Nuove opzioni per il trattamento delle infezioni da lieviti

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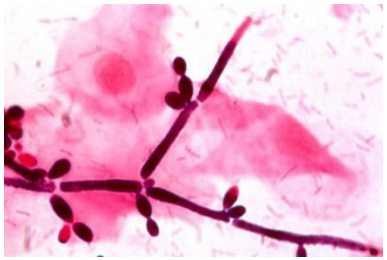
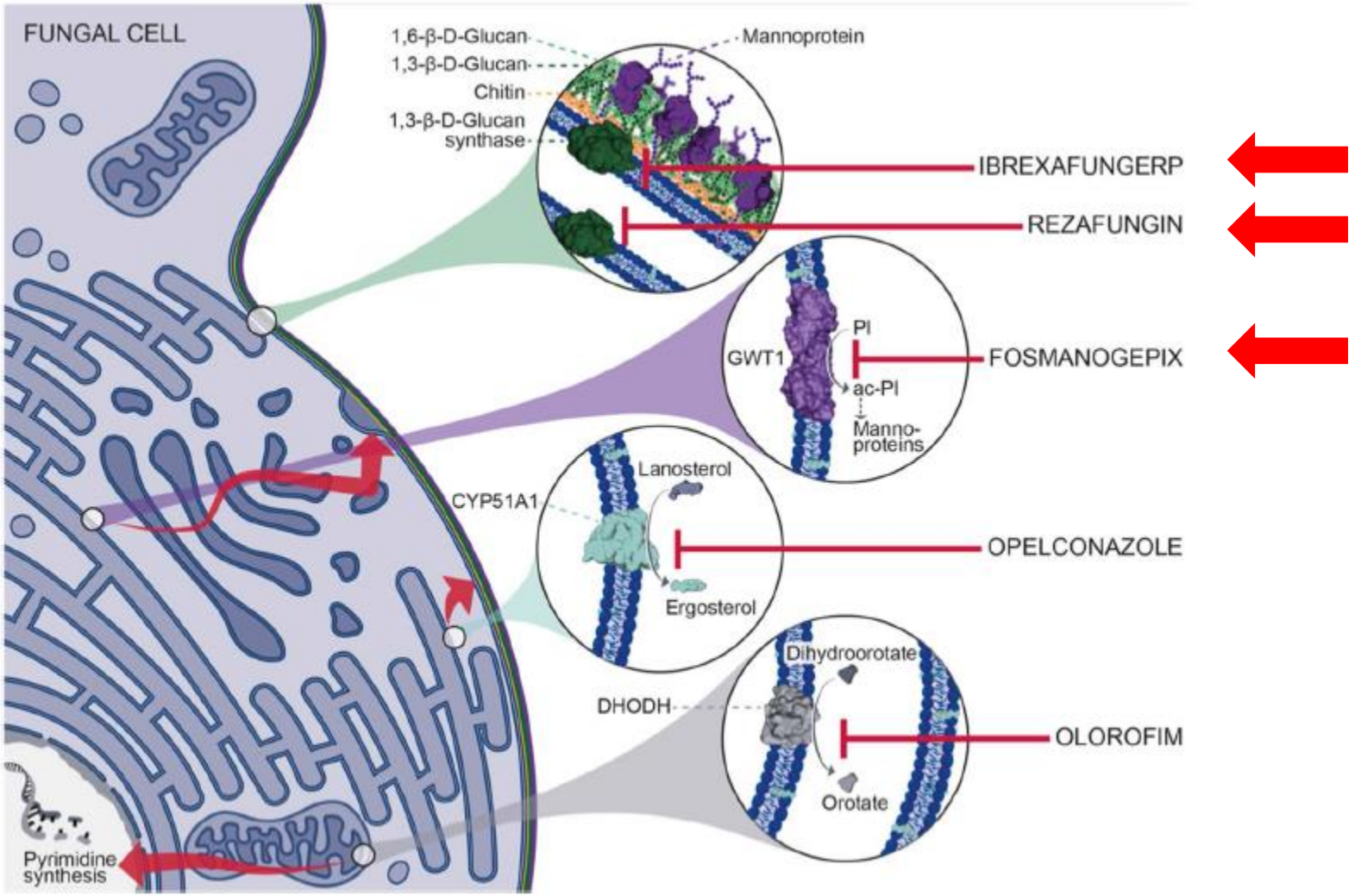
Università Politecnica delle Marche Ancona

Malattie Infettive
Azienda Sanitaria Territoriale
Pesaro Urbino

The best we can get ...

	% favorable response
	
FLU	60%
VORI	65%
ISA	…..
POSA	…..
ANIDULA	76%
CASPO	73%
MICA	76%
L-AmB	70%

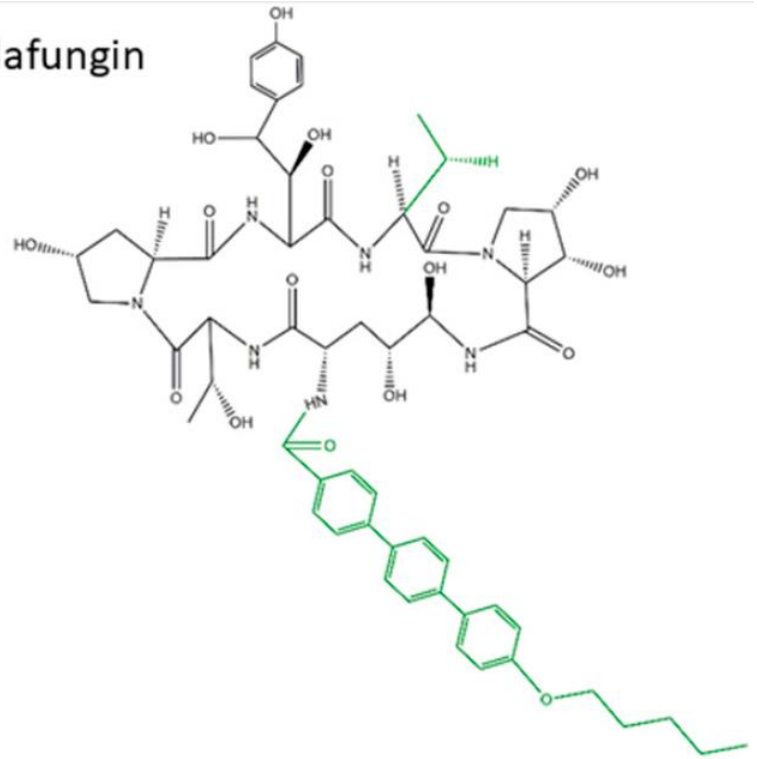
Antifungal Drugs in Clinical Development



