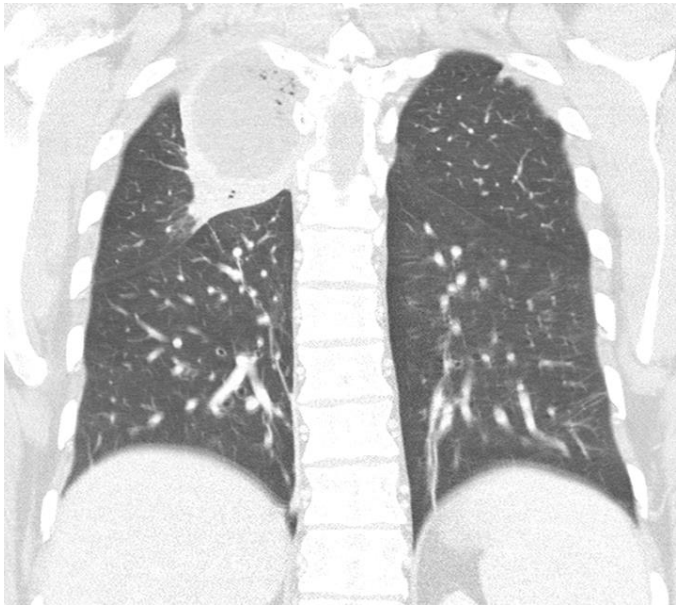
West Coast Transplant ID

Morgan Hakki

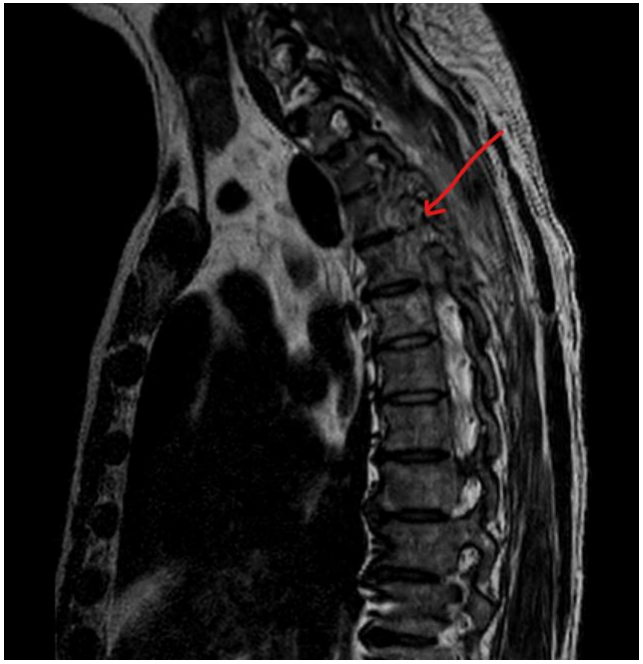
OHSU

Oct 1, 2025

- [redacted] yo with hx of multiple myeloma s/p auto HCT 201[redacted] then B-ALL treated with VIA CALGB 10403 (vincristine, daunorubicin, pegasparagase, prednisone) 8/24 admitted 10/[redacted]/24 for workup of RUL consolidation found incidentally on CXR for PICC placement check
  - Neutropenic 8/18/24-9/4/24
  - Prophylaxis: acyclovir, micafungin while neutropenic
- Endorsed R shoulder pain x 1 month but no other sx
- Social hx: born in Mexico, moved to US 2004, lived in AZ x 18 years, then OR



- CT chest: right upper lobe posterior segment consolidation containing a 5.2 x 4.6 x 3.7 cm fluid collection with multiple internal foci of gas. Associated peripheral soft tissue thickening and hyperenhancement extends to involve the adjacent right pleural surface, with additional extension into the adjacent right thoracic neural foramina



- MRI spine: Rim-enhancing fluid collection centered in the right posterior pleura/chest wall at T3 and T4 with adjacent vertebral and rib osteonecrosis/devitalization

- Underwent IR drain placement 10/13 into pleural cavity -> cx+ Rhizopus microsporus -> Ambisome
  - Susceptibilities requested
- Underwent RUL wedge resection, pleural decortication, soft tissue debridement, T3-T5 laminectomy 10/18-10/21
  - Pleura culture -> Rhizopus
  - Lung parenchyma and Spine cx negative
- 10/29: pt doing well on ambisome but susceptibilities never sent, Lab says it will take 7-14 days (sendout to reference lab)

What do you do now?

A. Keep [redacted] in-house on ambisome pending susceptibilities
B. Keep [redacted] in-house pending susceptibilities but step down to posaconazole
C. Discharge on ambisome
D. Discharge on posaconazole

Susceptibility patterns of amphotericin B, itraconazole, posaconazole, voriconazole and caspofungin for isolates causing invasive mould infections from the SENTRY Antifungal Surveillance Program (2018–2021) and application of single-site epidemiological cutoff values to evaluate amphotericin B activity

Organism/ organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC/MEC (mg/L) of														MIC_{50}	MIC_{90}
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	> [a]		
Rhizopus microsporus group (18)																
Amphotericin B								0	10	8					0.5	1
								0.0	55.6	100.0						
Itraconazole								0	1	5	8	2	0	2	2	>8
								0.0	5.6	33.3	77.8	88.9	88.9	100.0		
Posaconazole							0	1	9	6	0	0	0	2	0.5	>8
							0.0	5.6	55.6	88.9	88.9	88.9	88.9	100.0		

Mycoses. 2023;66:854–868.

In Vitro Antifungal Drug Resistance Profiles of Clinically Relevant Members of the Mucorales (Mucoromycota) Especially with the Newer Triazoles

	MIC (mg/L)									
Amphotericin B	**0.03**	**0.06**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**≥16**
Rhizopus microsporus (96)	–	1	13	31	38	12	1	–	–	–

	MIC (mg/L)									
Posaconazole	**0.03**	**0.06**	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**≥16**
Rhizopus microsporus (83)	-	1	1	14	36	13	7	3	1	6

	MIC (mg/L)									
Isavuconazole	**≤0.03**	0.06	0.125	0.25	0.5	1	2	4	8	≥16
Rhizopus microsporus (23)	-	-	-	-	-	6	7	7	2	1

