REVIEW ARTICLE

Rezafungin for Candidemia and Invasive Candidiasis: A Focus on the Pharmaceutical Development, Related Patents, and Prospects

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Abstract

Infections caused by *Candida* are extremely dangerous and pose a serious threat to public health. Echinocandins are an important drug class used to combat fungal infections. A new echinocandin, Rezafungin (REZ), has been approved by the United States Food and Drug Administration (USFDA) on March 22, 2023, to treat invasive candidiasis and candidemia. This review article discusses the pharmaceutical development, patent literature, and the future directions of REZ-based therapy for fungal diseases. The literature for this article was obtained from authentic websites (USFDA, Cidara Therapeutics, and clinicaltrial.gov), PubMed, and various free patent databases (Espacenet, Patentscope, and USPTO) utilizing different keywords. REZ was invented by Seachaid Pharmaceuticals, which disclosed its chemical structure in 2012. Later Cidara Therapeutics acquired the patent rights of REZ from Seachaid Pharmaceuticals. REZ provides better patient compliance (once-a-week dosing) and cost-effective treatment than other marketed echinocandins. REZ demonstrates low CYP450-associated drug interactions but on limited drugs. The pharmacovigilance studies will provide more details of the pharmacokinetic properties, interaction (drug, food, and disease), and use in the special population (children, elderly, pregnant, and lactating women). Echinocandin, including REZ, is effective against many species of *Candida*. Drug-resistance development has been observed among the drugs of the echinocandin class. This issue must be considered while using REZ. The patent literature of REZ revealed some important REZ-based inventions. The patent literature of the REZ is likewise lacking. The authors predict a promising future for creating numerous patented inventions based on REZ.

Key words: Candidemia, invasive candidiasis, invention, patents, prospects, rezafungin

INTRODUCTION

Candida is a genus of yeasts that can cause fungal infections in humans.[1] Different pathogenic species of *Candida* are known, including *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida dubliniensis*, *Candida krusei*, *Candida lusitaniae*, *Candida guilliermondii,* and *Candida auris*.[2] Some *Candida* species, like *C. albicans*, are normally found in the human body parts as normal microbiota (skin, mucous membranes, digestive tract, mouth, genital area, etc.) in balance with other

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microorganisms.[1-5] However, *Candida* can overgrow and cause infections (called candidiasis) in some situations based on certain risk factors [Figure 1]. The different types of candidiasis include candidiasis of the mouth (oropharyngeal and esophageal), skin (cutaneous), nail (onychomycosis), genital, organs or invasive (eye, heart, lung, spleen, intestine, liver, kidney, abdomen, brain, and bones), and blood (candidemia).[2,6] Invasive candidiasis (IC) and candidemia (yeast in the blood) are similar conditions but are not identical. In short, candidemia is a type of IC specifically referring to a bloodstream infection, whereas IC encompasses candidemia and infections of different human body organs. Accordingly, IC patients develop organ-specific symptoms during the infections.[3-5,7,8] The important information about IC and candidemia is depicted in Figure 1.

IC and candidemia are life-threatening illnesses requiring immediate medical care.[2] The current United States Food and drug administration (USFDA) approved treatment of IC encompasses echinocandins, azoles, polyenes, and a single member of the antimetabolite class (flucytosine) [Figure 1 and Table 1].[2,8] Echinocandin antifungal therapy is recommended as the first-line therapy for treating candidemia and IC except in instances involving the central nervous system, the eyes, or the urinary tract.[1,5,7]

IC and candidemia are related to considerable morbidity and mortality (25 to >50% death), leading to prolonged hospital stays, high-cost treatment, and financial burden on patients and their families.[2-5,7,8] The current treatments have a relatively short half-life, need daily dose administration, and have slower clearance of candidemia, leading to high-cost treatment [Table 1]. On March 22, 2023, the USFDA approved long-acting Rezafungin (REZ) (half-life of about 152 h), having a faster clearance of candidemia to treat IC and candidemia, making it a cost-effective treatment for the patient [Table 2].[12-15]

This review article discusses the pharmaceutical development, patent literature, and the future directions of REZ-based therapy for treating IC, candidemia, and other fungal diseases. This article would be useful to the scientific fraternity devoted to developing and inventing patentable REZ-based antifungal therapies. The non-patent literature for this article was obtained from authentic websites (USFDA, Cidara Therapeutics, and clinicaltrial.gov), PubMed, and various free patent databases utilizing different keywords (REZ, Rezzayo, SP-3025, CD-101, and Cidara) or a combination of these keywords.

REZ (REZZAYO)

REZ [Figure 2; Synonyms: Rezzayo, SP-3025 and CD-101; Chemical Formula: $C_{63}H_{85}N_8O_{17}$; Molecular weight: 1226.411; CAS Registry Number: 1396640-59-7] is a stable long-acting intravenous semisynthetic lipopeptide antifungal agent of echinocandin class.[13,16,17]

Echinocandins are fungicidal drugs for *Candida* species with fewer side effects than azoles and polyenes.[16,17] Three antifungal echinocandins (caspofungin [CSF], micafungin [MCF], and anidulafungin [ANF]) have been approved by the USFDA [Table 1].[16] REZ is a derivative of ANF and is the first representative of the second-generation echinocandin