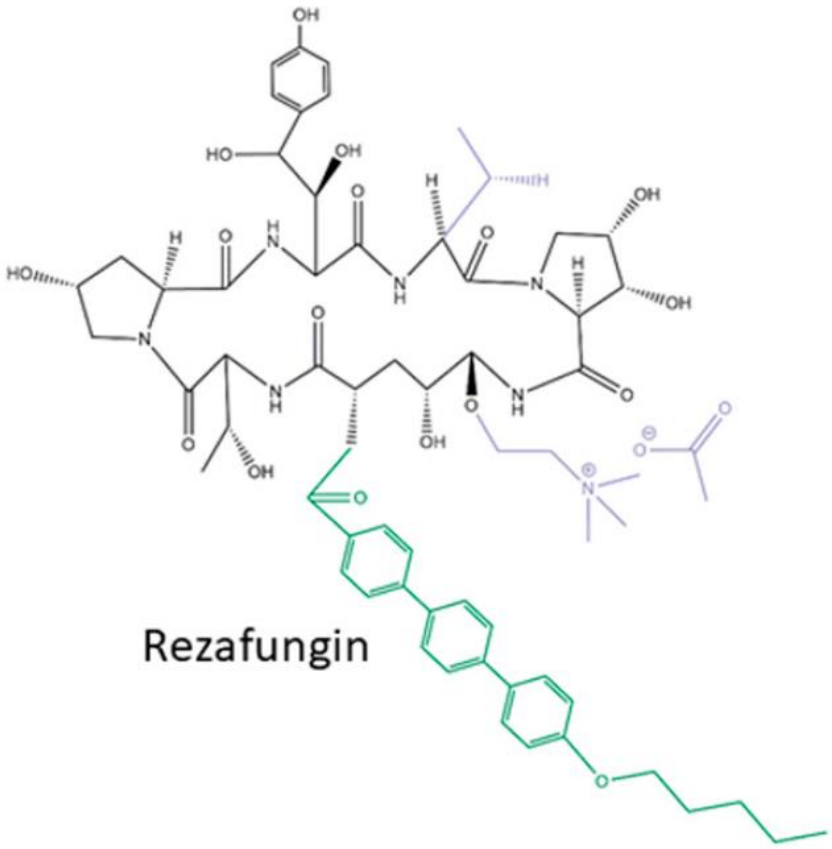
Drugs (2021) 81:1703–1729
https://doi.org/10.1007/s40265-021-01611-0

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

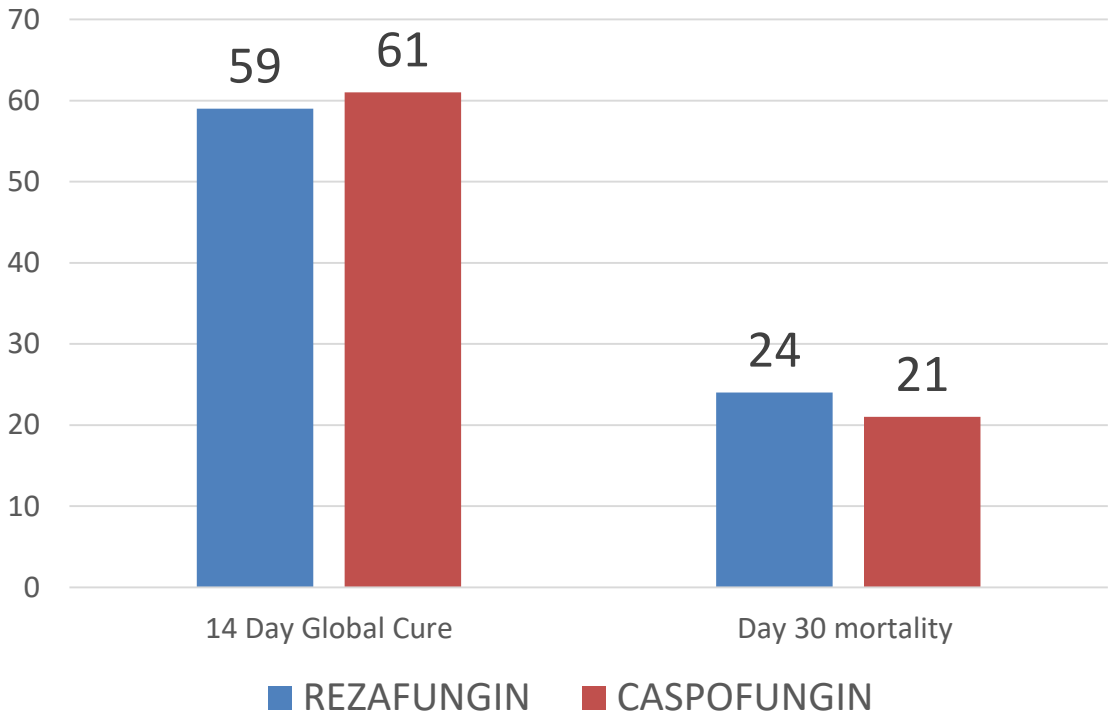
100 pts → REZA
99 pts → CAS

Primary endpoints:

- **global cure**

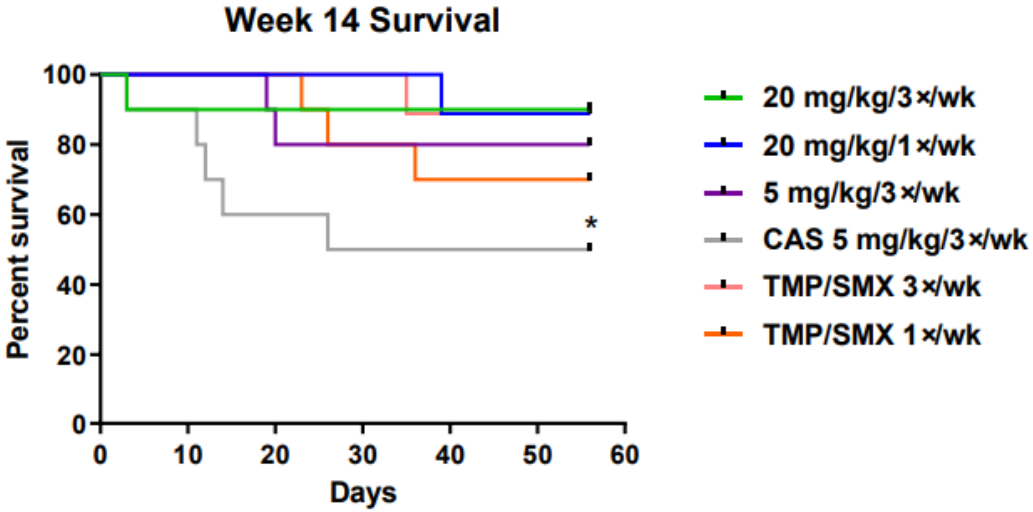
clinical cure
radiological cure
mycological eradication
} 14 days

