Tackling pharmacokinetic and pharmacodynamic challenges in antifungal therapy

Guest speakers: Wan-Yu (Wendy) Chu, Francelise Bridi Cavassin & David Andes

Moderator: Dallas Smith

Host: Shirine Derakhshani

17 September 2026

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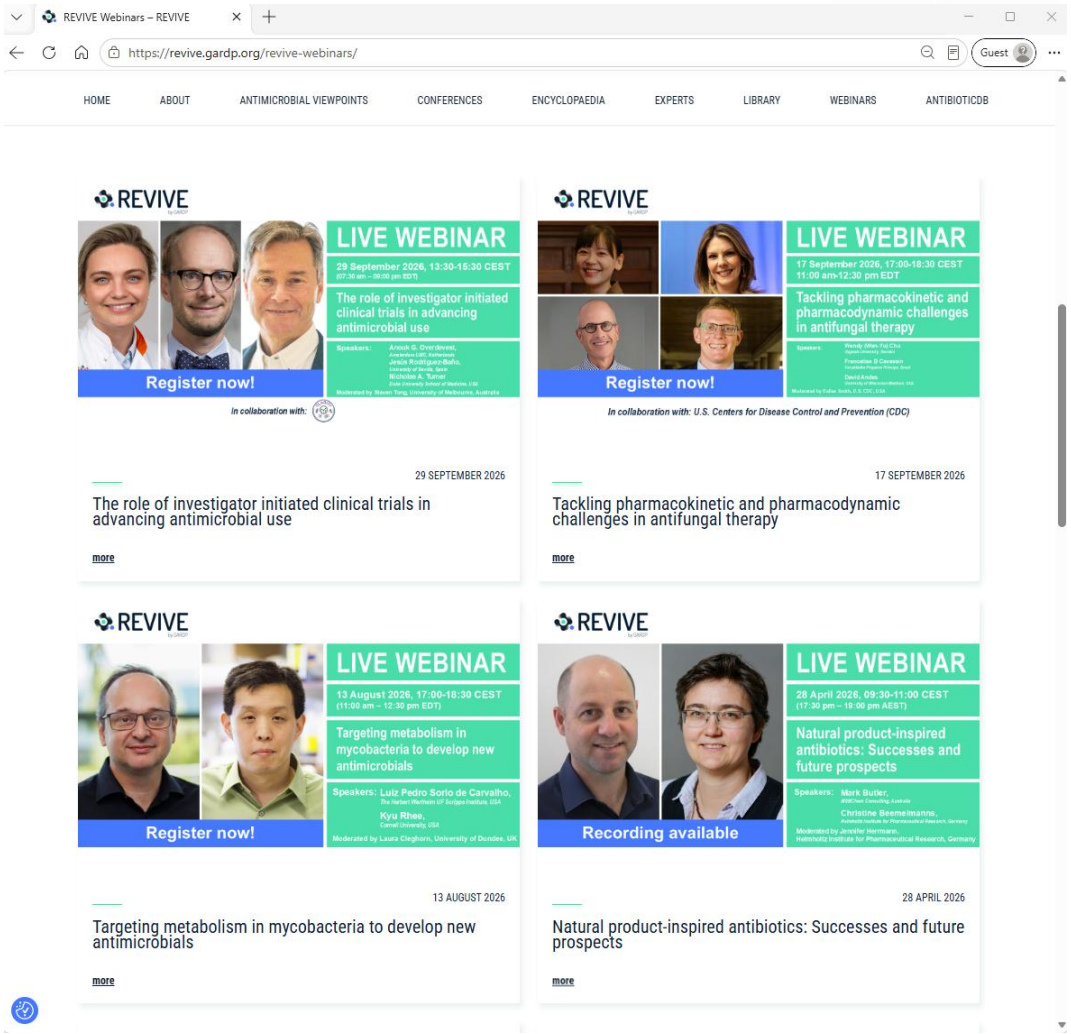

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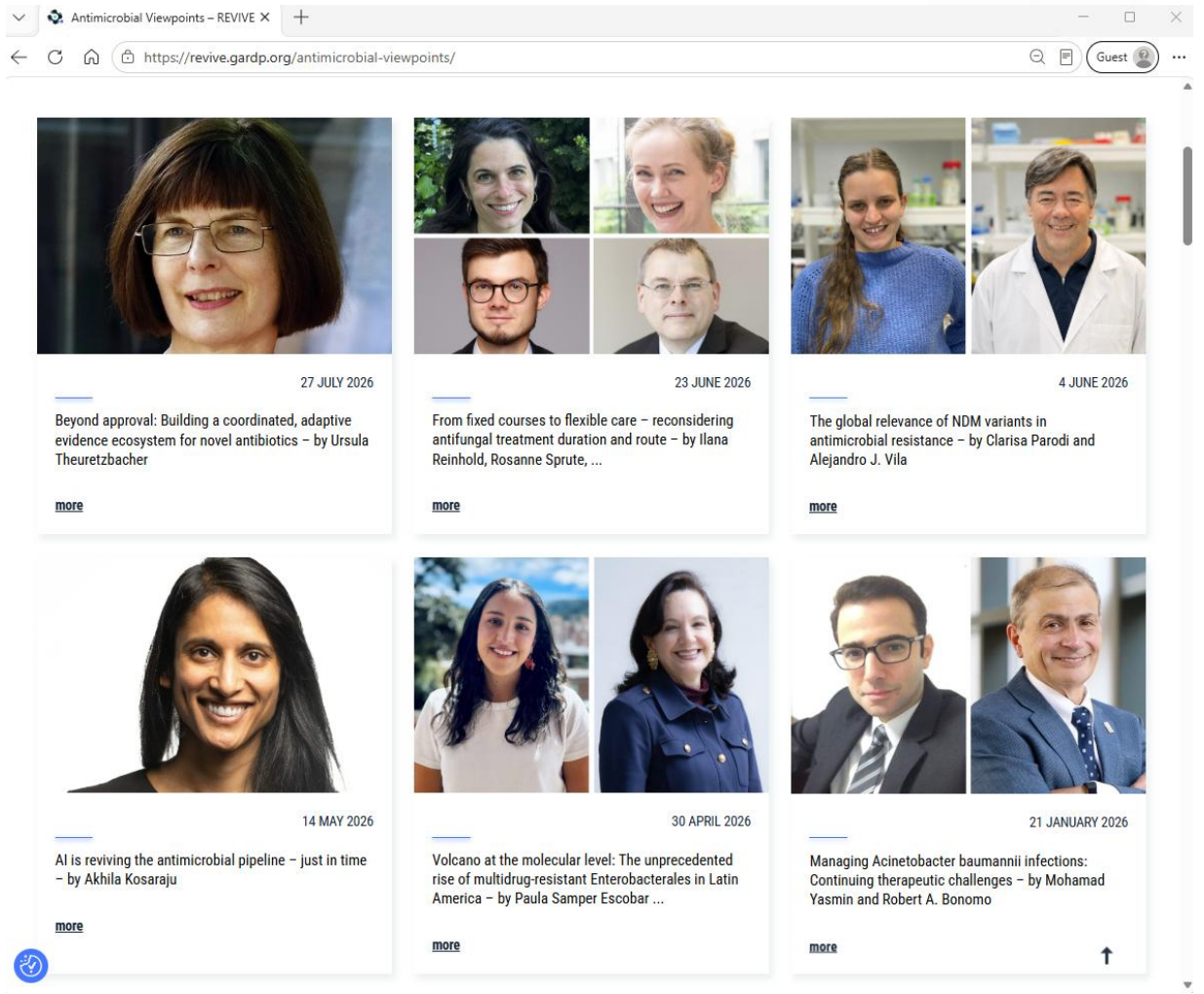

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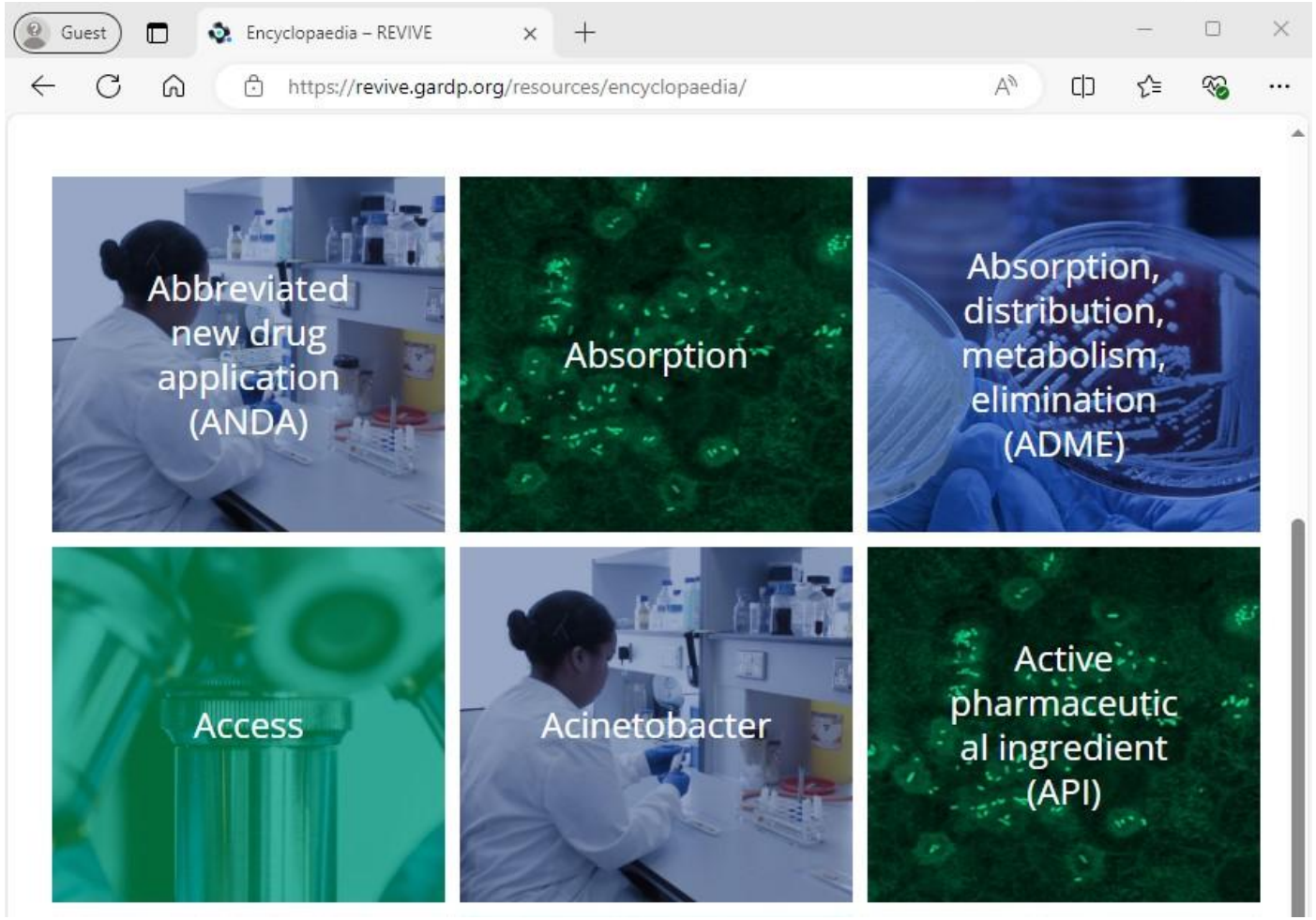

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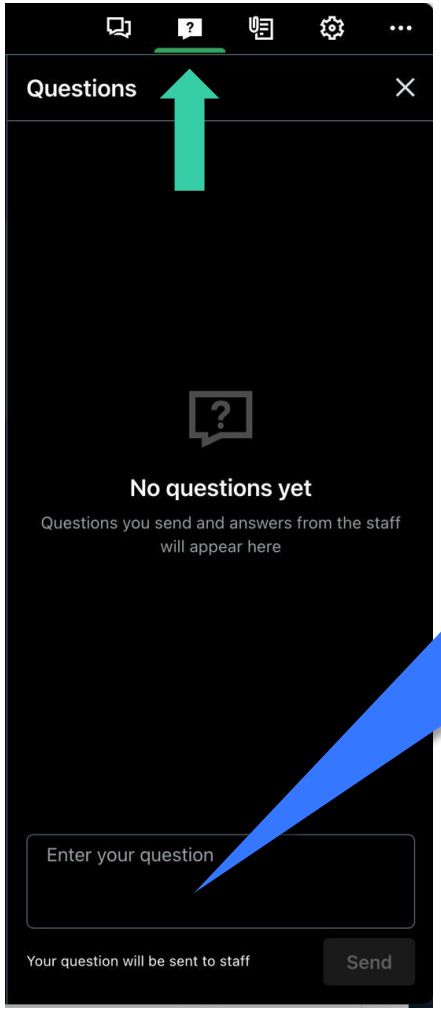


Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

Today's speakers

REVIVE by GARDP

An introduction to antibiotic research and development (R&D)

Moderator:
Dallas Smith
Centers for Disease Control and Prevention
U.S. CDC, USA

Wan-Yu (Wendy) Chu
Uppsala University, Sweden

Francelise Bridi Cavassin
Faculdades Pequeno Príncipe, Brazil

David Andes
University of Wisconsin-Madison, USA

Tackling Pharmacokinetic and Pharmacodynamic Challenges in Antifungal Therapy

Antifungal resistance is a growing global threat

‘A growing threat to human health’: we are ill-equipped for the dangers of fungal infections

About 2 million people die a year as a result of a core group of fungi, and the WHO is concerned we are unprepared for the future

MARYN MCKENNA SCIENCE AUG 25, 2023 6:00 AM

The Battle Against the Fungal Apocalypse Is Just Beginning

Fungal infections are rising worldwide and climate change may be to blame. Medicine isn’t ready.

FUNGUS

A New Drug-Resistant Fungus Is Spreading in Hospitals. Is It *The Last of Us* in Real Life?

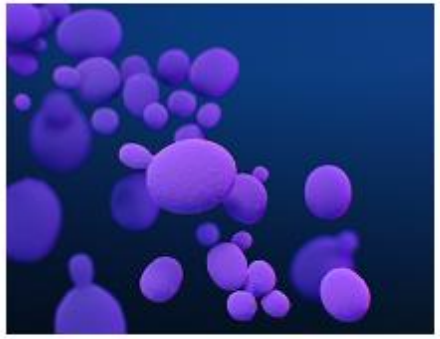
Candida auris **isn’t going to “cause a zombie apocalypse tomorrow,” says CARB-X director Kevin Outterson—but researchers do need to take it seriously**

Several fungal diseases and fungi are developing resistance domestically and globally

Aspergillus

Candida

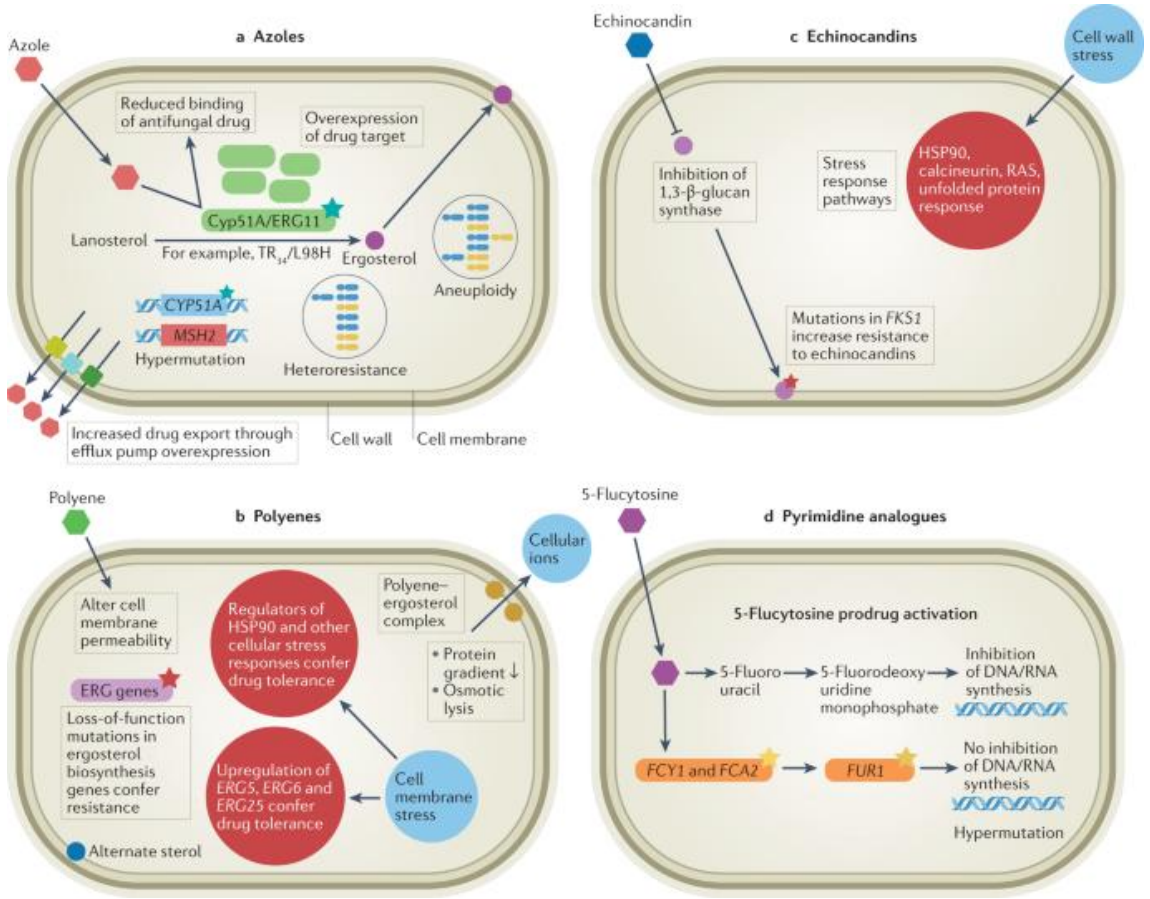
Candida auris



Ringworm

[Antimicrobial-Resistant Fungi | Fungal Diseases | CDC]

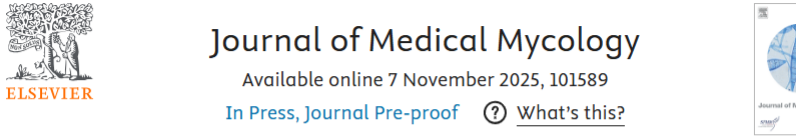
Resistance is developing to all currently available antifungal classes

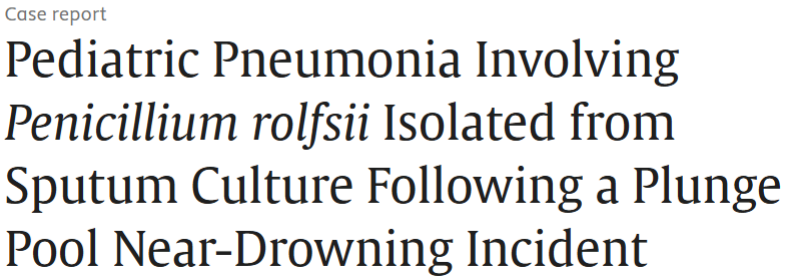


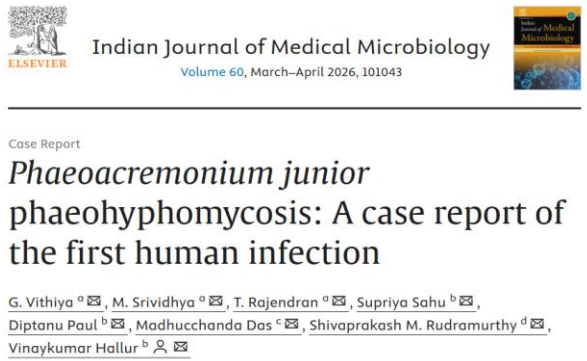
Tackling the emerging threat of antifungal resistance to human health | Nature Reviews Microbiology

Emerging fungi are causing human infections

- **Examples:**
  - *Rhodosporidiobolus fluvialis*
  - *Chrysocorona lucknowensis*
  - *Penicillium rolfsii*
  - *Candida berthetii*
  - *Phaeoacremonium junior*







Antifungal penetration into tissues and body fluids relative to plasma concentration

Compound	Eye			Skin			Vagina		Heart		Liver	Pancreas	Kidney	Bone		Prostate		Brain		Lung			Spleen	Muscle	Reference
	Aqueous	Vitreous	Cornea	Tissue	Interstitial fluid	Nail	Tissue	Fluid	Tissue	Pericardial fluid				Tissue	Synovial fluid	Tissue	Fluid	Tissue	CSF	Tissue	Alveolar cells	ELF			
Fluconazole	X	X	O	X	X	X	X	X	X	X	X	X	X	X O	X	X X	X	X	X	X		O	X	X	(67, 70, 72, 120, 137, 200-203, 205, 219, 237, 238)
Itraconazole	O X	O[2] X	O	X X	X	X	X X	X X	O		X	O	X	X	X	X	X	O	X	X X[5]	X	X	X	X	(25, 56, 73, 74, 120, 121, 140, 220, 221, 239-242)
Voriconazole	X	X		O	O				X X[◇]		X X		X X	X	X			X	X	X X	X	X X[•]	X X	O	(58, 80, 81, 83, 114, 142, 153, 154, 208, 224, 243, 252, 253)
Posaconazole		X		X		X												O	X		X	X			(57, 59, 85-89, 223, 244)
AmBd	X X	X							O X[◇]		X	X X	X	O	X			X X	X	O O[4]		X[3] O	X		(37, 52, 53, 91, 115, 123, 148, 151, 156, 210, 245-247, 249)
ABLC	O[2]	O[2]							X		X		X	O				O	X	X[◇]		X[•] X	X[◇]		(90, 92, 117, 125, 147, 155, 210, 246, 249)
L-AMB	O[2]	O[2]	O[2]	X[□]					O X		X[◇]		X[◇]	O				X	X	X		X[•] X	X[◇]		(34, 53, 60, 90, 125, 147, 155, 210, 248, 249)
5-FC	O	X		O					O		O		O O	O	O			O	X X	O[4]		O[3]	O	O	(91, 96, 115, 116, 151, 156, 174, 250)
Anidulafungin	O	O		O					O		O		O	O				O	O	O O	X	X	O O		(58, 100, 102, 175, 251)
Caspofungin	X O[2]	X	O[2]						O		O		O					O	X	O	X		O	O	(44, 103, 105, 113, 126, 130, 149)
Micafungin	O[2]	O[2]		X[◇]							O O	X[•]	O O					X	X X	O O	X	X X[•]	O		(61, 62, 106-108, 127, 150, 252)

Red, from below level of detection to ≤0.5 times the plasma concentration; yellow, from >0.5 times to ≤5 times the plasma concentration; green, >5 times the plasma concentration; white, no data

Documented and likely intrinsic antifungal resistance against fungi

Fungus	Amphotericin B	Fluconazole	Voriconazole	Isavuconazole	Posaconazole	Itraconazole	Anidulafungin	Caspofungin	Micafungin	Rezafungin	Olorofim	Fosmanogepix	Ibrexafungerp	Flucytosine
Candida species											■			
Pichia kudriavzevii		■									■	■		■
Cryptococcus gattii & deuterogattii							■	■	■	■	■			
Cryptococcus neoformans							■	■	■	■	■			
Rhodotorula species		■					■	■	■	■	■			
Trichosporon species		■					■	■	■	■	■			
Aspergillus species		■												
A. terreus species complex	■	■												■
A. alliaceus	■	■												■
Mucorales		■	■				■	■	■	■	■		■	■
Fusarium species		■					■	■	■				■	■
Scedosporium species	■	■											■	■
Lomentospora prolificans	■	■					■	■	■				■	■
Purpureocillium lilacinum	■	■											■	■
Scopulariopsis species		■												■
Rasamsonia argillaceae species complex		■	■	■										
Malassezia furfur											■			■

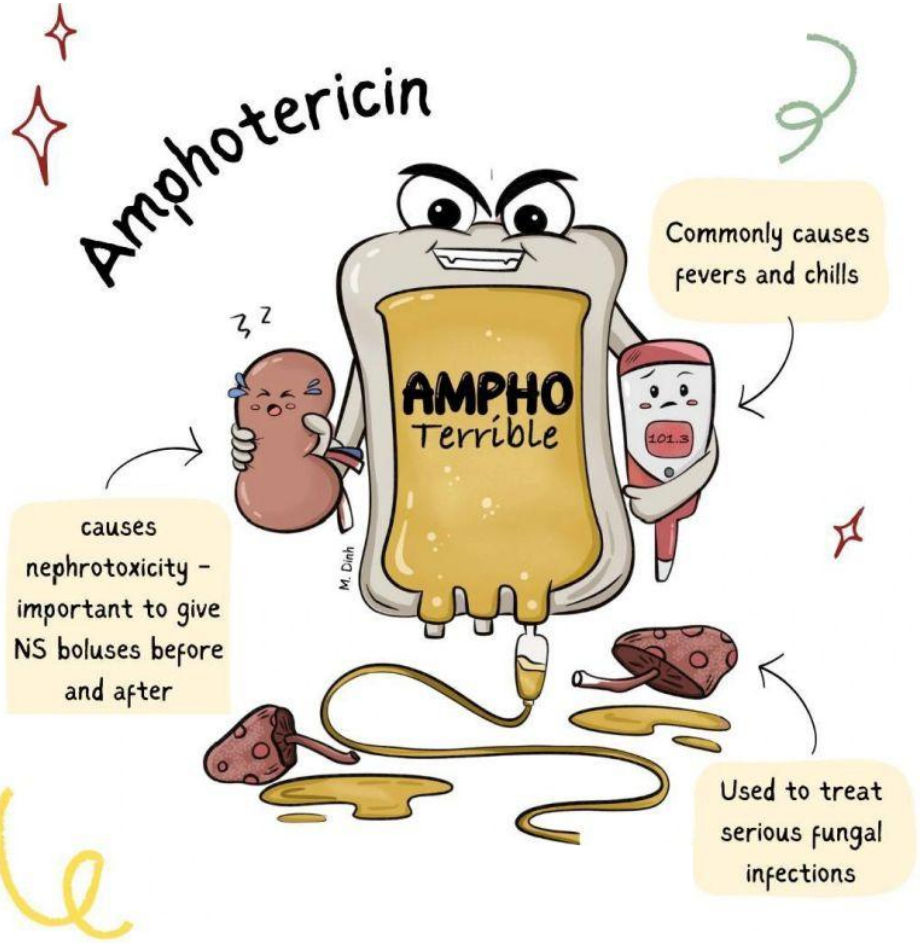
*Black boxes indicate documented or likely intrinsic antifungal resistance

Some azole antifungal agents have attributes that warrant therapeutic drug monitoring

	Flucytosine	Itraconazole	Voriconazole	Posaconazole
Efficacy	✓	✓	✓	✓
Toxicity	✓	✓	✓	
Pharmacokinetic variability	✓	✓	✓	✓ (suspension[a])
Altered PK in pediatrics		✓	✓	✓
Genetic polymorphisms			✓	
Patient adherence or reduced absorption	✓	✓	✓ (pediatrics[b])	✓ (suspension[a])
Elevated MIC or treatment failure		✓	✓	✓
Drug–Drug interactions		✓	✓	✓
Extremes of body weight	✓	✓	✓	✓

Full article: Therapeutic drug monitoring of systemic antifungal agents: a pragmatic approach for adult and pediatric patients (tandfonline.com)

Other antifungals have limitations that prevent use in patients, certain fungal diseases, and outpatient care



Bottom line: we need new antifungals with better pharmacokinetic and pharmacodynamic profiles

Wendy (Wan-Yu) Chu

Wendy (Wan-Yu) Chu is a postdoctoral researcher in the Tropical Pharmacology and Therapeutics Group at the Department of Pharmacy, Uppsala University.
Her research applies pharmacometric modeling to optimize treatment strategies for poverty-related and neglected tropical diseases, including leishmaniasis, malaria, and mycetoma.

