safety: The Cancidas SmPC includes warnings regarding cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN); the proposed Rezzayo SmPC does *not include any such warnings.* DDIs: Concomitant use of caspofungin and ciclosporin may increase the risk for liver enzyme elevations and close monitoring of liver enzymes is recommended. Caspofungin reduced the trough concentrationof tacrolimus by 26% in *healthy adult volunteers. For patients receiving both therapies, standard monitoring of tacrolimus blood concentrations and appropriate tacrolimus dosage adjustments are mandatory. Caspofungin dose adjustment may be required with concomitant use of metabolic enzyme inducers such as rifampicin, dexamethasone, phenytoin, efavirenz, nevirapine, or carbamazepine. No drug-drug interactions were identified for rezafungin during the clinical development program.*

	A recent observational cohort study of 64 hospitals *located in 20 European countries has shown hospital stay was extended solely due to and for the purpose of completing parenteral antifungal treatment in 100 (16%) of 621 patients by a median of 14 days (IQR 3–23) (Egger et al., 2023).* • When asked as part *of ReSTORE if once-weekly rezafungin were available and they did not need to administer a daily echinocandin, investigators said 16% of patients were considered ready for discharge, a median of 5-6 days earlier than the actual discharge date. Caspofungin is only available as a daily IV infusion.* Network meta-analysis (comparisons of individual antifungals) (Demir et al., 2021): • Rank probability analysis suggested that rezafungin was the preferred choice for successfully treating invasive candidiasis (26.2%), followed closely by micafungin (25.8%) and anidulafungin (21.9%).
Mycamine (micafungin)	Safety: The Mycamine SmPC includes a black box warning regarding the development of foci of altered hepatocytes (FAH) and hepatocellular tumours in rats *after a treatment period of 3 months. Other warnings for micafungin includes reports of exfoliative skin reactions (SJS, TEN), reports of rare cases of haemolysis, risk of renal failure and abnormal renal functions tests, the risk of amphotericin B deoxycholate toxicities when coadministered with amphotericin B, and the risk of sirolimus, nifedipine, or tacrolimus toxicity when the respective products are administered concomitantly with micafungin. The proposed Rezzayo SmPC does not include any such warnings.* Mycamine is not recommended for use in patients with severe hepatic impairment. The proposed Rezzayo SmPC does not include this restriction. DDIs: Co-administration of micafungin with amphotericin B, sirolimus, nifedipine or itraconazole should be clos*ely monitored as exposure to these products may be increased which increases the risk for toxicity; no such interaction is listed for rezafungin.* A recent observational cohort study of 64 hospitals located in 20 European countries has shown hospital sta*y was extended solely due to and for the purpose of completing parenteral antifungal treatment in 100 (16%) of 621 patients by a median of 14 days (IQR 3–23) (Egger et al., 2023).* • When asked as part of ReSTORE if once-weekly rezafungin were available and *they did not need to administer a daily echinocandin, investigators said 16% of patients were considered ready for discharge, a median of 5-6 days earlier than the actual discharge date. Micafungin is only available as a daily IV infusion.* Network meta-an*alysis (comparisons of individual antifungals) (Demir et al., 2021):* • Rank probability analysis suggested that rezafungin was the preferred choice for successfully treating IC (26.2%), followed closely by micafungin (25.8%) and anidulafungin (21.9%).
Ecalta (anidulafungin)	A recent observational cohort study of 64 hospitals located in 20 European countries has shown hospital stay was extended solely due to and for the purpose of completing parenteral antifungal treatment in 100 (16%) of 621 patients by *a median of 14 days (IQR 3–23) (Egger et al., 2023).* • When asked as part of ReSTORE if once-weekly rezafungin were available and they did not need to administer a daily echinocandin, investigators said 16% of patients were considered ready for discharge, *a median of 5-6 days earlier than the actual discharge date. Anidulafungin is only available as a daily IV infusion.* Network meta-analysis (comparisons of individual antifungals) (Demir et al., 2021):

	• Rank probability *analysis suggested that rezafungin was the preferred choice for successfully treating invasive candidiasis (26.2%), followed closely by micafungin (25.8%) and anidulafungin (21.9%).* Network meta-analysis (comparisons of individual antifungals; incl. 13 trials (n = 3632 patients) that were pu*blished between 1996 and 2020) (Domingos et al., 2022)* • Overall, caspofungin, micafungin, and rezafungin were associated with better efficacy (>60%) and a manageable safety profile (discontinuation <45%).
Polyenes **Echinocandins, including *rezafungin, provide significant benefit over currently available polyenes.*** • Similar efficacy has been demonstrated against both micafungin and caspofungin, however, renal toxicity was higher with liposomal amphotericin B and amphotericin B deoxycholate was significantly more toxic (Cornely et al., 2012).	
AmBisome (Liposomal Amphotericin B)	ESCMID 2012 Guideline recommendation: B (Moderately supports a recommendation for use) Safety: AmBisome *has the potential to cause nephrotoxicity and pulmonary toxicity.* DDIs: Concurrent administration of AmBisome with other nephrotoxic agents (for example ciclosporin, aminoglycosides, polymixins, tacrolimus and pentamidine) may enhance the potential for drug-induced renal toxicity. Concurrent use of antineoplas*tic agents may enhance the potential for renal toxicity, bronchospasm and hypotension. Acute pulmonary toxicity has been reported in patients given amphotericin B (as sodium deoxycholate complex) during or shortly after leukocyte transfusions. Concurrent use of corticosteroids, ACTH and diuretics (loop and thiazide) may potentiate hypokalemia. AmBisome-induced hypokalemia may potentiate digitalis toxicity. AmBisome-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (e.g. tubocurarine).* A network meta-analysis to compare the efficacy of individual antifungals showed that rezafungin was associated with a comparable outcome (i.e., treatment success) than liposomal amphotericin B (OR 1.149, 95% CI 0.346-3.719) (an odds ratio >1 r*epresents a relatively favourable outcome) (Demir et al., 2021).* Network meta-analysis (comparisons of individual antifungals; incl. 13 trials (n = 3632 patients) that were published between 1996 and 2020) (Domingos et al., 2022) • SUCRA demonstrated that a*mphotericin B [and fluconazole (400 mg)] had the highest probabilities of causing abnormal liver function (87% [and 68%, respectively]), whereas caspofungin 150 mg was the safest alternative.* • Amphotericin B [and fluconazole (400 mg)] were highly *associated with discontinuation (88% [and 65%, respectively]), whereas rezafungin was the best tolerated alternative.* • Regimens containing amphotericin had moderate-high efficacy (around 50%) but were associated with higher rates of discontinuation due to adverse events.
Abelcet (Amphotericin B Lipid Complex)	ESCMID 2012 *Guideline recommendation: C (Marginally supports a recommendation for use)* Safety: Abelcet has the potential to cause nephrotoxicity. Renal impairment including *acute renal failure is listed as a common adverse reaction.* DDIs: Close monitoring should be performed while administering Abelcet concomitantly with nephrotoxic drugs, zidovudine, and cyclosporin. Caution should be taken when using Abelcet with other drugs that are known to interact with amphotericin B containing products such as antineoplastic agents, corticosteroids and corticotrophin