J. Fungi **2021**, *7*, 271. https://doi.org/10.3390/jof7040271

- Pt discharged 10/[redacted]/24 on posaconazole
- Treatment of ALL continued with blinatumomab (CD19/3 bispecific Ab)
- Seen in follow up 12/[redacted]/24: doing well, no new symptoms
  - ANC 4730
  - Posaconazole trough 1.6
- CT chest: There is soft tissue mass along the staple line, measuring 53 x 20 mm (soft tissue axial 39). More involvement of the superior medial chest wall with eroding the adjacent costovertebral joint and posterior medial right 3rd-4th rib with pathologic fracture.
- MRI spine: Compared to prior exam on 10/12/2024, interval increase in diffuse irregular marrow signal and inflammatory change throughout the T2 and T3 vertebral bodies. Additional extension into the right greater than left pedicles of T3 and associated posterior elements. Findings are concerning for worsening infection/osteomyelitis. Additional increase in irregular signal and inflammatory change throughout the posterior aspect of the T4 vertebral body and associated right pedicle and posterior elements.
- Rhizopus microsporus susceptibility testing (MICs in mcg/mL):
  - Ampho = 4
  - Posa = 4
  - Isavu = > 16

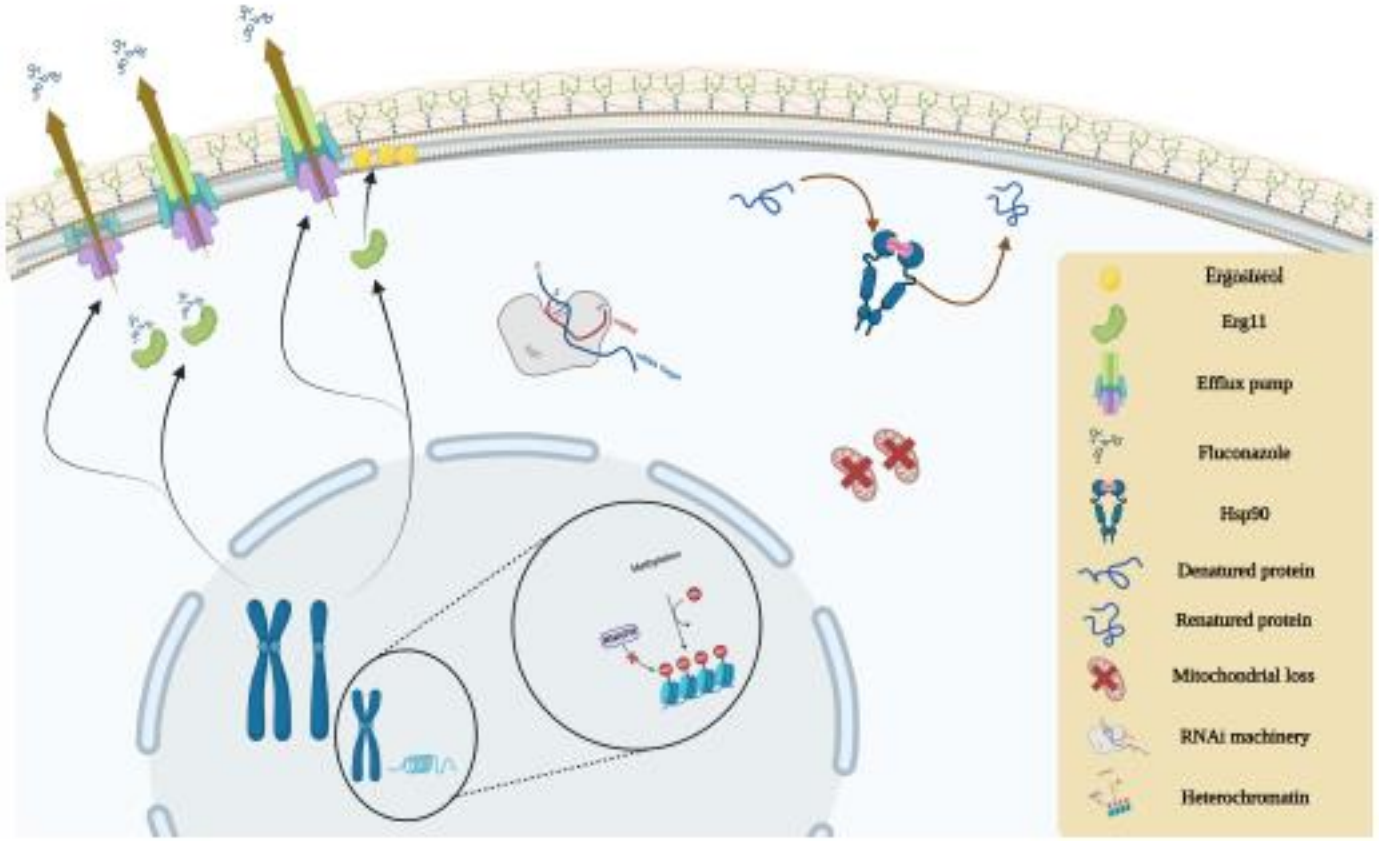


FIG 3 Mechanisms generally governing antifungal resistance. Azole resistance involves multiple mechanisms, including the overexpression of efflux pumps (CDR1 and MDR1) due to hyperactive Tac1 and Mrr1, and the overexpression of the drug target using hyperactive UPC2. The drug target mutation is universal for both azole and echinocandin resistance. Mechanisms underpinning AmB resistance have not been shown.

- You admit for surgical evaluation. What do you do with [redacted] antifungal therapy in the right now?

A. Continue posaconazole, increase dose
B. Stop posaconazole, start high(er) dose ambisome (≥5 mkg/kg/day)
C. Stop posaconazole, start high(er) dose ambisome and echinocandin
D. Stop posaconazole, start nothing
E. None of the above (write-in your vote)

- [redacted] undergoes:
- C6-T8 PIF, T2-4 complete costotransversectomies, bilateral T2-T3 laminectomies and T2-T4 corpectomies with fibula free graft spinal reconstruction
  - Cultures negative
  - Path with fungal forms c/w Rhizopus
- Redo thoracotomy w/ redo RUL lung wedge resection and RLL wedge resection in addition to radical posterior pleurectomy
  - Cultures negative, BRPCR+ Rhizopus microsporus
- Renal function fluctuates but Ambisome continued with dose adjustments prn

What is your long-term antifungal therapy plan?

