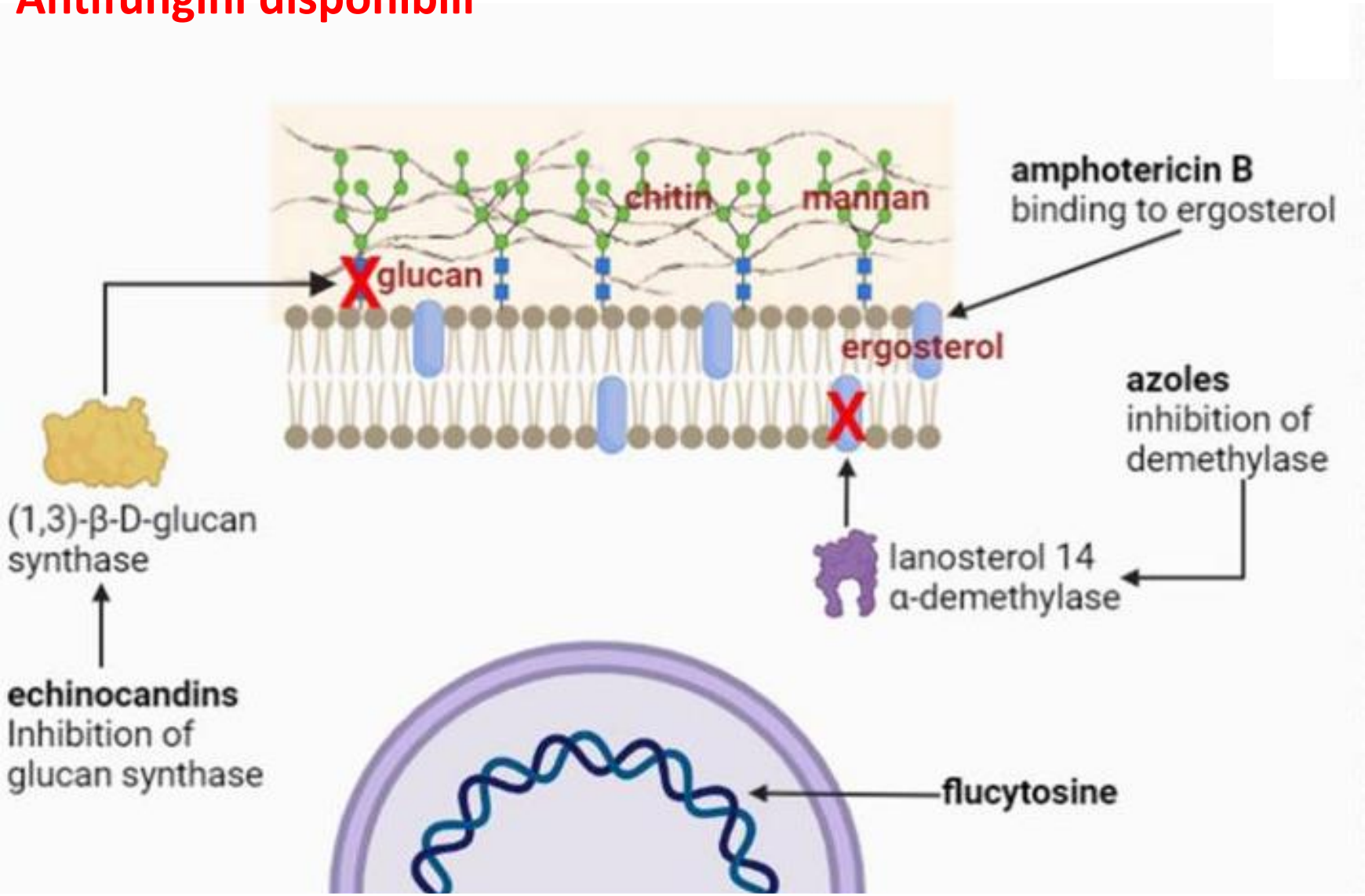
Nuove opzioni terapeutiche nelle infezioni fungine invasive

Francesco Barchiesi

Dipartimento di Scienze Biomediche
e Sanità Pubblica
Università Politecnica delle Marche Ancona

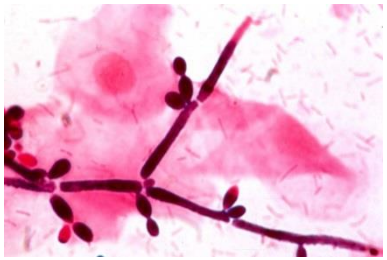
Malattie Infettive
Azienda Sanitaria Territoriale
Pesaro Urbino

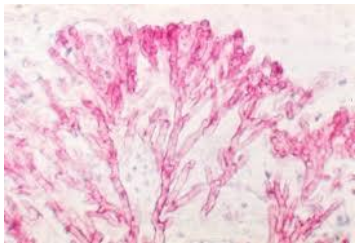
Antifungini disponibili



The best we can get ...