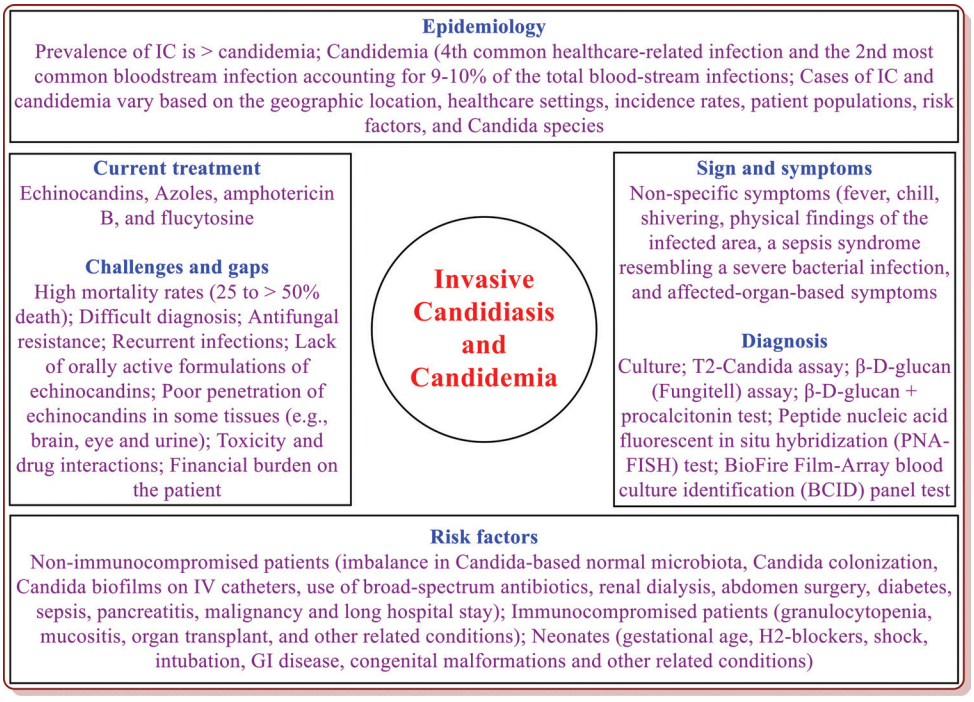

Figure 1: Epidemiology, risk factors, symptoms, diagnosis, treatment, and challenges of IC and candidemia[2-9]

Table 1: Current treatments for IC and candidemia[2,8,10,11]

Drug (Brand name)	Route; dose; half-life	Adverse reactions
Micafungin (mycamine)	IV; 100 mg once daily for a mean duration of 15 days; 14–17 h	Hypersensitivity; hematological, hepatic and renal effects; infusion site reactions
Caspofungin (Cancidas)	IV; 70 mg loading dose then 50 mg/day; 9–11 h	Hepatic effects and hypersensitivity
Anidulafungin (Eraxis)	IV; 200 mg loading dose, then 100 mg/day; 40–50 h	Hepatic effects; anaphylactic and hypersensitivity reactions
Fluconazole (diflucan)	Oral; 400 mg daily; 20–50 h	Hepatic injury; anaphylaxis; skin disorders; potential of drug interactions
Voriconazole (Vfend)	IV and oral; 3–4 mg/kg (IV) 200 mg (oral) 2 times a day; dose-dependent half-life	Liver, kidney, and embryo-fetal toxicity; arrhythmias; infusion site-related and skin reactions; visual disturbances; photosensitivity; pancreatitis; significant drug interactions
Posaconazole (Noxafil)	IV; 300 mg twice a day loading dose, then 300 mg once a day; 20 to 66 h	Hepatic and renal impairment; arrhythmias; toxicity of calcineurin inhibitor, midazolam, vincristine and venetoclax; drug interactions
Itraconazole (sporanox)	Oral; 200 mg 2 times a day; 21 h	Cardiac and hepatic effects; significant drug interactions
Isavuconazonium sulfate (cresemba)	IV and oral; 372 mg 2 times a day as a loading dose, then 372 mg once a day; 80–130 h	Hepatic and embryo-fetal effects; infusion site-related reactions; hypersensitivity; drug interactions
Amphotericin (Ambisome)	Intravenous (IV); 3–5 mg/kg/day; About 7–24 h	Renal insufficiency
Flucytosine (Ancobon)	Oral; 50–150 mg/kg/day; 2.4–4.8 h	Caution in patients with impaired renal function and bone marrow depression; drug toxicity with dihydropyrimidine dehydrogenase

IC: Invasive candidiasis

Table 2: Rx data of rezafungin

Proprietary name (active ingredient; therapeutic class; applicant; application number)	Approval date (dosage form; route; Strength; marketing status)	Marketing exclusivity	Approved indication
Rezzayo (Rezafungin Acetate; echinocandin antifungal; Cidara Therapeutics; N217417)	March 22, 2023 (Sterile white or pale-yellow powder/cake for injection; Intravenous; 200 mg base/vial; Prescription)	New Chemical Entity (GAIN) exclusivity expires on March 22, 2033, and Orphan Drug Exclusivity (GAIN) expires on March 22, 2035	Treatment of candidemia and invasive candidiasis in patients (≥18 years of age) having limited or no alternative options