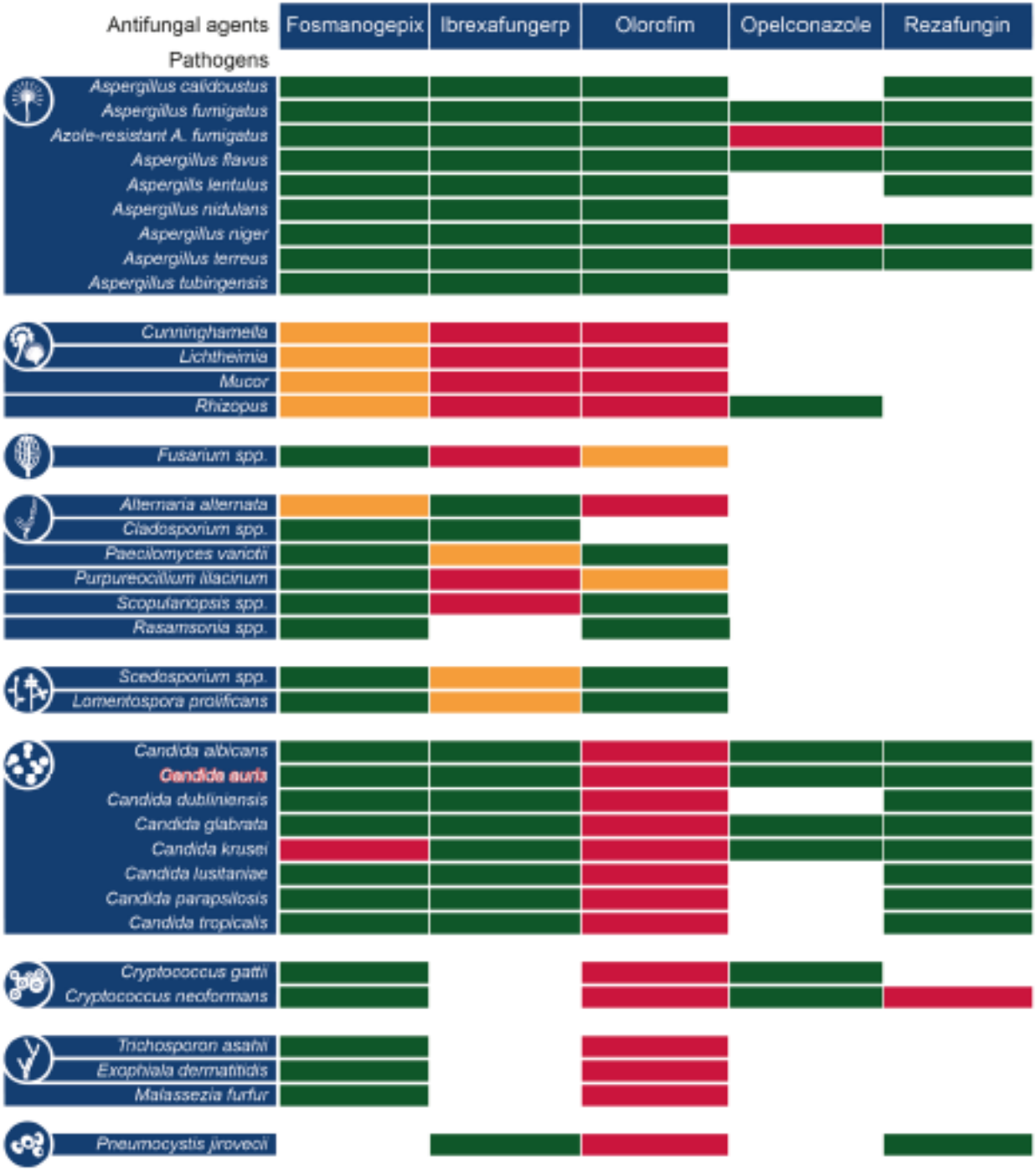
A. High dose ambisome
B. Fosmanogepix
C. Olorofim
D. Ibrexafungerp
E. Opelconazole

- Approval for fosmanogepix sought and received
- Pt started fosmanogepix 1/17/25
- Discharged 1/26/25 on fosmanogepix + TIW ambisome
  - Unfortunately no isolate available for fosmanogepix susceptibility testing
- Ambisome eventually stopped 2/4
- Fosmanogepix continued through 6/25 with no e/o recurrence clinically or radiographically at EOT
- Continues blinatumomab

Fosmanogepix

- Prodrug that is metabolized by systemic phosphatases to the active moiety manogepix (formerly APX001A).
- Interferes with cell wall synthesis by targeting fungal glycosylphosphatidylinositol-anchored cell wall transfer protein with resultant loss of cell viability