	(ACTH), digitalis glycosides, flucytosine, and skeletal muscle relaxants. Abelcet is not recommended for use in patients who have received leukocyte transfusions due to the potential for pulmonary toxicity.
Fungizone (Amphotericin B)	ESCMID 2012 Guideline recommendation: D (Supports a recommendation against use) Safety: Fungizone has the potential to cause nephrotoxicity. Accidental overdose of *Fungizone can result in potentially fatal cardiac or cardiorespiratory arrest. Leucoencephalopathy has been reported very occasionally following the use of amphotericin B injection in patients who received total body irradiation.* DDIs: Concomitant use of *nephrotoxic drugs or antineoplastic drugs should be avoided. The hypokalaemia following amphotericin B therapy may potentiate the toxicity of digitalis glycosides or enhance the curariform actions of skeletal muscle relaxants. Corticosteroids and Corticotrophin (ACTH) may increase the potassium loss due to amphotericin B. Flucytosine toxicity may be enhanced during concomitant administration, possibly due to an increase in its cellular uptake and/or impairment of its renal excretion. Acute pulmonary reactions have occasionally been observed in patients given amphotericin B during or shortly after leukocyte transfusions. It is advisable to separate these infusions as far as possible and to monitor pulmonary function.* A network meta-analysis to compare the ef*ficacy of individual antifungals showed that rezafungin was associated with a more favourable outcome (i.e., treatment success) than amphotericin B deoxycholate (OR 1.752, 95% CI 0.596-5.009) (an odds ratio >1 represents a relatively favourable outcome) (Demir et al., 2021).* Network meta-analysis (comparisons of individual antifungals; incl. 13 trials (n = 3632 patients) that were published between 1996 and 2020) (Domingos et al., 2022) • SUCRA demonstrated that amphotericin B [and fluconazole (400 mg)] *had the highest probabilities of causing abnormal liver function (87% [and 68%, respectively]), conventional amphotericin B (0.6-0.7mg/kg) was found to be significantly more related to the incidence of this event compared with caspofungin 150 mg (OR 0.08 [95% CI 0.00- 0.95]).* • Amphotericin B [and fluconazole (400 mg)] were *highly associated with discontinuation (88% [and 65%, respectively]), whereas rezafungin was the best tolerated alternative.* Regimens containing amphotericin had moderate-high efficacy (around 50%) but were associated with higher rates of discontinuation due to adverse events.

Abbreviations: ACTH = Adrenocorticotropic hormone; AF = anti-fungal; CI = confidence interval; DDIs = drug-drug interactions; CYP = cytochrome P450; DRESS = drug re*action with eosinophilia and systemic symptoms, ESCMID = European Society of Clinical Microbiology and Infectious Diseases; FAH = foci of altered hepatocytes; HMG-CoA = β-Hydroxy β-methylglutaryl- coenzyme A; IC = invasive candidiasis; incl. = including; IV = intravenous; IQR = Interquartile Range; MIC = minimum inhibitory concentration; mITT = modified Intent-to-Treat; OR = odds ratio; SJS = Stevens-Johnson syndrome; SmPC = Summary of Product Characteristic; SUCRA = surface under the cumulative ranking; TEN = toxic epidermal necrolysis*

Lower potential for drug-drug interactions (DDIs) versus currently approved treatments

The sponsor argued that further benefit of rezafungin is its potential for fewer drug-drug interaction (DDIs), which is a limitation associated with currently approved products in the EU (e.g., fluconazole, posaconazole, voriconazole, itraconazole, caspofungin, and amphotericin B).

In vitro, rezafungin is stable across species (including human) after incubation with liver and intestinal microsomes and with hepatocytes, suggesting little or no biotransformation, and comparative metabolite profiling experiments yielded no identifiable metabolites. Rezafungin is stable when

incubated in phosphatebuffered saline, with no evidence of formation of reactive intermediates (Ong et al., 2016). In addition, rezafungin was found not to be a substrate for the ATP-binding cassette (ABC) transporters: Breast Cancer Resistance Protein (BCRP), P-glycoprotein (P-gp) and Multi-drug resistance protein 2 (MRP2), or the human solute carrier (SLC) transporters: organic anion transporting polypeptide (OATP) OATP1B1 and OATP1B3, or organic cation transporters (OCT) OCT1, OCTN1, and OCTN2. As rezafungin undergoes minimal metabolism in vitro and does not appear to be a substrate of the main drug transporter proteins assessed, it is unlikely that coadministration of rezafungin with other drugs will result in a change in the exposure of rezafungin.

