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REVIEW

The Upcoming Antifungal Drugs in Clinical Development for the Treatment of Invasive Candidiasis

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Background: Invasive candidiasis (IC) is a major cause of morbidity and mortality among hospitalized patients, and treatment success relies on early diagnosis and prompt initiation of an appropriate antifungal agent. The increasing rates of resistance to first-line antifungal agents (azoles, echinocandins, and polyenes), along with changes in the epidemiology of IC and the spread of multidrug-resistant *C. auris*, pose further challenges for the management of IC. Limited therapeutic options and routes of administration, drug–drug interactions, and drug toxicities of commonly utilized antifungals further complicate management in the acute hospital setting and create barriers for long-term outpatient treatment. This article provides a review of the current literature on the upcoming antifungal agents that are being actively investigated as treatment options for invasive candidiasis, including those in early- and late-stage clinical development.

Areas Covered: We will discuss the spectrum of activity of novel antifungal agents, mechanisms or resistance, pertinent in vivo and vitro data, as well as data from the clinical trials evaluating efficacy and safety of novel antifungals.

Expert Opinion: Rezafungin holds promise as an excellent option for outpatient antimicrobial therapy programs due to its favorable safety profile and convenient once-weekly dosing. Ibrexafungerp has broad-spectrum antifungal activity, including activity against fluconazole- and echinocandin-resistant *Candida* spp. and is available in an oral formulation, making it an attractive option for step-down therapy after treatment with echinocandins or as an alternative to echinocandins. Fosmanogepix has a novel mechanism of action, a favorable side-effect profile, and a broad spectrum of clinical activity. However, further data from clinical trials are necessary to further establish its role in the management of invasive candidiasis. The role of agents in early clinical development, including BAL2062 and ATI2307, as well as repurposed agents with antifungal activity, such as miltefosine, in the management of invasive candidiasis remains to be determined.

Keywords: invasive candidiasis, fosmanogepix, rezafungin, ibrexafungerp, *Candida glabrata*, *Candida auris*, fluconazole resistance, echinocandins, BAL2062, ATI2307, miltefosine

Introduction and Epidemiology

Invasive candidiasis is a major cause of morbidity and mortality in hospitalized patients. The most common presentation of invasive candidiasis is candidemia, and the majority of cases are healthcare-associated.[1] According to the Centers for Disease Control and Prevention (CDC), 25,000 new cases of candidemia are diagnosed every year.[2] The CDC's Emerging Infections Program (EIP) conducted a laboratory surveillance of candidemia cases in 2017–2020 at centers in 10 states.[3] According to the surveillance data, the incidence was found to be 7.4 cases per 100,000 population, with an all-cause in-hospital mortality rate of 32.8%.[3] Candidemia used to be the fourth most common healthcare-associated bloodstream infection in the US, however it was estimated to be the second most common cause of bloodstream infections in certain geographical locations and is considered a leading cause of healthcare-associated bloodstream infections according to the CDC.[2,4,5] Overall, the incidence of candidemia in the US has declined since 2004.[2,6] The retrospective analysis of all candidemia patients from 130 Veterans Health Administration (VHA) hospitals suggested that the two major changes in hospital-onset candidemia incidence occurred shortly after the publication of the CRBSI prevention guidelines and the expansion of the infection control resources within the

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VHA system, underscoring the role of infection control practices and guideline adherence in decreasing the candidemia rates.[6] Invasive candidiasis among patients in the intensive care units poses challenges in both diagnosis and management.[7] Based on the surveillance data across 23 European ICUs, the cumulative incidence of invasive candidiasis was 7.07 per 1000 ICU admissions, with candidemia and intraabdominal candidiasis accounting for 5.52/1000 and 1.84/1000 episodes, respectively.[8] According to inpatient data from 2009 through 2017, the incidence of invasive candidiasis (IC) was 90 per 100,000 hospitalized patients.[9] Candidemia, intra-abdominal candidiasis (IAC), and non-abdominal sterile site IC accounted for 51/100,000, 32/100,000, and 5.7/100,000 hospitalizations, respectively.[9] While the incidence of candidemia has declined and remained stable over the past decade, the incidence of intraabdominal candidiasis has increased, becoming the second most common form of IC among ICU patients.[9,10] However, an increase in the incidence of candidemia was observed during the COVID-19 pandemic.[10] Lapses in infection control practices, increased healthcare exposures in patients with COVID-19 and high acuity conditions, leading to prolonged hospital stays and placement of invasive devices, are probable risk factors resulting in an increase in hospital-acquired cases of candidemia during the COVID-19 pandemic.[10]

Historical data suggest that attributable mortality in nosocomial candidemia can be as high as 49%.[11–13] The recently published results from ECMM Candida III multinational European Observational Cohort Study estimated the overall mortality among patients with candidemia is approximately 40.4% and the attributable mortality was 18.2%. However, the mortality varied depending on the *Candida* species involved.[14] *Candida tropicalis* was found to confer the highest attributable mortality in this study at approximately 63.6%.[14]

Although *C. albicans* remains the leading cause of candidemia, according to the CDC, non-*albicans* species are now responsible for up to two-thirds of cases of candidemia, with *C. glabrata* becoming one of the primary causes of candidemia in the US.[2,15] An emerging pathogen, *C. auris*, has caused large outbreaks in multiple parts of the world and is becoming a global threat, owing to its multidrug resistance, as well as the ability to spread in the healthcare settings, posing a challenge to infection control practices.[10]

Widespread use of antifungals has significantly contributed to the development of resistance to antifungal agents among *Candida* spp., as well as a shift in epidemiology, leading to increased incidence of infections caused by non-albicansspecies.[16] Extensive use of antifungal drugs for treatment and prophylaxis, as well as the presence of intravascular catheters and other devices, a growing population of immunocompromised hosts, such as patients with hematological malignancies, solid organ and stem cells transplant recipients, and recipients of immunosuppressive therapies have resulted in an increased numbers of patients at increased risk of developing invasive candidiasis and candidemia.[17] These shifts in the prevalence of *Candida* spp. and distribution of resistance patterns lead to significant challenges in the management of candidemia and invasive candidiasis, frequently rendering first-line antifungal agents ineffective and jeopardizing patient care (Table 1).

Table 1 Relative Activity of Antifungal Agents Available in Clinical Practice or in Late-Stage Clinical Development Against Different Candida Species

	C. albicans	**C. glabrata**	**C. krusei**	**C. parapsilosis**	**C. tropicalis**	**C. auris**
Fluconazole	Active	Variable	Resistant	Active	Active	Resistant
Voriconazole	Active	Variable	Active	Active	Active	Variable
Posaconazole	Active	Variable	Variable	Active	Active	Variable
Isavuconazole	Active	Variable	Active	Active	Active	Variable
Oteseconazole	Active	Active	Active	Active	Active	No data
Echinocandins (including rezafungin)	Active	Active	Active	Active	Active	Active
Polyenes	Active	Active	Active	Active	Active	Variable
Fosmanogepix	Active	Active	Resistant	Active	Active	Active
Ibrexafungerp	Active	Active	Active	Active	Active	Active

Significant advances in the development and approval of new and novel antifungal agents have been made recently. Many of the newly developed antifungal agents exhibit unique mechanisms of action and may enhance our current antifungal armamentarium.