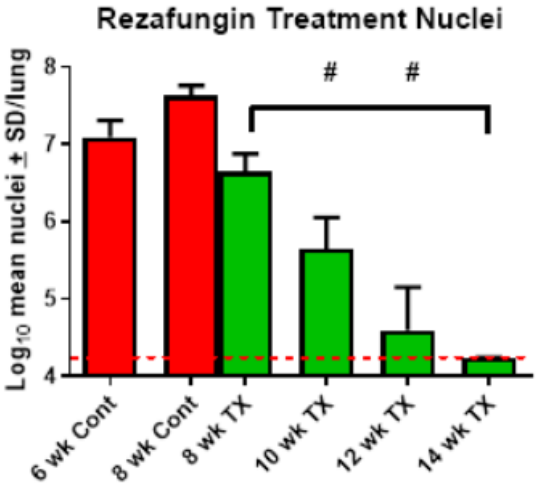
- **30-day all-cause mortality**

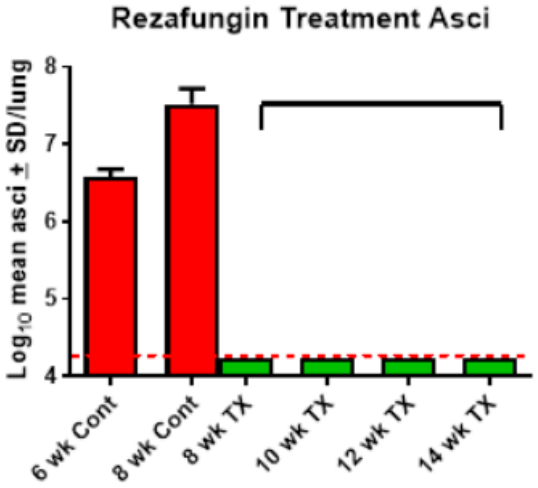


Lancet. 2023 Jan 7;401(10370):49-59.

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)

Study of Rezafungin Compared to Standard Antimicrobial Regimen for Prevention of Invasive Fungal Diseases in Adults Undergoing Allogeneic Blood and Marrow Transplantation (ReSPECT)

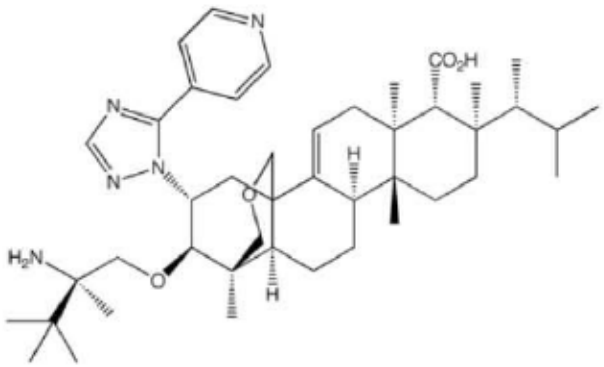
ReSPECT, NCT04368559: Recruiting

- 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	–

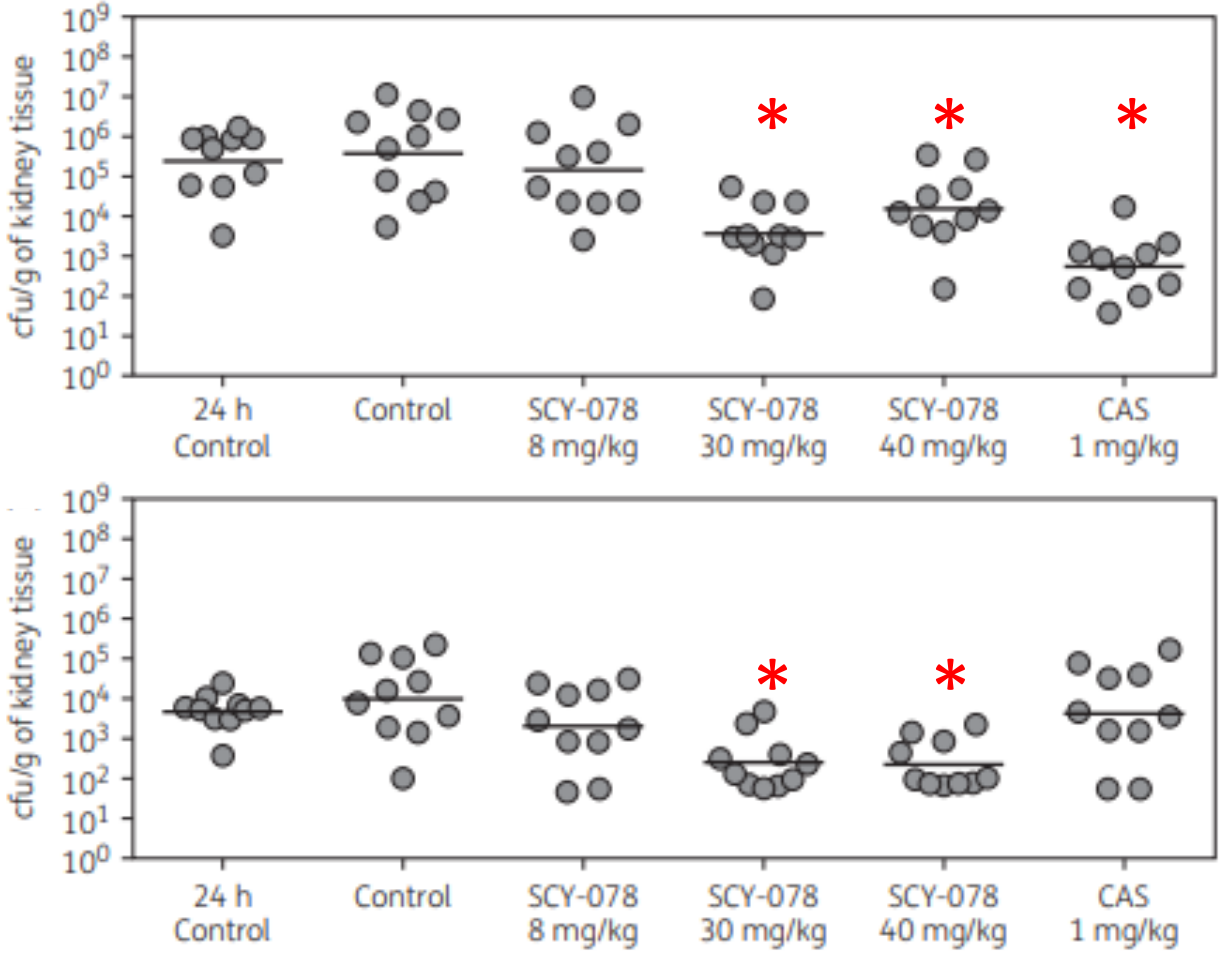
A. flavus	+
A. fumigatus	+
A. niger	+
A. terreus	+