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



Drugs (2021) 81:1703–1729

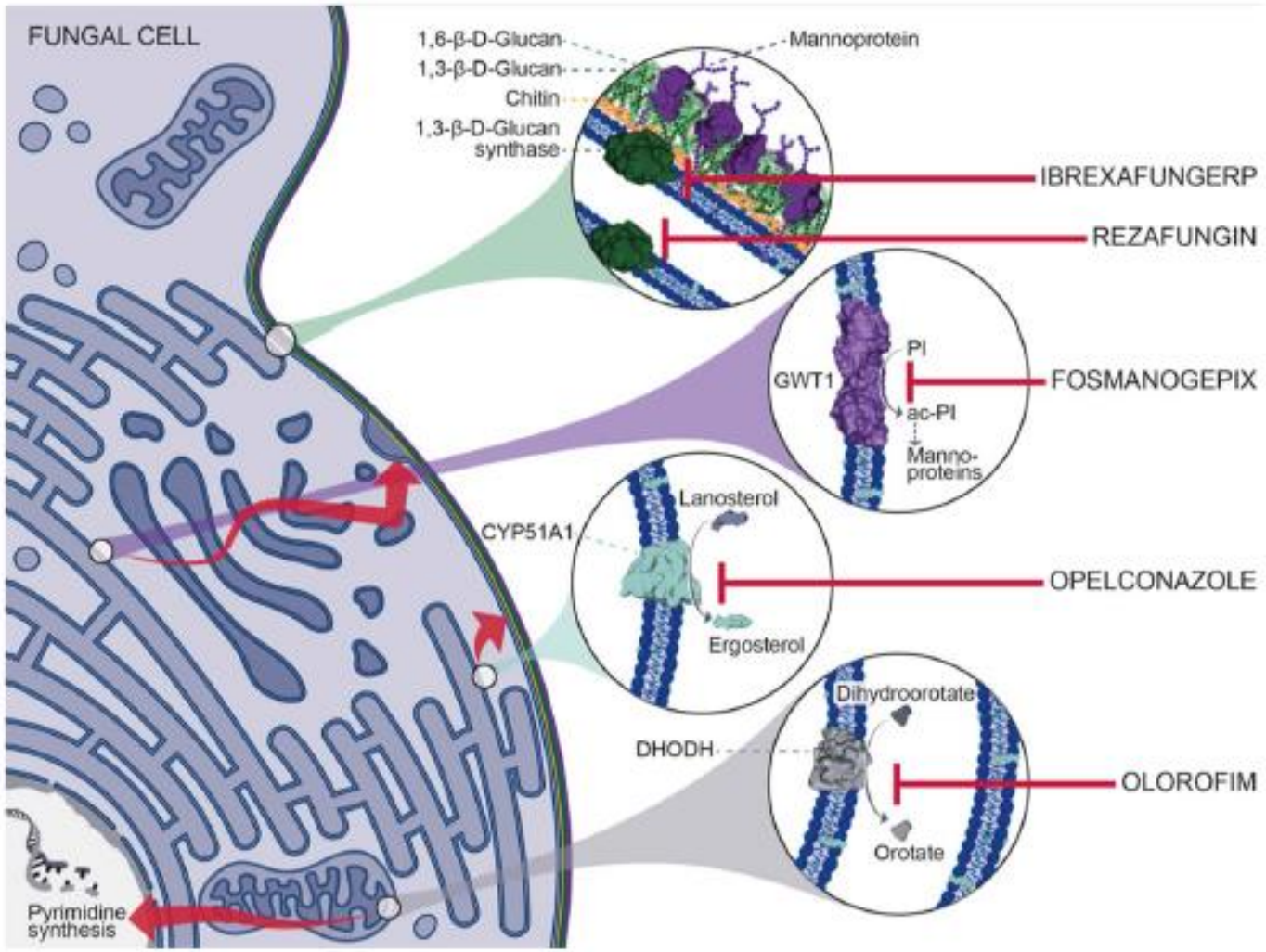


Fig. 1 Mechanism of action of novel antifungal drugs discussed in this review. *DHODH* dihydroorotate dehydrogenase

Activities of Manogepix and Comparators against 1,435 Recent Fungal Isolates Collected during an International Surveillance Program (2020)

Organism	MIC or MEC (mg/L)						
	Manogepix	Anidulafungin	Caspofungin	Micafungin	Posaconazole	Voriconazole	Amphotericin B
Rhizopus microsporus group	2	>4	>4	>4	0.5	8	0.5
Rhizopus microsporus group	2	>4	>4	>4	0.5	8	1
Rhizopus microsporus group	>8	>4	>4	>4	1	8	1
Rhizopus microsporus group	>8	>4	>4	>4	0.5	8	1
Rhizopus oryzae	4	>4	>4	>4	0.5	8	0.5
Rhizopus oryzae species complex	>8	>4	>4	>4	0.5	>8	0.5

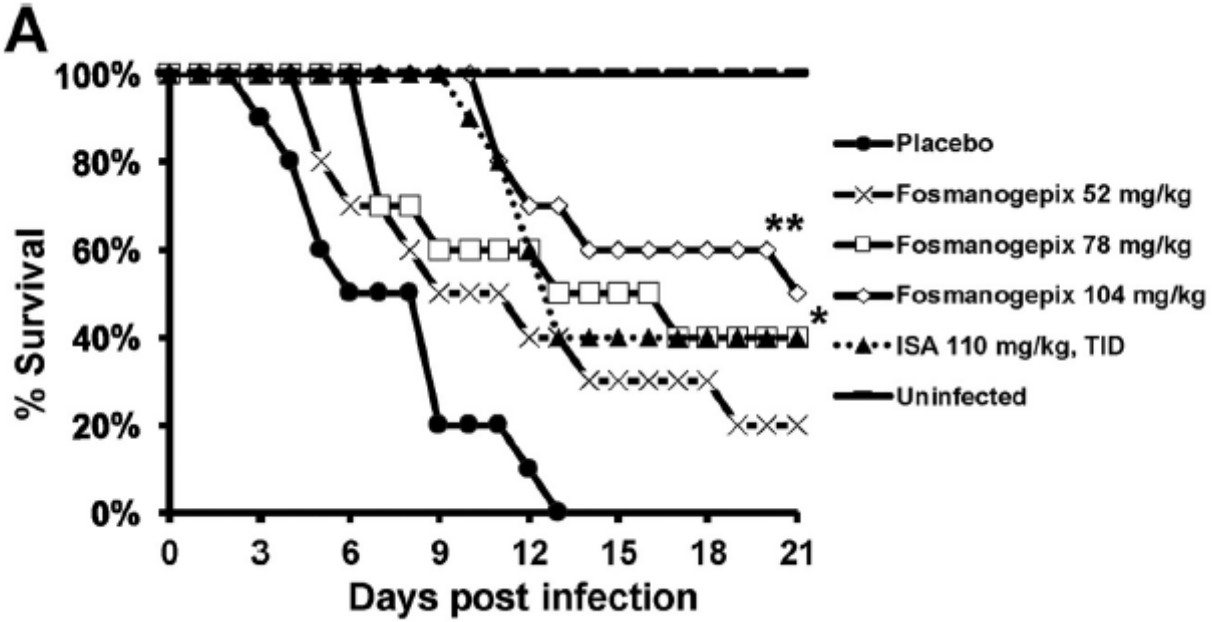
Fosmanogepix (APX001) Is Effective in the Treatment of Pulmonary Murine Mucormycosis Due to *Rhizopus arrhizus*

TABLE 1 Antifungal susceptibility of clinical isolates of *R. arrhizus* var. *delemar* and *R. arrhizus* var. *arrhizus*[a]

Isolate	Assessment type	MEC or MIC in μg/ml		
		MGX	POSA	ISA
R. arrhizus var. *delemar* ($n = 19$)	Range	0.25–8.0	0.125–1.0	1.0–8.0
	MEC/MIC_{50}	0.5	0.25	2.0
	MEC/MIC_{90}	4.0	1.0	4.0
	GM MEC/MIC	0.75	0.36	2.5
R. arrhizus var. *arrhizus* ($n = 17$)	Range	0.25–8.0	0.06–0.5	0.25–2.0
	MEC/MIC_{50}	8.0	0.125	1.0
	MEC/MIC_{90}	8.0	0.25	1.0
	GM MEC/MIC	3.84	0.15	0.85

Fosmanogepix (APX001) Is Effective in the Treatment of Pulmonary Murine Mucormycosis Due to *Rhizopus arrhizus*