https://www.uu.se/en/contact-and-organisation/staff?query=N23-809

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Pharmacokinetics and pharmacodynamics of ravuconazole and itraconazole in Sudanese patients with eumycetoma

REVIVE webinar
2026-09-17

Speaker: Wendy Chu, Uppsala University

About me

- Postdoctoral researcher
- Uppsala University, Sweden
- Department of Pharmacy, Pharmacometrics group
- Tropical Pharmacology and Therapeutics

Poverty-related diseases

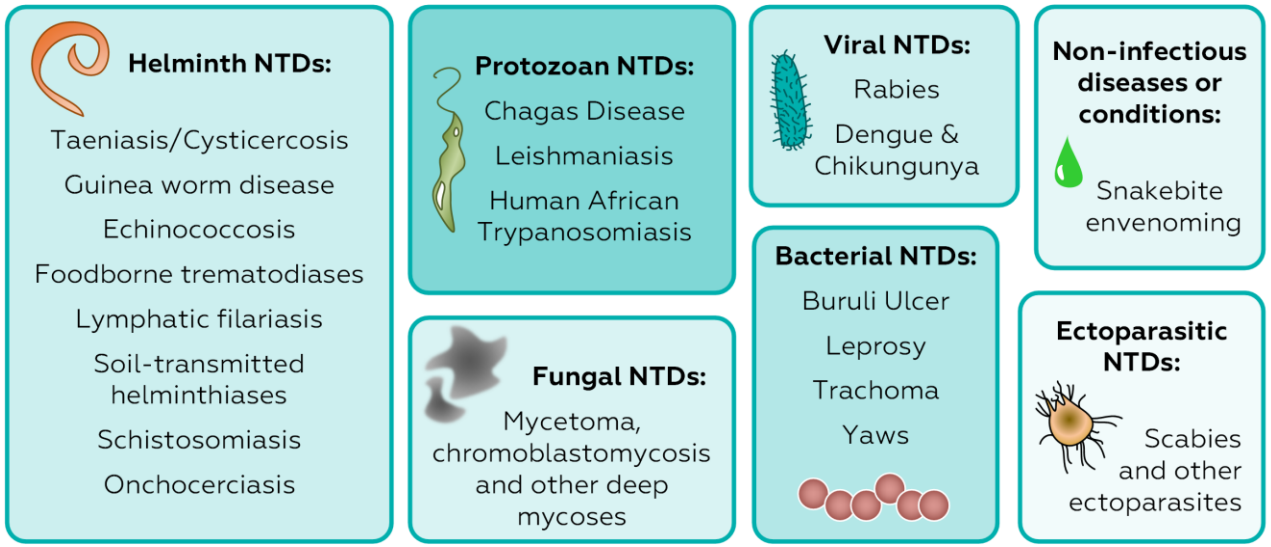
NTDs

Malaria

Tuberculosis

HIV/AIDS

The 20 neglected tropical diseases (NTDs)



Life Chemicals, *World Neglected Tropical Diseases Day 2021.*

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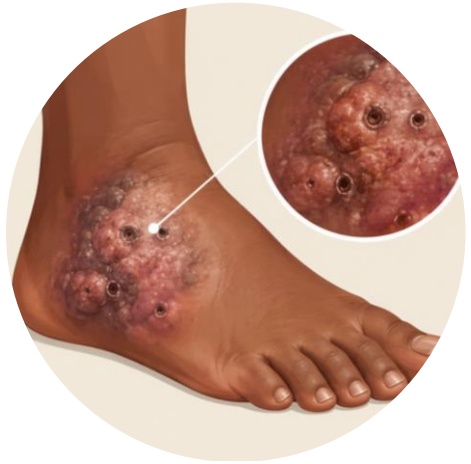
Overview

Fungal NTD: Mycetoma

Pharmacokinetic (PK) –Pharmacodynamic (PD) modelling

Dose selection for the clinical development of fosravuconazole

Mycetoma

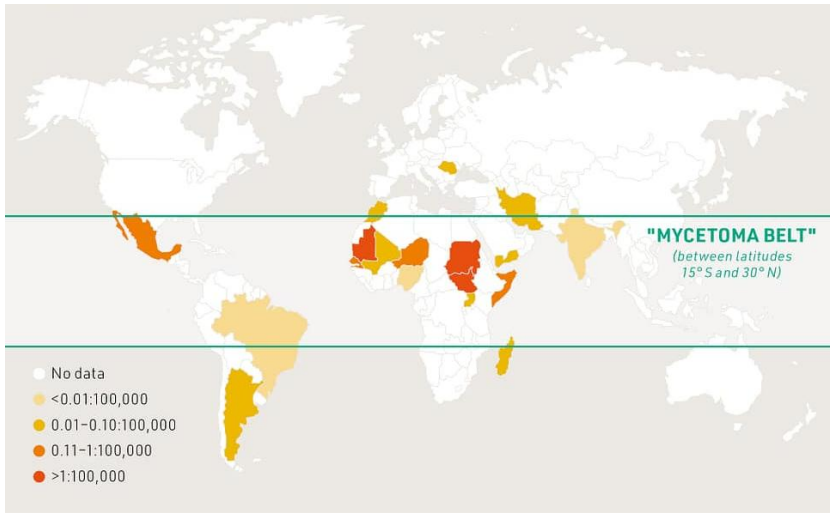


- Caused by bacteria (actinomycetoma) or fungi (eumycetoma)
- Usually starts in the foot, when bacteria or fungi enter through a small cut or injury
- Causes painless swelling, small openings in the skin, and discharge
- A slowly progressing infection that can spread deeper over time

  Skin → deeper tissues → bone
- In severe cases, it can cause serious damage and disability

Mycetoma

- Mainly found in tropical and subtropical regions, especially in Africa
- Particularly common in an area known as the “mycetoma belt” [1]
- The true number of people affected worldwide is still unknown
- Often affects young adults in rural communities
- People who work outdoors and walk barefoot are particularly at risk



1. van de Sande WWJ (2013)

Standard treatment for eumycetoma

(Fungal mycetoma caused by Madurella mycetomatis)

Current standard treatment → More than 12 months of oral itraconazole (twice-daily)

- Limited evidence of effectiveness
  - No randomized clinical trials
  - Reported cure rates <30%
- Expensive and difficult to access in endemic areas
  - Older, less safe drugs may be used instead (e.g., ketoconazole)
- Surgery is often needed to remove infected tissue
  - Severe cases may require amputation

Fosravuconazole: a potential new treatment

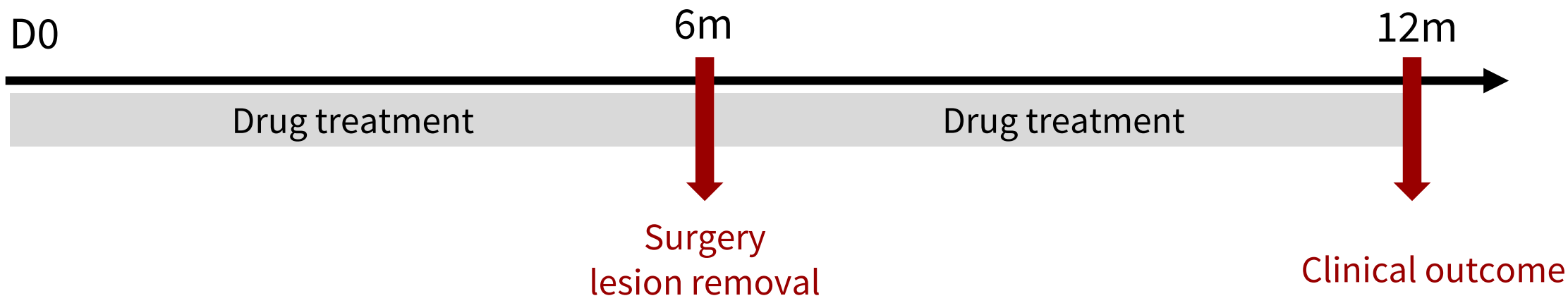
- The first randomized clinical trial for eumycetoma treatment was conducted in 2017 in Sudan.[2]
- The trial investigated fosravuconazole, an antifungal drug originally developed for nail fungal infection (onychomycosis).

Why fosravuconazole?

- Superior in vitro activity against *M. mycetomatis*
- Increased half-life to ≈10 days → potential for less frequent dosing
- Can be taken with or without food
- Fewer drug-drug interactions compared with older antifungal drugs
- Good solubility and stability

2. Fahal et al. (2024)

First clinical study in mycetoma



Arm 1: Itraconazole 400 mg **daily** dose (Standard treatment)

Arm 2: Fosravuconazole 200 mg **weekly** dose (D1-D3, 200 mg loading dose)

Arm 3: Fosravuconazole 300 mg **weekly** dose (D1-D3, 200 mg loading dose)

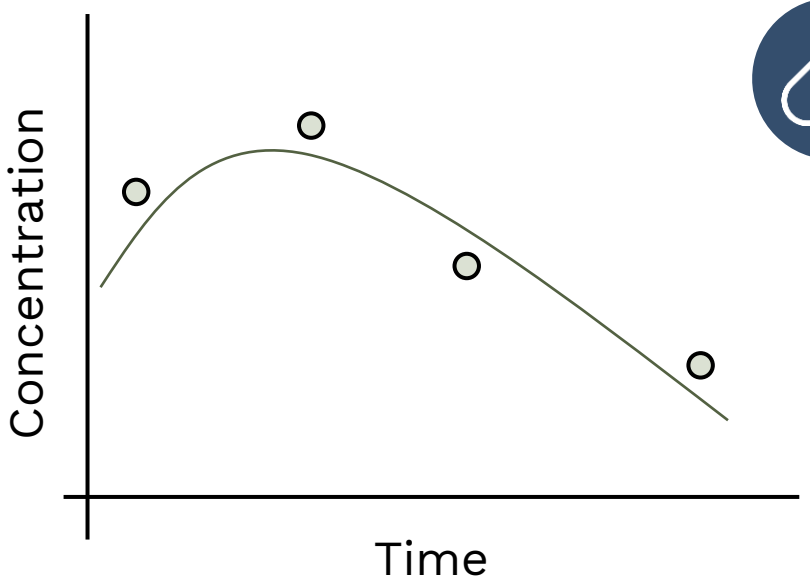
Aims

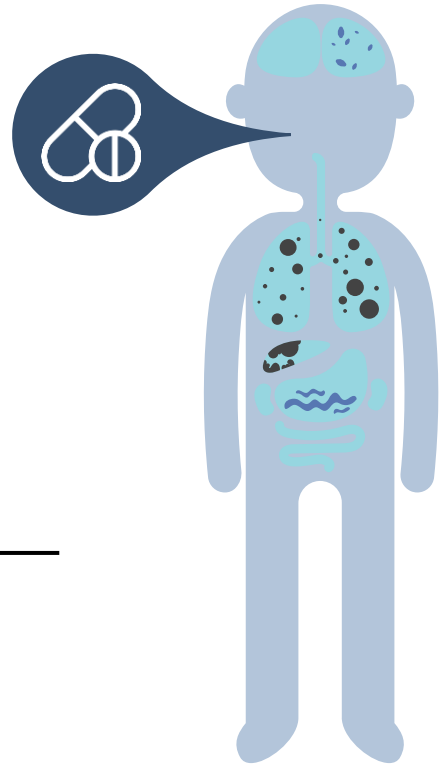
1. Describe the PK of antifungals in patients with eumycetoma
    - Fosravuconazole
    - Itraconazole and active metabolite hydroxyitraconazole
2. Explore potential relationships between drug exposures and responses
    - Reduction in lesion size at 6 months (before surgery)
    - Cure at 12 months
3. Dose selection between fosravuconazole 200 mg OR 300 mg

Pharmacometrics: PK & PD

Pharmacokinetics (PK)

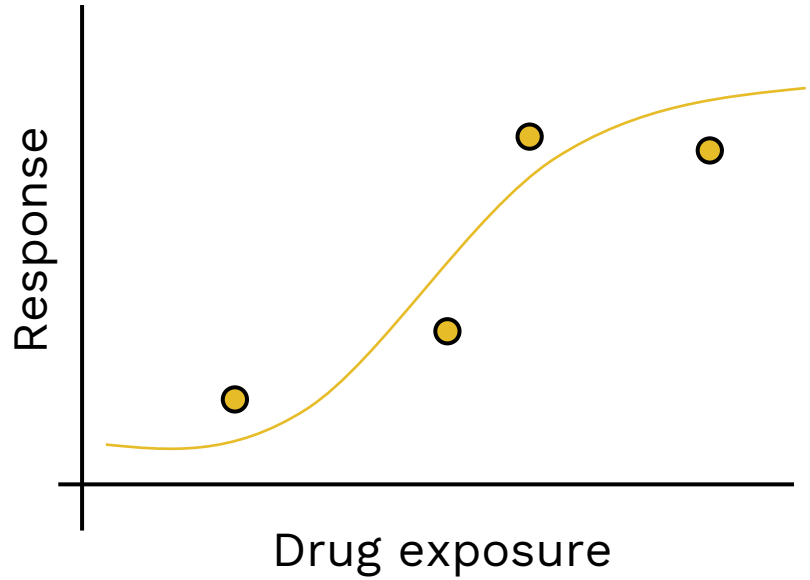
How the body interacts with the drug



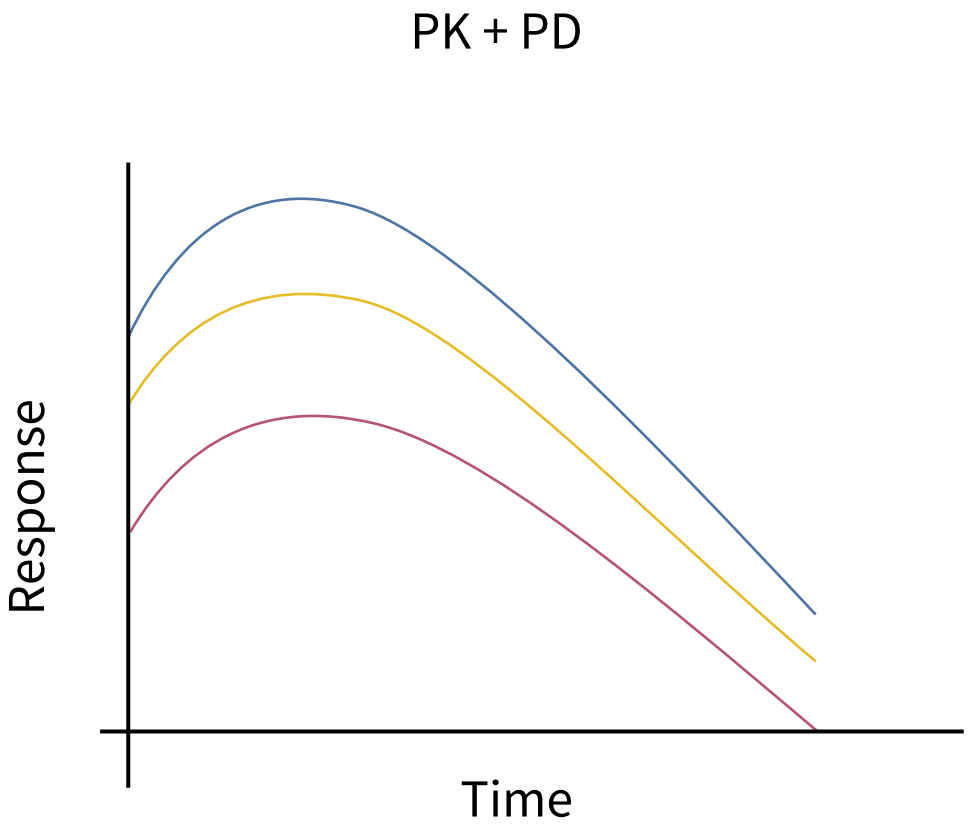


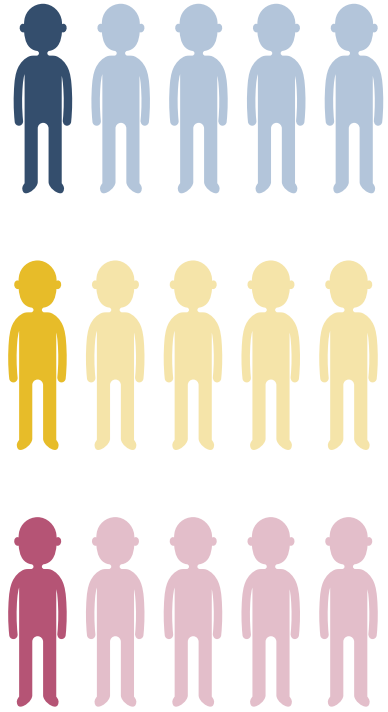
Pharmacodynamics (PD)

How the drug affects the body



Pharmacometrics: Patient variability





Treatment optimization

Clinical trial design

Data & Demographics

Treatment arm	Fosravuconazole 200 mg	Fosravuconazole 300 mg	Itraconazole 400 mg
	(N=20) [a]	(N=19) [a]	(N=13) [a]
Age (years)	24.0 [20.0,29.0]	30.0 [25.5,37.5]	22.0 [19.0,27.0]
Height (m)	1.72 [1.62,1.77]	1.70 [1.67,1.74]	1.71 [1.60,1.77]
Weight (kg)	56.3 [51.8,65.6]	60.0 [55.0,67.0]	67.0 [51.0,72.0]
Male	16 (80.0%)	18 (94.7%)	9 (69.2%)
Lesion size (cm^2)			
Baseline	11.7 [7.77,20.8]	17.0 [12.7,25.5]	12.5 [4.90,25.1]
Before surgery	6.17 [3.06,16.7]	16.7 [6.13,29.4] [b]	10.8 [4.08,15.8]
Treatment outcome			
Cured	**17 (85.0%)**	**12 (63.2%)**	9 (69.2%)

[a] All data indicated as median [IQR] for continuous values or number (%) for binary/categorical values.

[b] N = 17

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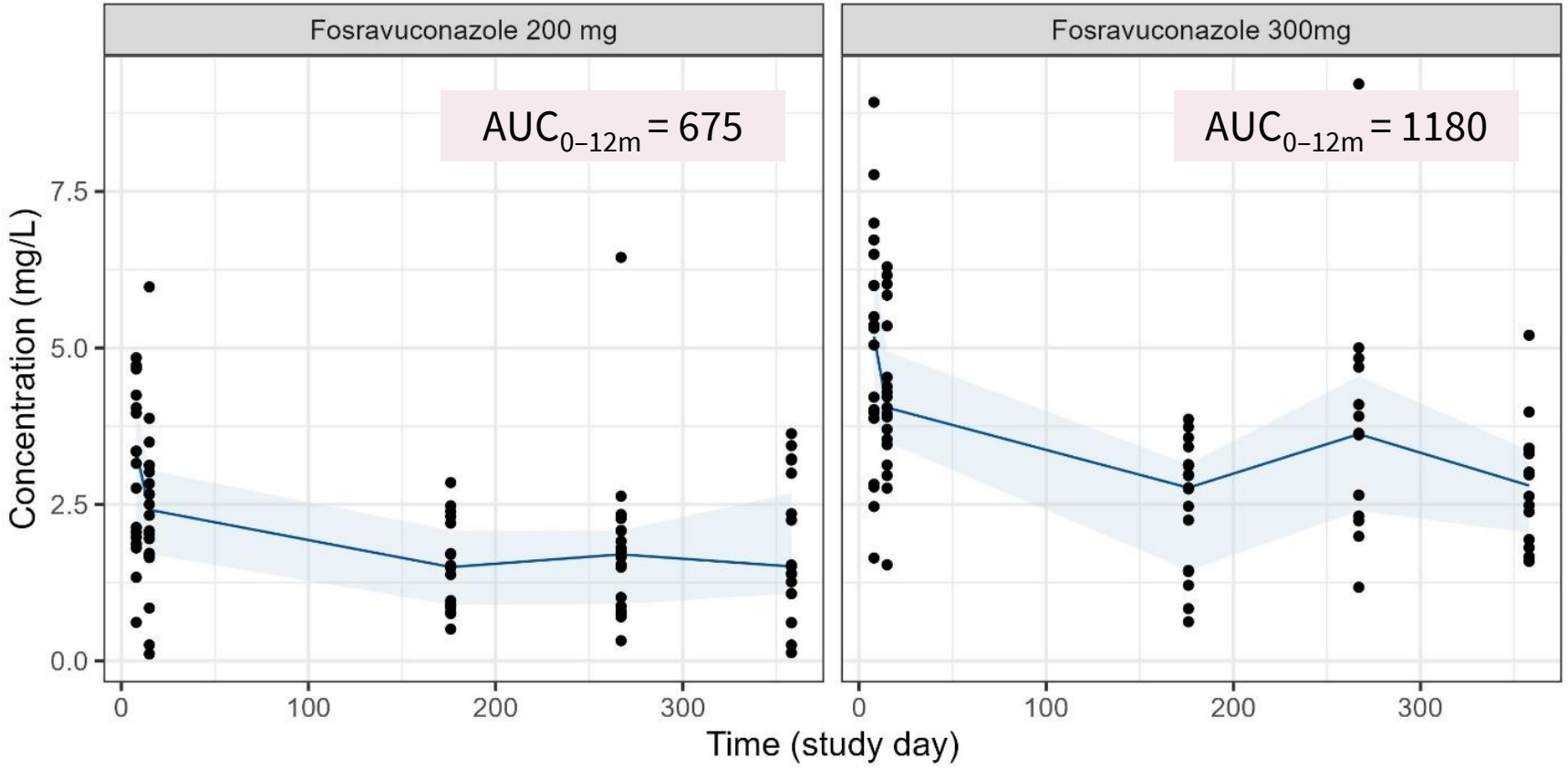
Fosravuconazole PK: more than dose-proportional exposure

200-mg vs 300-mg regimen:
50% dose increase → 75% higher AUC_{0-12m}

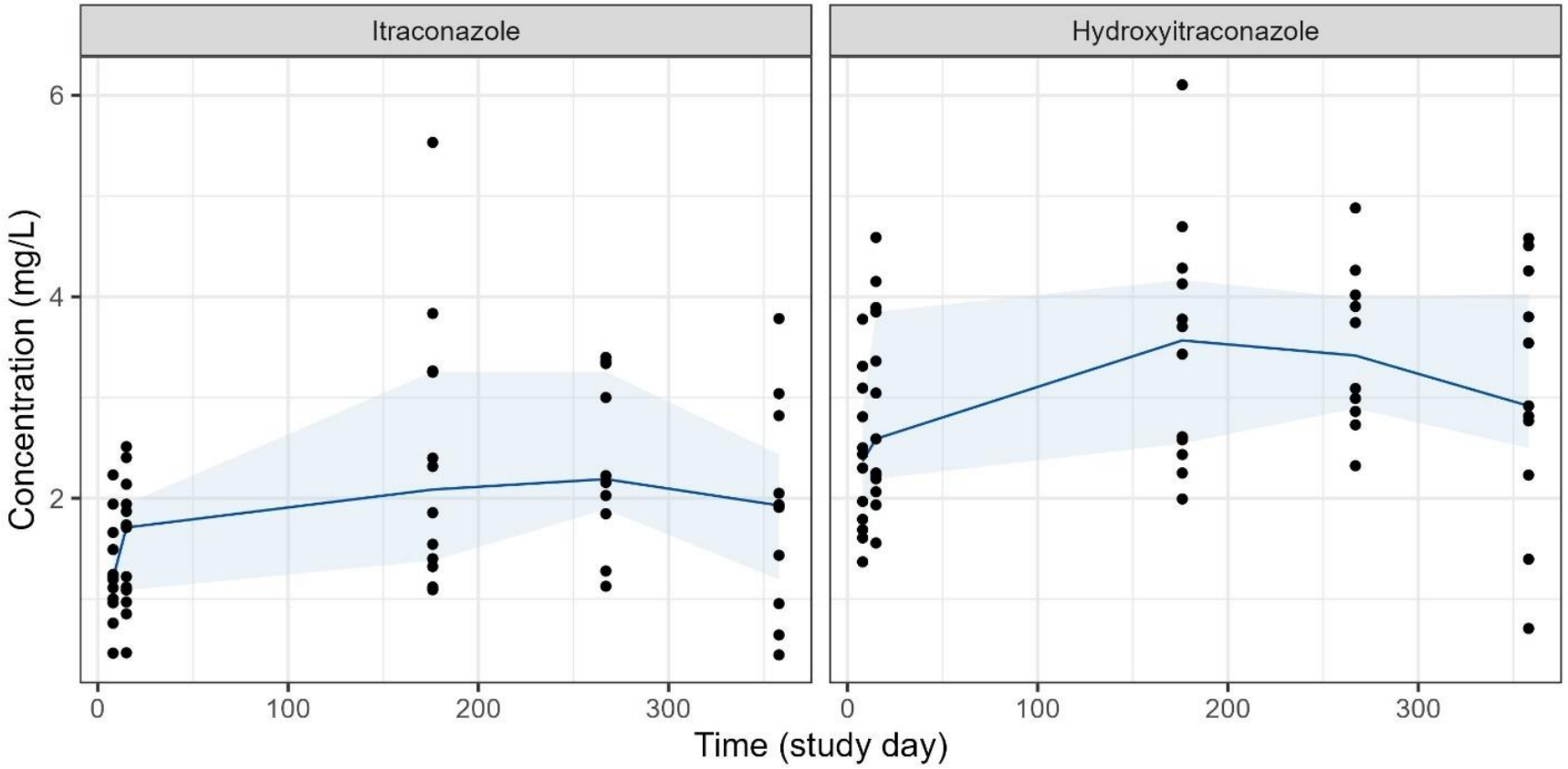
Pre-dose concentration versus time (median, IQR)



Itraconazole and hydroxyitraconazole PK

Hydroxyitraconazole vs itraconazole:
1.5-fold higher trough concentrations → first-pass effect

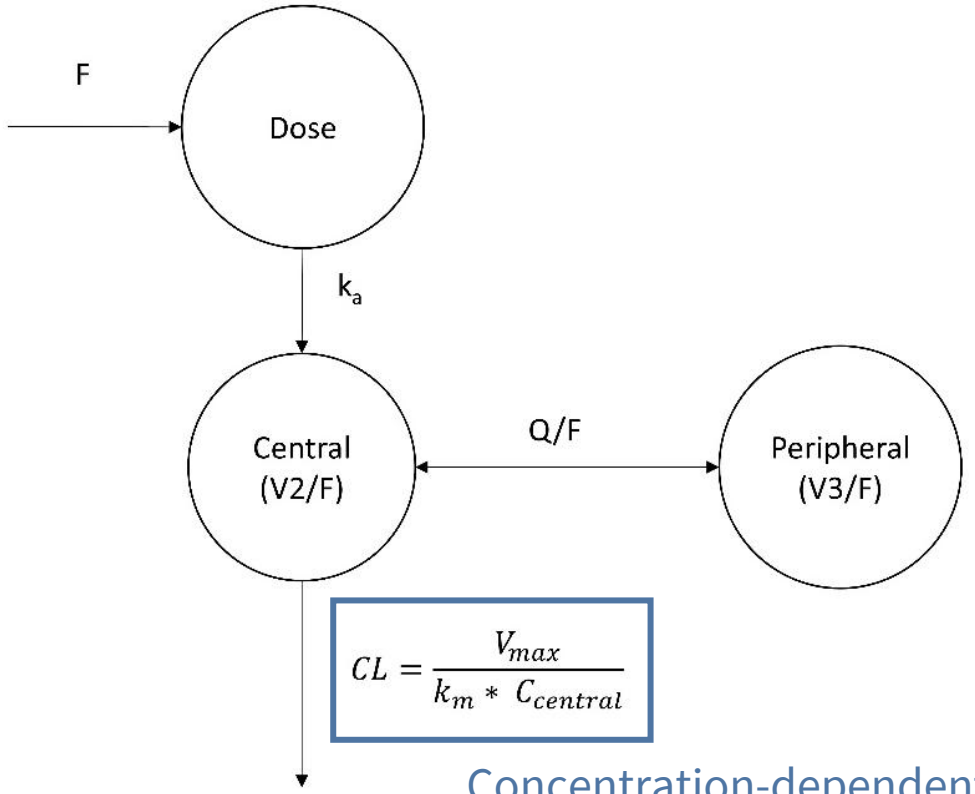
Pre-dose concentration versus time (median, IQR)



Non-linear PK characteristics

Changes in dose do not necessarily translate into proportional changes in drug exposure!

