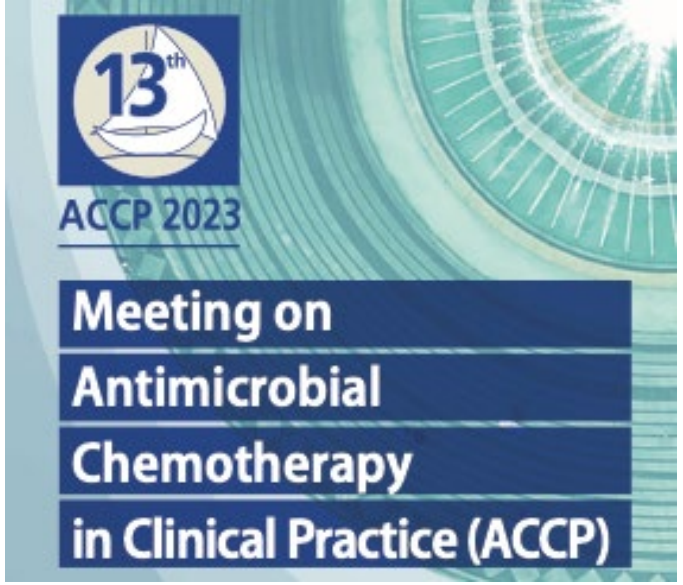


Nuovi antifungini

Silvia Corcione

Dipartimento di Scienze Mediche

Malattie Infettive

Università di Torino

Antifungal targets: New antifungals

Lamoth F. et al. Clin Infect Dis 2022

Cell membrane

Azoles
Inhibition of lanosterol 14α demethylase
(SUBA-itra and tetrazoles)

Polyenes
Punctures the ergosterol containing fungal membrane
(Amphotericin B cochleate)

Allylamines
Inhibition of squalene monooxygenase

Cell wall

Echinocandins
Inhibition of 1,3 β glucan synthase
(Rezafungin)

Ibrexafungerp
Inhibition of 1,3 β glucan synthase

Fosmanogepix
GPI inhibitor

Nikkomycin
GPI inhibitor

Intracellular targets

Antimetabolites (5-FC)

Olorofim
Inhibition of DHODH

AR-12
Inhibition of fungal achetil CoA

MGCD290
Hos2 inhibitors

VL2397/ASP2397 Siderophore

Promising antifungals in late stage: Phase 2- Phase 3 Trial

Lamoth F. et al. Clin Infect Dis 2022
Hoenigl M et al. Drugs 2021

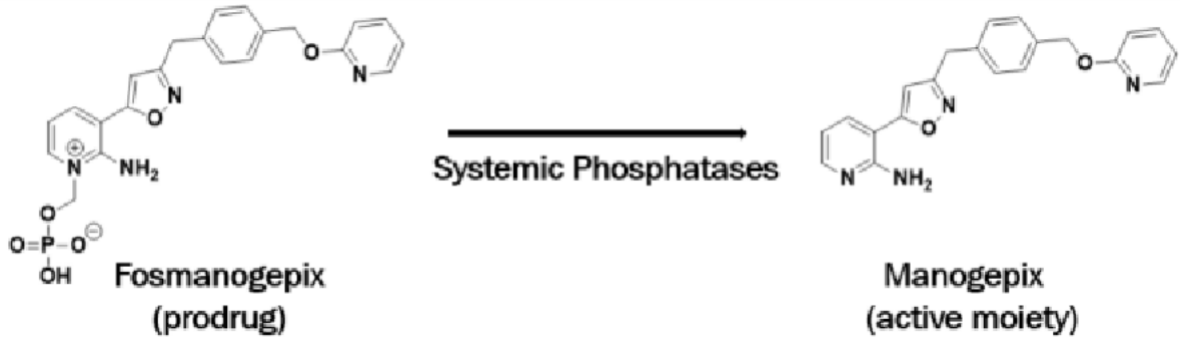
	Candida spp	*Crypto*	*P. jirovecii*	*Aspergillus*	*Fusarium*	Mucorales	*Scedosporium spp Lomentospoprium*
Fosmanogepix/ Manogepix	*C. krusei (!)*						
Ibrexafungerp		Unkown					
Olorofirm							
Opelconazole	*C.dublinensis C.lusitaniae C.parapsilosis C. tropicalis*			*A.niger (!)* Azole-R *A.fumigatus (!)*		*Rhizopus*	
Encholeated Amphotericin B							
Rezafungin		*C.neoformans (!)*		*A. niger*			