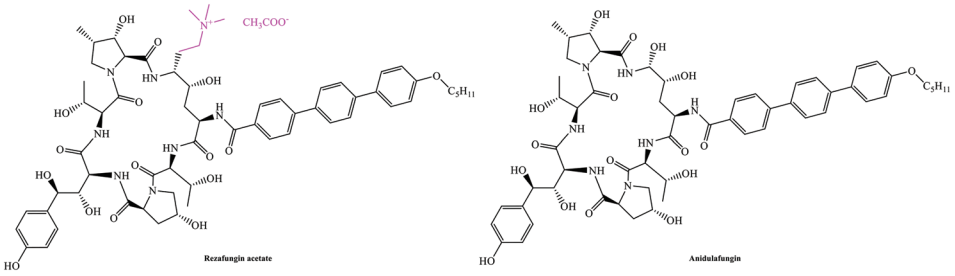

Figure 2: Chemical structure of Rezafungin acetate and anidulafungin

[Figure 3].[11,16,17] Adding the choline ether group at the C-5 ornithine position of ANF provided REZ. This change improved the chemical stability, decreased the degradation, enhanced the water solubility, better the pharmacokinetic profile, and prolonged the half-life of REZ.[16] The IV injection of REZ can irritate the injection site (pain, tenderness, itching, bruising, swelling, venous discoloration, and skin rash) due to its precipitation at the injection site.

This issue was overcome by developing REZ acetate salt.[18] Accordingly, the marketed REZ injection contains REZ acetate (A water-soluble hygroscopic white or off-white powder; Chemical Formula: $C_{63}H_{85}N_8O_{17}.C_2H_3O_2$; Molecular weight: 1285.46; CAS Registry Number: 1631754-41-0) as the active pharmaceutical ingredient along with histidine, mannitol, polysorbate 80, and pH adjustor (hydrochloric acid or sodium hydroxide).[14]

Mechanism of action of REZ

The current treatments for IC and candidemia [Table 1] exert their antifungal action by diverse mechanisms. The general anatomy of yeast and the sites of actions of different antifungal agents is provided in Figure 3.

Glucans are glucose polysaccharides connected by glycosidic linkages. They are classified as α-glucans (α-glycosidic linkage) and β-glucan (β-glucosidic linkage) depending on their molecular arrangement and characteristics. The cell wall of fungi, including *Candida*, comprises β-glucans, particularly β-1,3-glucan.[16,19,20] The β-1,3-glucan provides structural support, integrity, strength, and rigidity to the fungal cell wall. It also protects the cell wall from environmental stresses and mechanical damage and prevents the entry of harmful substances into fungi.[19,21] The β-1,3-glucan synthase enzyme complex, encoded by two primary genes (FSK1 and FSK2) and one secondary gene (FSK3), is involved in the synthesis of β-1,3-glucan from glucose in the plasma membrane of the fungi.[20,22] REZ inhibits the β-1,3-glucan synthase enzyme complex [Figure 4]. This event prevents the fungal cell wall synthesis and causes osmotic instability, destabilization of the structural support, and death.[1,13,16]

Microbiology

REZ's *in vitro* activity data against various *Candida* species are well presented in the literature.[11,17,20,23-25] A summary of the minimum inhibitory activity concentration (MIC) of REZ against important *Candida* species concerning ANF, CSF, and MCF is provided in Table 3.

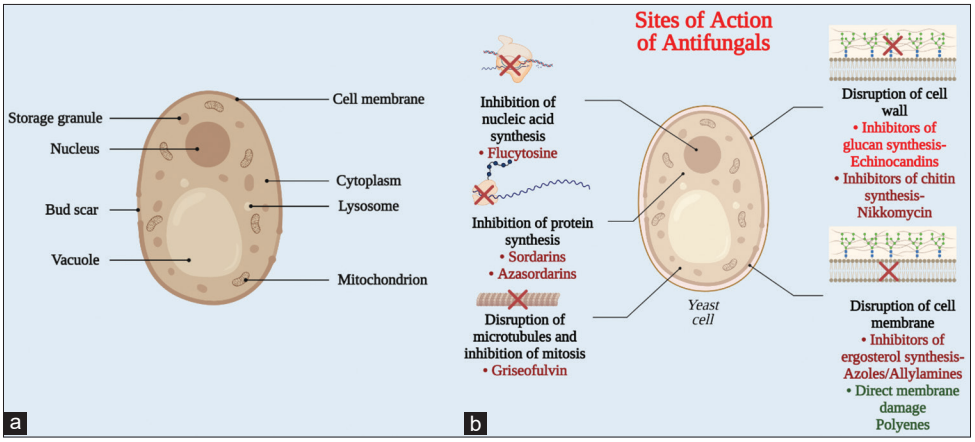

Figure 3: General fungal anatomy (a) and site of actions of antifungals (b) (Created with Biorender.com)