Ibrexafungerp

Mechanism of Action, Spectrum of Activity, and Resistance

Ibrexafungerp is a member of the triterpenoid class of compounds. It acts as an inhibitor of the 1,3-β-D-glucan synthase enzyme complex, affecting the integrity of the fungal cell wall, disrupting the osmotic pressure and eventually leading to cell wall lysis.[18–20] It has high oral bioavailability, and its oral formulation is approved by the Food and Drug Administration (FDA) for use in the treatment of vulvovaginal candidiasis, whereas the intravenous formulation is not yet available for clinical use.[21] The oral formulation of ibrexafungerp may be a convenient step-down therapy after parenteral treatment with echinocandins.[22]

Despite a similar mechanism of action to echinocandins, limited cross-resistance between echinocandins and ibrexafungerp exists due to the different binding sites.[19,22] The echinocandins act through the non-competitive inhibition of 1,3-β-D-glucan synthase enzyme, which is encoded by several *FKS* genes.[22] Resistance to echinocandins among *Candida* spp. is frequently mediated by mutations in the hotspots in the *FKS* genes, specifically *FKS1* and *FKS2*.[23] There is only a partial overlap of the binding sites for echinocandins and ibrexafungerp which results in retained activity of ibrexafungerp against many echinocandin-resistant strains of *Candida*.[24] However, because the molecular target conferring resistance to ibrexafungerp displays overlap with that of the echinocandins, certain mutations can result in increased minimal inhibitory concentrations (MICs) to both drugs.[25–27] Examples of the mutations of the *FKS* genes leading to decreased activity of ibrexafungerp include F641S in *FKS1* HS1 in *C. albicans*, and *FKS2* HS1 F658del, F659S, F659del, as well as E655A upstream *FKS2* HS1, and W715L downstream *FKS2* HS1 in *C. glabrata*.[25–30] The *FKS2 Phe659del* mutation in *C. glabrata* results in a >121-fold increase in ibrexafungerp MIC_{50}, while also exhibiting a 44-fold increase in the MIC_{50} to micafungin and the acquisition of *FKS1 Phe625del* in a 40-fold and 11-fold increase, respectively.[25] However, Ibrexafungerp has demonstrated activity against echinocandin-resistant *Candida* spp. harboring mutations in the *FKS1* and *FKS2* hotspots in in vitro and in vivo studies, including *C. glabrata*.[26,28,31,32] In the study by Pfaller et al of the 36 isolates of *Candida* spp. harboring FKS mutations, 83.3% were non-wild type to one or more echinocandins, whereas 75% remained susceptible to ibrexafungerp, with a similar distribution among *FKS*-mutant isolates of *C. glabrata*.[26] It also demonstrates excellent activity against fluconazole-resistant *Candida* spp., including *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. lusitaniae*, *C. guilliermondii*, and *C. glabrata*.[20,33–35] The ibrexafungerp MICs for *C. lusitaniae* and *C. krusei* are higher than other *Candida* spp.[18] In the study by Marcos-Zambrano et al, ibrexafungerp MIC values against *C. parapsilosis* were significantly lower than micafungin, while demonstrating higher MICs than micafungin against the remaining *Candida* spp.[36]

Ibrexafungerp exhibits potent activity against *C. auris* in vitro.[19,21,24,37] It is active against both planktonic and biofilm forms of *Candida* spp., including *C. auris*.[38,39] The study of 16 isolates *of C. auris* recovered from patients in different geographical regions evaluated the effects of ibrexafungerp on growth, ultrastructure, and biofilm production.[39] Ibrexafungerp resulted in the fusion of the *C. auris* cells and a loss of their ability to divide.[39] Furthermore, ibrexafungerp also had a potent effect on biofilm production, significantly reducing the thickness and metabolic activity of the *C. auris* biofilms.[39] Evaluation of activity of ibrexafungerp against 122 *C. auris* strains, including eight with resistance to anidulafungin and micafungin, showed consistent and potent activity against the isolates.[40] Zhu et al evaluated the in vitro activity of ibrexafungerp against 200 *C. auris* isolates including five pan-resistant isolates and demonstrated that ibrexafungerp was highly active against all of the isolates, with all five pan-resistant isolates demonstrating in vitro susceptibility to ibrexafungerp.[41]

In addition to its fungicidal activity against *Candida* spp., it also demonstrates fungistatic activity against *Aspergillus* spp., including cryptic species and azole-resistant strains.[19,27,42,43] Ibrexafungerp has also demonstrated efficacy against dimorphic fungi, and the asci form of *Pneumocystis*, however, it lacks activity against Mucorales and *Fusarium* spp.[20,22,44]

Clinical Trials

Several clinical trials are currently being conducted to determine the clinical efficacy of ibrexafungerp in the management of invasive candidiasis and determine its role in patient management. In 2019, Spec et al published the results of a multinational open-label study, assessing the efficacy of two dosing regimens of oral ibrexafungerp.[45] The primary goal was to evaluate the safety and tolerability of two dosing regimens, as well as the determination of the study drug dose achieving the target AUC in >80% of the patients. Twenty-seven subjects were enrolled, seven received ibrexafungerp 500 mg, seven received 750 mg, and eight were standard of care controls. The subjects were non-neutropenic patients with documented invasive candidiasis for whom ibrexafungerp was utilized as a step-down therapy following initial therapy with echinocandins vs. standard of care. Among the study participants with invasive candidiasis, a favorable global response was achieved with the 750 mg twice daily dosing which was also estimated to achieve the target exposure.[45] A relapse was reported in one patient in the 500 mg twice-daily dosing and occurred after the end of treatment after a biliary stent manipulation. No differences in treatment-associated adverse events were noted between the study drug and the standard of care treatment and, although 18/22 patients (86%) experienced at least one adverse event associated with treatment, none of them required study drug discontinuation or changes in treatment plan. There was no difference observed between the two groups regarding types or frequency of the adverse events.[45]

The efficacy and safety of ibrexafungerp among patients with fungal disease with limited treatment options due to intolerance to standard of care or refractory disease was evaluated in a multicenter, open-label, non-comparator study (FURI trial, NCT03059992).[46] The treatment regimen included a loading dose of 1500 mg/day for 2 days, followed by 750 mg/daily orally. The prespecified duration of treatment with ibrexafungerp was up to 180 days, with extension beyond 180 days permitted under special circumstances.[46] The interim results presented during several conferences showed favorable response to treatment with ibrexafungerp among patients with invasive candidiasis and candidemia, including those difficult to treat and those with *non-albicans Candida* species.[47,48] The study has been completed with some of the results available for review.[49] The available data is suggestive of 65.6% success in the intention-to treat (ITT) analysis of participants with acute invasive candidiasis including candidemia and 75.5% success in the per-protocol analysis.[49]

Step-down therapy with ibrexafungerp after initial treatment with echinocandins in patients with candidemia and invasive candidiasis is currently being evaluated in a multicenter, double-blind Phase 3 trial (MARIO, NCT05178862).[18] The study group will be compared to participants who were treated with echinocandins followed by fluconazole as step-down therapy. The primary outcomes include all-cause mortality and global response at the end of treatment. However, the study has been terminated early by the pharmaceutical company.[50]