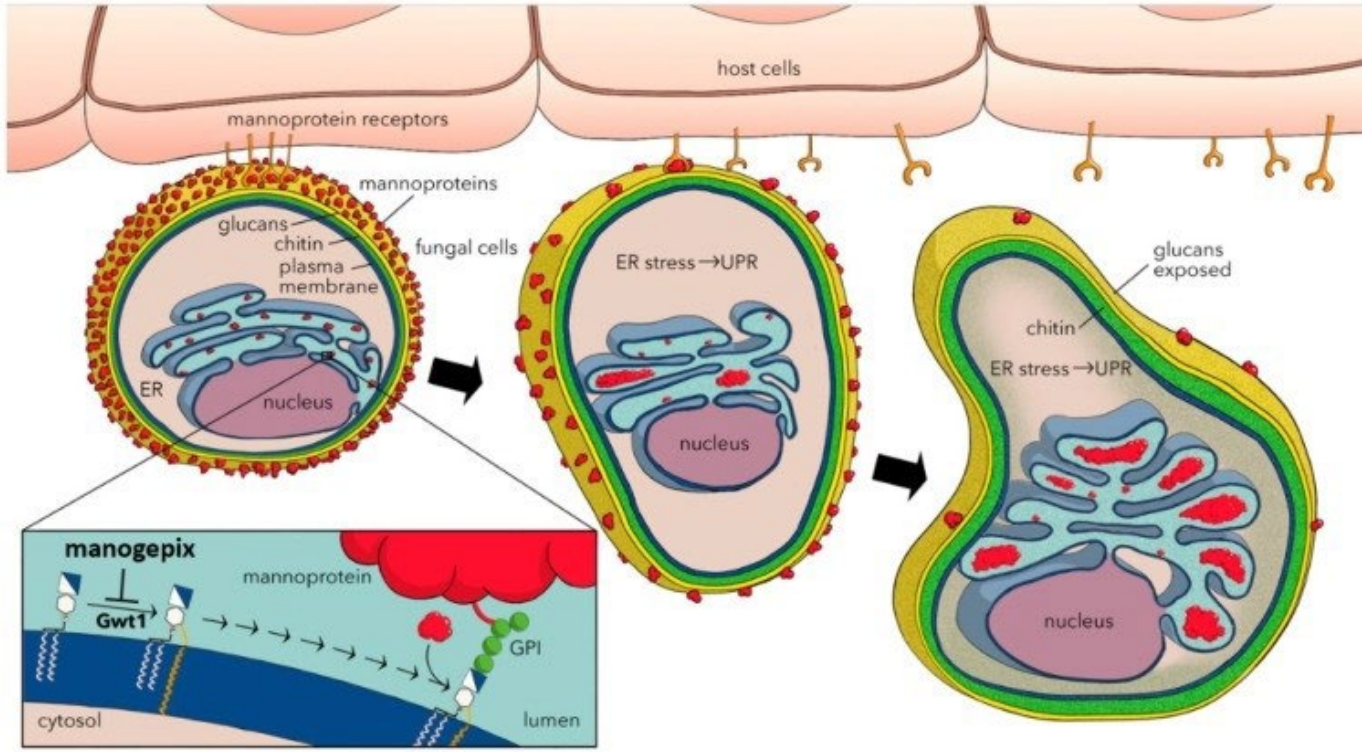
Fosmanogepix

Shaw KJ, Ibrahim AS. J Fungi; 2020; Hoenigl M, et al. Drugs. 2021

- Inositol acyltrasferasis GWT1 inhibitor
- Essential for trafficking and anchoring mannoproteins
  - Impairs cell wall integrity, adhesion, pathogenicity, host immune evasion
- Spectrum of activity:
  - Candida – but NOT C. krusei or C. kefyr
  - Aspergillus, Scedosporium, Lomentospora, Fusarium, Coccidioides, Mucorales unclear

- Intravenous and oral formulations
- Oral bioavailability >90%





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

Jose A. Vazquez[a], Peter G. Pappas[b], Kenneth Boffard[c], Fathima Paruk[d], Paul A. Bien[e], Margaret Tawadrous [f], Eric Ople[e], Pamela Wedel[e], Iwona Oborska[e], Michael R. Hodges[e]

American Society for Microbiology | Antimicrobial Agents and Chemotherapy

- Phase 2
- > 18 years, invasive candidiasis or candidemia C. auris
- FMGX (loading dose 1000mg IV twice daily followed by 600mg IV daily – switch to oral (800 mg qd) allowed on day 4
- 1º endpoint – treatment at EOST: 89% success
  - No treatment discontinuations or study drug related AEs
- MIC_{range}: CLSI, 0.008–0.015 µg/mL

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

Peter G. Pappas[1], Jose A. Vazquez[2], Ilana Oren[3]†, Galia Rahav [4,5], Mickael Aoun[6], Pierre Bulpa[7], Ronen Ben-Ami[5,8], Ricard Ferrer[9], Todd Mccarty[1], George R. Thompson III [10], Haran Schlamm[11], Paul A. Bien[12], Sara H. Barbat[11], Pamela Wedel[11], Iwona Oborska[11], Margaret Tawadrous [12*] and Michael R. Hodges[11]

Journal of Antimicrobial Chemotherapy

- Phase 2
- > 18 years, first-line treatment for candidemia, non neutropenic
- FMGX (loading dose 1000mg IV twice daily followed by 600mg IV daily – switch to oral (700 mg) allowed on day 4
- 1º endpoint – treatment at EOST: (16/20) 80% success
  - No treatment discontinuations or study drug related Aes
- MICrange: CLSI, 0.002–0.03 µg/mL

Available through compassionate use program

Vazquez JA, et al. **Antimicrob Agents Chemother**. 2023. 67(5):e014922.

Pappas PG, et al. **J Antimicrob Chemother**. 2023: Online ahead of print.

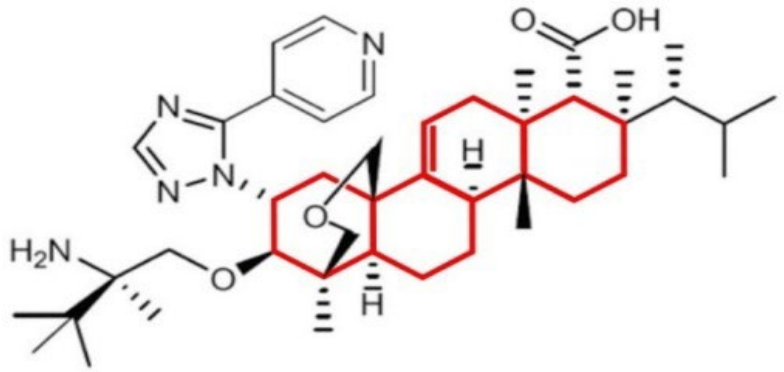
Other ongoing studies

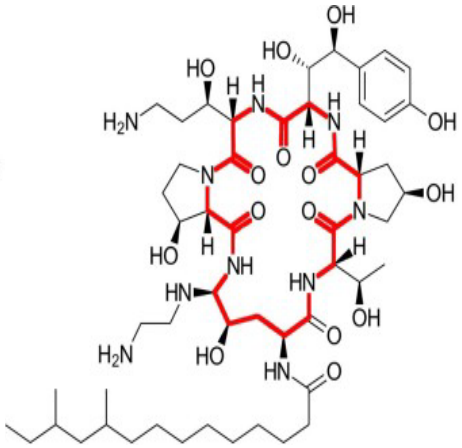
- Open-label study of fosmanogepix for treatment of **patients with IA and other rare molds** (e.g., *Scedosporium* spp., *Fusarium* spp and *Mucorales*) with limited or no treatment options because of resistance, toxicity or lack of clinical response to SOC (AEGIS, NCT04240886).