When considering the potential of rezafungin to cause DDIs when co-administered with other drugs, in vitro data showed that rezafungin did not cause meaningful competitive (IC50 values >25 μM) or time dependent inhibition of the major human CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4). In hepatocytes from three separate donors, no evidence of CYP induction was seen for CYP1A2 and CYP2B6 although, in the case of CYP3A4, one out of the three donors tested showed a 2.68-fold induction of mRNA expression at the highest feasible concentration tested (3 μM). Whilst rezafungin was not found to be a substrate for any of the human drug transporters tested, it was an inhibitor of transporters P-gp, OATP1B1, OATP1B3, OAT1, OCT2, OCT1, MATE1 and MATE2-K. In cases where a possible interaction was identified or could not be definitively ruled out by in vitro studies, DDI potential was assessed clinically.

Two Phase 1 studies in healthy volunteers have been conducted (Flanagan et al., 2023). The first DDI study in healthy subjects assessed the effect of rezafungin on several probe substrates of CYP enzymes and/or drug transporter proteins. The second DDI study in healthy subjects assessed the effect of rezafungin on drugs likely to be co-administered with rezafungin, namely cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax. The results of these show that rezafungin has a low DDI liability where 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 (Flanagan et al., 2023). In addition, the need for dose adjustments is considered unlikely for the following commonly coadministered medicinal products: tacrolimus, cyclosporine, ibrutinib, mycophenolate mofetil and venetoclax, when administered with rezafungin (Flanagan et al., 2023).

COMP conclusion:

Based on the results of the NMA, the echinocandins showed a higher rate of successful treatment compared to the polyenes (OR 1.41, 95% CI 1.04–1.92) and the triazoles (OR 1.82, 95% CI 1.35–2.51) overall. This points in the correct direction for the class of drugs, and there seems to be reasonable evidence from this that the class effect exists. The NMA therefore becomes a 3-way analysis and is robust enough for the COMP to agree with the sponsor and conclude on the echinocandin class effect, based on the endpoint used in the NMA of "treatment success".

The sponsor also argued that a further benefit of rezafungin is its potential for fewer DDIs, which is a limitation associated with currently approved products in the EU (e.g., fluconazole, posaconazole, voriconazole, itraconazole, caspofungin, and amphotericin B). Indeed, rezafungin does not undergo extensive oxidative metabolism and is not a substrate of drug transporting proteins, so it is unlikely that other drugs will alter rezafungin exposure. However, this argument on itself cannot justify a significant benefit over other existing methods, for the purpose of the OD legislation.

The COMP concluded that rezafungin offers a clinically relevant advantage over fluconazole, posaconazole, voriconazole, itraconazole, caspofungin, and amphotericin B based on the published NMA (Demir et al 2021).

B) Significant benefit of rezafungin versus caspofungin only

The sponsor claimed significant benefit based on a clinically relevant advantage of rezafungin group compared to caspofungin.

- *Rapid mycological clearance*

The sponsor presented the rapid mycological clearance results observed in ReSTORE and STRIVE study (Table 3).

Table 3. Mycological Clearance (Derived) at 24 h, 48 h and Day 5 in ReSTORE and in STRIVE/ReSTORE pooled analyses

Mycological clearance	**ReSTORE**		**STRIVE/ReSTORE pooled analyses**		
			Overall		
	Rezafungin n/N (%)	**Caspofungin n/N (%)**	**Rezafungin n/N** (%)	**Caspofungin n/N (%)**	**Difference (R-C) (95% CI)** [3]
24 hours [1]	36/67 (53.7)	30/65 (46.2)	63/105 (60.0)	57/116 (49.1)	-
48 hours [1]	49/66 (74.2)	41/64 (64.1)	80/103 (77.7)	73/115 (63.5)	-
Day 5 [2]	64/93 (68.8)	58/94 (61.7)	102/139 (73.4)	100/155 (64.5)	10.0 (-0.3, 20.4)

Abbreviations: C = caspofungin; R = rezafungin
[1] mITT Population with positive blood culture before randomisation. Subjects censored prior to 24 and 48 hours are excluded from the denominator for 24 hours and 48 hours, respectively.
[2] mITT Population
[3] Two-sided 95% CI for the weighted treatment difference estimate in eradication rates, rezafungin minus caspofungin, is calculated using the stratified (by study and Part A and B) methodology of Miettinen and Nurminen.

The key secondary endpoint of mycological response assessed by eradication rate at Day 5 was analysed in subjects with positive Candida culture more proximal to randomisation (mITT2 population). It was shown that the rate of mycological success at Day 5 (as confirmed by DRC) was >20% higher in the rezafungin group as compared to the caspofungin group (95% CI: -0.2, 40.2). This evidence of a more effective early response to rezafungin shows consistency with results from the Phase 2 STRIVE study where improved mycological success at Day 5 in the equivalent rezafungin (400/200 mg) treatment group was also evident. These results confirm that the high front-loaded exposure allows rezafungin to achieve a greater degree of early fungal killing following initiation of treatment than can be achieved with caspofungin.

In pooled analyses for the mITT2 Population (subjects who had a positive culture more proximal to randomisation), the rate of subjects with mycological eradication at Day 5 was 75.5% and 54.9% in the rezafungin and caspofungin groups, respectively. These results demonstrate that the improved early clearance response with rezafungin is effective in active infections, and not influenced by the window applied for defining the positive blood cultures in the mITT Population.

- *Benefits in subjects with no prior antifungal therapy*

The sponsor claimed that rezafungin shows clear benefits when subjects were analysed by status according to administration of systemic antifungals in the 48 hours preceding randomisation. In subjects who had not received prior therapy, and thus were more likely to have an active infection, mycological eradication rates at Day 5 were 19.2% (95% CI: -9.4, 43.0) higher in those who received

rezafungin compared with caspofungin-treated subjects. Global cure rates at Day 5 were also 9.8% higher in rezafungin-treated subjects compared to those treated with caspofungin (95% CI: -18.6, 35.4).