The efficacy and safety of oral ibrexafungerp against invasive candidiasis and candidemia, caused by *C. auris*, were evaluated in the CARES trial, a multicenter, open-label, single-arm study.[11,51,52] Some of the results are available for review.[52] The global success rate, which was defined as complete or partial resolution of signs and symptoms caused by candidemia and/or invasive candidiasis and mycological eradication, as determined by the data monitoring committee, was 21/30 (70%) among the intent-to-treat population.[52] Among the participants who achieved global success at the end of treatment, only one out of 21 subjects (4.8%) experienced a recurrence of the baseline fungal infection.[52] The reported all-cause mortality was 26.67% (8/30).[52] In the analysis of efficacy of ibrexafungerp against urinary tract infections, including five subjects from the CARES study and two subjects from the FURI trial, six out of seven (86%) participants achieved a complete response to ibrexafungerp, including three cases of *C. auris* UTI and one case of a mixed *C. parapsilosis*/*C. auris* infection.[53]

Ibrexafungerp may become a valuable tool in the treatment of resistant candidal infections because of its oral formulation, its favorable safety profile, few drug interactions, and its broad spectrum of activity. In the future, it may be considered an alternative to parenteral echinocandins or as a step-down treatment after initial echinocandins therapy.[22,44] Further clinical data is necessary to establish the appropriate use of ibrexafungerp in the management of invasive candidiasis.

Rezafungin

Mechanism of Action, Spectrum of Activity, and Resistance

Rezafungin is a second-generation echinocandin, which was FDA-approved in 2023 for treatment of candidemia and invasive candidiasis in adult patients with limited or no alternative treatment options.[22,54] It is designed as a structural

analog of anidulafungin, however the C5 ornithine residue in anidulafungin was replaced by a choline aminal ether side-chain in rezafungin, resulting in both increased stability and solubility, as well as a prolonged half-life (~80 hours after the first dose and ~150 hrs after the second dose) allowing us to achieve target drug levels with once-weekly dosing.[55,56] Studies have demonstrated that rezafungin is well-tolerated, with a good safety profile and no meaningful drug–drug interactions with commonly co-prescribed drugs.[56,57] Rezafungin acts as an inhibitor of cell wall formation by inhibiting the 1,3-β-d-glucan synthase enzyme complex, which leads to osmotic instability and cell wall lysis.[56] The major route of elimination is via excretion in feces as an unchanged drug, and a small proportion is also eliminated in the urine as an inactive metabolite.[21,58] Since rezafungin is mostly eliminated via the non-renal route, there are no recommendations for dose adjustments for any degree of renal function impairment, including patients receiving renal replacement therapy or hemodialysis.[59,60] Dose adjustment in any degree of liver dysfunction is also not required, however, monitoring of liver function tests should be considered.[60]

Rezafungin demonstrates certain additional features that make it an important tool in management of invasive candidiasis. In the study by Zhao et al investigating spatial and quantitative distributions of micafungin and rezafungin in tissue lesions in a murine model of invasive candidiasis, a single dose of rezafungin demonstrated an extensive penetration into the infected lesion and distribution within the infective tissue, resulting in thorough diffusion into infective lesions at 48 hours. Additionally, it accumulated in necrotic areas of the lesions at 72 hours, whereas micafungin was only detected from lesion centers at steady state (after 3 doses).[61] Moreover, accumulation of rezafungin exceeded the mutant prevention concentration when compared to micafungin, which may have implications for clinical outcomes as well as decreasing the possible emergence of resistance during treatment.[61]

Previous studies have shown significant activity of rezafungin against *C. albicans* biofilms, preventing the development of early biofilms into mature biofilms and thus eradicating mature biofilms. However, this activity seems to be species-specific, and varies across the different *Candida* spp., with lower efficacy against *C. parapsilosis* and *C. auris* biofilms.[38,62]

Rezafungin demonstrates potent activity against *Candida* spp. and *Aspergillus* spp. including azole-resistant strains and cryptic species.[54,63] In addition, it also demonstrated activity against the asci form of *Pneumocystis*, which may make it a useful tool for both prophylaxis and treatment.[54] However, it lacks activity against *Cryptococcus*, *Rhodotorula* spp., and *Trichosporon* spp., as these organisms are intrinsically resistant to echinocandins.[27] *Mucorales*, *Fusarium*, and *Basidiomycota* also possess intrinsic resistance to rezafungin.[55]

Among *Candida* spp., rezafungin exhibits potent activity against *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. krusei*, *C. auris*, and many other *Candida* spp. However, the activity against *Candida* spp. exhibiting reduced susceptibility (RES) phenotype, such as the members of *C. parapsilosis species complex*, as well as *C. guilliermondii* is decreased.[55,64] These species are known to harbor naturally occurring mutations in the *FKS1 gene*, which results in intrinsically reduced echinocandin susceptibility.[65,66] The MIC50 and MIC90 values for rezafungin are comparable to those of other echinocandins, however discrepancies have been noted. Emergence of secondary echinocandin resistance has been increasing recently, especially among *C. glabrata*. It is important to note that echinocandin resistance in *C. glabrata* is associated with cross-resistance to azole antifungals.[67,68] Mutations in the hotspots of the *FKS1* and *FKS2* genes, encoding the 1,3-β-D-glucan synthase enzyme complex, are responsible for resistance of *Candida* spp. to echinocandins.[69] The activity of echinocandins including rezafungin against *C. glabrata* isolates that were collected from 2014–2021 from European hospitals was studied by Castanheira et al.[70] Out of the 1,257 *C. glabrata* isolates, 26 were found to be non-wild type (NWT) to echinocandins, with 46.2% harboring *FKS1*/*2* hotspot mutations. In this same study, rezafungin exhibited in vitro activity against 73.1% of the echinocandin NWT *C. glabrata* isolates, whereas anidulafungin, caspofungin, and micafungin retained activity against 46.2%, 65.4%, and 57.7%, respectively.[70] Among the isolates harboring *FKS1*/*2* alterations, rezafungin remained active against 41.7% of isolates, while the susceptibility rates to anidulafungin, caspofungin, and micafungin were 8.3%, 25.0%, and 25.0%, respectively.[70] Overall, rezafungin MICs are similar to those of other echinocandins against *FKS1*/*2*-mutant *Candida* isolates.[27]

Rezafungin also demonstrates potent activity against *C. auris* in vivo and in vitro.[64,71] Among the 78 *C. auris* isolates submitted to the SENTRY Antifungal Surveillance Program in 2013–2022 from 148 hospitals in 44 countries, 82.1% were resistant to fluconazole, 17.9% were resistant to amphotericin B, and 1.3% were resistant to micafungin, caspofungin, or anidulafungin, while 96.2% remained susceptible to rezafungin.[72] In the study by Winkler et al,

rezafungin was active against 95.4% of *C. auris* isolates, collected as part of the SENTRY program in 2020–2022.[64] In vivo studies evaluating efficacy of rezafungin in murine models of invasive candidiasis, caused by *C. auris*, showed potent activity and efficacy in reducing the fungal burden.[73,74] Further clinical data is necessary to establish the use of rezafungin in the management of *C. auris* infections since the registration trials (ReSTORE and STRIVE) did not include patients with infections due to *C. auris*.[75,76]

