Fosmanogepix: A comprehensive review of its origin, mechanism, antifungal efficacy, and resistance (Review)

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Received June 11, 2026; Accepted September 15, 2026

DOI: 10.3892/br.2026.2204

Abstract. The escalating burden of invasive fungal infections, compounded by rising antifungal resistance and evolving pathogen epidemiology, underscores the urgent need for novel agents. There is a requirement for these novel agents to combine broad-spectrum activity with >90% oral bioavailability and a 48% acceptable safety profile. Fosmanogepix, an N-phosphonooxymethylene prodrug of manogepix (APX001A), is a first-in-class glycosylphosphatidylinositol (GPI)-anchored wall transfer protein 1 (Gwt1) inhibitor in Phase III clinical trials for invasive fungal infections. It is a potent inhibitor of the fungal enzyme Gwt1, which blocks GPI-anchored protein maturation and disrupts cell wall integrity. Manogepix has broad *in vitro* activity against yeasts and molds, including drug-resistant and intrinsically resistant pathogens. Fosmanogepix shows notable *in vivo* efficacy in mouse and rabbit models of disseminated candidiasis, coccidioidomycosis, fusariosis, pulmonary aspergillosis, scedosporiosis and mucormycosis. Clinical trials have demonstrated high oral bioavailability (90%), allowing seamless intravenous-to-oral switching. Favorable drug-drug interaction, tolerability and effective tissue distribution profiles make fosmanogepix an attractive option for treating invasive fungal infections. However, emerging resistance mechanisms, including Gwt1 target mutations (such as V162A/V163A), efflux pump overexpression mediated by transcription factor mutations (Tac1B, Tac1, Pdr1), and calcineurin-dependent calcium signaling activation, pose potential threats to its long-term clinical utility. The present narrative review summarized published findings on fosmanogepix, encompassing its origin, mechanism of action, antifungal efficacy, resistance mechanisms, and combination strategies through *in vitro*, *in vivo*, and clinical investigations.

Contents

1. Introduction

The global public health burden of invasive fungal infections (IFIs) has become increasingly severe, driven by an aging population and the increasing use of immunosuppressive therapies (1). The COVID-19 pandemic further aggravated this trend, leading to a marked surge in infections caused by *Aspergillus fumigatus (A. fumigatus)* and *Candida* species (2,3). Climate change has also expanded the geographic range and incidence of fungal diseases (4,5). A 2024 global study estimated that IFIs account for ~6.55 million cases and 3.75 million deaths annually, with ~2.55 million deaths directly attributable to these infections (1). Immunocompromised individuals remain the principal high-risk group, which includes recipients of solid organ or hematopoietic stem cell transplants, patients undergoing chemotherapy for cancer, and those on long-term immunosuppressive or corticosteroid therapy (6,7). Despite improvements in diagnostics and antifungal treatment, mortality from IFIs remains high: ~64% for invasive candidiasis (995,000 deaths among 1,565,000 annual cases), 18.5% for chronic pulmonary aspergillosis (340,000 deaths among 1,837,000 annual cases), and ~54% for other major life-threatening fungal infections (161,000 deaths among 300,000 annual cases) (1).

Currently available antifungals include polyenes (such as amphotericin B), azoles (such as fluconazole and voriconazole), echinocandins (such as caspofungin and micafungin),

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Key words: fosmanogepix, antifungal drug, origin, resistance mechanisms, antifungal efficacy

and pyrimidine analogs (such as 5-flucytosine) (8-10), however, each class has notable limitations. Amphotericin B use is restricted by nephrotoxicity and infusion-related adverse effects (11). Despite their high bioavailability and broad spectrum, azoles are limited by escalating antifungal resistance driven by *CYP51A* mutations and hepatotoxicity (12). Globally, azole-resistant *A. fumigatus* clinical isolates, especially those carrying environmental *CYP51A* mutations such as TR34/L98H and TR46/Y121F/T289A, have substantially increased treatment failure rates (5). Echinocandins have limited activity against filamentous fungi, cannot effectively cross the blood-brain barrier, and are increasingly associated with resistance in *Candida glabrata* and *Candida auris* (*C. auris*) (13,14). The antifungal 5-flucytosine, when used alone, rapidly selects for resistance and is therefore typically given in combination (15). Of particular concern, multidrug-resistant *C. auris* has caused outbreaks on six continents since its first identification in 2009, with fluconazole resistance >90% (16). Some strains are resistant to both amphotericin B and echinocandins, earning the label multidrug-resistant fungal pathogens (17). In 2022, the World Health Organization (WHO) issued its first fungal priority pathogens list, designating *Cryptococcus neoformans* (*C. neoformans*), *C. auris*, *Candida albicans* (*C. albicans*), and *A. fumigatus* as 'critical priority' pathogens, highlighting the urgent need for new antifungal agents (18).

Fosmanogepix (APX001) is a first-in-class N-phosphonooxymethylene prodrug that is rapidly converted *in vivo* by systemic phosphatases into its active metabolite, manogepix (APX001A, also known as E1210) (19). Manogepix selectively inhibits the fungal glycosylphosphatidylinositol (GPI)-anchored wall transfer protein 1 (Gwt1), a conserved enzyme that catalyzes the inositol acylation reaction in the GPI anchor biosynthesis pathway. This inhibition disrupts the maturation and cell wall anchoring of GPI-anchored proteins, thereby compromising cell wall integrity, hyphal formation, and biofilm development (19). Because the fungal target differs substantially from its mammalian homolog (PIGW), manogepix exhibits fungal-selective Gwt1 inhibition with minimal activity against human PIGW (20). Both *in vitro* and *in vivo* studies have consistently shown that manogepix has potent broad-spectrum activity, against a wide range of clinically relevant opportunistic fungal pathogens (21-23). Clinical trials have indicated that fosmanogepix has high oral bioavailability (>90%), along with a favorable drug-drug interaction profile and good tolerability, allowing convenient switching between intravenous and oral formulations. Multiple phase I and II clinical trials have been completed, and phase III clinical studies are ongoing (24,25).

Accordingly, the present narrative review aimed to: i) Summarize the origin and structural optimization of fosmanogepix from its precursor E1210 to the clinical candidate E1211; ii) elucidate the unique mechanism of action of manogepix targeting Gwt1 and its impact on fungal biofilm formation and virulence factors; iii) evaluate the *in vitro* and *in vivo* antifungal efficacy of fosmanogepix against susceptible and multidrug-resistant pathogens, including *Candida*, *Aspergillus*, and rare molds; iv) examine emerging resistance mechanisms, including *GWT1* target mutations, efflux pump overexpression, and calcineurin-mediated calcium signaling; v) assess the current evidence for combination therapy strategies; and vi) identify current knowledge gaps and future directions in the clinical development of fosmanogepix.

2. Literature search strategy and study selection

For the present narrative review, literature related to fosmanogepix (APX001), manogepix (APX001A, E1210) and Gwt1 inhibitors was searched using the PubMed database (https://pubmed.ncbi.nlm.nih.gov/), with search strategies informed by review methodology principles including database selection, search cut-off dates and effect size reporting approaches. The search terms included the following: 'manogepix', 'APX001', 'APX001A', 'E1210', 'E1211', 'Gwt1 inhibitor', 'inositol acyltransferase inhibitor', 'GPI anchor', 'antifungal', 'invasive fungal infections', '*C. auris*', '*A. fumigatus*', 'azole resistance', 'echinocandin resistance', 'biofilm', 'virulence', 'clinical trial', 'Phase II', 'Phase III', 'FAST-IC', 'FORWARD-IM', 'AEGIS', 'resistance mechanism', 'efflux pump', 'calcineurin', 'drug combination' and 'pharmacokinetics'. Combinations of search terms were also used, which included: 'fosmanogepix and *Candida*' or '*Aspergillus*', 'manogepix and resistance' or 'efflux pump', 'APX001 and clinical trial' or 'efficacy', 'Gwt1 inhibitor and biofilm' or 'virulence', 'fosmanogepix and combination therapy' or 'liposomal amphotericin B', and 'manogepix and calcineurin' or 'calcium signaling'. Original research articles, clinical trials, preclinical *in vivo* studies, *in vitro* susceptibility studies, and mechanistic studies published in English were selected.