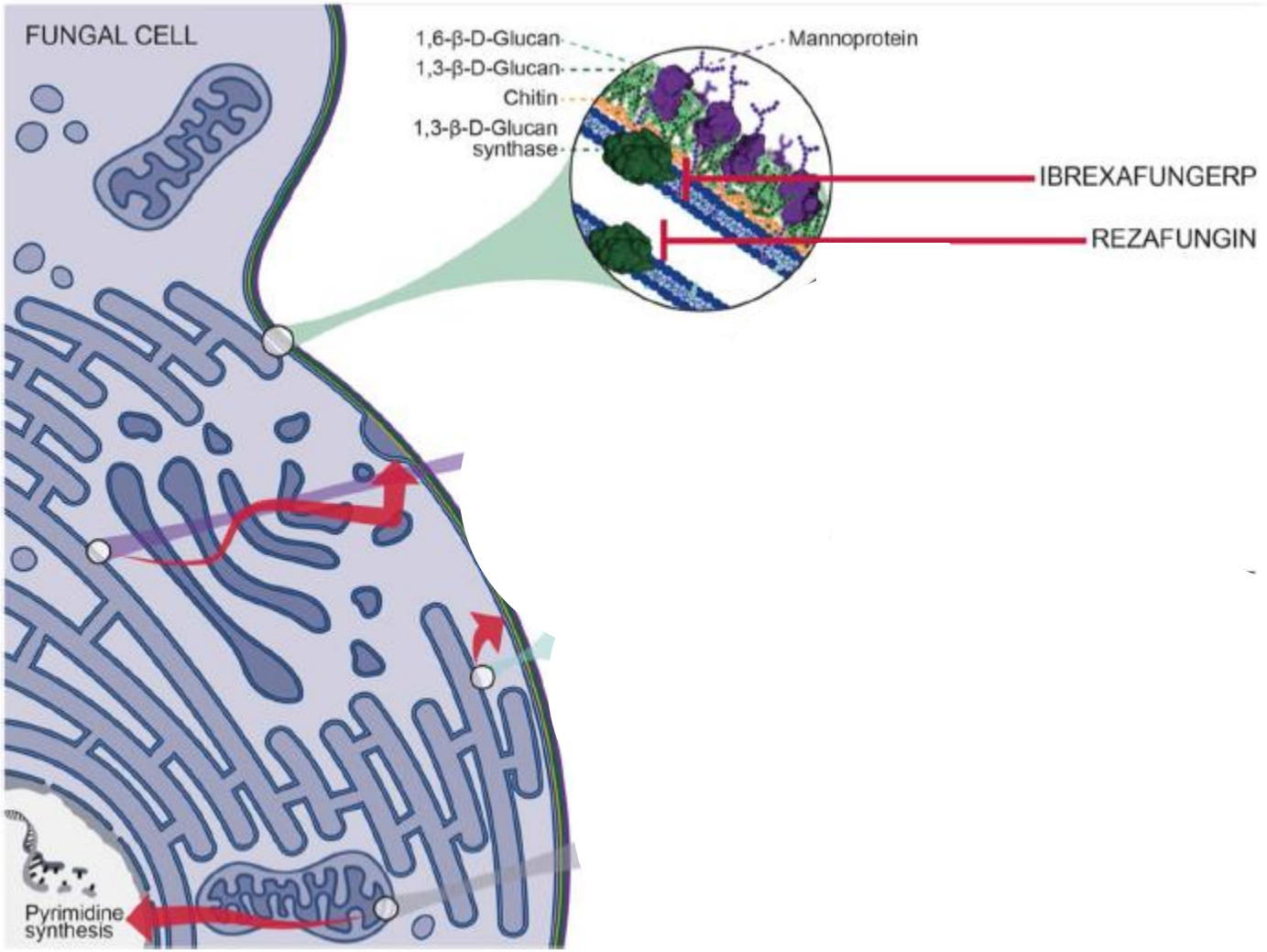
% favorable response





FLU	**60%**	**…..**
VORI	**65%**	**60%**
ISA	**…..**	**62%**
POSA	**…..**	**42%**
ANIDULA	**76%**	**…..**
CASPO	**73%**	**45%**
MICA	**76%**	**…..**
L-AmB	**70%**	**50%**

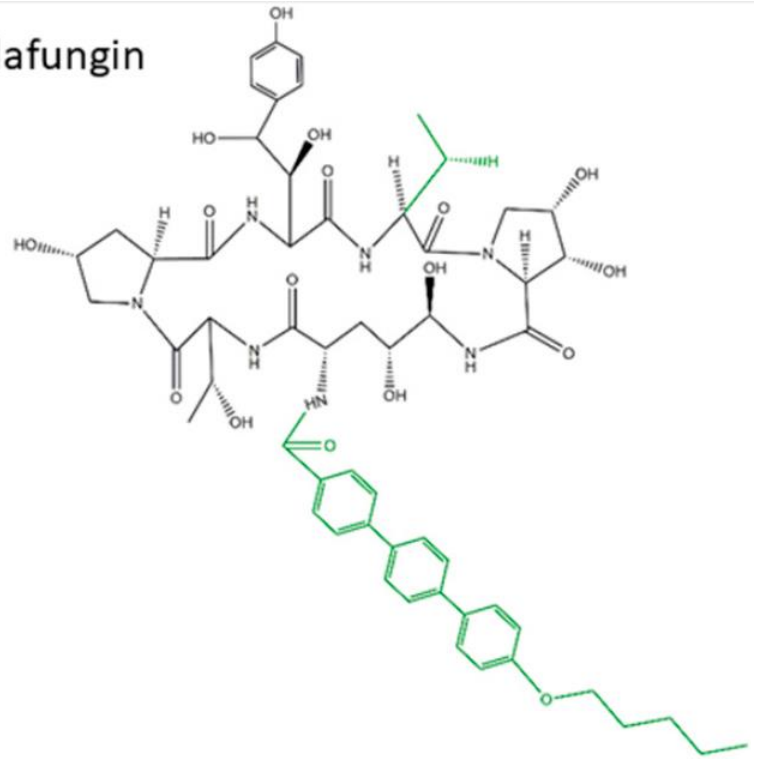
Antifungal Drugs in Clinical Development



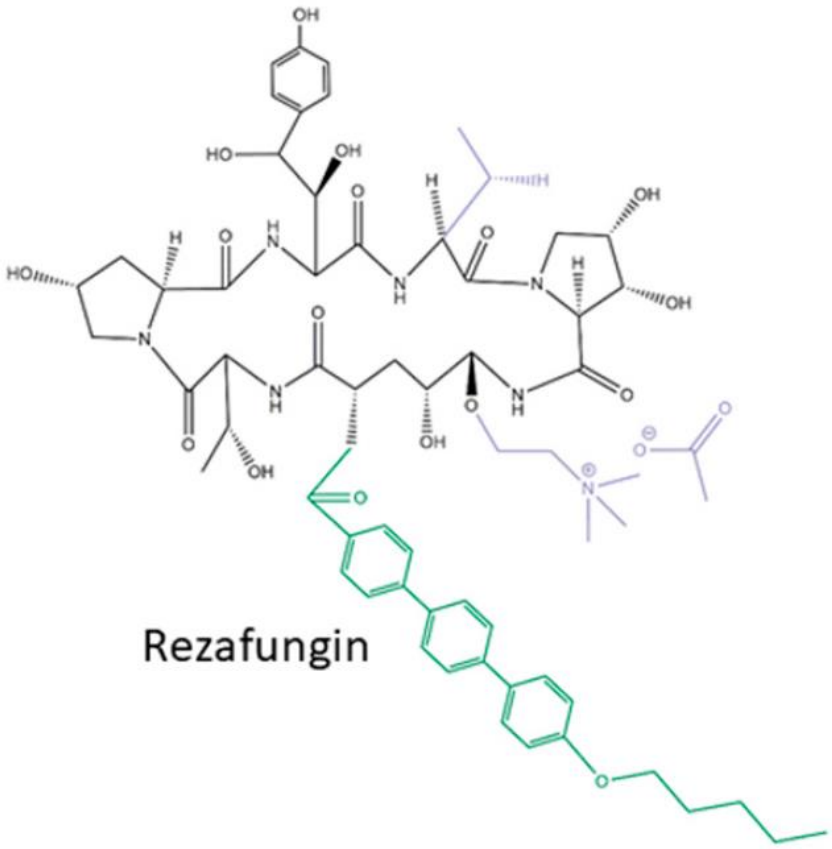
Drugs (2021) 81:1703–1729
https://doi.org/10.1007/s40265-021-01611-0

Anidulafungin vs Rezafungin

Anidulafungin



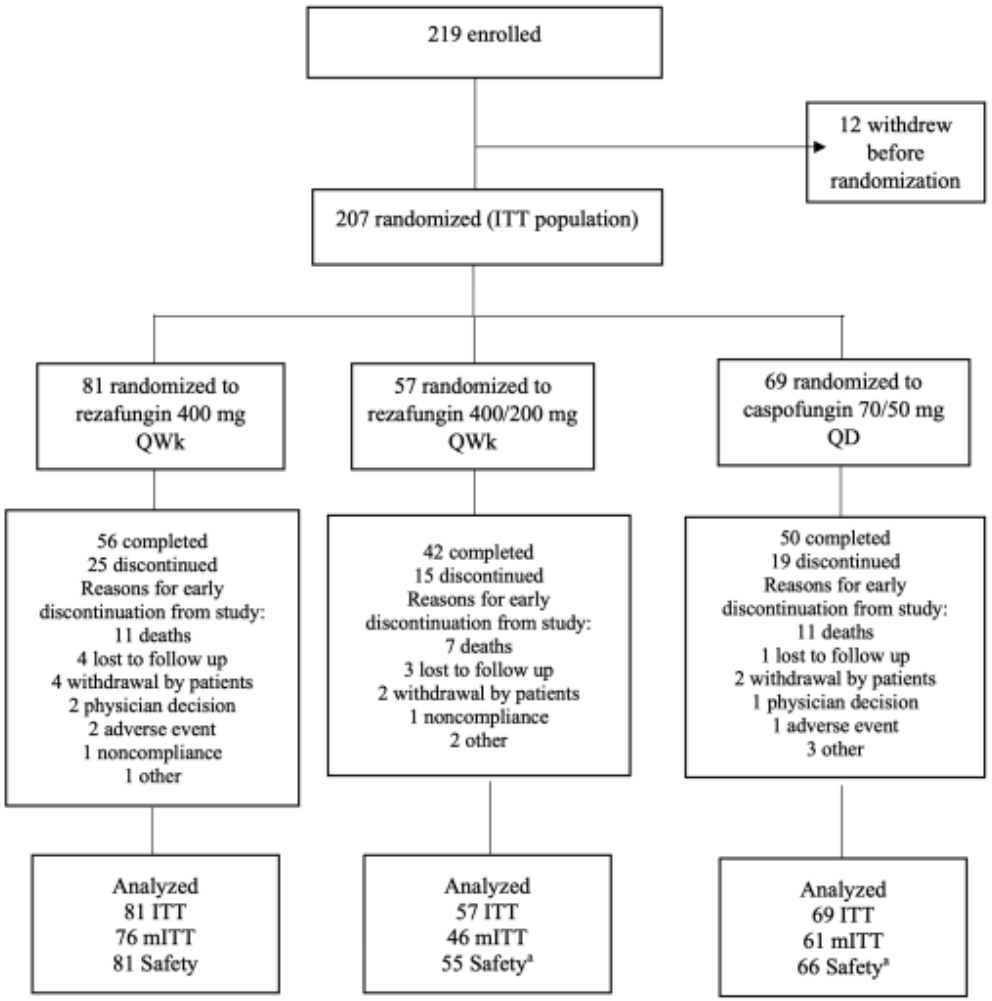
1. Greater stability
2. Prolonged half-life (≈ 130 h *vs* ≈ 24 h)

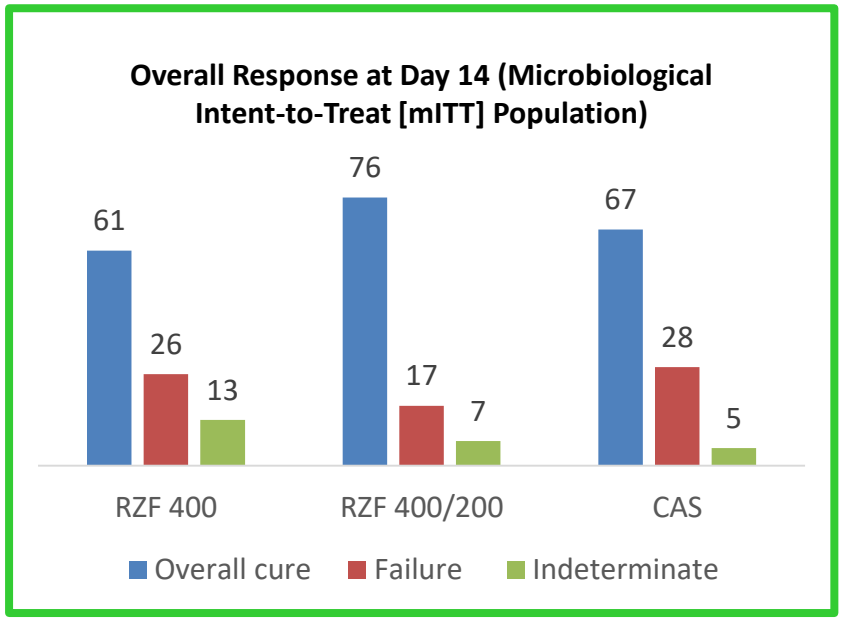


Rezafungin

J. Fungi **2022**, *8*, 857. https://doi.org/10.3390/jof8080857

Rezafungin Versus Caspofungin in a Phase 2, Randomized, Double-blind Study for the Treatment of Candidemia and Invasive Candidiasis: The STRIVE Trial





Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial

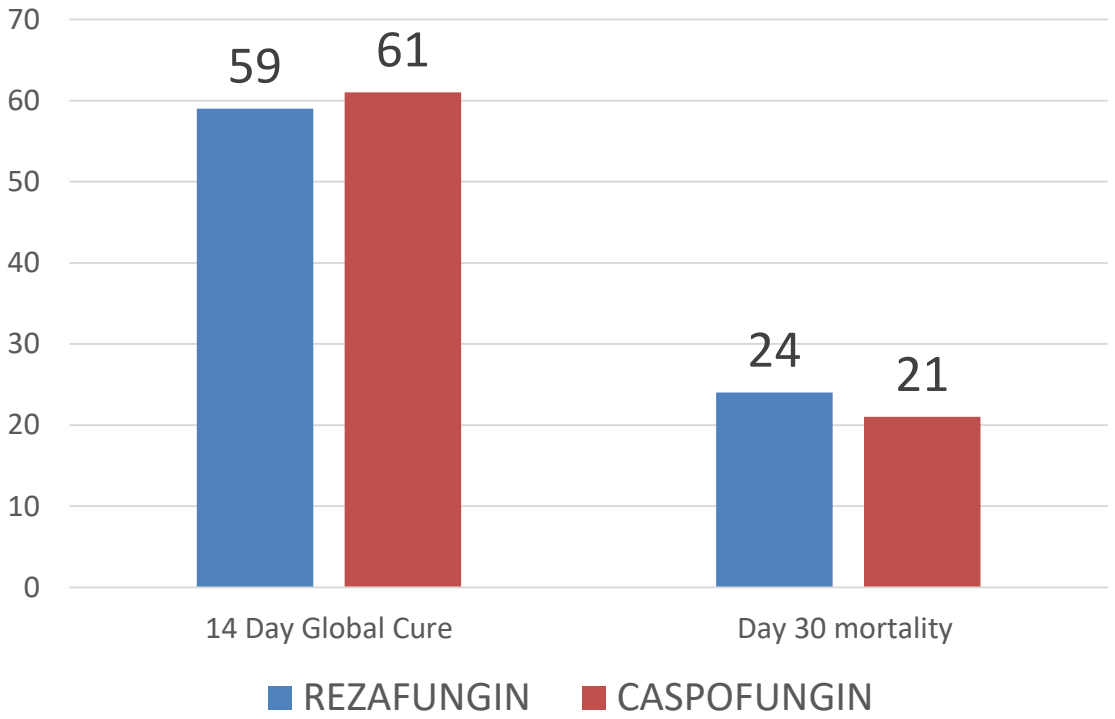
100 pts → REZA
99 pts → CAS

Primary endpoints:

- **global cure**

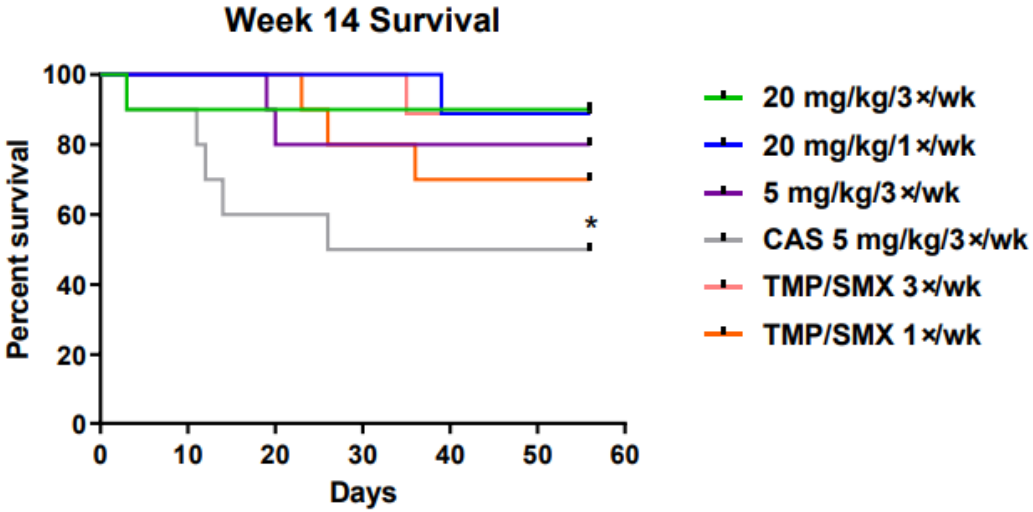
clinical cure
radiological cure
mycological eradication
} 14 days

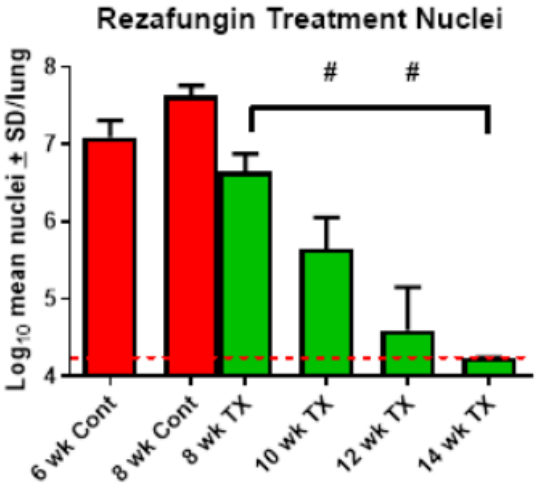
- **30-day all-cause mortality**

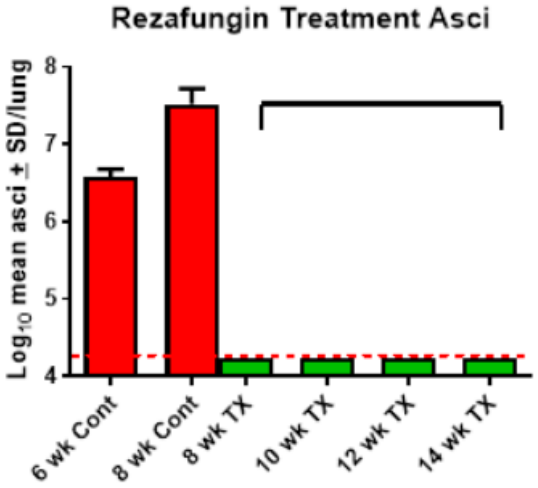


Lancet. 2023 Jan 7;401(10370):49-59.

The Long-Acting Echinocandin, Rezafungin, Prevents Pneumocystis Pneumonia and Eliminates Pneumocystis from the Lungs in Prophylaxis and Murine Treatment Models







J. Fungi **2021**, *7*, 747. https://doi.org/10.3390/jof7090747

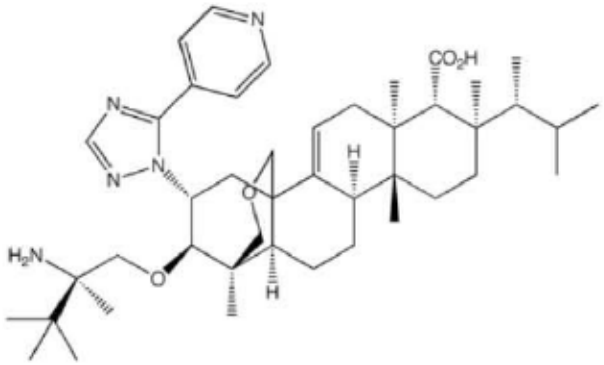
Ongoing Studies (Phase III)

ReSPECT, NCT04368559: Recruiting

- multicenter, randomized, double blind study
- RZF 400-mg/200-mg once weekly for the prevention of IFD including *Candida* spp., *Aspergillus* spp., and *P. jirovecii* in patients undergoing allogeneic blood and marrow transplantation
- active comparators: daily FLU, POS, and anti-*Pneumocystis jirovecii* prophylaxis with oral trimethoprim-sulfamethoxazole.

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Ibrexafungerp (SCY-078)



Triterpenoid - Non-competitive inhibition of 1,3-β-D-glucan synthase, depleting 1,3-β-D-glucan in cell wall
(*FKS1* and *FKS2*)

C. albicans	+
C. auris	+
C. glabrata	+
C. krusei	+
C. parapsilosis	+
C. tropicalis	+
C. gattii	–
C. neoformans	–
Rhodotorula	–
Trichosporon	–

A. flavus	+
A. fumigatus	+
A. niger	+
A. terreus	+

Blastomyces	+
Coccidioides	+
Histoplasma	+

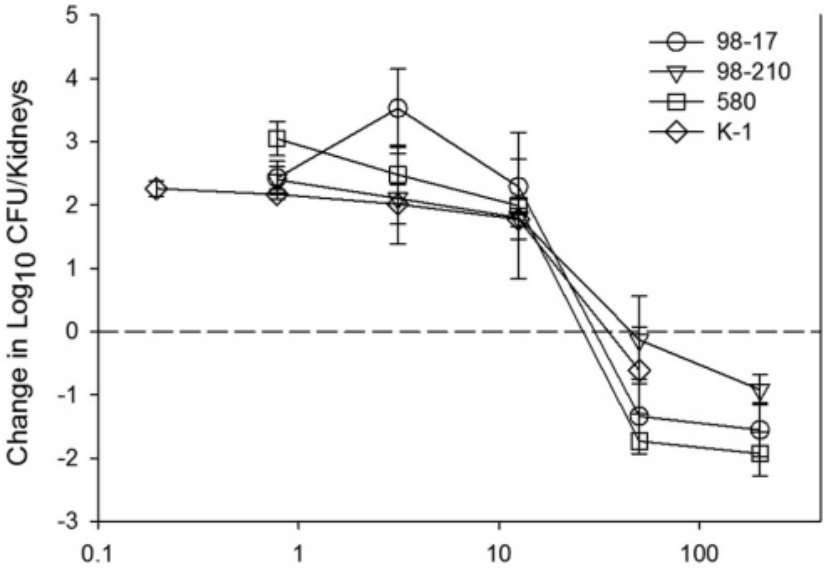
SCY-078-Ibrexafungerp (Scynexis, Inc., Jersey City, NJ, USA)

In vitro

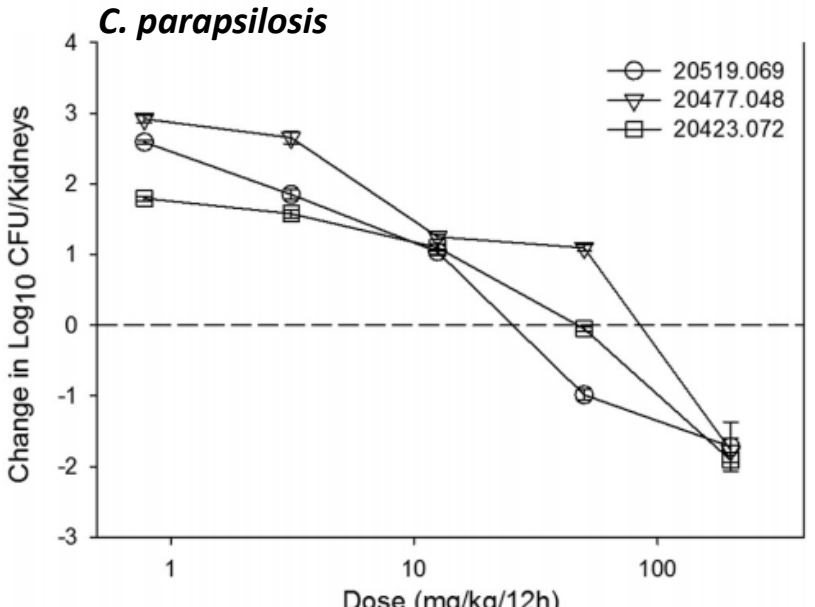
- *Candida spp.* similar to caspofungin but higher (eightfold) potency against *C. glabrata* strains
- It also retains activity against fluconazole-resistant strains and isolates harboring mutations in the hotspot of *fks1* or *fks2*
- Active *vs Aspergillus* spp.

In vivo

C. albicans



C. parapsilosis



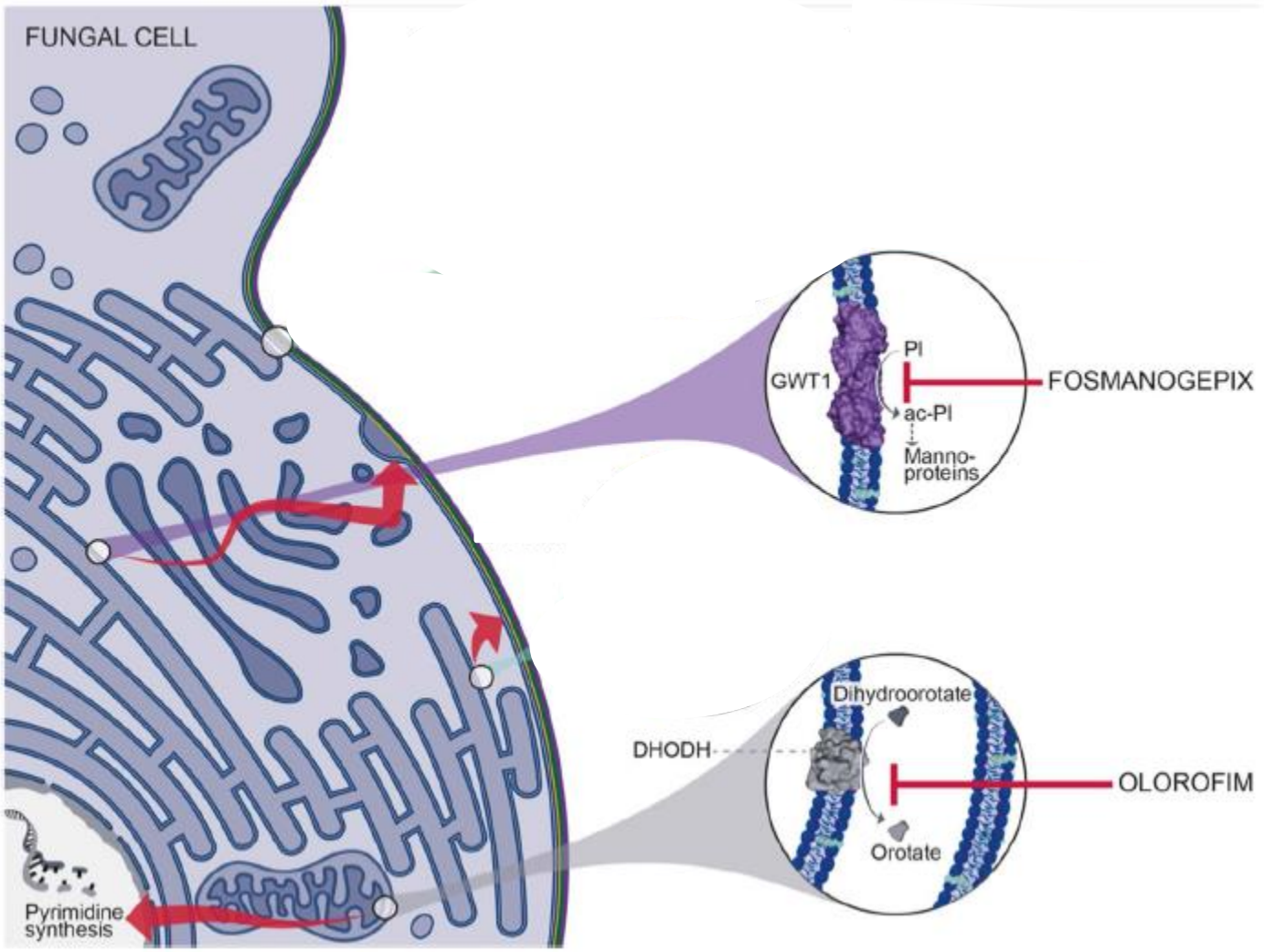
Antimicrob Agents Chemother. 2014;58(2):1248–51
Antimicrob Agents Chemother. 2011;55(11):5099–106
Antimicrob Agents Chemother. 2015;59(2):1265–72
Antimicrob Agents Chemother. 2015;59(7):4308–11.

Ongoing Studies

NCT02244606 Completed	IC; nonneutropenic adults	Phase II (randomized, open label) Arm 1: ibrexafungerp (oral) at 1000 mg (d 1), then 500 mg daily Arm 2: ibrexafungerp (oral) at 1250 mg (d 1), then 750 mg daily Arm 3: fluconazole (oral) or micafungin (intravenous)	Incidence of TEAE Dose of ibrexafungerp to assess the target AUC exposure
NCT03672292; SCYNERGIA Completed	Invasive pulmonary aspergillosis; adults	Phase II (randomized double blind) Arm 1: ibrexafungerp (oral) at 500 mg twice daily (d 1 and 2), then 500 mg daily + voriconazole (intravenous or oral) for 6–13 wk Arm 2: voriconazole (intravenous or oral) for 6–13 wk	Incidence of TEAE
NCT03059992; FURI Not recruiting	Intolerant or refractory invasive fungal infections	Phase III (open label, noncomparator, single arm) Ibrexafungerp (oral) at 750 mg twice daily for 2 d, then 750 mg daily for up to 180 d	Global response (up to 180 d)
NCT03363841; CARES Completed	*Candida auris* IC	Phase III (open label, noncomparator, single arm) Ibrexafungerp (oral) at 750 mg twice daily for 2 d, then 750 mg daily for up to 90 d	Global success at the end of therapy

NIH U.S. National Library of Medicine
ClinicalTrials.gov

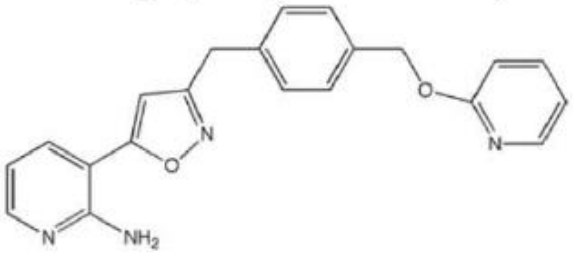
Antifungal Drugs in Clinical Development



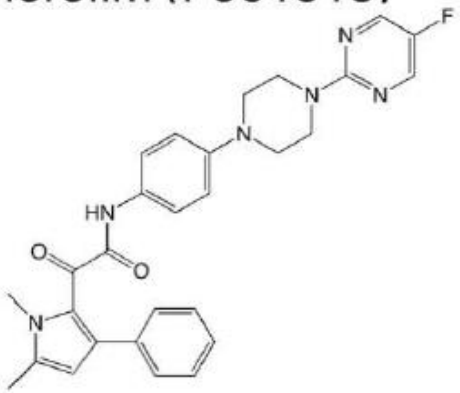
Drugs (2021) 81:1703–1729
https://doi.org/10.1007/s40265-021-01611-0

Novel Mechanisms of Action

Manogepix (APX001A)



Olorofim (F901318)



GPI-anchored proteins

- Integrity of the fungal cell wall
- Adherence and invasion of host tissues
- Hyphal growth
- Biofilm formation
- Filamentation
- Sensing the enviroment

Although mammalian cells also contain a form of this enzyme, the activity appears to be fungal specific.

(fos)manogepix

C. albicans	+
C. auris	+
C. glabrata	+
C. krusei	–
C. parapsilosis	+
C. tropicalis	+
C. gattii	+
C. neoformans	+
Rhodotorula	+
Trichosporon	+/–

A. flavus	+
A. fumigatus	+
A. niger	+
A. terreus	+
F. oxysporum	+
F. solani	+
Scedosporium	+
L. prolificans	+
Mucor	–
Rhizopus	+/–
Other Mucorales	–

Blastomyces	
Coccidioides	+
Histoplasma	

Fosmanogepix

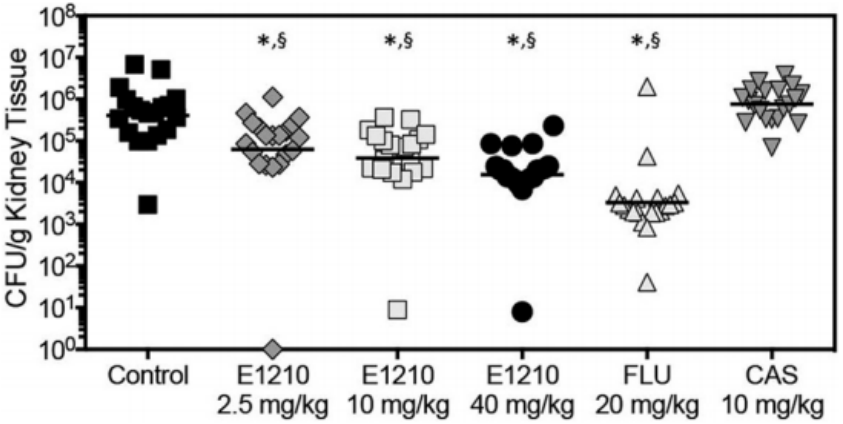
In vitro

Broad spectrum activity against:

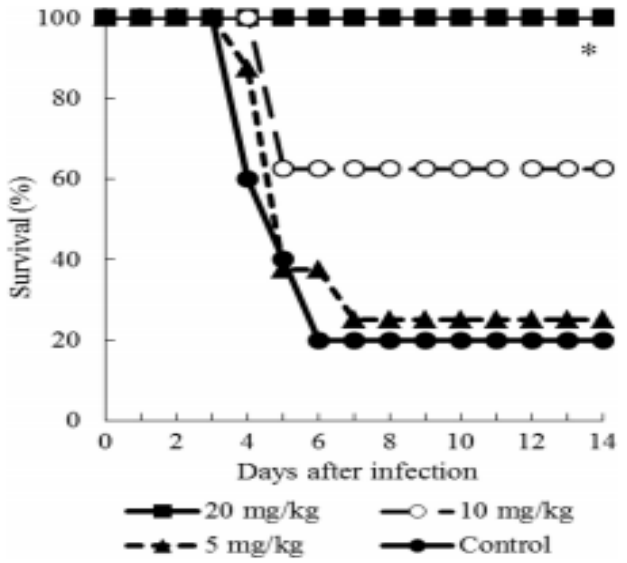
- *Candida* spp, including fluconazole resistant isolates (except for *C. kruzei*)
- *A. fumigatus, A. niger, A. flavus, A. terreus*
- *Fusarium* spp.
- *Pseudallescheria boydii*
- *L. prolificans*

In vivo

Candidosis

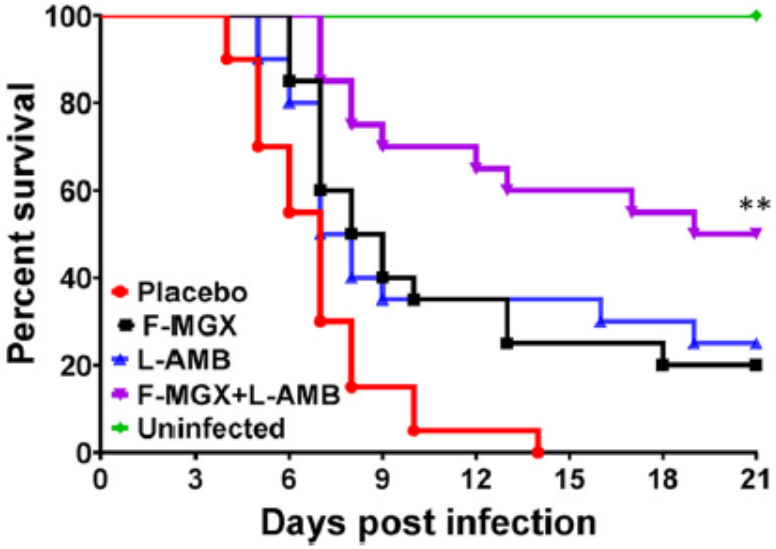


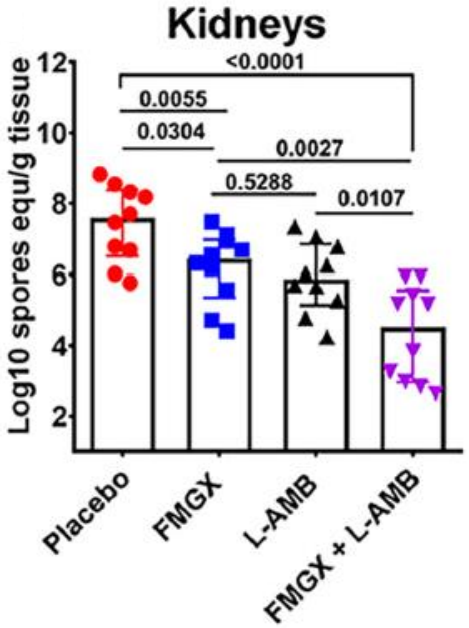
Fusariosis

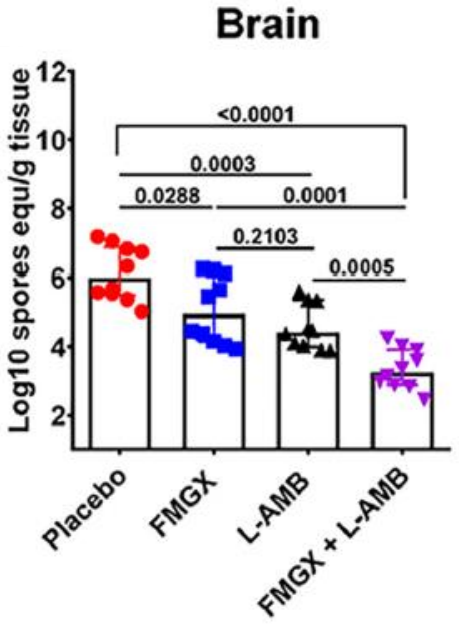


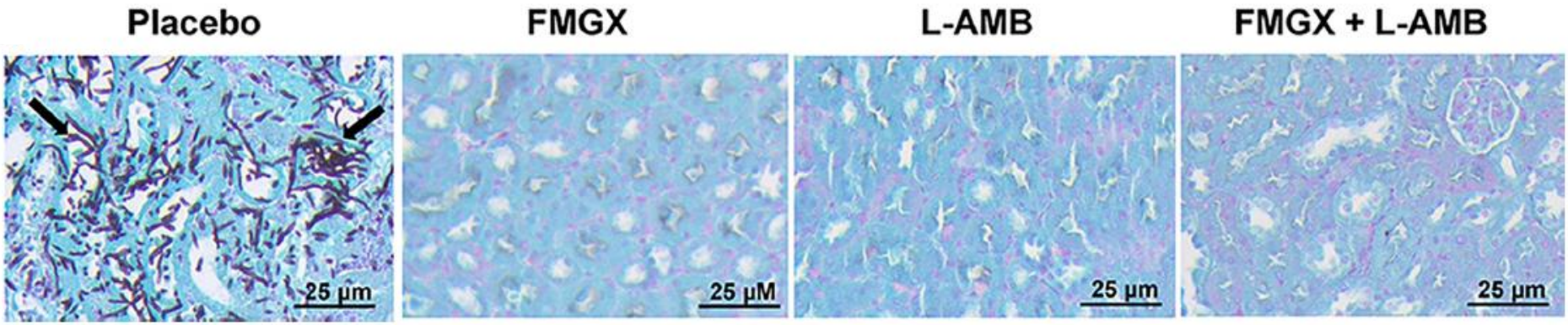
Antimicrob Agents Chemother. 2011;55:4652-8.
MMBR. 2008;72:495-544.
Antimicrob Agents Chemother. 2012;56:960-71.
Antimicrob Agents Chemother. 2011;55:5155-8.
Diagn Microbiol Infect Dis. 2011;71:167-70.
Antimicrob Agents Chemother. 2012;56:352-7.
Antimicrob Agents Chemother. 2015;59:690-2.
Antimicrob Agents Chemother. 2011;55:4543-51.

The Combination Treatment of Fosmanogepix and Liposomal Amphotericin B Is Superior to Monotherapy in Treating Experimental Invasive Mold Infections









Ongoing Studies: fosmagogepix

NCT03604705 Completed	Candidemia Nonneutropenic adults	Phase II (open label, noncomparator, single arm) Fosmanogepix (intravenous) at 1000 mg twice daily (d 1), 600 mg daily (d 2 and 3), and then 600 mg (intravenous) or 700 mg (oral) daily for up to 14 d	Global success at the end of therapy
NCT04148287; APEX Completed	*C. auris* IC; adults	Phase II (open label, noncomparator, single arm) Fosmanogepix (intravenous) at 1000 mg twice daily (d 1), 600 mg daily (d 2 and 3), and then 600 mg (intravenous) or 800 mg (oral) daily for up to 42 d	Treatment success up to 42 d
NCT04240886; AEGIS Completed	IA and other invasive mold infections; adults	Phase II (open label, noncomparator, single arm) Fosmanogepix (intravenous) at 1000 mg twice daily (d 1) and 600 daily (d 2 and 3), then 600 mg (intravenous) or 800 mg (oral) daily for up to 42 d	All-cause mortality (d 42)

NIH U.S. National Library of Medicine
ClinicalTrials.gov

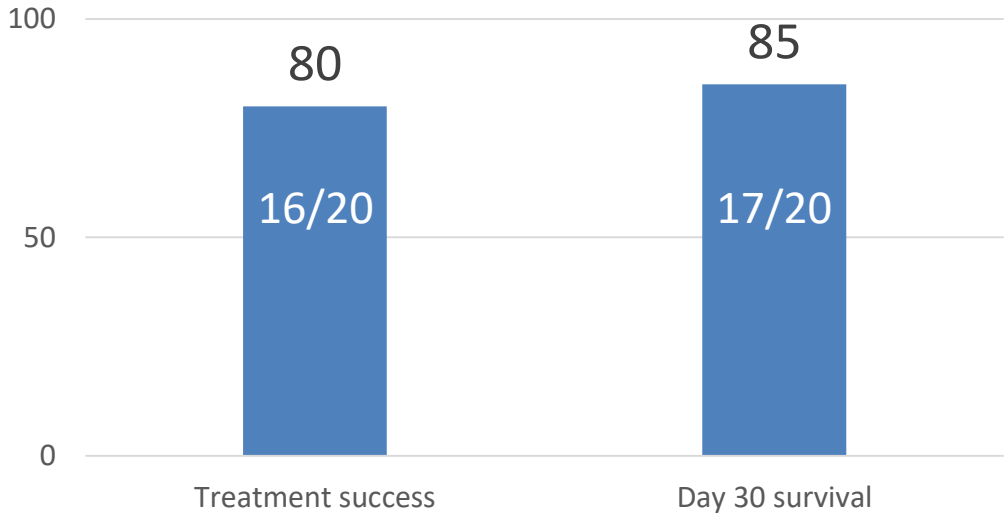
Clinical safety and efficacy of novel antifungal, fosmanogepix, for the treatment of candidaemia: results from a Phase 2 trial

Participants received fosmanogepix for 14 days:

1000 mg IV twice daily on **Day 1**

maintenance 600 mg IV once daily **Day 2**, **Day 3**

and optional switch to 700 mg orally once daily from **Day 4**



Reasons for mortality through D30:	
Gram-negative (*Acinetobacter*) sepsis (D12)	1/20
Progression of underlying cancers (D15)	1/20
Worsening of interstitial pneumonia (D30)	1/20

Success:

1. Clearance of *Candida* from blood cultures with no additional antifungal treatment
2. Survival at the EOST

J Antimicrob Chemother 2023; **78**: 2471–2480

Clinical Efficacy and Safety of a Novel Antifungal, Fosmanogepix, in Patients with Candidemia Caused by *Candida auris:* Results from a Phase 2 Trial

Endpoint	Fosmanogepix $N = 9$
Response at EOST[a]	
Treatment Success[b], *n* (%) [95% CI[c]][d]	8 (88.9) [51.8, 99.7]
Treatment Failure, *n* (%)	1 (11.1)
Reasons for failure at EOST	
Death, *n* (%)	1 (11.1)
Response at 2 wks after EOST	
Treatment Success Sustained, *n* (%) [95% CI][d]	6 (66.7) [29.9, 92.5]
Clinical Relapse (Positive culture), *n* (%)	1 (11.1)
Death, *n* (%)	1 (11.1)
Response at 4 wks after EOST	
Treatment Success Sustained, *n* (%)	6 (66.7)
Survival at Day 30, *n* (%)	8 (88.9)

Antimicrob Agents Chemother. 2023 May; 67(5): e01419-22.

olorofim

C. albicans	–
C. auris	–
C. glabrata	–
C. krusei	–
C. parapsilosis	–
C. tropicalis	–
C. gattii	–
C. neoformans	–
Rhodotorula	–
Trichosporon	–

A. flavus	+
A. fumigatus	+
A. niger	+
A. terreus	+
F. oxysporum	+/–
F. solani	–
Scedosporium	+
L. prolificans	+
Mucor	–
Rhizopus	–
Other Mucorales	–

Blastomyces	+
Coccidioides	+
Histoplasma	+
	–
Trichophyton	+

Olorofim (F2G Ltd – Eccles, UK)

In vitro

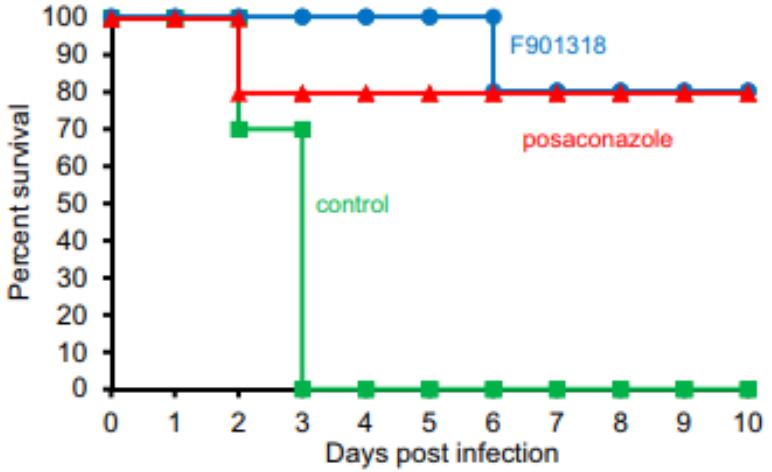
Filamentous and dimorphic fungi:

- *Aspergillus, Scedosporium, Acremonium, Paecilomyces,* and *Scopulariopsis species, Talaromyces marneffei, Blastomyces dermatitidis, Histoplasma capsulatum,* and *Coccidioides immitis/posadasii, Scedosporium prolificans, Fusarium* spp.