This benefit remained at Day 14: in subjects with no prior antifungal therapy within 2 days of study drug, subjects treated with rezafungin had a mycological eradication rate of 17.8% (95% CI: -9.6, 40.5) higher and a global cure rate 8.2% higher (95% CI: -19.5, 32.8) than those treated with caspofungin. According to the sponsor, this data showed consistent, sustained benefit of rezafungin in those subjects without prior systemic antifungal therapy and therefore more likely to have an active infection.

- *Improved target tissue distribution leading to improved response in candidaemia and deep-seated infections*

The sponsor also claimed that there is nonclinical evidence that rezafungin may offer superior target tissue distribution versus other echinocandins (Zhao et al., 2017), and this may be translated to the clinical setting. Although the numbers are small, the clinical benefits of the superior tissue penetration observed in non-clinical models were reflected in the mycological eradication rates observed in patients with deep-seated/visceral infections. Pooled analysis of patients with a diagnosis of invasive candidiasis with positive Candida culture proximal to randomisation showed an improvement of over 20% in mycological clearance a Day 5 and Day 14 in patients treated with rezafungin compared with caspofungin.

- *Efficacy Against Echinocandin-Resistant Infections*

The sponsor presented the global response by baseline candida species in phase 3 ReSTORE as assessed by the DRC at Day 14 (±1 day) for *C. glabrata*, *C. tropicalis*, and *C. parapsilosis.*

Table 4. Global response, investigator's assessment of clinical cure and mycological response (Eradication) as assessed by the DRC at Day 14 (±1 day) by baseline candida species in phase 3 ReSTORE – mITT population

Efficacy by Candida Species at Baseline n/N1 (%)	**Rezafungin 400/200 mg (N = 93)**	**Caspofungin (N = 94)**
Global Response as Assessed by the DRC, n/N1 (%)		
Candida albicans	21/39 (53.8)	23/40 (57.5)
Candida glabrata	16/24 (66.7)	14/25 (56.0)
Candida parapsilosis	6/8 (75.0)	11/17 (64.7)
Candida tropicalis	14/20 (70.0)	10/17 (58.8)
Investigator's Assessment of Clinical Response of Cure, n/N1 (%)		
Candida albicans	24/39 (61.5)	26/40 (65.0)
Candida glabrata	17/24 (70.8)	17/25 (68.0)
Candida parapsilosis	6/8 (75.0)	12/17 (70.6)
Candida tropicalis	15/20 (75.0)	9/17 (52.9)
Mycological Response of Eradication (Programmatically Derived), n/N1 (%)		
Candida albicans	22/39 (59.0)	24/40 (60.0)
Candida glabrata	20/24 (83.3)	15/25 (60.0)
Candida parapsilosis	6/8 (75.0)	14/17 (82.4)
Candida tropicalis	15/20 (75.0)	10/17 (58.8)

- *Additional Analyses of Subgroups*

Length of Stay in ICU

In the ReSTORE study, it was notable that the median total number of days in the intensive care unit (ICU) across all admissions was 5.0 days in the rezafungin group compared to 14.5 days in the caspofungin group (this excludes the patients that died in ICU). The median longest length of ICU stay was also lower in the rezafungin group compared to the caspofungin group (5.0 days vs 13.0 days, respectively) across all admissions. For pooled analyses across the Phase 2 and Phase 3 studies, the median total number days in ICU was 10.0 days in the rezafungin group compared to 16 days in the caspofungin group.

Further exploratory analyses were performed using only patients who were in ICU at randomisation (n=46 for rezafungin; n=67 for caspofungin). There was an imbalance between groups of patients that died in ICU (17/46 [37%] in the rezafungin arm vs. 16/67 [24%] in the caspofungin arm), and also an imbalance in the number of these patients who were mechanically ventilated (17/46 [37%] in the rezafungin arm vs 34/67 [51%] in the caspofungin arm). To account for this, a simulation exercise varying the length of stay for patients that died in ICU using a generalised linear model adjusted for mechanical ventilation was used to assess the robustness of the estimates. The data demonstrated that the most conservative benefit in length of stay in ICU was estimated as 2-3 days less in the rezafungin arm for patients who were in ICU at randomisation.

Given that increased length of stay in ICU is generally associated with increased morbidity and mortality, this evidence of reduced number of days in ICU amongst patients in the rezafungin arm compared to caspofungin could be a significant benefit both to patients and healthcare systems.

Promising Efficacy in Frail Patients

A trend towards increased efficacy has also been observed in the pooled analyses of the subgroup of patients who had an APACHE II score of ≥20 with ACM at Day 30 of 5/21 (23.8%) in the rezafungin group and 10/26 (38.5%) in caspofungin group. This coincided with improved mycological eradication at Day 5 in APACHE II of ≥20 (14/21; 81.0%) with rezafungin when compared to caspofungin (16/26; 61.5%). A similar pattern was seen at Day 14 (14/26; 66.7% vs 34/59; 57.6%, respectively).

According to the sponsor, there was also a suggestion of improved outcomes in older patients. Pooled analyses of the Phase 2 and Phase 3 data showed a lower mortality rate in those aged >65 years (ACM at Day 30 [-2 days] of 14.0%, 8/57 vs 31.7%, 20/63 in caspofungin arm). This reduced mortality again coincided with improved mycological eradication in subjects over 65 years at Day 5.

COMP conclusion

Phase 3 results from the ReSTORE study showed evidence of a more effective early response to rezafungin as indicated by increased mycological eradication at Day 5 (68.8% vs 61.7% in caspofungin group; difference = 7.1 (95% CI : 6.6, 20.6). In pooled analysis results were 73.4 % vs. 64.5% eradication, for both groups respectively (95% CI: -0.3; 20.4). However, the results are considered as "exploratory" and not valid to make inferences; note also that with increased sample size in pooled analysis, the expressed uncertainty of treatment difference involves the 0 value (i.e., negative lower bound of CI).