Fosravuconazole

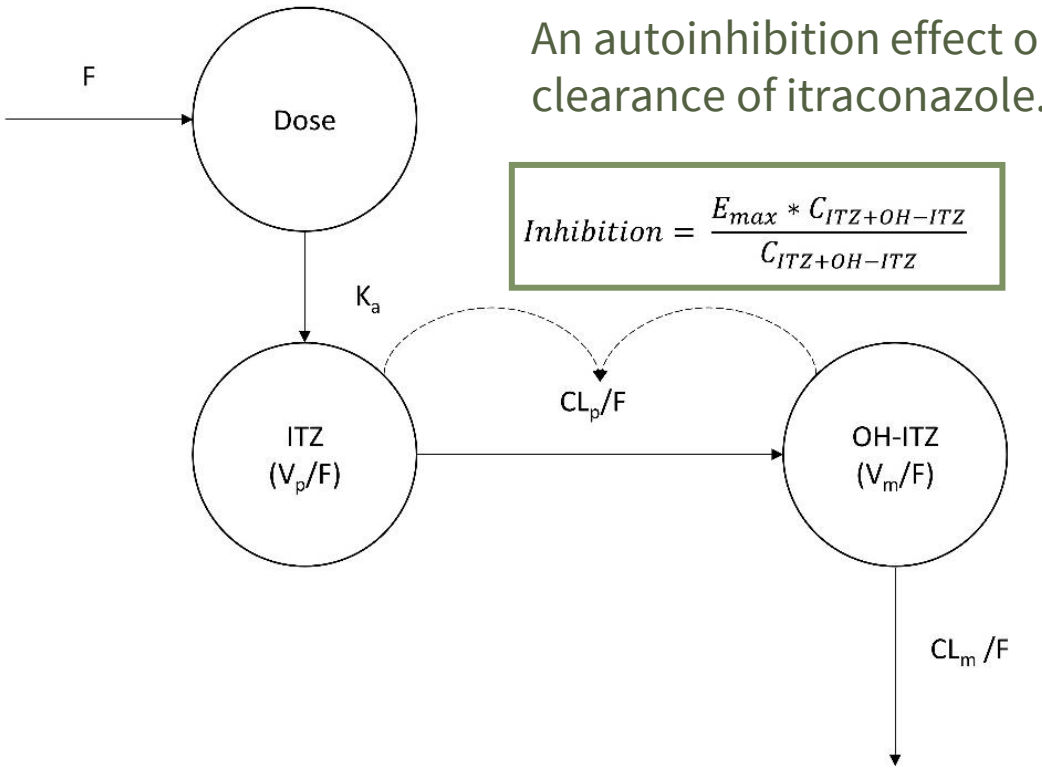


$$CL = \frac{V_{max}}{k_m * C_{central}}$$

Concentration-dependent saturable clearance.

Itraconazole

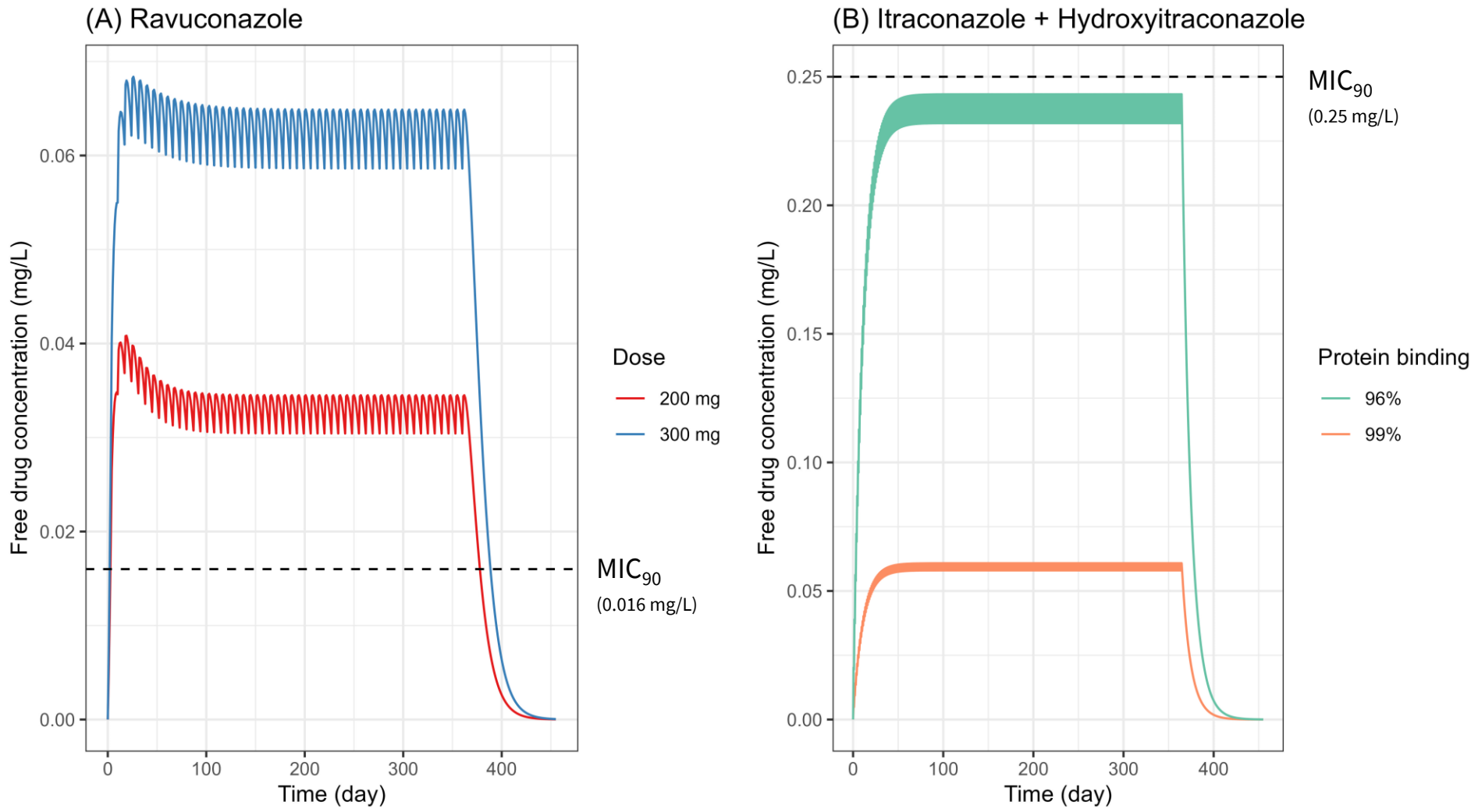
An autoinhibition effect on the clearance of itraconazole.



$$Inhibition = \frac{E_{max} * C_{ITZ+OH-ITZ}}{C_{ITZ+OH-ITZ}}$$

ITZ: Itraconazole
OH-ITZ: Hydroxyitraconazole

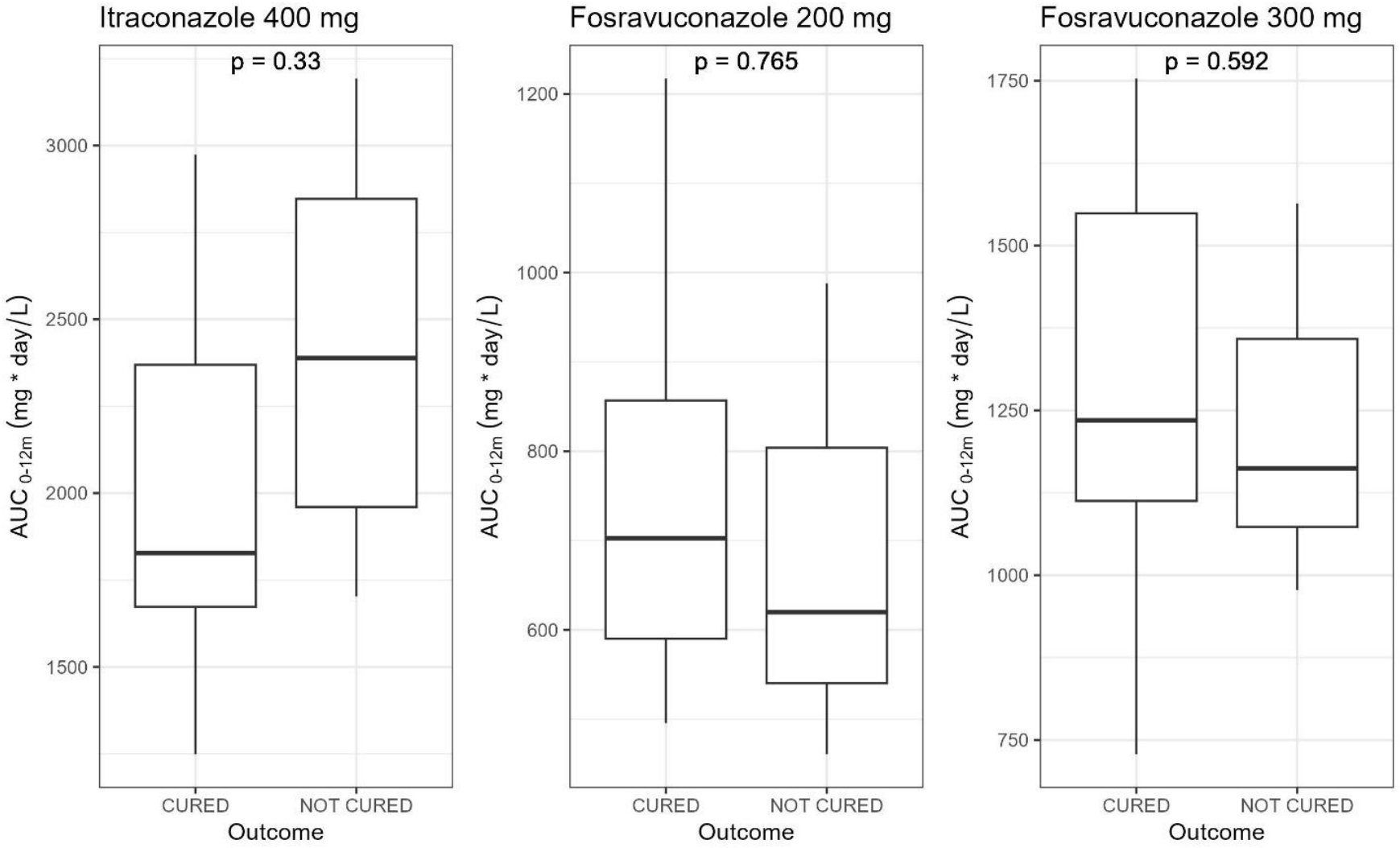
Free drug concentrations versus in vitro MIC_{90}



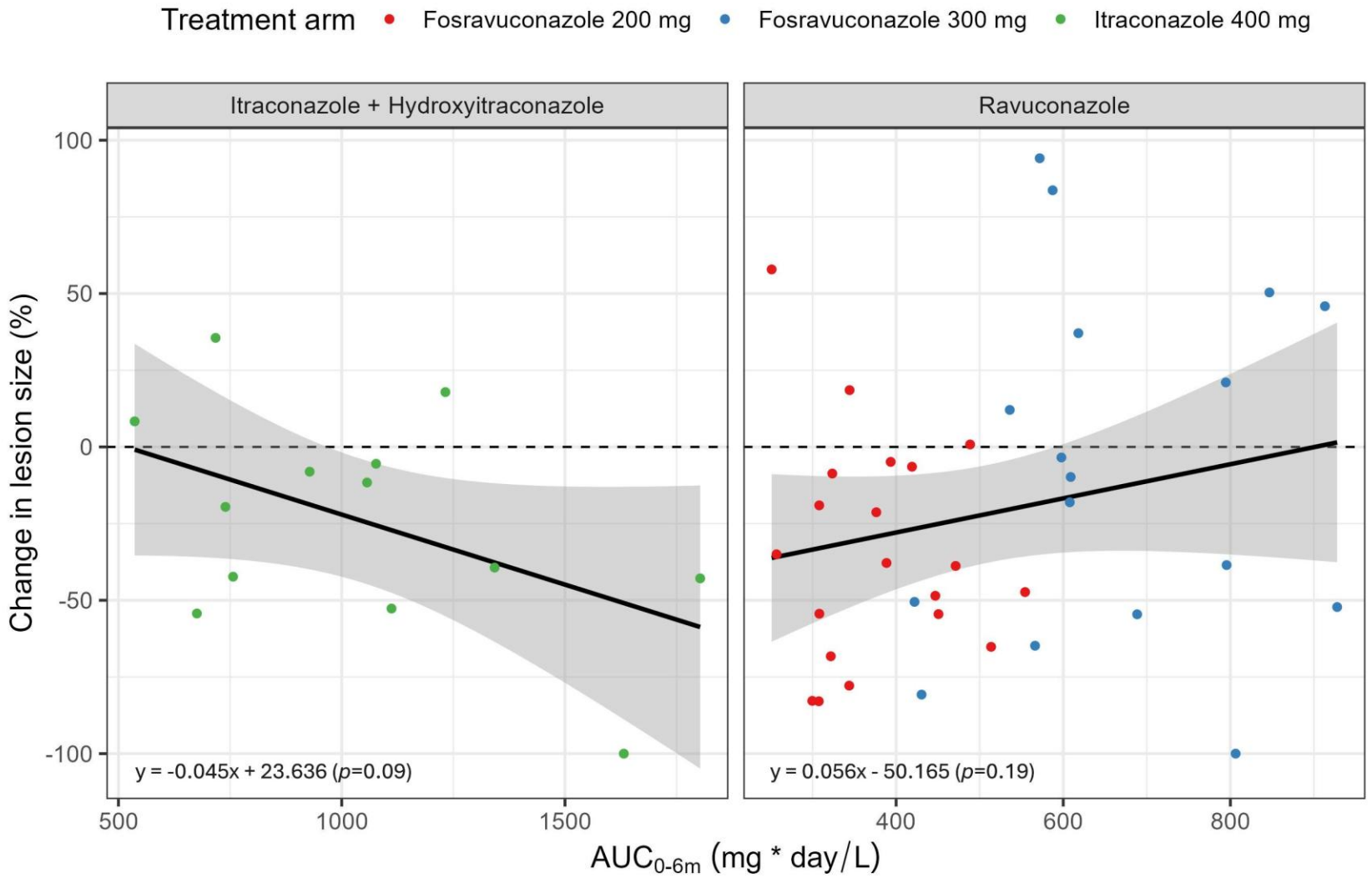
3. Ahmed et al. (2014)

MIC: minimum inhibitory concentration

Drug exposure vs complete cure

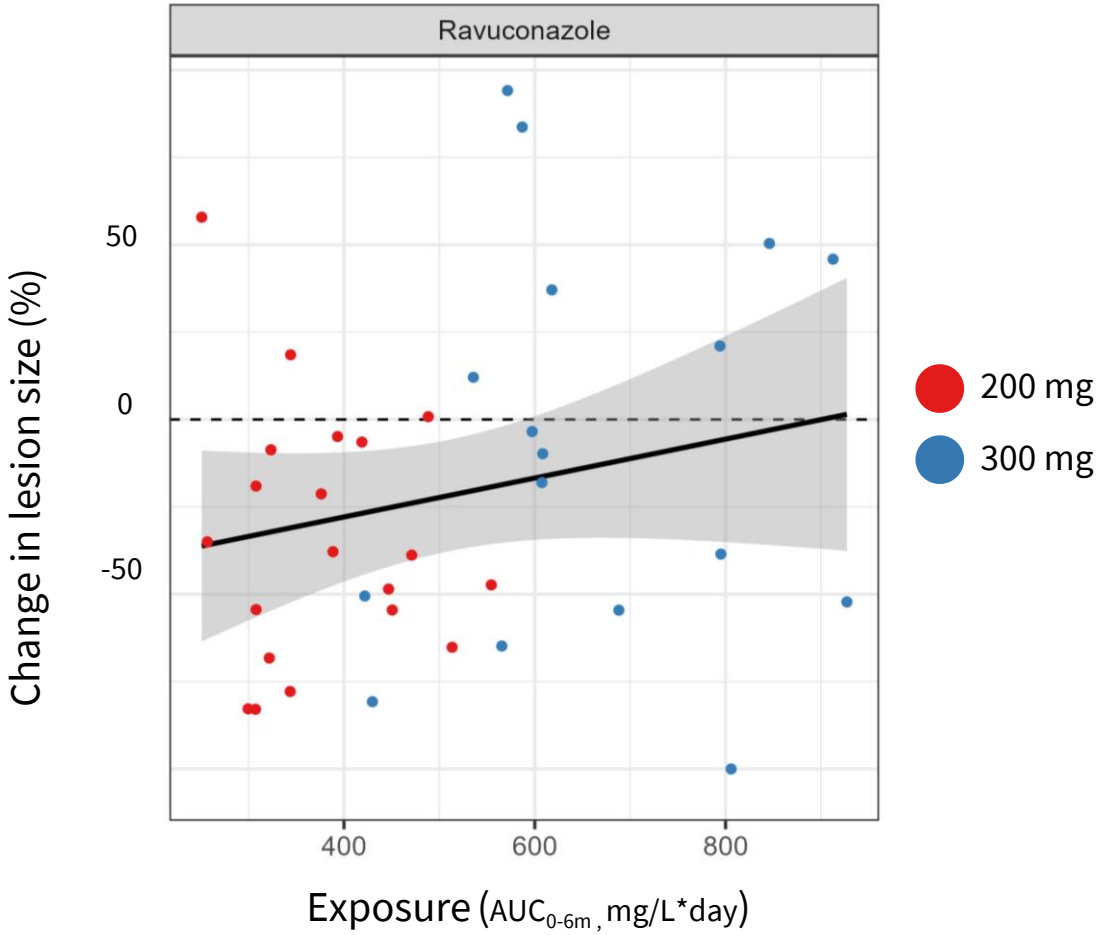


Drug exposure vs change in lesion size prior to surgery from baseline



Conclusion: Lower dose is preferred based on cost-effectiveness

Exposure-response relationship



Higher dose

=

Higher exposure

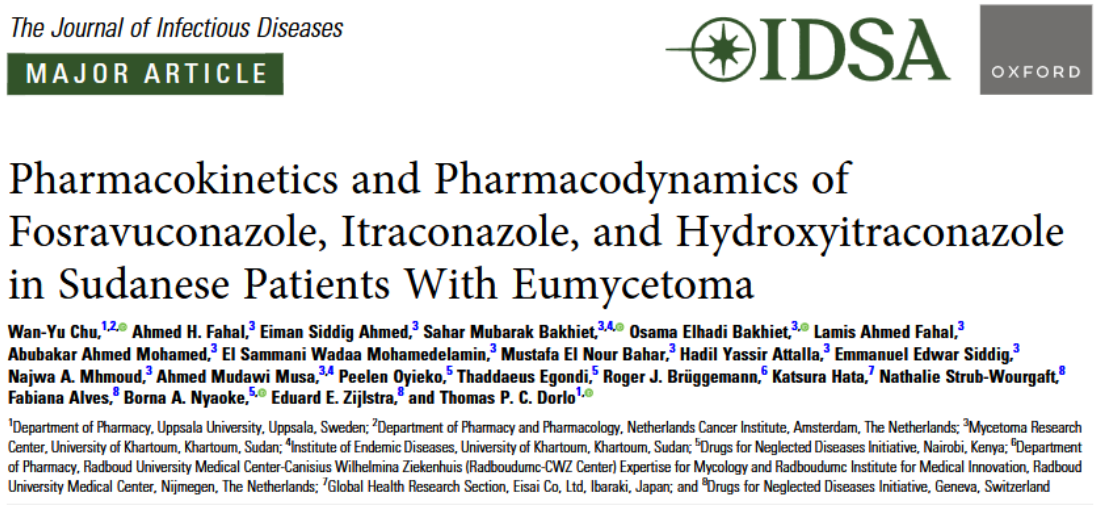
≠

Better response

200 mg

Acknowledgements

- Pharmacometrics group, Uppsala University, Uppsala, Sweden
  - Thomas Dorlo
- Patients involved in the clinical studies, their families and communities
- Co-investigators, nurses, laboratory personnel, and staff at Mycetoma Research Center, University of Khartoum, Khartoum, Sudan
- Drugs for Neglected Diseases initiative (DNDi)
  - Fabiana Alves
  - Borna Nyaoke
- Eisai Co, Ltd, Japan



The Journal of Infectious Diseases

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IDSA OXFORD

Pharmacokinetics and Pharmacodynamics of Fosravuconazole, Itraconazole, and Hydroxyitraconazole in Sudanese Patients With Eumycetoma

Wan-Yu Chu,[1,2] Ahmed H. Fahal,[3] Eiman Siddig Ahmed,[3] Sahar Mubarak Bakhiet,[3,4] Osama Elhadi Bakhiet,[3] Lamis Ahmed Fahal,[3] Abubakar Ahmed Mohamed,[3] El Sammani Wadaa Mohamedelamin,[3] Mustafa El Nour Bahar,[3] Hadil Yassir Attalla,[3] Emmanuel Edwar Siddig,[3] Najwa A. Mhmoud,[3] Ahmed Mudawi Musa,[3,4] Peelen Oyieko,[5] Thaddaeus Egondi,[5] Roger J. Brüggemann,[6] Katsura Hata,[7] Nathalie Strub-Wourgaft,[8] Fabiana Alves,[8] Borna A. Nyaoke,[5] Eduard E. Zijlstra,[3] and Thomas P. C. Dorlo[1]

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DNDi
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UPPSALA UNIVERSITET

Francelise Bridi Cavassin

Francelise Bridi Cavassin is a pharmacologist and adjunct professor at Faculdades Pequeno Príncipe in Brazil. Her areas of research are in pharmacology, clinical-epidemiological studies, and therapeutic strategies related to communicable and non-communicable diseases and tropical and neglected diseases.

Francelise obtained her PhD in Internal Medicine and Health Sciences, her Masters in Microbiology, Parasitology, and Pathology. She did an observership at the University of Cologne, Germany and a fellowship at the Pasteur Institute, France. She is titular member of the Advisory Technical Committee (CTA) of Medical Mycology Experts of the Mycoses Technical Group/CGTM/DATHI/SVSA/MS at the Brazilian Ministry of Health. She is member of the International Society for Human and Animal Mycoses (ISHAM), Society of Infectious Diseases Pharmacists (SIDP), and European Society of Clinical Microbiology and Infectious Diseases (ESCMID).

REVIVE by GARDP

U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

The Distinct Pharmacokinetic Profile of Rezafungin

Prof. Dr. Francelise Bridi Cavassin
Pharmacist, PhD. MSc.

Adjuntc Professor, Faculdades Pequeno Príncipe (FPP), Brazil
AHA Fiocruz & CDC/US Project, Hospital Oswaldo Cruz-PR, Brazil
Titular Member, CTA/GT Micoses - Brazilian Ministry of Health

A HORA É AGORA

HOSPITAL OSWALDO CRUZ

10 anos

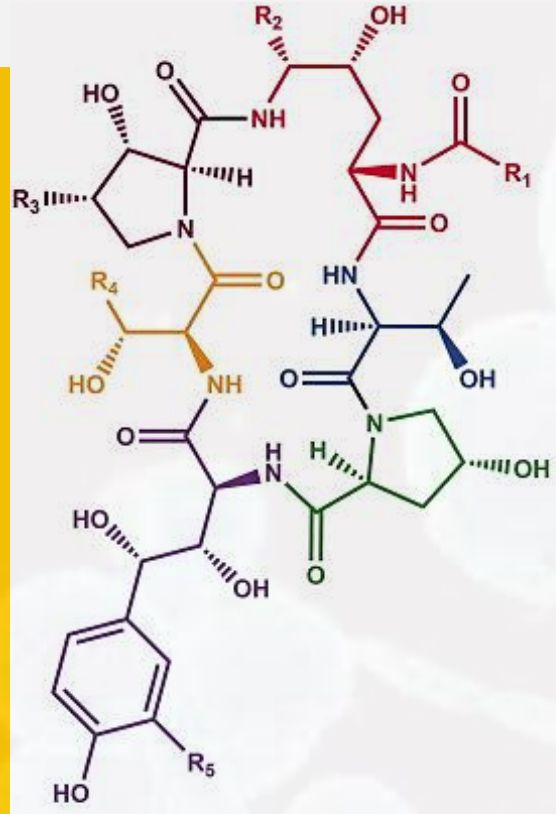
COMPLEXO pequeno PRÍNCIPE

Conflict of Interests

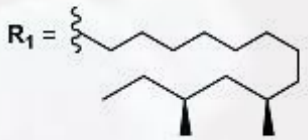
- I have no conflicts of interest to declare for this lecture.

- I receive/received remuneration for consulting or I am a speaker/lecturer for the following laboratories: Mundipharma, Knight Therapeutics, Gilead.