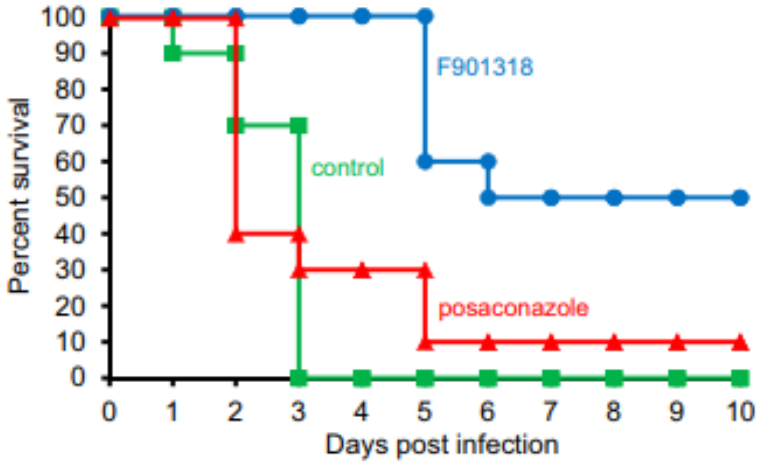
- Lacks yeasts / Mucorales

In vivo

***A. fumigatus* azole S**



***A. fumigatus* azole R**



Proc Natl Acad Sci USA. 2016;113(45):12809–14
J Antimicrob Chemother. 2017. doi:10.1093/jac/dkx065.
Int J Antimicrob Agents, 2018; 51:333-39

Ongoing Studies: olorofim

NCT03583164; FORMULA-OLS	Invasive mold infections with limited alternative therapeutic options	Phase II (open label, noncomparator, single arm) Olorofim at a maximum of 300 mg daily (dose adjusted according to TDM)	Overall response (d 42)

Recruiting

NIH U.S. National Library of Medicine
ClinicalTrials.gov

Investigational Antifungal Agents for Invasive Mycoses: A Clinical Perspective

Yeasts

Invasive candidiasis caused by azole-resistant *Candida* spp.
(e.g., *Candida auris*, *Candida glabrata*)

Current options: Echinocandins[a], lipid AMB

Future options: rezafungin[b], ibrexafungerp[b], fosmanogepix

Invasive candidiasis caused by echinocandin-resistant *Candida* spp.
(e.g., *Candida auris*, *FKS*-mutant *Candida glabrata*)

Current options: azoles, lipid AMB

Future options: ibrexafungerp, fosmanogepix

Early discharge of invasive candidiasis on a non-azole regimen

Current options: None

Future options: ibrexafungerp (oral)[b], rezafungin (iv 1/week)[b], fosmanogepix (oral)

Molds

Invasive aspergillosis caused by azole-resistant *Aspergillus* spp.
(e.g. *cyp51A* mutant *A. fumigatus*, cryptic *Aspergillus* spp.)

Current options: lipid AMB, (Echinocandins)[a,d]

Future options: olorofim, fosmanogepix, (ibrexafungerp, rezafungin)[d]

Invasive mucormycosis (*Mucorales*)

Current options: lipid AMB, posaconazole, isavuconazole

Future options: (fosmanogepix)[e]

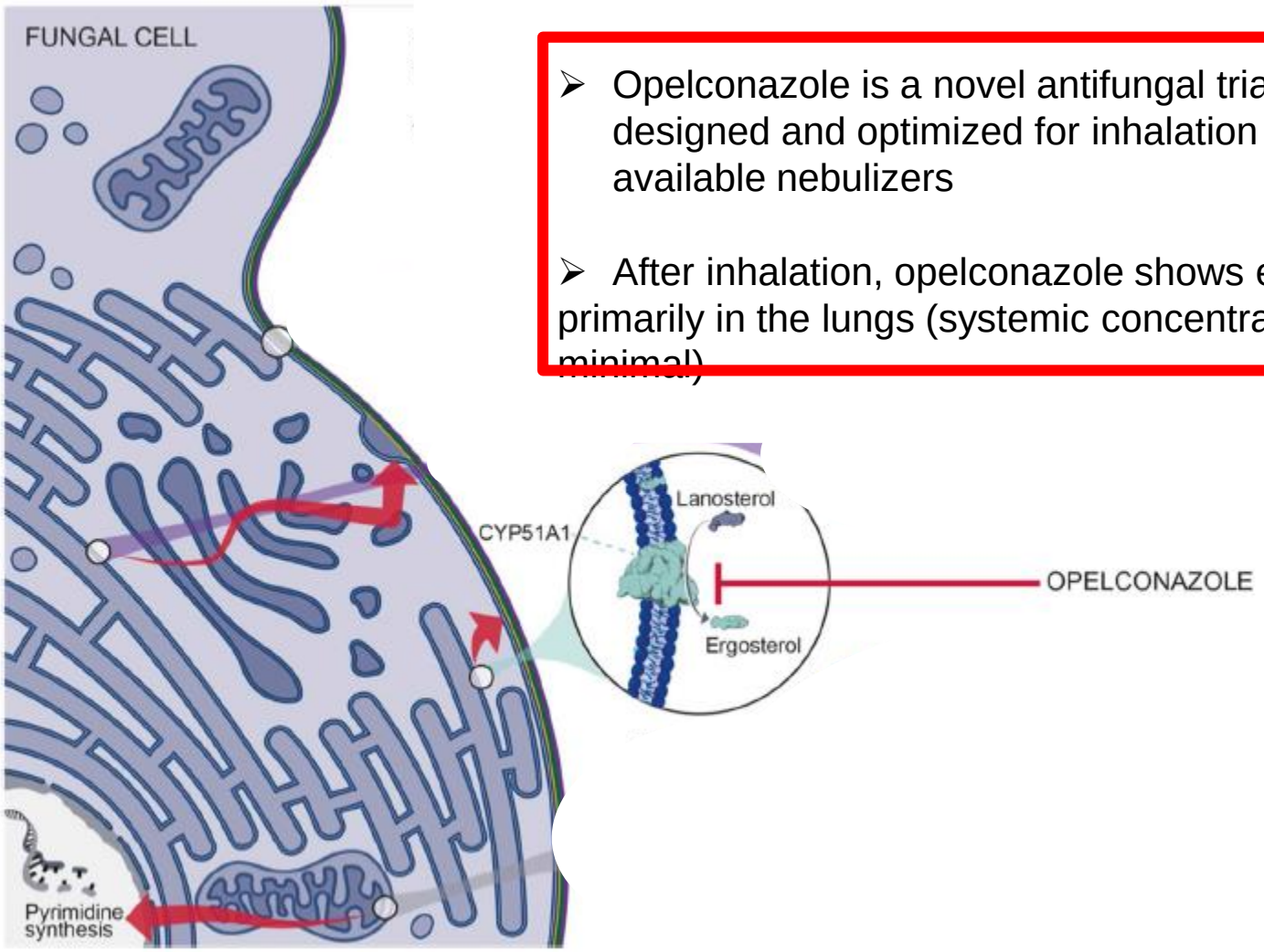
Disseminated fusariosis (*Fusarium* spp.)

Current options: lipid AMB, voriconazole

Future options: fosmanogepix[f], olorofim[f]

Grazie per l’attenzione

Antifungal Drugs in Clinical Development



- Opelconazole is a novel antifungal triazole that was designed and optimized for inhalation via commonly available nebulizers

- After inhalation, opelconazole shows efficacy primarily in the lungs (systemic concentrations are minimal)

Drugs (2021) 81:1703–1729
https://doi.org/10.1007/s40265-021-01611-0

Opelconazole