Post-hoc subgroup analyses were also performed to assess the impact of timing of sampling for culture in relation to study drug administration on mycological eradication rates (the component of the composite primary endpoint that focuses on the fungicidal activity of the study drugs). It was shown

that the rate of mycological success at Day 5 (as confirmed by DRC) was >20% higher in the rezafungin group as compared to the caspofungin group (95% CI: -0.2, 40.2).

In pooled analyses for the mITT2 Population (subjects who had a positive culture more proximal to randomisation), the rate of subjects with mycological eradication at Day 5 was 75.5% and 54.9% in the rezafungin and caspofungin groups, respectively. The sponsor states "results demonstrate that the improved early clearance response with rezafungin is effective in active infections, and not influenced by the window applied for defining the positive blood cultures in the mITT population". However, these seem to be post-hoc analyses and populations are smaller for mITT2 (38 on rezafungin/ 46 on caspofungin) than the mITT population (93 on rezafungin/ 94 on caspofungin) therefore do not allow for an adequate assessment of the observed differences.

In subjects who had not received prior therapy, and thus were more likely to have an active infection, mycological eradication rates (95% CI) were 19.2% (-9.4, 43.0) higher in those who received rezafungin compared with caspofungin-treated subjects at Day 5. The impact of antifungal therapy prior to randomisation continued to show a clear benefit for rezafungin-treated subjects, with a mycological eradication rate (95% CI) 17.8% (-9.6, 40.5) higher than caspofungin-treated subjects at Day 14. However, these are trends in the data, exploratory, and no inferences can be drawn.

There is nonclinical evidence that rezafungin may offer superior target tissue distribution versus other echinocandins (Zhao et al., 2017), and this may be translated to the clinical setting. Although the numbers are small, the clinical benefits of the superior tissue penetration observed in non-clinical models were reflected in the mycological eradication rates observed in patients with deep-seated/visceral infections. Pooled analysis of patients with a diagnosis of invasive candidiasis with positive Candida culture proximal to randomisation showed an improvement of over 20% in mycological clearance a Day 5 and Day 14 in patients treated with rezafungin compared with caspofungin. However, this is exploratory at this time and would need to be confirmed.

PK/PD modelling data put in the context of simulated clinical exposures showed that rezafungin is predicted to achieve high and prolonged target attainment over several weeks of therapy for both C. glabrata and C. albicans (Bader, Lakota, et al., 2018). The global response by baseline Candida species as assessed by the DRC at Day 14 (±1 day) for C. glabrata, C. tropicalis, and C. parapsilosis were higher in the rezafungin group (66.7%, 70.0%, and 75.0%, respectively) compared to the caspofungin group (56.0%, 58.8%, and 64.7%, respectively). Investigators' assessment of clinical response of cure at Day 14 (±1 day) were generally similar, although the response rate for C. tropicalis was higher in the rezafungin group (75.0%) compared to the caspofungin group (52.9%). Mycological response of eradication by baseline Candida spp. Shows eradication rates similar between rezafungin and caspofungin, although the eradication rate for C. glabrata was higher for rezafungin (83.3% versus 60.0%, respectively) and the eradication rate for C. parapsilosis was lower for rezafungin (75.0% versus 82.4%, respectively). Overall, this analysis has to be viewed as explorative and no major conclusion can be inferred.

New admissions to the ICU since Day 1 occurred in 12.9% versus 7.4% of rezafungin and caspofungin subjects, respectively. The median total number of days in the hospital across all admissions was 21.0 days and 24.0 days, respectively. Of note, the median total number of days in the ICU across all admissions was 5.0 days in the rezafungin compared to 14.5 days in the caspofungin group, and the median longest length of ICU stay was 5.0 days versus 13.0 days, respectively. Further exploratory analyses were performed using only patients who were in ICU at randomisation (n=46 for rezafungin; n=67 for caspofungin) which showed that the most conservative benefit in length of stay in ICU was estimated as 2-3 days less in the rezafungin arm for patients who were in ICU at randomisation. This is however an exploratory analysis and needs further confirmation with time.

Finally, anecdotal data gathered in a compassionate use programme cannot be a basis to support a claim of significant benefit.

C) Significant benefit of rezafungin versus caspofungin, micafungin and anidulafungin:

- *Justification for significant benefit on the basis of major contribution to patient care*

The arguments for the major contribution to patient care were based on the once-weekly dosing regimen and the fact that no dose adjustment is needed for the administration of rezafungin in special patient populations.

The currently available echinocandins require daily IV administration meaning patients have to remain hospitalised to complete the treatment. The sponsor refers to a recent observational cohort study of 64 hospitals located in 20 European countries (undertaken by The European Confederation of Medical Mycology (ECMM)) has shown hospital stay was extended specifically solely due to and for the purpose of completing parenteral antifungal treatment in 100 (16%) of 621 patients by a median of 14 days (IQR 3–23) (Egger et al., 2023). The sponsor thinks that this confirms that in the real world, the discharge date is being postponed allowing echinocandin administration in an in-patient setting in patients who are otherwise eligible for discharge.

By contrast, rezafungin has a once-weekly IV administration and thus offers patients the potential for earlier discharge, as a single administration covers 7 days of treatment. This concept was tested within rezafungin's Phase 3 clinical trial. The ReSTORE trial was double-dummy (with daily placebo administrations required) which could impact investigators' ability to exercise the discharge at their own discretion. To overcome this limitation, discharge eligibility was assessed during the follow-up visit. It was based on responses to a question on the case report form, for completion by the site principal investigator, which asked "*In your opinion, if you had the availability of once weekly IV rezafungin and did not need to administer daily placebo/caspofungin/fluconazole, would you have considered discharging this patient from hospital earlier than the actual discharge date (yes/no)? How many days earlie*r?" When asked as part of ReSTORE if once-weekly rezafungin were available and they did not need to administer a daily echinocandin, investigators said 16% of patients were considered ready for discharge, a median of 5-6 days earlier than the actual discharge date. This clinical trial outcome is in line with ECMM findings.