https://clinicaltrials.gov/

Ibrexafungerp

McCarthy MW; Drug 2022; Gamal A; Front Cell Infect Microbiol. 2021





Caspofungin

- Structurally distinct from other glucan synthase inhibitors (echinocandins)
- Activity vs. *Candida* (including FKS mutants and *C. auris*), *Aspergillus, (azole R)* and *P. jirovecii.*
- *No Mucorales or Fusarium*
- FDA **approved for vulvovaginitis** (VANISH-303 and VANISH 306)
- High tissue penetration (No CNS!)
- Favorable safety profile (no QT prolongation)
- **Low drug-drug** interactions (rifampicin).

- Oral bioavailability
- IV formulation in development

	PHASE 3 Open-label Single-Arm	PHASE 3 Open-label Single-Arm	PHASE 3 Open-label Single-Arm
	FURI	**CARES** (*Candida auris*)	**MARIO**
Potential Indication	Intolerance, refractory fungal infections including *Candida* spp, *Aspergillus* spp, Endemics	Treatment of *Candida auris* infections	Treatment of invasive candidiasis and candidemia
Trial Size	>200 patients in primary evaluable population (mITT)	~30	~220
Trial Status	Complete	Complete	Ongoing

MSG-10: a Phase 2 study of oral ibrexafungerp following initial echinocandin therapy in non-neutropenic patients with IC

Spec et al; J Antimicrob Chemother 2019

- Multinational, open-label study.
- Following initial echinocandin, IC pts were randomized to receive step-down therapy with: IBREX 500 mg vs IBREX 750 mg vs SOC

	Ibrexafungerp 500 mg (*N*=7), *n* (%)	Ibrexafungerp 750 mg (*N*=7), *n* (%)	SOC		All patients (*N*=22), *n* (%)
			fluconazole (*N*=7), *n* (%)	micafungin (*N*=1), *n* (%)	
EOT					
global response	5 (71)	6 (86)	5 (71)	1 (100)	17 (77)
clinical response	5 (71)	6 (86)	5 (71)	1 (100)	17 (77)
microbiological response	6 (86)	6 (86)	6 (86)	1 (100)	19 (86)
missing	1 (14)	1 (14)	0 (0)	0 (0)	2 (9)

d

- Similar favourable response
- The rate of adverse events was **similar** among patients receiving ibrexafungerp or SOC (mainly Gastrointestinal)
- ibrexafungerp 750 mg regimen is predicted to achieve the target exposure in ~85% of the population

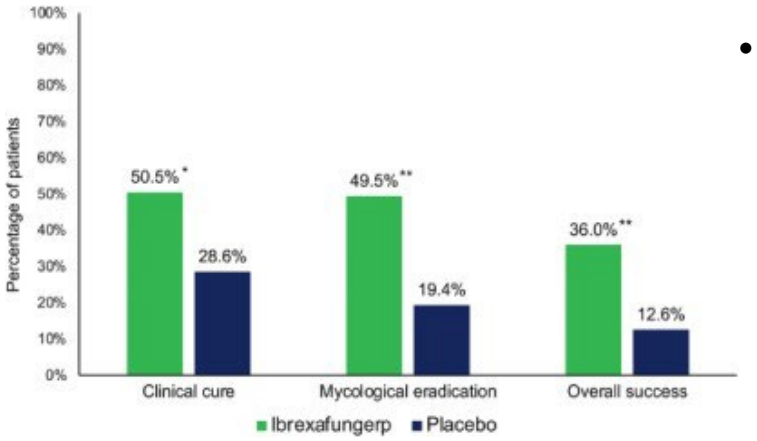
Vulvovaginal Candidiasis (Recurrent)

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

Clinical Infectious Diseases
MAJOR ARTICLE

Jane R. Schwebke,[1] Ryan Sobel,[2] Janet K. Gersten,[3] Steven A. Sussman,[4] Samuel N. Lederman,[5] Mark A. Jacobs,[6] B. Todd Chappell,[7] David L. Weinstein,[8] Alfred H. Moffett Jr,[9] Nkechi E. Azie,[10] David A. Angulo,[10] Itzel A. Harriott,[10] Katyna Borroto-Esoda,[11] Mahmoud A. Ghannoum,[12] Paul Nyirjesy,[2] and Jack D. Sobel[13]

- Oral ibrexafungerp for VVC
- 376 pts
  - IBREXA (N=249) 300mg
    - BID x 1 day
  - Placebo (N=127)
- 1º outcome: Cure at TOC (day 11) - Clinical Cure:
  - IBREXA (51%) vs placebo (29%) (P=0.001)
- AEs IBREXA (39%) vs placebo (17%)
  - AEs primarily GI and mild



