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DRUG EVALUATION

Rezafungin acetate for the treatment of candidemia and invasive candidiasis: a pharmacokinetic evaluation

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ABSTRACT

Introduction: Rezafungin, formerly SP3025 and CD101, is a next-generation echinocandin, chemically related to anidulafungin, with differentiated pharmacokinetic characteristics, including a prolonged half-life allowing extended-interval dosing.

Areas covered: Herein, we discuss the role of rezafungin in the treatment of candidemia and invasive candidiasis, with a specific focus on pharmacokinetics considerations.

Expert opinion: Rezafungin exhibits potent in vitro activity against most wild-type and azole-resistant *Candida* species, including *Candida auris*. The differentiated PK characteristics of rezafungin which enables once weekly dosing could reduce catheter overuse and provide a rapid transition to outpatient treatment for *Candida* infections in which azoles cannot be used, due to resistance or drug-drug interactions. Besides weekly dosing, other potential pharmacokinetic/pharmacodynamic advantages of rezafungin are its good penetration into anatomically challenging sites and a potentially reduced probability of local resistance promotion, making it an attractive option also for deep-seated infections that could warrant dedicated clinical investigation.

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KEYWORDS
Rezafungin; SP3025; CD101; PK/PD; echinocandins; candidemia; invasive candidiasis

1. Introduction

Candidemia and invasive candidiasis are important causes of morbidity and mortality with high health-care management associated costs, especially among critically ill patients in intensive care unit (ICU) [1–3]. Over the last decades, the management of candidemia has continuously evolved. Currently, the Infectious Diseases Society of America (IDSA) recommends starting echinocandins for moderate-to-severe cases, like those with hemodynamic instability, neutropenia, recent azole exposure, and high risk for *Candida glabrata* or *Candida krusei* infection [4]. The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend echinocandins as the first line treatment for invasive candidiasis due to their high fungicidal activity, broad-spectrum coverage and safety profile [5].

Rezafungin (Box 1) is a next-generation echinocandin, chemically related to anidulafungin, with differentiated pharmacokinetic characteristics, including a prolonged half-life (around 133 hours) allowing extended-interval dosing [6]. The documented potency, spectrum, and safety of previously approved echinocandins support their recommendation as a first-line therapy for candidemia [4,5]. However, they are not exempt from some important limitations, most notably the poor oral absorption and their relatively short half-lives, 14 hours [7]. For these reasons, short half-life echinocandins are administered intravenously and daily, thereby reducing suitability for outpatient use (especially in case of resistance to azoles precluding step-down to oral therapy). Against this background, the prolonged half-life of rezafungin may overcome these important limitations. Like other echinocandins, rezafungin exhibits potent *in vitro* activity against most wild-type and azole-resistant *Candida* species, including *Candida auris*, and it also shows activity against other fungal species (see Figure 1) [8–10].

Herein, we discuss the role of rezafungin in the treatment of candidemia and invasive candidiasis, with a specific focus on pharmacokinetics considerations.

2. Overview of the market

Rezafungin adds to three other echinocandins already approved for the treatment of candidemia and invasive candidiasis in US and Europe (caspofungin, anidulafungin, and micafungin, all administered daily and intravenously).

3. Pharmacodynamics

Rezafungin is a noncompetitive inhibitor of (1,3)-β-D-glucan (BDG) synthase which inhibits formation of BDG in fungal cells

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Article highlights

- Rezafungin is a next-generation echinocandin with differentiated pharmacokinetic characteristics, including a prolonged half-life
- The prolonged half-life of rezafungin enables and extended-interval dosing (once weekly)
- This could reduce catheter overuse and provide a rapid transition to outpatient treatment for Candida infections in which azoles cannot be used, due to resistance or drug-drug interactions
- The exact cost – benefit balance of this approach remains to be established, although some preliminary results suggested possible advantages