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.

Oral glucan synthase inhibitor SCY-078 is effective in an experimental murine model of invasive candidiasis caused by WT and echinocandin-resistant *Candida glabrata*

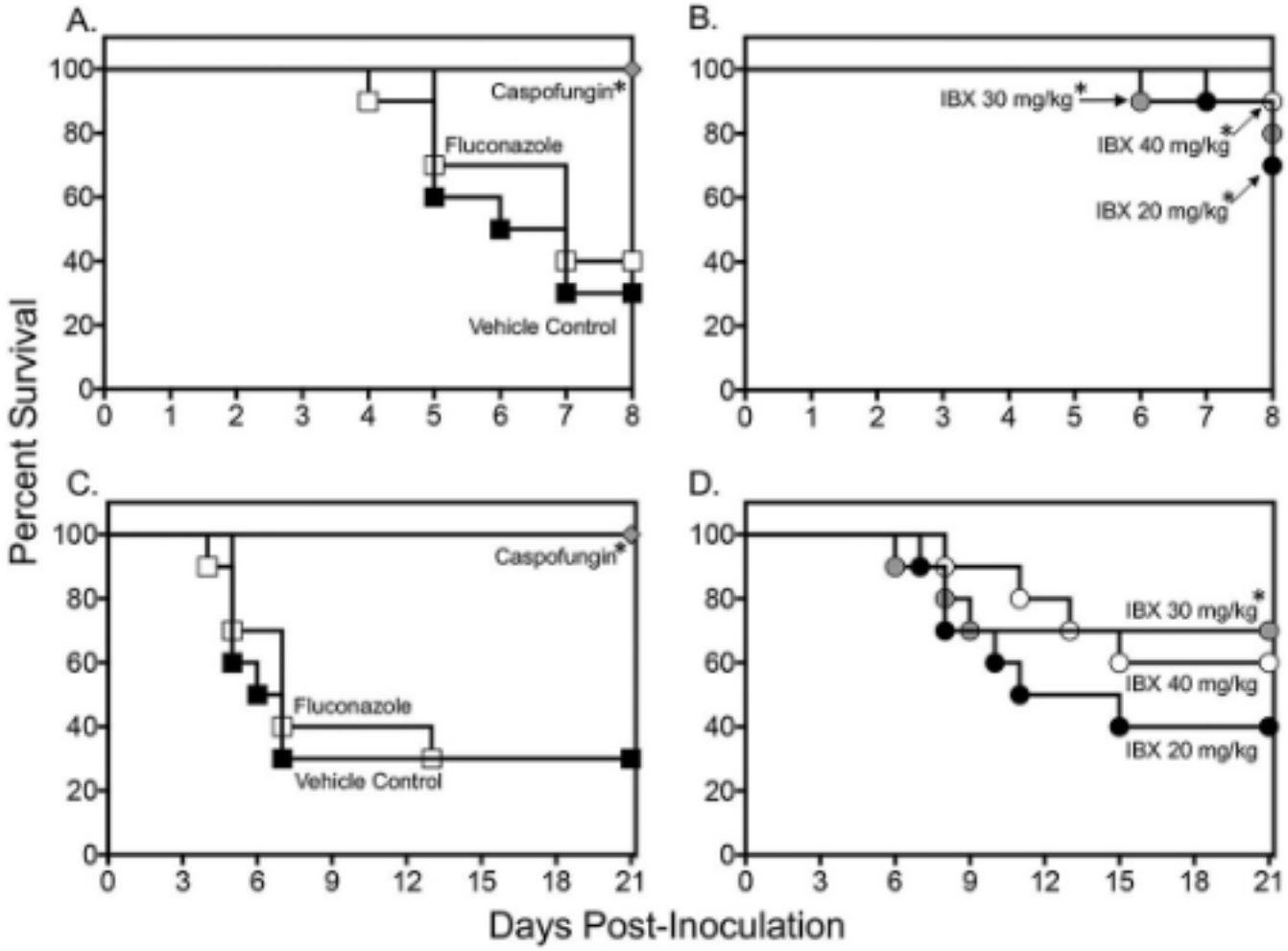
WT

R1379S Fks2p



J Antimicrob Chemother 2018; **73**: 448–451
doi:10.1093/jac/dkx422 Advance Access publication 21 November 2017

Ibrexafungerp Demonstrates *In Vitro* Activity against Fluconazole-Resistant *Candida auris* and *In Vivo* Efficacy with Delayed Initiation of Therapy in an Experimental Model of Invasive Candidiasis

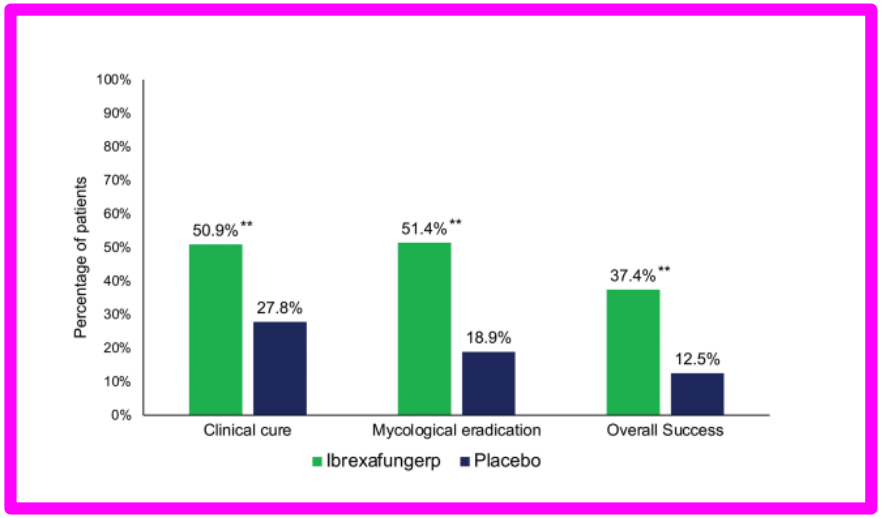


AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

EXPERIMENTAL THERAPEUTICS
June 2021 Volume 65 Issue 6 10.1128/aac.02694-20
https://doi.org/10.1128/aac.02694-20

Ibrexafungerp Versus Placebo for Vulvovaginal Candidiasis Treatment: A Phase 3, Randomized, Controlled Superiority Trial (VANISH 303)

Clinical Infectious Diseases
MAJOR ARTICLE
CID 2022:74 (1 June) •



Two phase 3 open-label, single-arm studies

NIH National Library of Medicine
National Center for Biotechnology Information

ClinicalTrials.gov

☐ **NCT03059992** **Completed**

Study to Evaluate the Efficacy and Safety of Ibrexafungerp in Patients With Fungal Diseases That Are Refractory to or Intolerant of Standard Antifungal Treatment

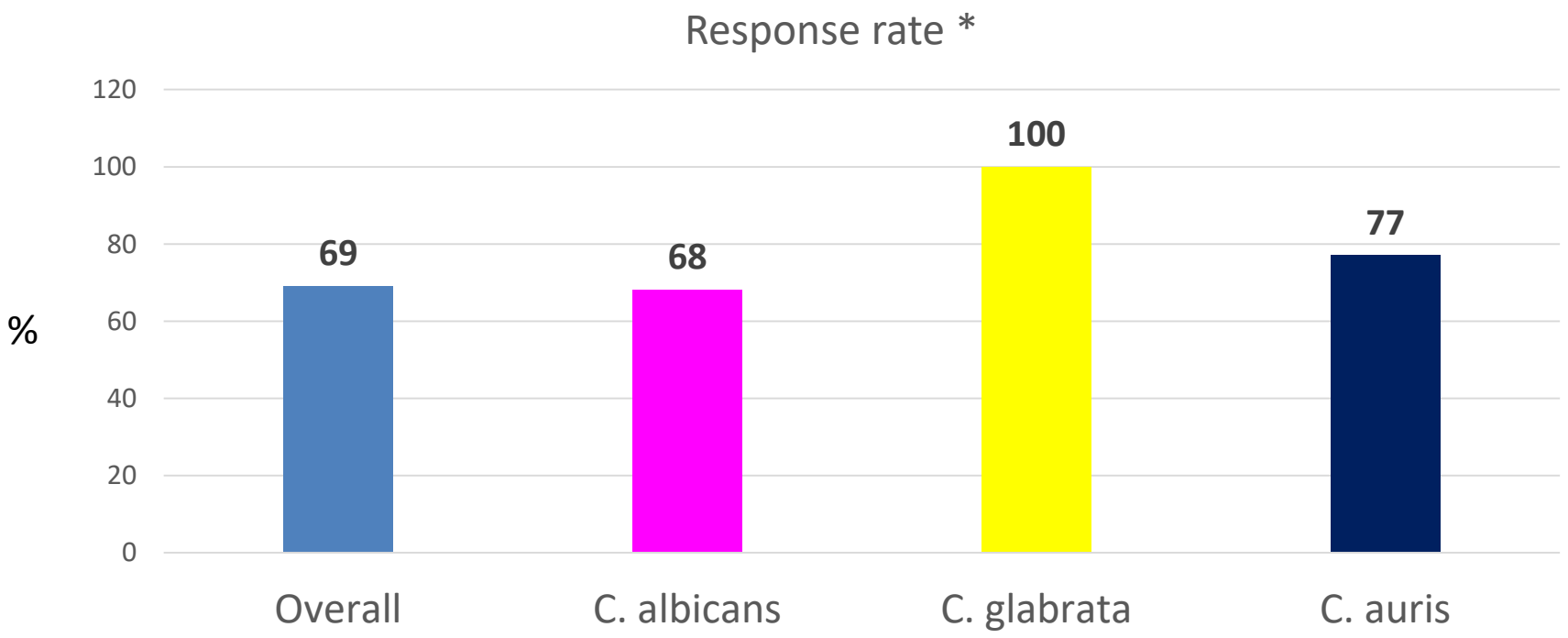
FURI Study

☐ **NCT03363841** **Completed** WITH RESULTS

Open-Label Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (SCY-078) in Patients With Candidiasis Caused by Candida Auris (CARES)

CARES Study

Oral ibrexafungerp outcomes in patietns with invasive candidiasis and candidemia from the FURI and CARES studies.

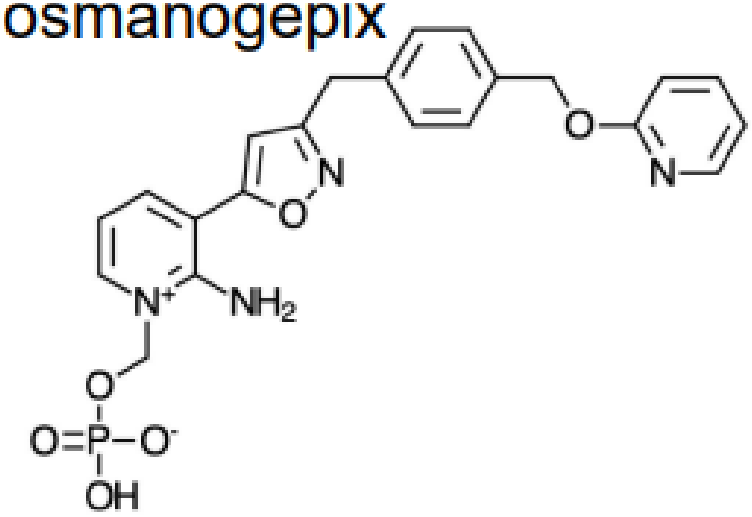


**clinical improvement, complete or partial response*

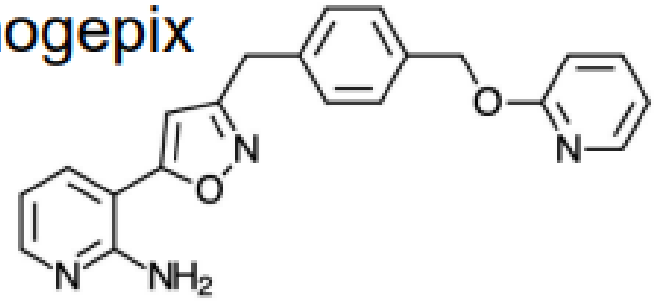
In Proceedings of the 32nd **ECCMID 2022**: European Congress of Clinical Microbiology & Infectious Diseases, Lisbon, Portugal, 23–26 April 2022.

(fos)manogepix

Fosmanogepix



Manogepix



N-phosphono-oxymethyl - Inhibition of acyltransferase Gwt1, part of GPI-anchored protein maturation pathway (*GWT1*)

GPI-anchored proteins

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

J. Fungi **2024**, *10*, 362. https://doi.org/10.3390/jof10050362

(fos)manogepix

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

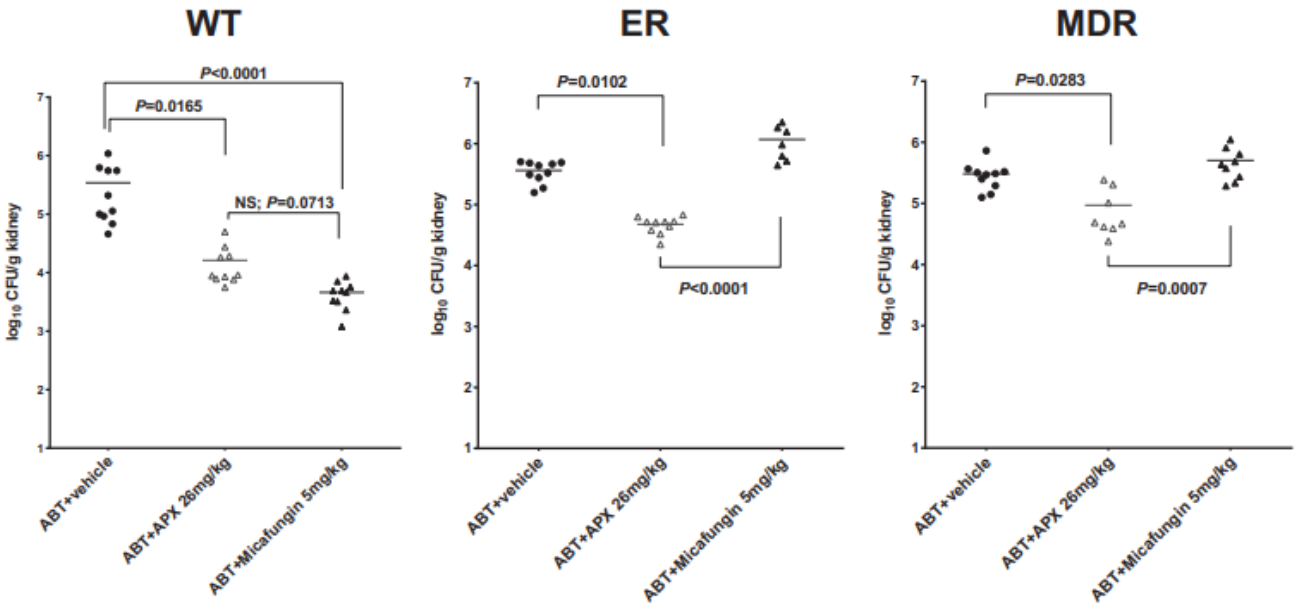
A. flavus	+
A. fumigatus	+
A. niger	+
A. terreus	+
F. oxysporum	+
F. solani	+
Scedosporium	+
L. prolificans	+