In addition, once weekly rezafungin will make the de-escalation approach easier to adhere to, without having to step down to oral fluconazole too early or switch to another oral azole due to non-adherence to daily IV echinocandin. Azoles are known to be associated with an adverse safety profile that includes hepatotoxicity and QT prolongation. The once-weekly dosing regimen for rezafungin also results in fewer healthcare touchpoints, thus reducing the risk of healthcare-associated infections. Additionally, once-weekly dosing allows a smaller volume of administration for antifungal treatment than daily dosing, which may be important in patients requiring fluid restriction.

The sponsor also claimed that the administration of rezafungin does not require any dose adjustment in patients with liver or renal impairment, or in elderly patients or based on weight. This represents an important benefit as dosing is simplified in the care of these particular groups of patients where dosing with alternative antifungals may require dose adjustment, and where drug dosing errors are common and for whom fewer therapeutic alternatives are available.

COMP conclusion:

A claim of major contribution to patient care may only be assessed once the equivalence of the candidate orphan product and the authorised product under comparison has been established in terms of efficacy, safety and benefit/risk balance. To that effect, reference is made to the "Commission notice

on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products" (available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN). The sponsor should first demonstrate that the efficacy, safety and benefit/risk balance of rezafungin is equivalent compared to the other products authorised for IC.

Based on the NAM, rank probability analysis suggested that rezafungin was the preferred choice for successfully treating invasive candidiasis (26.2%), followed closely by micafungin (25.8%) and anidulafungin (21.9%). In addition, the Phase 3 study (ReSTORE) demonstrated that rezafungin could be as effective as caspofungin in the treatment of invasive candidiasis. Therefore, the COMP concluded that the efficacy rezafungin has equivalent efficacy over the approved medicinal products in the same class for treatment of candidiasis (micafungin, anidulafungin and caspofungin).

The sponsor claimed major contribution to patient care of rezafungin compared to other echinocandins such as micafungin, anidulafungin and caspofungin. However, the sponsor should further elaborate on the argument of the major contribution to patient care of the proposed product versus caspofungin, micafungin and anidulafungin. The sponsor should provide any further justification and additional data in order to support the claim.

Overall COMP conclusion

The COMP agreed that significant benefit has been shown over the azoles and polyenes. Based on the primary analysis, which employed a 20% non-inferiority margin, the Phase 3 study demonstrated that rezafungin could be as effective as caspofungin in the treatment of invasive candidiasis. The sponsor has not been able to establish that rezafungin has any important advantages in terms of spectrum, efficacy or safety over the approved agents in the same class for treatment of candidiasis and there is therefore no clinically relevant advantage of rezafungin. As it is agreed that rezafungin is at least equivalent in terms of efficacy, safety and benefit/risk balance as compared with the echinocandins, the claim for a MCPC can be considered, however, the justification by the sponsor for this claim has not been sufficiently substantiated.

Comments on sponsor's response to the COMP list of issues

In the written response, the sponsor presented their responses to the COMP's list of questions: The sponsor should further elaborate on the argument of the major contribution to patient care of the proposed product versus caspofungin, micafungin and anidulafungin. The sponsor presented a summary of the major advantages for patient care in those with candidaemia and/or invasive candidiasis in a number of ways (Table 5)

Table 5. The major contributions to patient care offered by rezafungin over currently available echinocandins

	Rezafungin	**Caspofungin**	**Micafungin**	**Anidulafungin**
Dosing	Once per week	Daily	Daily	Daily
Hospital Stay (Days)	25.9	28.8-45.6	35.5-45.2	29.6
Number of Infusions (14 days therapy)	2	14	14	14
Volume of Infusions (mL; 14 days therapy)	500	3640	1400	1950
Potential for Outpatient Therapy	Yes	Low – daily infusions	Low – daily infusions	Low – daily infusions
Potential for Early Discharge	Yes	Poor	Poor	Poor
IV Line Risks	Low	Higher	Higher	Higher
Need for Oral Step-down Therapy	None	If not remaining in hospital	If not remaining in hospital	If not remaining in hospital
Dose Adjustments by Weight	No dose adjustment by weight	Dose adjustment by weight needed.	Dose adjustment by weight needed.	No dose adjustment by weight
Patients with Hepatic Impairment	Can be used in patients with hepatic impairment, no dose adjustment required	No clinical experience in patients with severe hepatic impairment and caspofungin should be used with caution in these patients. Dose adjustment needed in patients with moderate hepatic impairment.	Micafungin use is not recommended in patients with severe hepatic impairment	No dose adjustment is required in patients with hepatic impairment

The arguments on the major contribution to patients care are presented below:

1. Enabling echinocandin treatment to be provided in an outpatient setting

The introduction of rezafungin will enable appropriate patients to be transitioned to an outpatient setting while maintaining continuity of echinocandin treatment. This allows physicians to meet current treatment guidelines of a full 14 days of antifungal treatment, with no requirement to switch to another drug class with a different mode of action that may be less efficacious (Ioannidis et al., 2020).

In addition to earlier discharge for medically fit patients, the availability of rezafungin means an echinocandin can be readily used in an out-patient setting. Outpatient parenteral antimicrobial therapy has been recognised to benefit patients in terms of improved safety, efficacy, and patient satisfaction (Chapman et al., 2009; Durojaiye et al., 2018; Gil-Navarro et al., 2020).

2. Reducing clinical burden

As rezafungin only requires once-weekly administration compared to the daily IV administration needed for other currently available echinocandins, the burden of clinical care for patients over the recommended 14-day treatment course will be significantly reduced through:

- Reduction in the number of infusions and fewer complications resulting from an IV line

A reduction in the number of infusions required for full antifungal treatment over a period of at least 14 days (Table 6) will significantly reduce the burden of clinical care for patients, through fewer complications resulting from an intravenous line, less potential for fluid overload in patients requiring careful fluid management, and a single, simple dosing regimen.