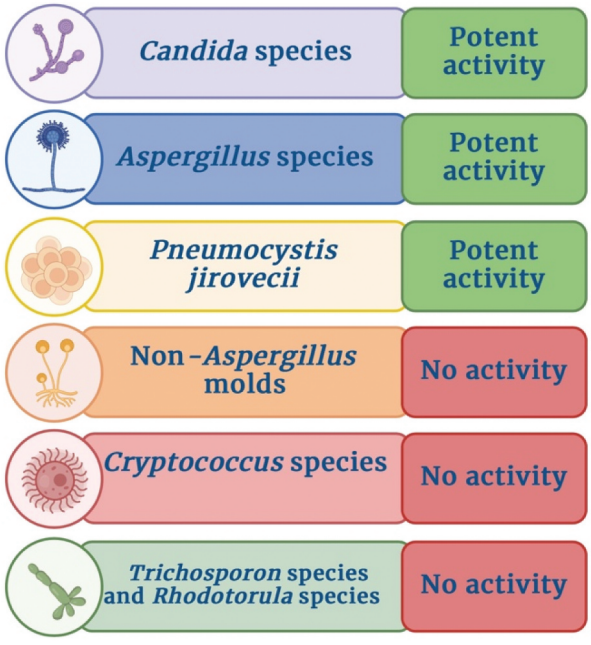

Figure 1. *In vitro* activity of rezafungin against different fungi.

legend. Activity of rezafungin according to *in vitro* studies [8–10]. Created with BioRender.com

walls causing osmotic instability and cell lysis [11]. Rezafungin exhibits both fungicidal and fungistatic activity against *Candida* and *Aspergillus* species, respectively [12]. It has a broad spectrum of *in vitro* activity against fungal species. *Candida* species are the most well studied with pooled susceptibility data of almost 8,000 strains being tested with mostly similar minimum inhibitory concentration (MIC) values (defined as the minimum concentration at which 50% and 90% of the isolates were inhibited, respectively) seen among echinocandin antifungals [13]. The pooled $MIC_{50/90}$ values for *Candida albicans*, *C. glabrata*, *C. krusei*, *Candida parapsilosis*, and *Candida tropicalis* were 0.03/0.06, 0.06/0.12, 0.03/0.12, 1/2, and 0.03/0.06 µg/mL, respectively. Rezafungin has displayed potent activity against *Candida auris* in both *in vitro* and *in vivo* pre-clinical models [14]. The primary resistance mechanism for rezafungin, and other echinocandins, is hot spot mutations in the target enzyme gene *FKS*, which encoded for the catalytic component (Fksp) of 1,3-β-d-glucan synthase (i.e. the echinocandins target), thus resulting in reduced sensitivity to echinocandins and elevated echinocandin MIC values

Box 1. Drug summary box

Drug name	Rezafungin
Phase	Phase IV
Adults	*European Medicines Agency (EMA)* • Treatment of invasive candidiasis, including candidemia Food and Drug Administration (FDA) • Treatment of candidemia and invasive candidiasis in patients who have limited or no alternative treatment options
Pharmacology description	Noncompetitive inhibition of the enzyme (1,3)-β-D-glucan synthase
Route of administration	Intravenous
Chemical structure	Structural analog of anidulafungin, with a key change at the echinocandin cyclic nucleus (hemiaminal region replaced with a choline aminal ether) which significantly reduces chemical degradation of the compound [18]
Pivotal RCT	Phase-2 (STRIVE, NCT02734862) and Phase-3 (ReSTORE, NCT03667690) randomized controlled trials (RCT) [6,22] for the treatment of candidemia and invasive candidiasis

RCT, randomized controlled trials.

across various *Candida* species [15]. For FKS mutants, rezafungin shares similar *in vitro* activity when compared with other echinocandins [16]. The pooled minimum effective concentration $(MEC)_{50/90}$ values (defined as lowest concentration to produce short and aberrant hyphal branching under the microscope at 50% and 90% of the isolates respectively) for *Aspergillus fumigatus*, *Aspergillus flavus*, and *Aspergillus terreus* were 0.03/0.03, 0.03/0.015, and 0.015/0.015 µg/mL, respectively [13]. In addition, rezafungin has good activity against azole-resistant *Aspergillus* species [17]. Rezafungin has good activity against *Pneumocystis jirovecii* but no activity against *Cryptococcus* species or Mucorales. Rezafungin exhibits concentration-dependent killing with the area under the curve (AUC)/MIC being the best pharmacodynamic index of killing. For *C. albicans* and *C. glabrata*, rezafungin 400 mg for 1 week followed by 200 mg weekly for 5 weeks achieved > 90% probability of target attainment for MIC_{90} values through to week 6 [16].