Mucor	–
Rhizopus	+/–
Other Mucorales	–

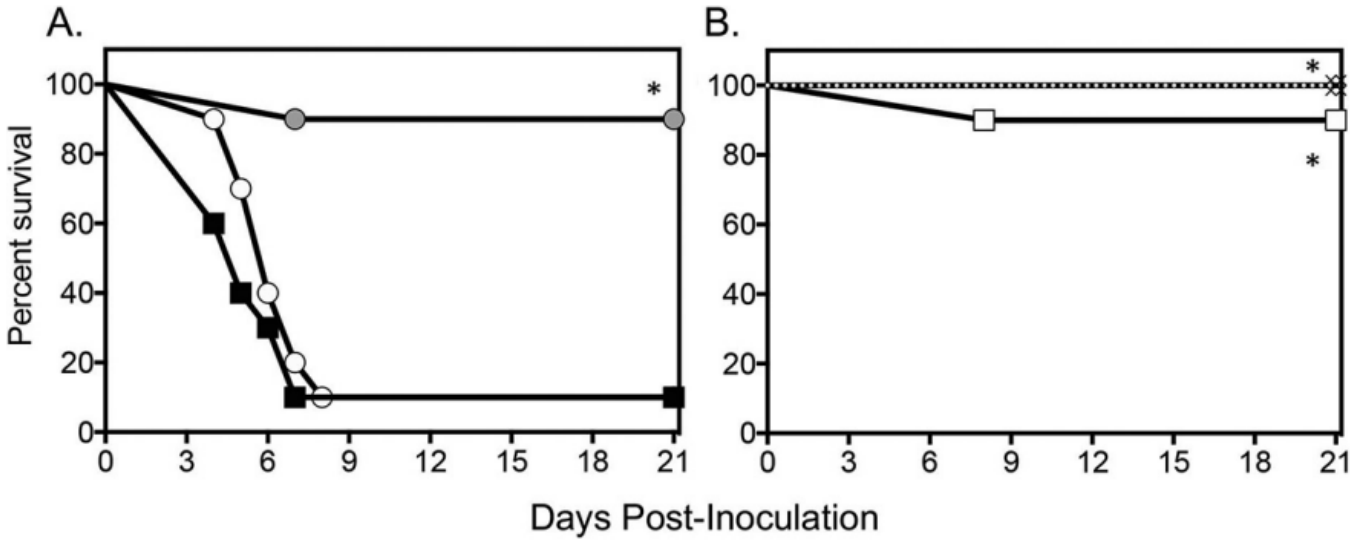
Blastomyces	
Coccidioides	+
Histoplasma	

J. Fungi **2024**, *10*, 362. https://doi.org/10.3390/jof10050362

Candida glabrata

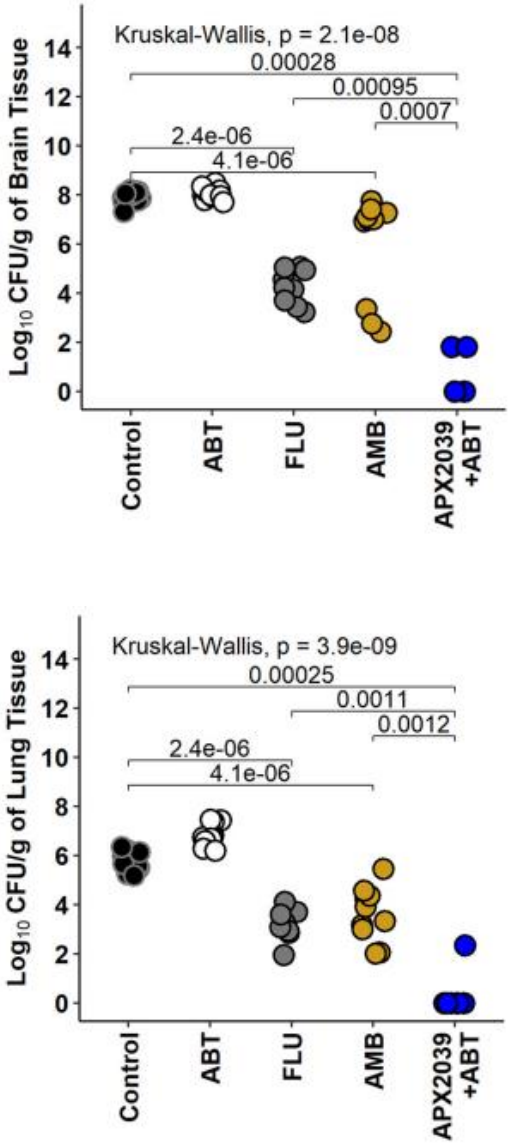


Candida auris



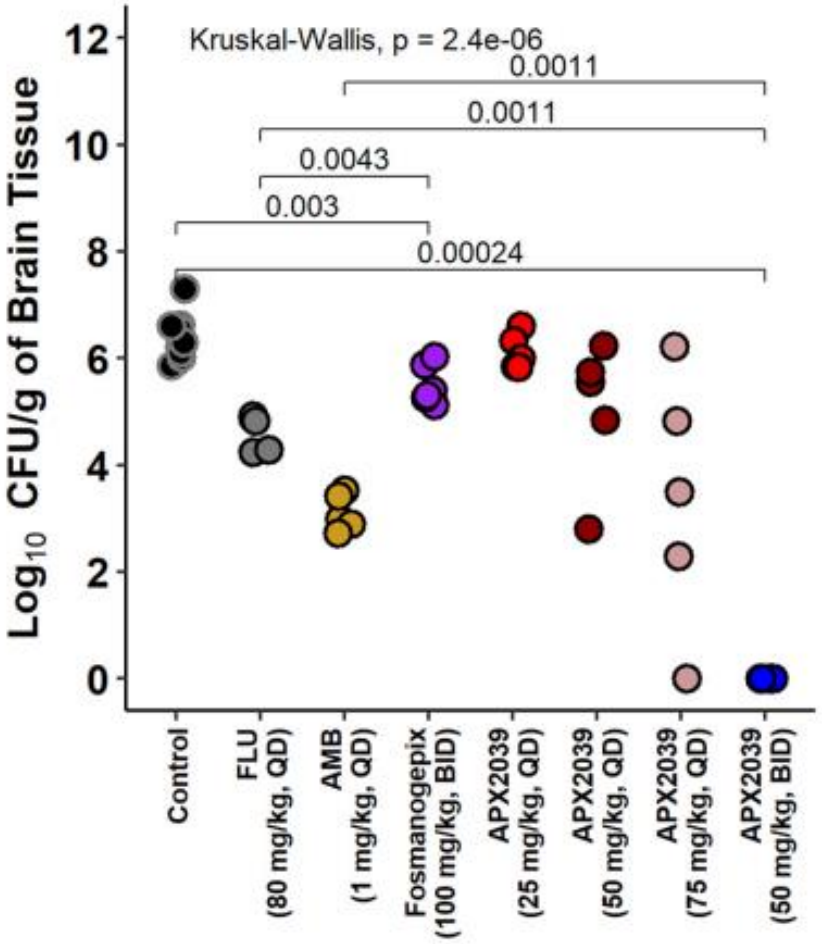
Antimicrob Agents Chemother. 2018 Sep 24;62(10):e00425-18. doi: 10.1128/AAC.00425-18.
Antimicrob Agents Chemother. 2019 Oct 22;63(11):e01120-19. doi: 10.1128/AAC.01120-19.

In Vitro and *In Vivo* Evaluation of APX001A/APX001 and Other Gwt1 Inhibitors against *Cryptococcus*



Antimicrobial Agents and Chemotherapy
August 2018 Volume 62 Issue 8 10.1128/aac.00523-18
https://doi.org/10.1128/aac.00523-18

Efficacy of APX2039 in a Rabbit Model of Cryptococcal Meningitis



November/December 2022 Volume 13 Issue 6
AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