Table 6. Comparison of Echinocandin Treatment Duration and Administration Time Required

Echinocandin	**Rezafungin**	**Caspofungin**	**Micafungin**	**Anidulafungin**
Treatment Duration Required	≥14 days	≥14 days	≥14 days	≥14 days
Minimum Infusions Required	2	14	14	14
Length of Each Infusion	Approx. 1 hour	Approx.1 hour	Approx. 1 hour	3* or 1.5 hours
Total Time Required for Infusions	2 hours	14 hours	14 hours	22.5 hours

* 3 hours is required for 200 mg loading dose of anidulafungin, the following 100 mg doses should be infused over 1.5 hours ; Information from REZZAYO (rezafungin) SmPC, CANCIDAS (caspofungin) SmPC, Mycamine (micafungin) SmPC and ECALTA (anidulafungin) SmPC

In addition, in patients with no need to keep intravenous catheters for administration of other medication during their hospital stay, the once-weekly IV administration of rezafungin allows for removal of the intravenous line between weekly administrations. Furthermore, temporary peripheral IVs are sufficient for outpatient courses of once weekly rezafungin, reducing the risk of procedure-related adverse outcomes.

This thereby eliminates the need for peripheral intravenous catheter (PIVC) placement (which is extremely unpleasant for patients) purely for the purposes of antifungal agent administration and reduces the risks associated with placement of any PIVC, in contrast to the need for a permanent

intravenous catheter through which to administer the other available echinocandins daily. This benefit is more likely to be enjoyed by patients in a general ward, rather than in the ICU where patients are likely to require a PIVC to deliver other medication and/or fluids.

- Less potential for fluid overload in patients requiring careful fluid management

Moving away from the daily administration required for caspofungin, micafungin or anidulafungin to the weekly administration of rezafungin will decrease the total administered intravenous fluid load to patients diagnosed with invasive candidiasis where an echinocandin is indicated (Table 7). This may be especially important in patients with fluid restriction, for instance those with congestive heart failure or renal impairment.

Table 7. Infusion Volumes Required for 14 Day Courses of Echinocandins

Product name	**Active ingredient**	**Volume for loading dose (mL)**	**Volume for subsequent doses (mL)**	**Instances of Administration Required in 14 days**	**Total volume (mL)**
Rezzayo[a]	Rezafungin	250	250	2	500
Cancidas[b]	Caspofungin	260	260	14	3640
Mycamine[c]	Micafungin	100	100	14	1400
Ecalta[d]	Anidulafungin	260	130	14	1950

[a]ReSTORE clinical trial. [b]CANCIDAS, INN-caspofungin (as acetate) (europa.eu). [c]MICAFUNGIN-PSJ, INN-Micafungin Sodium (europa.eu).[d]Ecalta, INN-anidulafungin (europa.eu).

- One single, simple dosing regimen

Rezafungin uses a single dosing regimen in all adults and does not require any dose adjustment based on weight, in patients with liver or renal impairment, or in elderly patients. This is in contrast to some of the currently available echinocandins: caspofungin and micafungin both require dose adjustment by weight of the patient, and caspofungin and micafungin use is not recommended in patients with severe hepatic impairment.

3. Reduced hospitalisation time

Rezafungin studies ReSTORE and STRIVE showed reduced ICU and hospital stays; both of which compared rezafungin with no oral stepdown to caspofungin with optional oral fluconazole step-down therapy. The shorter total hospital length of stay effect was seen in the rezafungin group in both survivor and all-patient analyses, and with and without adjustment for mechanical ventilation as per pooled data (Table 8).

Table 8. Total Length of Hospital Stay in the Pooled Analysis (mITT Population)

	Rezafungin (N=139)	**Caspofungin (N=155)**	**Absolute difference**
	All patients		
Unadjusted mean (SD)[a] LoS, days	25.2 (19.26)	28.3 (20.16)	3.1
Adjusted mean (95% CI)[a] LoS, days	25.9 (22.2,28.6)	28.8 (25.2,31.9)	2.9
	Survivors only[b]		
n (%)	112 (80.6)	125 (80.6)	-
Unadjusted mean (SD) LoS, days	25.7 (18.4)	28.7 (17.9)	3.0

CI, confidence interval; ICU, intensive care unit; LoS, length of stay; mITT, modified intention to treat; SD, standard deviation
A Generalised linear model, unadjusted or adjusted for mechanical ventilation status; b patients who did not die in hospital during the trial

Although the original randomised clinical trials of other echinocandins (micafungin and anidulafungin) did not report length of hospital stay (Kuse et al., 2007; Reboli et al., 2007), further studies have reported this, though different comparisons were used. Many analyses report on "excess" hospital length of stay rather than total length of stay, due to *Candida* species being a common hospital acquired infection, which does not allow comparison with the current data from randomised clinical trials collected for rezafungin.

From publications that do report full duration of hospitalisation (Table 9), length of stay for invasive candidiasis has been reported as 45.2 days for micafungin and 43.6 for caspofungin (Sidhu et al., 2009). A retrospective study to assess pharmacoeconomic outcomes of patients receiving a 100 mg once-daily dose of micafungin to treat candidaemia reported a length of hospital stay of 40.89 ± 22.3 days (n = 29), with a duration of micafungin treatment of 7.17 ± 3.6 days (Marfo & Guo, 2009). An economic study investigating the cost effectiveness of micafungin compared with liposomal amphotericin B (LAmB) in Germany found a length of hospital stay of 35.5 days (Cornely et al., 2008). Average length of hospitalisation was found to be 29.6 days in patients treated with anidulafungin (Reboli et al., 2011).