3. Origin and derivatives of manogepix

A unique feature of fungi is the incorporation of mannoproteins into cell wall glucan. Using a yeast cell phenotypic screening approach, researchers identified the lead compound 1-[4-butylbenzyl]isoquinoline (BIQ) (Fig. 1). In 2003, BIQ was first reported to effectively inhibit the cell wall localization of GPI-anchored mannoproteins in *Saccharomyces cerevisiae* (*S. cerevisiae*) and *C. albicans* (26). Further genetic studies revealed a previously uncharacterized gene, *GWT1*, which acted as a dose-dependent suppressor of the BIQ-induced phenotype. *GWT1* knockout strains exhibited cell wall structures and transcript profiles similar to those of BIQ-treated wild-type strains (27). Systematic structure-activity relationship studies based on BIQ optimized their pharmacological properties while preserving antifungal activity, ultimately leading to the preclinical candidate E1210 (manogepix) (28). In 2012, E1210 was reported as a pyridine-isoxazole broad-spectrum antifungal agent. It notably inhibited the inositol acylation activity of Gwt1p in *C. albicans* and *A. fumigatus* and exhibited no inhibitory activity against human PIGW, demonstrating fungal selectivity (28). Because manogepix has poor water solubility, researchers synthesized its N-phosphonooxymethylene prodrug, fosmanogepix (Fig. 2). This prodrug exhibits enhanced water solubility, enabling intravenous administration. *In vivo*, it is rapidly converted to the active compound manogepix by systemic phosphatases. Clinical trials demonstrated that fosmanogepix has an oral bioavailability of 90.6-101.2%, and both intravenous and oral formulations exhibit linear pharmacokinetics (PK) and

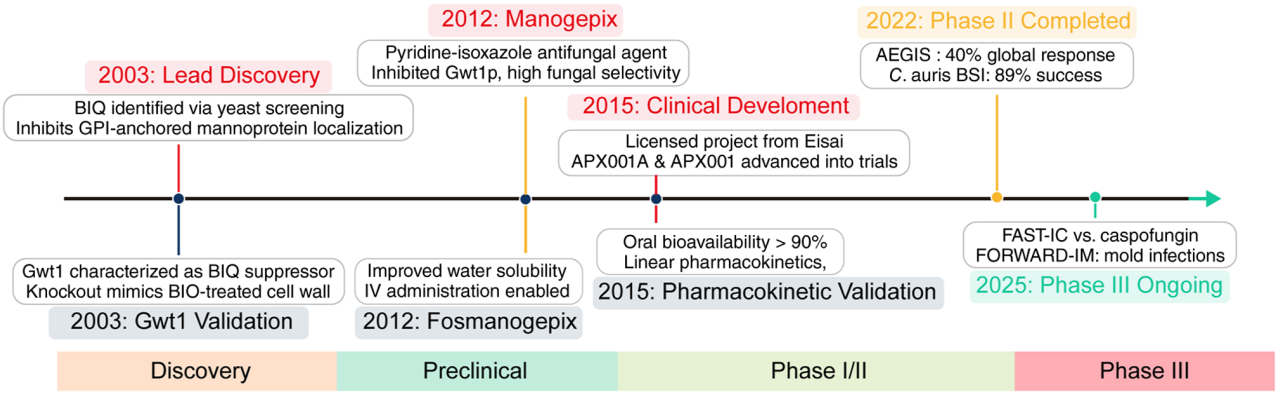

Figure 1. Timeline of fosmanogepix (APX001) development from lead discovery to Phase III clinical trials. The development of fosmanogepix spans over two decades, from the initial discovery of the lead compound BIQ in 2003 through current Phase III clinical trials. Key milestones include: i) Identification of GWT1 as the molecular target in 2003; ii) optimization to the preclinical candidate E1210 (manogepix) and synthesis of its prodrug E1211 (fosmanogepix) in 2012; iii) initiation of clinical development in 2015 with validated pharmacokinetic properties including >90% oral bioavailability and seamless IV-to-oral switching; iv) completion of Phase II trials in 2022 demonstrating 40% global response success in invasive mold diseases (AEGIS study) and 89% treatment success in *C. auris* bloodstream infections; and v) ongoing Phase III trials (FAST-IC and FORWARD-IM, expected completion 2028) evaluating fosmanogepix against caspofungin for candidemia/invasive candidiasis and for invasive mold infections, respectively. BIQ, 1-[4-butylbenzyl]isoquinoline; GWT1, GPI-anchored wall transfer protein 1; *C. auris*, *Candida auris*; GPI, glycosylphosphatidylinositol; BSI, bloodstream infection.

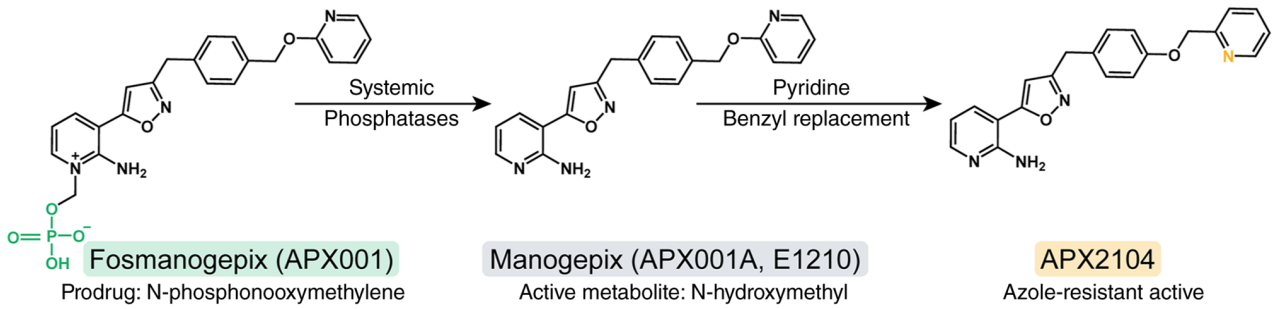

Figure 2. Structures of fosmanogepix, manogepix, and the next-generation candidate APX2104. Fosmanogepix (APX001) is an N-phosphonooxymethylene prodrug that is rapidly converted by systemic phosphatases to the active metabolite manogepix (APX001A, E1210) bearing an N-hydroxymethyl group. APX2104 represents a structural optimization with a benzyl group replacing the pyridine ring, maintaining potent activity against azole-resistant *Aspergillus fumigatus*.

favorable tolerability (24). In 2015, a biopharmaceutical company licensed the project from Eisai and advanced manogepix (APX001A) and fosmanogepix (APX001) into clinical development. Currently, fosmanogepix is undergoing phase III clinical trials for IFIs caused by *Candida*, *Aspergillus*, and rare molds (25).

In parallel with advancing manogepix into clinical development, researchers have been exploring structural optimizations to develop next-generation Gwt1 inhibitors. A new Gwt1 inhibitor, APX2041, and its prodrug APX2104 were reported in 2021 (29). APX2041 was synthesized by replacing the pyridine ring in the manogepix scaffold with a benzyl group (Fig. 2). It maintained equivalent *in vitro* activity against wild-type, azole-resistant, and echinocandin-resistant *A. fumigatus* strains. Its prodrug, APX2104, notably prolonged survival of neutropenic mice infected with wild-type and azole-resistant *A. fumigatus*, indicating potential for treating invasive aspergillosis (29). Progress has also been made in targeting other enzymes in the GPI anchor biosynthesis pathway. Using a chemical genomics-based screening platform, combining Gwt1 inhibitors with mannose-ethanolamine phosphotransferase (Mcd4) inhibitors produced marked chemical synergy, consistent with the synthetic lethality observed in *GWT1* and *MCD4* conditional mutant strains (30). This finding opens new avenues for combination antifungal therapies targeting the GPI biosynthesis pathway.

4. Antifungal mechanism and resistance mechanisms of manogepix

Mannoproteins are required for cell wall integrity, adhesion, pathogenicity and evasion of host immune responses. By inhibiting Gwt1, manogepix triggers a range of downstream effects: Reduced cell wall-associated mannoproteins, impaired hyphal formation, diminished biofilm production, abnormal cell morphology, exposure of the glucan layer and endoplasmic reticulum (ER) stress (31). As a result, immature GPI-anchored proteins accumulate in the ER and activate the cell wall stress response, ultimately leading to fungal cell death (Fig. 3). Manogepix has broad-spectrum antifungal activity. It notably inhibits *Candida* species (including echinocandin-resistant strains), *Aspergillus* species (including azole-resistant strains) and rare molds such as *Fusarium* and *Scedosporium* species. Research targeting *A. fumigatus* have

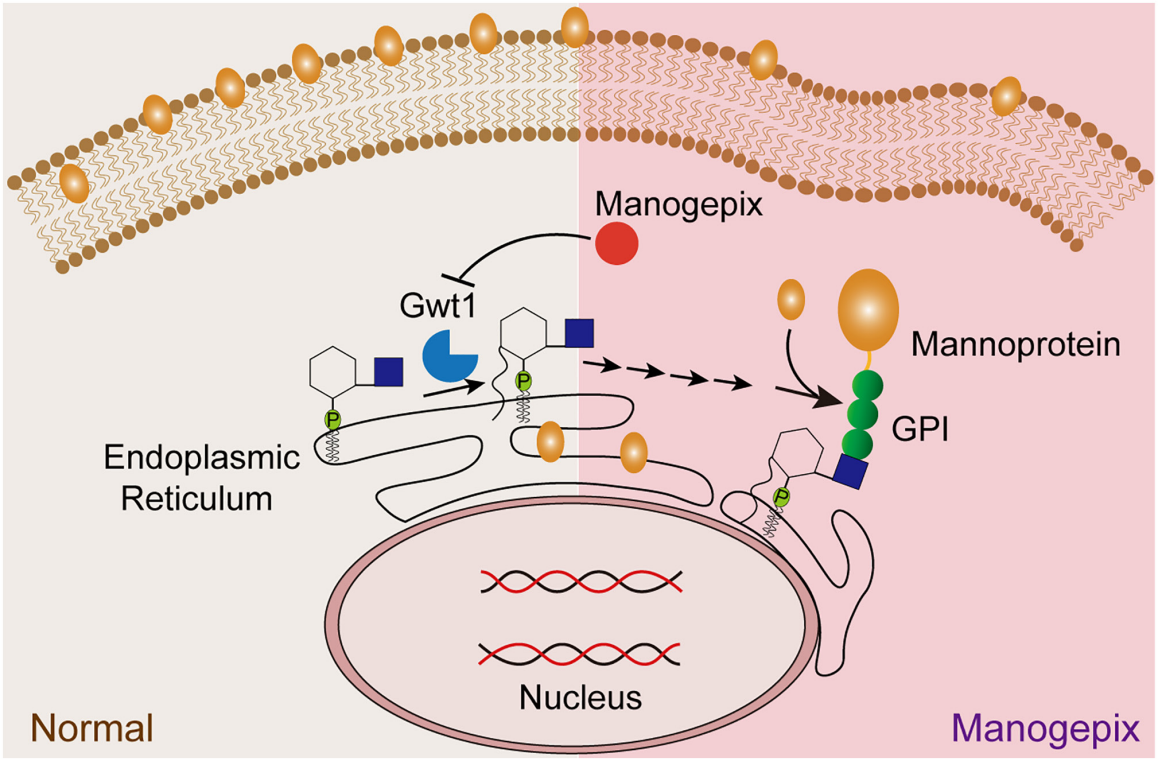

Figure 3. Mechanism of action of manogepix in fungi. Manogepix inhibits fungal Gwt1, an evolutionarily conserved inositol acyltransferase embedded in the ER membrane that catalyzes the early inositol acylation step in GPI anchor biosynthesis. Using palmitoyl-CoA as the acyl donor, Gwt1 catalyzes palmitoylation at the 2-position of the inositol ring of GlcN-PI, an essential step for GPI anchor maturation and proper anchoring of mannoproteins to the cell wall. By blocking this reaction, manogepix disrupts GPI anchor biosynthesis, impairs mannoprotein transport to the cell wall, and ultimately inhibits cell wall synthesis, leading to fungal cell death. GWT1, GPI-anchored wall transfer protein 1; ER, endoplasmic reticulum; GPI, glycosylphosphatidylinositol; GlcN-PI, glucosaminylphosphatidylinositol.

shown that manogepix sensitivity is inversely associated with *GWT1* expression and overexpression of *GWT1* leads to resistance to manogepix (32,33). Manogepix activates the cell wall integrity stress pathway but only occasionally induces cell lysis (33). Deletion of *WSC1* or *RHO4* causes only a mild increase in susceptibility, whereas deletion of *RHO2* or *MIDA* leads to improved growth under drug exposure and failure to properly upregulate cell wall chitin (33). These results suggest that Rho2-dependent cell wall remodeling plays a notable regulatory role in the antifungal activity of manogepix against *A. fumigatus*.

Impact of manogepix on biofilms and virulence factors. Fungal biofilms are complex aggregates formed when microbial cells adhere to biological or non-biological surfaces and secrete an extracellular matrix composed of polysaccharides, proteins, nucleic acids and lipids. This matrix provides mechanical stability and enhances resistance to antifungal agents (34). By inhibiting GPI anchor biosynthesis, manogepix affects multiple virulence-related phenotypes. At concentrations above its minimum inhibitory concentration (MIC), manogepix (E1210) inhibits *C. albicans* hyphal formation, adhesion to polystyrene surfaces and biofilm formation (35). In a murine model of oral candidiasis, oral administration of manogepix at 2.5, 5 and 10 mg/kg reduced viable fungal counts in a dose-dependent manner. Moreover, treated *C. albicans* cells showed notably lower expression of the GPI-anchored protein Als1 on their surface compared with untreated controls, confirming that manogepix inhibits GPI biosynthesis (28).

A 2025 study using the Calgary biofilm device assessed the activity of manogepix against mature *Candida* biofilms (35). The MIC for all tested strains, including *C. albicans*, *C. auris* and *Candida glabrata* (*C. glabrata*), was ≤2 µg/ml for planktonic cells; however, biofilm-related parameters were markedly higher (35). The MIC, minimum fungicidal concentration (MFC), minimum biofilm eradication concentration (MBEC) and minimum biofilm disruption concentration were 2- to 4,119-fold higher than those for planktonic cells (35). Among the various drugs tested, manogepix exhibited the lowest geometric mean MBEC (5.9 µg/ml) for *Candida* species (35). This demonstrates the highest anti-biofilm activity; however, activity varied among species: *C. auris* and *C. glabrata* biofilms required notably higher eradication concentrations than *C. albicans*, with manogepix being less effective against *C. auris* clade IV strains.

GWT1 mutations conferring resistance to manogepix. Similar to other antifungal drugs, fungi can reduce their sensitivity to manogepix through multiple mechanisms. Mutations in the target gene *GWT1* represent one of the core resistance mechanisms. A systematic evaluation of spontaneous resistance mutation frequencies in various *Candida* species revealed relatively low values: In *C. albicans*, *C. glabrata*, and *Candida parapsilosis* (*C. parapsilosis*), frequencies ranged from $<1.85\text{x}10^{-8}$ to $3\text{x}10^{-8}$, indicating a low inherent potential for

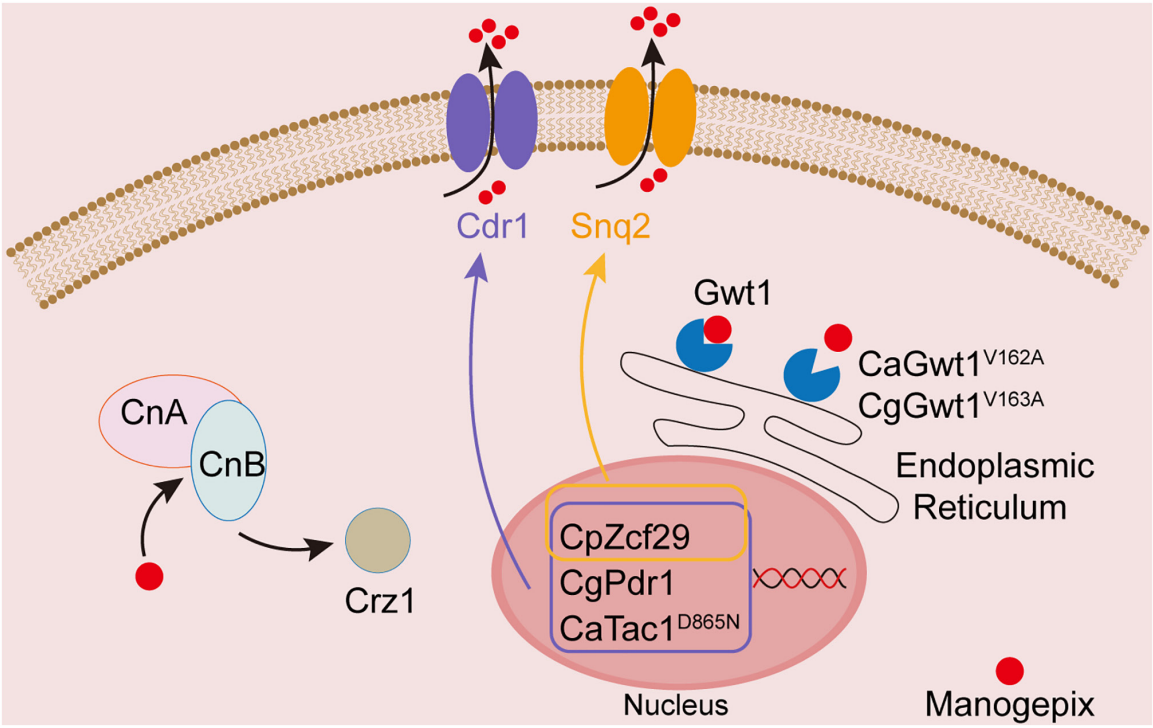

Figure 4. Resistance mechanisms of manogepix. GWT1 target mutations: Missense mutations (for example V162A/V163A) alter the drug-binding pocket conformation, reducing manogepix affinity for Gwt1 and conferring resistance. Efflux pump overexpression: Gain-of-function mutations in transcription factors (Zcf29 in *C. albicans*, Tac1 in *C. auris*, and Pdr1 in *C. glabrata*) upregulate ABC or MFS transporters (Cdr1, Cdr11, and Mdr1), enhancing drug efflux and decreasing intracellular accumulation. Calcium signaling activation: Calcineurin-dependent stress response serves as an essential tolerance mechanism to manogepix by activating cell wall repair pathways. GWT1, GPI-anchored wall transfer protein 1; GPI, glycosylphosphatidylinositol; Zcf29, zinc cluster transcription factor 29; *C. albicans*, *Candida albicans*; Tac1, transcriptional activator of CDR genes; *C. auris*, *Candida auris*; Pdr1, pleiotropic drug resistance 1; *C. glabrata*, *Candida glabrata*; ABC, ATP-binding cassette; MFS, major facilitator superfamily; Cdr1, *Candida* drug resistance 1; Cdr11, *Candida* drug resistance 11; Mdr1, multidrug resistance 1.

resistance development (Fig. 4) (36). Whole-genome sequencing identified key mutations in the Gwt1 of resistant isolates; for example, *C. glabrata* acquired a V163A mutation, while *C. albicans* developed the corresponding heterozygous V162A mutation. CRISPR-based validation experiments confirmed that these mutants had markedly reduced sensitivity to manogepix and the MIC for the V163A mutant was 16-fold higher than that for the wild-type strain. This suggests that the valine residue at this position is a notable binding site for manogepix across different fungal species. Cryo-electron microscopy of the *S. cerevisiae* Gwt1-manogepix complex (at 3.5 Å resolution) provided structural insights into these resistance mutations (37). Manogepix occupies the hydrophobic cavity of the palmitoyl-CoA binding site and competes with the endogenous substrate for binding. Key residues in the TM4-TM5 loop region of Gwt1 are involved in substrate recognition and catalysis. These residues play a notable role in drug binding. Missense mutations in this region (such as V162A/V163A) can alter the conformation of the drug-binding cavity, thereby weakening the affinity between manogepix and Gwt1. Collectively, these studies systematically reveal the molecular mechanisms underlying manogepix resistance mediated by target gene mutations. They integrate genetic, molecular biology and structural biology perspectives. In addition, these studies provide a theoretical foundation for the future development of next-generation Gwt1 inhibitors capable of overcoming such resistance (37).

Role of efflux pumps in manogepix resistance. In addition to *GWT1* target mutations, overexpression of drug efflux pumps represents another central mechanism underlying *Candida* resistance to manogepix (Fig. 4). This mechanism exhibits species-specific differences rather than universal conservation across Candida species. In *C. albicans*, gain-of-function mutations in the transcription factor *ZCF29* were shown to activate expression of the ABC transporter genes *CDR11* and *SNQ2*, reducing manogepix susceptibility (38). In *C. parapsilosis*, mitochondrial deficiency was found to induce upregulation of the MFS transporter gene *MDR1*, indicating that this species employs a distinct pump type and regulatory network for efflux-mediated evasion (38). In *C.* auris, the D865N mutation in *TAC1b* was shown to upregulate the ABC transporter *CDR1*, as demonstrated by *in vitro* induction combined with CRISPR-Cas9 gene editing (39). In *C. glabrata*, gain-of-function mutations in *PDR1* were demonstrated to decrease manogepix sensitivity through ABC transporter-dependent pathways, particularly *CDR1* (40). These findings indicate that different *Candida* species can achieve efflux-mediated evasion of manogepix through divergent transcriptional regulatory networks and distinct pump types.

These studies have also revealed marked cross-resistance between pump-mediated manogepix resistance and azole antifungals. Gain-of-function mutations in *TAC1B* of *C. auris*, *TAC1* of *C. albicans* and *C. parapsilosis*, and *PDR1* of *C. glabrata* were all shown to reduce manogepix sensitivity

through ABC transporter-dependent pathways, indicating a potential cross-resistance risk between fluconazole-resistant clinical isolates and manogepix (40). The MIC elevations currently attributed to efflux pump overexpression are relatively modest, typically 2- to 4-fold. However, multidrug-resistant clinical isolates often harbor multiple concurrent resistance mechanisms, and efflux pump inhibitors hold potential clinical utility as synergistic agents. Therefore, pump-mediated resistance remains a non-negligible challenge for the clinical use of manogepix and warrants focused attention in resistance surveillance and combination therapy strategies.

Calcium signaling in manogepix resistance. The calcium signaling pathway, particularly the calcineurin signaling cascade, plays a central regulatory role in fungal adaptation to cell wall integrity damage and antifungal drug tolerance (41). Manogepix inhibits Gwt1, blocking GPI-anchored protein maturation and impairing mannoprotein trafficking to the cell wall. This triggers ER stress and cell wall integrity defects (31). In response, fungi activate conserved stress pathways, including protein kinase C, the high-osmolarity glycerol response, and the Ca^{2+}-calcineurin cascade, which facilitate adaptive repair. Calcineurin, a serine/threonine phosphatase, regulates cell wall repair gene expression by dephosphorylating the transcription factor Crz1, thereby mediating tolerance to cell wall-targeting agents (Fig. 4) (42). Chemical-genetic screening has shown that calcineurin signaling is essential for fungal tolerance to manogepix and represents a core resistance mechanism against GPI anchor pathway inhibition. Notable negative chemical-genetic interactions were observed between the calcineurin inhibitor FK506 and 11 GPI anchor biosynthetic genes and combining FK506 with manogepix markedly enhanced fungicidal activity.

However, excessive activation of calcium signaling may also drive resistance. Manogepix, as a chemical stressor, can pre-activate calcineurin, increasing the tolerance and persistence of *C. glabrata* to echinocandins. Thus, manogepix exposure may induce cross-tolerance to other antifungals via a calcineurin-dependent mechanism. This illustrates the dual role of calcium signaling in manogepix resistance; it is both an essential stress-response pathway for fungal survival and a mediator of cross-protection against drug resistance (43). Although calcineurin inhibitors alone may raise the risk of IFIs due to immunosuppression, their combination with fosmanogepix could leverage calcium signal blockade to enhance antifungal activity. This combination may also offset the infection risk, as manogepix treatment exposes immunostimulatory glucan components that potentially counterbalance immunosuppression. Together, these findings support a mechanism-based combinatorial strategy to overcome drug-resistant fungal infections (31).

5. Antifungal efficacy of manogepix

In vitro antifungal activity of manogepix. As a novel agent targeting the GPI anchor biosynthetic pathway, manogepix exhibits a distinctive spectrum of antifungal activity against a broad range of pathogenic fungi (Table I) (20,21,44-46). Extensive *in vitro* studies have consistently confirmed its potent and broad-spectrum activity against susceptible clinical isolates. For *C. albicans* tested by CLSI M27 broth microdilution, manogepix $MIC_{50}/_{90}$ values were 0.004/0.008 μg/ml, compared with fluconazole $MIC_{50}/_{90}$ of 0.12/0.25 μg/ml (21,47-52). For *Aspergillus* species, the $MEC_{50}/_{90}$ values were reported to be 0.015/0.03 μg/ml. For *C. neoformans*, the $MIC_{50}/_{90}$ values ranged from 0.25-0.5/1-2 μg/ml (53,54). In the 2020-2021 SENTRY global surveillance program, manogepix retained high activity against 2,810 invasive fungal isolates derived from bloodstream infections, pneumonia, and skin/soft tissue infections (55). Notably, the *in vitro* activity of manogepix against clinically uncommon yeasts, including *C. auris*, *Saprochaete clavata*, and *Rhodotorula* species Manogepix also shows activity against rare and refractory molds such as *Scedosporium* species, *Lomentospora prolificans* (*L. prolificans*) and *Fusarium* species. It further demonstrates favorable inhibition of challenging pathogens such as *Paecilomyces* species and *Magnusiomyces capitatus* (52,56).

Notably, manogepix retains marked activity against multidrug-resistant clinical and environmental isolates. Against fluconazole-, amphotericin B-, echinocandin- and even pan-resistant clinical and environmental isolates of *C. auris*, manogepix exhibited MIC values ranging from 0.002 to 0.06 μg/ml (21,36,45,57,58). Potent activity is also maintained against multidrug-resistant and pan-resistant *C. auris* strains isolated during the New York outbreak (59,60). Regarding resistant *Aspergillus* isolates, surveillance data from ten tertiary hospitals in China during 2019-2024 demonstrated that manogepix remains effective against triazole-resistant clinical *Aspergillus* isolates (61). For azole-resistant and amphotericin B non-wild-type cryptic species within *Aspergillus terreus*, the MEC_{90} was only 0.125 μg/ml (21). Complete activity is preserved against clinical *Aspergillus* isolates harboring *CYP51A* mutations such as TR34/L98H and TR46/Y121F/T289A (62). Moreover, azole-resistant *A. fumigatus* from environmental sources in Denmark carry the same resistance mutations as clinical strains, yet manogepix retains full activity against these isolates, indicating that environmental-clinical cross-resistance does not affect this agent (63), however, the antifungal spectrum of manogepix is not all-encompassing. Activity against Mucorales fungi is relatively limited, with MIC/MEC values for *Rhizopus arrhizus* and *Cunninghamella bertholletiae* frequently exceeding 4 μg/ml, suggesting that manogepix is unsuitable as monotherapy for mucormycosis. Although hyphal morphological alterations can be observed in certain inherently resistant rare molds such as *L. prolificans* and some *Fusarium* species, the concentrations required for complete inhibition are relatively high (64,65).

In vivo antifungal activity of manogepix. Extensive preclinical studies have consistently demonstrated that fosmanogepix has notable *in vivo* antifungal activity against susceptible isolates (Table II) (22,66-71). Oral E1210 demonstrated dose-dependent efficacy in murine models of disseminated candidiasis, invasive pulmonary aspergillosis, and disseminated fusariosis, notably improving survival. It was effective against both *A. flavus* and *A. fumigatus* pulmonary infections, and notably against disseminated fusariosis caused by *Fusarium solani*, an infection refractory to numerous antifungals (22).

Table I. Summary of the *in vitro* activity of fosmanogepix against fungi.

Organism (of strains)	Method	MIC_{50}/MEC_{50} (μg/ml)	MIC_{90}/MEC_{90} (μg/ml)	(Refs.)
C. albicans (1425)	CLSI	0.004-0.015	0.008-0.016	(47-52)
C. albicans (641)	EUCAST	0.008	0.016	(45,46,51)
C. auris (938)	CLSI	0.002-0.016	0.008-0.125	(21,46,52,57,59,60,66,87)
C. auris (122)	EUCAST	0.016	0.03	(46)
C. neoformans (208)	CLSI	0.25	0.5	(48,52)
C. glabrata (1103)	CLSI	0.03-0.06	0.008-0.25	(21,47,48,50-52)
C. glabrata (287)	EUCAST	0.06-0.12	0.002-0.25	(45,46,51)
A. fumigatus (680)	CLSI	0.015	0.03-0.06	(21,48,52,88)
A. fumigatus (121)	EUCAST	nt	0.06	(62)
F. solani (34)	CLSI	0.016	0.03-0.06	(52,58)
F. oxysporum (33)	CLSI	0.03	0.25-16	(52,56,58)
F. verticilloides (10)	CLSI	nt	16	(56)
L. prolificans (29)	CLSI	0.03	0.06	(52,56)
M. circinelloides (18)	CLSI	2	8	(52,56)
S. apiospermum (76)	CLSI	0.03	0.0.3-16	(21,52,56)
S.aurantiacum (24)	CLSI	0.03	0.03-0.06	(21,52,56)
S. boydii (14)	CLSI	0.03	0.03-0.12	(21,56)

MIC_{50}, minimum inhibitory concentration inhibiting 50% of isolates; MEC_{50}, minimum effective concentration inhibiting 50% of isolates; MIC_{90}, minimum inhibitory concentration inhibiting 90% of isolates; MEC_{90}, minimum effective concentration inhibiting 90% of isolates; *C. albicans*, *Candida albicans*; CLSI, Clinical and Laboratory Standards Institute; *C. auris*, *Candida auris*; *C. neoformans*, *Cryptococcus neoformans*; *C. glabrata*, *Candida glabrata*; EUCAST, European Committee on Antimicrobial Susceptibility Testing; *A. fumigatus*, *Aspergillus fumigatus*; nt, not tested; *F. solani*, *Fusarium solani*; *F. oxysporum*, *Fusarium oxysporum*; *F. verticillioides*, *Fusarium verticillioides*; *L. prolificans*, *Lomentospora prolificans*; *M. circinelloides*, *Mucor circinelloides*; *S. apiospermum*, *Scedosporium apiospermum*; *S. aurantiacum*, *Scedosporium aurantiacum*; *S. boydii*, *Scedosporium boydii*.