4. Pharmacokinetics and metabolism

Rezafungin is a structural analog of anidulafungin, with a key change at the echinocandin cyclic nucleus (hemiaminal region replaced with a choline aminal ether) which significantly reduces chemical degradation of the compound (see Figure 2) [18]. This alteration increases drug stability and solubility when compared with anidulafungin, giving it the

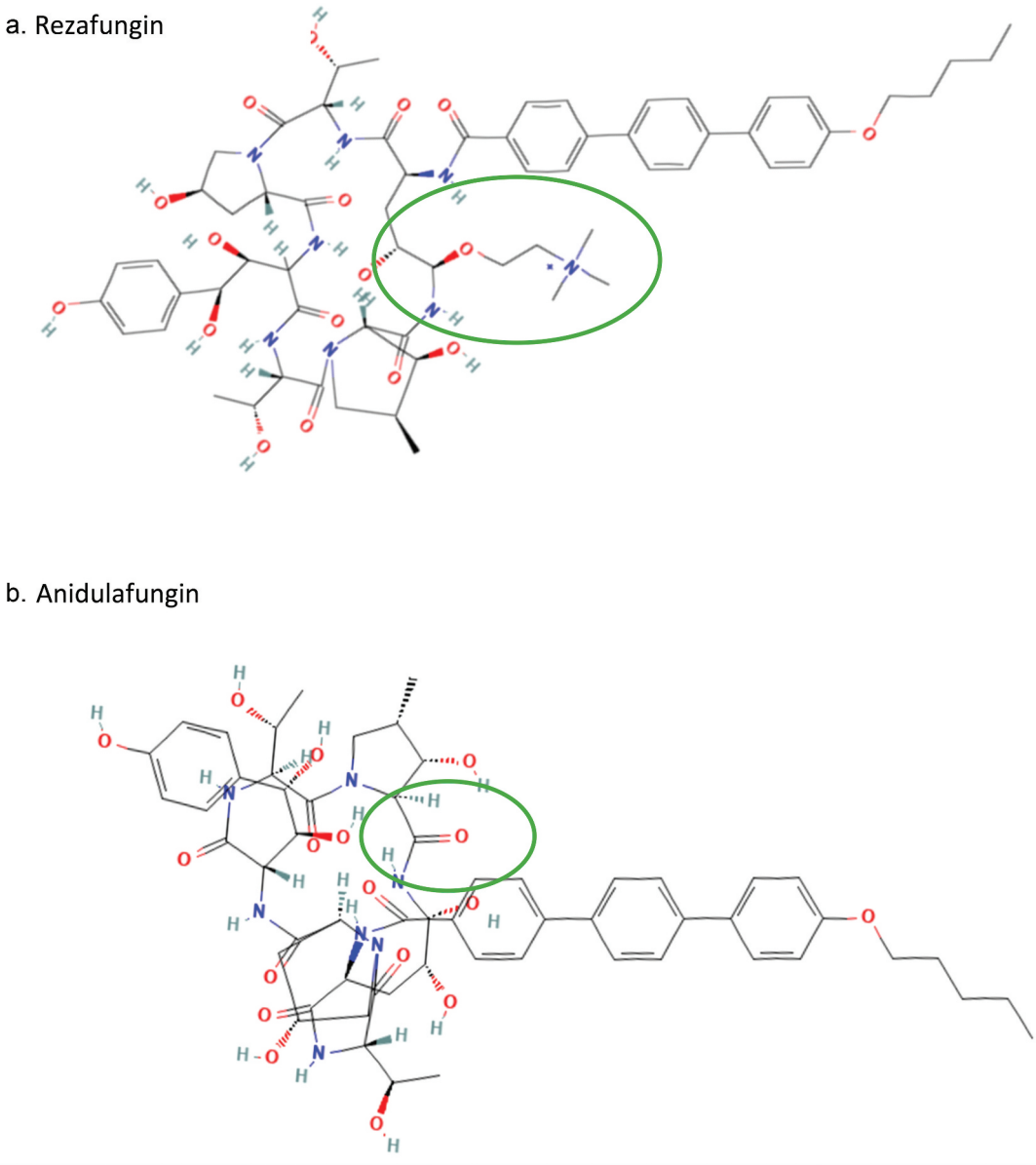

Figure 2. Differences in structural formulas of (a) rezafungin and (b) anidulafungin.