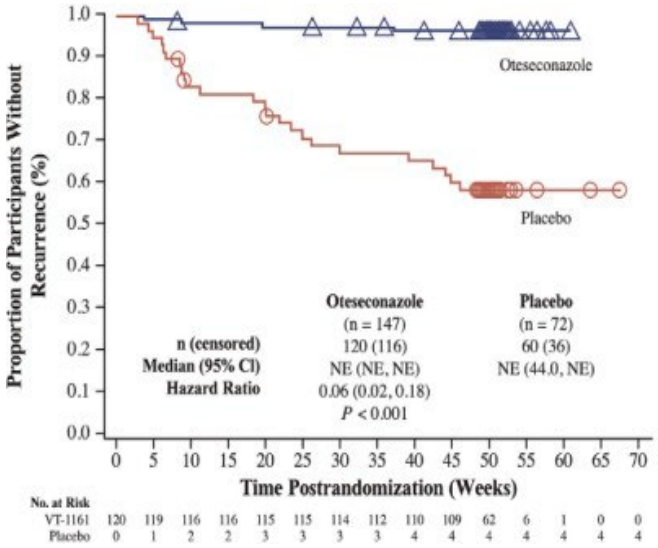
Schwebke JR, et al. Clin Infect Dis 2022

Phase 3 study evaluating the safety and efficacy of oteseconazole in the treatment of recurrent vulvovaginal candidiasis and acute vulvovaginal candidiasis infections

AJOG American Journal of Obstetrics & Gynecology

Mark G. Martens, MD, FACOG; Bassem Maximos, MD, MPH, FACOG; Thorsten Degenhardt, PhD; Karen Person, MSc; Stacey Curelop, MPH; Mahmoud Ghannoum, PhD; Amy Flynt, PhD; Stephen R. Brand, PhD

- Oral oteseconazole (tetrazole) for prevention of recurrent VVC through 50 weeks
- 219 pts with recurrent VVC
- >12 yrs and recurrent VVC (N=219)
  - OTE (N=147) 600mg day 1; 450 on day 2; once weekly thereafter
  - FLU (N=72) 150mg doses, days 1,4&7
- 1º outcome: relapse – OTE (5%) vs FLU (42%) (P<0.001)
- Day 14 cure: OTE (93%) vs FLU (96%)



Ibrexafungerp : Ongoing clinical studies

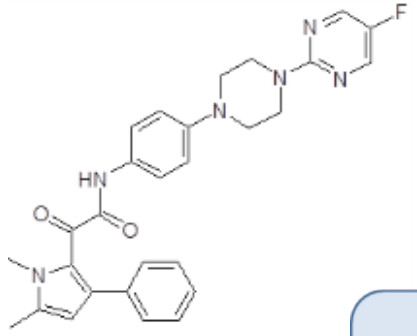
https://clinicaltrials.gov/

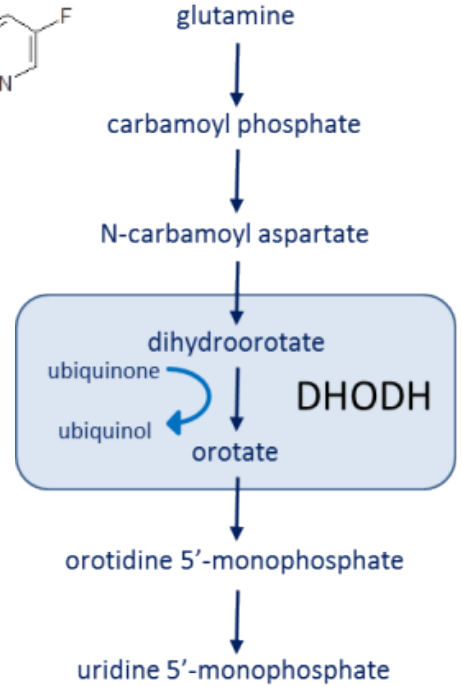
Invasive Candidiasis And Refractory Invasive Fungal Infections

- FURI- Open label study in Refractory/Intolerant IFIs (interim Results; 33 patients (30 IC e 3 IA): clinical success 70%, stable 21%, failure 9%)
- CARES- Open label study in IC by *C. auris* (interim Results; 10 patients: clinical response 80%, death 10%, indeterminate 10%)
- SCYNERGIA- Multicenter Randomized Double Blind Trial Evaluating Ibrexafungerp as A Combination Therapy For IPA

Olorofim

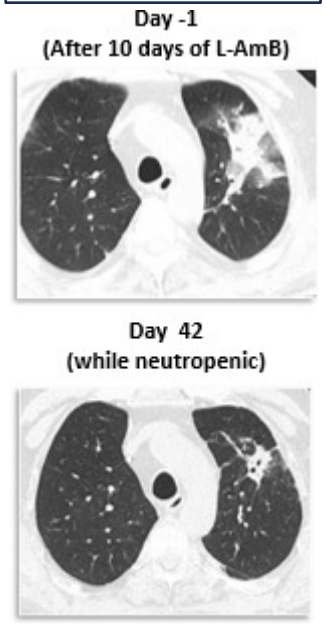
Hammond S, et al. ECCMID 2023. #01141 Slavin M, et al. ECCMID 2023. #01135 Thompson GR, et al. CSG 2023 #140



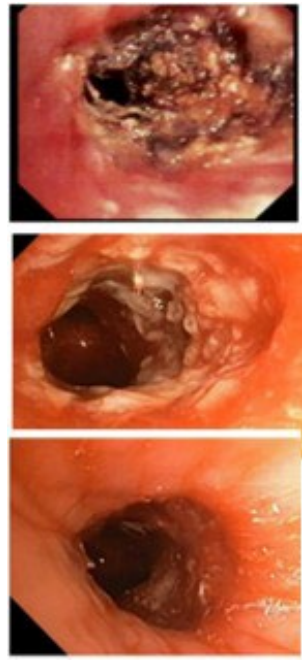


- **F901318 is a potent inhibitor of A. fumigatus DHODH**
  - DHODH (dihydroorotate dehydrogenase) is a key enzyme involved in pyrimidine biosynthesis
- **Spectrum of activity:** highly active against moulds/endemics including resistant Lomentospora, Scedosporium, and Aspergillus
- IV and oral distribution; good penetration in tissues including CNS
- Phase II trial for refractory, resistant, or intolerance (studio 32)