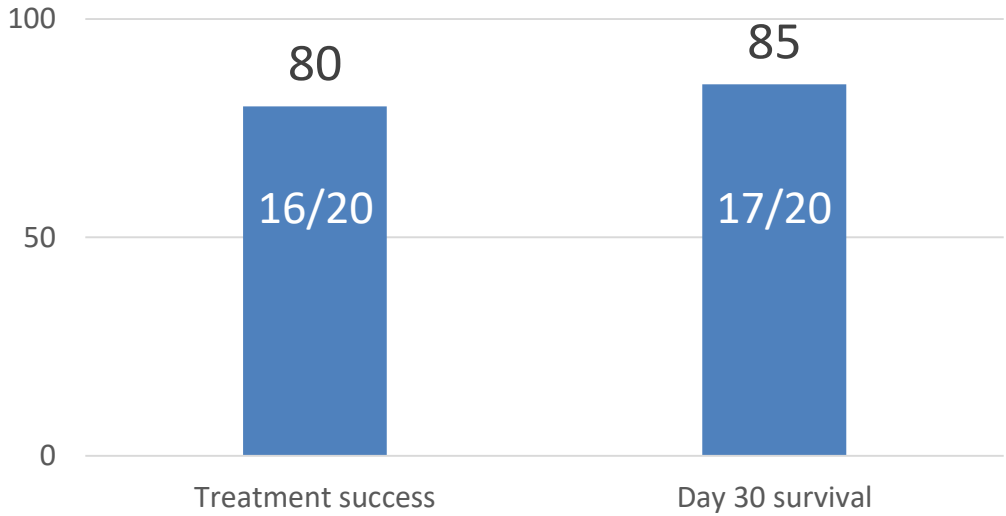
Clinical safety and efficacy of novel antifungal, fosmanogepix, for the treatment of candidaemia: results from a Phase 2 trial

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

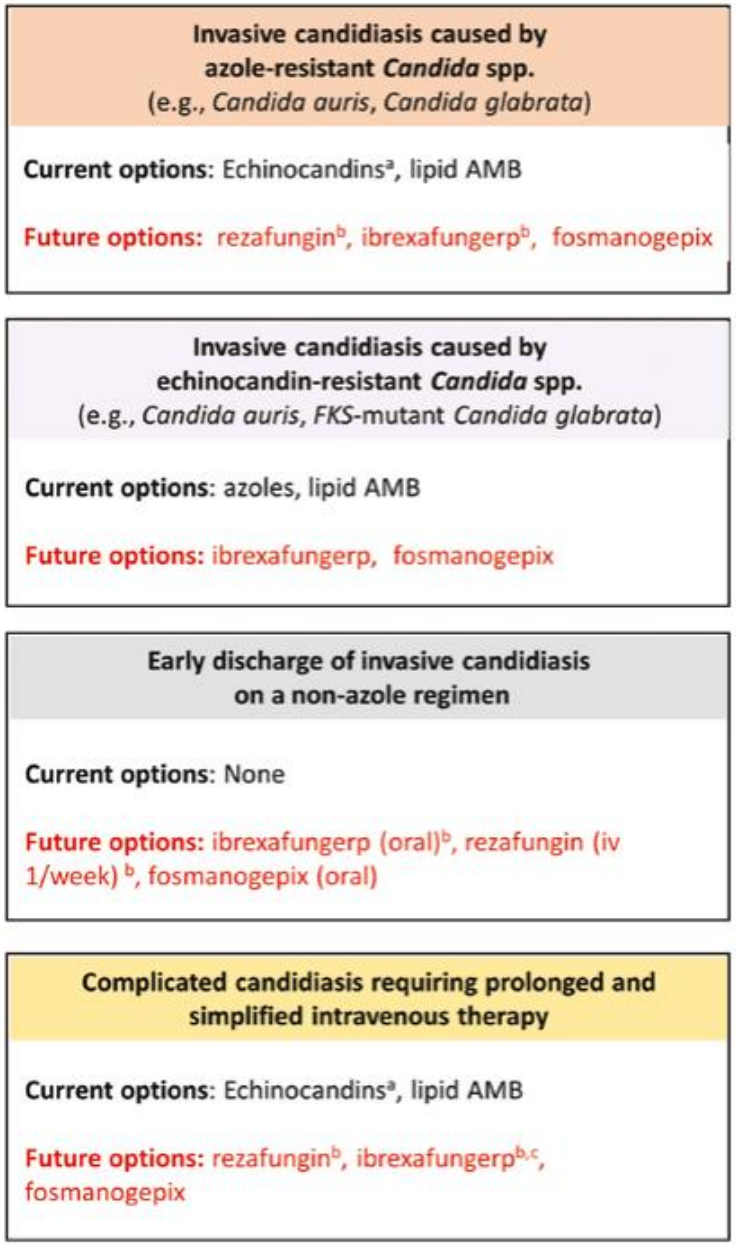
J Antimicrob Chemother 2023; **78**: 2471–2480

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.

Investigational Antifungal Agents for Invasive Mycoses: A Clinical Perspective



Oral Lipid Nanocrystal Amphotericin B for Cryptococcal Meningitis: A Randomized Clinical Trial

Boulware et al., 2023 | *Clinical Infectious Diseases*

IDSA Infectious Diseases Society of America

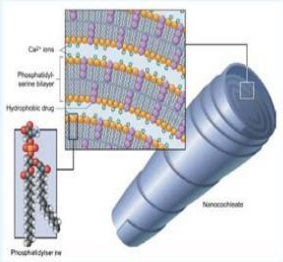
BACKGROUND: We conducted a randomized clinical trial to evaluate the antifungal efficacy of oral lipid nanocrystal (LNC) amphotericin (MAT2203) with flucytosine (5FC) in the treatment of cryptococcal meningitis.

PARTICIPANTS: We recruited adults with HIV diagnosed with cryptococcal meningitis from three hospitals in Uganda.

METHODS

Study participants had a positive CSF CrAg, Glasgow Coma Scale score = 15, and had to be able to tolerate oral medication. Participants were randomized to either the IV amphotericin control arm or to an interventional arm.

	ARM 1: 7 doses of IV Amphotericin + 5FC	ARM 2: 2 doses of IV Amphotericin + MAT2203 + 5FC	ARM 3: Oral MAT2203 + 5FC
	N=41	N=40	N=40
18-week Survival	85%	90%	85%
2-week CSF Sterility	67.6%	62.2%	63.6%
Grade 3-4 Hgb AEs	43.9%	20%	22.5%
Grade 3-4 K+ AEs	17%	5.1%	5%



Clinical antifungal activity did not differ between oral LNC-amphotericin and IV amphotericin

CONCLUSION: Oral LNC-amphotericin B with 5FC demonstrated similar antifungal activity, similar survival, and less toxicity than IV amphotericin and 5FC. Oral LNC-amphotericin B appears to be a promising antifungal candidate to be moved forward in future clinical trials for the treatment of severe fungal infections.

Clinical Infectious Diseases https://doi.org/10.1093/cid/ciad440

Clin Infect Dis, Volume 77, Issue 12, 15 December 2023, Pages 1659–1667, https://doi.org/10.1093/cid/ciad440

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Grazie per l’attenzione