legend. Both rezafungin (a) and anidulafungin (b) share a cyclic hexapeptide core attached to a fatty acid side chain. Rezafungin contains a long lipophilic side chain with an oxygen substitution which enhances its stability and prolongs its half-life (green circle), whereas anidulafungin has a different side chain with a simpler aliphatic structure (green circle). Adapted from https://pubchem.ncbi.nlm.nih.gov/

unique feature of a prolonged half-life of approximately 133 hours, with a half-life of approximately 80 hours following the first dose in healthy adults (more than 5 times the half-life of other echinocandins) [19]. This enables favorable once-weekly intravenous dosing. The volume of distribution of rezafungin is similar to other echinocandins, with a mean value at steady state ranging from 25 to 32 liters [19]. Rezafungin is highly protein bound and has a slow mean total body clearance of approximately 0.2 L/h [19]. These pharmacokinetic properties allow for high-level front-loaded plasma drug exposure with a low rate of total plasma clearance. This means reaching effective drug exposures immediately after dosing which maximizes drug effect early in the course of therapy. Early phase clinical trial data has described key pharmacokinetic parameters of rezafungin in healthy adults. Area under the curve (AUC) and maximum concentration in plasma increased in a dose-proportional manner in single ascending dose studies. Renal elimination of parent drug is minimal (<1%) indicating its minor contribution in rezafungin excretion. The majority of elimination is through feces with 74.3% recovered at 60 days, compared with 25.7% in urine [20]. There is very minimal biotransformation with mainly parent drug being recovered up to 60 days post-administration [20]. Rezafungin is mainly retained in plasma and not the cellular portion of whole blood. Current recommended dosing regimen is 400 mg loading dose followed by 200 mg weekly. The mean C_{max} and AUC values ranged from 10.6 to 12.4 µg/mL (day 1 to day 8) and from 570 813 µg • h/mL (day 1 to day 8) in healthy adults (200 mg dosing) [19]. Following IV administration, the population pharmacokinetics (PK) of rezafungin using data from five

Table 1. Population pharmacokinetic parameters in patients with candidemia or invasive candidiasis following rezafungin administration (initial 400 mg loading dose, followed by a 200 mg dose once weekly).

Parameter	Value	
Exposure	Day 1	Day 15
Cmax (μg/mL)	19.2±5.9	11.8±3.5
AUC (μg · h/mL)	827±252	667 ± 224
Cmin (μg/mL)	2.4 ± 0.9	2.2±0.9
Distribution		
% bound to human plasma proteins	Mean estimates varied from 87.5% to 93.6% in patients Mean estimates varied from 95.6% to > 98.6% in healthy adults	
Volume of distribution (L)	67 ± 28	
Elimination		
Clearance (L/hr)	0.35 ± 0.13	
Terminal half-life (hr)	152 ± 29	
Metabolism		
Metabolic pathways	Hepatic metabolism of rezafungin has not been observed. It is unlikely that rezafungin is a clinically relevant substrate of CYP450 enzymes	
Excretion		
Major route of elimination	Faecal excretion	
% feces	74.3% of recovered radioactivity, primarily as rezafungin	
% urine	25.7% of recovered radioactivity, primarily as inactive metabolites	

Adapted from [30].

Phase 1, one Phase 2, and one Phase 3 study was best described as a linear three-compartment model impacted by weight which is typical for the echinocandin class of antifungals. Indeed, albumin concentrations, body surface area (BSA), and disease state impacted model parameters [21]. Although, these covariates were not associated with clinically meaningful PK changes. This indicates that a common dose regimen is appropriate for all adult patients with a variety of disease states. A summary overview of the main pharmacokinetic parameters of rezafungin is available in Table 1.

5. Clinical efficacy

The clinical efficacy of rezafungin for treating candidemia and invasive candidiasis was assessed in Phase-2 (STRIVE, NCT02734862) and Phase-3 (ReSTORE, NCT03667690) randomized controlled trials (RCT) [6,22].