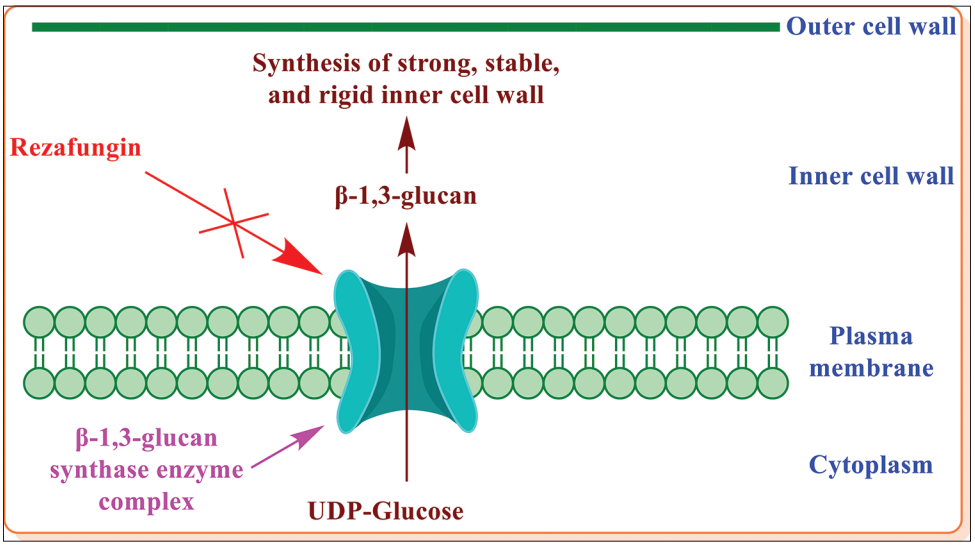

Figure 4: Mechanism of action of Rezafungin

Table 3: The MIC values (μg/mL) of REZ, ANF, CSF, and MCF against important *Candida* species[11,17,20,23]

***Candida* species**	**REZ**		**ANF**		**CSF**		**MCF**	
	MIC_{50}	**MIC_{90}**	**MIC_{50}**	**MIC_{90}**	**MIC_{50}**	**MIC_{90}**	**MIC_{50}**	**MIC_{90}**
Candida species (wild-type with FKS genes)								
C. albicans	0.022	0.050	0.012	0.027	0.053	0.069	0.022	0.021
C. glabrata	0.044	0.085	0.045	0.085	0.080	0.140	0.027	0.030
C. parapsilosis	1.260	2.000	1.219	2.245	0.435	0.758	1.122	1.414
C. tropicalis	0.030	0.072	0.012	0.034	0.046	0.092	0.030	0.050
C. dubliniensis	0.060	1.360	0.034	0.270	0.036	0.370	0.030	0.105
C. krusei	0.033	0.078	0.045	0.085	0.280	0.248	0.108	0.153
C. lusitaniae	0.120	0.250	0.042	0.060	0.500	1.000	0.038	0.250
C. guilliermondii	1.00	1.00	1.00	2.00	0.50	1.00	1.00	2.00
C. auris	0.153	0.500	0.391	0.250	0.707	1.000	0.630	0.500
FKS-mutated *Candida* species								
C. albicans	0.71	1.00	0.50	1.00	0.50	1.00	1.00	-
C. glabrata	0.50	1.00	0.25	1.00	0.50	1.00	1.00	-
C. tropicalis	0.71	1.00	0.50	1.00	1.00	2.00	2.00	-
C. krusei	0.35	1.00	0.50	2.00	1.00	16.00	1.00	-
C. auris	8.00	8.00	8.00	-	4.00	-	4.00	-

C. albicans: *Candida albicans*, *C. glabrata*: *Candida glabrata*, *C. parapsilosis*: *Candida parapsilosis*, *C. tropicalis*: *Candida tropicalis*, *C. dubliniensis*: *Candida dubliniensis*, *C. krusei*: *Candida krusei*, *C. lusitaniae*: *Candida lusitaniae*, *C. guilliermondii*: *Candida guilliermondii*, *C. auris*: *Candida auris*. MIC: Minimum inhibitory activity concentration, REZ: Rezafungin, ANF, CSF: Caspofungin, MCF: Micafungin

The data in Table 3 reflect similar MIC values for REZ, ANF, CSF, and MCF. The potency of REZ against FKS-mutant was also comparable to ANF, CSF, and MCF. These observations indicate that REZ shares analogous antifungal activity profiles ANF, CSF, and MCF.

Pre-clinical studies

The pharmacokinetic and pharmacodynamic activity data of REZ have been documented (*in vitro* and *in vivo* studies) in various animals, including mice, rats, monkeys, rabbits, dogs, and chimpanzees, to validate REZ's nonclinical safety. The authors summarize the REZ animal study data in the following Table 4.

Clinical studies (computed tomography)

The REZ-related clinical studies were searched on the clinical trial database.[34] A short description of important clinical studies is mentioned in Table 5.

Pharmacological parameters

The important pharmacokinetic and Rx data of REZ are described in Table 6.[10,11,13,15,33,42-44]

The development timeline of REZ

It is provided in Figure 5.

PATENTS

The relevant patent literature for REZ was searched on a free patent database (USPTO, Patentscope, and Espacenet) employing various keywords (REZ; SP-3025; SP3025; CD-101; and CD101).[45-47] The patent literature claiming the inventions related to REZ are segregated and summarized [Table 7].