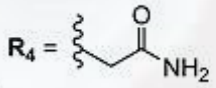
ECHINOCANDINS | History



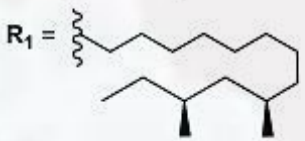
Pneumocandin B_0



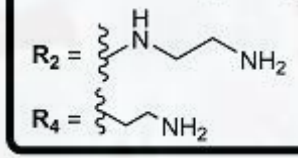
R_2 = OH R_3, R_5 = H



Caspofungin



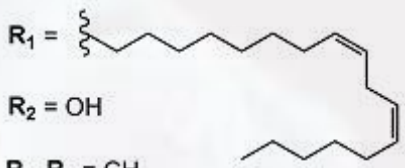
R_3, R_5 = H



Approved for commercialization in:

USA 2001
EUR 2002
BRA 2001

Echinocandin B

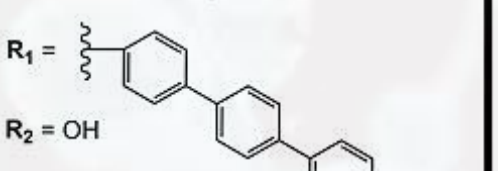


R_2 = OH

R_3, R_4 = CH_3

R_5 = H

Anidulafungin



R_2 = OH

R_3, R_4 = CH_3

R_5 = H

Approved for commercialization in:

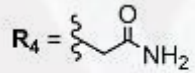
USA 2006
EUR 2007
BRA 2008

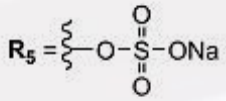
FR901379

Coleophoma empetri (Japan, 1994)

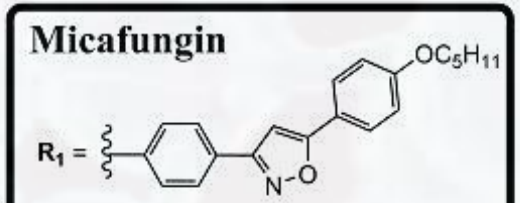
R_1 = $C_{15}H_{31}$ R_2 = OH

R_3 = CH_3





Micafungin

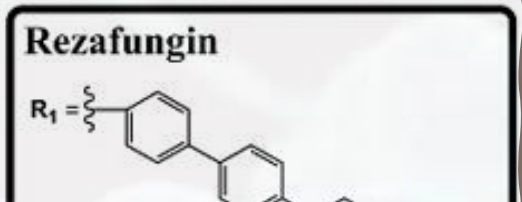


R_2 = OH R_3 = CH_3

Approved for commercialization in:

USA 2005
EUR 2008
BRA 2010

Rezafungin



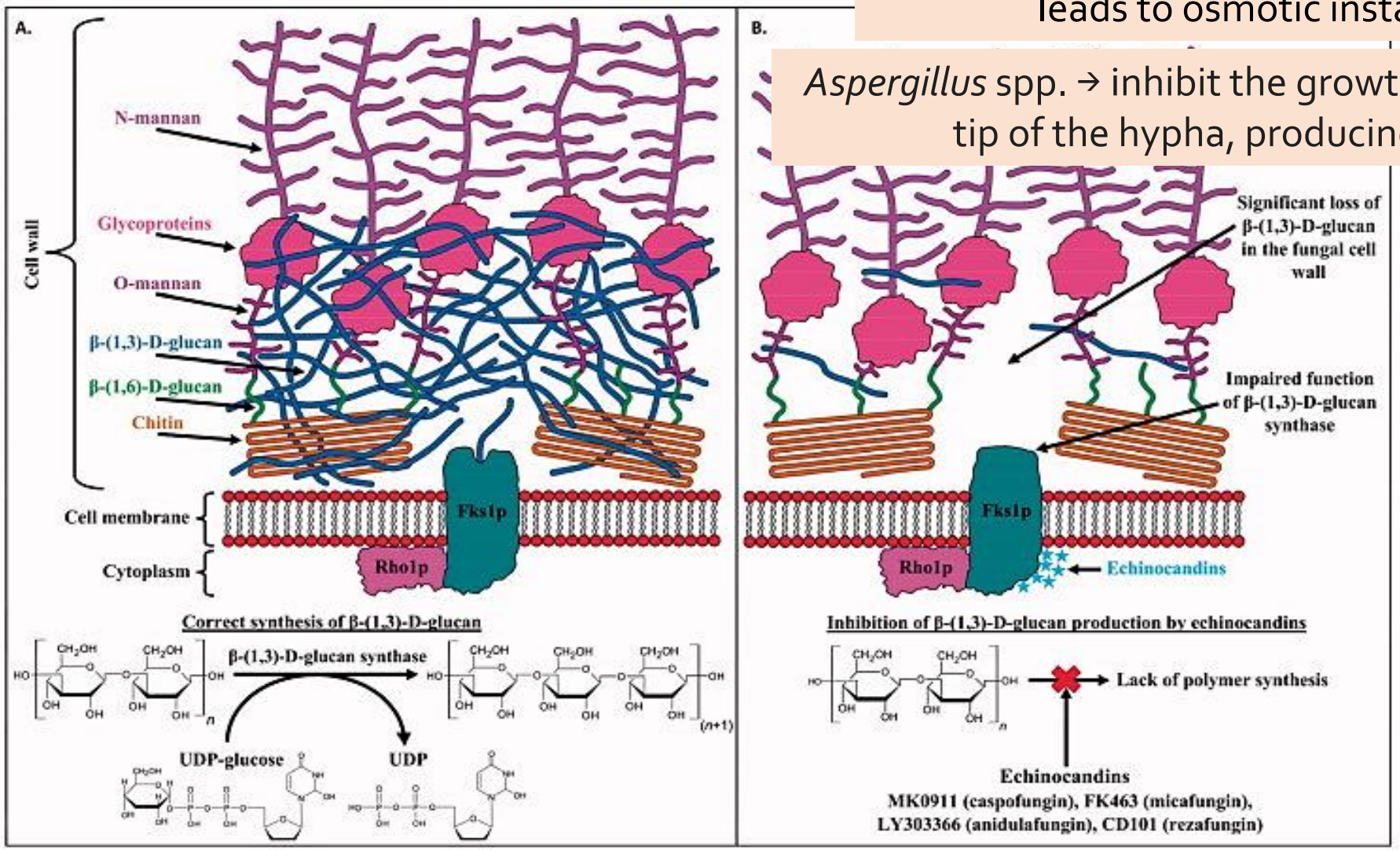
R_3, R_4 = CH_3 R_5 = H

Kanasaki R et al. *J Antibiot*. 2006.; Szymański M et al. *J Enzyme Inhib Med Chem.* 2022.

ECHINOCANDINS | Mechanism of action

The inability of the fungus to synthesize (1,3)-β-D-glucan leads to osmotic instability and cell death.

Aspergillus spp. → inhibit the growth of the cell wall mainly at the tip of the hypha, producing a fungistatic effect.



GS and β-(1,3)-D-glucan
↓
absent in humans
↓
good target for action
↓
AEs e DI differences associated with other antifungal agents

AEs: advers events, DI: drug interactions

Szymański M et al. *J Enzyme Inhib Med Chem*. 2022.

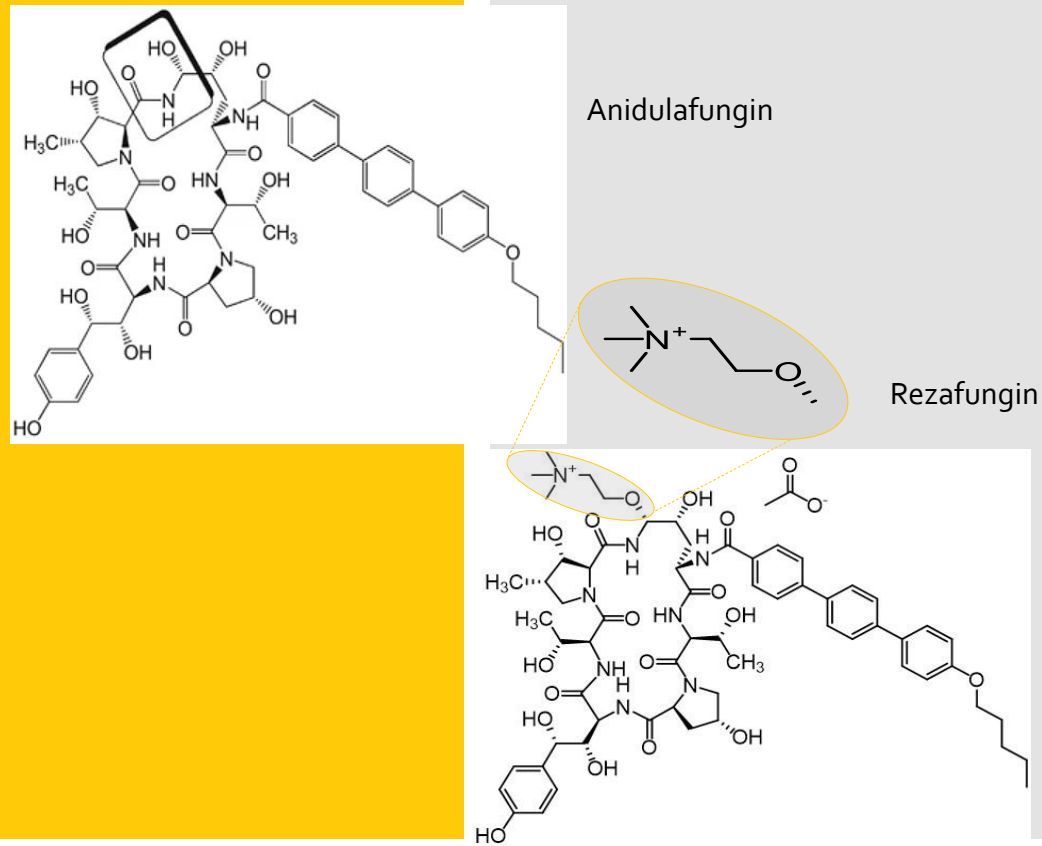
REZAFUNGIN | key-points

- Analogous to anidulafungin;
- Initial load ↑ maximizes the antifungal effect due to ↓ clearance and long half-life;
- Changes in structure = ↑ chemical stability in plasma, aqueous solution and at elevated temperature;
- PK/PD profile allows IV formulation 1x / week;
- ↓ hospital admissions, ↓ cost of outpatient services ↑ adherence and ↓ toxicity;
- Retains general activity and safety of the class.

J Infect Dis. 2024 Aug 16;230(2):505-513. doi: 10.1093/infdis/jiae146.

Regulatory Considerations in the Approval of Rezafungin (Rezzayo) for the Treatment of Candidemia and Invasive Candidiasis in Adults

Heidi L Smith [1], Timothy J Bensman [2], Shrimant Mishra [1], Xianbin Li [3], Cheryl A Dixon [3],



PK: pharmacokinetics; PD: pharmacodynamics

Krishnan BR et al. *J Antibiot (Tokyo)*. 2017.; Chang CC et al. *Arch Toxicol*. 2017.; Syed YY. *Drugs*. 2023; Smith HL et al. *J Infect Dis.* 2024.

Review > J Antimicrob Chemother. 2025 Jan 3;80(1):18-28. doi: 10.1093/jac/dkae415.

The distinctive pharmacokinetic profile of rezafungin, a long-acting echinocandin developed in the era of modern pharmacometrics

David Andes [1], Roger J Brüggemann [2], Shawn Flanagan [3], Alexander J Lepak [1], Russell E Lewis [4], Voon Ong [3], Christopher M Rubino [5], Taylor Sandison [3]

- A pharmacometrics-based approach was adopted throughout the development of rezafungin, which contrasts with older echinocandins;
- Dosage regimens were largely empirically derived and only recently based on pharmacometrics guidance.

State-of-the-art approach → used model-based simulations incorporating preclinical and clinical data as they became available to optimize the dosing regimen for rezafungin.

Andes D et al. *Antimicrob Agents Chemother*. 2025.

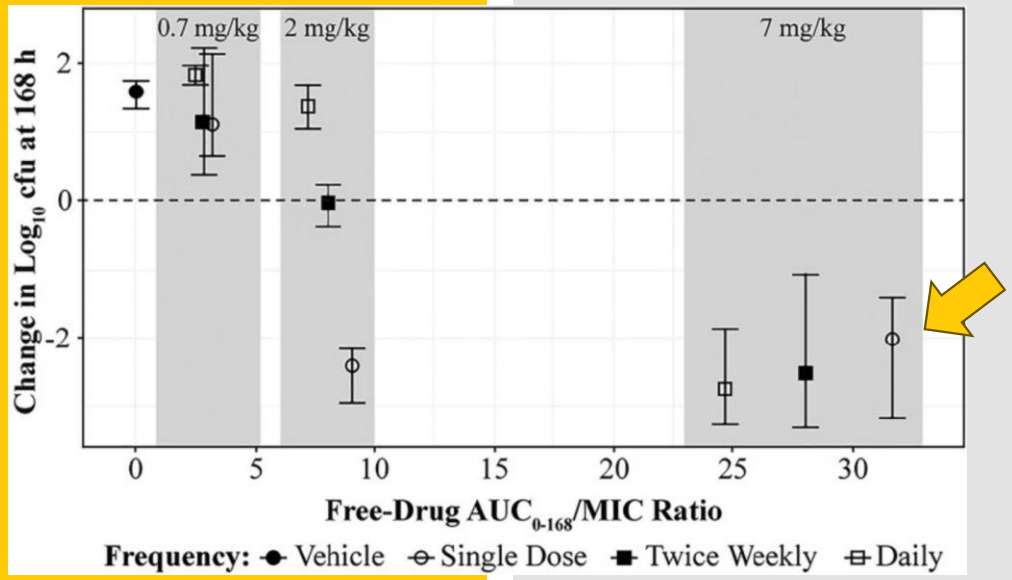
REZAFUNGIN | Properties

- Adults (>18 years old)

- Dosage schedule
  Attack 400 mg
  Maintenance 200 mg

Once a week: steady state is reached with the first loading dose.

- *In vivo* action spectrum
  Candida spp.
  Aspergillus spp.
  Pneumocystis spp.



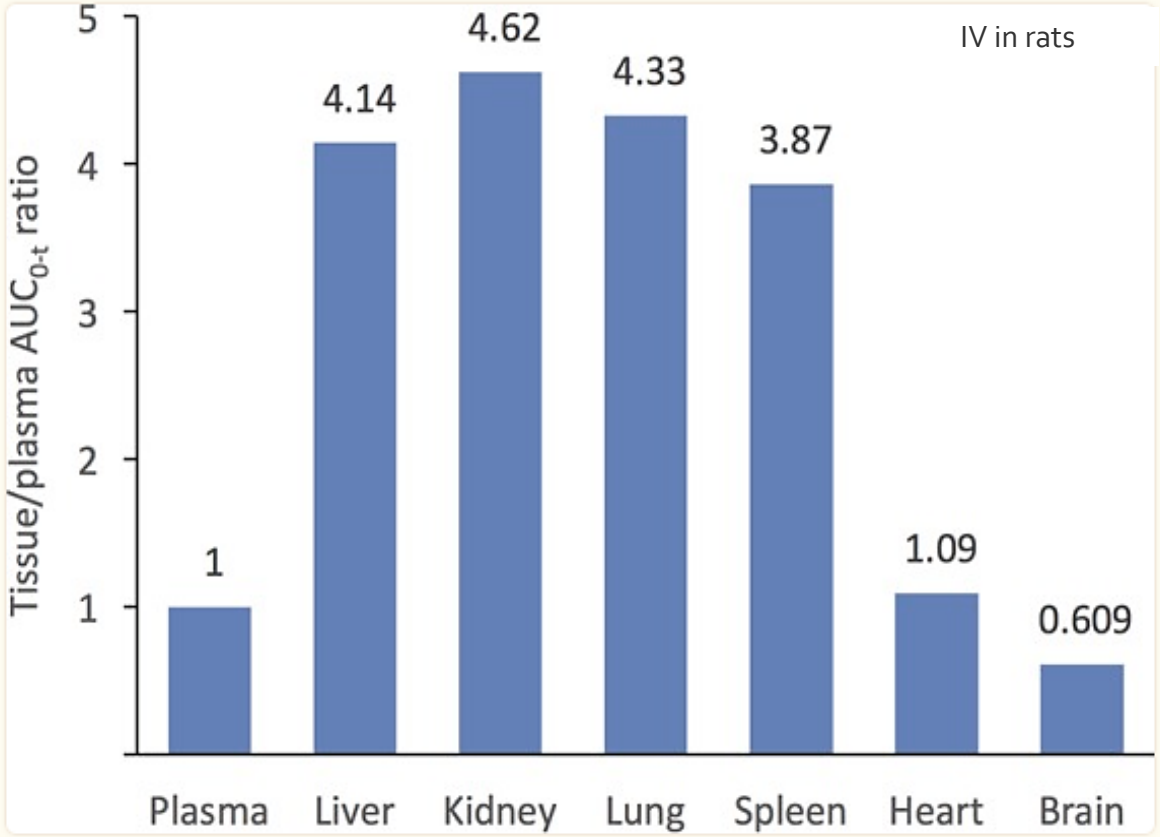
Front-loaded dosage (high initial cc.) → greater fungicidal activity than fractionated doses.

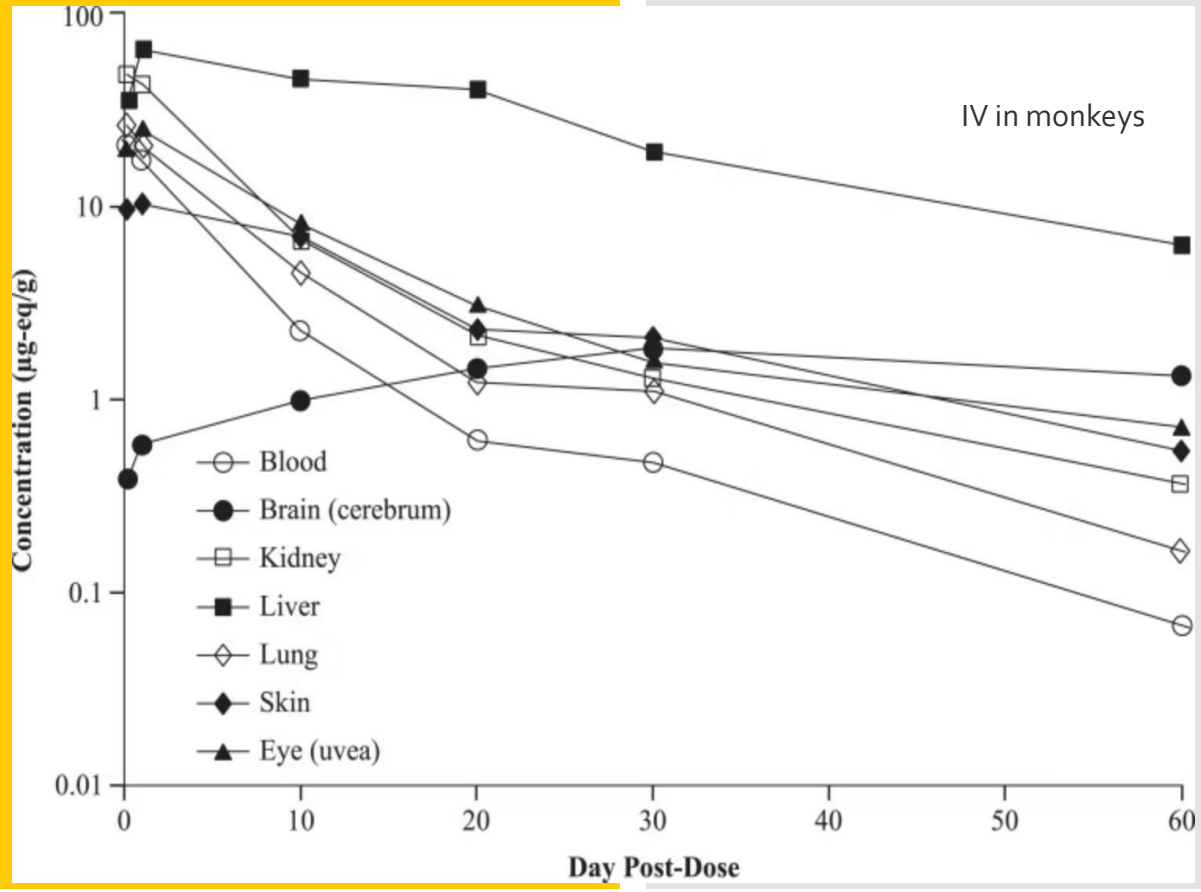
- *Pregnancy risk summary*: Animal studies have not detected adverse embryo-fetal or postnatal outcomes.

Zhao Y, Perlin DS. *J Fungi (Basel).* 2020.; Cushion MT, Ashbaugh A, *J Fungi (Basel)*. 2021.; Syed YY. *Drugs*. 2023.; Lakota EA et al. *Antimicrob Agents Chemother* 2017.; www.accessdata.fda.gov/drugsatfda_docs/nda/2023/217417Orig1s000IntegratedR.pdf.

REZAFUNGIN | Tissue distribution

Given the frontal exposure and greater tissue penetration, RZF may be associated with a ↓ risk of emergence of resistance compared to other echinocandins.

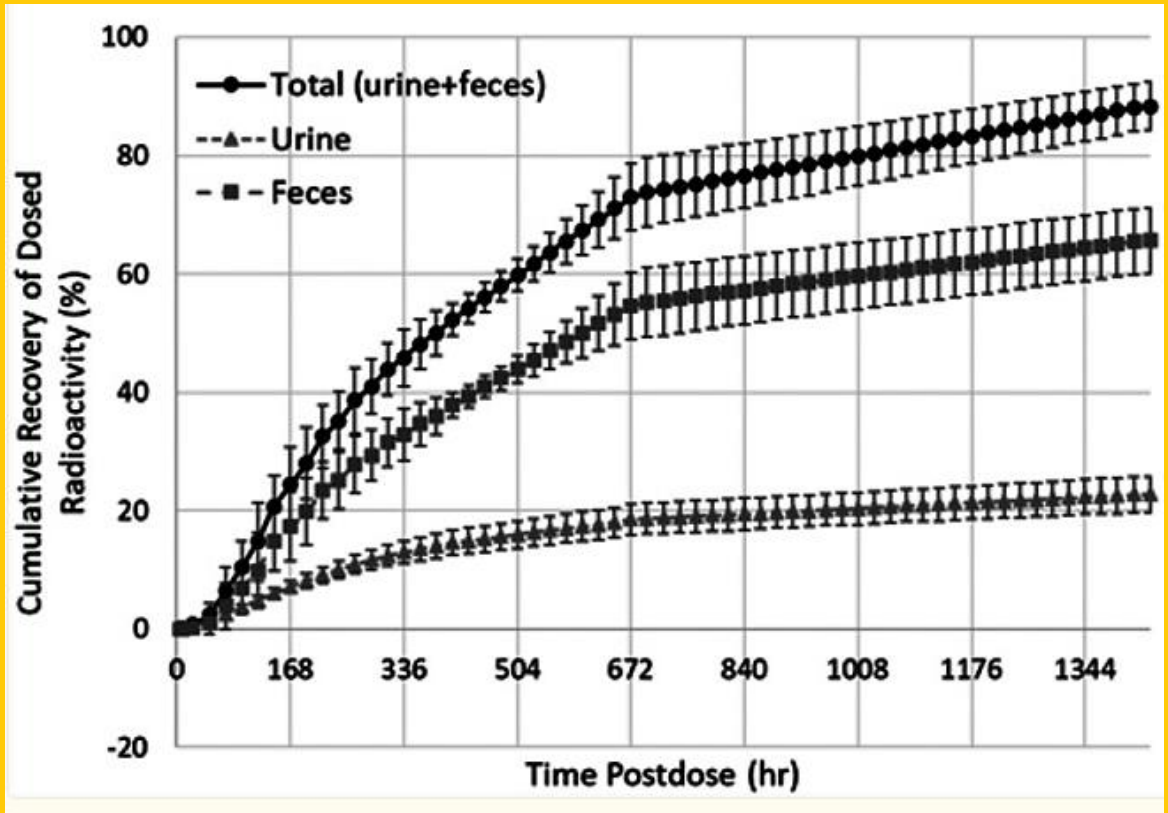




Ong V et al. *Antimicrob Agents Chemother*. 2017.; Ong V et al. *Antimicrob Agents Chemother*. 2022; Ordaya EE et al. *Mycopathologia*. 2023.; Garcia-Effron G. *J Fungi*. 2020.

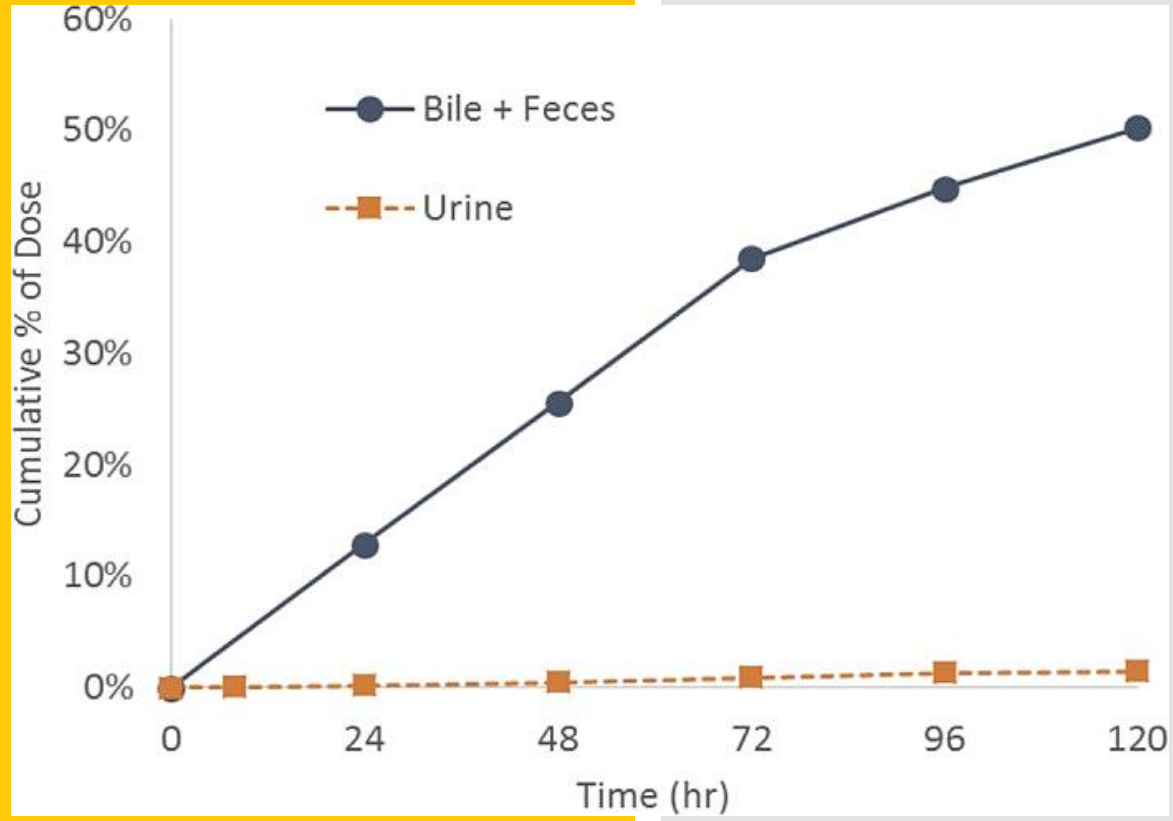
REZAFUNGIN | Metabolism/Excretion

Single dose IV 400 mg in humans



Ong V et al. *Antimicrob Agents Chemother*. 2022.

Single dose IV 5 mg/kg in rats



Ong V et al. *Antimicrob Agents Chemother*. 2017.

REZAFUNGIN | Safety

Laboratory findings

	No. (%) of subjects (n = 6)								
	Single-ascending-dose study[a]					Multiple-ascending-dose study[b]			
	CD101 dose (mg)				Rezafungin	CD101 dose (mg)			
Laboratory result	**50**	**100**	**200**	**400**	**Pooled Placebo (n = 8)**	**100**	**200**	**400**	**Pooled Placebo**
Hematology[c] (hemoglobin, white blood cell count, and platelets)									
Normal	78 (87)	80 (99)	89 (99)	88 (98)	115 (96)	136 (94)	137 (95)	198 (100)	159 (98)
Abnormal—not clinically significant	12 (13)	2 (2)	1 (1)	2 (2)	5 (4)	8 (6)	7 (5)	0	3 (2)
Abnormal—clinically significant	0	0	0	0	0	0	0	0	0
Chemistry[c] (calcium, chloride, bicarbonate, potassium, albumin, blood urea nitrogen, creatinine, glucose, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, protein, and sodium)									
Normal	461 (96)	432 (100)	465 (97)	475 (99)	619 (96.5)	699 (97)	696 (97)	969 (98)	790 (98)
Abnormal—not clinically significant	19 (4)	0	16 (3)	5 (1)	18 (3)	21 (3)	24 (3)	21 (2)	20 (3)
Abnormal—clinically significant	0	0	0	0	2 (0.5)	1[d]	0	0	0

Yang YL et al. *Front Pharmacol*. 2021.

Sandison T et al. *Antimicrob Agents Chemother*. 2017.

REZAFUNGIN | Drug interaction

Drug	Possible mechanism(s)	Observation[a]		Suggested action
		C_{max}	AUC	
Tacrolimus	CYP3A4, P-gp	↔	↓ ~14%	No change in dose
Repaglinide	CYP2C8, OATP	↔	↑ ~16% (0–∞)	No change in dose
Metformin	OCT, MATEs	↔	↔	No change in dose
Rosuvastatin	BCRP, OATP	↑ ~12%	↑ ~15%	No change in dose
Pitavastatin	OATP	↔	↔	No change in dose
Caffeine	CYP1A2	↔	↔	No change in dose
Efavirenz	CYP2B6	↔	↔	No change in dose
Midazolam	CYP3A4	↔	↔	No change in dose
Digoxin	P-gp	↔	↔	No change in dose
Cyclosporine	CYP3A4, P-gp	↔	↔	No change in dose
Ibrutinib	CYP3A4, P-gp, BCRP	↓ ~17%	↔	No change in dose
Mycophenolate mofetil[c]	Other[b]	↓ ~19%	↔	No change in dose
Venetoclax	CYP3A4, P-gp	↔	↓ ~10%	No change in dose

› Microbiol Spectr. 2023 Jun 15;11(3):e0133923. doi: 10.1128/spectrum.01339-23. Epub 2023

Absence of Clinically Meaningful Drug–Drug Interactions with Rezafungin: Outcome of Investigations

Shawn Flanagan [1], Helen Walker [2], Voon Ong [1], Taylor Sandison [1]

- Absence of clinically relevant interactions with multiple drugs.