A

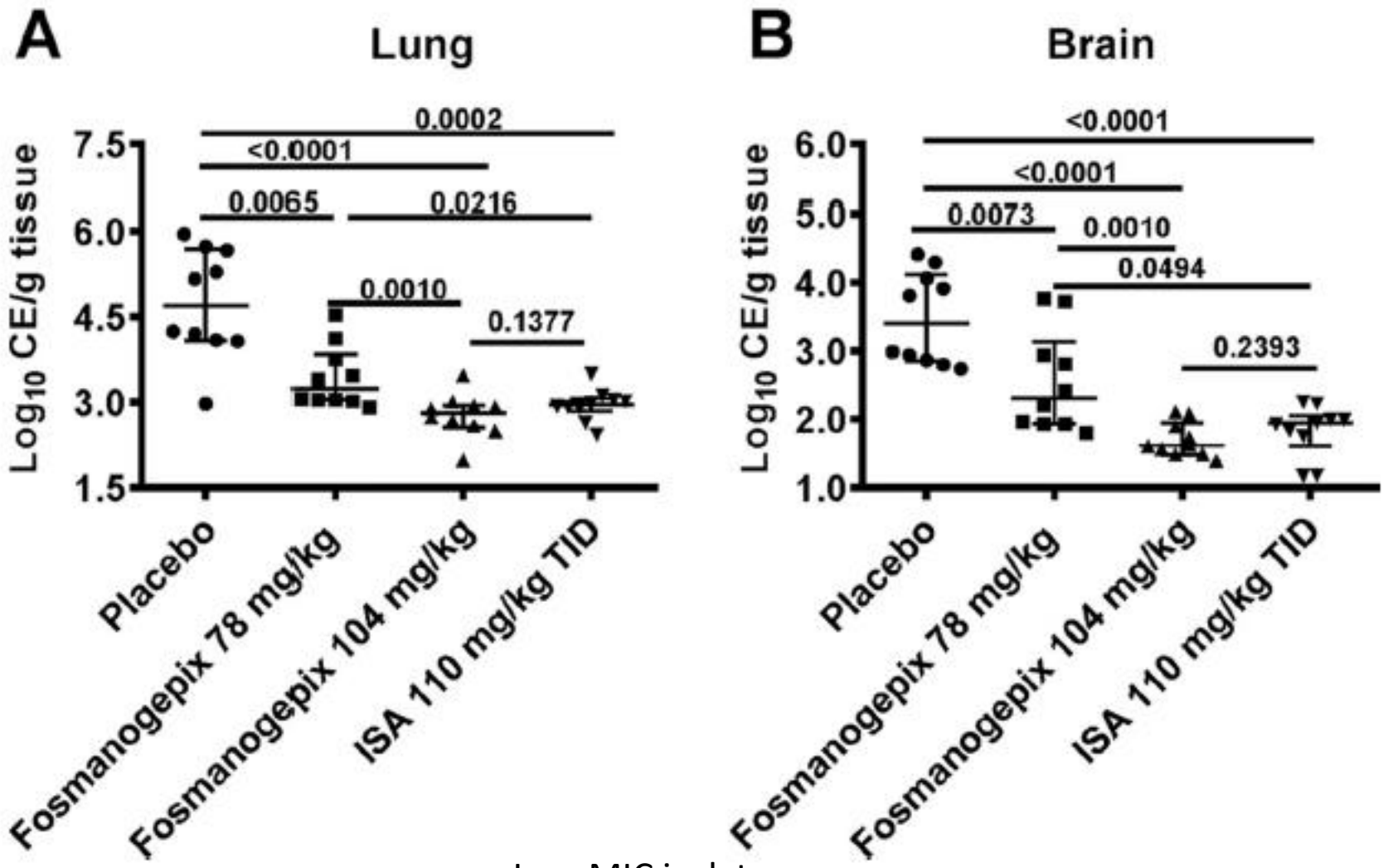


B

	Placebo	Fosmanogepix + ABT QD			ISA TID
		52 mg/kg	78 mg/kg	104 mg/kg	110 mg/kg
Median Survival	6	9	13	21	13
Percent Survival	0%	20%	40%	50%	40%

Low MIC isolate

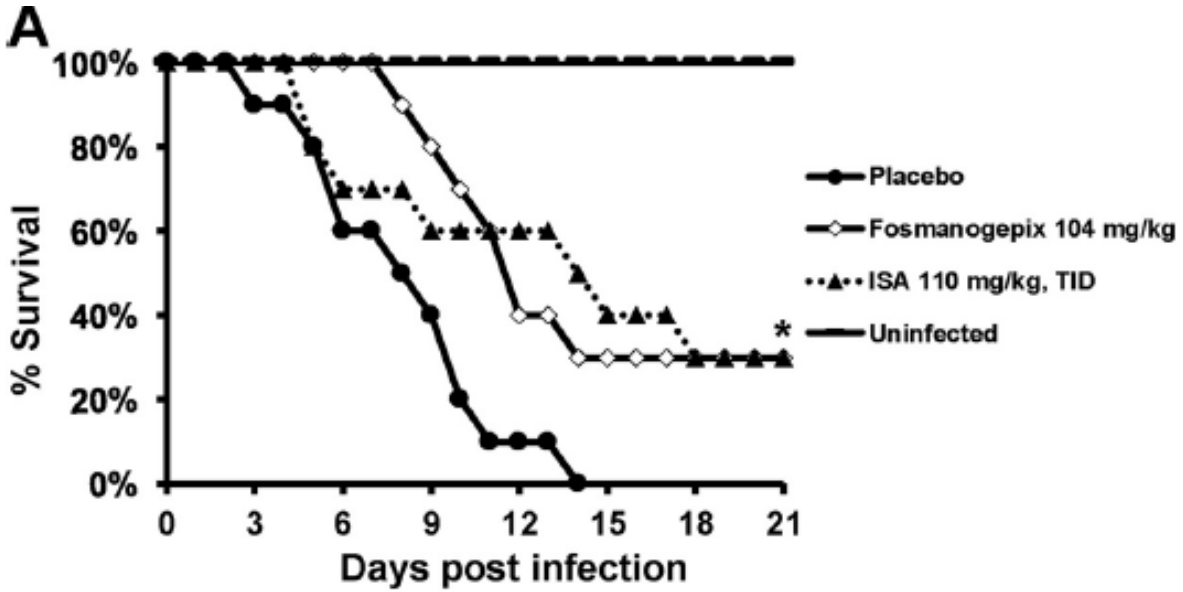
Fosmanogepix (APX001) Is Effective in the Treatment of Pulmonary Murine Mucormycosis Due to *Rhizopus arrhizus*



Low MIC isolate

Fosmanogepix (APX001) Is Effective in the Treatment of Pulmonary Murine Mucormycosis Due to *Rhizopus arrhizus*

A

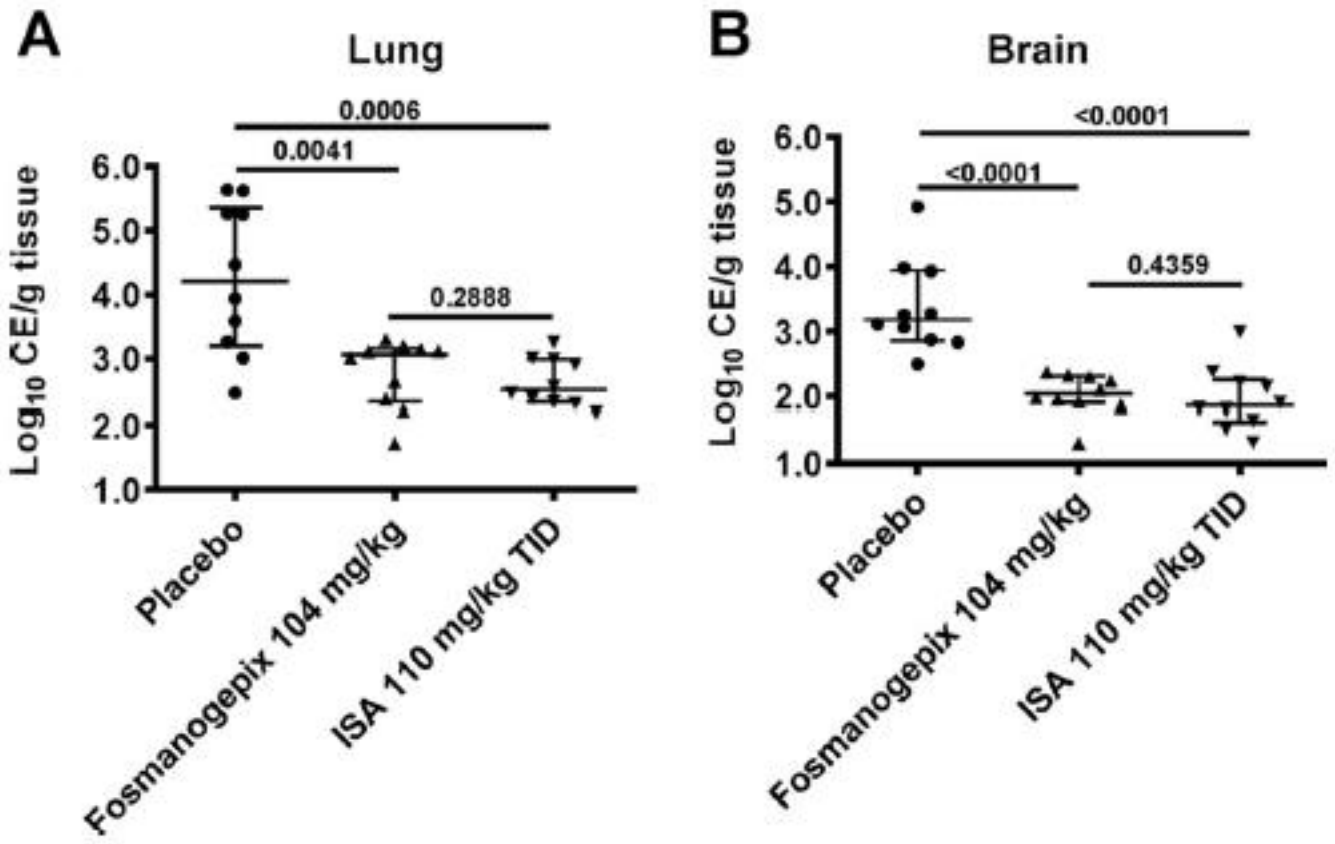


B

	Placebo	Fosmanogepix + ABT QD	ISA TID
		104 mg/kg	110 mg/kg
Median Survival	8	12	14
Percent Survival	0%	30%	30%

High MIC isolate

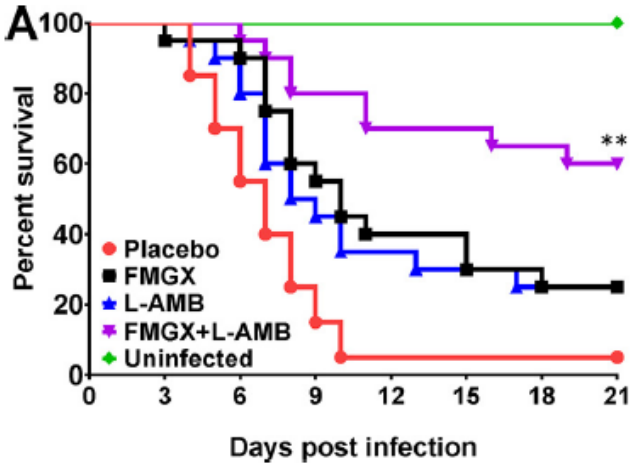
Fosmanogepix (APX001) Is Effective in the Treatment of Pulmonary Murine Mucormycosis Due to *Rhizopus arrhizus*



High MIC isolate

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

Survival of immunosuppressed mice infected with *A. fumigatus*.

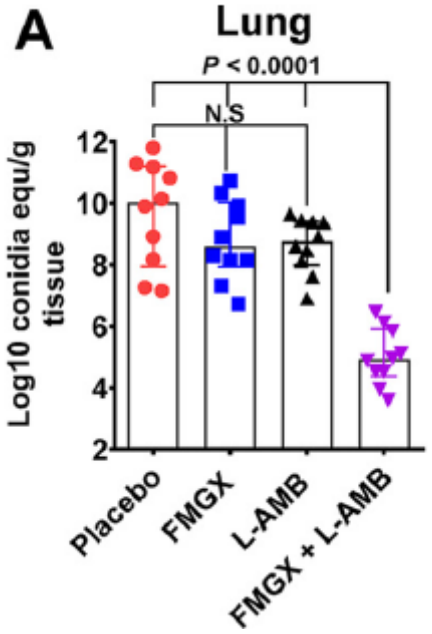


B

Treatment	Median survival (days)	% Survival	*P* value (*vs.* placebo)
Placebo	7	5	N/A
FMGX	10	25	0.004
L-AMB	8.5	25	0.02
FMGX + L-AMB	>21	60	<0.0001

TABLE 1 Antifungal susceptibilities

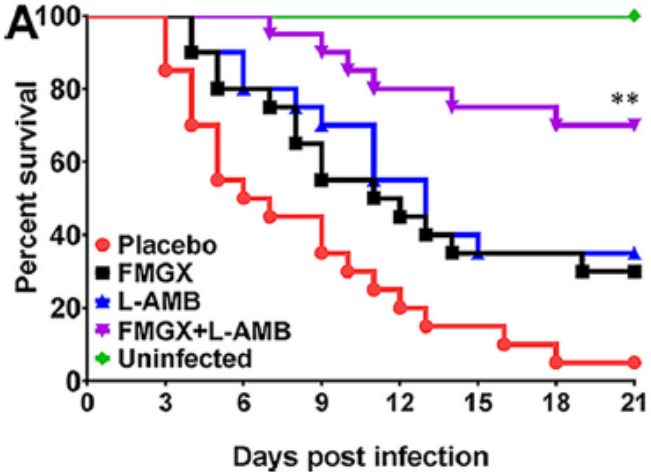
	Value (μg/mL) for:	
Clinical isolate	MGX MEC	AMB MIC
Aspergillus fumigatus AF293	0.03	0.25
Rhizopus arrhizus var. *delemar* strain 99-880	0.25	0.25
Fusarium solani 95-2478	0.03	4.0



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

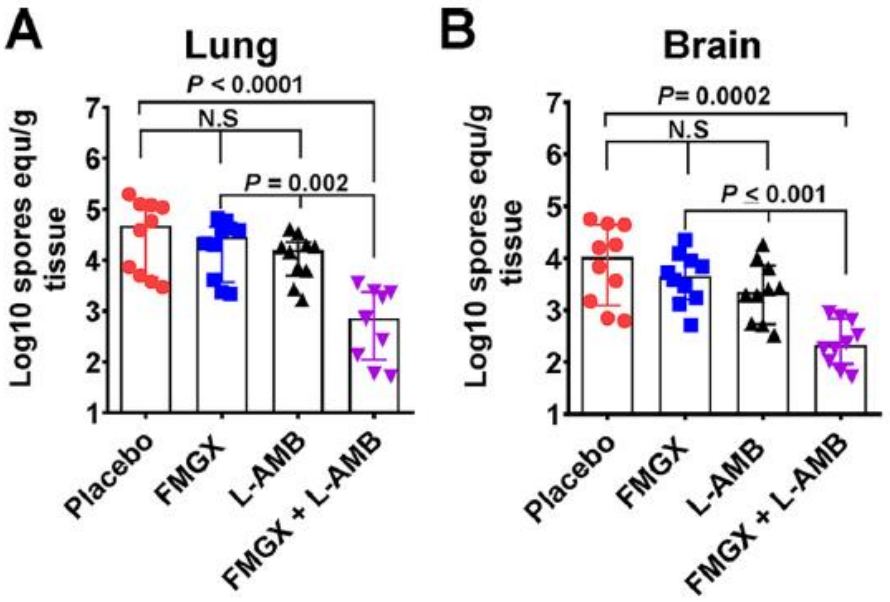
Survival of immunosuppressed mice infected with *R. arrhizus* var. *delemar*.

A



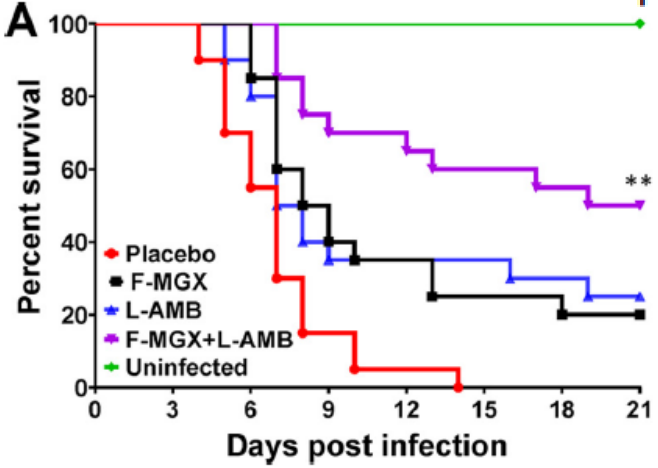
B

Treatment	Median survival (days)	% Survival	*P* value (*vs.* placebo)
Placebo	6.5	5	N/A
FMGX	11.5	30	0.02
L-AMB	13	35	0.005
FMGX + L-AMB	>21	70	<0.0001



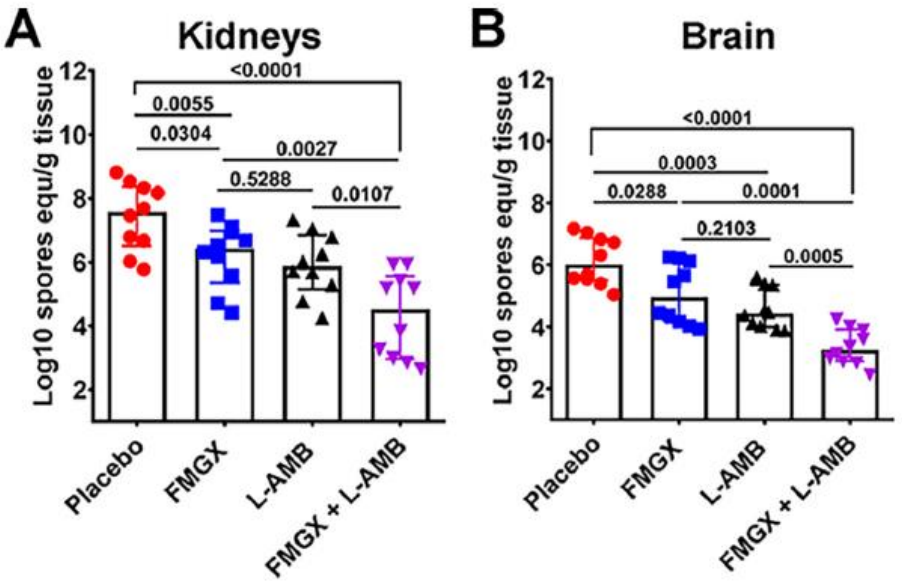
The Combination Treatment of Fosmanogepix and Liposomal Amphotericin B Is Superior to Monotherapy in Treating Experimental Invasive Mold Infections

Survival of immunosuppressed mice infected with *F. solani*.



B

Treatment	Median survival (days)	% Survival	*P* value (*vs.* placebo)
Placebo	7	0	N/A
FMGX	8.5	20	0.003
L-AMB	7.5	25	0.007
FMGX + L-AMB	20	50	<0.0001



Fosmanogepix for Candida infections

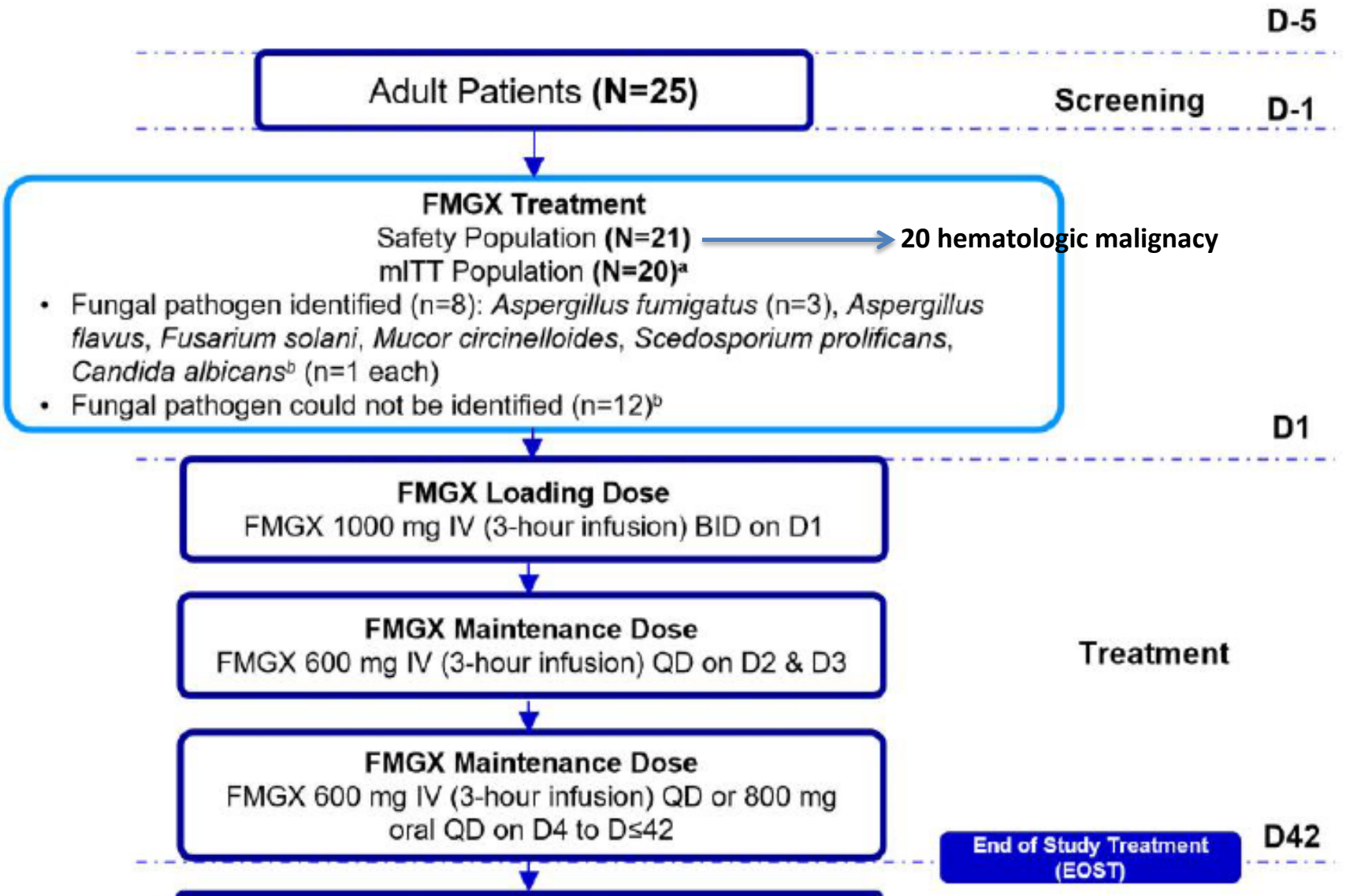
- Two phase II studies have evaluated the safety of fosmanogepix in patients with *Candida* infections:
  - multicenter, open-label, non-comparative, single-arm study in non-neutropenic patients with candidemia (NCT03604705)
    - The primary endpoint was observed in 16/20 (80%) of participants in the mITT population
  - multicenter, open-label, single-arm phase II study for the treatment of candidemia/invasive candidiasis caused by *C. auris* (NCT04148287)
    - Of 9 participants, 8 (89%) met the primary endpoint.
- Current phase III study for the treatment of candidemia and/or invasive candidiasis (NCT05421858)

Fosmanogepix for the Treatment of Invasive Mold Diseases Caused by *Aspergillus* Species and Rare Molds: A Phase 2, Open-Label Study (AEGIS)

- Phase II, open-label, multicenter, non-comparative study in adult patients Jan 2020-May 2022
  - Those with limited treatment options, resistance, contraindications or intolerance, lack of response to SOC
- Study terminated early to prioritize a randomized comparative Phase III study in the same indication (NCT06925321) (only 1 location listed as actively recruiting – Wash U)
- Endpoints:
  - Day 42 all-cause mortality
  - Global response at end of therapy (secondary efficacy endpoint)

CID • Hodges et al published online 9 April 2025

Fosmanogepix for the Treatment of Invasive Mold Diseases Caused by *Aspergillus* Species and Rare Molds: A Phase 2, Open-Label Study (AEGIS)



Fosmanogepix for the Treatment of Invasive Mold Diseases Caused by *Aspergillus* Species and Rare Molds: A Phase 2, Open-Label Study (AEGIS)

Table 2. Efficacy Endpoints (mITT Population)

Efficacy Endpoints	FMGX Cohort N = 20
Primary: Day 42 All-Cause Mortality, n (%); 80% CI	5 (25); 12.7–41.5
Secondary: DRC assessed global response at EOST/ET	
Treatment success, n (%); 80% CI	8 (40); 24.9–56.7
Complete response, n (%)	4 (20)
Partial response, n (%)	4 (20)
Stable disease, n (%)	2 (10%)
Treatment failure, n (%)	10 (50)
Progression of disease, n (%)	6 (30)
Death, n (%)	4 (20)

An adjusted survival of 55% (ie, mortality rate: 45%) was considered for the AMB historical control.

Fosmanogepix for the Treatment of Invasive Mold Diseases Caused by *Aspergillus* Species and Rare Molds: A Phase 2, Open-Label Study (AEGIS)

Table 3. Summary of Overall Safety (ITT Population)

Safety Parameters	FMGX Cohort N = 21
Overall safety summary, n (%)	
Number of TEAEs	258
Participants with TEAEs	21 (100)
Serious TEAEs	13 (61.9)
Grade 3 or 4 TEAEs	11 (52.4)
Grade 5 TEAEs	6 (28.6)
Discontinuations from study due to TEAEs	0
Discontinuation of FMGX due to TEAEs[a]	7 (33.3)
Total deaths	9 (42.9)
Through EOST[b]	4
EOST through follow-up visit	2
Post follow-up visit[c]	3

Opelconazole

- first-in-class inhaled triazole antifungal
- achieves high and prolonged concentrations in the lung
- broad spectrum activity against yeasts (Candida spp including C auris, Cryptococcus), Aspergillus, and Rhizopus (limited testing)
- Case report of use in ABPA
- OPERA-S: Safety study of opelconazole prophylaxis or pre-emptive therapy against pulmonary aspergillosis in lung transplant recipients (NCT05037851) (completed)
- OPERA-T: Safety and efficacy of opelconazole in combination with other antifungal therapy for the treatment of refractory invasive pulmonary aspergillosis (NCT05238116) (ongoing)

In Vitro and *In Vivo* Antifungal Profile of a Novel and Long-Acting Inhaled Azole, PC945, on *Aspergillus fumigatus* Infection

TABLE 6 Antifungal effects of PC945 and posaconazole on other fungal species

Species (strain[s])	No. of strains tested	Culture method	MIC (μg/ml)[a]		
			PC945	Voriconazole	Posaconazole
Mucor circinelloides (ATCC 8542)	1	CLSI	>8	>8	>8
Rhizomucor pusillus (ATCC 16458)	1	CLSI	>8	>8	>8
Rhizopus oryzae (ATCC 11145)	1	CLSI	2	>8	>8

Thank you!