PROSPECT

Candida infections are one of the deadliest diseases that a person may have and a major public health concern. Some medicines of different chemical classes (echinocandin, azole, and polyenes) are available to treat *Candida* infections [Figure 1 and Table 1]. Echinocandin is an important chemical class of antifungal agents.[60] Echinocandin, including REZ, inhibits the β-1,3-glucan synthase enzyme. This enzyme is absent in humans. This feature makes β-1,3-glucan synthase a terrific drug target for developing antifungal drugs.[71] The poor aqueous solubility, low potency, and hemolytic action of natural echinocandins make them unsuitable as treatments. Therefore, clinically relevant echinocandins are semisynthetic derivatives of natural echinocandin.[72] CSF was the first echinocandin marketed in 2001, whereas REZ is the latest marketed echinocandin antifungal agent with potent activity against *Candida* and *Aspergillus*.[57]

Table 4: Summary of the animal study data of REZ

Parameters	Summary
Pharmacokinetics	Long Half-life in hours by IV route (Mouse=25; Rat=39; Dog=53; cynomolgus monkey=40; chimpanzee=81); Low clearance in mL/min/kg (mouse=0.10; rat=0.47; dog=0.30; cynomolgus monkey=0.41; chimpanzee=0.06); Volume of distribution (mL/kg) in all major organ tissues, excluding brain and heart (mouse=206; rat=1390; dog=not determined; cynomolgus monkey=597; chimpanzee=400); Approximately 4 times higher concentration in tissues than plasma; biliary and fecal elimination was the main route of excretion; Once a week dose was expected due to long half-life, wide tissue distribution and low clearance rate.[26]
Pharmacodynamics	The ratio of the AUC (area under the curve) and MIC (*Candida tropicalis*=0.93; *C. dubliniensis*=0.72; *C. albicans*=2.92; *Candida glabrata*=0.07; *Candida parapsilosis*=2.61) indicated good efficacy of REZ against *C. tropicalis* and *C. dubliniensis* in neutropenic mouse candidiasis model.[27,28]
Multiple dosing regimens	The multiple dosing regimens (2 mg/kg once a week; 1 mg/kg 2 times a week; 0.29 mg/kg/day for 1 week) studies in *C. albicans* infected neutropenic mice demonstrated that once-a-week dosing had the greatest efficacy than other dosing regimens. Similar results were obtained in another study.[29,30]
Stability (chemical and metabolic), safety, and efficacy	Demonstrated metabolic stability (monkey, rats, dog, and human liver); minimum interaction with cytochrome P450 enzymes; plasma protein binding >98% (mouse, rat, and human); well-tolerated concerning body weight, coagulation, hematology, and urinalysis in rats than anidulafungin; no hepatotoxicity (2–20 mg/kg/day); did not produce reactive intermediates unlike anidulafungin; and exhibited antifungal activity in neutropenic mice against *Candida* and *Aspergillus*.[31]
Quantitative distribution in tissue lesions in an intra-abdominal candidiasis mouse model	REZ and micafungin accumulated in lesions standard at therapeutic dose. The penetration of REZ was 4–6 times higher than micafungin.[32]
Adsorption and transmembrane clearance (CLTM)	This validated *ex vivo* study demonstrated that REZ is not separated by continuous venovenous hemofiltration (CVVH) by membrane indication no likely need to adjust the dose among critical patients receiving CVVH.[33]

C. tropicalis: *Candida tropicalis*, *C. dubliniensis*: *Candida dubliniensis*, MIC: Minimum inhibitory activity concentration, REZ: Rezafungin

The chemical structure of REZ was first disclosed in 2012 by Seachaid Pharmaceuticals.[48] The intellectual property (patent) of REZ was acquired by Cidara Therapeutics from Seachaid Pharmaceuticals in 2014 [Figure 5]. On March 22, 2023, the USFDA approved REZ to treat IC and candidemia [Table 1]. REZ provides better patient compliance (once-a-week dosing) and cost-effective treatment than other marketed echinocandins.[73,74] REZ also demonstrates low CYP450-associated drug interactions.[44] However, these studies are performed on limited drugs, warranting further research with more medications. Drug-food interactions and drug-disease interactions are also important studies that need further exploration. No REZ-based study has been conducted on special populations.[15] This area also needs study to understand the utility among children, elderly, pregnant, and lactating women. Echinocandin, including REZ, is effective against many species of *Candida*. Drug-resistance development has been observed among the drugs of the echinocandin class.[7] It is imperative to note that a mutation in FSK genes (preferable in highly conserved regions (HS1 and HS2 regions of FSK1 and FSK2 genes) can alter β-1,3-glucan synthesis and cell wall components. This incident causes resistance to echinocandin-based antifungal drugs.[20,22,75] The development of drug resistance triggers the development of better antifungal drugs.

The patent literature of REZ revealed some important REZ-based inventions. The stability of echinocandins is very poor. They are easily hydrolyzed, dimerized, or oxidized and produce a variety of degradable impurities. Many echinocandin products are stored at low temperatures and transported in the cold chain.[60] One patent application provides a stable echinocandin antifungal pharmaceutical composition comprising an echinocandin antifungal agent, an antioxidant, and meglumine.[60] Some companies have filed patent applications related to the conjugates/prodrugs of REZ.[59,76] The development of conjugates/prodrug echinocandins can also solve their stability issues. The use of echinocandin antifungals, including REZ, has been claimed as a cytoprotective drug (for treating psoriasis).[58] This is an example of drug repurposing.[77] Accordingly, finding a second indication for REZ is interesting for scientists. The particle size of a drug is crucial for its delivery at the site of action, pulmonary fungal infection.[78] The drug's delivery at