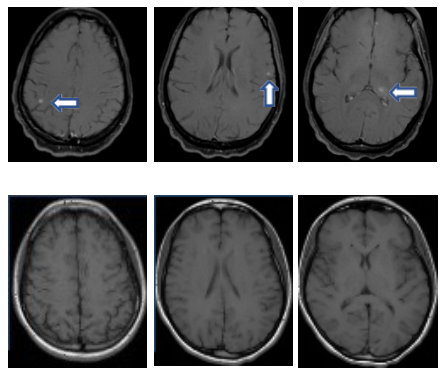
Resistant Aspergillosis



Scopulariopsis of anastomosis



Refractory CNS Coccidioidomycosis



Study 32: Open-Label Study in Patients with Limited Treatment Options (NCT03583164)

Data from first 100 subjects available

1. Proven Invasive Fungal Infection *or* Probable Pulmonary IA*

AND

2. Limited treatment options

→ Olorofim for up to 90 Days

All dosing has been with the 30 mg tablet

→ EOT at or before 90 days

F/U 4 weeks after EOT

51 of first 100 subjects

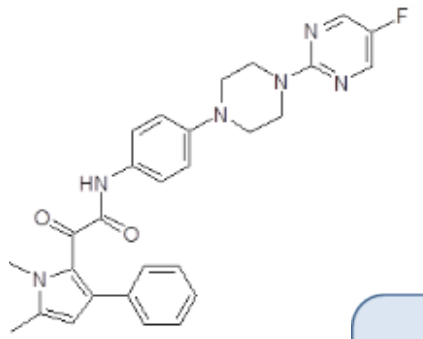
→ Extended therapy for as long as thought useful

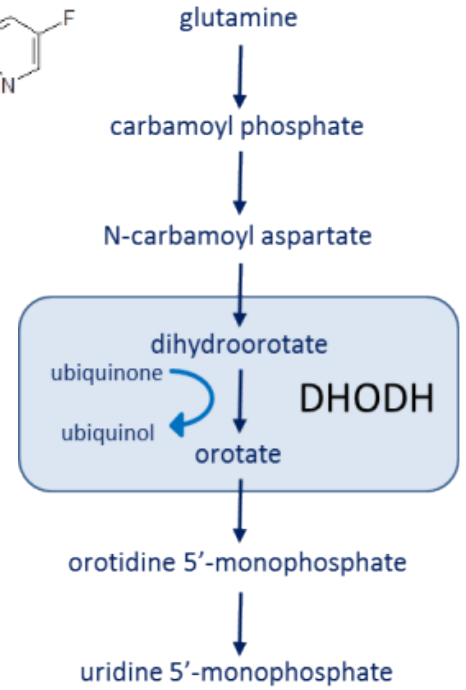
49 of first 100 subjects

*All definitions based on EORTC-MSG definitions. Probable Pulmonary IA required host factors, mycology and radiology; Probable was not accepted for any other fungus or body site

ID Week 2022 abstracts 754 and 870

Olorofim

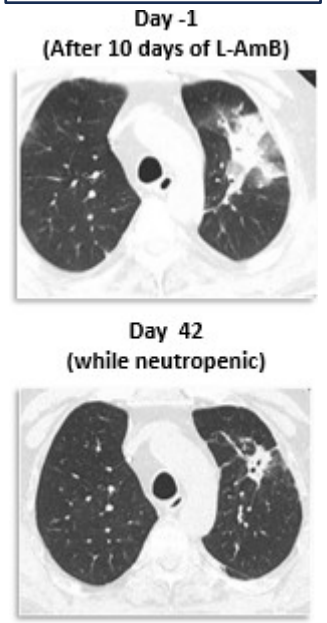




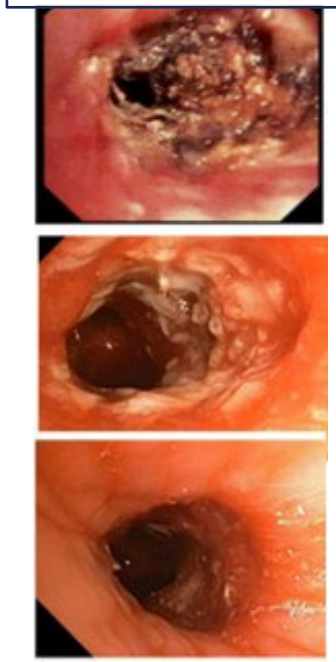
- **F901318 is a potent inhibitor of A. fumigatus DHODH**
  - DHODH (dihydroorotate dehydrogenase) is a key enzyme involved in pyrimidine biosynthesis
- **Spectrum of activity:** highly active against moulds/endemics including resistant Lomentospora, Scedosporium, and Aspergillus.

- Phase II trial for **refractory, resistant, or intolerance (studio 32)**
- First 100 patients:
  - d42 overall complete/partial response – 43%; stable 26%
  - d84 overall complete/partial 37%; stable 22%
  - AEs gastrointestinal (mild) and hepatic (9.9% rate of ALT/AST elevations judged at least possibly due to olorofim; managed with dose reduction or pause; discontinued in 2.5%)

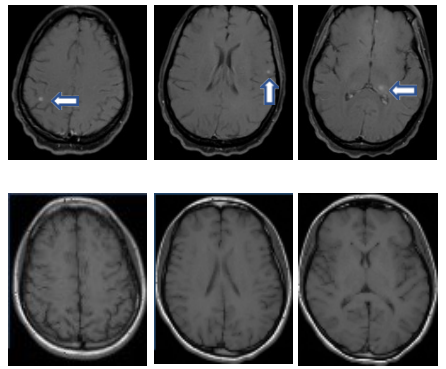
Resistant Aspergillosis



Scopulariopsis of anastomosis



Refractory CNS Coccidioidomycosis



Hammond S, et al. ECCMID 2023. #01141 Slavin M, et al. ECCMID 2023. #01135 Thompson GR, et al. CSG 2023 #140