Table 9. Comparison of Echinocandin Length of Hospital Stay

Echinocandin	**Rezafungin**	**Caspofungin**	**Micafungin**	**Anidulafungin**
Length of Hospital Stay (days)	25.9	28.8 – 43.6	35.5 – 45.2	29.6
Source	ReSTORE and STRIVE pooled studies	ReSTORE and STRIVE pooled studies, (Sidhu et al., 2009)	(Cornely et al., 2008; Marfo & Guo, 2009; Sidhu et al., 2009)	(Reboli et al., 2011)

Due to the complexity of ICU patients, and the inability to control for confounding factors such as APACHE II/SOFA scores, and/or mechanical ventilation status, data on ICU length of stay can only be compared in a head-to-head study setting; thus, for this outcome, rezafungin has only been compared with caspofungin using pooled data from the ReSTORE and STRIVE studies.

Patients treated with rezafungin had a numerically shorter mean ICU stay than patients in the caspofungin group in both survivor and all-patient analyses of the pooled data set. In all patients with an ICU stay, the mean ICU stay was 16.1 days versus 21.6 days for rezafungin and caspofungin, respectively (Table 10). In patients admitted to ICU who did not die in hospital during the trial, the difference was greater, with a mean ICU stay of 15.9 days in the rezafungin group and 23.0 days in the caspofungin group. However, there was an imbalance in the number of ICU patients who were mechanically ventilated in both the ReSTORE and STRIVE studies (16/55 [29.1%] in the pooled rezafungin arm versus 33/71 [46.5%] in the pooled caspofungin arm). When adjusting for this imbalance in all patients with an ICU stay, patients in the rezafungin group still demonstrated reduced ICU stays compared to the caspofungin group: 17.3 days in the rezafungin group compared to 21.4 days in the caspofungin group.

Table 10. Length Of ICU Stay In STRIVE/ReSTORE Pooled Analysis (Patients with an ICU Stay, mITT Population)

	Rezafungin (N=139)	**Caspofungin (N=155)**	**Absolute Difference**
All patients			
N (%) with ICU stay	55 (39.6)	71 (45.8)	-
Unadjusted mean (SD)[a] LoS, days	16.1 (15.2)	21.6 (18.0)	5.5
Adjusted mean (95% CI)[a] LoS, days	17.3 (13.4,20.6)	21.4 (17.3,26.8)	4.1
Survivors Only[b]			
n (%)	35 (25.2)	53 (34.2)	-
Unadjusted mean (SD) LoS, days	15.9 (16.4)	23.0 (19.6)	7.1

CI = confidence interval; ICU = intensive care unit; LoS = length of stay; mITT = modified intention to treat; SD = standard deviation
[a]Generalised linear model, unadjusted or adjusted for mechanical ventilation status; [b]patients who did not die in hospital during the trial.

This evidence of reduced number of days in ICU and general hospital wards amongst patients treated with rezafungin could be a significant benefit both to patients and healthcare providers. Infection risk increases with increased length of stay in both hospital and ICU (Jeon et al., 2012; Mujagic et al., 2018; Playford et al., 2007).

Longer ICU stay is also associated with worse health-related quality of life outcomes (HR-QoL) after discharge (Granja et al., 2005; Oeyen et al., 2010). Data from a large single-centre study of 32,270 patients in London found that short length of stay in hospital was associated with favourable post-discharge outcomes such as reduced rates of early readmission and mortality (Han et al., 2022). ICU stay also impacts mental health, which can have a large impact on quality of life post-discharge (Teixeira et al., 2021). Overall, these associations mean that increased length of stay in hospital and ICU is associated with increased morbidity and mortality (Han et al., 2022; Moitra et al., 2016; Williams et al., 2010), risks which a shorter length of stay facilitated by rezafungin treatment will decrease.

Another advantage of reduced ICU and hospital length of stay is the increased rate at which facilities will become available for other patients in need. Concerns around scarcity of critical care resources began before the SARS-CoV-2 pandemic, which put an extreme strain on ICU facilities and personnel. Recent UK analysis of the demand for complex services in health care (projections for 2018-2030) demonstrates that more hospital capacity will almost certainly be required to meet people's health needs over this decade, irrespective of if another pandemic is likely or not (Rocks & Rachet-Jacquet, 2022).

COMP discussion

The COMP agreed that there are well-described risk factors associated with invasive candidiasis that apply to all hospitalized persons but especially to those in the ICU. Some risk factors are intrinsic to the host or the disease state, whereas others are the result of iatrogenic interventions. The most common individual risk factors include the presence of an indwelling central venous catheter, exposure to broad-spectrum antibacterial agents, long-term ICU stay with or without assisted ventilation, recent major surgery, necrotizing pancreatitis, any type of dialysis, total parenteral nutrition and iatrogenic immunosuppression.

From the data submitted above the COMP concluded that a major contribution to patient care can be justified based on the reduced hospital stay in ICU, the potential for earlier patient discharge, the lower risk of IV fluid overload, which is a significant risk in patients with renal impairment or requiring dialysis and the reduced clinical burden for the patients. In conclusion, the flexibility of using a weekly dosed rezafungin for treating invasive candidiasis would be a major contribution to patient care in clinical practice.

COMP conclusion

The COMP concluded that the sponsor has provided clinical data showing improved efficacy compared to the azoles and polyenes which corresponds to a clinically relevant advantage. In addition, the reduced hospital stay in intensive care unit constitutes a major contribution to patient care over the other echinocandins. The major contribution to patient care is also supported by the once weekly administration of rezafungin, over the daily intravenous administration of the other echinocandins.

4. COMP position adopted on 13 November 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of invasive candidiasis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 1.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening with above 50% mortality in the acute phase in intensive care unit;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union for all the patients covered by Rezzayo, the assumption that Rezzayo may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data showing improved efficacy compared to the azoles and polyenes which corresponds to a clinically relevant advantage. In addition, the reduced hospital stay in intensive care unit constitutes a major contribution to patient care over the other echinocandins. The major contribution to patient care is also supported by the once weekly administration of rezafungin, over the daily intravenous administration.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Rezzayo, rezafungin acetate, for treatment of invasive candidiasis (EU/3/20/2385) is not removed from the Community Register of Orphan Medicinal Products.