STRIVE was a phase-2, double-blind RCT comparing rezafungin either administrated 400 mg weekly or 400 mg for the first week and 200 mg weekly thereafter with caspofungin (once daily and optional switch to oral fluconazole) for the treatment of candidemia and invasive candidiasis, for a total of two to four weeks of treatment [6]. The primary efficacy population was the microbiological intent-to-treat (mITT) population, including patients receiving any amount of study drug and with a documented *Candida* infection at baseline. The primary efficacy endpoint was overall cure, defined as resolution of signs of infection and mycological eradication at day 14. Overall, 183 patients were included in the mITT population (76 in the rezafungin 400 mg arm, 46 in the rezafungin 400/200 mg arm, and 61 in the caspofungin arm). The overall cure was 60.5%, 76.1%, and 67.2% in rezafungin 400 mg, rezafungin 400/200 mg, and caspofungin arms, respectively. Notably, candidemia (registered in 76.5%, 80.7%, and 81.2% of patients in rezafungin 400/200 mg, rezafungin 400 mg, and caspofungin arms, respectively) cleared more rapidly in patients treated with rezafungin compared to those in the caspofungin arm (mycological eradication rates at day 5 were 80.0% for rezafungin vs 67.8% for caspofungin), suggesting a potential enhancement in fungicidal activity, possibly due to the high initial rezafungin concentrations [23,24].

ReSTORE was a multicentre, double-blind, double-dummy, non-inferiority, phase-3 RCT including adults with candidemia or invasive candidiasis [22]. Patients were randomly assigned (1:1) to receive either intravenous rezafungin once weekly (400 mg for the first week and 200 mg weekly thereafter, for a total of two to four doses) or intravenous caspofungin (70 mg loading dose on day 1, followed by 50 mg daily, for a total of two to four weeks). The primary study population was the modified ITT population, defined as patients with documented *Candida* infection and receiving at least one dose of study drug. The FDA primary endpoint was all-cause mortality at day 30, whereas the EMA primary endpoint was global cure at day 14, defined as clinical cure as assessed by the investigator, radiological cure, and mycological eradication. The non-inferiority margin was 20%. The modified ITT population included 187 patients (93 patients in the rezafungin arm and 94 patients in the caspofungin arm). Candidemia only occurred in 70% and 69% of patients in rezafungin and caspofungin arms, respectively, whereas invasive candidiasis (with or without candidemia) was diagnosed in 30% and 31% of patients in rezafungin and caspofungin arms, respectively. All-cause mortality at day 30 was 24% and 21% in rezafungin and caspofungin arms, respectively (observed difference 2.4%, with 95% confidence interval [CI] from 14.9 to 12.7), whereas global cure at day 14 was 59% and 61% in rezafungin and caspofungin arms, respectively (weighted difference – 1.1%, with 95% CI from – 14.9 to 12.7). Regarding efficacy in subgroups by *Candida species*, rates of all-cause mortality and global cure were comparable between study arms and did not appear to be impacted by MIC values for either rezafungin or caspofungin [25]. Main efficacy results of the ReSTORE RCT are summarized in Table 2.

Pooled data from STRIVE and ReSTORE trials (including a total of 294 patients) confirmed similar all-cause mortality at day 30 (weighted difference – 1.5%, with 95% CI from – 10.7 to 7.7) [26]. In subgroup analyses, a larger difference was noted in patients with candidemia only, who represented > 70% of the pooled population (weighted difference 12.9%, with 95% CI from 1.5 to 24.3), and in those with a positive blood culture proximal to randomization (i.e. from a blood sample obtained within 12 hours before or 72 hours after randomization or a sample from a normally sterile site obtained within 48 hours before or 72 hours after randomization; weighted difference 19.2%, with 95% CI from 3.0 to 35.5).

An ongoing phase-3, multicenter, prospective, randomized, double-blind RCT (ReSPECT, NCT04368559) aims to assess the efficacy of rezafungin for the prevention of invasive fungal diseases in patients undergoing allogeneic blood and marrow transplantation, in comparison to

Table 2. Summary of efficacy results from the ReSTORE trial.

	Rezafungin 400 mg/200 mg N = 93 n (%)	Caspofungin N = 94 n (%)	Difference (95% CI)
All-Cause Mortality (Day 30)	22 (23.7)	20 (21.3)	2.4 (−9.7, 14.4)
Global Cure			
Day 5	52 (55.9)	49 (52.1)	3.8 (−10.5, 17.9)
Day 14	55 (59.1)	57 (60.6)	−1.5 (−15.4, 12.5)
Clinical Cure			
Day 5	59 (63.4)	70 (74.5)	−11.0 (−24.0, 2.3)
Day 14	62 (66.7)	63 (67.0)	−0.4 (−13.8, 13.1)
Day 30	51 (54.8)	52 (55.3)	−0.5 (−14.6, 13.7)
Mycological eradication/presumed eradicated			
Day 5	64 (68.8)	58 (61.7)	7.1 (−6.6, 20.6)
Day 14	63 (67.7)	62 (66.0)	1.8 (−11.7, 15.2)

Adapted from [30].

a standard regimen containing daily azole prophylaxis with fluconazole or posaconazole and anti-*Pneumocystis jirovecii* pneumonia prophylaxis with oral trimethoprim-sulfamethoxazole. Finally, in the phase-2 RADIANT RCT (NCT02733432), a topical formulation of rezafungin was compared to oral fluconazole for the treatment of vulvovaginal candidiasis (VVC), showing good tolerability but lower cure rates in comparison to fluconazole for VVC [27].

6. Safety

Phase-1 studies assessing safety of rezafungin in healthy adults consisted of two dose-escalation studies up to 400 mg once weekly for 3 consecutive weeks (NCT02516904 and NCT02551549) [19]. Most adverse events (AE) reported were mild, mostly chest discomfort, constipation, flushing, nausea, and myalgia. In the multiple-ascending-dose study, there was a tendency toward higher rates of AE in patients receiving the highest dose of rezafungin (400 mg once weekly for 3 weeks). Nevertheless, no serious AE (SAE), withdrawals because of AE, or deaths were reported, and no safety issues related to laboratory results, physical examination, or vital signs were registered.

A randomized, double-blind, phase-1 study conducted in healthy volunteers evaluated cardiac effects of single doses of intravenous rezafungin vs. intravenous placebo (with moxifloxacin as positive control) on the QT interval. Two rezafungin doses (600 mg and 144 mg) were administered to achieve therapeutic and supratherapeutic exposures of up to approximately 2.5-fold higher than produced by the highest dose used in the STRIVE phase-2 RCT (400 mg once weekly). No clinically significant effects of concern were registered [28].

With regards to safety of rezafungin in the STRIVE RCT and ReSTORE RCT, treatment-emergent AE occurred at a similar rate to the comparator AE occurring ≥ 5% were diarrhea, vomiting, nausea, abdominal pain, and constipation [6,22]. Infusion-related and hepatic adverse reactions were registered with 9.3% discontinuing rezafungin due to the adverse reaction compared with 9.0% in the comparator arm.

Dose-related neurotoxicity, including tremors and neurodegeneration, was observed in non-clinical studies in nonhuman primates treated with rezafungin, but no neurotoxic concerning AEs were observed in completed clinical studies [29]. It is nonetheless worth mentioning that, due to safety concern in non-clinical studies, additional eligibility criteria were added in ReSTORE trial to exclude patients with potential for increased risk of neurotoxicity, and neurological sign and symptoms were monitored in the study [30]. In the RADIANT trial of topical formulations of rezafungin for VVC, treatment-emergent AE were unrelated to the study drugs, and all were mild or moderate in intensity, with no SAE reported [27]. Finally, an assessment of subcutaneous route of administration for rezafungin was explored in another phase I study (NCT04117607) conducted in healthy subjects to determine the safety of subcutaneous application (single dose of escalated doses from 1 to 200 mg). The study was terminated after cohort 2 (10 mg) due to concerns of tolerability at higher doses related to the formation of injection-site skin nodules [31].

7. Drug-drug interactions

Echinocandins are not known to cause major drug-drug interactions [32]. Indeed, in vitro studies demonstrate that rezafungin is not a substrate (inhibitor or inducer) of cytochrome P450 enzymes or drug transporters [33]. Furthermore, in vitro studies did not show evidence of antagonism between rezafungin and other antifungals (azoles, amphotericin B, flucytosine) or between rezafungin and common antibacterial agents with respect to bacterial killing. Phase 1 clinical trial data in healthy subjects showed an absence of clinically meaningful drug-drug interactions with rezafungin. Indeed, intravenous rezafungin was co-administered with known oral probe substrates of cytochrome P450 enzymes or drug transporter proteins. In general, the C_{max} and AUC remained within the equivalence range for most probes. Medication likely to be co-administered with rezafungin (e.g. ibrutinib for cancer therapy) were also assessed for drug-drug interactions. Ibrutinib, tacrolimus, venetoclax, and mycophenolic acid had their AUC or C_{max} reduced, although not resulting in a clinically significant reduction in drug exposure (<20% reduction of AUC and C_{max} [33]). Like other echinocandins, rezafungin is not associated with serious drug-drug interactions. Conversely, azoles are as associated with significant drug-drug interactions with drug conversion occurring in liver microsomes. Rezafungin is chemically and metabolically stable in liver microsomes and hepatocytes.

8. Dosing routes

Rezafungin is administered as a 250 mL intravenous solution (parent drug with 0.9% sodium chloride) over 1 hour. The recommended dose is 400 mg as a load, followed by 200 mg once weekly.

9. Regulatory affairs

Rezafungin was approved in March 2023 by the FDA and in December 2023 by the EMA for the treatment of invasive candidiasis in adults [29]. The drug approval was driven by favorable results from ReSTORE phase-3 RCT [22] and STRIVE phase-2 RCT [6], discussed in previous sections.

10. Conclusion

Rezafungin is a promising therapeutic option for candidemia and invasive candidiasis, owing to its differentiated pharmacokinetic characteristics that enable weekly dosing, good penetration into anatomically challenging sites and low probability of resistance emergence.

11. Expert opinion

The differentiated PK characteristics of rezafungin which enables once weekly dosing could reduce catheter overuse and provide a rapid transition to outpatient treatment for *Candida* infections in which azoles cannot be used, due to resistance or drug-drug interactions.

Regarding the apparent difference in overall cure rates between the rezafungin 400/200 mg and rezafungin 400 mg arms (60.5% vs. 76.1%) observed in the phase-2 STRIVE RCT, it has been proposed that they could be related to the *in vitro* phenomenon of paradoxical fungal growth with higher concentrations of echinocandins [34]. However, the differences with rezafungin occurred on day 5, when both treatment arms had received a similar doses, so a paradoxical growth effect therefore appears unlikely [23]. Therefore, a difference due to chance alone could not be excluded, also considering the generally limited sample size of phase-2 studies for definite efficacy conclusions. On the other hand, a reduced paradoxical effect of rezafungin vs. other echinocandins cannot be excluded, as suggested by an *in vitro* study [35], and could merit further investigation to explore the presence of any possible clinically relevant implication.

Rezafungin has demonstrated a low potential for resistance development in *Candida* species *in vitro*. [36]. Rezafungin showed to have species-specific *in vitro* activity similar to that of anidulafungin and micafungin against the most common *Candida* species [37]. Nonetheless, it was also seen that *FKS-1* mutations raised rezafungin MIC notably less than anidulafungin and micafungin MIC in *Candida auris* [37].

With regard to specific site of invasive candidiasis, and the related possible prevention of local resistance development [38], at least theoretically, tissue/plasma AUC ratios in rats following intravenous administration of rezafungin were high for highly perfused organs (approximately 4- to 5-fold higher in kidney, lung, liver, and spleen than in plasma), with the exception of the heart and brain tissues [39]. A recent study has also investigated the tissue distribution of micafungin and rezafungin by means of matrix-assisted laser desorption ionization (MALDI) mass spectrometry imaging in a mouse model of intra-abdominal candidiasis, registering a reduced fungal burden in the livers of mice treated with rezafungin compared to micafungin (sterilization of liver tissue achieved in 80% of the mice in the rezafungin treatment arm compared to none in the micafungin group) [40,41]. In a study evaluating the efficacy of rezafungin in the treatment of disseminated *Candida auris* infection using a mouse model of disseminated candidiasis, rezafungin showed to reduce fungal burden on infected kidneys in comparison to amphotericin B and micafungin-treated mice [42]. The use of rezafungin for other forms of invasive candidiasis such as osteomyelitis, endocarditis or myocarditis, and endophthalmitis could be attractive, but still deserving dedicated investigation.

Finally, regarding cost-effectiveness aspects, the exact cost – benefit balance remains to be established, although some preliminary results suggested possible advantages. For example, a German cost-of-illness study evaluated the potential cost savings due to the administration of rezafungin in patients with *Candida* infections [43]. The model was based on a 5-day reduction of ICU length of stay shown by the STRIVE study and showed a potential median cost-saving of €7175 per hospital case, with accumulated cost savings for 37 patients of €283 335 [43].

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Declaration of interest

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