Clinical ongoing trials: Olorofim Aspergillus Infection Study (OASIS)

- Phase 3 trial
- To compare treatment with olorofim versus treatment with liposomial amphotericin B followed by standard of care (SOC) in patients with IFD caused by proven IA or probable lower respiratory tract disease Aspergillus species (invasive aspergillosis, IA)
- Entry criteria:
    1. Patients with proven IA at any site or probable LRTD IA per EORTC/MSG 2019 criteria as adapted for this study
    2. Patients requiring therapy with an antifungal agent other than a mould-active azole on the basis of IA refractory to mould-active azole therapy, proven resistance to the mould active azoles, breakthrough infection on mould-active triazole prophylaxis, or azole drug-drug interactions (or potential for drug-drug interactions).
- Outcomes:
    1. All cause mortality at day 42-84 and EOT

https://clinicaltrials.gov/

Rezafungin

- Long-acting new generation echinocandin
- Novel, once-weekly IV echinocandin
- Analogue of anidulafungin, designed for increased stability and improved PK (1/2 life=133h)
- Long-acting PK enables once-week dosing and front-loaded plasma exposure

- **Spectrum of activity** (low risk of R development)
  - *Candida*, including azole-resistant strains (e.g. *C. krusei, C. auris*)
  - *Aspergillus,* including azole-R *A. fumigatus* isolates and cryptic specie
  - *Pneumocistis spp*

	PHASE 3 TREATMENT TRIAL	PHASE 3 PROPHYLAXIS TRIAL
	ReSTORE	ReSPECT
Potential Indication	Treatment of candidaemia & invasive candidiasis	Prophylaxis against IFD caused by *Aspergillus*, *Candida* & *Pneumocystis* in allogeneic blood and marrow transplant patients
Trial Size	187 patients in primary evaluable population (mITT)	462 patients
Trial Status	Complete	Ongoing

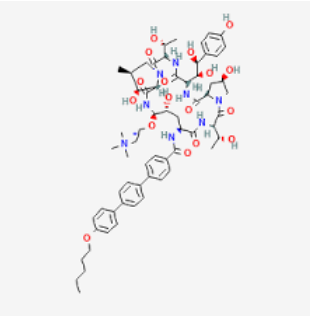
Rezafungin VS Caspofungin: STRIVE TRIAL

Thompson III G. et al. Clin Infect Dis 2021 6;73(11):e3647-e3655.

- Phase 2, RCT double blind for the treatment of candidemia and IC, n=207

ARM	OVERALL CURE
RZF 400 mg once weekly for 2–4 weeks.	60.5% (46/76)
RZF at 400 mg on week 1 followed by 200 mg on subsequent weeks.	76.1% (35 /46)
CAS (70→50 MG) once daily with an optional stepdown available after 3 d	67.2% (41/61)

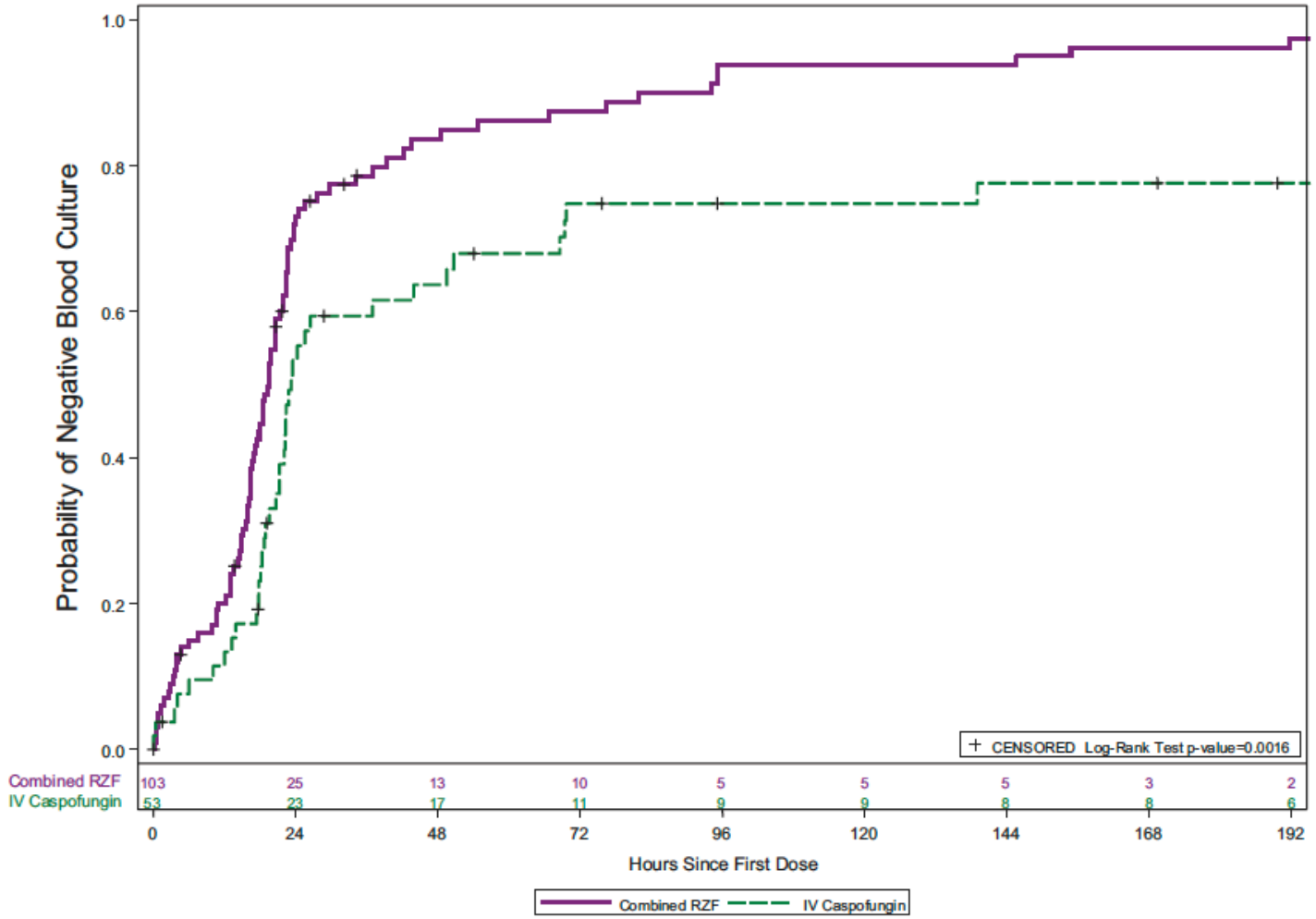
Resolution of signs of candidemia/IC + Mycological eradication



STRIVE TRIAL: Time to negative blood culture

Thompson III G. et al. Clin Infect Dis 2021 6;73(11):e3647-e3655.

Median time to negative BC: RZF 19.5 hrs VS CAS 22.8 hrs (p=0.02)

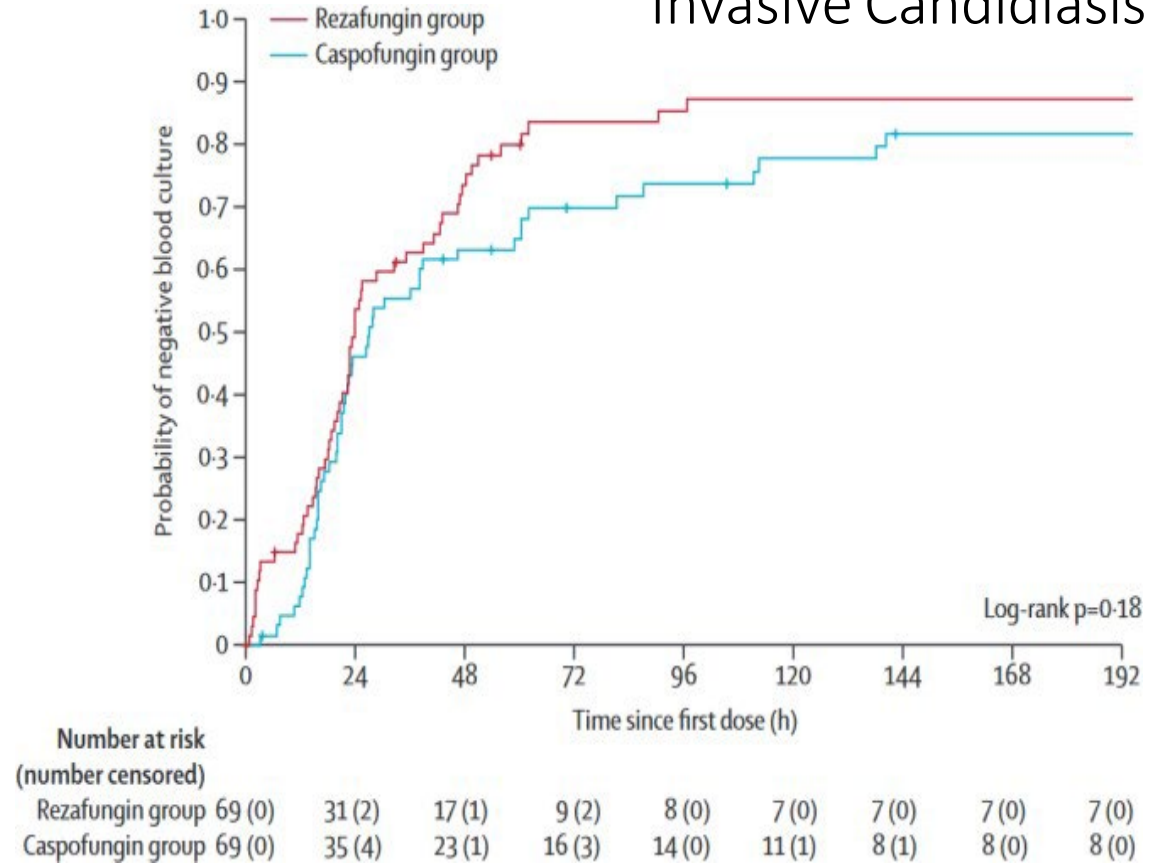


ReSTORE Trial: Reza Vs. Caspo for Candidaemia & Invasive Candidiasis: A Double-blind, double-dummy, randomized phase 3 Trial

Thomson III GR et al, Lancet 2023; 401:49-59

- 199 pts with invasive candidiasis (rezafungin (100) or CASPO followed by FLUCO (100))
  - REZA 400mg IV on day 1, 200mg day 8
  - CAS 70mg IV x 3 days min; FLU following improvement
- Primary endpoint global response at day 14 (EMA):
  - Cure – REZ 55 (59%) vs CAS 57 (61%)
- Primary endpoint all cause 30-day mortality (FDA):
  - REZ 22 pts (24%) vs CAS 20 (21%)
- More rapid clearance of BCx in REZ group (P=0.18)
- AEs similar between groups; drug-related AEs (<3% in both)
- Led to FDA Approval