Clinical Trials

The efficacy and safety of rezafungin was compared to caspofungin in patients with candidemia or invasive candidiasis (IC) in the STRIVE trial (Phase 2, randomized double-blind study).[75] Eligible participants were adult patients with clinical signs of infection and mycological confirmation of candidemia or invasive candidiasis (IC). Patients with certain forms of invasive candidiasis, such as septic arthritis in a prosthetic joint, osteomyelitis, endocarditis, or myocarditis, ocular *Candida* infections, central nervous system (CNS) infections due to *Candida* spp., as well as neutropenia, liver aminotransferases levels exceeding 10-fold the upper limit of normal, or severe hepatic impairment with and history of chronic cirrhosis (Child-Pugh score >9) were excluded. The trial consisted of parts A and B with differing randomization schedules. Rezafungin was administered on days 1 and 8, with optional doses on day 15 and an additional optional dose on day 22 for IC, whereas caspofungin was limited to 21 days for candidemia and up to 28 days for IC (with or without candidemia), with a possible step-down to fluconazole. The primary endpoint was global response at day 14, which consisted of clinical resolution of IC/candidemia and evidence of mycological eradication. In the modified intent-to-treat population, which included 183 patients, the overall cure on day 14 was achieved among 60.5% (46/76) of patients in the rezafungin 400 mg/weekly group, 76.1% (35/46) among the rezafungin 400 mg/200 mg weekly cohort, and 67.2% (41/61) of those subjects on caspofungin.[75] When the patients with indeterminate response were excluded from the analysis, the overall cure rates were 69.7%, 81.4%, and 70.7%, respectively. The highest clinical cure rates at day 14 by baseline *Candida* species (*albicans vs. non-albicans*) were achieved in the rezafungin 400/200 mg group (84.2% vs 81.3%, respectively). The most common treatment-associated adverse events (TAEs) included hypokalemia, diarrhea, and vomiting. Most adverse effects were mild.[75] The 400/200 mg group outperformed the two other comparator groups by achieving higher overall cure on day 14 and demonstrating the lowest all-cause mortality on day 30. Notably, the differences in efficacy between the two rezafungin arms were first evident on day 5, at which point both groups had received the same 400 mg dose of rezafungin.[75]

In the Phase 3 study, the efficacy and safety of rezafungin among patients with candidemia and invasive candidiasis (IC) was compared to those of caspofungin in a multicenter, double-blind, randomized trial (ReSTORE).[76] Eligible patients with mycological confirmation of candidemia or IC were randomized by 1:1 to receive either rezafungin 400 mg loading dose, followed by 200 mg weekly for a total of two to four doses or intravenous caspofungin (70 mg loading dose on day 1, followed by 50 mg daily) for no more than 4 weeks. In the caspofungin cohort, if step-down criteria were met, patients could be switched to an oral step-down therapy (fluconazole) and a placebo was provided for the rezafungin cohort. The primary endpoints included a composite endpoint of global cure (comprised of clinical cure, radiological cure, and mycological eradication) on day 14 and the 30-day all-cause mortality with a non-inferiority margin of 20%.[76] Secondary endpoints included global cure on day 5, day 30, end-of-treatment, and at the follow-up visits. Additional secondary outcomes included mycological eradication, clinical cure, and radiological cure for invasive candidiasis on day 5, day 30, end-of-treatment, and the follow-up visits. A total of 199 patients were enrolled in the study, 100 in the rezafungin arm and 99 in the comparator group. Results included a global cure on day 14 at 55/93 (59%) in the rezafungin group and 57/94 (61%) in the caspofungin group. Death or unknown survival status was documented among 22/93 (24%) in the rezafungin group and 20/94 (21%) in the caspofungin group. Non-inferiority of rezafungin was met when compared to caspofungin and was seen in both primary endpoints. However, a numerical trend toward higher rates of mycological eradication was observed in the rezafungin group both on day 5 and day 14. This possibly suggests that front-end loading with rezafungin enhances the mycological effect and the eradication of candidemia, which may be beneficial in serious infections.[73,76,77] The most common adverse events in the rezafungin group included pyrexia (14%), hypokalemia (13%), pneumonia (10%), and septic shock (10%). Analysis of outcomes by *Candida* spp. demonstrated comparable rates of mycological eradication and global cure rate in both study groups.[76] There were two isolates that were non-wild type to echinocandins, both in the rezafungin group with candidemia: one isolate of *C. dubliniensis* was

non-susceptible to rezafungin, the other one was a *C. glabrata* isolate harboring the *F659V FKS2* HS1 alteration, susceptible to rezafungin, however intermediate to caspofungin. The patient with *C. dubliniensis* candidemia had an indeterminate global cure response on day 14, while failure to achieve global cure on day 14 was reported for the patient with *C. glabrata* infection. However, mycological eradication on day 14 and treatment success based on the 30-day all-cause mortality endpoint was achieved in both cases.[76,78]

Rezafungin is currently being evaluated as an antifungal prophylactic regimen among recipients of allogeneic stem cell transplants (allo-SCT).[79,80] The ReSPECT trial is a phase 3, multicenter, randomized, double-blind study, with subjects randomized 2:1 to receive posttransplant prophylaxis with either once weekly rezafungin or the standard prophylaxis with trimethoprim/sulfamethoxazole and oral fluconazole/posaconazole.[80] The study will assess the efficacy of rezafungin prophylaxis of fungal diseases, as well as toxicity and tolerability, as compared to standard drugs.[79] The study is closed to enrollment achieving 600 subjects and is currently in the follow-up phase of the protocol.

Overall, rezafungin appears to be a valuable addition to the antifungal armamentarium for a variety of reasons including its once weekly dosing, no meaningful drug–drug interactions, minimal metabolism and favorable side-effect profile which is similar to that of other echinocandins. It has become an important tool in the management of patients with invasive candidiasis and candidemia, as it should decrease the length of stay and the duration of inpatient stay, decrease hospitalization-associated costs. In addition, it represents a reasonable option for outpatient parenteral antimicrobial therapy (OPAT) programs, as well as an option for long-term and suppressive management in the presence of implantable hardware or devices, or when azole therapy is not an option and when placement of a central line is not desirable.[2,33,81–83]