In neutropenic mice with disseminated infection caused by fluconazole-resistant *C. auris*, delayed fosmanogepix therapy (104-260 mg/kg) initiated 24 h post-infection notably improved survival in all dose groups compared with controls. The highest dose (260 mg/kg twice daily) achieved reductions in renal and cerebral fungal burden (66,67). In a rabbit non-neutropenic model, fosmanogepix was effective against *C. albicans* endophthalmitis and hematogenous meningoencephalitis; intraocular and central nervous system drug concentrations were positively associated with fungal clearance, underscoring its effective tissue penetration. For cryptococcal meningitis, fosmanogepix monotherapy reduced cerebral fungal load in mice, but combination with fluconazole produced improved outcomes (54). Fosmanogepix reduced pulmonary fungal burden by 4.2-7.6 log conidial equivalents/g in immunosuppressed murine models of invasive pulmonary aspergillosis, improving survival with efficacy comparable to posaconazole (68); in a murine model of coccidioidal pneumonia, it reduced lung fungal burden and prevented splenic dissemination to an extent comparable to fluconazole and moreover prolonged survival longer than fluconazole after treatment cessation (69).

Fosmanogepix maintains *in vivo* efficacy against clinical and environmental isolates of drug-resistant fungi, and its activity is not constrained by existing resistance mechanisms. Against azole-resistant *A. fumigatus* (including clinical and environmental isolates with *CYP51A* mutations), fosmanogepix performed well against susceptible strains, confirming that azole resistance does not affect its therapeutic efficacy (20). The drug was also effective against disseminated fusariosis and invasive pulmonary scedosporiosis in immunosuppressed mice, extending median survival from 7 to 10-13 days and reducing fungal burden in lungs, kidneys and brain, efficacy comparable to that of clinically dosed liposomal amphotericin B (10-15 mg/kg) (70). In pulmonary mucormycosis caused by *Rhizopus arrhizus* (*R. arrhizus*), fosmanogepix markedly reduced fungal burden in the lungs and brain by 1-2 log conidial equivalents per gram of tissue, improved survival, and showed efficacy comparable to clinically relevant doses of isavuconazole (65). Notably, in delayed-treatment models of invasive pulmonary aspergillosis, mucormycosis and fusariosis, combining fosmanogepix with liposomal amphotericin B yielded markedly better outcomes than either drug alone, improving both survival and tissue fungal clearance (71).

Clinical evidence. Fosmanogepix clinical development was supported by three phase I studies (Table III). In healthy volunteers, single ascending IV doses (10-350 mg) and multiple ascending IV doses (50-600 mg daily for 14 days) showed linear, dose-proportional PK, a half-life of ~2.5 days, and accumulation; a single 350 mg dose sustained plasma levels above the MIC for *Candida* and *Aspergillus* for one week (72). A subsequent randomized, double-blind, placebo-controlled study confirmed linear PK, oral bioavailability >90%, and accumulation with multiple oral doses (500/1,000 mg daily; $AUC_{0\text{-}24}$ 192/325 μg h/ml), and a high-fat meal did not

Table II. Summary of animal efficacy models for fosmanogepix.

Infection model	Immune status	Dose	Comparator	Primary outcomes	(Refs.)
Murine invasive candidiasis (*C. auris*)	Cyclophosphamide-induced immunosuppression	200 mg/kg (day-3) and 150 mg/kg (day+1)	Untreated control	80-100% survival in all groups, significant FB reduction (1.03-1.83 $\log_{10}$ CFU/g) in kidney, lung and brain vs. untreated control	(66)
Murine invasive candidiasis (*C. auris*)	Cyclophosphamide-induced immunosuppression	150 mg/kg (day-4), 100 mg/kg (day-1) and 100 mg/kg (day+2)	Untreated control	ED50: 7.14±4.54 Stasis fAUC/MIC target: 14.67±8.30	(89)
Murine invasive candidiasis (*C. auris*)	Neutropenic	104 and 130 mg/kg (TID) or 260 mg/kg (BID) x7 days	Untreated control Fluconazole Caspofungin	Survival: Significant improvement in all fosmanogepix groups and caspofungin vs. vehicle; Fungal burden: Reduction in kidneys and brains at highest fosmanepix dose and all fosmanogepix groups; Fluconazole: No survival or fungal burden improvement	(67)
Murine invasive candidiasis (*C. albicans*)	Neutropenic	26 mg/kg APX001 + ABT, once daily	Untreated control	Kidney sterilization (APX001 + ABT) vs. 0.2 $\log_{10}$ CFU/g reduction (APX001 alone)	(90)
Murine invasive candidiasis (*C. glabrata*)	Neutropenic	26 mg/kg APX001 + ABT, once daily x2 days	Micafungin	Potent kidney burden reduction in susceptible, echinocandin-resistant, and multidrug-resistant strains; micafungin ineffective against resistant isolates	(90)
Murine invasive cryptococcosis (*C. neoformans*)	Immunocompetent	APX001A: MIC 0.004-0.5 μg/ml; APX001 + fluconazole combination	Fluconazole	Brain fungal burden: APX001 -0.78 $\log_{10}$ CFU/g; fluconazole -1.04 $\log_{10}$ CFU/g; combination -3.52 $\log_{10}$ CFU/g	(54)
Murine invasive pulmonary aspergillosis (*A. fumigatus*)	Neutropenic	81-768 mg/kg/day APX001; fractionated q3h, q6h, q8h x 96 h; 40-1,536 mg/kg q3h x 96 h (additional strains)	Untreated control	PK/PD index: AUC/MEC best correlated with efficacy (R^2=0.79); free drug AUC/MEC targets: Stasis 47.6, 1-log-kill 89.4	(91)
Murine invasive pulmonary aspergillosis (*A. fumigatus*)	Immunosuppressed (cyclophosphamide + cortisone acetate)	APX001 78 mg/kg QD, 78 mg/kg BID, or 104 mg/kg QD (with ABT 50 mg/kg)	Posaconazole	Enhanced median survival; prolonged day 21 postinfection survival; reduced lung fungal burden (4.2-7.6 $\log_{10}$ conidial equivalents/g); resolved infection on histopathology; comparable to posaconazole	(68)
Murine invasive pulmonary aspergillosis (*A. fumigatus*)	Immunosuppressed	78 mg/kg QD or 104 mg/kg QD (oral; with 50 mg/kg ABT pretreatment to extend half-life)	Posaconazole	Galactomannan reduction correlated with survival and fungal burden; dose-dependent efficacy	(92)
Pulmonary scedosporiosis	Immunosuppressed (cyclophosphamide	78 mg/kg + ABT; 104 mg/kg + ABT	Placebo; liposomal	Median survival: 7→13 days (78 mg/kg), 7→11 days	(70)

Table II. Continued.

Infection model	Immune status	Dose	Comparator	Primary outcomes	(Refs.)
(*S. apiospermum*)	+ cortisone)		amphotericin B (10-15 mg/kg)	(104 mg/kg); ~2-$\log_{10}$ reduction in lung/kidney/ brain CE; reduced abscesses on histopathology	
Hematogenously disseminated fusariosis (*F. solani*)	Immunosuppressed (cyclophosphamide + cortisone)	78 mg/kg + ABT; 104 mg/ kg + ABT	Placebo; liposomal amphotericin B (10-15 mg/kg)	Median survival: 7→12 days (78 mg/kg), 7→10 days (104 mg/kg); 2-3-$\log_{10}$ reduction in kidney/brain CE; reduced abscesses on histopathology	(70)

C. auris, *Candida auris*; FB, fungal burden; ED_{50}, 50% effective dose; fAUC/MIC, free-drug area under the concentration-time curve to minimum inhibitory concentration ratio; TID, three times daily; CFU/g, colony-forming units per gram; BID, twice daily; ABT, 1-aminobenzotriazole; *C. albicans*, *Candida albicans*; *C. glabrata*, *Candida glabrata*; *C. neoformans*, *Cryptococcus neoformans*; MIC, minimum inhibitory concentration; *A. fumigatus*, *Aspergillus fumigatus*; q3h, every 3 h; q6h, every 6 h; q8h, every 8 h; PK/PD, pharmacokinetic/pharmacodynamic; MEC, minimum effective concentration; AUC, area under the concentration-time curve; QD, once daily; *S. apiospermum*, *Scedosporium apiospermum*; CE, conidial equivalents; *F. solani*, *Fusarium solani*.

affect absorption. Both studies were well tolerated, with no dose-limiting toxicities and mostly mild, transient adverse events (AEs) (73). In a third phase I study in 21 neutropenic patients (10 IV and 11 oral; 18 PK-evaluable), 26 treatment-related AEs occurred in 9 patients (42.9%), generally mild to moderate with none serious or leading to discontinuation (nausea most common, 14.3%); one IV administration was interrupted due to chills (74).

In a multicenter, open-label, single-arm phase II study, nine intensive care unit patients with candidemia caused by *C. auris* received fosmanogepix [1,000 mg intravenously (IV) twice daily on Day 1, followed by 600 mg IV once daily]). The independent data review committee (DRC)-assessed treatment success at the end of study treatment (EOST) and Day 30 survival were both 89% (8/9), with no treatment-related AEs or study drug discontinuations. Fosmanogepix also demonstrated potent *in vitro* activity against all *C. auris* isolates (MIC range, 0.008-0.015 mg/ml), consistent with its favorable safety, tolerability, and efficacy profile in candidemia caused by *C. auris* (75). In a separate phase II clinical trial, 20 patients with candidemia received fosmanogepix as first-line treatment (1,000 mg IV twice daily on Day 1, then 600 mg IV once daily, with an optional switch to 700 mg orally once daily from Day 4). The DRC-assessed treatment success at EOST was 80% (16/20), and Day 30 survival was 85% (17/20; all three deaths were unrelated to fosmanogepix) (76).

In another phase II, open-label AEGIS study (NCT04240886), 21 patients with invasive mold diseases caused by *Aspergillus* species and rare molds were enrolled and constituted the safety population, of whom 20 comprised the modified intent-to-treat (mITT) population [mean age, 61.9 years; females, 2 (10%)]; efficacy was evaluated in this mITT population (n=20), in which the Day-42 all-cause mortality rate was 25% (80% CI, 12.7-41.5%) and the independent DRC-assessed global response success rate was 40% (80% CI, 24.9-56.7%). Safety was evaluated in the full safety population (n=21), in which a total of 258 AEs were reported, with 15 participants experiencing 36 fosmanogepix-related AEs and 2 participants experiencing 3 serious AEs; 3 participants (14.3%) discontinued study treatment due to fosmanogepix-related AEs, and 9 deaths (43%) were reported during the study (25).

Notably, two phase III registrational studies are underway: FAST-IC (NCT05421858) compares fosmanogepix with caspofungin for candidemia/invasive candidiasis, and FORWARD-IM (NCT06925321) evaluates its efficacy and safety in invasive mold infections, with completion expected in 2028. Additionally, under an expanded access program, fosmanogepix showed efficacy in coccidioidomycosis (8/11 successful cases, including six with meningitis) and in drug-resistant strains during a *Fusarium solani* meningitis outbreak in Mexico (77). Fosmanogepix has a unique mechanism (Gwt1 inhibition) and broad-spectrum activity against drug-resistant pathogens. Together, the preclinical and early clinical evidence positions it as a candidate for treatment of multidrug-resistant infection. The ongoing phase II trials will provide more robust evidence to guide its clinical use.

Combination of manogepix with other antifungal agents. Combination therapy can enhance fungicidal activity through synergistic or additive interactions among agents with distinct mechanisms of action. It also mitigates the risk of resistance emergence associated with monotherapy. Consequently, it has become an increasingly important strategy in combating multidrug-resistant fungal infections (78). Because manogepix targets Gwt1, a unique fungal enzyme, it shows considerable potential for synergy with several established antifungals (79). Checkerboard assays performed against both multidrug-resistant and susceptible isolates of *C. auris* revealed pronounced synergism between anidulafungin and manogepix [fractional inhibitory concentration index (FICI) 0.28-0.75]. Microfluidic live-cell imaging corroborated this finding, showing that the combination significantly prolonged colony doubling time and attenuated biomass accumulation. In the same study,

Table III. Summary of clinical studies of fosmanogepix.

Design	Number of patients	Type of infection	Treatment regimen	Efficacy endpoints	Safety findings	Study status	(Refs.)
Phase I (SAD and MAD, IV)	8 subjects per cohort (6 SAD, 4 MAD cohorts)	Healthy volunteers	SAD: Single IV infusion 10-350 mg; MAD: Daily IV 50, 150, 300, 600 mg x14 days	PK parameters: Linear, dose-proportional exposure; half-life ~2.5 days; accumulation observed; single 350 mg dose sustained levels >MIC for *Candida*/*Aspergillus* for 1 week; AUC_{0-24} of 245 μg·h/ml for 600 mg/day on Day 14	Commendable tolerability; no dose-limiting toxicities; majority of AEs mild/transient; headache most prevalent; 1 subject discontinued due to fluconazole	Completed	(72)
Phase I, randomized, double-blind, placebo-controlled	Cohorts of 8-10 subjects	Healthy volunteers	Single IV 200 mg; Single oral 100-500 mg; Cohort 1b: Oral 400 mg (fed/fasted); MAD: Oral 500 and 1,000 mg daily for 14 days	PK parameters: Linear, dose-proportional exposure; Half-life ~2.5 days; Oral bioavailability >90%; Accumulation observed in MAD cohorts (AUC0-24 192 and 325 μg·h/ml for 500 and 1,000 mg, respectively)	High-fat/high-calorie meal did not impact rate or extent of absorption (other specific safety findings not detailed in this section)	Completed	(73)
Phase I	21 (10 IV, 11 oral) for safety; 18 for PK	Neutropenic patients with AML undergoing remission induction chemotherapy	IV and oral administration (specific doses not provided in text)	Safety (primary endpoint); PK analysis	26 related AEs in 9 patients (42.9%); generally mild to moderate; none serious or led to discontinuation; most common AEs: Nausea (14.3%); vomiting, ALT increase, delirium (9.5% each); 1 IV cohort administration interrupted due to chills	Completed	(74)
A first phase II	9	Candidemia or invasive candidiasis caused by *C. auris*	IV fosmanogepix (all received IV only; option to switch to 800 mg orally once daily from Day 4 existed)	Treatment success at EOST and Day 30 survival (assessed by DRC): 89% (8/9)	No treatment-related adverse events; no study drug discontinuations	Completed	(75)

Table III. Continued.