Invasive Candidiasis



Opelconazole

Hoenigl M et al. Drugs 2021

- First <u>in-class-inhaled</u> antifungal triazole
- Spectrum of Activity:
  - *Candida* spp, *Aspergillus spp*, *Cryptococcus spp* and *Mucorales*
- Advantages
  - High lung concentration with prolonged lung retention, slow absorption from the lung and low plasma concentrations.
  - Low drug-drug interactions or systemic adverse reactions.
- Clinical studies
  - Phase 2: Invasive aspergillosis in cystic fibrosis and lung transplant (NCT03905447; NCT03870841)
  - Phase 2: Prophylaxis/Pre-emptive therapy of IA in lung Tx (closed October 2023)

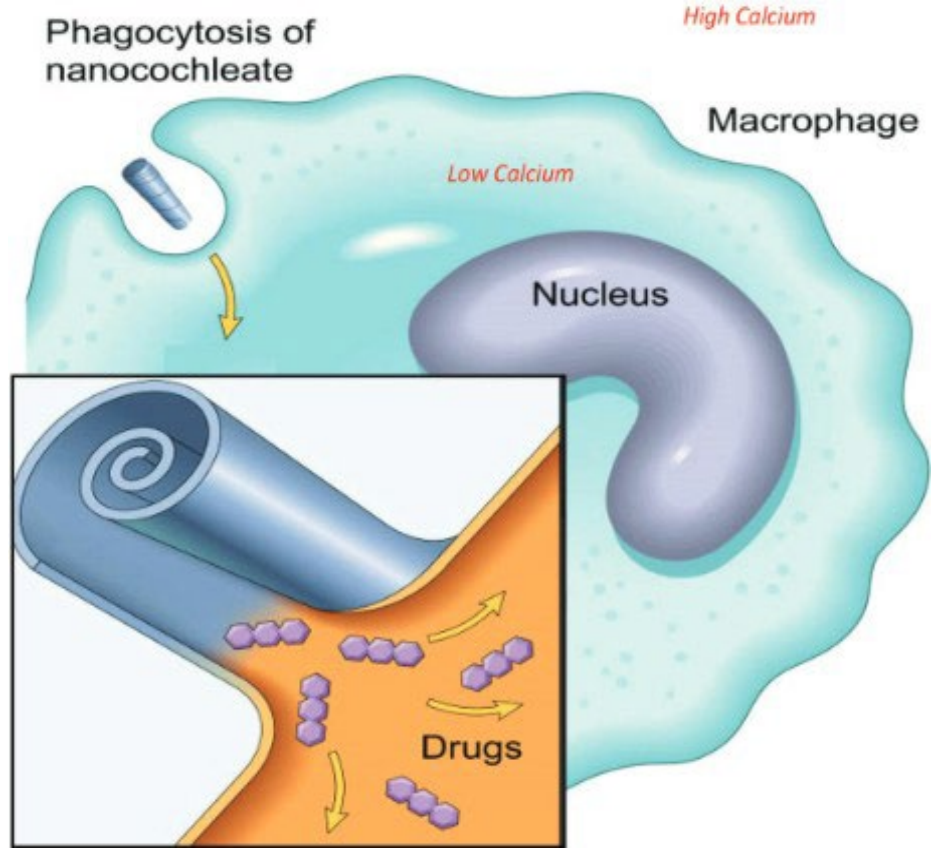
- **Clinical role**

  - Mono (Airway) or combo (ANGIO) therapy for invasive aspergillosis
  - Prophylaxis after lung Tx or in clinical setting where itsrole is not yet firmly established (e.g. ALL or critically ill covid-19 patients).

Encochleated lipid nanocrystal amphotericin B (LNC Am-B)

Gonzalez-Lara et al Drugs 2017; Skipper CP AAC October 2020 ; Hoenigl M et al. Drugs 2021

- Novel lipid-based delivery system
- Allows oral formulation
- Spectrum: similar to AMB (polyene)
- Advantage: oral formulation of amphotericin B delivered by cochleate.
- Clinical Phase: Phase 2
  - Murine models of *C. albicans*, cryptococcal meningitis and IA
  - Vulvovaginal candidiasis-completed (failed)
  - Cryptococcal meningitis (EnACT)-recruiting



Oral encochleated LNC Am-B: Phase II Trial

Boulware DR, Atukunda M et al CID 2023

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

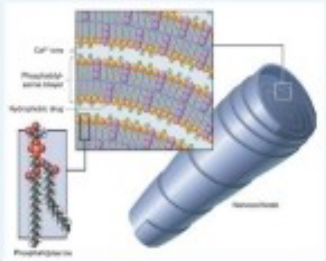
BACKGROUND: We conducted a randomized clinical trial to evaluate the antifungal efficacy of oral lipid nanocrystal (LNC) amphotericin (MAT2203) with flucytosine (5FC) in the treatment of cryptococcal meningitis.

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.

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Strategies for place in therapy

Drugs	Place in therapy
Fosmanogepix	Treatment of DTR infections (scedosporiosis; fusariosis) Invasive candidiasis Azole R IA
Ibrexafungerp	Step-down/long term therapy for IC (azole resistant or echinocandin R-strains) Switch to oral treatment in case of azole-R Aspergillus fumigatus (?)
Olorofim	MDR mould infection, including azole- resistant Aspergillosis, L. prolificans or endemic mycoses such as Coccidiodomycoses
Rezafungin	Earlier hospital discharge IC Second line therapy for IA due to azole resistant A. fumigatus Prophylaxis in HIV patients, HSCT or SOT patients

Conclusions

- Epidemiology of IFI is changing; changing population at risk (e.g. COVID-19)
- Old drugs: Drug-drug interactions, drug related adverse events and low availability of oral medications
- Interesting new entries.. **prudent enthusiasm** (few phase 3 studies; no phase 4 study)
- **Better spectrum:** (activity against MDR moulds): olorofirm, fosmanogepix, ibrexafungerp
- **Reduced toxicity:** CAMB, olorofim,fosmanogepix
- Less drug drug interactions and convenient route of administration
- New strategies for therapy but also for prophylaxis