Table 5: Summary of important REZ-related clinical studies

NCT number (other IDs; title acronym; sponsor; location)	Conditions (intervention; allocation; numbers enrolled; Purpose)	Phase (status; start date; completion date; last update)	Key findings
NCT03667690 (CD101. IV.3.05; ReSTORE; Cidara Therapeutics; Multinational)[13,17,35-39]	Candidemia, IC, mycoses, and fungal infection (Comparison of intravenous REZ and IV caspofungin with optional stepdown to oral fluconazole in the caspofungin arm in adults with candidemia and IC; Randomized; 199 aged ≥ 18 years; Treatment)	3 (Completed; October 7, 2018; October 7, 2021; January 6, 2023)	Intravenous REZ (400 mg loading dose in the 1st week followed by 200 mg per week) was effective in treating Candidemia and IC and non-inferior to caspofungin, supporting its further development
NCT02734862 (CD101.IV.2.03 and 2015-005599-51; STRIVE; Cidara Therapeutics; Multinational)[13,37,38-41]	Candidemia, IC, mycoses, fungemia and fungal infection (Safety and efficacy of REZ vs. caspofungin; Randomized; 207; Treatment)	2 (Completed; July 26, 2016; July 2019; December 8, 2020)	Intravenous REZ (400 mg loading dose in the 1st week followed by 200 mg per week) displayed better efficacy than caspofungin
NCT02516904 (CD101. IV.1.01; Not mentioned; Cidara Therapeutics; United States)[13,38,39,41]	Safety, tolerability, and pharmacokinetics of REZ (Single ascending dose of REZ; Randomized; 32; Treatment)	1 (Completed; July 2015; October 2015; May 22, 2024)	No major safety issues observed
NCT02551549 (CD101. IV.1.02; Not mentioned; Cidara Therapeutics; United States)[13,38,39,41]	Safety, tolerability, and pharmacokinetics of REZ (Multiple ascending dose of REZ; Randomized; 24; Treatment)	1 (Completed; September 2015; January 2016; June 26, 2017)	No major safety issues observed
NCT04368559 (CD101. IV.3.08 and 2017–004981–85; ReSPECT; Cidara Therapeutics; Multinational)[13,41]	Candidemia, IC, fungemia, fungal infections, mycoses, Pneumocystis, *Aspergillus* and mold infection (Safety and efficacy of REZ; Randomized; 462; Treatment)	3 (Recruiting; May 11, 2020; August 2024; July 26, 2024)	Study in progress
NCT05534529 (MR907–1501; Not mentioned; Mundipharma Research Limited; Not mentioned)[13]	Safety, tolerability, and pharmacokinetics of REZ in pediatric patients (REZ acetate; Not mentioned; 32; Treatment)	1 (Suspended; May 31, 2023; December 1, 2027; June 21, 2024)	Study in progress
NCT02733432 (CD101. TP. 2.01; Not mentioned; Cidara Therapeutics; United States)[13,41]	Candidiasis, monilial, yeast infection, and vulvovaginal mycoses (Gel and ointments of REZ; Randomized; 126; Treatment)	2 (Completed but discontinues; June 8, 2016; December 23, 2016; August 31, 2020)	The topical formulations were safe and effective, but the cure rate was not better than fluconazole
NCT05835479 (MR907–2501; Not mentioned; Mundipharma Research Limited; Not mentioned)[34]	Pneumocystis Pneumonia (Combination of REZ and co-trimoxazole; Randomized; 50; Treatment)	2 (Recruiting; October 2023; September 2024; March 29, 2024)	Study in progress

REZ: Rezafungin, IC: Invasive candidiasis

the site of action achieves a high drug concentration, keeps the plasma concentration low, and reduces unwanted systemic effects of the drug. Cipla Technologies filed dry particles (powder) based patent application of REZ to treat pulmonary fungal infection.[62] Some patent/patent applications claim the use of the combinations of echinocandin with chitinase,[66] defensing,[67] anti-hsp90 antibody,[68] and anti-sweating agents[69] as antifungal combinations. However, they do not specifically claim the combination of REZ but may cover it generically. The combination of REZ with chitinase,

Table 6: Pharmacological parameters and Rx data of REZ

Parameter	Summary
Dosing regimen	Initial loading dose (intravenous 400 mg) followed by once-a-week dose (intravenous 200 mg). Normal treatment duration is up to 4 weekly doses because no safety is established beyond four doses.[15]
Limitations	REZ has not been examined in *Candida*-related meningitis, osteomyelitis, and endocarditis.[15]
Absorption	C_{max} (μg/mL) = 19.2 on day 1 and 11.8 on day 15; AUC_{0-168} (μg-h/mL) = 827 on day 1 and 667 on day 15; C_{min} (μg/mL) = 2.4 on day 1 and 2.2 on day 15; Half-life=152±29 h; Plasma protein binding=87.5% to>98.6% in healthy adult and 87.5–93.6% in patients; No clinically relevant effects of age, race, sex, weight, and hepatic impairment has been observed on the pharmacokinetic profile of REZ.[11,13,15]
Volume of distribution	67±28 L[11,13,15]
Metabolism	REZ is metabolized by hydroxylation to produce hydroxylated metabolites (2'-hydroxylpentyl rezafungin, 3'-hydroxylpentyl rezafungin, and 4'-hydroxylpentyl rezafungin). Despentyl-rezafungin is another metabolite produced by the O-dealkylation of REZ. REZ metabolism is not a clinically relevant substrate of CYP450 enzymes and major drug transporters.[11,13,15]
Primary excretion pathways (% dose)	REZ is excreted primarily unchanged in feces (74.3%), and its inactive metabolites are excreted in urine (25.7%).[15]
Clearance	0.35±0.13 L/h[11,15]
Adverse effects	The main adverse events relate to the infusion site, photosensitivity, and hepatic adverse events.[11,15]
Warning	Infusion-related reactions, photosensitivity, and abnormal liver tests.[15]
Contraindication	Patients with hypersensitivity to REZ or other echinocandins.[11,15]
Toxicity/Overdose	No overdose cases were reported during clinical trials. The high protein binding may make REZ non-dialyzable.[15]
QT prolongation	No clinically relevant QTc interval prolongation was observed at 1400 mg.[11,15]
Use in special populations	No data is available on the effects of REZ among pregnant and lactating women, pediatric patients, and geriatric patients.[15]
Drug interactions	REZ metabolism is not clinically relevant to CYP450 enzymes and major drug transporters. Therefore, fewer drug interactions are expected.[11,15]
Food interaction	No relevant study was done.[11,15]
Renal/Hepatic impairment	No dose adjustment is recommended in these conditions.[11,15]

REZ: Rezafungin

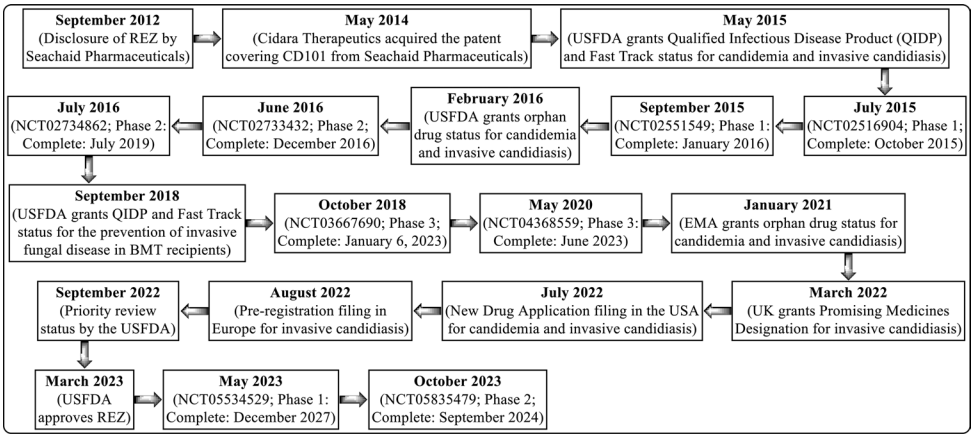

Figure 5: The development timeline for Rezafungin

defensin, anti-hsp90 antibody, anti-sweating agents, and other antimicrobials may be explored to provide a better antifungal treatment. A patent may be granted for various pharmaceutical inventions.[79-81] There is also a shortage in the REZ's patent literature. The authors foresee a bright scope in developing many REZ-based patentable inventions.

Table 7: Patent literature of REZ

S. No.	Patent/application number (applicant/assignee; status)	Summary
1	US8722619B2 (Seachaid Pharmaceuticals; Valid patent)	This patent specifically claims REZ and its salts, including REZ acetate salt. It also claims oral, intravenous, topical, subcutaneous, and inhalation formulations of REZ generically for treating fungal infections. This OB-listed patent has an estimated expiry date of March 2, 2032.[48] A 5-year patent term extension is possible by the USPTO based on the recommendation of the USFDA.[49]
2	US9526835B2 (Cidara Therapeutics; Valid patent)	A pharmaceutical composition for treating a fungal infection comprising REZ or its salt in a lyophilized composition that loses<5% potency when stored for 3–4 months and wherein stabilizers are absent. This OB-listed patent has an estimated expiry date of March 14, 2033.[50]
3	US10702573B2 (Cidara Therapeutics; Valid patent)	A method of treating a fungal infection using an intravenous solution of REZ or its acetate salt, wherein the solution is administered at an interval of one dose every 5–8 days (preferably 7 days). The solution may be administered for 2, 4, 8, or 12 weeks. This OB-listed patent has an estimated expiry date of March 14, 2033.[51]
4	US11197909B2 (Cidara Therapeutics; Valid patent)	An aqueous pharmaceutical composition for intravenous injection comprising at least 85% (w/w) water, 0.4–10 mg/mL of REZ acetate, 0.12–6% (w/w) of a saccharide, and an intravenous solubility promoter, wherein the weight to weight (w/w) ratio of the intravenous solubility promoter to the REZ acetate is at least 2, and the pharmaceutical composition has a pH of between 5 and 7. This OB-listed patent has an estimated expiry date of July 14, 2038.[18]
5	US11654196B2 (Cidara Therapeutics; Valid patent)	A method of treating or preventing a fungal infection using an aqueous intravenous infusion (0.50–3 mg/mL) or intravenous aqueous solution bolus (25–500 mg/mL) of REZ. It further claims an injectable device containing a needle and aqueous solution of REZ for injection (0.05–10 mL). This OB-listed patent has an estimated expiry date of March 2, 2032.[52]
6	US10016479B2 (Cidara Therapeutics; Valid patent)	A treatment method comprising reconstituting a lyophilized composition to form an aqueous solution for subcutaneous administration, wherein the lyophilized composition comprising REZ or its salt is formulated to release REZ or its salt immediately.[53]
7	US11819533B2 (Cidara Therapeutics; Valid patent)	An aqueous pharmaceutical composition for intravenous injection comprising at least 85% (w/w) water, 0.4–10 mg/mL REZ, and an intravenous solubility promoter, wherein the pharmaceutical composition exhibits reduced local irritation upon intravenous administration to a subject.[54]
8	US11712459B2 (Cidara Therapeutics; Valid patent)	A dosing regimen for treating invasive candidiasis using REZ in acetate salt or neutral form.[55]
9	US2020164023A1 (Cidara Therapeutics; Abandoned)	A method of treating intra-abdominal candidiasis by administering a pharmaceutical composition of REZ in salt or neutral form.[56]
10	CN115850383A (Jiangsu Jiuyang Biological Pharmaceutical; Under examination)	An industrially applicable chromatographic method for purifying REZ. The method adopts the mixed solution of acetonitrile and water as a mobile phase to carry out isocratic and gradient elution to get pure REZ (HPLC purity>99%) in high yield (70%).[57]
11	US11458189B2 (Balmes Transplantation; Valid patent)	A method for treating psoriasis by administering a compound of the echinocandin family (caspofungin, anidulafungin, REZ, etc.), or a salt, ester or ester salt thereof, as a cytoprotective drug.[58]
12	US2023218652A1 (Centre National De La Recherche Scientifique; Under examination)	It claims the prodrug of the compound of the echinocandin family (caspofungin, anidulafungin, REZ, etc.) and its use for treating fungal infections.[59]
13	CN112741894A (Jiangsu Hengrui Medicine; Withdrawn)	An antifungal pharmaceutical composition comprising an echinocandin antifungal agent (caspofungin, anidulafungin, REZ etc.), an antioxidant (sodium bisulfite, ascorbic acid, reduced glutathione, vitamin E, α-tocopherol, etc.), and meglumine.[60]
14	WO2022253297A1 (Jiangsu Hengrui Pharmaceuticals; Entered in national phase)	A preparation method of REZ and its acetate salt.[61]