Fosmanogepix

Mechanism of Action, Spectrum of Activity, and Resistance

Fosmanogepix is a prodrug of manogepix, which can be administered orally and intravenously, and is rapidly converted to its active form, manogepix (APX001A).[22,27,46] It acts by inhibiting the Gwt1 protein, which is a part of the glycosylphosphatidylinositol (GPI)-anchored protein biosynthesis pathway.[27,84] GPI-anchored mannoproteins are essential for maintaining cell wall integrity and for adhesion to host epithelial and mucosal surfaces, thereby enabling fungal colonization and infection.[27,84,85] The cellular target Gwt1 plays a key role in trafficking and anchoring mannoproteins to the cell wall.[84] Inhibition of Gwt1 affects the localization and maturation of the GPI-anchored mannoproteins, leading to a decrease in the amount of cell wall-linked mannoproteins, cellular malformation, endoplasmic reticulum strain, exposure of the highly immunogenic cellular glycan layer, impaired surface adherence, and hyphal formation, which directly affects the fungal virulence.[21,84] Manogepix demonstrated concentration-dependent inhibition of Als1 adhesin protein surface expression in *C. albicans*.[84] Another important property of manogepix is its ability to inhibit biofilm formation by pathogenic fungi.[38] In a study by Ceballos-Garzon et al, the activity of several antifungal agents, including amphotericin B, caspofungin, ibrexafungerp, manogepix, and rezafungin, was evaluated against planktonic cells and mature biofilms of *Candida* spp.[38] Manogepix demonstrated the highest activity among the tested antifungal agents against a variety of *Candida* spp., except for mature biofilms of *C. auris*.[38] The closest mammalian ortholog (phosphatidylinositol glycan-class W protein (PigW)) is not affected by manogepix due to low structural and chemical similarities at active sites.[38,84]

Fosmanogepix has demonstrated efficacy in invasive candidiasis, including CNS and ocular infections in experimental animal models.[86] In the study by Petraitiene et al, administration of fosmanogepix in nonneutropenic rabbits with *Candida* endophthalmitis and hematogenous meningoencephalitis resulted in a significant reduction in the *C albicans bio*burden in the choroid and vitreous humor. Administration of fosmanogepix also resulted in a decline in the fungal burden in the cerebrum, cerebellum, spinal cord, meninges and cerebral spinal fluid. Doses of 50 mg/kg twice a day (BID) or 100 mg/kg BID were equally effective in terms of fungal burden reduction as was treatment with amphotericin B deoxycholate.[86] Manogepix was evaluated in the murine model of intraabdominal candidiasis, caused by *C.albicans*.[87] Robust accumulation of manogepix in liver abscesses was observed after 3 days of repeated dosing, with high concentrations in the necrotic core and enhanced drug penetration into the liver lesion with repeat dosing.[87] Fungal

clearance was observed in all experimental models in the 4-day treatment fosmanogepix arm, with histopathological examination in this group showing no detectable fungi or morphologically damaged, necrotic hyphal elements of unknown viability.[87] The histopathological examination of the liver lesions in the comparator group, who received a 4-day course of micafungin, demonstrated a robust network of fungal filaments in the lesion core, suggesting only a marginal reduction in fungal burden.[87] The results of this study suggest that fosmanogepix may be a promising agent for the treatment of intra-abdominal candidiasis. Efficacy in animal models of disseminated candidiasis, including those caused by azole- and echinocandin-resistant strains, has been demonstrated in multiple studies.[88,89] The APX001A (former name of fosmanogepix) demonstrated improved survival in the murine model of disseminated candidiasis, caused by *C. auris*, as well as a greater reduction in brain tissue fungal burden, compared to both placebo and anidulafungin groups.[90] In a murine neutropenic model of invasive candidiasis caused by *C. auris* similar efficacy was demonstrated even if the initiation of therapy was delayed by 24 hours post-inoculation.[91]

Manogepix has also demonstrated in vitro activity against a variety of dimorphic fungi, molds, including *Scedosporium* spp., *Fusarium* spp., *Lomentospora* (*Scedosporium*) *prolificans*, *Aspergillus* spp., including azole-resistant strains, *Cryptococcus neoformans* and *C. gattii*.[27,92–94] Among *Candida* spp., manogepix demonstrated in vitro activity against *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*.[93] In vitro studies, however, demonstrated limited activity against certain *Candida* spp., such as *C. krusei*, *C. inconspicua*, *C. kefyr*, and *Pichia kluyveri*.[27,95] There is a statistically significant correlation between manogepix and fluconazole MICs in *C. albicans*, *C. dubliniensis*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* isolates that are non-wild type to manogepix, often being non-wild type (NWT) or resistant to fluconazole as well.[95] No such correlation was observed between manogepix and micafungin or amphotericin B MICs for any species, except for a similar correlation between manogepix and micafungin MICs in *C. tropicalis*.[96] However, most fluconazole-resistant and NWT strains remain susceptible to manogepix, suggesting drug efflux as a possible mechanism of resistance.[93,96] Manogepix demonstrated a low potential for development of resistance, with low frequencies of spontaneous mutations and low potential for cross-resistance to other antifungals.[97]

Manogepix non-wild type isolates of *Candida* spp. are uncommon.[93] In the study by Pfaller et al, manogepix inhibited 100% of 460 *C. glabrata* isolates, including seven isolates with *FKS* alterations with echinocandin MICs greater than epidemiologic cut-off values (ECVs) and 6.3% of isolates that were fluconazole resistant.[93] In the same study, all isolates of *C. auris* (total of 11 isolates from the USA and Panama) were inhibited by ≤0.06 mg/L manogepix, while 63.6% of the isolates were fluconazole resistant.[93] In vitro data from another study also showed potent activity of manogepix against *C. auris* isolates, outperforming echinocandins.[98] Among 200 *C. auris* isolates, obtained during the *C. auris* outbreak in the New York metropolitan area, all isolates were wild-type to manogepix, and manogepix remained active to pan-resistant *C. auris* isolates.[99] Moreover, fosmanogepix in combination with anidulafungin demonstrated synergistic activity against *C. auris* isolates in vitro.[100] One of the mechanisms of the development of decreased susceptibility to manogepix in *C. auris* is mediated by the D865N amino acid mutation in *TAC1b*, leading to upregulation of expression of *CDR1* and increased activity of drug efflux pumps.[101] Mutations in the *gwt1* target genes, such as valine to alanine mutation at position 163 (V163A) in the Gwt1 protein in *C. glabrata* or V162A in *C. albicans* results in the reduced susceptibility to manogepix without affecting susceptibility to azoles and echinocandins.[84] Other mechanisms of resistance in *Candida* spp. may also include upregulation of drug efflux pumps, such as upregulation of the *MDR1*, the major facilitator superfamily gene, as well as increased expression of AATP-binding cassette transporter genes *CDR11* and *SNQ2*.[84]

Fosmanogepix has a prolonged half-life of about 60 hours, a high oral bioavailability (>90%), and has oral and intravenous formulations.[102] It exhibits wide tissue distribution, and it is mostly eliminated via the biliary tract.[11]

Clinical Trials

Published data from several clinical trials suggest that administration of fosmanogepix is well-tolerated, with low rates of serious adverse events.[103–106] In the Phase 1b open-label study, the investigators utilized a single dose of ^{14}C-radiolabeled fosmanogepix to evaluate its pharmacokinetics and metabolism in healthy male participants.[103] Several major routes of metabolism of fosmanogepix were demonstrated, mainly via conversion to manogepix, and included oxidation, oxidative deamination, and conjugation. Manogepix elimination occurs equally via renal and hepatic routes.[99] In the phase 1b trial evaluating safety and pharmacokinetics of fosmanogepix in patients with acute myeloid leukemia and neutropenia, the study drug demonstrated

a favorable safety profile, with no serious adverse events necessitating discontinuation of fosmanogepix.[104] Most common study-drug associated adverse events were gastrointestinal disturbances (nausea, vomiting, increase in ALT level) and delirium and, apart from one instance of Grade 3 hypertension, all study-drug related adverse events were mild or moderate.[104]