Flanagan S et al. *Microbiology Spectrum*, 2023.

REZAFUNGIN | *In vivo* efficacy

Comparative Study > Antimicrob Agents Chemother. 2016 Oct 21;60(11):6872-6879.
doi: 10.1128/AAC.00701-16. Print 2016 Nov.

Preclinical Evaluation of the Stability, Safety, and Efficacy of CD101, a Novel Echinocandin

Voon Ong [1], Grayson Hough [2], Michael Schlosser [2], Ken Bartizal [2], James M Balkovec [2], Kenneth D James [3], B Radha Krishnan [3]

Objectives	Methods	Results
Evaluate the efficacy of RZF in preclinical models of systemic infection	Neutropenic mouse/ *C. albicans* disseminated Single IV injection 2 h after infection	Potent antifungal efficacy up to 72 h after a single dose of RZF

> Antimicrob Agents Chemother. 2017 Oct 24;61(11):e00758-17. doi: 10.1128/AAC.00758-17.
Print 2017 Nov.

Pharmacological Basis of CD101 Efficacy: Exposure Shape Matters

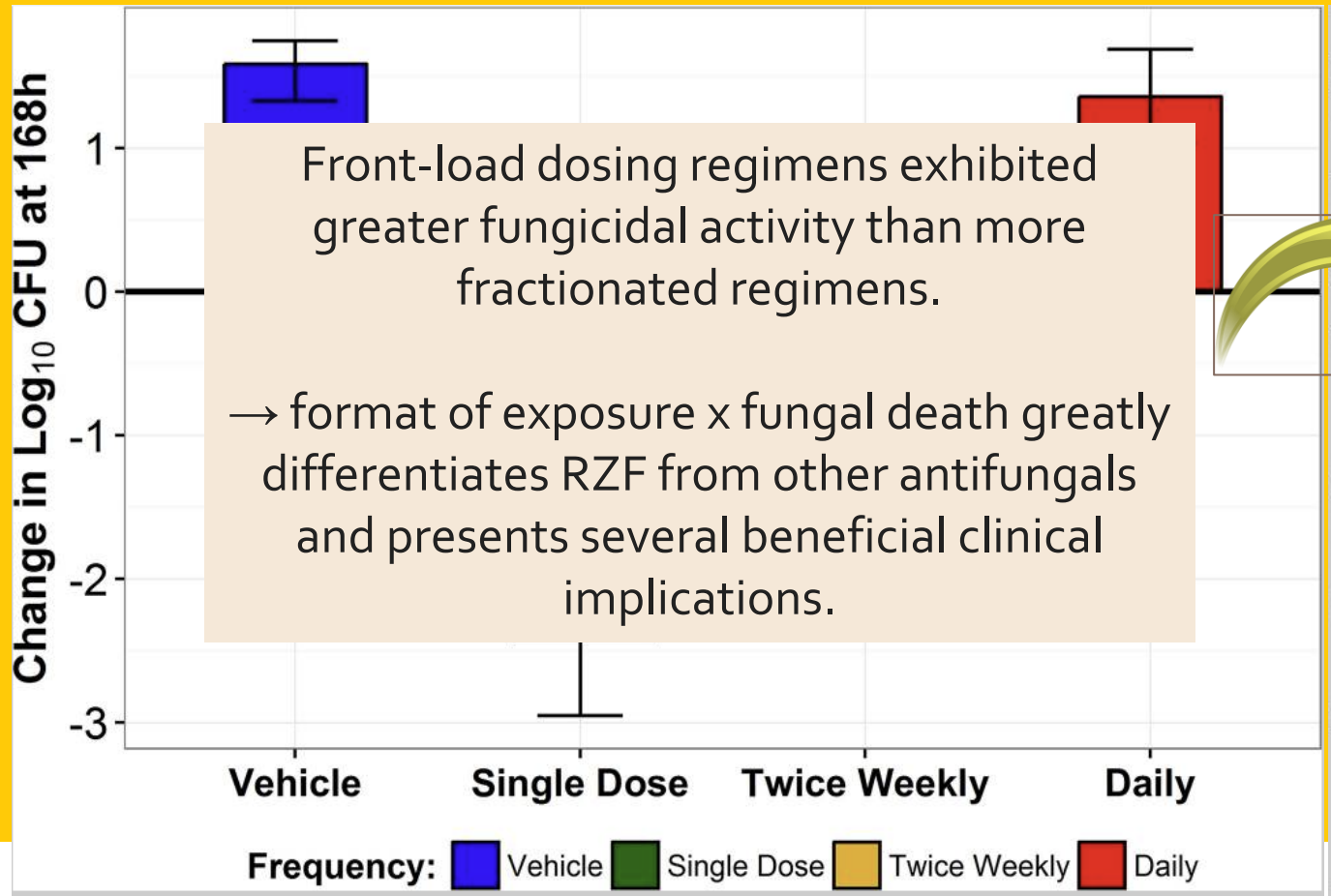
Elizabeth A Lakota [1], Justin C Bader [2], Voon Ong [3], Ken Bartizal [3], Lynn Miesel [4], David R Andes [5], Sujata M Bhavnani [2], Christopher M Rubino [2], Paul G Ambrose [2], Alexander J Lepak [5]

Objectives	Methods	Results
Evaluate the effects of front-loading dosing regimens on the efficacy of RZF	Neutro penic mouse/*C. albicans* disseminated 3 regimens: single dose, 2x/week and daily	PK/PD: efficacy due to initial dosage load and exposure format

PK: pharmacokinetics; PD: pharmacodynamics; RZF: rezafungin

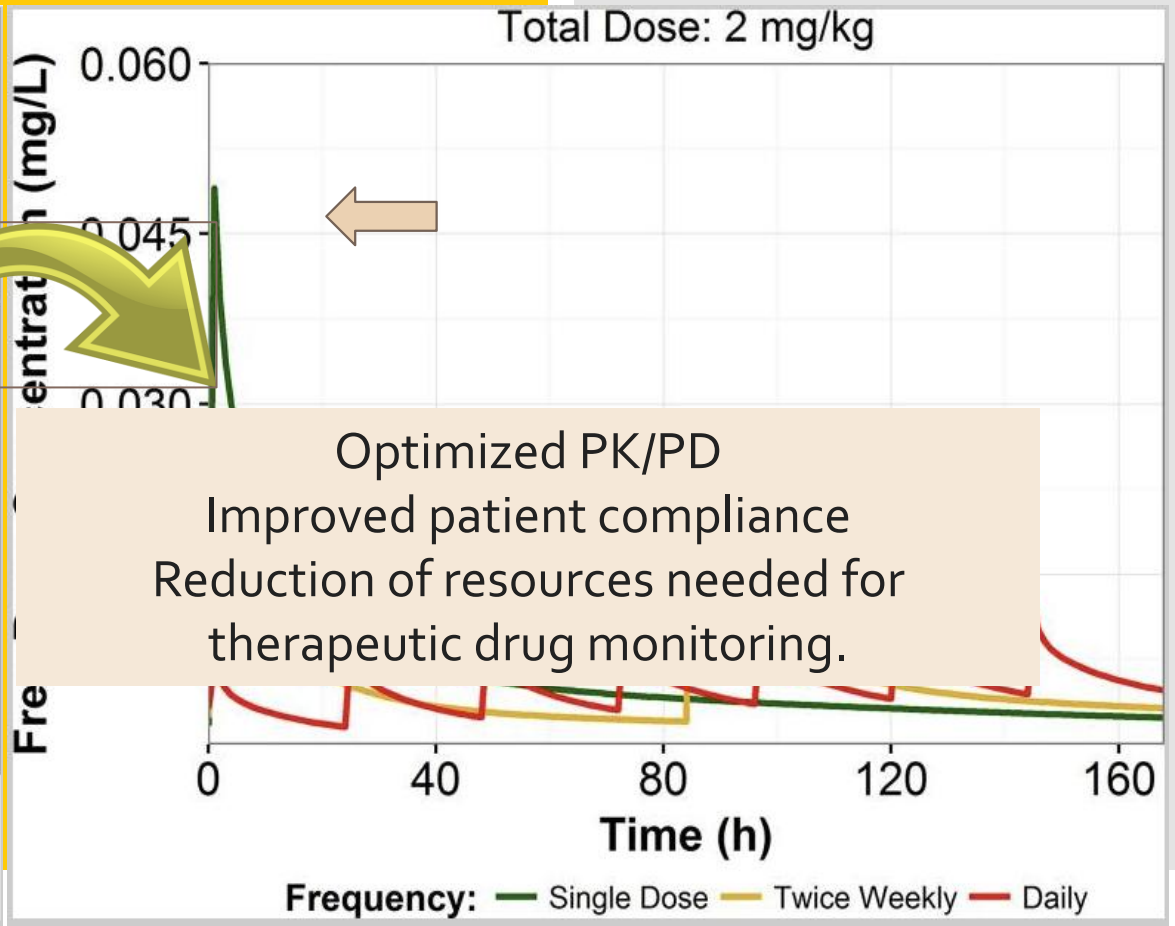
2 mg/kg single dose - 1 mg/kg 2x/week - 0,29 mg/kg daily

Greater degree of elimination of fungal burden compared to the same dose divided into twice-weekly or daily regimens.



Front-load dosing regimens exhibited greater fungicidal activity than more fractionated regimens.

→ format of exposure x fungal death greatly differentiates RZF from other antifungals and presents several beneficial clinical implications.



Optimized PK/PD
Improved patient compliance
Reduction of resources needed for therapeutic drug monitoring.

Lakota E et al. *Antimicrob Agents Chemother*. 2017.

REZAFUNGIN | *In vivo* efficacy

Antimicrob Agents Chemother. 2017 Sep 22;61(10):e01009-17. doi: 10.1128/AAC.01009-17. Print 2017 Oct.

Unraveling Drug Penetration of Echinocandin Antifungals at the Site of Infection in an Intra-abdominal Abscess Model

Yanan Zhao [1], Brendan Prideaux [2], Yoji Nagasaki [2], Min Hee Lee [2], Pei-Yu Chen [2], Landry Blanc [2], Hsinpin Ho [2], Cornelius J Clancy [3], Minh Hong Nguyen [3], Véronique Dartois [2], David S Perlin [1]

Objectives
To evaluate the effects of RZF exposure on tissue

Methods
Rat/Intra-abdominal *C. albicans*

Single IP injection on day 3 post-infection

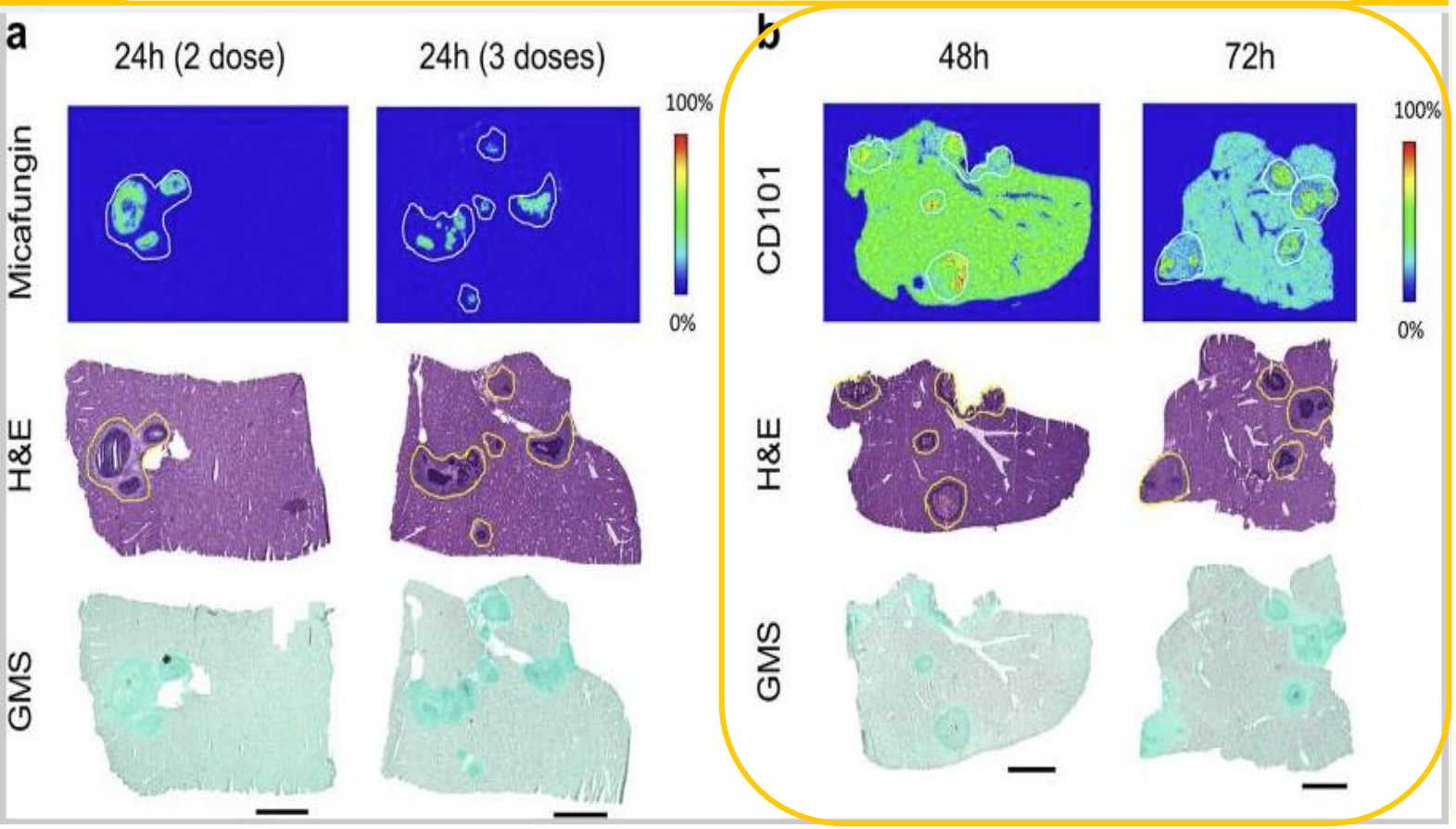
Results
RZF provides greater tissue exposure and lesion penetration compared to MCF

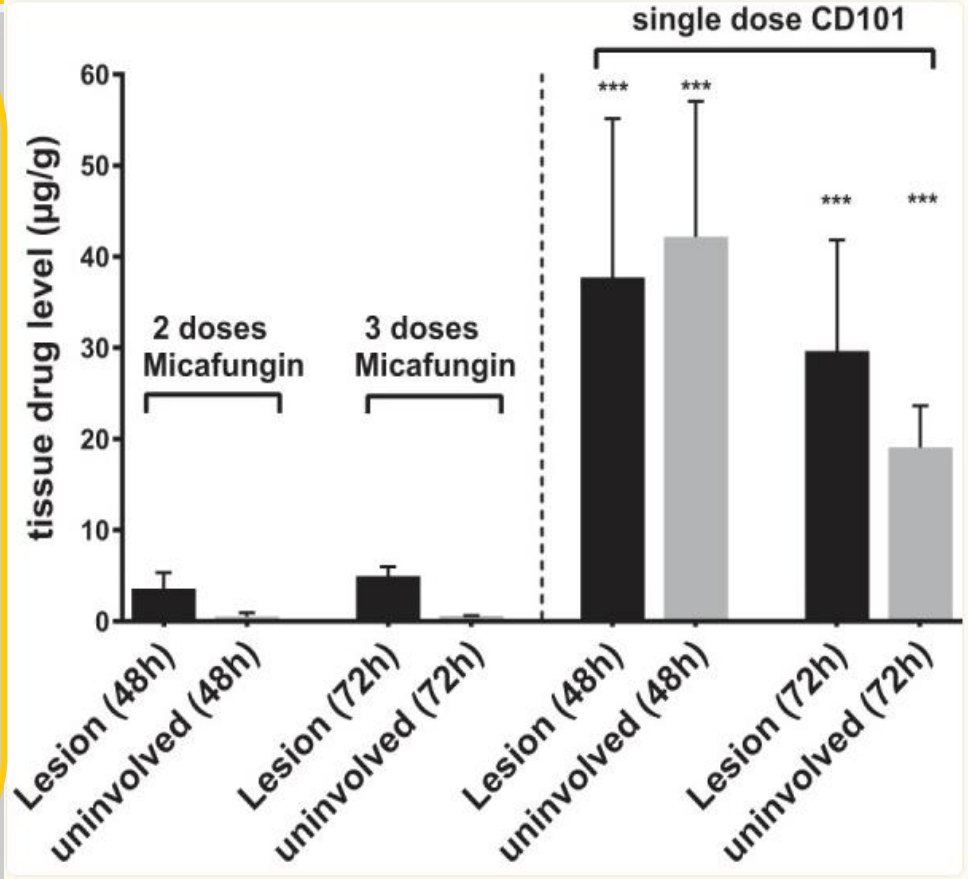
RZF: rezafungin

REZAFUNGIN | *In vivo* efficacy

The prolonged PK property not only differentiates RZF from other echinocandins but also results in greater drug penetration into the infected tissue site.

RZF diffused completely into the lesions 48 hours after the single dose and accumulated in necrotic areas within 72 h.





PK: pharmacokinetics; RZF: rezafungin

Zhao Y et al. . *Antimicrob Agents Chemother*. 2017.

REZAFUNGIN | *In vivo* efficacy

J Antimicrob Chemother. 2018 Aug 1;73(8):2085-2088. doi: 10.1093/jac/dky153.

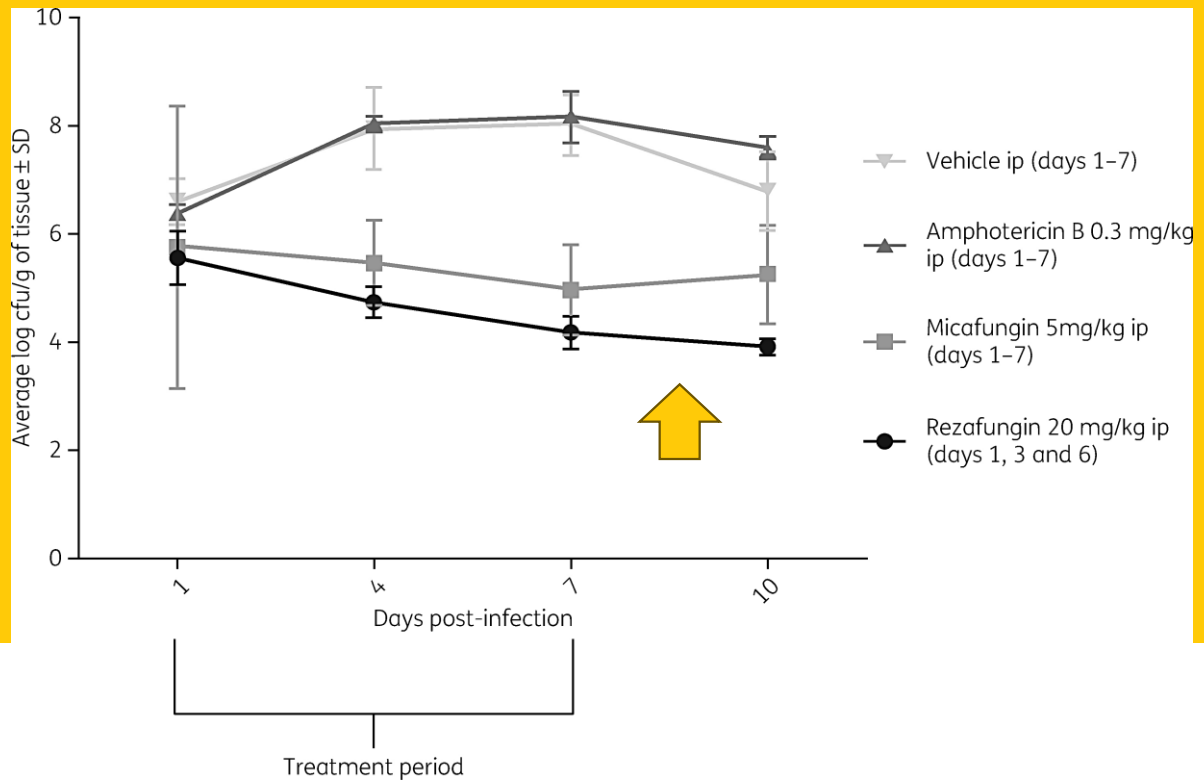
Evaluation of the efficacy of rezafungin, a novel echinocandin, in the treatment of disseminated Candida auris infection using an immunocompromised mouse model

Christopher L Hager [1], Emily L Larkin [1], Lisa A Long [1], Mahmoud A Ghannoum [1]

Objectives
To evaluate the efficacy of rezafungin in the treatment of disseminated *C. auris* infection.

Methods
Murine model of disseminated candidiasis.
RZF 20mg/kg
AMB 0.3mg/kg
MCF 5mg/kg

Results
Significantly lower mean log 10 cfu/g of tissue compared to AMB and MCF.



- Efficacy was measured by counting fungal colonies in the kidneys at various time points.
- RZF significantly reduced fungal colony counts more than AMB and MCF on D10.
- Authors: Potent antifungal agent against disseminated *C. auris* infection.

Hager CL et al. . *Antimicrob Agents Chemother*. 2018.

REZAFUNGIN | PK/PD meta

Antimicrob Agents Chemother. 2018 May 25;62(6):e02614-17. doi: 10.1128/AAC.02614-17. Print 2018 Jun.

Overcoming the Resistance Hurdle: Pharmacokinetic–Pharmacodynamic Target Attainment Analyses for Rezafungin (CD101) against Candida albicans and Candida glabrata

Justin C Bader [1], Elizabeth A Lakota [2], Shawn Flanagan [3], Voon Ong [3], Taylor Sandison [3], Christopher M Rubino [2], Sujata M Bhavnani [2], Paul G Ambrose [2]

JOURNAL ARTICLE

We can do better: a fresh look at echinocandin dosing FREE

Justin C Bader, Sujata M Bhavnani, David R Andes, Paul G Ambrose ✉

Journal of Antimicrobial Chemotherapy, Volume 73, Issue suppl_1, January 2018, Pages i44–i50, https://doi.org/10.1093/jac/dkx448

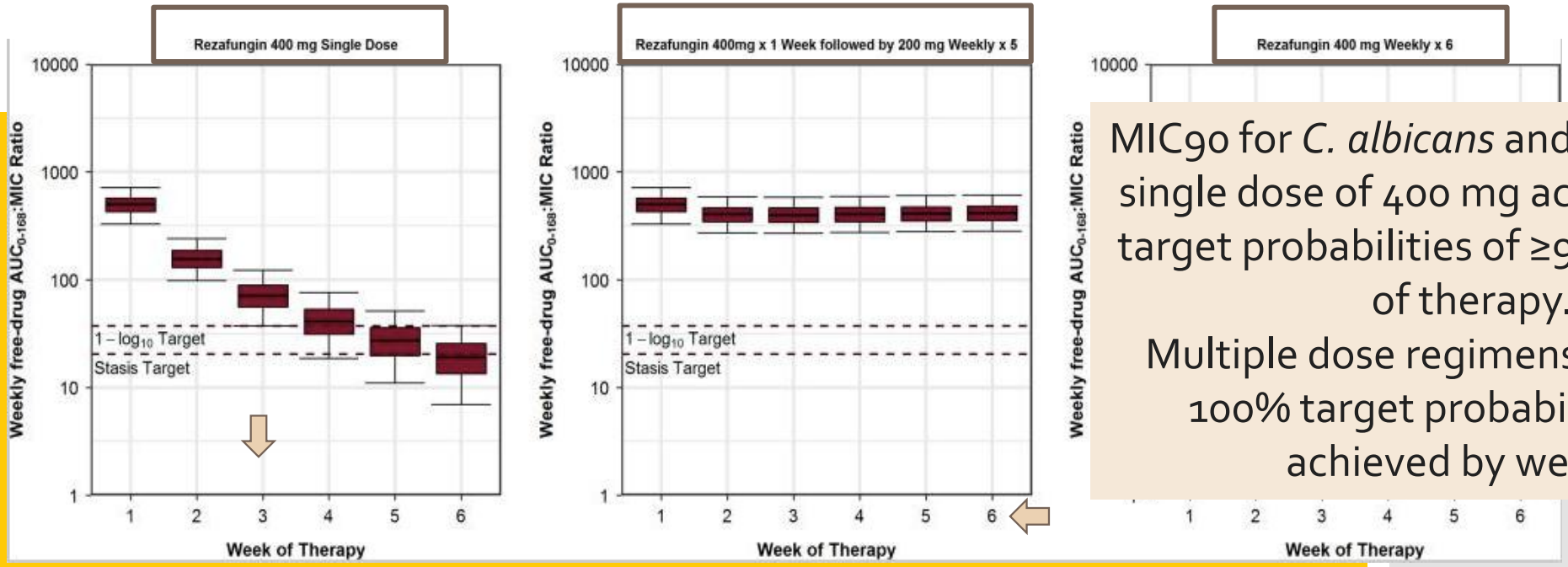
Objectives To evaluate the single and once-weekly dosage of RZF.

Methods Population-based PK model, and *in vitro* surveillance data obtained through Monte Carlo simulation.

Results RZF achieved 100% of its PK-PD target by week 6.

PK: pharmacokinetics; PD: pharmacodynamics; RZF: rezafungin

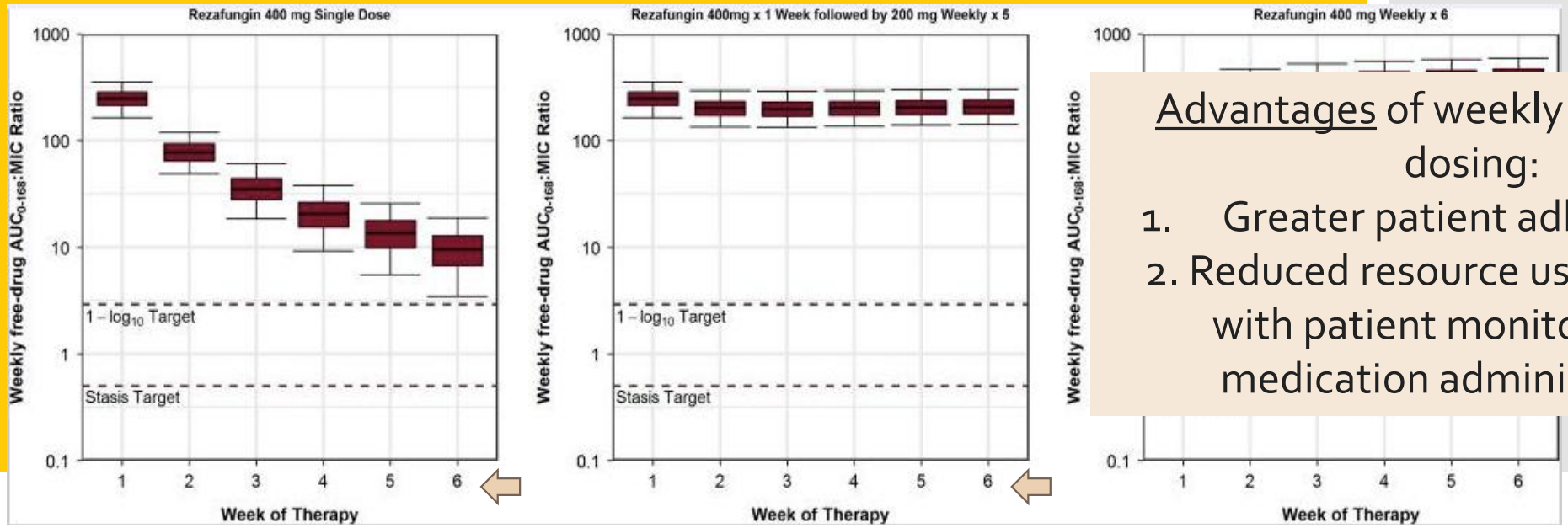
C. albicans



MIC90 for *C. albicans* and *C. glabrata* → single dose of 400 mg achieved PK/PD target probabilities of ≥90% by week 3 of therapy.