Design	Number of patients	Type of infection	Treatment regimen	Efficacy endpoints	Safety findings	Study status	(Refs.)
A second phase II	20	Candidemia (first-line treatment in non-neutropenic patients	1,000 mg IV twice daily on day 1, then 600 mg daily thereafter; option to switch to oral therapy (700 mg once daily) after day 4 (total IV + oral duration for 14 days)	Success (clearance of *Candida* from blood cultures and survival to day 42): 80% (16/20); mean time to first negative blood culture: 2.4 days	One patient experienced recurrent candidemia due to *C. glabrata* 2 weeks after end of treatment (manogepix MIC increased >30-fold); one patient experienced a clinical relapse secondary to a *C. albicans* biliary infection (manogepix MIC remained the same)	Phase 2 completed	(76)
Phase II study (NCT04240886)	21	Invasive mold infections (*Aspergillus* or rare molds); 20 with probable/ proven IMI	Day 1: 1,000 mg IV (3-h infusion) BID; Days 2-3: 600 mg IV QD; Days 4-42: 600 mg IV QD or 800 mg oral QD (optional switch)	Primary: Day 42 all-cause mortality (25%; 80% CI, 12.7-41.5%); Secondary: DRC-assessed global response success at EOST (40%; 80% CI, 24.9-56.7%)	258 TEAEs reported (n=21); 36 FMGX-related TEAEs in 15 participants (71.4%); 3 SAEs in 2 participants; 3 discontinuations due to FMGX-related AEs (14.3%); 9 deaths (43%)	Completed; NCT04240886	(25)

SAD, single ascending dose; MAD, multiple ascending dose; IV, intravenous; PK, pharmacokinetic; AUC_{0-24}, area under the concentration-time curve from 0 to 24 h; MIC, minimum inhibitory concentration; AE, adverse event; *C. auris*, *Candida auris*; EOST, end of study treatment; DRC, Data Review Committee; *C. glabrata*, *Candida glabrata*; *C. albicans*, *Candida albicans*; IMI, invasive mold infection; BID, twice daily; QD, once daily; NCT, National Clinical Trial; CI, confidence interval; TEAE, treatment-emergent adverse event; FMGX, fosmanogepix; SAE, serious adverse event.

anidulafungin combined with 5-flucytosine also exhibited synergistic effects (FICI 0.36-1.02). However, the manogepix plus 5-flucytosine combination predominantly yielded partial synergism or additive effects. This underscores the necessity of tailoring combination regimens to specific drug pairings. With respect to rare pathogens, manogepix in combination with itraconazole displayed *in vitro* synergistic activity against *Madurella mycetomatis* in 70% of isolates tested. However, this combination failed to demonstrate improved survival compared with monotherapy in a *Galleria mellonella* larval infection model. This highlights the need for cautious interpretation when extrapolating *in vitro* synergy to clinical outcomes (80). Systematic evaluations of uncommon yeasts and molds from the SENTRY surveillance program have provided essential baseline data to guide combination strategies involving manogepix (52).

In vivo models have further validated the benefits of combination therapy. In delayed-treatment murine models of invasive pulmonary aspergillosis, mucormycosis, and fusariosis, fosmanogepix plus liposomal amphotericin B markedly improved survival and reduced target organ fungal burden compared with either drug alone (20,71). For mucormycosis

caused by *R. arrhizus*, adding liposomal amphotericin B to fosmanogepix further enhanced efficacy, offering an option for this lethal infection (65,81). Mechanistic complementarity between novel antifungals also holds promise. Olorofim is active against various drug-resistant molds (such as *L. prolificans*) but has limited activity against yeasts and Mucorales; fosmanogepix has broad-spectrum activity against both yeasts and molds. Their combination could therefore provide complementary coverage (78). Additionally, the effective tissue penetration of fosmanogepix, demonstrated in rabbit models of candidal endophthalmitis and central nervous system infections, provides a pharmacokinetic foundation for dose optimization and regimen design in combination approaches (82).

6. Clinical positioning of fosmanogepix

Fosmanogepix acts via a novel mechanism and avoids cross-resistance to existing antifungal classes. Its most supported application is in multidrug-resistant infections where conventional options are exhausted. Phase II data provide preliminary evidence for use in *C. auris* candidemia (89% treatment success, 8/9 patients) and invasive mold diseases caused by *Aspergillus* and rare molds (40% global response success in AEGIS) (25,75). High oral bioavailability (>90%) and seamless IV-to-oral transition from Phase I studies support its potential for oral step-down therapy, although this has not been prospectively evaluated (73). Effective distribution into the central nervous system and ocular compartments, demonstrated in rabbit models of *Candida* meningitis and endophthalmitis, suggests theoretical utility for central nervous system and intraocular infections, but clinical validation in these sites is lacking (54). Preclinical combination studies with liposomal amphotericin B or calcineurin inhibitors show synergistic/additive effects in murine models of aspergillosis, mucormycosis, and fusariosis, yet no randomized human trials have been conducted (65,79,81). Expanded-access experience in coccidioidomycosis offers anecdotal data without controlled efficacy evidence.

Despite these promising findings, definitive efficacy, optimal positioning vs. existing antifungals, and long-term safety are still unproven for all proposed clinical uses. The two ongoing Phase III trials will establish superiority, non-inferiority, or equivalence within adequately powered cohorts. FAST-IC (NCT05421858) compares fosmanogepix against caspofungin for candidemia and invasive candidiasis, and FORWARD-IM (NCT06925321) evaluates fosmanogepix relative to standard-of-care for invasive mold infections. Pending trial outcomes, fosmanogepix remains investigational. Its putative clinical roles, such as first-line treatment for multidrug-resistant infections, combination therapy for refractory disease, and oral step-down regimens, remain hypothetical and need prospective validation.

7. Conclusion

Fosmanogepix is a first-in-class antifungal agent that targets the fungal enzyme Gwt1. By blocking the maturation of GPI-anchored proteins, it disrupts cell wall integrity and avoids the cross-resistance commonly associated with existing drugs (83). The compound offers several pharmacological advantages, including high oral bioavailability (>90% in Phase I studies), a prolonged half-life (~2.5 days), and the availability of both intravenous and oral formulations. It demonstrates broad-spectrum activity against several clinically notable pathogens listed in the WHO fungal priority pathogens list. The evidence base is comparatively robust for *C. auris* and *A. fumigatus*, encompassing *in vitro* susceptibility data, animal models, and preliminary Phase II clinical trials. For *Mucorales*, *Fusarium*, *Scedosporium* and *L. prolificans*, current evidence is largely derived from *in vitro* investigations and animal models, while clinical evidence remains scarce. Both *in vitro* and *in vivo* studies consistently confirm that fosmanogepix is potent against susceptible strains as well as against multidrug-resistant clinical and environmental isolates. Combining it with liposomal amphotericin B or calcineurin inhibitors shows synergistic or additive effects in preclinical models (84).

However, several important limitations must be acknowledged. Fosmanogepix remains an investigational agent; Phase II clinical evidence is preliminary and derived from open-label, single-arm studies with small sample sizes. These studies enrolled heterogeneous patient populations with limited treatment options, and their findings may not be generalizable to broader clinical settings. The two ongoing Phase III registrational studies, FAST-IC (NCT05421858, clinicaltrials.gov/study/NCT05421858) and FORWARD-IM (NCT06925321, clinicaltrials.gov/study/NCT06925321), have not yet reported comparative efficacy or safety data. Optimal clinical positioning, resistance breakpoints, and long-term safety profiles in diverse patient populations therefore remain to be established. Additionally, the transferability of animal model data to human disease requires cautious interpretation, and publication bias cannot be excluded.

Several resistance mechanisms, however, threaten the long-term utility of fosmanogepix. These include *GWT1* target mutations (such as G387S and L432F), efflux pump overexpression driven by transcription factor mutations such as *TAC1b*, and calcineurin-mediated calcium signaling activation. Of particular concern, the agricultural fungicide aminopyrifen shares the same Gwt1 target as manogepix (85). Its widespread environmental use could accelerate resistance dissemination through One Health pathways. Future priorities should focus on advancing phase III clinical trials, developing next-generation Gwt1 inhibitors that overcome known resistance mutations, deepening mechanism-based combination therapy research, and establishing cross-sectoral resistance surveillance networks (86). These measures are essential to preserve the long-term clinical value and sustainability of this novel antifungal agent.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 32400026), the Natural Science Foundation of the Jiangsu Higher Education

Institutions of China (grant no. 24KJB180025), the Fundamental Research Funds of Taizhou University (grant no. TZXYQD2025A116).

Availability of data and materials

Not applicable.

Authors' contributions

GZ designed the scope and structure of the review, and performed structured literature searches. GZ and NZ critically synthesized and interpreted the findings. GZ, NZ, PZ and YM wrote and revised major sections of the manuscript. All authors reviewed the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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