Safety and efficacy of fosmanogepix as the first line for treatment of candidemia *was* evaluated in a multicenter, non-comparative phase 2 trial.[105] Eligible participants were diagnosed with candidemia within less than 96 hours prior to study enrollment, had suspected or documented resistance to at least one systemic antifungal and received less or equal to 2 days of effective systemic antifungals. Neutropenic patients, pregnancy, patients with infections due to *C. krusei*, and cases of deep-seated invasive candidiasis and hepatosplenic candidiasis were excluded. Treatment consisted of an IV loading dose of fosmanogepix (1000 mg twice daily for 24 hours) followed by the maintenance dose of 600 mg IV daily, with a possible consideration of transitioning to oral fosmanogepix 700 mg daily on day 4 of study, provided the blood cultures remained negative for *Candida*. Total duration of treatment with fosmanogepix (IV+PO) was 14 days, with an optional step-down therapy with an azole or other guideline-recommended antifungal permitted if treatment needed to be extended beyond 14 days.[105] The primary endpoint of the study was treatment success at the end of study (EOST, day 14 of IV/PO fosmanogepix). In addition, other significant outcomes were evaluated as well, including success at 2 weeks after the end of treatment, overall survival on day 30, time to blood culture clearance, mycological outcomes and adverse events. A total of 16 of the 21 participants completed 14 days of treatment, with 21 patients included in the intention-to-treat population (ITT) and 20 participants included in the modified intention-to-treat population (mITT). Baseline pathogens included *C. glabrata* (10), *C. albicans* (8), *C. parapsilosis* (3), and *C. dubliniensis* (1). Treatment success at the end of the study/end of treatment (EOST/EOT) was defined as clearance of the blood cultures and survival at the EOST/EOT without the use of additional systemic antifungals. Treatment success at EOST was achieved in 16 patients in the mITT population, with four cases of treatment failure, including three cases of persistent candidemia and the death of one participant. Treatment success at EOT was achieved in 15 patients (75%), including three subjects who received step-down therapy with fluconazole. No serious adverse events related to the study drug were observed, and no study drug-related adverse events resulting in the discontinuation of the study drug were observed.[105]

Clinical efficacy and safety of fosmanogepix in patients with candidemia and/or invasive candidiasis, caused by *C. auris* with limited treatment options, was evaluated in a Phase 2, multicenter, single-arm, open-label study.[106] The study protocol permitted treatment with fosmanogepix for no longer than 42 days with an IV loading dose of 1000 mg twice daily, followed by 600 mg IV daily and the possibility of switching to an 800 mg oral fosmanogepix once daily starting on day 4. The study cohort included only nine subjects with documented candidemia. All were enrolled in the intensive care units in South Africa and received IV fosmanogepix only. Treatment success was defined as the eradication of *C. auris* without the use of additional antifungals. Survival of the participants at the end of the study treatment was the primary outcome of the study. Fosmanogepix demonstrated a high success rate, with both treatment success at EOST and survival on day 30 reaching 89% (8/9 patients). There was one death during the study at EOST which was the reason for the single failure. However, it was later determined that it was not related to the study drug. The mean time to first negative blood culture was 8.7 (SD =5.51) days. Eradication of *C. auris* from the bloodstream was achieved in six of nine participants. There was one case of recurrence after stopping the fosmanogepix with subsequent eradication of the candidemia and no further relapses. Fosmanogepix was well-tolerated with no serious adverse events related to study treatment. Low MIC values to manogepix were observed across all tested *C. auris* isolates, with a high agreement between CLSI and EUCAST MICs, and no shift in fosmanogepix susceptibility was noted during study treatment.[106]

A phase 3, randomized, multicenter study in patients with candidemia and/or invasive candidiasis comparing safety and efficacy of fosmanogepix to caspofungin, followed by oral fluconazole, is currently in the recruitment phase.[107]

The data from these two trials suggest that fosmanogepix may become a valuable option in the treatment of candidemia and invasive candidiasis, including those cases with limited therapeutic options such as multidrug resistant *Candida* spp., such as *C. glabrata* and *C. auris*. However, further clinical trials are necessary to establish its place in clinical practice.

Antifungal Agents in Early Clinical Development

Encochleated Amphotericin B (CAmB, Formerly MAT2203)

CAmB represents a novel formulation of amphotericin B, with the active compound encapsulated in a cochleate, providing a novel delivery vehicle for amphotericin B, that increases the stability of the drug and permits oral administration.[108,109] Cochleates consist of a negatively charged lipid and a divalent cation, and encapsulate amphotericin B, incorporating it within the multilayered lipid matrix at the interior of the calcium-phospholipid anhydrous crystal.[108,109] It has demonstrated an efficacy in a murine model of invasive candidiasis due to *C. albicans* with a 100% survival of the treated murine models at 16 days postinfection when compared to empty cochleates that were used as negative control. Moreover, it showed a significant dose-dependent reduction in fungal burden in the kidneys and lungs.[109] The Phase I open label trial (part of the EnACT trial) evaluated the safety and tolerability of CAmB.[110] CAmB lacked the toxicity commonly observed with IV amphotericin B and was generally well-tolerated by the study participants.[110] No serious adverse events were observed, with the most common adverse events being GI disturbances.[110] No human studies in invasive candidiasis or candidemia are available. However, the results of two clinical trials evaluating safety, efficacy, and tolerability of CAmB in patients with chronic mucocutaneous candidiasis and moderate to severe vulvovaginal candidiasis (VVC) are available.[11]

ATI2307 (T-2307)

ATI2307 is a novel arylamidine compound that has demonstrated broad-spectrum in vitro activity against a wide variety of fungal pathogens, including *C. neoformans*, *A. fumigatus*, as well in vitro activity against *Candida* spp., such as *C. albicans*, *C. glabrata*, and *C auris*, including echinocandin-resistant and azole-resistant *C. auris* strains.[46,111,112] ATI2307 mechanism of action and antifungal effect on yeast cells is by inducing mitochondrial dysfunction through the inhibition of the respiratory chain enzyme complexes III and IV in the inner mitochondrial membrane, causing the collapse of the mitochondrial membrane potential.[112,113] The studies also suggested that ATP production is inhibited in a dose-dependent fashion. In addition, ATI2307 has been shown to have significantly greater affinity to yeast mitochondria when compared to the mammalian cells.[111–113] T-2307 demonstrated a dose-dependent improvement in survival in a neutropenic murine model of disseminated candidiasis caused by a wild-type strain of *C. albicans*, achieving 100% survival at day 15 among animal models receiving 0.02 mg/kg once daily.[114] Improved survival and reduced kidney fungal burden were observed in a non-neutropenic murine model of disseminated candidiasis, caused by echinocandin-resistant *C. albicans*, compared to placebo controls and caspofungin.[115] In vivo efficacy has been demonstrated in echinocandin-susceptible and echinocandin-resistant *C. glabrata* disseminated infections in murine neutropenic models, as well as in disseminated *C. auris* infection.[116–118] A significant reduction in ocular fungal burden, as well as ocular trough concentrations above the MIC were observed in vivo in a disseminated wild-type *C. albicans* infection model, suggesting potential use of T-2307 in ocular candidiasis.[119] There is no data evaluating its clinical efficacy in invasive candidiasis in human subjects at this point.

VT-1598

VT-1598 is a novel 1-tetrazole-based antifungal drug candidate.[120] It acts as a Cyp51 inhibitor with improved selectivity for the fungal enzymes, thus minimizing the binding to the human Cyp450 enzymes.[120] Its primary metabolite, VT-11134 also exhibits antifungal activity.[120] It has demonstrated in vitro activity against a broad range of yeasts, molds, and endemic fungi.[121] In addition, it retains in vitro activity against *Candida* spp. isolates, including those that are either resistant or with reduced susceptibility to fluconazole.[121] VT-1598 also demonstrated in vitro and in vivo activity against *C. auris* in animal models.[122] A neutropenic murine model of invasive candidiasis caused by *C. auris* treatment with VT-1598 resulted in a dose-dependent improvement in survival, as well as a dose-dependent reduction in kidney and brain fungal burden.[122] The safety and pharmacokinetics of VT-1598 have been evaluated in a phase 1, placebo-controlled study using single-ascending oral doses. In this study, there were no severe adverse events, death, or early withdrawals from the study due to adverse events.[120] The safety and PK profiles, observed in this phase 1 study, support its further clinical development.[120] However, no further data in human studies among patients with invasive candidiasis is yet available.

Oteseconazole

Oteseconazole (formerly VT-1161) is novel tetrazole antifungal, a member of the new generation of azoles with increased affinity to fungal Cyp51 enzyme (ie., lanosterol 14α-demethylase).[27,46] Oteseconazole inhibited *C. albicans* Cyp51 and culture growth with >2000-fold selectivity over human Cyp51 enzyme.[123] It also showed a weak inhibitory effect on other human Cyp enzymes, suggesting low risk of drug–drug interactions.[123] It demonstrated activity against multiple *Candida* spp., such as *C. albicans*, including some fluconazole-resistant strains, fluconazole- and echinocandin-resistant *C. glabrata* and fluconazole-resistant *C. krusei*.[27,124,125] Additionally, it is active against *Cryptococcus* spp., *Trichophyton rubrum*, and *Coccidioides immitis/posadasii*, as well as some Mucorales species (ie., *R. arrhizus* var. *arrhizus*) and it showed promise in vivo as a prophylactic agent and as a treatment agent against pulmonary mucormycosis caused by *R. arrhizus* var. *arrhizus* in immunosuppressed murine models.[126–130] Oteseconazole showed efficacy in animal models of oropharyngeal and vulvovaginal candidiasis, as well as onychomycosis.[131–133]

Oteseconazole was FDA approved in April 2022 for the treatment of recurrent vulvovaginal candidiasis for females who are not of reproductive potential.[46,134] In clinical trials evaluating safety and efficacy of oteseconazole in acute and recurrent VVC and onychomycosis oteseconazole exhibited a favorable safety profile and was well-tolerated by the study participants, with most adverse events ranging from mild to moderate.[135–138] Oteseconazole has a half-life of about 138 days, and is contraindicated in pregnant and lactating women, as well as females of reproductive potential.[46] Currently there are no plans for its development as a treatment option in invasive candidiasis.[11]

BAL2062 (Former GR2397, VL-2397)

BAL2062 is a non-ribosomally synthesized cyclic hexapeptide isolated from the Malaysian fungus *Acremonium persicinum* MF-347833. Its exact mechanism of action is still unknown.[139] It has a siderophore-like molecule and selective affinity for fungal cells, as it is being transported into the fungal cell via Sit1 transporter, which is not present in mammalian cells.[139] Because of the dependence on the Sit1 transporter, the spectrum of activity of BAL2062 is limited to Sit1-positve *Candida* spp., such as *C. glabrata*, including azole- and echinocandin-resistant insolates, and *C. kefyr*.[11] *C. albicans* also encodes the Sit1 protein, however it is resistant to BAL2062.[139] Possible explanations include different intracellular targets, the inability of the *C. albicans* Sit1 ortholog to recognize BAL2062 as a substrate for uptake, or the inability to express the Sit1 ortholog by some species under the specific conditions utilized for in vitro susceptibility testing.[139] There is limited data regarding the in vivo efficacy of BAL2062, however it demonstrated efficacy in a murine model of invasive candidiasis caused by *C. glabrata*, including multidrug-resistant strains.[140] The safety, tolerability, and pharmacokinetics of BAL2062 in healthy adults was evaluated in a Phase 1, placebo-controlled, dose-escalation study.[141] Elimination via renal route plays a major role in total body clearance of BAL2062 at doses above 10 mg, with a substantial amount of BAL2062 excreted in urine in the form of unmetabolized drug.[141] Clinical data regarding efficacy and tolerability of BAL2062 in human subjects with invasive candidiasis are lacking. The potential applications of BAL2062 include targeted therapy of infections caused by *C. glabrata* and *C. kefyr*, and its use in infections of the urinary tract due to its high renal excretion.[11]

Miltefosine

Miltefosine was originally developed as an antitumor agent and was later repurposed for treatment of leishmaniasis.[142] It has demonstrated broad antifungal activity against a wide range of fungi, including *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., *Fusarium* spp., *Scedosporium* spp., *Histoplasma capsulatum*, *Rhizopus* spp., and *Sporothrix schenckii*.[142,143] In vitro data suggested that miltefosine has activity against planktonic cells of *C. albicans*, including fluconazole-resistant strains, as well as an inhibitory effect on biofilm formation and activity against mature biofilms viability of *C. albicans*.[142] Subsequent studies showed that it is also active against the planktonic cells of multiple non-*albicans Candida* spp., including *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, and *C. auris*. In addition, it also exhibits an inhibitory effect on the development of candidal biofilms, as well as efficacy against preformed biofilms.[142,144–146] Treatment with miltefosine, either as a free drug or as miltefosine alginate nanoparticles, in *Galleria mellonella* larvae infected with fluconazole-sensitive and fluconazole-resistant strains of *C. albicans*, resulted in prolonged survival and reduced fungal burden.[147] In the *Galleria mellonella* larval model of candidiasis, caused by *C. auris*, administration of miltefosine, either in the form of a free drug or miltefosine-loaded alginate nanoparctiles,

reduced the fungal burden in tissues and dissemination, as well as increased granuloma formation.[145] Increased granuloma formation suggests an enhanced immune response to the fungal infection, which leads to a higher larval survival rate.[145] Use of alginate nanoparticles helps mitigate the toxic effects of miltefosine.[145,147] Treatment with topical miltefosine was effective in a murine model of oropharyngeal candidiasis caused by wild-type *C. albicans*, resulting in reduced tissue colonization, inhibition of hyphal formation, decreased invasive features on histological sections, and reduced biofilm formation.[142] A reduction in fungal burden has been observed after topical miltefosine treatment in murine models of vulvovaginal candidiasis caused by *C. albicans*.[148] The exact mechanism of action remains unclear.[46] Various possible mechanisms of action have been demonstrated among fungal species.[149,150] One of the possible mechanisms described in *C. albicans*, *C. krusei*, *Cryptococcus* spp., *Scedosporium* spp., and *A. fumigatus* involves the destruction of mitochondria, increased production of reactive oxygen species, and the induction of apoptosis.[146,149,150] Human studies evaluating the safety and efficacy of miltefosine in invasive candidiasis are yet to be performed. However, in 2021, miltefosine was granted an orphan drug designation by the FDA for the treatment of invasive candidiasis.[151]

Table 2 Novel Antifungals and Their Characteristics

Antifungal Agent	Class	Mechanism of Action	Activity	Advantage	Limitations	Dosage in Candidiasis
Ibrexafungerp	Triterpenoid	Inhibitor of the 1,3-β-D-glucan synthase enzyme complex	*Candida* spp, including *C. auris* and *C. glabrata* Fungicidal against *Candida* spp, fungistatic against *Aspergillus* spp Asci form of *Pneumocystis* Endemic yeasts: *H.capsilatum, C.immitis, B.dermatitidis* Molds: *Alternaia alternata, Cladosporium* spp.	Oral and IV preparation; minimal side-effects; high tissue penetration, anti-biofilm properties, activity against echinocandin-resistant strains due to only partial overlap of binding sites	IV preparation in studies, currently available only as PO form	750 mg BID x 2 days, followed by 750 mg PO daily In combination with azoles: 500 mg PO BID, then 500 mg PO daily
Rezafungin	Echinocandin	Glucan synthase inhibitor	*Candida* spp. *C. auris* *Aspergillus* spp *P. jiroveci*	Weekly IV dosing with long half-life Lack of significant drug–drug interactions Favorable safety profile	No oral formulation Reduced potency against *C.* parapsilosis spp. complex and *C. guilliermondii*	400 mg loading dose, followed by 200 mg weekly afterwards
Fosmanogepix	N-phosphono-oxymethyl/ Prodrug of manogepix	Gwt1 inhibitor	*Candida* spp. Including azole resistant species *Cryptococcus* spp.; *Trichosporon asahi, Malassezia.furfur* Molds: *Aspergillus* spp.; *Fusarium* spp.; *Scedosporium* spp., *Cladosporium* spp., *Lomentospora prolificans, Rasamsonia* spp., etc. Some mucorales Endemic yeasts: *Histoplasma* spp.; *Coccidioides* spp., *B. dermatitidis*, etc.	Favorable side-effect profile; broad spectrum of activity against yeast and molds; synergy with polyenes, antibiofilm properties, low potential for development of resistance and low potential for cross-resistance with other antifungals (in vitro data)	Phase III studies pending, no activity against *C. krusei, C. inconspicua*, and *C. kefyr*	1000 mg IV BID x 1 day, followed by 600 mg IV daily x at least 2 days, and 600 mg daily IV or 700 mg PO daily

(*Continued*)

Table 2 (Continued).

Antifungal Agent	Class	Mechanism of Action	Activity	Advantage	Limitations	Dosage in Candidiasis
Encochleated amphotericin B (CAmB, formerly MAT2203)	Polyene	Encochleated oral formulation of amphotericin B	*Candida* spp. *Cryptococcus* spp. *Aspergillus* spp.	Oral formulation Reduced toxicity, as compared to IV formulations of amphotericin Potent anticandidal activity in kidneys and CNS	No human studies in IC Suboptimal in chronic mucocutaneous candidiasis (CMC), compared to standard of care Moderate-to-severe VVC: inferior to fluconazole	No dosing schedule for IC/candidemia Treatment of CMC: 400 mg or 800 mg qd Treatment of VVC: 200 mg or 400 mg qd for 5 days
Oteseconazole	Azole	Tetrazole	*Candida* spp, including fluconazole-resistant *C. krusei*, and fluconazole- and echinocandin -resistant *C. glabrata* *Cryptococcus* spp.,*Trichophyton rubrum* *Coccidioides immitis/posadasii* Some *Mucorales* species (i.e. *R. arrhizus var. arrhizus*)	Favorable side-effect profile, minimal CYP450 interaction when compared to other azoles	No IV preparation Very long-half life and contraindicated in women of reproductive potential Approved for recurrent VVC only, no plans for development as treatment for IC currently	No dosing schedule for IC or candidemia Treatment of VVC: 150–300 mg once weekly treatment of onychomycosis: 300–600 mg qd for 2 weeks followed by once weekly dosing for 10–22 weeks
ATI2307 (T-2307)	Aromatic diamidine	Induces mitochondrial dysfunction through the inhibition of the respiratory chain enzyme complexes	*Candida* spp., including echinocandin-resistant *C. albicans* and *C. glabrata*, *C. auris*, including echinocandin-resistant and azole-resistant *C. auris* strains *C. neoformans/gattii* *M. furfur* Select filamentous fungi and *Aspergillus* spp.	Further data from clinical studies are needed, however holds promise as a treatment option for IC caused by azole- and echinocandin-resistant strains	No data in human studies of IC	No data yet available
VT-1598	1-tetrazole-based antifungal drug candidate	Selective inhibitor of fungal Cyp51 enzyme Primary metabolite VT-11134 also with antifungal activity	Broad range of yeasts, molds, and endemic fungi *Candida* spp, including resistant/with reduced susceptibility to fluconazole *C. auris*	Further data from clinical studies needed	No data in human studies of IC	No data yet available

(*Continued*)

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Table 2 (Continued).

Antifungal Agent	Class	Mechanism of Action	Activity	Advantage	Limitations	Dosage in Candidiasis
BAL2062 (former GR2397, VL-2397)	Non-ribosomally synthesized cyclic hexapeptide isolated from the Malaysian fungus Acremonium persicinum	Mechanism unclear, however depends on activity of Sit1 transporter	Limited to Sit1-positve *Candida* spp., such as *C. glabrata*, including azole- and echinocandin-resistant insolates, and *C. kefyr* *Aspergillus* spp. including azole-resistant strains *Fusarium solanii*	Further data from clinical studies needed Possible future use as a targeted treatment of infections due to *C. glabrata* and *C. kefyr* Renal excretion: potential for use in urinary tract infections caused by *C. glabrata* and *C. kefyr*	No data in human studies of IC	No data yet available
Miltefosine	Alkyl phosphocholine analogue	Exact mechanism is still unclear, however mechanism involving destruction of mitochondria, increased production of reactive oxygen species and induction of apoptosis has been described in some species	*Candida* spp. In vitro activity against *Aspergillus* spp., *Cryptococcus* spp., certain *Mucorales* and endemic fungi, *Fusarium* spp., *Scedosporium* spp., and *Sporothrix* spp.	Further data from clinical studies needed	No data in human studies of IC	No data yet available

Abbreviations: IC, invasive candidiasis; IV, intravenous; VVC, vulvovaginal candidiasis.

Conclusions

There continues to be a significant unmet need for newer antifungal agents in the clinical arena. The increase in antifungal resistance, as well as epidemiological shifts in *Candida* spp. distribution from a susceptible species to a more resistant species are significant factors contributing to high morbidity and mortality rates in patients with candidemia and invasive candidiasis. Novel antifungal agents are important tools necessary to tackle these challenging aspects and management of IC. However, further clinical studies are still necessary to determine the role of these newer antifungal agents in management of candidemia and invasive candidiasis. Key features of the novel antifungals are summarized in Table 2.

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