Multiple dose regimens (weekly) → 100% target probabilities were achieved by week 6.

C. glabrata



<u>Advantages</u> of weekly versus daily dosing:

1. Greater patient adherence and;
2. Reduced resource use associated with patient monitoring and medication administration.

PK: pharmacokinetics; PD: pharmacodynamics; MIC: minimum inhibitory concentration

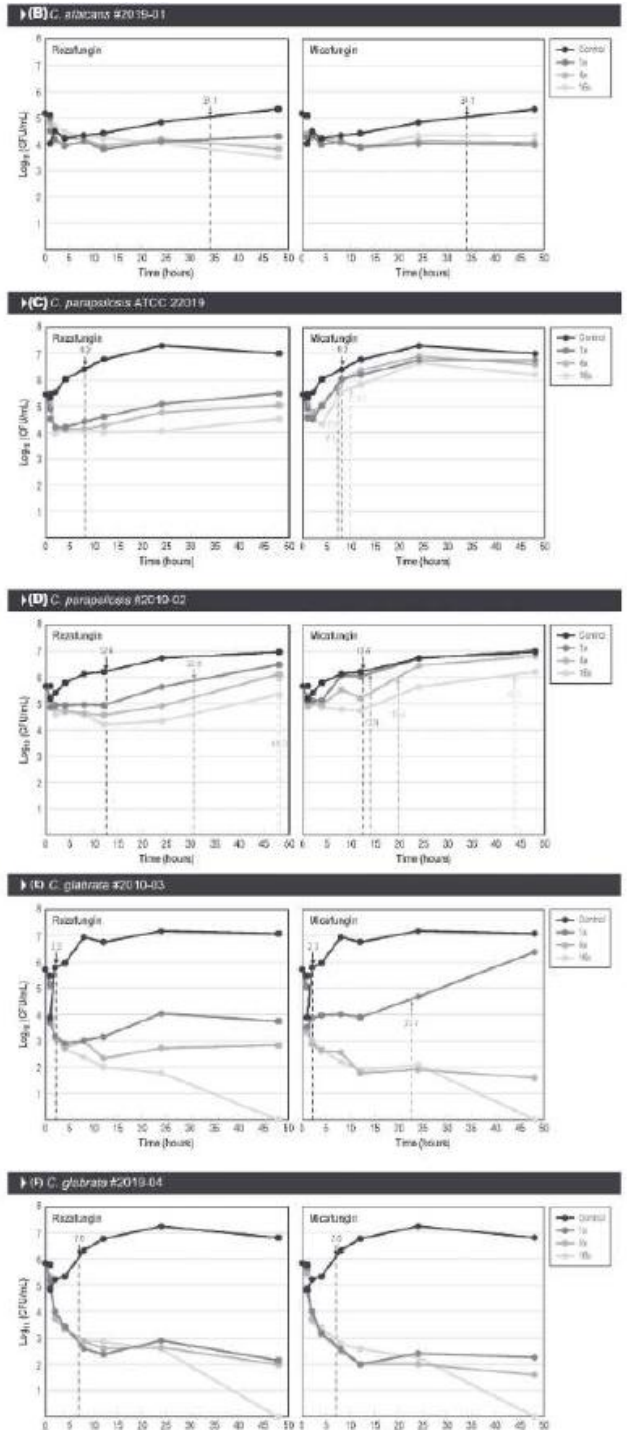
Mycoses
Diagnosis, Therapy and Prophylaxis of Fungal Diseases

ORIGINAL ARTICLE

Evaluation of the Post-Antifungal Effect of Rezafungin and Micafungin against *Candida albicans*, *Candida parapsilosis* and *Candida glabrata*

Cecilia G. Carvalhaes, Paul R. Rhomberg, Michael A. Pfaller, Jeffrey B. Locke, Mariana Castanheira

- **Post-antifungal effect (PAFE)** → RZF was compared to MCF;
- Sustained growth inhibition even after drug withdrawal for all *Candida* species tested;
- Particularly prolonged effects against C. *parapsilosis isolates*.
- RZF exhibited similar or longer PAFE values compared to MCF:
  RZF = MCF C. *albicans* (>14.9 h)
  RZF = MCF C. *glabrata* (>40 h)
- RZF ↑ MCF C. *parapsilosis* (18.4 to 40 h): no MCF PAFE or a short PAFE (1.8 to 7.4 h) was observed, except in 16x bMIC.



RZF: rezafungin; MCF: micafungin; MIC: minimum inhibitory concentration

Carvalhaes CG et al. *Mycoses*, 2022.

| Clinical Microbiology | Research Article | 28 November 2023

Population pharmacokinetic modeling and target attainment analyses of rezafungin for the treatment of candidemia and invasive candidiasis

Authors: Stefan Roepcke, Julie Passarell, Helen Walker, Shawn Flanagan | AUTHORS INFO & AFFILIATIONS

Population-based PK with data from: five Phase 1 studies, one Phase 2 study, and one Phase 3 study.

Significant covariates: body surface area, disease status, and albumin concentration.

Covariates were not associated with clinically significant changes in PK, nor with any other patient factors, including sex, BMI, renal function, and age.

No dose adjustment is necessary, indicating that the common dosing regimen is suitable for all adult patients.

Simulations to estimate the probability of hitting PK/PD targets across the entire MIC range for six *Candida* species indicated success for most individuals (96%).

PK: pharmacokinetics; PD: pharmacodynamics; BMI: body mass index; MIC: minimum inhibitory concentration

Roepcke S et al. *Antimicrob Agents Chemother*. 2023.

Clinical trials development program

PHASE 2

STRIVE

NCT02734862

DESIGN

Randomized, double-blind

POPULATION

207 patients randomized

COMPARISON

Rezafungin (2 regimens) vs. caspofungin

PRIMARY ENDPOINT

Overall cure at Day 14

PHASE 3

ReSTORE

NCT03667690

DESIGN

Randomized, double-blind, double-dummy, noninferiority

POPULATION

199 patients (mITT: 93 vs. 94)

COMPARISON

Rezafungin 400/200 mg vs. caspofungin 70/50 mg

PRIMARY ENDPOINT

Day 14 global cure (EMA) and Day 30 mortality (FDA)

POOLED

Species analysis

STRIVE + ReSTORE

DESIGN

Post hoc, pooled data

POPULATION

294 patients (RZF 139 / CAS 155)

COMPARISON

Stratification by Candida species and baseline MIC

PRIMARY ENDPOINT

Day 14 global cure, Day 30 mortality, mycological eradication

Thompson et al., Clin Infect Dis 2021; Thompson et al., Lancet 2023; Soriano et al., Clin Microbiol Infect 2024

STRIVE PHASE 2

Clinical Trial > Clin Infect Dis. 2021 Dec 6;73(11):e3647-e3655. doi: 10.1093/cid/ciaa1380.

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

George R Thompson [1], Alex Soriano [2], Athanasios Skoutelis [3], Jose A Vazquez [4], Patrick M Honore [5], Juan P Horcajada [6], Herbert Spapen [7], Matteo Bassetti [8], Luis Ostrosky-Zeichner [9], Anita F Das [10], Rolando M Viani [11], Taylor Sandison [11], Peter G Pappas [12]

DESIGN

Phase 2, randomized, double-blind, multicenter trial in adults with systemic signs and mycological confirmation of candidemia and/or invasive candidiasis.

TREATMENT ARMS

- Rezafungin 400 mg, once weekly
- Rezafungin 400 mg (Week 1) followed by 200 mg once weekly
- Caspofungin 70 mg (loading dose) followed by 50 mg daily, for up to 4 weeks

ENDPOINTS ASSESSED

Primary: overall cure at Day 14 (clinical resolution + mycological eradication).
Secondary: investigator-assessed clinical response (D14), 30-day all-cause mortality, time to negative blood culture.

207

patients
randomized

183

microbiological
intent-to-treat population
46 (400mg)/ 76 (400/200mg)/ 61 (CAS)

CLINICAL TRIAL REGISTRATION

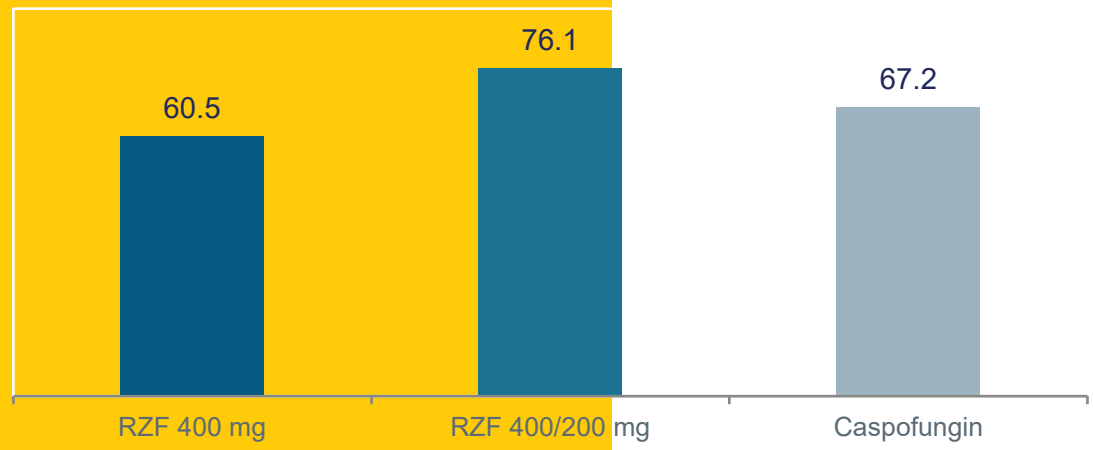
NCT02734862

Comparison of two rezafungin dosing strategies (fixed weekly dose vs. loading-and-maintenance regimen) against standard-of-care caspofungin.

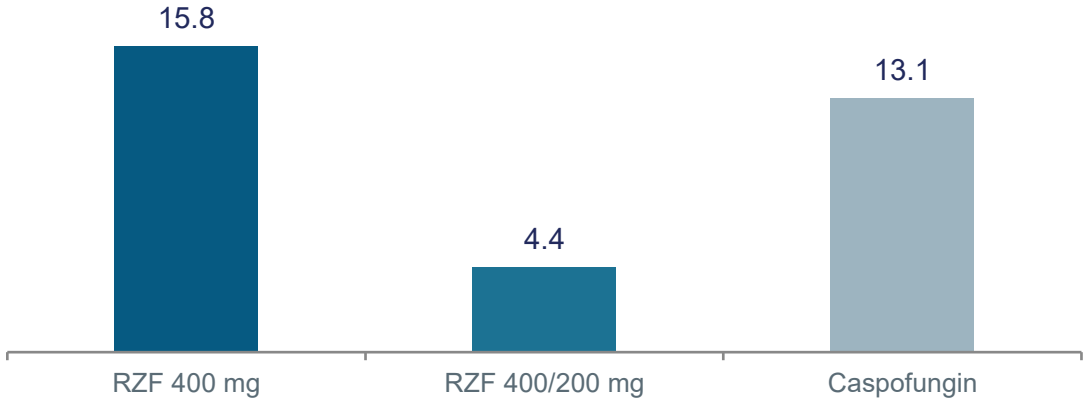
Thompson GR 3rd et al. Rezafungin versus caspofungin in a phase 2 trial. Clin Infect Dis. 2021;73(11):e3647–e3655.

STRIVE

Overall cure at Day 14 (%)



30-day all-cause mortality (%)



69.7 / 80.4 / 70.5%

Investigator-assessed clinical cure (D14), RZF 400 mg / RZF 400-200 mg / CAS

19.5 vs. 22.8 h

Time to negative blood culture, rezafungin vs. caspofungin

15.2 vs. 18.8%

Overall mortality through follow-up, rezafungin vs. caspofungin

No concerning safety trends between groups; comparable adverse event profile between rezafungin and caspofungin.

Thompson GR 3rd et al. Rezafungin versus caspofungin in a phase 2 trial. Clin Infect Dis. 2021;73(11):e3647–e3655.

ReSTORE PHASE 3

Clinical Trial > Lancet. 2023 Jan 7;401(10370):49-59. doi: 10.1016/S0140-6736(22)02324-8. Epub 2022 Nov 25.

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

George R Thompson 3rd [1], Alex Soriano [2], Oliver A Cornely [3], Bart Jan Kullberg [4], Marin Kollef [5], Jose Vazquez [6], Patrick M Honore [7], Matteo Bassetti [8], John Pullman [9], Methee Chayakulkeeree [10], Ivan Poromanski [11], Cecilia Dignani [12], Anita F Das [13], Taylor Sandison [14], Peter G Pappas [15]; ReSTORE trial investigators

DESIGN

Phase 3, multicenter, randomized, double-blind, double-dummy, noninferiority trial in adults with candidemia and/or invasive candidiasis.

TREATMENT ARMS

- Rezafungin 400 mg (loading dose) followed by 200 mg once weekly
- Caspofungin 70 mg (loading dose) followed by 50 mg daily
- Treatment for up to 4 weeks, with optional oral fluconazole step-down in the caspofungin arm

PRIMARY ENDPOINTS

Day 14 global cure (EMA criterion) and 30-day all-cause mortality (FDA criterion). Noninferiority margin: upper 95% CI < 20% (mortality); weighted lower bound > −20% (global cure).

199

patients randomized

93 / 94

mITT population rezafungin / caspofungin

CLINICAL TRIAL REGISTRATION

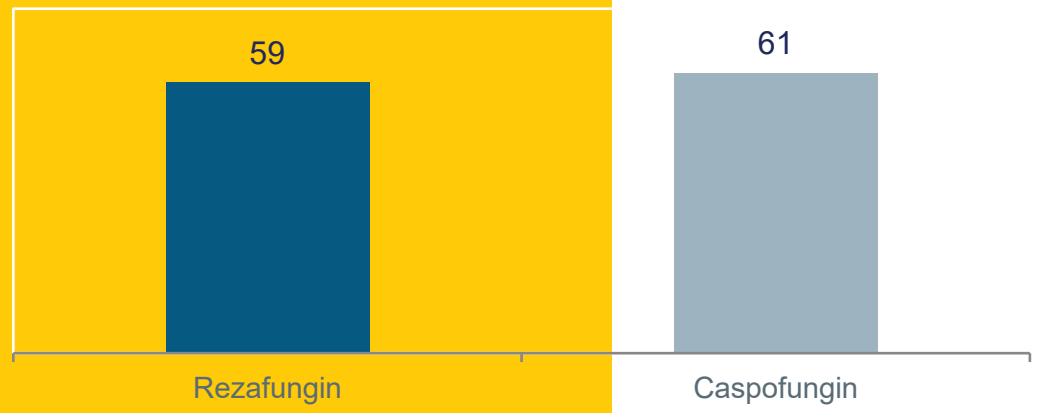
NCT03667690

Pivotal trial supporting rezafungin's regulatory approval, including a China extension cohort for local registration.

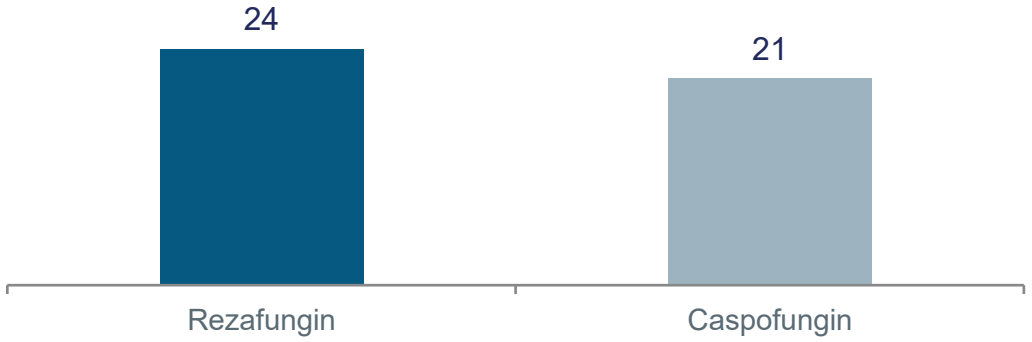
Thompson GR 3rd et al. Rezafungin versus caspofungin (ReSTORE). Lancet. 2023;401(10370):49–59.

ReSTORE

Global cure - Day 14 (%)



All-cause mortality - Day 30 (%)



Noninferiority of rezafungin versus caspofungin was confirmed for both primary endpoints. No concerning trends were observed in treatment-emergent or serious adverse events between groups.

Thompson GR 3rd et al. Rezafungin versus caspofungin (ReSTORE). Lancet. 2023;401(10370):49–59.

Pooled analysis

STRIVE + RESTORE

Clinical Trial > Clin Microbiol Infect. 2025 Feb;31(2):250-257. doi: 10.1016/j.cmi.2024.11.029. Epub 2024 Nov 22.

Clinical and mycological outcomes of candidaemia and/or invasive candidiasis by Candida spp. and antifungal susceptibility: pooled analyses of two randomized trials of rezafungin versus caspofungin

Alex Soriano [1], Jeffrey B Locke [2], Oliver A Cornely [3], Emmanuel Roilides [4], Antonio Ramos-Martinez [5], Patrick M Honoré [6], Mariana Castanheira [7], Cecilia G Carvalhaes [7], Saad Nseir [8], Matteo Bassetti [9], Nick Manamley [10], Taylor Sandison [11], Maiken C Arendrup [12]

METHODS

- Post hoc analysis using pooled data from the STRIVE (Phase 2) and ReSTORE (Phase 3) trials
- Inclusion: documented Candida infection within 96 hours of randomization, with receipt of ≥1 dose of study drug
- Comparison: rezafungin 400/200 mg once weekly vs. caspofungin 70/50 mg once daily
- Susceptibility testing: broth microdilution per EUCAST E.Def 7.4 methodology, with Tween 20-supplemented medium for rezafungin
- Outcomes assessed by *Candida* species and by baseline minimum inhibitory concentration (MIC)

294

patients with documented Candida infection
(RZF n=139 · CAS n=155)

SUSCEPTIBILITY FINDING

3 isolates

non-susceptible to rezafungin identified at baseline screening

Soriano A et al. Clinical and mycological outcomes by Candida spp. and antifungal susceptibility. Clin Microbiol Infect. 2024.

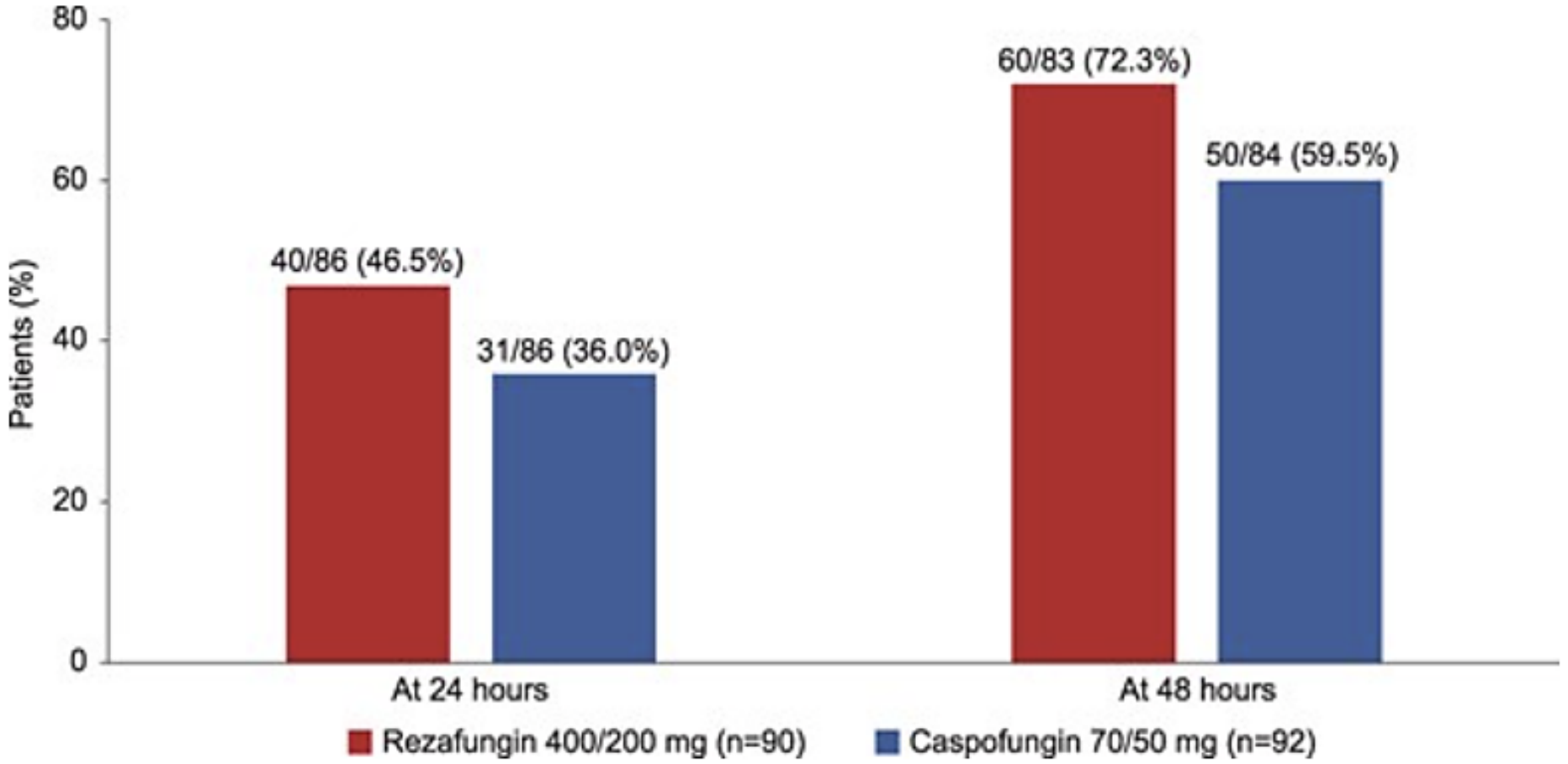
Pooled analysis

RESTORE + China extension

Clinical Trial > Open Forum Infect Dis. 2025 Sep 15;12(9):ofaf555. doi: 10.1093/ofid/ofaf555. eCollection 2025 Sep.

Rezafungin Versus Caspofungin for the Treatment of Candidemia and Invasive Candidiasis: Results from the Double-blind, Randomized, Phase 3 ReSTORE Trial Including the China Extension Study

George R Thompson [1], Haihui Huang [2], Sizhou Feng [3], Yunsong Yu [4], Alex Soriano [5], Oliver A Cornely [6], Bart Jan Kullberg [7], Peter G Pappas [8], Marin Kollef [9], Jose A Vazquez [10], Patrick M Honore [11], Laura Cox [12], Matteo Bassetti [13]



Proportions of patients with negative blood cultures were higher with rezafungin than caspofungin at 24 h and 48 h after the first dose

Thompson GR et al. ReSTORE + China extension. Open Forum Infect Dis. 2025;12(9):ofaf555.

Independent observational cohorts

REAL-WORLD EVIDENCE

Across independent cohorts in Europe and the United States, rezafungin has enabled outpatient parenteral antifungal therapy, earlier hospital discharge, and treatment of chronic or hard-to-treat invasive candidiasis.

EARLY ACCESS PROGRAM · ITALY / GERMANY

Long-term outpatient use in hard-to-treat IC

Prospective early access program; 6 adults with chronic, hard-to-treat invasive candidiasis (incl. C. parapsilosis)

Once-weekly outpatient IV infusion for up to 39 weeks — replaced daily antifungal infusions a… enabled hospital discharge

Trapani F et al. Open Forum Infect Dis. 2025;12(3):ofaf034.

FUNGISCOPE REGISTRY · EUROPE + US

Multinational registry experien…

Retrospective analysis, C… median age 6…

…esponse in

OUTPATIENT UTILI…

R… …iders, May–Dec 2024; 86 patients re…

47/8… …om inpatient to outpatient care; 66% resolved, 21% improved, 13% unsuc… …al

Van Hise N et al. Open Forum Infect Dis. 2026;13(Suppl 1):ofaf695.1393.

… / CONSOLIDATION COHORT · SPAIN

Single-center experience, deep-seated sites

Retrospective cohort, Hospital 12 de Octubre (Madrid), Sept 2022–Dec 2025; 13 patients, mean age 59.4y

Intravascular Candida infection (38.5%); surgical-site and intra-abdominal candidiasis (23.1% each)

Real-World Clinical Practice study. Mycoses. 2025/2026.

Independent, non-interventional cohorts; sample sizes are small and hypothesis-generating.

PK/PD rationale and ongoing clinical study

DEEP-SEATED INFECTION · PK/PD

PHARMACOKINETIC RATIONALE

- Extended half-life (~133–152 hours) with front-loaded, high early plasma exposure supports sustained tissue concentrations between weekly doses
- Preclinical and PK/PD modelling data indicate higher penetration into hepatosplenic and other deep abdominal tissues than standard-dose echinocandins
- Pharmacokinetics unaffected by age, sex, body weight, renal function (including continuous renal replacement therapy), or hepatic impairment (Child-Pugh B/C)
- Front-loaded exposure and higher tissue penetration are proposed to lower the risk of on-therapy resistance emergence at deep-seated infection sites

ONGOING CLINICAL STUDY

NCT06985758

Pharmacokinetic study of rezafungin in patients with suspected intra-abdominal candidiasis. Objective: characterize peritoneal and tissue-level rezafungin concentrations in patients with suspected or confirmed intra-abdominal/peritoneal candidiasis.

CURRENT EVIDENCE STATUS

Human PK and efficacy data specific to intra-abdominal candidiasis are still emerging. Current evidence rests on preclinical models, PK/PD modelling, and case-level real-world experience, with dedicated prospective studies underway.

Wasmann et al. Crit Care 2023 (PK/PD review); ClinicalTrials.gov NCT06985758; Microbiol Spectrum. 2023;11(6):e01339-23.

Cost-effectiveness versus daily echinocandins

PHARMACOECONOMICS

Mycoses. 2026 Feb;69(2):e70148. doi: 10.1111/myc.70148.

Cost–Effectiveness of Once Weekly Rezafungin for the Treatment of Invasive Candidiasis in the United Kingdom

Noemi Muszbek [1], Alisha Angdembe [1], Carolina Garcia-Vidal [2], Inga Bielicka [3], Keith R Abrams [1], Keith Tolley [4], Markus Ruhnke [5], Maximilian Lebmeier [6], Neil Hawkins [1], Nick Manamley [3], Sara Dickerson [3]

MODEL

- Hybrid model: short-term decision tree (≤30-day treatment) + long-term Markov model (lifetime horizon)
- UK NHS perspective; comparators: caspofungin, micafungin, anidulafungin (daily echinocandins)
- Base case: cost-minimisation (comparable efficacy assumed); scenario: cost-utility analysis
- Early hospital discharge modeled for 16% of rezafungin patients, averaging 5.9 days earlier

DISCOUNTED INCREMENTAL COST OF REZAFUNGIN (COST-SAVING)

−£7,789	−£8,344	−£8,705
vs. caspofungin	vs. micafungin	vs. anidulafungin

Cost-effective at the UK NHS willingness-to-pay threshold of £20,000 per QALY, with a net monetary benefit of £7,154–£8,069 versus daily echinocandins. Interpretation: the benefit is driven largely by avoided inpatient days and modeled pathways; prospective comparative cost data remain limited.

