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The Antifungal Pipeline: Fosmanogepix, Ibrexafungerp, Olorofim, Opelconazole, and Rezafungin

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Abstract

The epidemiology of invasive fungal infections is changing, with new populations at risk and the emergence of resistance caused by the selective pressure from increased usage of antifungal agents in prophylaxis, empiric therapy, and agriculture. Limited antifungal therapeutic options are further challenged by drug–drug interactions, toxicity, and constraints in administration routes. Despite the need for more antifungal drug options, no new classes of antifungal drugs have become available over the last 2 decades, and only one single new agent from a known antifungal class has been approved in the last decade. Nevertheless, there is hope on the horizon, with a number of new antifungal classes in late-stage clinical development. In this review, we describe the mechanisms of drug resistance employed by fungi and extensively discuss the most promising drugs in development, including fosmanogepix (a novel Gwt1 enzyme inhibitor), ibrexafungerp (a first-in-class triterpenoid), olorofim (a novel dihydroorotate dehydrogenase enzyme inhibitor), opelconazole (a novel triazole optimized for inhalation), and rezafungin (an echinocandin designed to be dosed once weekly). We focus on the mechanism of action and pharmacokinetics, as well as the spectrum of activity and stages of clinical development. We also highlight the potential future role of these drugs and unmet needs.

1 Introduction

The epidemiology of invasive fungal infections has changed over the last 2 decades, with broad-spectrum antifungal prophylaxis reducing prevalence and improving survival in patients with traditional risk factors. Selective pressure of antifungal prophylaxis (as well as advances in molecular testing) may be contributing to the emergence of formerly less common fungal pathogens, including rare yeasts and rare molds [1–5] that are often resistant to currently available classes of antifungal treatments. The diagnosis of these breakthrough infections can be challenging even under optimal circumstances, owing to insufficient sensitivities of current diagnostics [6]. At the same time, the emergence of *Candida auris* [7], as well as azole-resistant *Aspergillus fumigatus* [8], and cryptic species that are morphologically

indistinguishable by classical methods within main *Aspergillus* sections [9] pose additional threats to our current antifungal armamentarium. In addition, new manifestations of disease in the intensive care population such as coronavirus disease 2019 (COVID-19)-associated aspergillosis [10–13] and mucormycosis [14, 15] are posing major problems because of extensive drug–drug interactions of antifungal drugs [16].

Despite the need for more antifungal drug options, no new classes of antifungal drugs have become available over the last two decades, and only one single new agent, isavuconazole [17], from a known antifungal class has been approved in the last decade. Fortunately, there are finally a number of new antifungal classes in late-stage clinical development. In this review, we discuss extensively the most promising drugs in development, including fosmanogepix (a novel Gwt1 enzyme inhibitor), ibrexafungerp (a first-in-class triterpenoid), olorofim (a novel dihydroorotate dehydrogenase enzyme inhibitor), opelconazole (a novel triazole optimized for inhalation), and rezafungin (an echinocandin designed to be dosed once weekly). We also highlight the potential future role of these drugs, the clinical trials currently evaluating them, and the spectrum of activity of these drugs.

Martin Hoenigl and Rosanne Sprute contributed equally to the article.

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Key Points

The epidemiology of invasive fungal infections is changing, with new populations at risk and the emergence of antifungal resistance.

Despite the need for more antifungal drug options, no new classes of antifungal drugs have become available over the last two decades, but there is finally hope on the horizon, with a number of new antifungal classes in late-stage clinical development.

In this review, we discuss the most promising antifungal drugs in development, focusing on the mechanism of action and pharmacokinetics, as well as the spectrum of activity and stages of clinical development.

We also highlight the potential future role of these drugs and unmet needs.

A literature search in July 2021 included: PubMed search for each compound name (old and new names) separately, searching the reference lists for additional studies, as well as search through abstracts presented at major scientific meetings in the field during the last 10 years.

2 Antifungal Resistance

Drug-resistant fungal pathogens have emerged and pose a significant clinical problem as treatment options are limited and infections may be associated with poor outcomes. Furthermore, some patients do not respond to antifungal therapy despite infection with a pathogen displaying susceptibility to the agent being used, a concept termed tolerance, which is discussed in more detail later. Thus, clinical therapeutic failure is a multifaceted phenomenon involving not only the mostly immunocompromised human host, but—although to a lesser extent—also the antifungal drug, and pathogenic fungi [18] and a combination of factors may contribute to therapeutic failure of antifungal drugs. Moreover, the concept of resistance laid out in the following will include mechanisms observed for three most predominant genera of fungi, namely *Candida*, *Cryptococcus*, and *Aspergillus*.

2.1 Drug Tolerance Definition and Its Clinical Importance

In the literature, the terms antifungal resistance and tolerance are frequently incorrectly used and resistance, resulting

from a stable genetic change, needs to be distinguished from tolerance, resulting from unstable genomic, epigenomic, and physiologic changes. Both adaptive and transient resistance tolerates high drug concentrations beyond minimum inhibitory concentrations (MICs); this concept is different from classical resistance and is attributed to clinical failure and therefore we discuss this briefly (this concept is poorly studied in *Aspergillus*, while numerous studies have explored this phenomenon in both *Candida* and *Cryptococcus*). Once a fungus is exposed to a stressful environment, such as azole drugs, the most important priority for the cell is to survive. Therefore, employing transient and rapid mechanisms rewiring the transcriptomics and genomics landscape takes place, allowing a subpopulation of cells to grow slowly and survive at drug concentration beyond the MIC [19]. Because this phenotypic growth is slow, the tolerance measure is assayed at 48 h, which is beyond the 24-h timepoint suggested by standard guidelines [19]. There is more attention to the concept of drug tolerance owing to the link between tolerance and azole therapeutic failure [19–23] and virulence [24]. Chromosomal duplications or aneuploidy may play a role in tolerance, as chromosomes housing the drug target and efflux pumps, and the resultant copy number variations are associated with a higher expression of the aforementioned genes. This may lead to more efficient expulsion of the drug out of the cells as well as allow for more available drug target to keep up with the excess of antifungal drugs, which ultimately provides a permissive state for cell survival [25–27]. These chromosomal changes are not stable and disappear following progressive passage on drug-free media [25–27]. Although tolerance and heteroresistance have many similarities regarding the underlying mechanisms and both survive at the concentration above the MIC [25, 27], it should be noted that the subpopulation size in tolerance (5–90%) is larger than what has been noted for heteroresistance (much less than 1%) [19]. Nonetheless, both phenomena are regarded as a window for gaining a stable drug resistance phenotype by allowing the tolerant minority subpopulation to survive in the presence of a high drug concentration [28–30]. Indeed, a new wave of studies has found the clinical importance of azole tolerance in therapeutic failure [22, 23, 31] and future studies are underway to better understand the underlying mechanism, with the hope of identifying novel targets impairing this mechanism to thwart the emergence of resistance. Thus, tolerance is an emerging entity potentially affecting clinical success, which results from physiologic and unstable genomic changes.

2.2 Drug Resistance Definition and Major Azole Resistance Mechanisms

Unlike tolerance, drug resistance is a stable phenotypic growth beyond the MIC, which can be recorded at a 24–72-h

time period and will not disappear after successive passage on drug-free media [19, 29]. Mechanisms involved in drug resistance have major overlaps among the three genera of fungi, but the mechanisms vary depending on the antifungal drug. Herein, our discussion includes the most predominant mechanisms believed to play a role against azoles.

Azoles are a class of antifungal drugs targeting one of the key enzymes involved in ergosterol biosynthesis, 14 α -lanosterol demethylase, which is encoded by *ERG11* in *Candida* and *Cryptococcus* and *CYP51A* in *Aspergillus* [29, 32]. Acknowledging that resistance to azoles is multifactorial and there might be numerous factors functioning simultaneously with yet unidentified mechanisms, currently, it is thought that three major mechanisms are involved, namely drug target change, overexpression of drug target, and overexpression of efflux pumps [32].

1. Drug target changes due to mutations modulating the azole-binding site appear to be one of the most prevalent causes of azole resistance. Although several mutations have been found throughout the *ERG11* in yeasts, Y132F, corresponding to Y145F in *Cryptococcus*, and G458S, corresponding to G484S in *Cryptococcus*, are among the most prevalent amino acid substitutions, which result in therapeutic failure [7, 31, 33–36]. Interestingly, it has been shown that *Candida parapsilosis* isolates carrying Y132F are associated with a high mortality rate in addition to causing azole therapeutic failure [36, 37]. More concerning is the emergence of azole-resistant *C. parapsilosis* isolates carrying Y132F in azole-naïve patients, possibly via environmental sources such as the hands of healthcare workers or devices routinely used in the clinic [37]. Of note, a growing number of studies show that the list of *ERG11* mutations associated with azole resistance is expanding [37]. In *A. fumigatus*, the azole target has two copies, *CYP51A* and *CYP51B*, and the occurrence of mutations in the former appear to be more accountable for resistance against mold-active triazoles [32]. Studies have shown that insertion of tandem repeats (TRs) with a length of 34bps and 46bps (TR34 and TR46) in conjunction with L98H and Y121F+T289A, respectively, are the most predominant mutations found that confer azole resistance [32]. Of note, *A. fumigatus* is intrinsically resistant to fluconazole due to a T301I amino acid substitution in *CYP51A* [38]. Moreover, numerous studies have also found azole-resistant isolates without mutations in the drug target, which has led to the discovery of new mechanisms and revealing the complexity of azole resistance [24, 25].
2. Overexpression of the drug target is another strategy employed to overcome azoles and employed by both yeasts and *Aspergillus* spp. Overexpression of the drug

target results in the overproduction of ergosterol in the presence of the abundant azole drug, resulting in maintaining the membrane integrity. The occurrence of specific mutations in transcription factor/s regulating the drug target render them hyperactive, which is translocated into the nucleus, followed by binding to the promoter of the drug target and its overexpression as a result [39]. Such gain-of-function (GOF) mutations occur in *UPC2* in *Candida* reported in numerous studies [40–42]. Expression of *CYP51A* in *A. fumigatus*, however, is regulated by the transcription factor *SrBA* [43]. Of note, the TR34/TR46 provide an extra binding site for *SrBA* and, therefore, strains carrying such TRs have an overexpressed *CYP51A* combined with mutations modulating the binding of the mold-active azoles [43].

3. Overexpression of efflux pumps expel the drug out of the cell and therefore help the fungus to mitigate the overwhelming concentrations of the azole drug. Efflux pumps belong to two major classes, including major facilitator superfamily (MFS), such as *MDR1*, and ATP-binding cassette (ABC) transporters, such as *CDR1* [19]. *AFR1* and *AFR2* correspond to *CDR1* and *MDR1* in *Cryptococcus* [44, 45]. In pathogenic yeasts, ABC and MFS transporters are mainly overexpressed by GOF mutations in *TAC1* and *MRR1*, respectively [19, 30, 46]. Although azole resistance to ABC and MFS are well studied in *Candida albicans* [46], their functions and the importance of respective GOF mutations remain to be elucidated for other non-*albicans* *Candida* species. In *C. glabrata*, numerous GOF mutations in *PDR1* have been catalogued, which confer azole resistance, a higher virulence, as well as immunoevasion [47, 48]. *CDR1B* is the main ABC transporter found in *A. fumigatus*, which is controlled by *AtrR* [49]. *AtrR*, in collaboration with *SrBA*, control the expression of *CYP51A* [50]. Of note, GOF mutations have not been described for *AtrR* and cataloging potential GOF mutations, followed by functional analysis to observe if they confer azole resistance, may potentially lead to the discovery of new pathways and/ or other players involving in azole resistance. Finally, *ATRF* is an MFS transporter, which has been found to be controlled by *Yap1* in *Aspergillus flavus* [51]. Therefore, its involvement in azole resistance and overexpression of *ATRF* in *A. fumigatus* is yet to be identified. It is noteworthy that these transcription factors play pivotal roles in virulence aside from drug resistance [52–54]. For instance, lines of evidence suggest that fluconazole resistant *C. glabrata* isolates carrying GOF mutations in *PDR1* are more immunoevasive and less identified by macrophages compared with their wild-type counterparts and paradoxically such isolates are more adherent to epithelial cells, which is mainly due to upregulation of EPA genes [52, 53]. Although roles of

such GOF mutations in SRBA and ATRR are not studied in *A. fumigatus*, current data suggest that both of these transcription factors play an important role in ergosterol biosynthesis, iron metabolism, nitrate assimilation, and adaptation to hypoxia. Therefore, mutant strains for lacking either or both of these genes have a significantly lower virulence relative to their wild-type backgrounds [54–56]. Clearly such data suggest that such transcription factors have pleiotropic biological functions, which extend beyond drug resistance, and play important roles in the survival of pathogenic fungi once exposed to various stresses, including adaptation to host-related niches.

2.3 Resistance Mechanisms Against Echinocandins and Polyenes

Resistance mechanisms against echinocandins appear to be straightforward, which does not require the involvement of a complex network. The major mechanisms found so far include the mutation in the hotspot regions of the catalytic subunit of β -1,3-D-glucan synthase, *FKS* [31, 57–61]. It is noteworthy that in some cases mutations found in the hotspot regions does not confer in vitro resistance to echinocandins, while the infected patient experiences echinocandin therapeutic failure [62]. More recently, a change in the lipid composition of the microenvironment surrounding the *FKS* gene is another proposed mechanism involved in echinocandin resistance [63]. Resistance against polyenes is relatively rare and mechanisms are poorly understood [32]. In most cases, the target is ergosterol, the mechanisms of action are ergosterol sequestration, and decreased membrane ergosterol and *ERG* mutations are responsible for intrinsic or acquired resistance, including with *C. auris* and *A. terreus* [32].

3 Antifungal Drugs in Clinical Development

3.1 Fosmanogepix/Manogepix

Manogepix (APX001A, Amplyx Pharmaceuticals, Inc., San Diego, CA, USA; formerly E1210, Eisai Co., Ltd., Tokyo, Japan) is the active moiety of the N-phosphonooxymethyl prodrug fosmanogepix (APX001, formerly E1211). Following oral or intravenous administration, systemic phosphatases rapidly convert fosmanogepix to manogepix [64]. Recently, Pfizer, Inc. acquired Amplyx Pharmaceuticals.

3.1.1 Mechanism of Action and Pharmacokinetics/Pharmacodynamics

Manogepix has a novel mechanism of action that targets glycosylphosphatidylinositol-anchored protein maturation through inhibition of the fungal enzyme Gwt1, an inositol

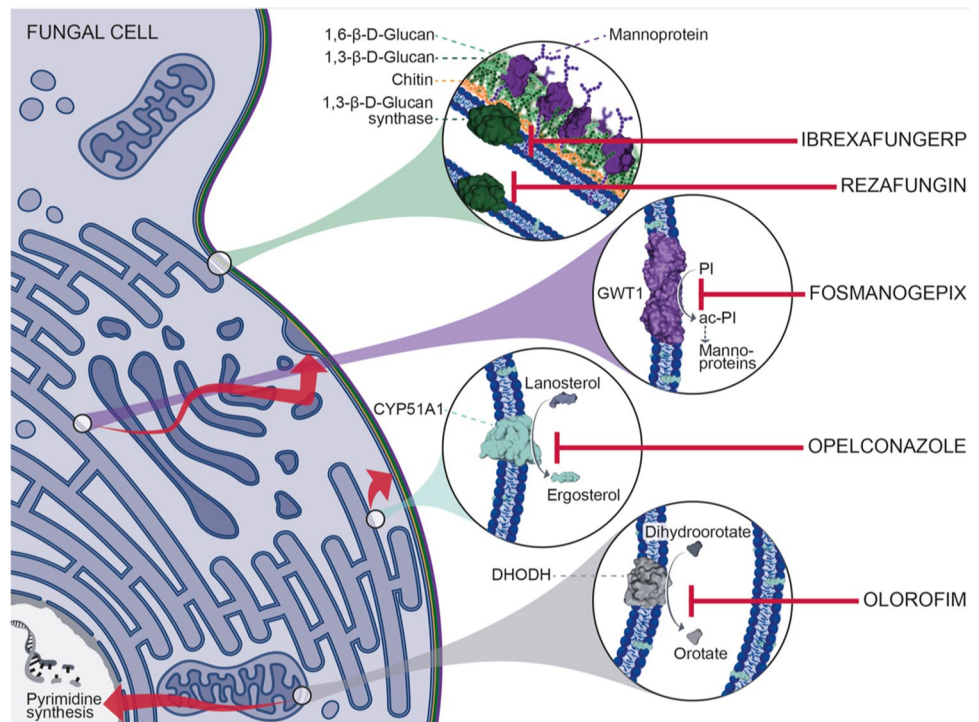
acyltransferase that is essential for trafficking and anchoring mannoproteins to the fungal cell membrane and wall (Fig. 1) [65, 66]. Glycosylphosphatidylinositol-anchored mannoproteins serve as adhesions that allow fungi to adhere to mucosal and epithelial surfaces within the host prior to colonization and infection [67]. Some fungal adhesins and virulence factors are derived from glycosylphosphatidylinositol-anchored proteins [67–71]. The action of manogepix appears to be fungal pathogen specific, as it does not inhibit human inositol acylation by the closest mammalian ortholog, PIGW [64, 72].

Experimental mouse models of invasive candidiasis caused by different species of *Candida*, including *C. albicans*, *C. glabrata*, and *C. auris*, have demonstrated that the AUC/MIC is the pharmacokinetic/pharmacodynamic (PK/PD) parameter most closely associated with in vivo efficacy followed by maximum plasma concentration (C_{max})/MIC [73–75]. In one study, the median free fraction area under the curve (AUC)/MIC ratios associated with stasis ranged from 1.35 to 22.54, which correspond to total AUC/MIC targets of 675.5 to 11,270 [73]. Similarly, the AUC/MEC was the PK/PD target associated with efficacy in a neutropenic murine model of invasive aspergillosis [76]. Against wild-type *A. fumigatus* isolates and azole-resistant strains with *CYP51A* mutations, the median free fraction AUC/MEC ratio associated with a 1-log reduction in fungal burden was 89.39 (total AUC/MEC 5258.2).

3.1.2 Spectrum of Activity

Manogepix has broad-spectrum activity against numerous pathogenic fungi (Fig. 2). Potent in vitro activity has been reported against *Candida* spp., including isolates of *C. albicans*, *C. auris*, and *C. glabrata* that are resistant to the azoles and echinocandins, *Cryptococcus neoformans* and *C. gatti*, *Coccidioides* spp., *Aspergillus* spp., including azole-resistant *A. fumigatus*, *Fusarium* spp., *Scedosporium* spp., *Lomentospora prolificans*, and other rare molds [65, 74–94]. Manogepix has been reported to lack in vitro activity against *C. krusei* and some of the Mucorales [65, 77], including variable activity against *Rhizopus* and *Lichtheimia* [89, 95], as well as *Mucor* and *Cunninghamella* [65, 89]. However, recent work has demonstrated activity in mouse models against *Rhizopus deleamar* [96], and both in vitro and in vivo activity against *Rhizopus arrhizus/oryzae*, a frequent cause of mucormycosis in humans [97, 98]. In a mouse model, a combination of manogepix with liposomal amphotericin B showed a string synergistic effect reducing lung fungal burden and improving survival in invasive pulmonary aspergillosis, and reducing both lung and brain fungal burden and improving survival in mucormycosis [99]. It should be noted that, similar to the echinocandins, owing to its mechanism of action to compromise cell wall growth

Fig. 1 Mechanism of action of novel antifungal drugs discussed in this review. *DHODH* dihydroorotate dehydrogenase



and hyphal elongation, the endpoint used for manogepix susceptibility against filamentous fungi is the minimum effective concentration (MEC). This is defined as the lowest concentration that results in morphologic changes to the fungus (i.e., short, stubby, abnormally branched hyphae) but not inhibition of growth as used for amphotericin B and the azoles [64, 100]. The use of MEC leads to more stable and reproducible measurements in echinocandins. Manogepix has been shown to induce a similar morphological change to that of echinocandins in filamentous fungi [65]. The clinical relevance remains to be determined. The *in vitro* activity of manogepix has also translated into *in vivo* efficacy when fosmanogepix has been administered in experimental models of candidiasis, cryptococcosis, coccidioidomycosis, aspergillosis, fusariosis, scedosporiosis, and mucormycosis [73, 76, 81, 82, 84, 90, 98, 101].











3.1.3 Clinical Studies

3.1.3.1 Safety Four phase I clinical trials have been completed illustrating the safety and tolerability of fosmanogepix (Fig. 3; Table 1 of the Electronic Supplementary Material [ESM]). The initial study in humans was a randomized, double-blind, placebo-controlled, single ascending dose and multiple ascending dose-escalation study (NCT02956499). Six cohorts of eight healthy subjects per cohort were enrolled and randomized to receive 3-hour infusions of fosmanogepix or placebo. Those randomized to the single ascending dose study received 10–350 mg, while those ran-

domized to multiple ascending doses received 50–600 mg once daily over 14 days duration. Fosmanogepix was well tolerated across all administered doses with no significant adverse events (AEs) [all described as mild, transient, and requiring no treatment]. Transient headache was the most frequently described AE [102]. There were no dose-limiting toxicities. The maximum tolerated dose was not determined in this study.

A second phase I study evaluated the safety, pharmacokinetics, bioavailability, and food effects of orally administered fosmanogepix (NCT02957929). Patients in this study were randomized to single intravenous doses of 200 mg infused over 3 hours followed by single oral dosing (tablet) of 100, 300, and 500 mg each separated by a 14-day washout period. They were also evaluated under fed and fasting conditions following a single oral dose of 400 mg. As in the initial phase I study, fosmanogepix was well tolerated across all studied doses with no clinically significant AEs observed. All subjects completed their assigned dosing regimen, and no dose-limiting toxicity was described. All AEs were, again, mild, transient, and required no specific treatment with headache that most frequently observed [103].

Additional phase I studies have also been performed: Safety and Pharmacokinetics of Intravenous and Oral APX001 in Patients With Acute Myeloid Leukemia (AML) and Neutropenia (NCT03333005), and A Drug-Drug Interaction Study of CYP3A4 Inhibition and Pan-CYP Induction on APX001 (NCT04166669). Although these results have not yet been published.

Antifungal agents		Fosmanogepix	Ibrexafungerp	Olorofim	Opelconazole	Rezafungin
Pathogens						
	<i>Aspergillus calidoustus</i>	Potent activity	Potent activity	Potent activity		Potent activity
	<i>Aspergillus fumigatus</i>	Potent activity	Potent activity	Potent activity		Potent activity
	Azole-resistant <i>A. fumigatus</i>	Potent activity	Potent activity	Potent activity	No activity	Potent activity
	<i>Aspergillus flavus</i>	Potent activity	Potent activity	Potent activity		Potent activity
	<i>Aspergillus lentulus</i>	Potent activity	Potent activity	Potent activity		Potent activity
	<i>Aspergillus nidulans</i>	Potent activity	Potent activity	Potent activity		Potent activity
	<i>Aspergillus niger</i>	Potent activity	Potent activity	Potent activity	No activity	Potent activity
	<i>Aspergillus terreus</i>	Potent activity	Potent activity	Potent activity	Potent activity	Potent activity
	<i>Aspergillus tubingensis</i>	Potent activity	Potent activity	Potent activity		Potent activity
	<i>Cunninghamella</i>	Variable activity	No activity	No activity		
	<i>Lichtheimia</i>	Variable activity	No activity	No activity		
	<i>Mucor</i>	Variable activity	No activity	No activity		
	<i>Rhizopus</i>	Variable activity	No activity	No activity	Potent activity	
	<i>Fusarium spp.</i>	Potent activity	No activity	Variable activity		
	<i>Alternaria alternata</i>	Variable activity	Potent activity	No activity		
	<i>Cladosporium spp.</i>	Potent activity	Potent activity			
	<i>Paecilomyces variotii</i>	Potent activity	Variable activity	Potent activity		
	<i>Purpureocillium lilacinum</i>	Potent activity	No activity	Variable activity		
	<i>Scopulariopsis spp.</i>	Potent activity	No activity	Potent activity		
	<i>Rasamsonia spp.</i>	Potent activity		Potent activity		
	<i>Scedosporium spp.</i>	Potent activity	Variable activity	Potent activity		
	<i>Lomentospora prolificans</i>	Potent activity	Variable activity	Potent activity		
	<i>Candida albicans</i>	Potent activity	Potent activity	No activity	Potent activity	Potent activity
	<i>Candida auris</i>	Potent activity	Potent activity	No activity	Potent activity	Potent activity
	<i>Candida dubliniensis</i>	Potent activity	Potent activity	No activity		Potent activity
	<i>Candida glabrata</i>	Potent activity	Potent activity	No activity	Potent activity	Potent activity
	<i>Candida krusei</i>	No activity	Potent activity	No activity	Potent activity	Potent activity
	<i>Candida lusitanae</i>	Potent activity	Potent activity	No activity		Potent activity
	<i>Candida parapsilosis</i>	Potent activity	Potent activity	No activity		Potent activity
	<i>Candida tropicalis</i>	Potent activity	Potent activity	No activity		Potent activity
	<i>Cryptococcus gattii</i>	Potent activity		No activity	Potent activity	
	<i>Cryptococcus neoformans</i>	Potent activity		No activity	Potent activity	No activity
	<i>Trichosporon asahii</i>	Potent activity		No activity		
	<i>Exophiala dermatitidis</i>	Potent activity		No activity		
	<i>Malassezia furfur</i>	Potent activity		No activity		
	<i>Pneumocystis jirovecii</i>		Potent activity	No activity		Potent activity
	<i>Blastomyces dermatitidis</i>	Potent activity	Potent activity	Potent activity		
	<i>Coccidioides immitis</i>	Potent activity	Potent activity	Potent activity		
	<i>Histoplasma capsulatum</i>	Potent activity	Potent activity	Potent activity		
	<i>Fonsecaea pedrosoi</i>	Potent activity		No activity		
	<i>Madurella mycetomatis</i>			Potent activity		
	<i>Talaromyces marneffei</i>			Potent activity		
	<i>Phialophora verrucosa</i>	Potent activity				
Antifungal agents		Fosmanogepix	Ibrexafungerp	Olorofim	Opelconazole	Rezafungin

Legend		!!!
Potent activity		
Variable activity	!?	
No activity	X	
Unknown / currently investigated	?	

Fig. 2 Activity of the new antifungal drugs in the pipeline against most common fungal pathogens

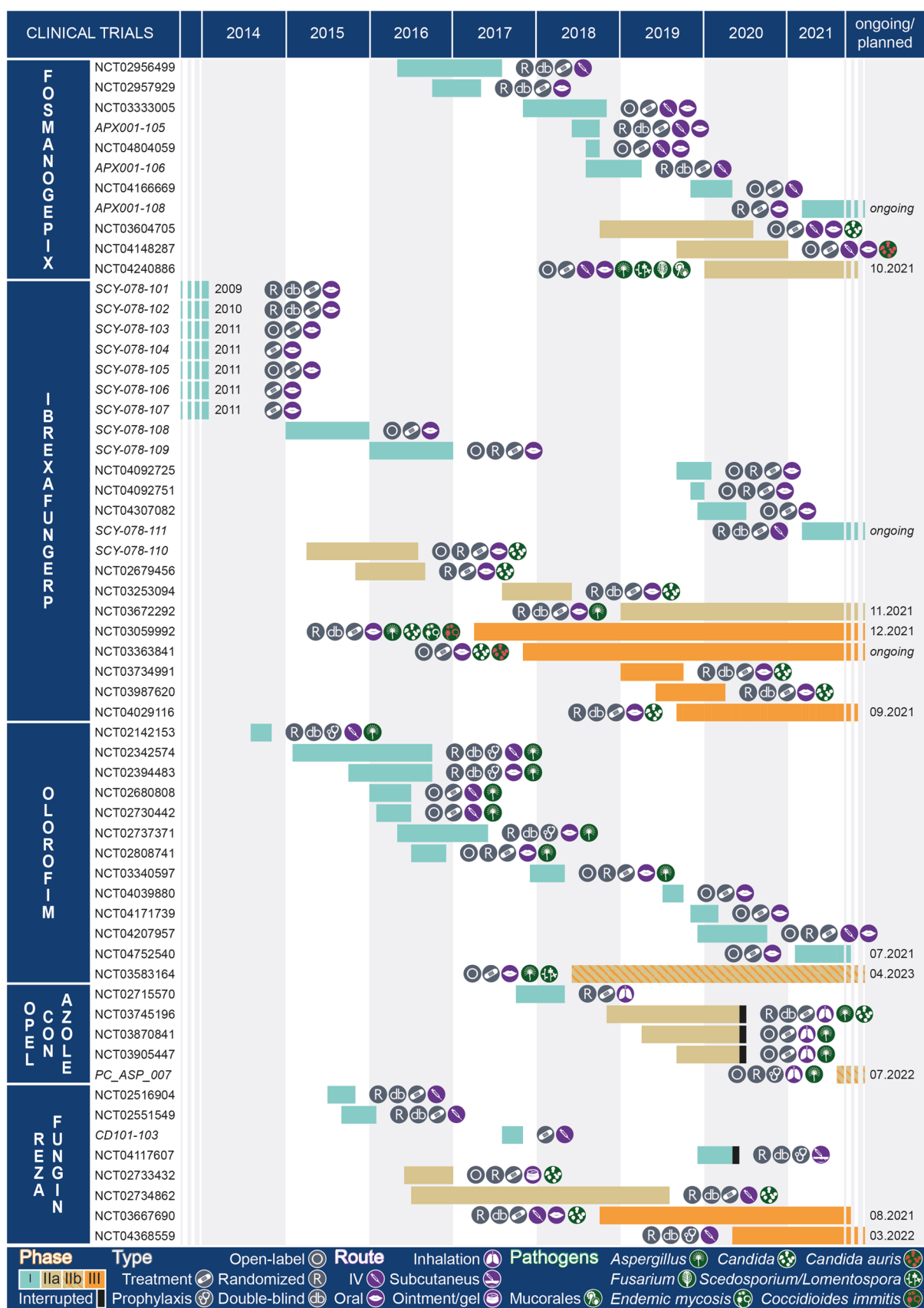


Fig. 3 Timetable of clinical trials evaluating fosmanogepix, ibrexafungerp, olorofim, opelconazole, and rezafungin. IV intravenous

In a phase II, multicenter, open-label, non-comparative, single-arm study of fosmanogepix for the treatment of invasive candidiasis in non-neutropenic patients, fosmanogepix was well tolerated with no treatment-related serious AEs or discontinuation in the modified intention to treat (MITT) group of 20 patients [104]. Patients with a recent diagnosis of candidemia defined as positive blood culture for *Candida* spp. within 96 hours prior to study entry, with ≤ 2 days of prior antifungal treatment were eligible. Patients with neutropenia, *C. krusei* infection, or deep-seated *Candida* infections were excluded. Sixty-six of patients in this study had renal insufficiency and no worsening of renal function was observed. There was no evidence of drug-related nephrotoxicity and no dose adjustments were required suggesting that fosmanogepix may be safe in patients with impaired renal function [105]. Manogepix was also well tolerated in a cohort of nine intensive care unit patients with candidemia [106].

3.1.3.2 Efficacy In the above-mentioned phase II study, fosmanogepix was initiated as first-line therapy and patients were treated for up to 14 days [104]. Patients were prescribed fosmanogepix 1000 mg intravenously twice a day for 1 day, then 600 mg intravenously once daily for at least 2 days, followed by either 600 mg intravenously once daily or 700 mg orally once daily. The primary efficacy endpoint was the outcomes as adjudicated by an independent data review committee at the end of the study treatment. A successful outcome was defined as clearance of *Candida* spp. from blood with no additional antifungal therapy and survival at the end of study therapy. A success rate of 80% was observed in the MITT population. Negative blood cultures were observed after 2.4 days (mean) of fosmanogepix initiation, and efficacy was observed in isolates resistant to amphotericin B and/or anidulafungin. Among the patients who did not respond to therapy at the end of study therapy, 15% had persistently positive cultures, while one patient experienced an AE (leukopenia) and died because of bacterial sepsis. Overall survival at day 30 was 85% and none of the deaths was considered by the data review committee as related to fosmanogepix. In an interim analysis of nine intensive care unit cases with *C. auris* candidemia, treatment success and survival were achieved in 8/9 (89%) of cases with one patient not responding to treatment [106].

3.1.3.3 Ongoing Studies An evaluation of fosmanogepix in the treatment of *C. auris* (APEX, NCT04148287) has recently been completed (Fig. 3; Table 1 of the ESM). This was a multicenter, open-label, non-comparative, single-arm study to evaluate the efficacy and safety of APX001 for the treatment of candidemia and/or invasive candidiasis caused by *C. auris* in patients aged 18 years and over with limited antifungal treatment options. Treatment was adminis-

tered for a maximum of 42 days with a follow-up period of 4 weeks after the end of study therapy. An evaluation of fosmanogepix in the treatment of invasive aspergillosis and other rare molds (e.g., *Scedosporium* spp., *Fusarium* spp., and Mucorales fungi) is ongoing (AEGIS, NCT04240886). This study will enroll patients with limited or no treatment options because of documented or anticipated resistance, contraindication, intolerance, or a lack of clinical response to standard of care (SOC) antifungal therapy. The primary outcome is all-cause mortality at day 42 with key secondary outcomes of the global response at the end of study treatment or day 42 and all-cause mortality at day 84. Phase III trials for the treatment of invasive candidiasis and endemic fungal infections are planned.

3.1.4 Future Role

Fosmanogepix has been given fast track status by the US Food and Drug Administration (FDA) for invasive candidiasis, aspergillosis, scedosporiosis, fusariosis, mucormycosis, cryptococcosis, and coccidioidomycosis. Multiple ongoing studies will further define the role of this agent for the treatment of invasive fungal infections, although the favorable side-effect profile and activity against multiple pathogens with limited treatment options make this an attractive option and addition to the therapeutic armamentarium for a broad range of mold (variable activity only against Mucorales) and yeast infections (other than those caused by *C. krusei*) as well as endemic mycoses. The synergism with liposomal amphotericin B may increase attractiveness for using manogepix in combination for the most difficult-to-treat infections (Table 1).

3.2 Ibrexafungerp

Ibrexafungerp (MK-3118 and SCY-078; developed by Scynexis, Jersey City, NJ, USA) is a first-in-class oral glucan synthase inhibitor.

3.2.1 Mechanism of Action and Pharmacokinetics/ Pharmacodynamics

Ibrexafungerp is a triterpenoid antifungal inhibiting the biosynthesis of 1,3-beta-D-glucan in the fungal cell wall, as already known from echinocandins. Ibrexafungerp inhibits the 1,3-beta-D-glucan synthase enzyme and acts fungicidally on *Candida* spp. and fungistatically on *Aspergillus* spp. (Fig. 1) [107, 108]. Although the mechanism of action for ibrexafungerp and echinocandins is similar, the binding sites for both antifungal drugs are different with only a partial overlap. This results in very limited cross-resistance between ibrexafungerp and echinocandins [109–111]. Some *Candida glabrata* isolates with certain mutations in the *FKS1*

Table 1 Future roles for new antifungal agents once approved in routine clinical use

Antifungal drugs	Substance class	Novel aspects	Future areas of use	Special clinical settings	Advantages	Limitations/disadvantages	Standard dosage from clinical trials
Fosmanogepix/ Manogepix	N-phosphono-oxymethyl (pro)drug	Inhibition of Gwt1, targets GPI-anchored protein maturation	Invasive infections with <i>Candida</i> spp. except <i>C. krusei</i> , <i>Aspergillus</i> spp., <i>Scedosporium</i> spp., <i>Fusarium</i> spp., Mucorales, <i>Cryptococcus</i> spp. Endemic mycoses, including coccidioidomycoses	Difficult-to-treat infections	Activity against fungi with limited treatment options Favorable side-effect profile Synergism with amphotericin B	Variable activity against Mucorales, no activity against <i>C. krusei</i>	Treatment of invasive infection: 1000 mg IV bid for 1 day, then 600 mg IV qd for at least 2 days, followed by either 600 mg IV qd or 700 mg PO qd
Ibrexafungerp	Triterpenoide	Glucan synthase inhibitor with alternative binding site	Invasive candidiasis including <i>C. auris</i> and <i>C. glabrata</i> Resistant invasive pulmonary aspergillosis Vulvovaginal candidiasis	Oral step-down therapy Outpatient setting	Favorable side effect profile Limited drug–drug interactions High tissue penetration Oral application	No activity against Mucorales IV formulation still in early stage of clinical testing	Treatment of invasive infection: 750 mg PO bid for 2 days, then 750 mg PO qd In combination with azoles: 500 mg PO bid for 2 days, the 500 mg PO qd Treatment of VVC: 300 mg PO bid for 1 day
Olorofim	Orotomide	Inhibition of dihydroorotate dehydrogenase, targets pyrimidine synthesis	Invasive infections with multi-resistant molds, including resistant <i>Aspergillus</i> spp. and <i>L. proliferans</i> Endemic mycoses, including coccidioidomycoses	Breakthrough infections Difficult-to-treat infections	Activity against fungi with limited treatment options Antibiofilm activity	No broad-spectrum antifungal with no activity against yeasts or the Mucorales group Potential drug–drug interactions: Metabolized by multiple CYP450 enzymes, weak inhibitor of CYP3A4	Treatment of invasive infection: 150 mg PO bid for 1 day, then 90mg (- 150 mg) PO bid
Opelconazole	Triazole	Triazole with inhaled administration	Invasive aspergillosis including COVID-19 associated pulmonary aspergillosis Allergic bronchopulmonary aspergillosis Chronic pulmonary aspergillosis	Intolerance to high systemic azole concentrations Prophylaxis in lung transplants, ICU setting	Avoidance of systemic toxicity Limited drug–drug interactions High local concentrations	Small range of application in terms of patient population and diseases	Treatment of invasive infection: 5 mg nebulized qd

Table 1 (continued)

Antifungal drugs	Substance class	Novel aspects	Future areas of use	Special clinical settings	Advantages	Limitations/disadvantages	Standard dosage from clinical trials
Rezafungin	Echinocandin	Echinocandin with prolonged half-life	Invasive infections with <i>Candida</i> spp., <i>Aspergillus</i> spp., <i>Pneumocystis jirovecii</i>	Outpatient setting Prophylaxis in HSCT and SOT	Favorable side effect profile Limited drug–drug interactions Once weekly IV application	Subcutaneous administration failed in clinical trials Unfavorable results of topical formulations in vulvovaginal candidiasis	Treatment and prophylaxis of invasive infection: 400 mg IV in week 1, then 200 mg IV once weekly

bid twice daily, *COVID-19* coronavirus disease 2019, *GPI* glycosylphosphatidylinositol, *Gwt1* GPI-anchored wall transfer protein 1, *HSCT* hematopoietic stem cell transplant, *ICU* intensive care unit, *IV* intravenous, *PO* per os, *qd* once daily, *SOT* solid organ transplant

or *FKS2* genes, which are resistant to echinocandins, might also show resistance against ibrexafungerp. However, usually ibrexafungerp has potent activity against echinocandin resistant *C. glabrata* isolates with FKS mutations [111, 112] (see below for activity).

Ibrexafungerp is currently available as an oral formulation (an intravenous formulation is still in phase I developments) and has a good oral absorption with a bioavailability rate of 35–50% and high protein binding of 99% [113, 114]. Human data showed a peak plasma concentration within 4–6 h and a linear decline with a mean half-life of approximately 20–30 hours supporting a once-daily dosing strategy [115]. In ongoing studies, a once-daily dosage is used after 2 days of a twice-daily loading dose (FURI, NCT03059992). Although a high-fat meal increased the bioavailability, it delayed the median time to C_{\max} from 4 h (fasted state) to 6 h [114]. Based on data from animal models, ibrexafungerp shows a high tissue penetration with the following tissue-to-blood AUC ratios: spleen 54-fold; liver 50-fold; lung 31-fold; bone marrow 25-fold; kidney 20-fold; skin 12-fold to 18-fold; vaginal tissue nine-fold; and skeletal muscle four-fold, although tissue concentrations are known to not always infer site activity. Ibrexafungerp shows a minimal distribution to central nervous system tissues [116, 117]. In another study, ibrexafungerp accumulation was shown in vaginal tissue and fluid with a tissue concentration of twofold to fivefold higher than plasma concentrations and supporting the recent approval for the treatment of *Candida* vaginitis using a single-day 600-mg treatment (300 mg twice-daily dosage) [118]. Whereas penetration into the lens is poor, ibrexafungerp shows high concentrations in the uvea [116]. Ibrexafungerp is mainly eliminated via feces and is marginally recovered from urine (approximately 1%) [116]. Ibrexafungerp is a CYP3A4 substrate and a reversible inhibitor of CYP2C8 and CYP3A4. However, the interaction with certain drugs and influence on drug concentrations is markedly weaker than observed with azoles. Ibrexafungerp has no effect on the maximum blood concentration of tacrolimus, a CYP3A4 substrate, with only a 1.4-fold increase in systemic exposure to tacrolimus. These findings support the coadministration of ibrexafungerp and tacrolimus without the need for an initial dose adjustment for tacrolimus [119]. Coadministration of strong CYP3A inducers (e.g., rifampin, St. John's wort) and ibrexafungerp should be avoided as ibrexafungerp might not reach sufficient drug concentrations, whereas coadministration of CYP3A inhibitors (e.g., ketoconazole or itraconazole) requires a dose reduction of ibrexafungerp (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214900s0001bl.pdf). In animal *Pneumocystis* models, ibrexafungerp reduced the fungal burden and improved survival. The results were comparable to trimethoprim-sulfamethoxazole standard therapy in one study and

better for trimethoprim-sulfamethoxazole in another study [120–122].

3.2.2 Spectrum of Activity

Ibrexafungerp has in vitro activity against *Aspergillus* and *Candida* spp., with slightly weaker activity against *C. lusitanae* and *C. krusei* compared with other *Candida* spp. (Fig. 2) [123]. Ibrexafungerp shows high activity against *Candida* isolates resistant to azoles (e.g., *C. albicans*, *C. krusei*, *C. glabrata*) but activity against echinocandin-resistant *Candida* spp. is variable [123]. Overall, most echinocandin-resistant FKS mutants in *Candida* spp. are susceptible to ibrexafungerp, especially *C. glabrata* and *C. auris* isolates [112, 123–126], but some echinocandin-resistant FKS mutants with the F641S, F649del, F658del, and F659del mutations also showed reduced susceptibility to ibrexafungerp [124, 127–129]. Ibrexafungerp is a potent inhibitor of *Aspergillus* spp. growth, including *A. fumigatus*, *A. niger*, *A. terreus*, cryptic species [130], and azole-resistant strains [108, 109, 127]. Ibrexafungerp has no activity against Mucorales and *Fusarium* spp. but is very active against *Alternaria* and *Cladosporium* spp. [131, 132].

3.2.3 Clinical Studies

3.2.3.1 Safety Ibrexafungerp has already demonstrated good tolerability in single-dose and multiple-dose phase I/II studies, with non-serious AEs increased with exposed dosage and duration of therapy (Fig. 3; Table 2 of the ESM) [133]. The most common AEs are mild to moderate and due to gastrointestinal tract symptoms, including nausea, diarrhea, abdominal pain, and vomiting, that may be dose limiting [115, 134–136] [133]. In a phase II study, the safety of two dosing regimens of ibrexafungerp was investigated. Whereas one group including seven patients received 1000 mg of ibrexafungerp as a loading dose followed by 500 mg daily, the second group containing six patients received a 1250-mg loading dose followed by 750 mg daily. As already observed in the phase I trial, most reported AEs were gastrointestinal tract symptoms; however, there was no distinct difference in AE frequency between the two groups and none of the AEs was considered severe enough to warrant the discontinuation of treatment [135]. Interim results of the ongoing phase III study show that oral ibrexafungerp was generally well tolerated, with the most common drug-related AEs being mild-to-moderate diarrhea, nausea, and less frequently vomiting [137]. In contrast to several other orally available antifungal agents, ibrexafungerp did not cause a clinically relevant prolongation of the QTc interval in a group healthy volunteers [138]. Last, safety data for long-term treatment in humans are needed, although in

preliminary animal data, 9 months of ibrexafungerp in dogs was well tolerated [139].

3.2.3.2 Efficacy In a randomized, phase II clinical trial investigating the efficacy, safety, and tolerability of different oral doses of ibrexafungerp in patients with invasive candidiasis, patients were randomized to receive oral step-down therapy after initial echinocandin treatment with either ibrexafungerp or fluconazole [135]. In the intention-to-treat analysis at the end of treatment, a favorable overall response was similar among the different study arms, with 71% of patients in the ibrexafungerp 500-mg group with a favorable outcome compared with 86% in the ibrexafungerp 750-mg group and 71% in the fluconazole group. Of interest, six out of eight patients with *Candida krusei* or *C. glabrata* infections showed a favorable outcome when treated with ibrexafungerp. As oral therapy with azoles in these two species is challenging or not possible because of resistance, ibrexafungerp may represent a promising treatment option for such infections.

After completion of the phase II trial for patients with invasive candidiasis, there are currently multiple ongoing phase III trials. In an open-label, single-arm trial (FURI, NCT03059992), patients with invasive candidiasis who are refractory or intolerant to SOC antifungal treatment and patients with aspergillosis are being treated with oral ibrexafungerp (750 mg twice daily for 2 days followed by 750 mg once daily; up to 180 days of treatment) with safety and efficacy as endpoints. This study is ongoing, although an interim analysis has been completed. Of 41 patients who were treated with oral ibrexafungerp for intra-abdominal infection, oropharyngeal or esophageal candidiasis, candidemia, or other forms of invasive candidiasis, 56% were considered as a partial or complete response and 15% as progressive disease [134]. Two patients with *C. albicans* and *Candida tropicalis* spondylodiscitis were also successfully treated with oral ibrexafungerp [140]. Given the need for a long treatment duration of *Candida* bone infections and the rising amount of azole-resistant and reduced susceptibility to *Candida* spp. [141], non-azole oral agents are needed to treat such infections in an outpatient setting. In the most recent interim analysis of 33 patients treated in 2019 and 2020 (each 45.5% with invasive candidiasis and mucocutaneous candidiasis, and 9% with invasive pulmonary aspergillosis), complete/partial response or clinical improvement was observed in 70%, with 21% stable disease as a global response at the end of treatment (9% unable to determine) [137]. A second single-arm, open-label, phase III trial (CARES, NCT03363841) is evaluating patients with *C. auris* infections (invasive candidiasis and candidemia) with oral ibrexafungerp (add on to ongoing intravenous therapy or ibrexafungerp monotherapy) as emergency treatment. Among the first ten patients enrolled were eight patients

(80%) who had a complete response, one patient died of other causes, and one patient outcome was indeterminate [142].

In addition, ibrexafungerp has been studied in patients with vulvovaginal candidiasis (VVC). In a randomized, multicenter, evaluator-blinded study of 96 patients with moderate or severe VVC, patients were randomized to receive oral ibrexafungerp for 3 days, ibrexafungerp for 5 days, or fluconazole [143]. In the intention-to-treat analysis, both ibrexafungerp treatment regimens showed similar efficacy with a clinical cure rate of 78% in the ibrexafungerp-treated patients vs 66% in the patients receiving fluconazole by day 24 following randomization. Based on two phase III trials, VANISH-303 and VANISH-306, ibrexafungerp was recently approved by the FDA for oral use in adult and post-menarchal pediatric female patients with VVC with a recommended dose of 300 mg twice daily for 1 day (Brexafemme®). In the multicenter, randomized, double-blinded VANISH-303 trial [144, 145], patients in the USA were randomized in a 2:1 ratio to treatment with either ibrexafungerp 600 mg once daily or placebo. The VANISH-306 trial has the same design as the VANISH-303 trial but allowed patient inclusion not only in the USA but also in Bulgaria. The primary endpoint for both studies was clinical cure (resolution of all signs and symptoms) at the test-of-cure (TOC) visit (day 11 ± 3 days). Overall, 290 patients (190 in the ibrexafungerp group and 100 in the placebo group) and 278 (189 in the ibrexafungerp group and 89 in the placebo group) were included in the modified intent-to-treat analysis (requiring isolation of yeasts at baseline) in the VANISH-303 and VANISH-306 study, respectively. In both trials, ibrexafungerp was superior to placebo regarding clinical cure at the TOC visit [risk ratio 1.70 (95% confidence interval 1.2–2.5) for the VANISH-303 trial and risk ratio 1.35 (95% confidence interval 1.06–1.73) for the VANISH-306 trial]. In addition, ibrexafungerp was superior for secondary endpoints including mycological eradication at TOC, overall success at TOC, clinical improvement at TOC, and clinical cure at follow-up [145].

3.2.3.3 Ongoing Studies The FURI and CARES phase III trials are currently ongoing (Fig. 3; Table 2 of the ESM). Data on the efficacy and safety of ibrexafungerp for the treatment of mold infections are lacking, apart from three cases with invasive pulmonary aspergillosis. In a recent in vitro and in vivo animal model study, combination ibrexafungerp and isavuconazole resulted in a synergistic in vitro interactions and the combination of ibrexafungerp (7.5 mg/kg bodyweight daily) plus isavuconazole (40 mg/kg bodyweight daily) not only reduced pulmonary fungal burden in a neutropenic rabbit model but also prolonged survival [146]. Currently, there is an ongoing phase II, multicenter, randomized, double-blind trial evaluating the efficacy and

safety of ibrexafungerp as combination therapy in patients with invasive pulmonary aspergillosis (SCYNERGIA, NCT03672292). In addition, the role of ibrexafungerp for the prevention of VVC is currently being investigated in a phase III trial (CANDLE, NCT04029116).

3.2.4 Future Role

Ibrexafungerp was approved by the FDA for the treatment of VVC on 1 June, 2021, with other approvals likely to follow soon. Echinocandins are considered the standard treatment for invasive *Candida* infections; however, they are only available as intravenous formulations and oral alternatives with similar activity are often lacking. A recent multinational European study showed that hospital stay was prolonged because of parenteral therapy in 21% of cases with invasive *Candida* infections [147] owing to a lack of a reliable oral alternative. Ibrexafungerp will fill the gap and will likely be used for primary and oral step-down therapy of invasive *Candida* infections. Ibrexafungerp will also fill the gap of being an oral antifungal drug with limited contraindications, resistance, or potential drug–drug interactions as well as high tissue penetration and broad and fungicidal activity particularly against yeasts including *C. auris*. For invasive pulmonary aspergillosis, it may serve a role as therapy for resistant cases, particularly in combination therapy with an azole or amphotericin B lipid formulations (Table 1).

3.3 Olorofim

Olorofim (F901318, developed by F2G, Inc., Manchester, UK) is a member of a novel class of antifungal drugs named ortomides.

3.3.1 Mechanism of Action and Pharmacokinetics/Pharmacodynamics

Olorofim inhibits fungal growth through inhibition of the fungal dihydroorotate dehydrogenase enzyme involved in pyrimidine synthesis, and without any significant cross-reactivity with the human dihydroorotate dehydrogenase, limiting the compounds on target drug toxicity (Fig. 1) [117, 148, 149]. The compound itself has poor water solubility and is highly protein bound, but excellent tissue distribution including the kidney, liver, lung, and the brain (at lower levels). Oral dosing is 45% bioavailable. Susceptible fungi exhibit time-dependent killing effect after dosing. Olorofim is metabolized by multiple CYP450 enzymes including CYP3A4 and is thus susceptible to strong CYP3A4 inhibitors and inducers [117]. Olorofim does not appear to have any effect on the CYP450 enzymes, and has a low potential for drug interactions [117, 150].

3.3.2 Spectrum of Activity

Olorofim is not a broad-spectrum antifungal; however, it does have significant novelty and a spectrum of activity that will be relevant in the future. Olorofim exhibits no activity for yeast, *Exophiala dermatitidis* [151], or the Mucorales group [152] of thermally monomorphic molds, and also no activity against *Alternaria alternata* [153], but does have activity against several clinically important groups of fungi, including dimorphic molds (e.g., *Histoplasma* and *Coccidioides* spp.), the hyaline hyphomycetes (e.g., *Aspergillus* spp.), and dematiaceous molds (e.g., *Scedosporium* spp.) (Fig. 2) [117, 154–156]. Olorofim was highly active in vitro and in vivo against central nervous system coccidioidomycosis in a mouse model [157]. Olorofim has shown excellent in vitro activity against both mold and yeast phases of *Talaromyces marneffei* [158], and also against *Madurella mycetomatis*, the main causative agent of eumycetoma [159] as well as dermatophytes including *Trichophyton* spp. [153]. By virtue of its novel target enzyme and mechanism of action, olorofim has activity against isolates that are resistant to current treatment options, including several species that can be resistant to all commercially available antifungal drugs such as *Scedosporium apiospermum*, *L. prolificans*, *Rasamsonia* spp., *Penicillium* spp., and *Scopulariopsis* spp. (including *Scopulariopsis brumptii*) [117, 151, 153, 160–164]. Olorofim also maintains good activity against azole resistant *A. fumigatus* isolates [151, 165], including *CYP51A* active mutants and hard-to-treat cryptic species of *Aspergillus*, such as *A. nidulans*, *A. tubingensis*, *A. lentulus*, and *A. calidoustus* [152, 154, 166, 167]. Of the common hyaline molds, olorofim exhibits overall good activity against *Fusarium solani* species complex and *Fusarium oxysporum*, with some isolates demonstrating MICs up to 4mg/L, while others demonstrate low MICs [152, 168].

3.3.3 Clinical Studies

3.3.3.1 Safety There is currently not much known about the adverse-effect profile of olorofim as clinical studies are ongoing, although it appears to be safe. Olorofim was well tolerated in a phase I study of once-daily oral olorofim dosed for 10 days in healthy volunteers (Fig. 3; Table 3 of the ESM). No serious AEs were reported, although two participants experienced nausea and diarrhea and one experienced dizziness [169]. In a multiple-dose study of 40 healthy male volunteers (NCT02142153), there also were no serious AEs reported [170], with a frequency of non-serious AEs as follows: musculoskeletal pain in 0/30 participants in the olorofim group vs 1/10 in the placebo group; paresthesias or headache in 2/30 in the olorofim group vs 0/10 in the placebo group; epistaxis in 2/30 in the olorofim group vs 1/10 in the placebo group; and eczema in 1/30 participants in the

olorofim group vs 0/10 in the placebo group [171]. Last, in the olorofim group, infusion-related reactions including dizziness (67%), infusion-site pain (44%), and phlebitis (39%) were reported; each of these AEs was reported in 17% of participants in the placebo group [170].

In November of 2019, olorofim was granted Breakthrough Therapy designation for the treatment of invasive mold infections in patients with limited or no treatment options by the FDA and again in October 2020 for the treatment of central nervous system coccidioidomycosis refractory to SOC therapy. In addition, olorofim was granted orphan drug designation in March 2020 for the treatment for invasive aspergillosis, *L. prolificans*, and *Scedosporium* spp. infections followed by coccidioidomycosis in June of 2020. Last, it was granted Qualified Infectious Disease Product designation in June of 2020 for the treatment of invasive aspergillosis, invasive scedosporiosis, invasive lomentosporiosis, coccidioidomycosis, invasive scopulariopsis, and invasive fusariosis.

3.3.3.2 Efficacy There are no published reports describing the clinical efficacy of olorofim, although there are a number of case reports that have been presented in abstract form at conferences. In one case, a 56-year-old woman with acute T-cell lymphoblastic leukemia underwent HyperCVAD and developed disseminated *L. prolificans* infection involving her bloodstream, lungs, and aortic valve, and she developed L4/5 vertebral osteomyelitis and endophthalmitis. She underwent surgical debulking of the spine and did not respond to dual antifungal therapy with voriconazole plus terbinafine. After 11 months from the onset of infection, she was started on olorofim monotherapy (loading dose of 180 mg followed by 60 mg twice daily followed by 90 mg twice daily). After 6 months, she developed radiologic improvement with decreased uptake on a positron emission tomography scan and clinically improved with weight gain and stabilization of vision. She ultimately received a year of olorofim without any adverse effects [172]. In another case report, a 49-year-old woman developed disseminated *L. prolificans* following a right breast implant, which spread to her soft tissue, ribs, and sternum. Despite implant removal, repeated debridement, hyperbaric oxygen therapy, and multiple antifungal treatment including voriconazole plus terbinafine, miltefosine, posaconazole, and anidulafungin, her infection persisted. She was started on olorofim (60 mg twice daily followed by 90 mg twice daily followed by 120 mg twice daily) for a total of 322 days. This was well tolerated and eventually the surgical site healed [173]. Last, a 45-year-old man with insulin-dependent diabetes mellitus developed disseminated coccidioidomycosis infection with central nervous system involvement. He did not respond to antifungal treatment with fluconazole, voriconazole, itraconazole, liposomal amphotericin B plus posaconazole, and

posaconazole plus micafungin and continued to clinically deteriorate. After 8 months, he was switched to posaconazole plus olorofim (120 mg twice daily). Radiographic and clinical improvement was noted and his *Coccidioides* complement fixation titer decreased from 1:128 to 1:32 within 5 months [174].

3.3.3.3 Ongoing Studies Currently, olorofim is being evaluated in an open-label, single-arm, phase IIb clinical trial for the treatment of invasive mold infections with limited treatment options (FORMULA-OLS, NCT03583164), including infections due to *L. prolificans*, *Scedosporium* spp., *Aspergillus* spp., *Coccidioides* spp., and other invasive molds with resistance to commercially available antifungal drugs or for patients who are not responding to traditional therapy (Fig. 3; Table 3 of the ESM) [175].

3.3.4 Future Role

Olorofim will have a central role in the treatment of multi-resistant mold infections, including azole-resistant aspergillosis. In particular for *L. prolificans*, where other treatment options are scarce because of pan resistance [2, 4, 176, 177], olorofim may present a “breakthrough” treatment option [151], as it is not only associated with very low MICs but also has antibiofilm activity [178]. In addition, olorofim will have a very important role in the treatment of endemic mycoses, particularly coccidioidomycoses, but also infections caused by *T. marneffei* [158], and *Madurella mycetomatis* (Table 1).

3.4 Opelconazole

Opelconazole (PC945, developed by Pulmocide Ltd., London, UK) is a first-in-class inhaled antifungal drug from the class of broad-spectrum triazoles.

3.4.1 Mechanism of Action and Pharmacokinetics/Pharmacodynamics

Opelconazole is a novel antifungal triazole that was designed and optimized for inhalation via commonly available nebulizers [179]. After inhalation, opelconazole shows efficacy primarily in the lungs (systemic concentrations are minimal), making it a promising agent for treating pulmonary aspergillosis in non-neutropenic patients without disseminated infection. Its primary mechanism of action is familiar and comparable to established azoles, as opelconazole also contains the typical heterocyclic triazole scaffold. By inhibiting lanosterol 14 α -demethylase (CYP51A1), lanosterol conversion to ergosterol is inhibited, leading to a reduction in ergosterol synthesis and hence dysfunction of fungal membrane structure, preventing further growth (Fig. 1)

[180]. Recent in vitro and in vivo studies have shown distinctive pharmacological characteristics, differentiating from commonly used azoles. Chemical and physical attributes of opelconazole, namely increases in lipophilic compounds and micronized drug particles, result in high local concentrations, prolonged lung retention, slow absorption from the lung, and as a consequence, low plasma concentrations [179].

These findings are promising given the low potential for systemic adverse drug effects and drug–drug interactions. Additionally, some data suggest cellular persistence of opelconazole in local immune and epithelial cells, which is potentially valuable in terms of use in prophylaxis or enhancement of antifungal activity [181, 182].

3.4.2 Spectrum of Activity

Opelconazole shows broad-spectrum antifungal activity against yeasts and molds, including *Candida* spp. including *C. albicans*, *C. glabrata* and *C. krusei*, *C. neoformans*, and *gattii* and *Aspergillus* spp. including *A. fumigatus*, *A. carbonarius*, and *A. flavus*. For the emerging yeast *C. auris*, which will potentially constitute a pathogen with limited treatment options because of its multi-drug-resistant nature, potent inhibition was noted [14]. Remarkable potency was also seen against *Rhizopus arrhizus/oryzae* (Fig. 2) [180]. Opelconazole has shown in vitro superiority over posaconazole, itraconazole, and voriconazole in azole-susceptible and azole-resistant strains of *A. fumigatus*. Against 96 clinically isolated *A. fumigatus* strains, opelconazole showed 2.5-fold more potency compared with voriconazole and comparable potency for posaconazole [180]. CLSI methods, as well as the EUCAST microdilution method, validated superiority over voriconazole. In immunocompromised mice, comparable in vivo findings were seen [180]. Opelconazole lacks activity against *Aspergillus niger*, *Lichteimia corymbifera*, *Fusarium graminearum*, *Penicillium chrysogenum*, and *Penicillium citrinum*. [180]. Remarkable synergistic effects were reported in an in vitro human alveolus bilayer model when opelconazole was administered apically combined with basolateral posaconazole or voriconazole, illustrating an in vitro model of concomitant topical lung and systemic therapy [182]. Interestingly, these effects were not present when combining posaconazole or voriconazole locally and systemically, highlighting the superiority of opelconazole pharmacokinetics regarding local drug activity, compared with established azoles [182].

3.4.3 Clinical Studies

3.4.3.1 Safety To date, a small number of phase I and phase IIa studies have investigated clinical safety (Fig. 3; Table 4 of the ESM). Cass et al. analyzed safety profiles in 29 sub-

jects, of whom 20 were healthy and nine had mild asthma. Following inhaled single doses of 5 mg in the mild asthma cohort, single doses between 0.5 and 10 mg in healthy cohort one and repeated doses of 5 mg for 7 days in healthy cohort two [179], the geometric mean plasma C_{\max} after the 5-mg single dose did not significantly differ between healthy subjects and subjects with mild asthma. A dose-proportional increase in the AUC from 0 to 24 h and C_{\max} was found between dosages of 0.5 mg to 10 mg. However, oral inhalation of PC945 resulted in low systemic exposure as demonstrated by a mean plasma C_{\max} of 0.951 ng/mL following 5-mg doses once daily for 7 days, suggesting that it will have a negligible systemic antifungal effect and a much lower drug–drug interaction risk than orally administered triazole antifungal drugs. In addition to mild-to-moderate AEs (e.g., cough, throat tightness, headache, nausea, fatigue), which all resolved by the end of the study, no severe events were observed. Compared with the placebo cohort, no significant differences in spirometry values, electrocardiogram recording, vital signs, or mean laboratory values were noted. In the mild asthma cohort, no significant decrease in lung function or triggering of bronchospasm was identified [179]. Inhibitory effects were found on CYP3A4/5 substrates but opelconazole showed no interaction with other CYP isoforms [179]. These first in-human clinical findings underline that pharmacokinetic (PK) properties of PC945 and drug administration via inhalation will likely lead to a superior safety profile compared with systemic application.

3.4.3.2 Efficacy The efficacy of inhaled opelconazole was investigated in *A. fumigatus*-infected neutropenic mice, focusing on fungal burden, dynamics of biomarkers (BALF, Serum GM), and fungus-related inflammatory response after various treatment regimens, including for prophylaxis. Results showed strong inhibition of fungal burden in lung tissue, substantial decrease of GM, and suppression of inflammatory cell accumulation in dose-dependent relations [183]. Opelconazole showed marked superiority to voriconazole and posaconazole when evaluating the aforementioned parameters and very high dosages of voriconazole and posaconazole were needed to achieve similar results, once more highlighting that the strength of opelconazole is sustained lung retention and persistent antifungal activity [183].

3.4.3.3 Ongoing Studies In an ongoing study, opelconazole has shown promising results when used as part of its compassionate use program, acting as a last resort in patients who have not responded to standard antifungal therapies (Fig. 3; Table 4 of the ESM). Of nine patients treated, positive clinical results were observed in eight. An open-label randomized phase IIb study will start in 2021, focusing on the safety and tolerability of opelconazole prophylaxis and

treatment of invasive aspergillosis in lung transplant recipients.

3.4.4 Future Role

Currently available antifungal agents have been approved for oral or intravenous application, but the emergence of primary airway invasive aspergillosis in non-traditional risk groups has lately increased the interest in inhaled antifungal agents. In order to achieve local efficacy, high systemic concentrations, which are frequently associated with treatment limiting complications, are required. Thus, other modes of delivery highlight unmet needs in antifungal treatment. Topical or inhaled administration may maximize local efficacy while avoiding systemic toxicity, decreasing the need for high drug concentrations and potential toxicity. Established drugs were tried to be repurposed but do not meet PK/pharmacodynamic (PD) properties and airway tolerability allowing sufficient local treatment. Particularly for combination therapy approaches in invasive aspergillosis, opelconazole would be a new therapeutic option of potential great value by achieving high local concentration without systemic drug concentrations and toxicity, specifically attractive for primarily airway invasive aspergillosis in non-neutropenic patients, including those with COVID-19-associated pulmonary aspergillosis [10, 184]. Other roles may include antifungal prophylaxis after lung transplantation and in the intensive care unit setting or also in other settings where mold-active prophylaxis is not yet firmly established (e.g., induction chemotherapy for acute lymphocytic leukemia or stem cell transplantation early phase) as well as combination therapy with a systemic antifungal agent for cases with angioinvasive pulmonary aspergillosis (Table 1).

3.5 Rezafungin

Rezafungin (formerly SP3025 and CD101; Cidara Therapeutics, San Diego, CA, USA) is considered the first member of second-generation echinocandins with enhanced PK/PD pharmacometrics [185]. This novel drug is currently investigated in two phase III trials (ReSTORE, NCT03667690 and ReSPECT, NCT04368559) to assess its therapeutic use in candidemia and other invasive candidiasis and its potential to prevent invasive fungal disease (IFD).

3.5.1 Mechanism of Action and Pharmacokinetics/Pharmacodynamics

Rezafungin was designed to optimize PK properties and avoid hepatotoxicity by reducing degradation while maintaining the potent antifungal activity and safety profile of the echinocandin class [186]. Echinocandins are lipopeptide antifungal drugs that have a cyclic depsipeptide core and

an N-linked acyl lipid side-chain [187] that is considered essential for the antifungal activity [188]. Consistent with other echinocandins, the antifungal activity of rezafungin is carried out by inhibition of the cell-wall enzyme complex β -1,3-D-glucan synthase (Fig. 1) [188]. Rezafungin is a chemical analog to anidulafungin with a similar alkoxy triphenyl moiety but a distinct structural modification at the C5 ornithine hemiaminal of the cyclic core, which is replaced by a choline aminal ether [189]. This modification results in a considerably longer half-life, as non-enzymatic chemical degradation occurs on the hemiaminal of anidulafungin [189]. Rezafungin is stable to biotransformation in liver microsomes or hepatocytes, reducing the risk of hepatotoxicity, similar to other echinocandins [186]. As with other echinocandins, in vitro cytochrome inhibition studies suggest minimal interaction with CYP450 enzymes [186].

Pharmacokinetic results from two phase I dose-escalation studies (NCT02516904 and NCT02551549) have shown a mean half-life of approximately 80 hours after the first dose and 150 hours after the second or third dose indicating linear pharmacokinetics [190]. This allows rezafungin to be administered at extended intervals, such as once weekly. Mean plasma C_{\max} and AUC have been shown to increase in proportion to dose [190]. Renal clearance plays a minor role in the excretion of rezafungin with fractions excreted < 1% at all dose concentrations [190]. In healthy subjects, no relevant PK interactions were monitored when dosing rezafungin concomitantly with several probe drugs [191].

3.5.2 Spectrum of Activity

In vitro susceptibility testing of rezafungin has been performed in several studies for wild-type and resistant fungal isolates using reference EUCAST and CLSI methodologies, which have been shown to have an excellent level of concordance for testing rezafungin [192]. The activity of rezafungin against *Candida* spp. is comparable to that of other members of the echinocandin class (Fig. 2) [192]. *Candida albicans* appears to be very susceptible to rezafungin, as the majority of isolates were inhibited by ≤ 0.125 $\mu\text{g/mL}$ in different laboratories using CLSI and EUCAST methods [193, 194]. *Candida dubliensis*, *C. fabianii*, *C. glabrata*, *C. inconspicua*, *C. kefyr*, *C. krusei*, *C. lipolytica*, *C. pulcherrima*, *C. sojae*, and *C. tropicalis* were also inhibited by MIC values ≤ 0.125 $\mu\text{g/mL}$ and were susceptible to other echinocandins using epidemiological cut-off value (ECV) interpretive criteria [194, 195]. For *C. lusitanae* and *C. auris* isolates, MICs were 0.25 $\mu\text{g/mL}$ by CLSI methodology [195]. Minimum inhibitory concentrations of 0.5 $\mu\text{g/mL}$ were found for *C. metapsilosis* and 1 $\mu\text{g/mL}$ for *C. orthopsilosis* and *C. guilliermondii* [195]. *Candida parapsilosis* was the least susceptible organism with MICs up to 4 $\mu\text{g/mL}$ [194]. Intrinsically elevated MICs for *C. parapsilosis* are similarly described

for other echinocandins and attributed to a polymorphism in the *FKS* gene of *C. parapsilosis* [196]. However, consistent treatment failures have not yet been demonstrated [196]. For isolates harboring *FKS* mutations, elevated rezafungin MICs were described with a similar or slightly better activity against mutant *Candida* spp. compared to other echinocandins [193, 197]. In summary, rezafungin demonstrates potent in vitro activity against most wild-type and azole-resistant *Candida* spp., including *C. auris*. Rezafungin also has potent activity vs common dermatophytes (e.g., *Trichophyton mentagrophytes*, *T. rubrum*, *Microsporum gypseum*, *Epidermophyton floccosum*).

Rezafungin has also demonstrated efficacy for the treatment of invasive candidiasis in vivo, with potent activity against *C. albicans*, including azole-resistant *C. albicans*, *C. glabrata*, and *C. parapsilosis* strains in murine models of immunocompromised disseminated candidiasis [198, 199]. For *Aspergillus* spp., rezafungin MEC ranges of ≤ 0.015 – 0.125 $\mu\text{g/mL}$ and ≤ 0.015 – 2 $\mu\text{g/mL}$ were reported against *A. fumigatus* wild-type and azole-resistant species, respectively [200]. Against *A. flavus*, *A. niger*, and *A. terreus*, rezafungin was shown to be active with MECs of ≤ 0.008 – 0.03 $\mu\text{g/mL}$ [192]. Rezafungin also has activity against cryptic species, including *A. calidoustus*, *A. lentulus*, *A. thermomutatus*, and *A. udagawae* [200]. The activity of rezafungin against *Aspergillus* spp. is therefore comparable to other echinocandins. In a disseminated infection mouse model of aspergillosis caused by *A. fumigatus*, similar survival rates were shown with rezafungin compared to amphotericin B treatment [199]. In vivo efficacy has also been demonstrated in an murine model of disseminated aspergillosis caused by an azole-resistant *A. fumigatus* isolate harboring a TR₃₄/L98H *CYP51A* mutation [201]. Additional studies are warranted to determine whether this preclinical research translates to clinical experience and if rezafungin has the potential to prevent and treat infections caused by *Aspergillus* spp.

Echinocandins are not commonly used to treat or prevent *Pneumocystis jirovecii* infections. However, rezafungin has been shown to prevent *P. murina* infection in an immunosuppressed mouse model of *Pneumocystis jirovecii* pneumonia. A significant decrease in the number of trophic nuclei and reduced count of cystic forms have been demonstrated in the rezafungin-treated groups, with a comparable efficacy to the active control trimethoprim-sulfamethoxazole [202].

Like other echinocandins, rezafungin is inactive against non-*Aspergillus* molds, *Cryptococcus*, *Trichosporon*, and *Rhodotorula* isolates with MICs > 8 $\mu\text{g/mL}$ [188, 193]. Overall, rezafungin exhibits broad in vitro potency against fungal pathogens comparable to that of other echinocandins. To date, in vitro data are lacking for most of the rare and emerging molds and yeasts.

3.5.3 Clinical Studies

3.5.3.1 Safety Phase I studies of rezafungin consisted of two randomized, double-blind, placebo-controlled dose-escalation studies with doses up to 400 mg once weekly for 3 consecutive weeks (NCT02516904 and NCT02551549, Fig. 3; Table 5 of the ESM) [190]. Safety was assessed by the number of clinically significant AEs in healthy adults. The majority of AEs reported were mild, with chest discomfort, constipation, flushing, nausea, and myalgia being frequently reported. A tendency toward higher rates of AEs, including transfusion reactions, was observed in the group receiving the highest dose of rezafungin. All AEs were transient and resolved completely. No severe or serious AEs, withdrawals because of AEs, or deaths were reported. Furthermore, no safety issues related to laboratory results, physical examination, or vital signs were reported. Thus, rezafungin was shown to have a favorable safety profile at once-weekly doses of 400 mg.

In addition, a randomized, double-blind, phase I study was conducted in healthy volunteers to evaluate cardiac effects of single doses of intravenous rezafungin [203]. For echinocandins, data on QT prolongation among echinocandins are limited. For anidulafungin, QT prolongation is reported as an AE [204]. Rezafungin infusions did not prolong QT/QTc interval at doses up to 1400 mg, and there was no apparent effect on repolarization or QRS duration in a 12-lead electrocardiogram. Echocardiograms showed no change in ejection fraction or other cardiac parameters compared with baseline and an increase in PR interval was seen in the 1400-mg dose group, but was considered not clinically relevant. No serious AEs were reported, and no subjects discontinued the study because of an AE. The 1400-mg dose is six-fold higher than expected to be achieved at therapeutic steady-state exposures and was not associated with a higher number or severity of AEs, implying a high therapeutic index of rezafungin. Overall, no evidence for the adverse effects of rezafungin was found from electrocardiogram or echocardiogram data.

In the phase II evaluation, the randomized, double-blind STRIVE trial (NCT02734862) aimed to evaluate the safety and efficacy of intravenous rezafungin for the treatment of candidemia and invasive candidiasis [185]. The most common TEAEs were mild-to-moderate diarrhea, fever, hypokalemia, and vomiting. No trend was seen between the rezafungin and SOC groups, therefore the STRIVE trial was considered to further validate the robust safety profile of rezafungin at the once-weekly dosing regimen.

A second phase II study, the randomized, multicenter, open-label, sponsor-blinded, active-controlled, dose-ranging RADIANT trial (RADIANT, NCT02733432), was designed to investigate gel and ointment topical formulations of rezafungin for the treatment of acute VVC, with and without

a history of recurrence [205]. In three treatment arms, both rezafungin formulations and SOC with oral fluconazole were compared. Most treatment-emergent AEs were unrelated to the study drugs, and all were mild or moderate in intensity. Infections were the most common events across all treatment groups. Vaginal symptoms such as pain and dyspareunia occurred most frequently with the 6% rezafungin ointment and no serious AEs were reported. Overall, both topical formulations of rezafungin were safe and well tolerated.

For the assessment of subcutaneous route of administration for rezafungin, another double-blind, placebo-controlled phase I study (NCT04117607) was conducted in healthy subjects to determine the safety, tolerability, and pharmacokinetics of subcutaneous application. Despite reported good preclinical tolerability [206], the study was terminated because of the formation of injection-site skin nodules.

3.5.3.2 Efficacy In the phase II efficacy analysis of the STRIVE trial for the treatment of candidemia and invasive candidiasis, the primary efficacy endpoint was overall success at day 14 as demonstrated by mycological eradication and clinical cure [185]. Rezafungin was dosed at either 400 mg weekly or 400 mg for the first week and 200 mg weekly thereafter and compared to SOC with caspofungin once daily and optional switch to oral fluconazole. The rezafungin 400-mg/200-mg regimen showed the greatest overall cure with the highest clinical and mycological cure rates and lowest rate of all-cause mortality at day 30 across all treatment arms. Candidemia cleared more rapidly in the rezafungin-treated patients compared with SOC treatment, possibly reflecting greater fungicidal activity with front-loaded drug exposure, and demonstrated high rates of early treatment efficacy in patients with candidemia [207]. Clinical cure rates were also highest with rezafungin 400 mg/200 mg when differentiating between *C. albicans* and non-*albicans Candida* spp. Of note, certain forms of invasive candidiasis such as osteomyelitis, endocarditis or myocarditis, and endophthalmitis were excluded. Apparent differences between the two rezafungin groups raised the discussion of paradoxical growth with higher concentrations. Both in vitro and animal studies of other echinocandins have reported this phenomenon whereby the fungal burden increases at doses above a certain threshold [208]. However, the differences with rezafungin occurred on day 5, when both treatment arms had received a similar 400-mg dose [185]. A paradoxical growth effect therefore appears unlikely.

Efficacy outcomes of the phase II RADIANT trial were measured as clinical and mycological cures of acute VVC by changes in vaginal scoring system and mycological culture [205]. Two topical formulations of rezafungin were similar in efficacy to each other but lower in clinical and mycological cure rates compared with SOC. Fluconazole also maintained the highest cure rate regardless of infection

severity or recurrence. Most subjects with non-*albicans* *Candida* infections demonstrated treatment failure across all cohorts. Based on these unfavorable results, the development of topical formulation in VVC was discontinued [209]. A non-interventional extension study (NCT02888197) was conducted to follow up on participants who completed the RADIANT trial without recurrence at day 28 visit, although results are not yet available.

3.5.3.3 Ongoing Studies Currently, two phase III trials are recruiting patients to further determine the impact and future of rezafungin for the treatment of invasive candidiasis (ReSTORE, NCT03667690) and for the prevention of IFD (ReSPECT, NCT04368559) (Fig. 3; Table 5 of the ESM). The ReSTORE trial is a multicenter, randomized, double-blind study examining the rezafungin 400-mg/200-mg once-weekly regimen for the treatment of candidemia and invasive candidiasis. The active comparator is intravenous caspofungin followed by optional fluconazole step-down. The primary endpoint is day 30 all-cause mortality and day 14 global cure measured by clinical, radiological, and mycological indices.

The randomized, double-blind, controlled phase III trial ReSPECT is intended to evaluate rezafungin for the prevention of IFD including *Candida* spp., *Aspergillus* spp., and *P. jirovecii* in patients undergoing allogeneic blood and marrow transplantation. Rezafungin 400 mg/200 mg once weekly is compared with a standard regimen containing daily azole prophylaxis with fluconazole or posaconazole and anti-*Pneumocystis jirovecii* prophylaxis with oral trimethoprim-sulfamethoxazole. Fungal-free day 90 survival will be evaluated as the primary outcome.

3.5.4 Future Role

The strengths of the echinocandin class combined with the prolonged half-life and robust safety profile of rezafungin open several possibilities for future use. Rezafungin may enable earlier hospital discharge and extended outpatient access to the treatment of invasive candidiasis. Although in vitro susceptibility results are encouraging, further studies are needed to determine the efficacy of rezafungin in the treatment of invasive aspergillosis [192, 199]. Its use as a prophylactic agent for preventing invasive fungal disease caused by *Candida* spp., *Aspergillus* spp., and *P. jirovecii* could overcome current multidrug regimens, and the once-weekly dosing with limited drug–drug interactions may be attractive also for prophylaxis during the early phase after solid organ transplantation (e.g., liver) (Table 1). A front-loaded drug exposure suggests advantages in preventing the selection of resistant strains [210].

4 Discussion and Conclusions

There are a number of promising antifungal agents currently in late-stage clinical development. This review highlights the most advanced and promising candidates for timely regulatory approval. These antifungal treatments offer significant advantages in terms of spectrum of activity, tolerability, drug–drug interactions and/or route of administration that have the potential to significantly change the field of clinical mycology as we know it. While current clinical trials often focus on the treatment of refractory, resistant, or breakthrough infections [211], the drugs highlighted in this review—once approved—will likely soon have additional indications and broader clinical use because of the advantages in pharmacokinetics, limited drug–drug interactions, and generally very good tolerability. In addition, three of the drugs discussed in this review have novel mechanisms of action. While these new antifungal drugs are promising, there are still gaps of knowledge regarding their pharmacokinetics and pharmacodynamics, and whether therapeutic drug monitoring may be required. Only once they are used in real-world scenarios, we will find out how prone these new drugs will be to development of novel drug resistance mechanisms. Furthermore, some of the new drugs may have a narrower spectrum of activity compared with some of the currently available broad-spectrum agents and may therefore be less promising for empirical therapy.

In summary, fosmanogepix has a novel mechanism of action and inhibits the fungal enzyme Gwt1. Dosed orally or intravenously, fosmanogepix has a broad spectrum of action against most molds including most of the endemic fungi and most *Candida* spp., although it lacks activity against *C. krusei* and has variable activity against *Mucor* and *Rhizopus* spp. Given its favorable side-effect profile and broad spectrum of activity, fosmanogepix will likely serve as a good treatment option for a broad spectrum of infections. Ibrexafungerp, a first-in-class triterpenoid, is currently available only in oral formulation and is approved by the FDA for the treatment of VVC, although additional approvals are likely forthcoming and it is currently being evaluated to be given intravenously as well. It has good coverage against *Aspergillus*, most of the endemic fungi, and particularly *Candida* spp. although activity against other molds including *Mucor*, *Rhizopus*, *Fusarium*, and *Scopulariopsis* spp. is lacking. Given its oral formulation, ibrexafungerp will likely be a good primary and step-down option for infections from *Candida* spp., and it may play a role in the treatment of aspergillosis as well. Olorofim is a dihydroorotate dehydrogenase enzyme inhibitor available in oral formulation with good activity against *Aspergillus* spp., *L. prolificans*, and *Scedosporium* spp., and many of the endemic fungi. It appears well tolerated with few drug–drug interactions and

likely will play a role against difficult-to-treat infections such as those caused by *L. proliferans* and coccidioidomycoses, which require prolonged treatment courses. Opelconazole is a novel triazole that has been optimized for inhalation and has activity against *C. neoformans* and *gattii*, and many *Aspergillus* spp. Opelconazole may have a nice niche for the prophylaxis and treatment of primarily airway-invasive infections where high drug concentrations can be achieved via inhalation without the systemic side effects. Last, rezafungin is a once-weekly intravenous echinocandin with good activity against *Aspergillus* spp. and *Candida* spp. as well as *P. jirovecii*. Rezafungin may serve as a good option for prophylaxis after solid organ transplantation or allow for earlier hospital discharge and access to extended outpatient therapy given its once-weekly dosing.

Despite the promising antifungal drugs outlined in this review, there are still remaining unmet needs in the treatment of fungal infections. For example, even with these new options there are still too few antifungal drugs that are well tolerated and with good activity against the Mucorales, with novel treatment options for mucormycosis probably presenting the biggest need currently. In addition, while there are new treatment options against multi-resistant non-*Aspergillus* spp. including *Fusarium* spp., *Scedosporium* spp., and *L. proliferans*, given that these infections can be very difficult to treat and may develop further resistance, more treatment options are likely needed. Last, there are still no antifungal drugs that can eradicate disseminated infection from *Coccidioides* spp. and thus lifelong treatment is still required. Thus, despite the promise that these new antifungal drug options hold, continued research and development into new options including drugs from novel antifungal classes will help replenish the current antifungal armamentarium.

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Availability of Data and Material Data available upon request.

Authors contribution MH had the idea for the review and coordinated the review process. All authors performed the literature search and data analysis for their assigned sections and drafted their assigned sections. MH and RS created the first draft of the manuscript and developed the Figures and Tables in the review. All authors read, critically revised and approved the final manuscript.

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