(Contd...)

Table 7:*(Continued)*

S. No.	Patent/application number (applicant/assignee; status)	Summary
15	US2021113461A1 (Cipla Technologies; Under examination)	A method of treating pulmonary fungal infection using homogenous respirable dry particles (powder) of an anti-fungal agent (itraconazole, REZ, etc.) in crystalline particulate form and a stabilize.[62]
16	WO2022050369A1 (Osaka University; Entered in national phase)	A liposome preparation in which an antibacterial agent (oritavancin) or a cyclic lipopeptide-based antibacterial agent (daptomycin, caspofungin acetate, anidulafungin, and REZ) is bound outward to the surface layer of the liposome.[63]
17	WO2018191692A1 (Cidara Therapeutics; Abandoned)	A method of treating vulvovaginal candidiasis by subcutaneously administering doses (25–600 mg) of REZ in salt or neutral form.[64]
18	US2019374601A1 (Cidara Therapeutics; Abandoned)	A method of treating onychomycosis by subcutaneously administering doses (25–600 mg) of REZ in salt or neutral form.[65]
19	WO2018078626A1 (Gavish-Galilee Bio Applications; Abandoned)	A combination comprising chitinase (human CHITI) and at least one echinocandin (caspofungin, micafungin, or anidulafungin) for use in treating a fungal infection. This patent application does not specifically claim the combination of chitinase and REZ to treat the fungal infection.[66]
20	US10568930B2 (Hexima; Valid patent)	Use of a combination of a plant defensin (permeabilizing defensin of Class I defensin or a Solanaceous Class II defensin) and β-glucan synthase inhibitor (caspofungin). This patent does not specifically claim the combination of defensin and REZ for controlling pathogen infestation.[67]
21	RU2262952C2 (Newtech Pharma; Invalid due to non-payment of fees)	Use of a combination of a fungal anti-hsp90 antibody and at least one antifungal agent (amphotericin B or anidulafungin) for the treatment of fungal infections (mucormycosis, blastomycosis, or coccidioidomycosis). This patent does not specifically claim the combination of anti-hsp90 antibody and REZ for treating fungal infection.[68]
22	US11554108B2 (Xeropedix; Valid patent)	A method of treating a dermatophytic infection using actives selected from a group of antifungals (caspofungin, micafungin, and anidulafungin) and a group of anti-sweating agents (aluminium zirconium tetrachlorohydrexgly). This patent does not specifically claim the application of REZ and anti-sweating agents to treat dermatophytic infection.[69]
23	US11524980B2 (Cidara Therapeutics; Valid patent)	An easy and commercially applicable method of synthesizing REZ involves the reaction of boronate ester of anidulafungin. This method provides REZ with a higher yield, higher isomeric purity, elimination of a mutagenic impurity, and reduced waste stream.[70]

USFDA: United states food and drug administration

CONCLUSION

Candida infections are a leading cause of death and a serious public health problem. REZ is an avant-garde patient-compliant and cost-effective treatment for candidemia and IC. To date, REZ has a promising pharmacokinetic profile. The pharmacovigilance studies will expose further details of its pharmacokinetic properties and information about its drug resistance. The authors also foresee exploring many REZ-based pharmaceutical inventions for treating fungal infections and other diseases alone or in combination with other drugs.

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ETHICAL DISCLOSURE

None required.

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