Muszbek N et al. Cost-effectiveness of once weekly rezafungin for IC in the UK. Mycoses. 2026;69:e70148.

Cost-of-illness modelling

PHARMACOECONOMICS

JOURNAL ARTICLE

Health-economic modelling of cost savings due to the use of rezafungin based on a German cost-of-illness study of candidiasis

Julia Jeck, Florian Jakobs, Melina S Kurte, Oliver A Cornely, Florian Kron ✉
Author Notes

JAC-Antimicrobial Resistance, Volume 5, Issue 3, June 2023, dlad079,
https://doi.org/10.1093/jacamr/dlad079

METHODS

- Retrospective cost-of-illness study, University Hospital Cologne (Germany), real-world data 2016–2021
- 724 cases (652 patients) with Candida infections identified; 61% received ICU treatment, 29% mechanically ventilated
- Potential rezafungin savings modeled using the 5-day ICU length-of-stay reduction observed in the STRIVE trial

A candidemia-specific subgroup (ICD-10 B37.7) showed a median saving of €7,211, consistent with the overall model.

€7,175

median cost-saving potential per hospital case with invasive candidiasis or candidemia

€283,335

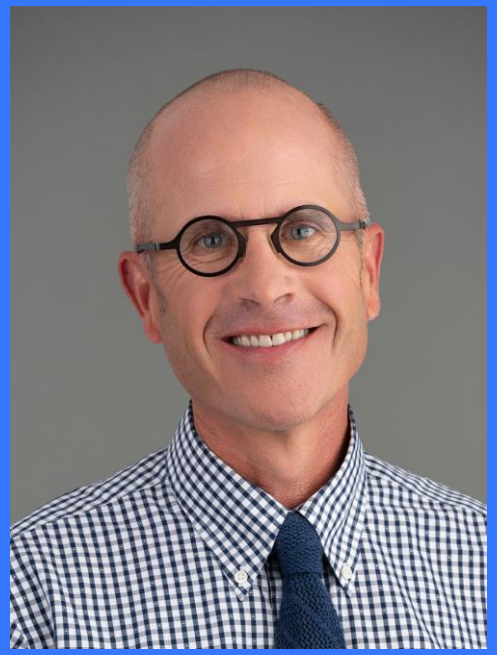
accumulated modeled savings across 37 evaluable patients

Jeck J et al. Health-economic modelling of cost savings due to rezafungin. JAC-Antimicrob Resist. 2023;5(3):dlad079.

REZAFUNGIN | Take-home messages

- Weekly dosing is supported by long half-life, front-loaded exposure, and tissue penetration.
- Pivotal trials support efficacy, safety, and tolerability comparable to established echinocandins.
- The greatest practical value may be in OPAT and prolonged therapy; access and reimbursement remain implementation barriers.
- Observational and economic findings are promising but should be interpreted as hypothesis-generating.
- **Take-home: clinical non-inferiority, weekly convenience, and potential system value.**

David Andes



David Andes, M.D. is the William Craig Professor in the Departments of Medicine, Medical Microbiology and Immunology, and Head of the Division of Infectious Diseases at the University of Wisconsin School of Medicine and Public Health.

David is a clinician-scientist with focus in the area of antimicrobial resistance.

https://www.medicine.wisc.edu/directory/andes_david

PHARMACOLOGY OF NEW ANTIFUNGALS

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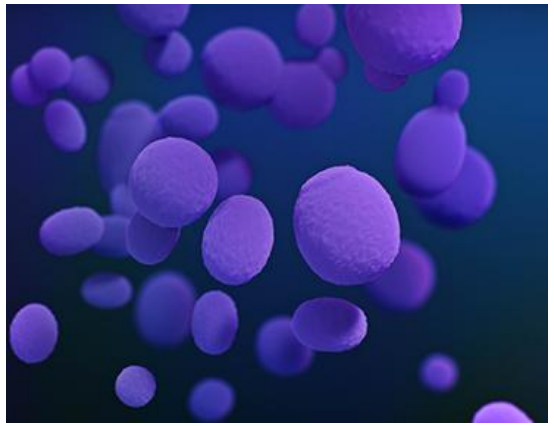
Disclosures

- Consultant: FDA, CDC, NIH, Astellas, Merck Scynexis, Basilea, Elion, F2G, Mundipharm

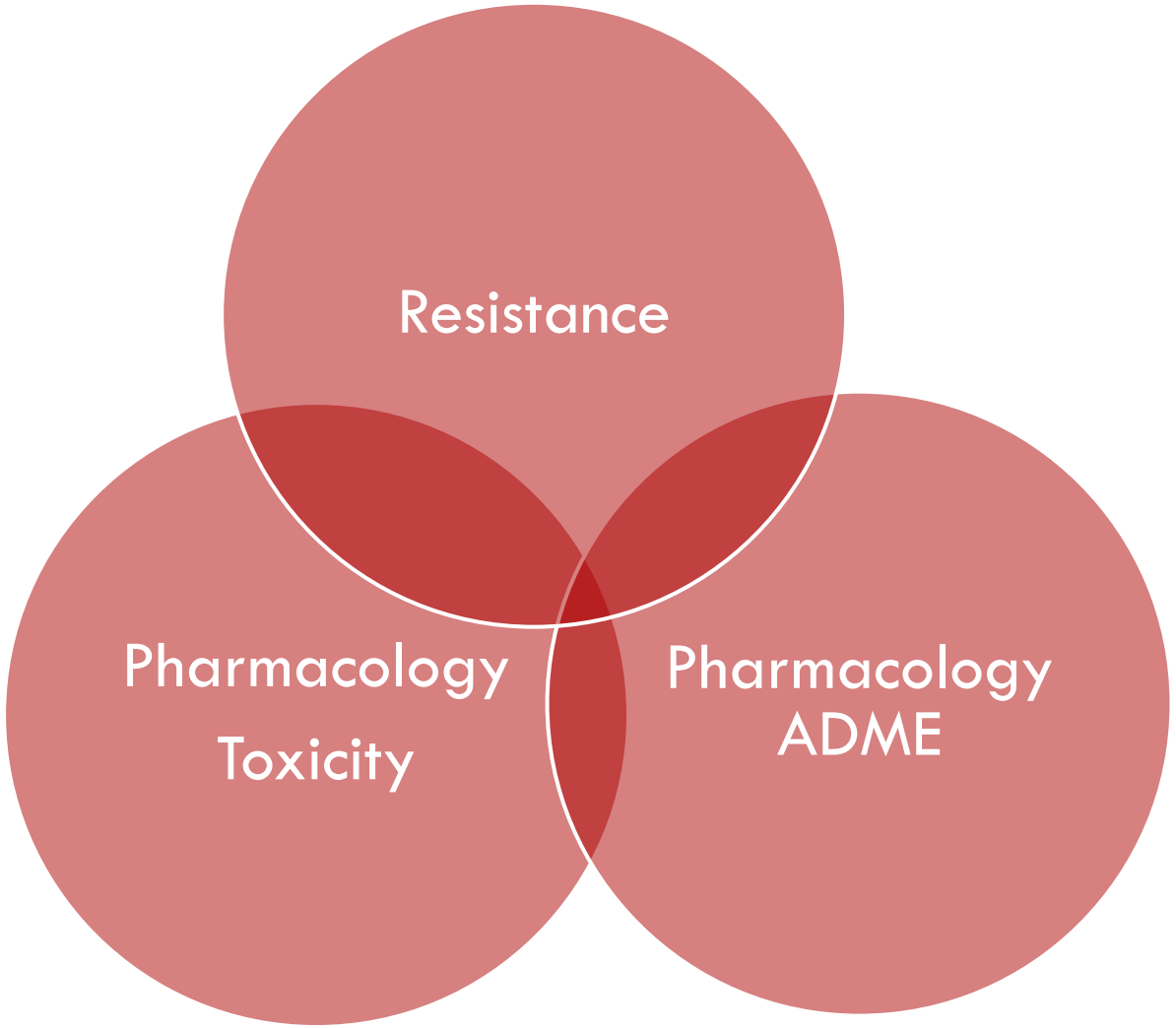
- Grant support: NIH, FDA, Merck, Astellas, Basilea, Scynexis, Cidara, Matinas, Elion

Outline

- Antifungal pharmacologic gaps
- New antifungal agents and pharmacologic potential



Antifungal Needs



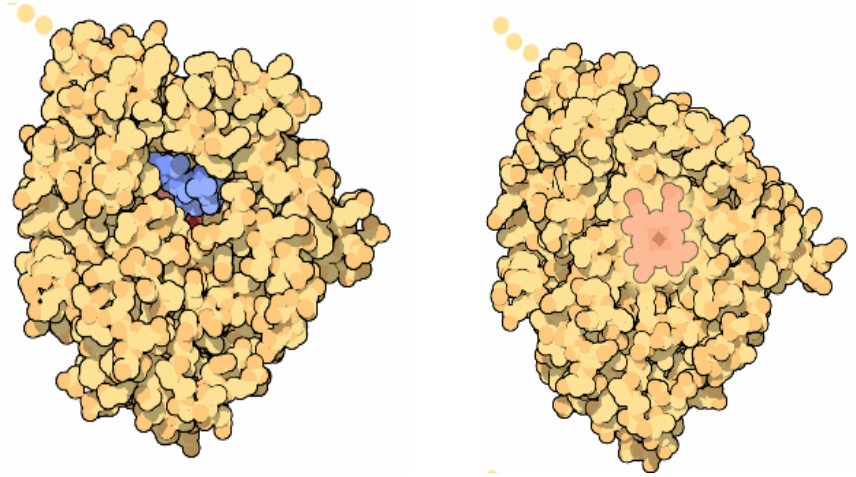
PK – Metabolism, Drug Interactions, Therapeutic Drug Monitoring (TDM), Toxicity

Challenging Efficacy vs Toxicity Bar

Eukaryotic conservation of cellular and metabolic biology limits exploitable fungal-specific drug targets

Metabolic

CYP51A CYP3A4



Homology of fungal and mammalian targets (e.g., P450 enzymes)

Drug-Interactions

- Triazole drug interactions
- Multicenter, N=6,962
  - >80% hospitalizations
  - 20-60% contraindicated

Andes D et al. Antimicrob Agents Chemother. 2016 doi: 10.1128/AAC.00054-16.

PK – Site of Infection and Drug Distribution

Key Pharmacologic Liabilities – Distribution to Common Fungal Sanctuaries

CNS Incidence

Candidiasis 15-64%

Aspergillosis 6%

Cryptococcosis 67-84%

Histoplasmosis 5-20%

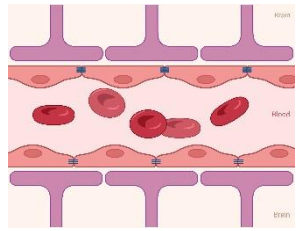
Disseminated

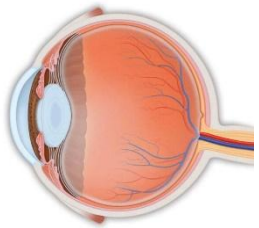
Coccidioidomycosis 25%

Disseminated

Blastomycosis 40%

HIV/transplant





CSF/Eye Accumulation

Fluconazole 80%

Flucytosine 75%

Voriconazole 60%

Ambisome > other polyenes

Everything else<1%

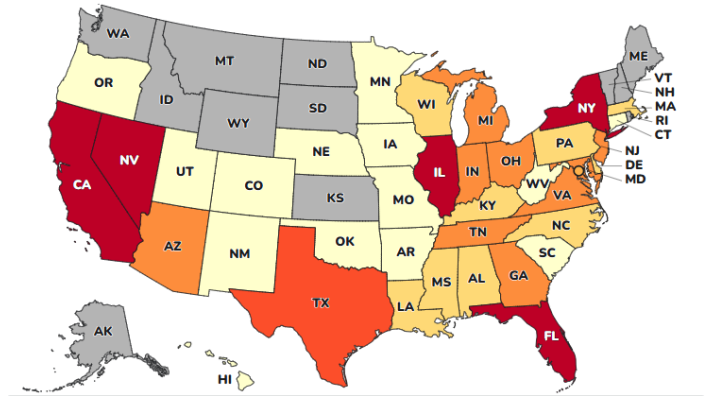
Lipton AJM 1984;76:101, Bayer Medicine 1976;55:477, Patterson Medicine 2000;79:250, Chapman CID 2000;30:679, Wheat CID 2000;30:688.
Nett Infect Dis Clin North Amer 2016

Antifungal Resistance and PK/PD Target

Emerging Resistance and PK/PD Target

C. auris

- 80% azole-R, 30% MDR
- Up to 60% mortality



Legend

From 2016-2023, there have been 10,788 clinical cases. There were an additional 22,931 screening cases not shown on the map. There were 9 clinical cases from 2013-2015 that were reported retrospectively.

- No new clinical cases
- 1 to 10
- 11 to 50
- 51 to 100
- 101 to 500
- 501 to 1000
- >1000

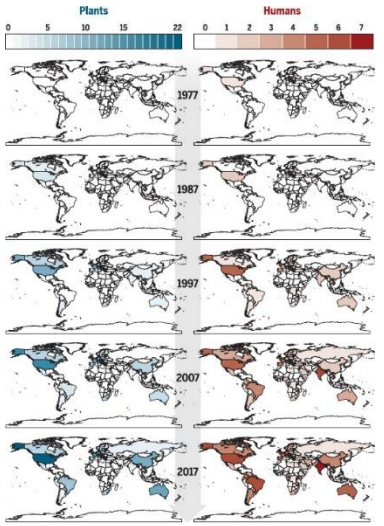
C. glabrata

- Echinocandin-R
- 2-15%

A. fumigatus

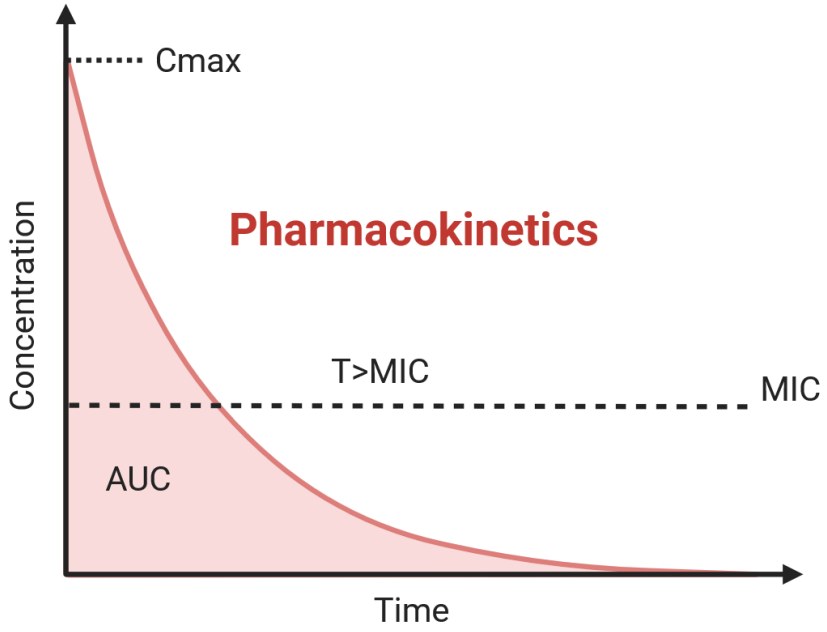
- Triazole-R 5-50% global, US 5%

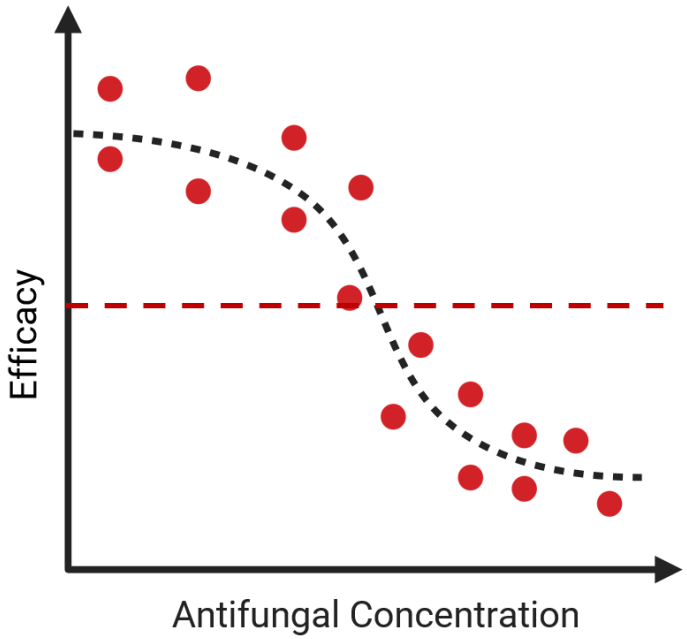
Emerging mold pathogens and dermatophytes



CDC.gov, WHO fungal priority list, NEJM 2025;392:2187, CMR 2024;37:1

PK/PD Predictions – Resistance, Mice, and Humans





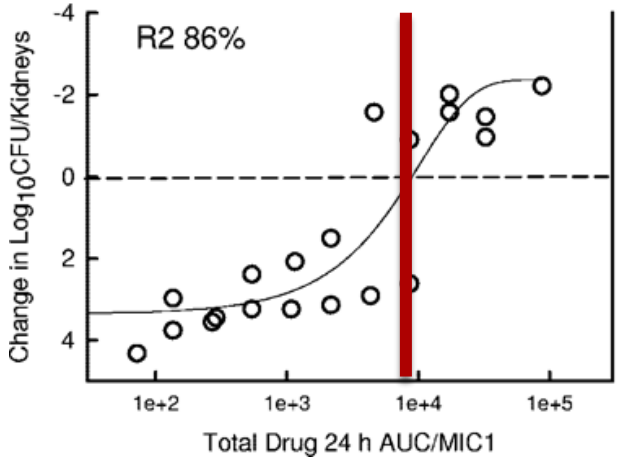
Preclinical Translation of PK-PD Targets for Candidemia

Micafungin

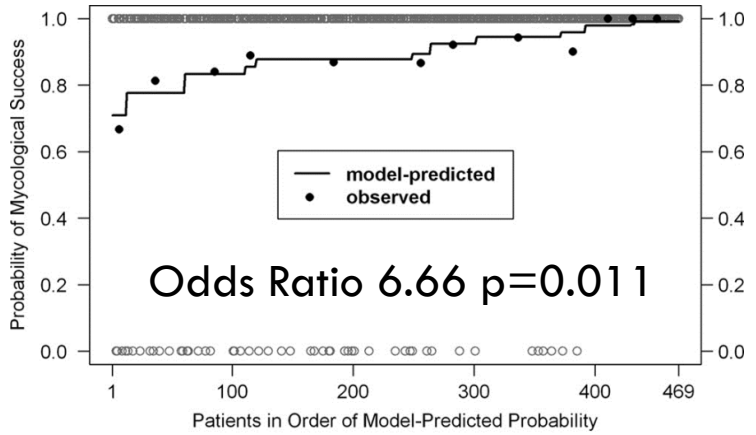
Animal-Derived

Clinically-Derived

Endpoint	Net fungal stasis
Total-drug AUC/MIC ratio target	~ 3000-5000



Endpoint	Mycological success
Total-drug AUC/MIC ratio target	3000



Andes D. Antimicrob Agents Chemother. 2008; 52(10):3497-3503.
Andes D,. Antimicrob Agents Chemother. 2011; 55(5):2113-2121.

Preclinical Translation of PK-PD Targets for Candidemia

Micafungin

Animal-Derived

Clinically-Derived

Despite:

- Faster half-life in small animals

BUT:

- Drug target is in the organism and NOT the host
- Exposure relative to MIC is the determinant

USE:

- Dose regimen selection
- Susceptibility breakpoint guidance

Total Drug 24 h AUC/MIC1

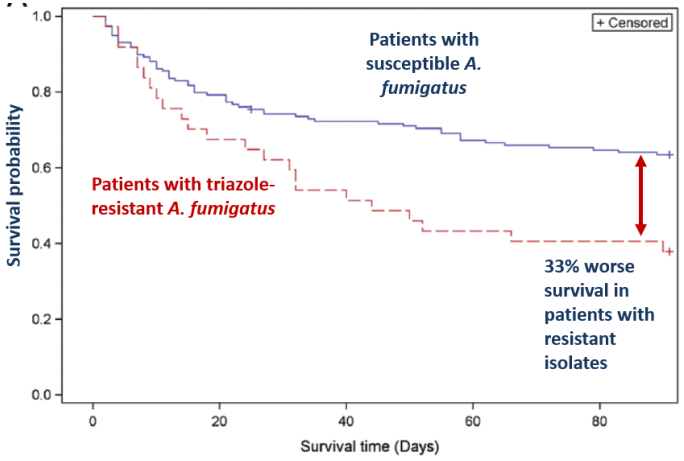
Patients in Order of Model-Predicted Probability

Andes D. Antimicrob Agents Chemother. 2008; 52(10):3497-3503.
Andes D,. Antimicrob Agents Chemother. 2011; 55(5):2113-2121.

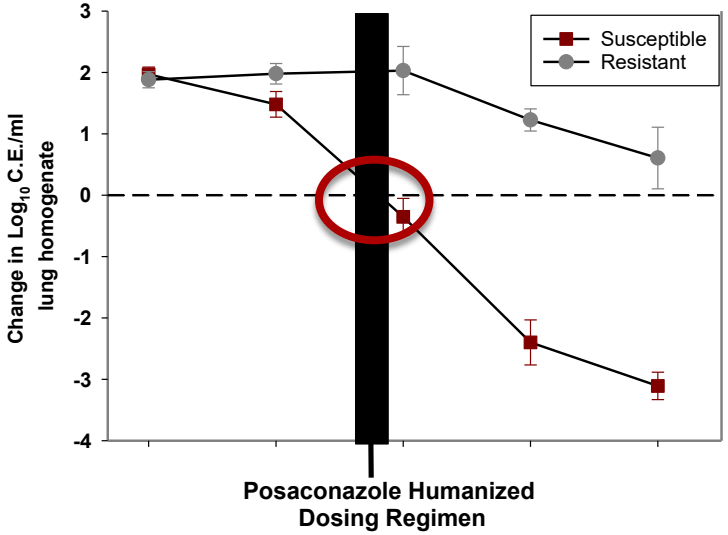
Preclinical Translation of PK-PD Targets for Resistant *Aspergillosis* – ***MIC Breakpoint***

Posaconazole

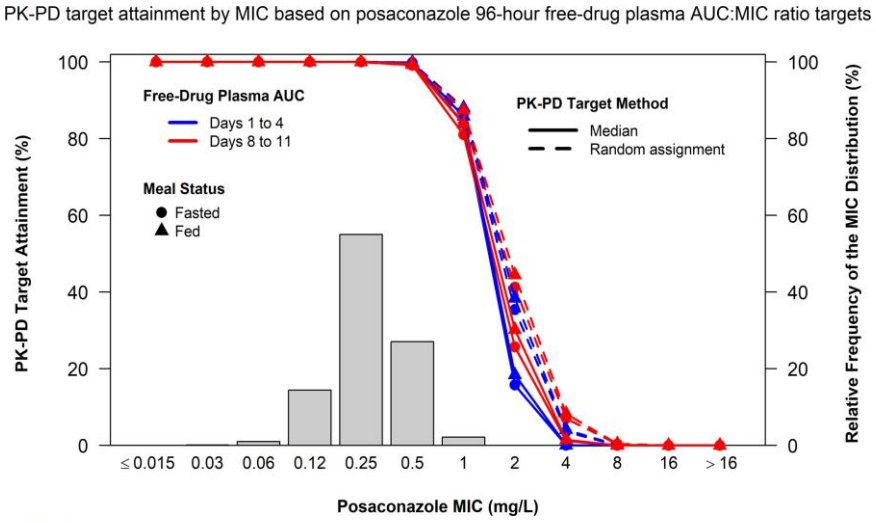
Clinical Signal



Animal-Derived



Clinically-Predicted



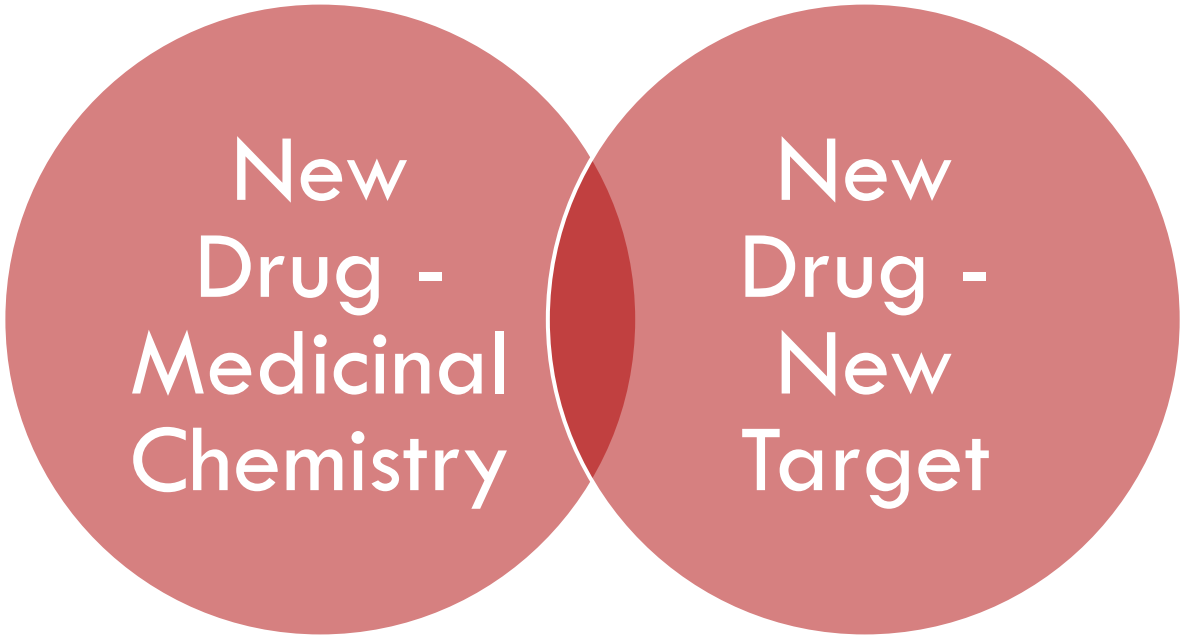
Resistance

Lestrade PP. Clin Infect Dis. 2019 68(9):1463-1471.

Andes D. Antimicrob Agents Chemother. 2008; 52(10):3497-3503.

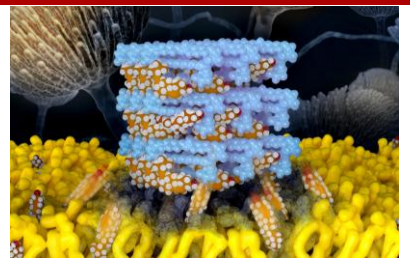
Lepak A. Antimicrob Agents Chemother. 2026 70(3):e0164325.

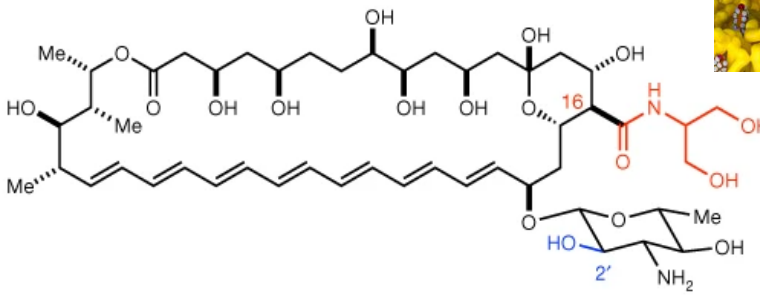
Antifungal Innovations



New Antifuganl
Similar Mechanism – Improved Features

- **AM-219/SF001/EL-219 (Turletricin)**
  - Elion Therapeutics
  - AmB analog
  - IV
  - Same spectrum
  - **Safer (preferential ergosterol vs cholesterol sequestration)**
  - Early trials
    - P1 safe
    - P2-3 NCT06666322 Cryptococcal meningitis (PLATFORM-CM)
    - P2 NCT107215273 – (TREAT-1) Suspected mold infection



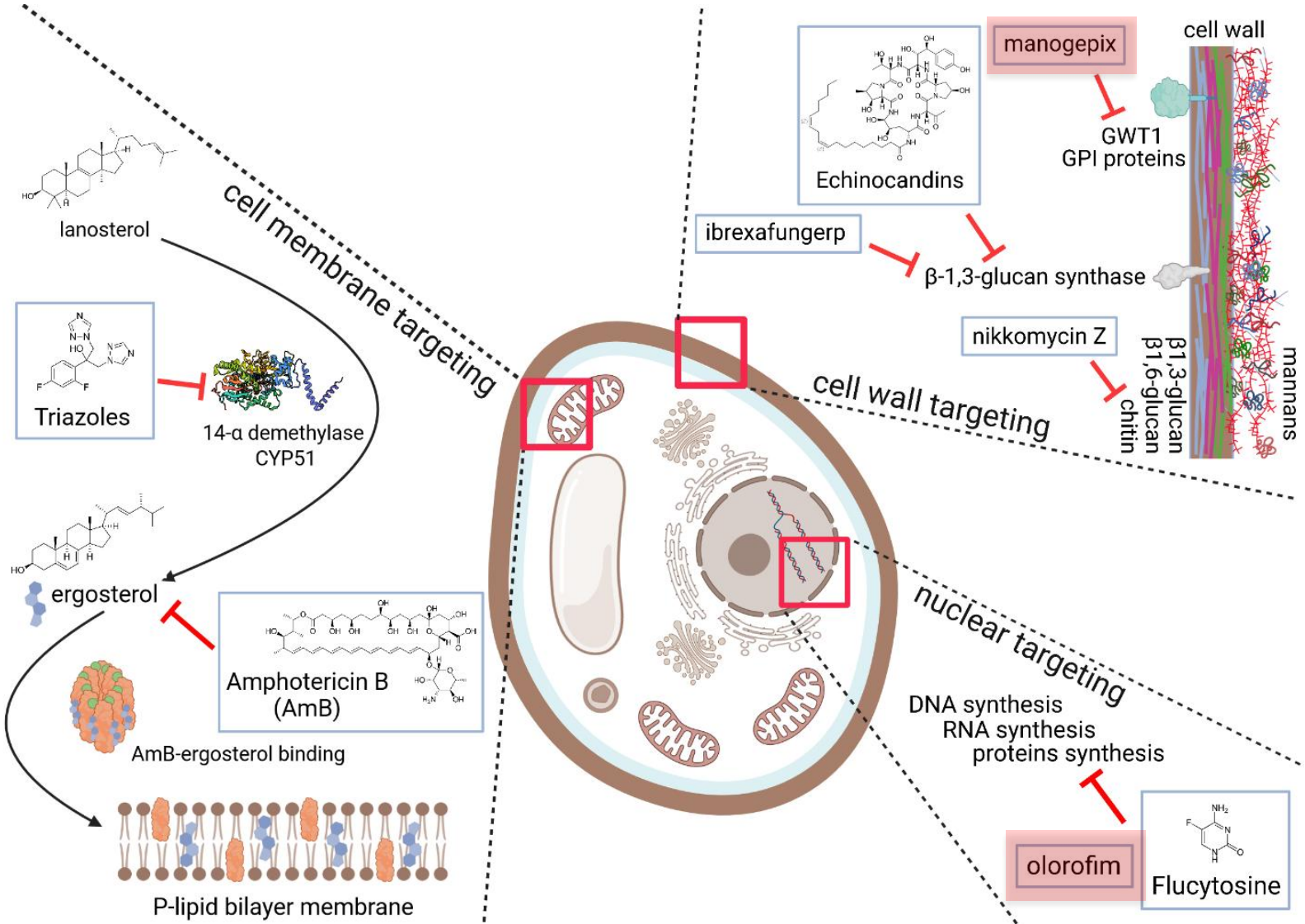


Ergosterol binding

Cholesterol binding

Nature. 2023;623(7989):1079-1085.

Novel Targets in Clinical Development



New Antifungal - Novel Target

Olorofim (*F901318*)

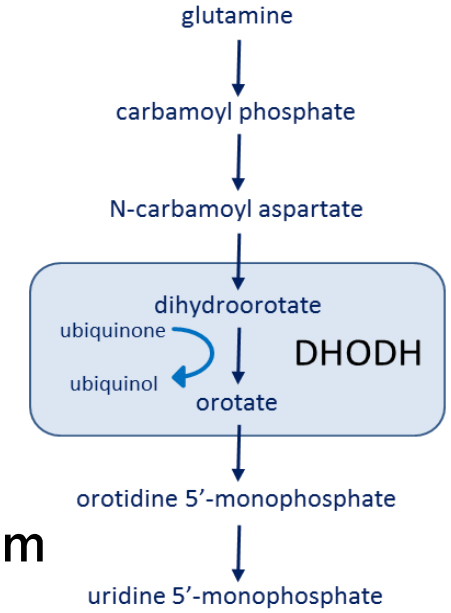
- Orotamide class
- DHODH (Dihydroorotate dehydrogenase) inhibitor

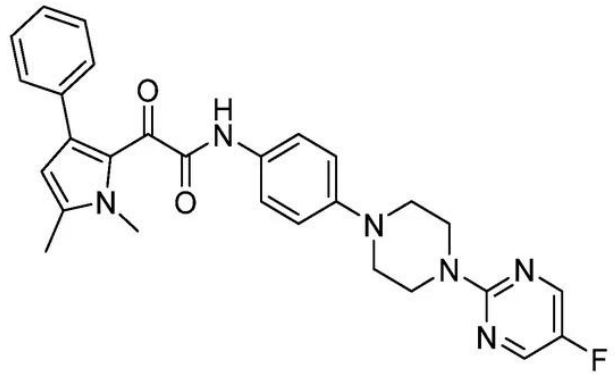
– 4th step pyrimidine biosynthesis (DNA/RNA)

2000X less activity against human DHODH

- Aspergillus, Scedosporium, Endemics, +/- Fusarium

(Not *Candida/Zygomycetes/Cryptococcus*)





Oliver et al. PNAS 113:12809-14, 2016.
Beckmann et al. ICAAC 2015; Fothergill et al. ICAAC 2015; Buil et al.JAC 2017; Rivero-Menéndez et al ECCMID 2017; Oliver et al PNAS 2016; Jorgensen et al. TIMM 2017

Olorofim - Pharmacology

Olorofim (*F901318*)

- Orotamide class
- DHODH (Dihydroorotate dehydrogenase) inhibitor

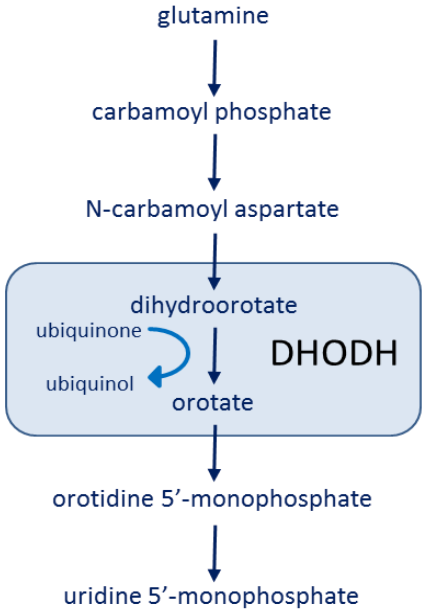
– 4th step pyrimidine biosynthesis (DNA/RNA)

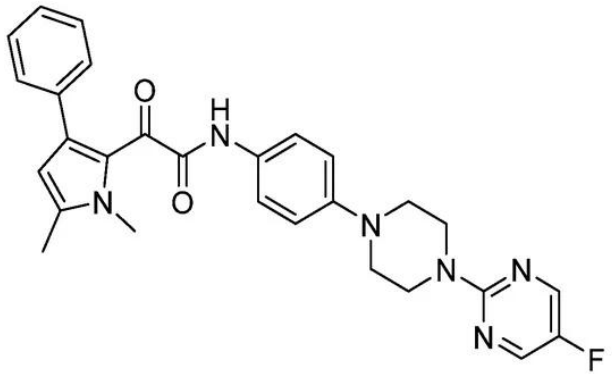
2000X less activity against human DHODH

- Aspergillus, Scedosporium, Endemics, +/- Fusarium

(Not *Candida/Zygomycetes/Cryptococcus*)

- **Oral and NG (>82% bioavailable)**
- **Twice daily dosing**
- **CNS penetration**
- **CYP3A4 weak inhibitor**
- **No organ dysfunction change**
- **No TDM**





Oliver et al. PNAS 113:12809-14, 2016.
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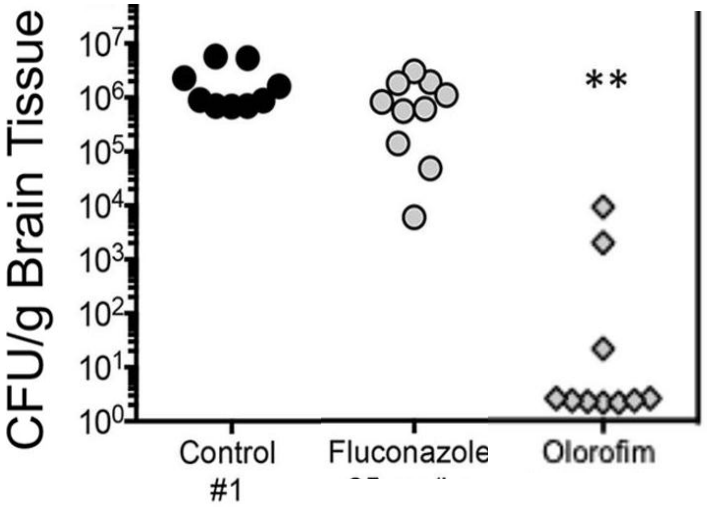
Fothergill et al. ICAAC 2015;
Buil et al.JAC 2017; Rivero-Menéndez et al ECCMID 2017;
Oliver et al PNAS 2016;
Jorgensen et al. TIMM 2017

Olorofim - Tissue Distribution and Efficacy

Preclinical

- ^{14}C labeled olorofim
- Rats - Extensive brain and eye radioactivity (1.6X plasma)
- Not urine (<0.3%)

Preclinical



Murine *Coccididoidomycoses* meningitis

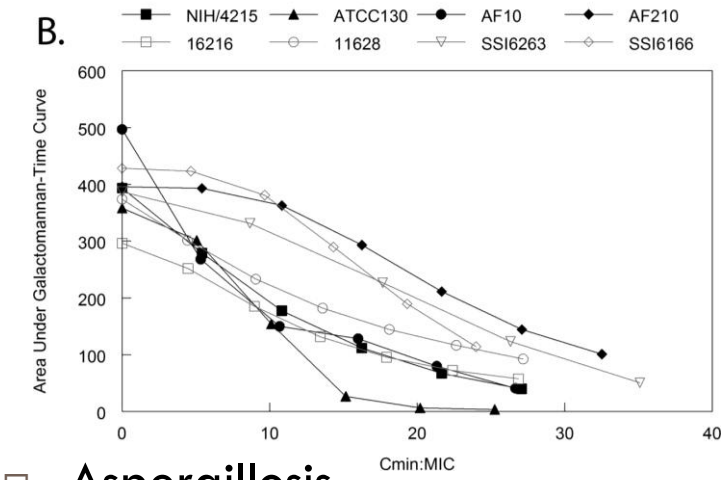
Clinical

>50 patients with CNS IFI in clinical trials

J Antimicrob Chemother. 2026 doi: 10.1093/jac/dkag120.
Antimicrob Agents Chemother. 2018 doi: 10.1128/AAC.00999-18.

Olorofim

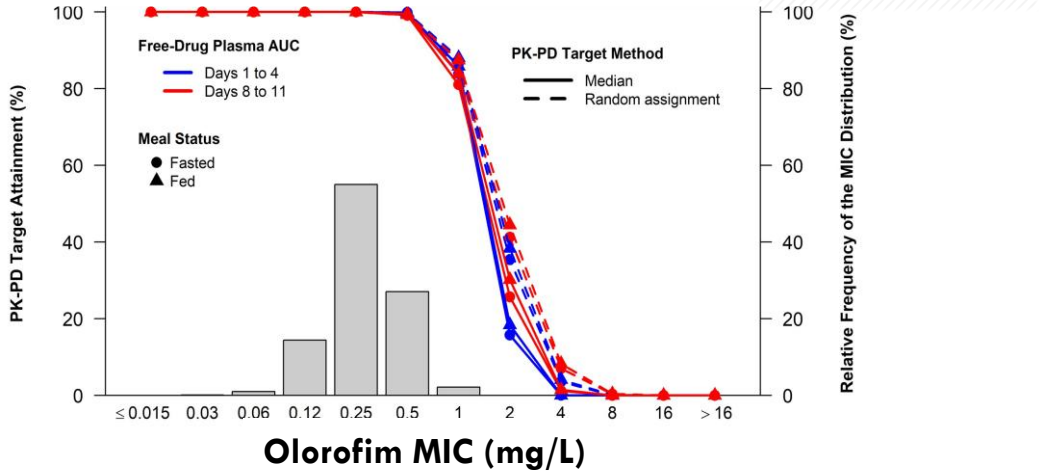
Animal-Derived



- Aspergillosis
- PK/PD driver = Cmin/MIC
- Humanized posaconazole = 27% GM
- Olorofim Cmin/MIC ~ 10

Hope WW et al. mBio. 2017 doi: 10.1128/mBio.01157-17.

Clinically-Predicted



- Target Cmin >0.1 µg/mL = 80% GM in mice
- Clinical trial dose (successful in Ph2 and 3 mold/cocci (150 mg bid load, then 90 mg bid)
- Target in >90% (no TDM?)

Maertens JA Lancet Infect Dis. 2025 doi: 10.1016/S1473-3099(25)00224-5.
Donovan FM et al. Ann Intern Med. 2026 doi: 10.7326/ANNALS-26-00103.

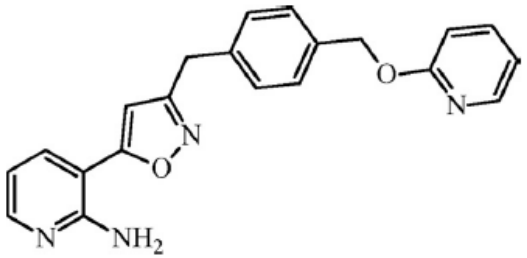
New Antifungal - Novel Target 2

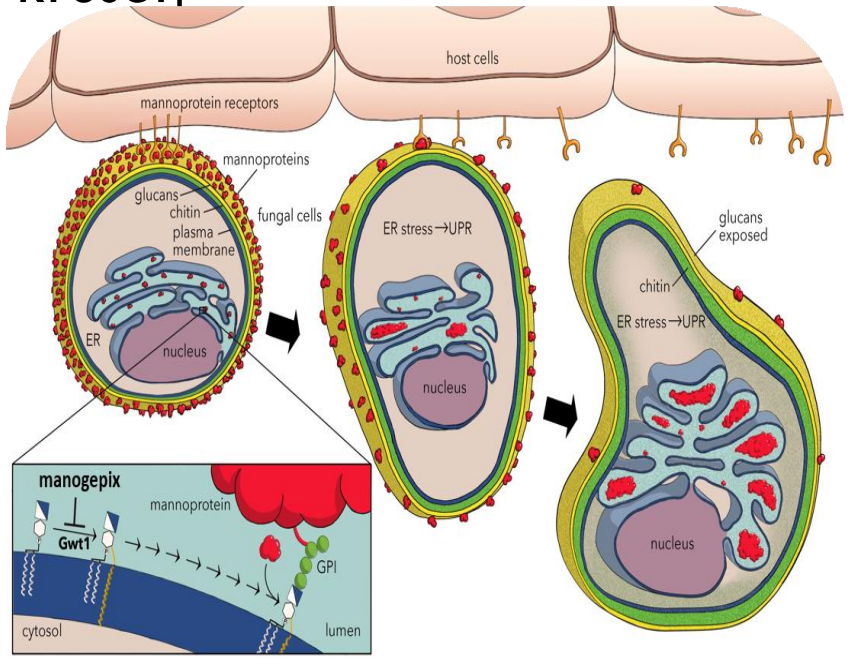
Fosmanogepix (APX-001/E1211, PF-07842805)

- GPI inhibitor (Gwt1= GPI-anchored wall protein transfer protein 1 = inositol acyltransferase)

  No activity vs human ortholog Pig-W

- Broad spectrum (Candida [except C. krusei] Aspergillus, Fusarium, Scedosporium, Zygomycetes, Endemics, Cryptococcus)

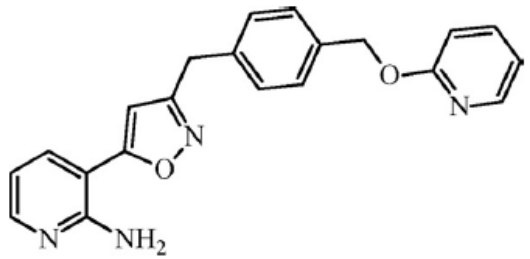


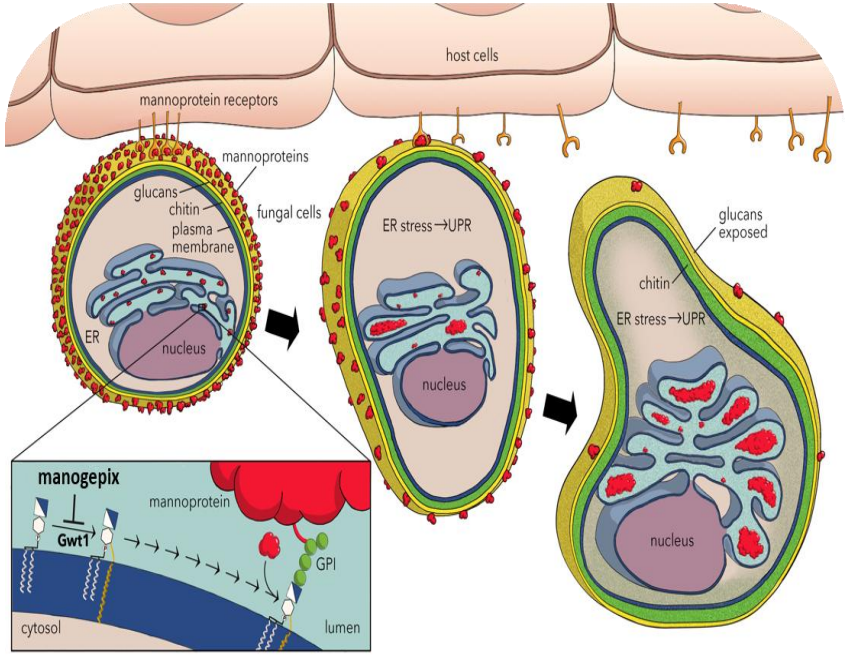


Fosmanogepix - Pharmacology

Fosmanogepix (APX-001/E1211, PF-07842805)

- GPI inhibitor (Gwt1= GPI-anchored wall protein transfer protein 1 = inositol acyltransferase)
  No activity vs human ortholog Pig-W
- Broad spectrum (Candida [except C. krusei] Aspergillus, Fusarium, Scedosporium, Zygomycetes, Endemics, Cryptococcus)
- **Oral (>90% bioavailable) and IV**
- **>2d half-life (daily dosing)**
- **CNS/eye penetration**
- **Low DDI**



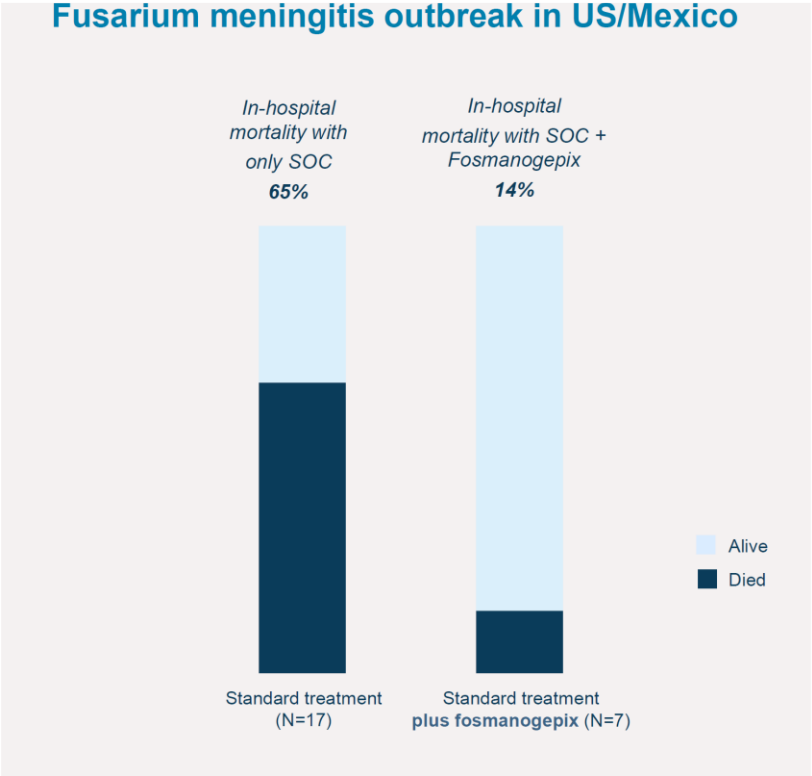


Fosmanogepix - Tissue Distribution and Efficacy

Preclinical

- ^{14}C labeled fosmanogepix
- Rats and monkeys
- Extensive brain and eye radioactivity
- Only 2.5% in urine

Clinical

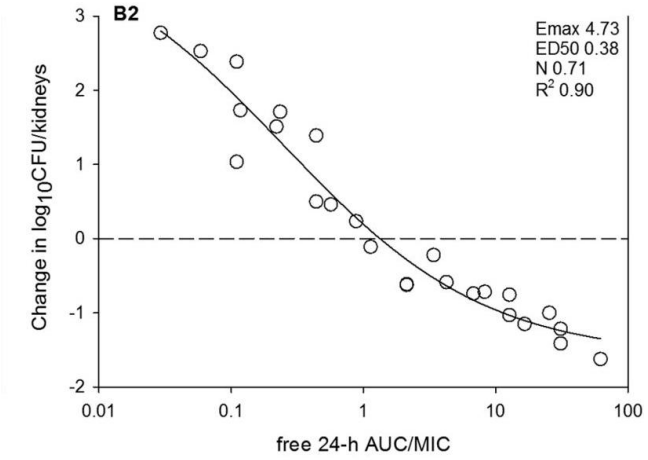


>100 patients in compassionate use program.
77% favorable response

Open Forum Infectious Diseases 2017 https://doi.org/10.1093/ofid/ofx163.1209
Clin Infect Dis 2025; https://doi.org/10.1093/cid/ciaf185

Fosmanogepix

Animal-Derived

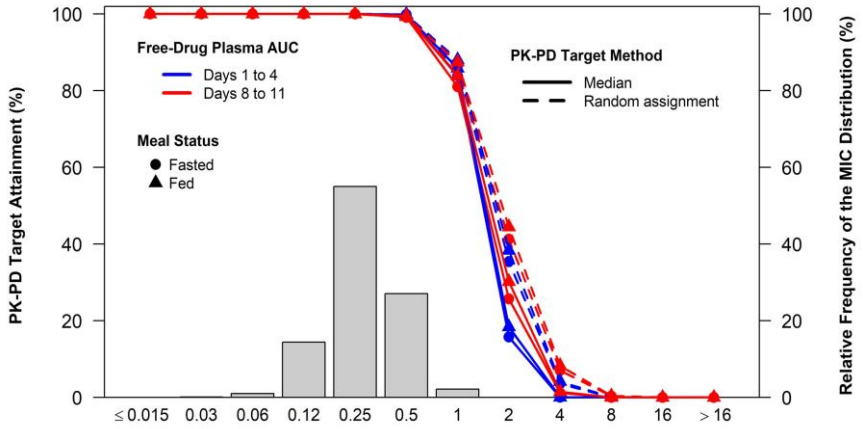


- *Candida and* Aspergillus
- PK/PD driver = AUC/MIC
- AUC/MIC target
  - Candida 10-20, A fumigatus 50

Zhao M et al. Antimicrob Agents Chemother. 2018 doi: 10.1128/AAC.02542-17.

Zhao M et al. Antimicrob Agents Chemother. 2019. doi: 10.1128/AAC.02372-18.

Clinically-Predicted



Manogepix MIC (mg/L)

- Human dose predicted effect (1000 mg IV bid, then 600 mg/d IV or 800 mg oral)
- Phase 2 AEGIS (aspergillosis)
- Phase 3 (candidemia) NCT05421858
- Phase 3 (mold) NCT06925321

Hodges MR et al Clin Infect Dis. 2025 doi: 10.1093/cid/ciaf185

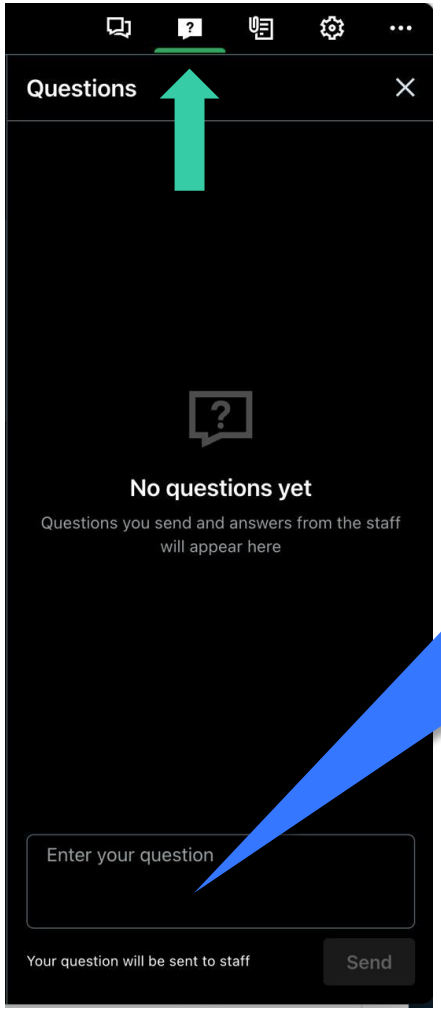
Summary

- Finding antifungal targets and drugs that kill fungi is relatively easy to find
- Finding antifungals that are safe and exhibit favorable pharmacologic properties is hard
- Promising agents on the horizon, including several with improved safety, CNS delivery, oral absorption, and MDR PK/PD predicted efficacy

How to submit your questions

REVIVE by GARDP

If your question is addressed to a specific speaker, please include their name when submitting the question.



Please submit your questions through the box provided after clicking the ‘questions’ button. We will review all questions and respond to as many as possible after the presentation.

Today's speakers

REVIVE by GARDP

An introduction to antibiotic research and development (R&D)

Moderator:
Dallas Smith
Centers for Disease Control and Prevention
U.S. CDC, USA

Wan-Yu (Wendy) Chu
Uppsala University, Sweden

Francelise Bridi Cavassin
Faculdades Pequeno Príncipe, Brazil

David Andes
University of Wisconsin-Madison, USA

Upcoming webinars

REVIVE by GARDP

The role of investigator initiated clinical trials in advancing antimicrobial use

With Anouk G. Overdevest, Nicholas A. Turner, Jesús Rodriguez-Bano

29 September 2026, 13:30-15:00 CEST

REVIVE
by GARDP

Thank you for joining us

Stay tuned, follow our activities on GARDP's social media channels: