



Rezafungina: una nuova echinocandina long-acting

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The diagram illustrates the structure of a fungal cell and the specific targets of various antifungal drugs. The cell contains organelles such as mitochondria and a nucleus. A red arrow indicates the pathway of pyrimidine synthesis. Five circular insets provide detailed views of the cell wall and membrane targets:

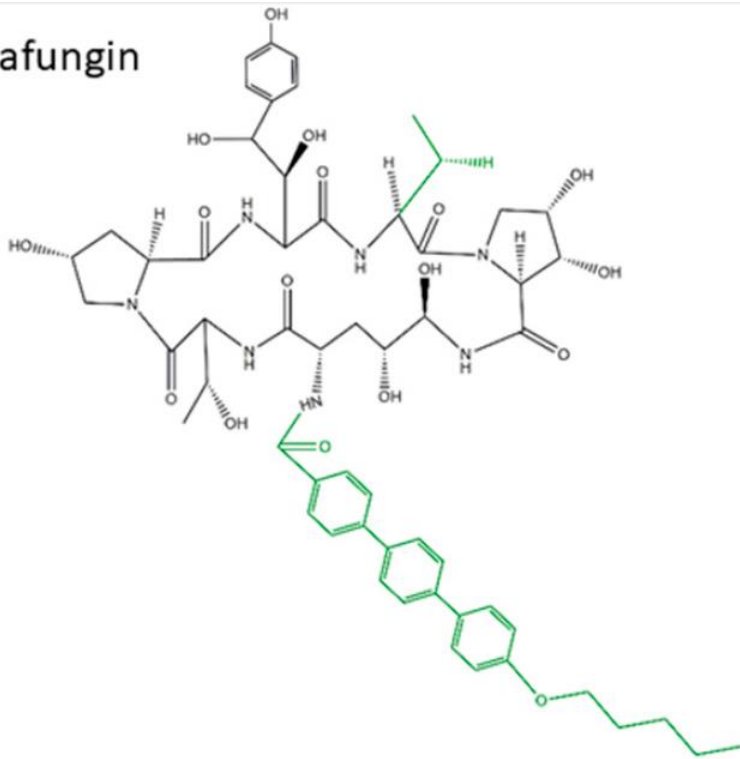
- IBREXAFUNGERP** and **REZAFUNGIN** target the synthesis of 1,6- β -D-Glucan, 1,3- β -D-Glucan, and Chitin by inhibiting 1,3- β -D-Glucan synthase.
- FOSMANOGEPIX** targets the conversion of PI to ac-PI by GWT1, which is necessary for the formation of Manno-proteins.
- OPELCONAZOLE** targets the conversion of Lanosterol to Ergosterol by CYP51A1.
- OLOROFIM** targets the conversion of Dihydroorotate to Orotate by DHODH.

Pyrimidine synthesis is shown as a red arrow originating from the nucleus and moving towards the cell periphery.

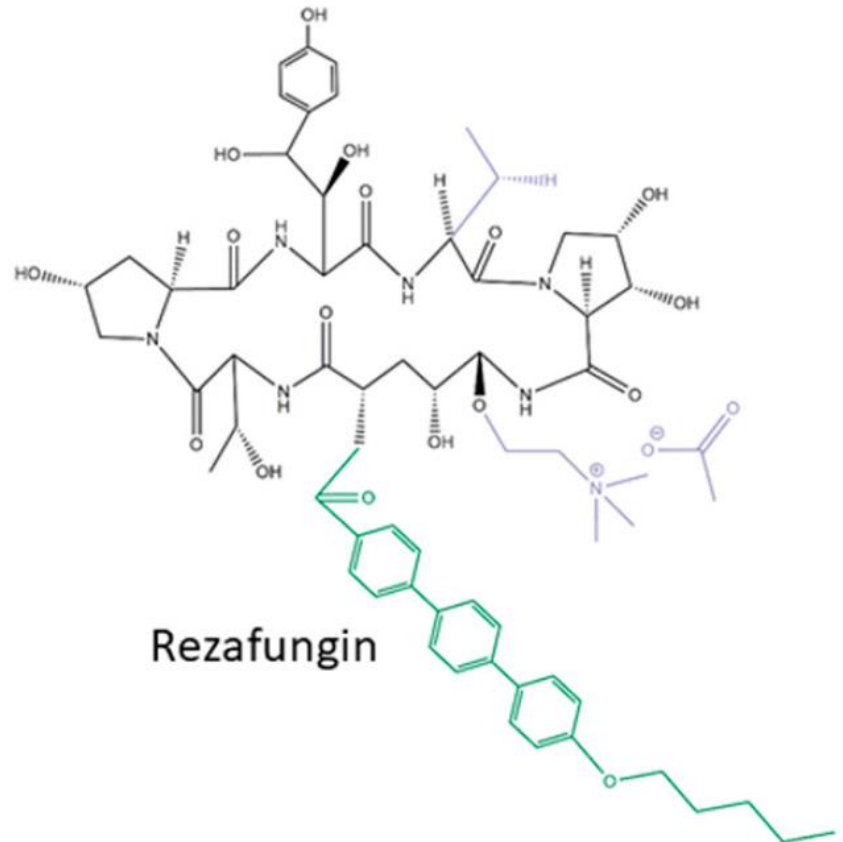
<https://doi.org/10.1007/s40265-021-01611-0>

Anidulafungin vs Rezafungin

Anidulafungin



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



Rezafungin

Pharmacodynamics, Mechanisms of Action and Resistance, and Spectrum of Activity of New Antifungal Agents

Antifungal	Manogepix	Olorofim	Ibrexafungerp	Rezafungin	Oteseconazole
Yeasts					
<i>C. albicans</i>	+	—	+	+	+
<i>C. auris</i>	+	—	+	+	+
<i>C. glabrata</i>	+	—	+	+	+
<i>C. krusei</i>	—	—	+	+	+
<i>C. parapsilosis</i>	+	—	+	+	+
<i>C. tropicalis</i>	+	—	+	+	+
<i>C. gattii</i>	+	—	—	—	+
<i>C. neoformans</i>	+	—	—	—	+
<i>Rhodotorula</i>	+	—	—	—	
<i>Trichosporon</i>	+ / —	—	—	—	

Antifungal	Manogepix	Olorofim	Ibrexafungerp	Rezafungin	Oteseconazole
<i>Aspergillus</i>					
<i>A. flavus</i>	+	+	+	+	—
<i>A. fumigatus</i>	+	+	+	+	—
<i>A. niger</i>	+	+	+	+	—
<i>A. terreus</i>	+	+	+	+	—
<i>Fusarium</i>					
<i>F. oxysporum</i>	+	+ / —	—		
<i>F. solani</i>	+	—	—		
<i>Scedosporium</i>					
<i>Scedosporium</i>	+	+	—		
<i>L. prolificans</i>	+	+	—		
Mucorales					
<i>Mucor</i>	—	—	—	—	
<i>Rhizopus</i>	+ / —	—	—	—	+ / —
Other Mucorales	—	—	—	—	

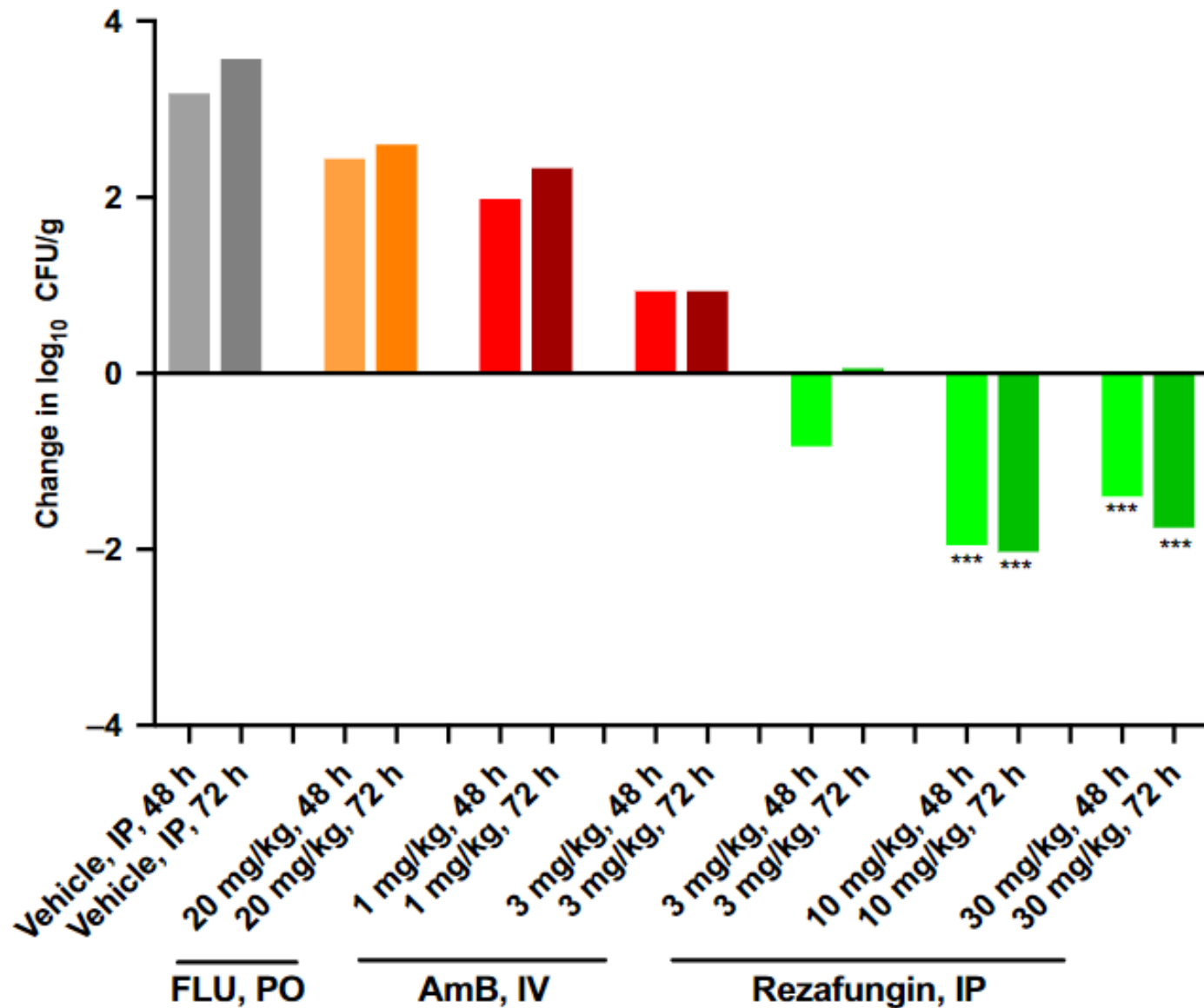
Rezafungin *In Vitro* Activity against Contemporary Nordic Clinical *Candida* Isolates and *Candida auris* Determined by the EUCAST Reference Method

Species	Rezafungin			Anidulafungin			Micafungin		
	MIC range (mg/liter)	Modal MIC (mg/liter)	% (n) >WT-UL	MIC range (mg/liter)	Modal MIC (mg/liter)	% (n) >ECOFF	MIC range (mg/liter)	Modal MIC	% (n) >ECOFF
Nordic clinical isolates									
<i>C. albicans</i>	0.016 to 1	0.06	1.9 (11)	0.004 to 0.25	0.004	1.1 (6)	0.004 to 2	0.016	6.2 (35) ^a
<i>C. glabrata</i>	0.03 to 2	0.125	3.0 (10)	0.008 to 1	0.03	3.3 (11)	0.008 to 0.5	0.016	4.9 (16)
<i>C. krusei</i>	0.03 to 1	0.125	1.2 (1)	0.016 to 0.25	0.03	2.4 (2)	0.06 to 4	0.125	3.7 (3)
<i>C. tropicalis</i>	0.03 to 2	0.125	2.7 (2)	0.008 to 2	0.03	2.7 (2)	0.016 to 2	0.03	2.7 (2)
<i>C. dubliniensis</i>	0.03 to 2	0.125	2.9 (2)	0.004 to 0.25	0.008	2.9 ^b (2)	0.08 to 2	0.03	2.9 ^b (2)
<i>C. parapsilosis</i>	1 to 4	2	0 (0)	0.25 to 2	1	0 (0)	0.25 to 4	2	0 (0)
<i>C. lusitaniae</i>	0.125 to 0.4	0.125	0 (0)	0.03 to 0.25	0.03	5.0 ^b (1)	0.03 to 0.5	0.06	5.0 ^b (1)
<i>S. cerevisiae</i>	0.125 to 0.5	0.25	0 (0)	0.016 to 0.125	0.06	0 ^b (0)	0.06 to 0.25	0.125	0 ^b (0)
Other <i>Candida</i>	0.03 to >4	0.06	ND ^f	0.004 to 4	0.25	ND	0.016 to 0.5	0.25	ND
Other yeast	0.03 to >4	>4	ND	0.004 to >4	>4	ND	0.008 to >4	>4	ND
Indian clinical isolates									
<i>C. auris</i>	0.06 to 16	0.25	14.8 ^c (18)	0.016 to >32	0.06	27.0 ^c (33) ^a	0.03 to >32	0.125	6.6 ^c (8)

Rezafungin *In Vitro* Activity against Contemporary Nordic Clinical *Candida* Isolates and *Candida auris* Determined by the EUCAST Reference Method

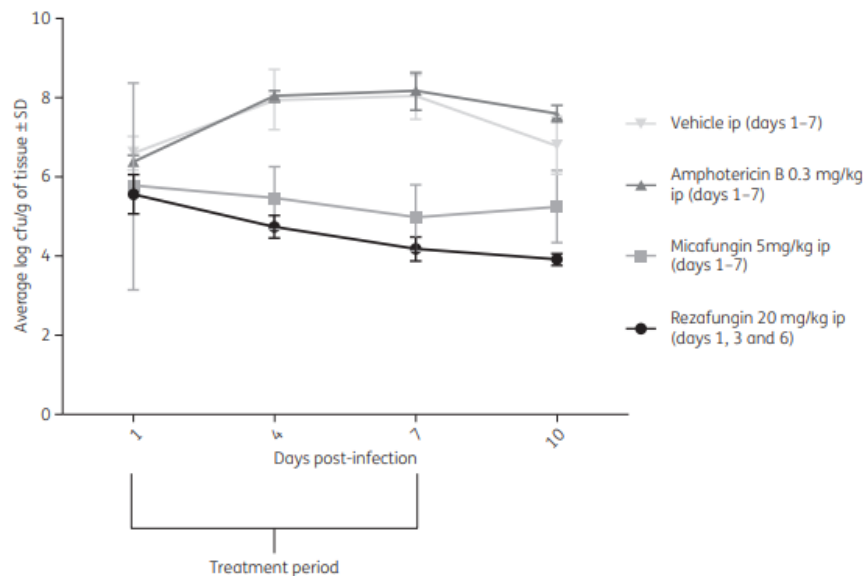
Organism	Mutation ^a		MIC ^b (mg/liter)			Increase in MIC ^c		
	Fks1	Fks2	RZF	ANF	MCF	RZF	ANF	MCF
<i>C. albicans</i>	S645P	NT	1	0.25	2	4	6	7
	D648Y	NT	0.5	0.06	0.125	3	4	3
	P1354S	NT	0.5	0.06	0.125	3	4	3
	P1354S	NT	0.25	0.016	0.06	2	2	2
	P1354S	NT	0.25	0.016	0.06	2	2	2
	P1354S	NT	0.25	0.016	0.06	2	2	2
	P1354P/S	NT	0.25	0.03	0.06	2	3	2
	P1354P/S	NT	0.25	0.06	0.06	2	4	2
	R1361R/S	NT	0.25	0.06	0.125	2	4	3
	R1361G	NT	0.25	0.06	0.125	2	4	3
	R1361G	NT	0.25	0.016	0.06	2	2	2
<i>C. glabrata</i>	L630Q	S663F	2	1	0.5	4	5	5
	L630Q	S663F	2	1	0.5	4	5	5
	WT	S663F	2	1	0.5	4	5	5
	WT	S663F	1	0.25	0.125	3	3	3
	WT	S663F	0.5	0.25	0.125	2	3	3
	WT	S663F	0.5	0.06	0.06	2	1	2
	WT	S663P	2	1	0.5	4	5	5
	WT	S663P	0.5	0.125	0.125	2	2	3
	Y1429X	Y658N/L664Q	0.5	0.125	0.06	2	2	2
	WT	F659del	0.5	0.06	0.06	2	1	2

RZF vs *C. albicans*

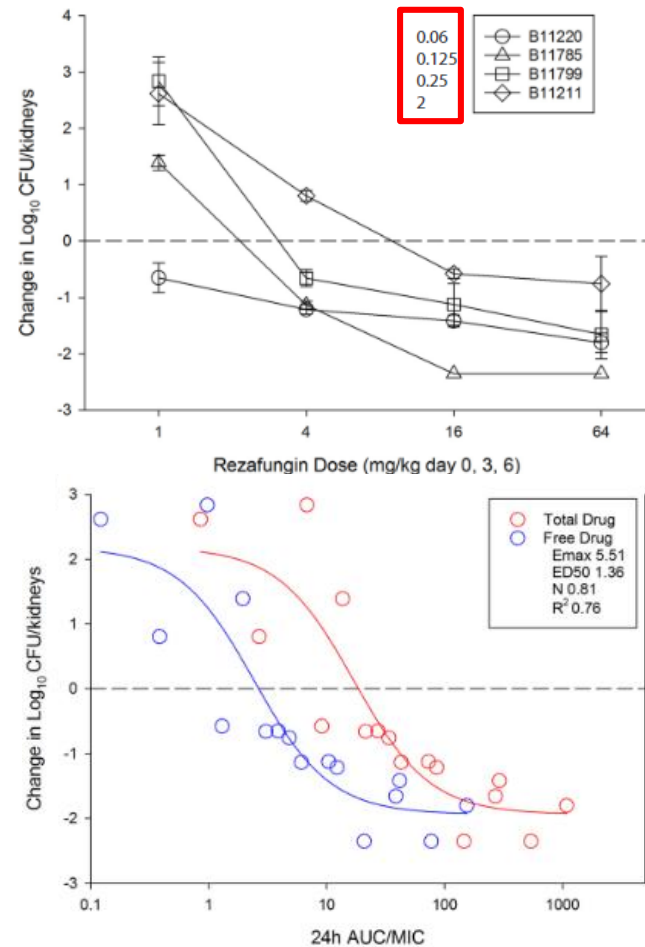


RZF vs *C. auris*

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

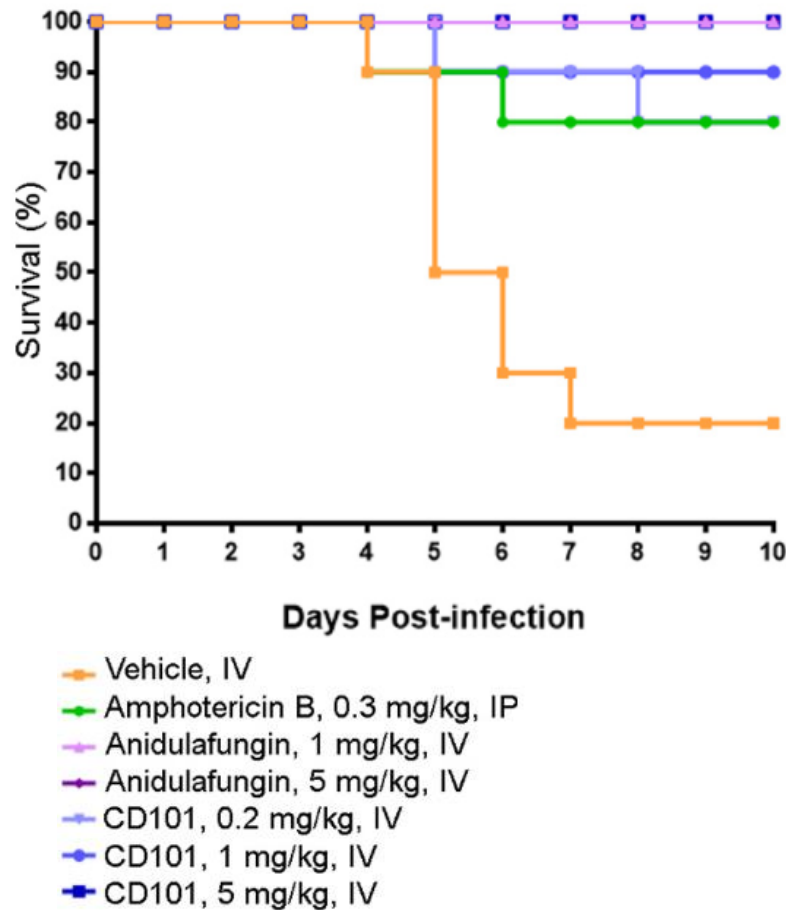


Pharmacodynamic Evaluation of Rezafungin (CD101) against *Candida auris* in the Neutropenic Mouse Invasive Candidiasis Model

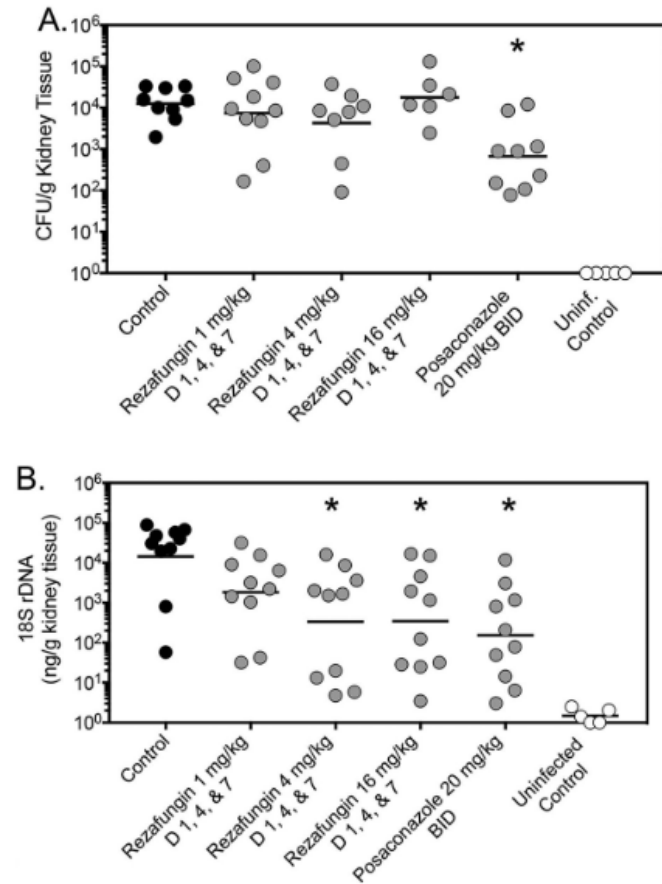


RZF vs *A. fumigatus*

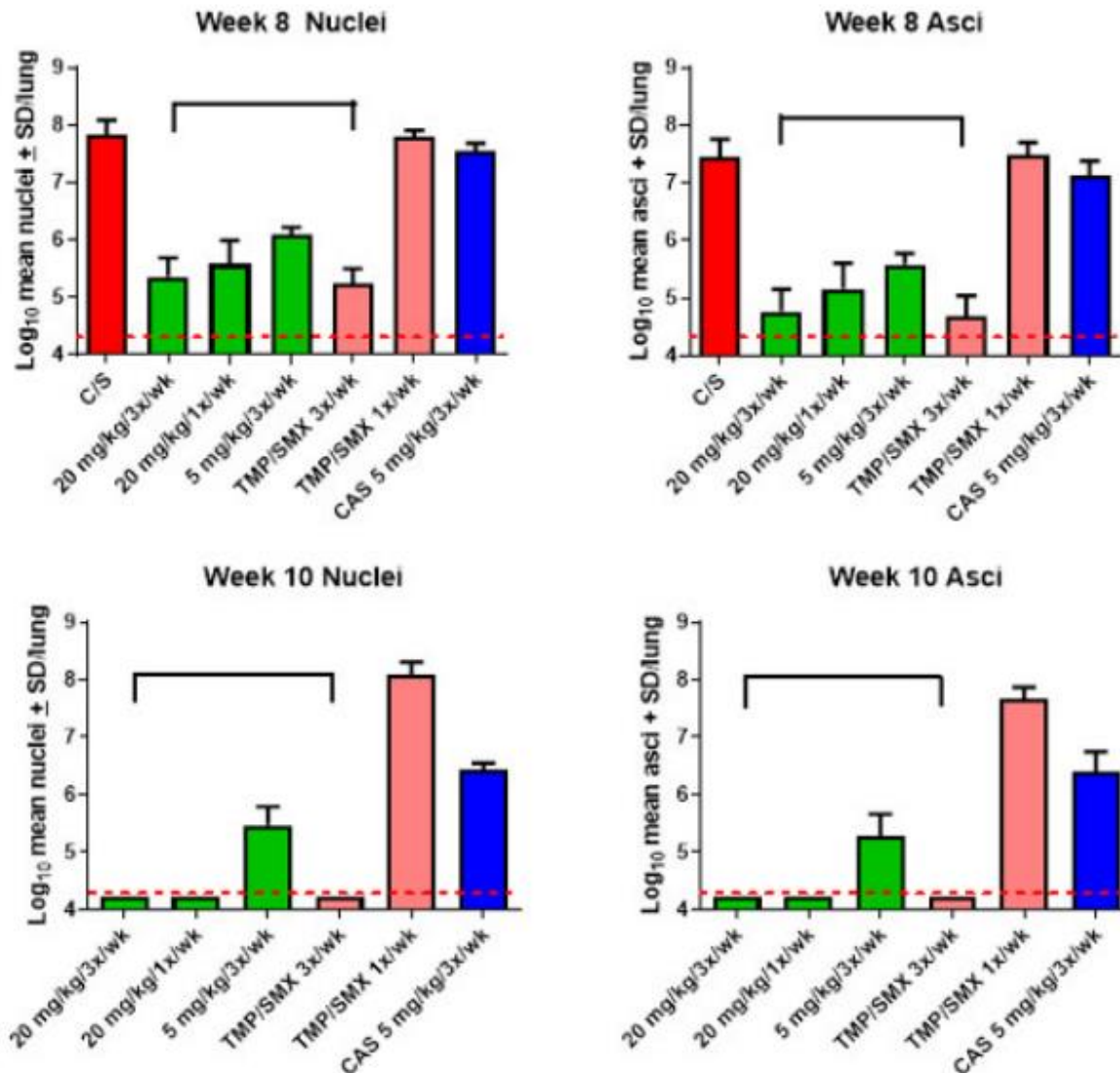
Preclinical Evaluation of the Stability, Safety, and Efficacy of CD101, a Novel Echinocandin



Extended-Interval Dosing of Rezafungin against Azole-Resistant *Aspergillus fumigatus*

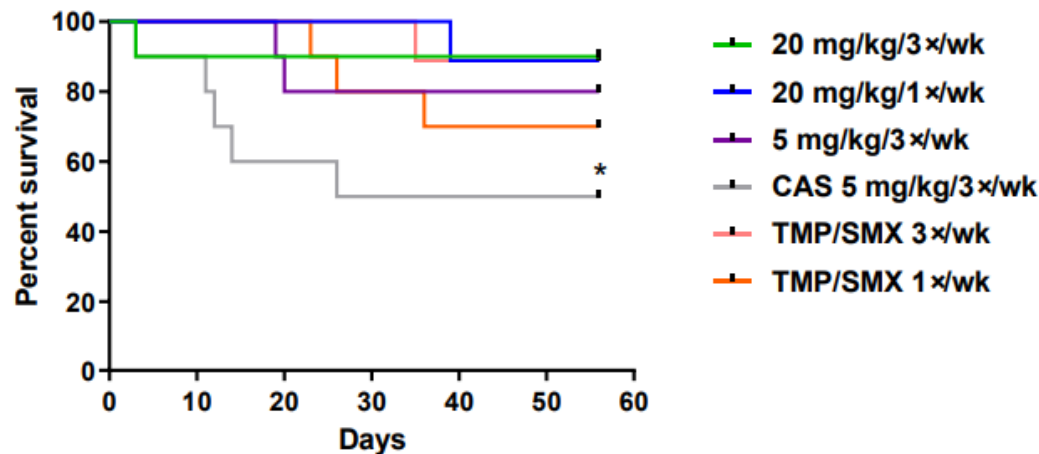


The Long-Acting Echinocandin, Rezafungin, Prevents Pneumocystis Pneumonia and Eliminates Pneumocystis from the Lungs in Prophylaxis and Murine Treatment Models

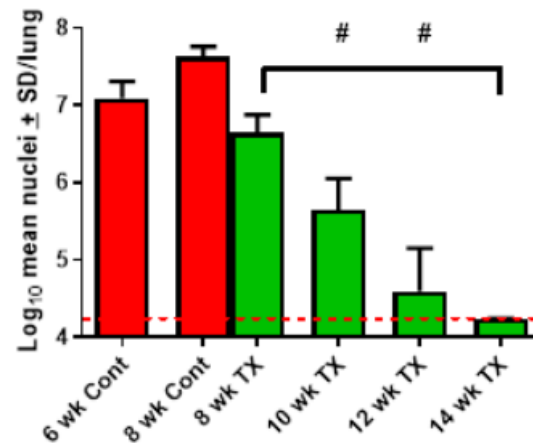


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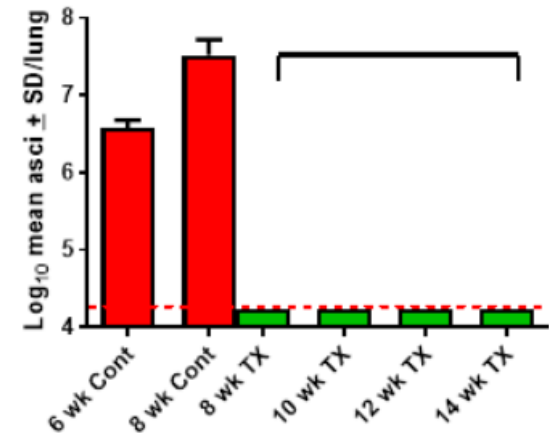
Week 14 Survival



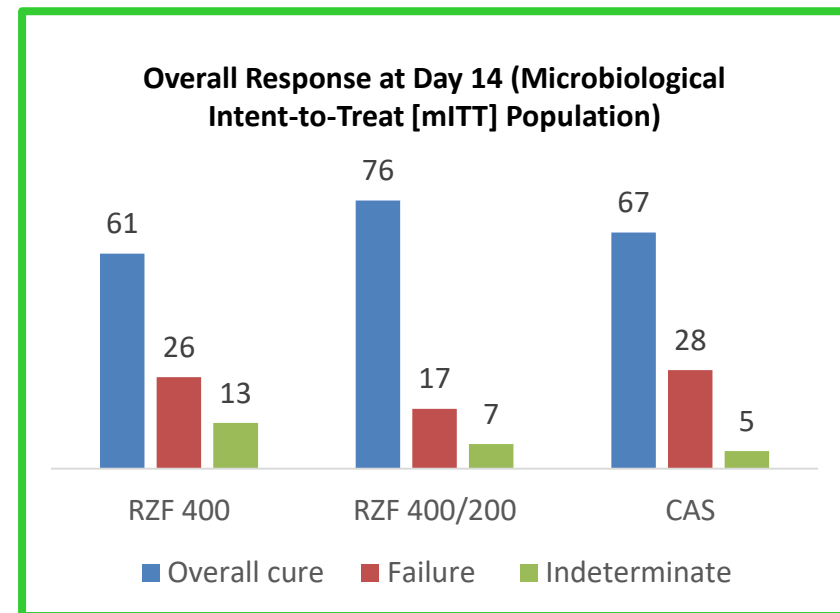
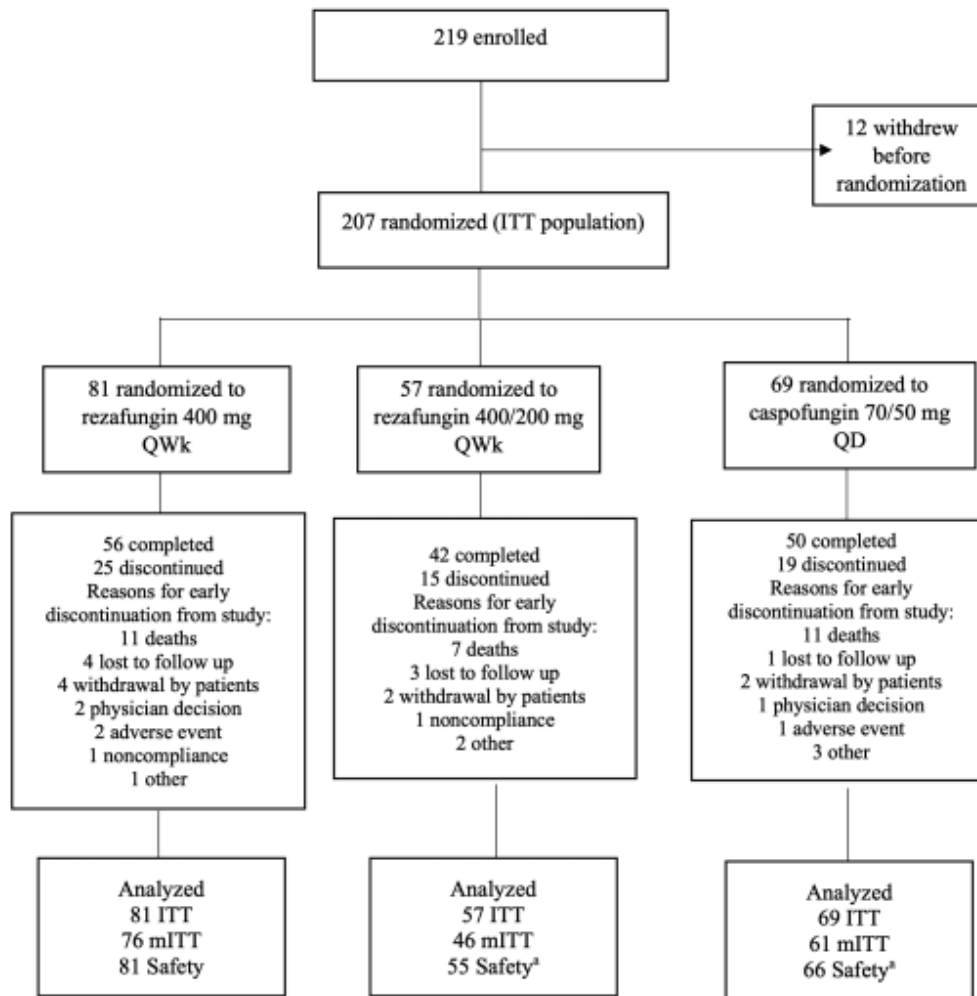
Rezafungin Treatment Nuclei



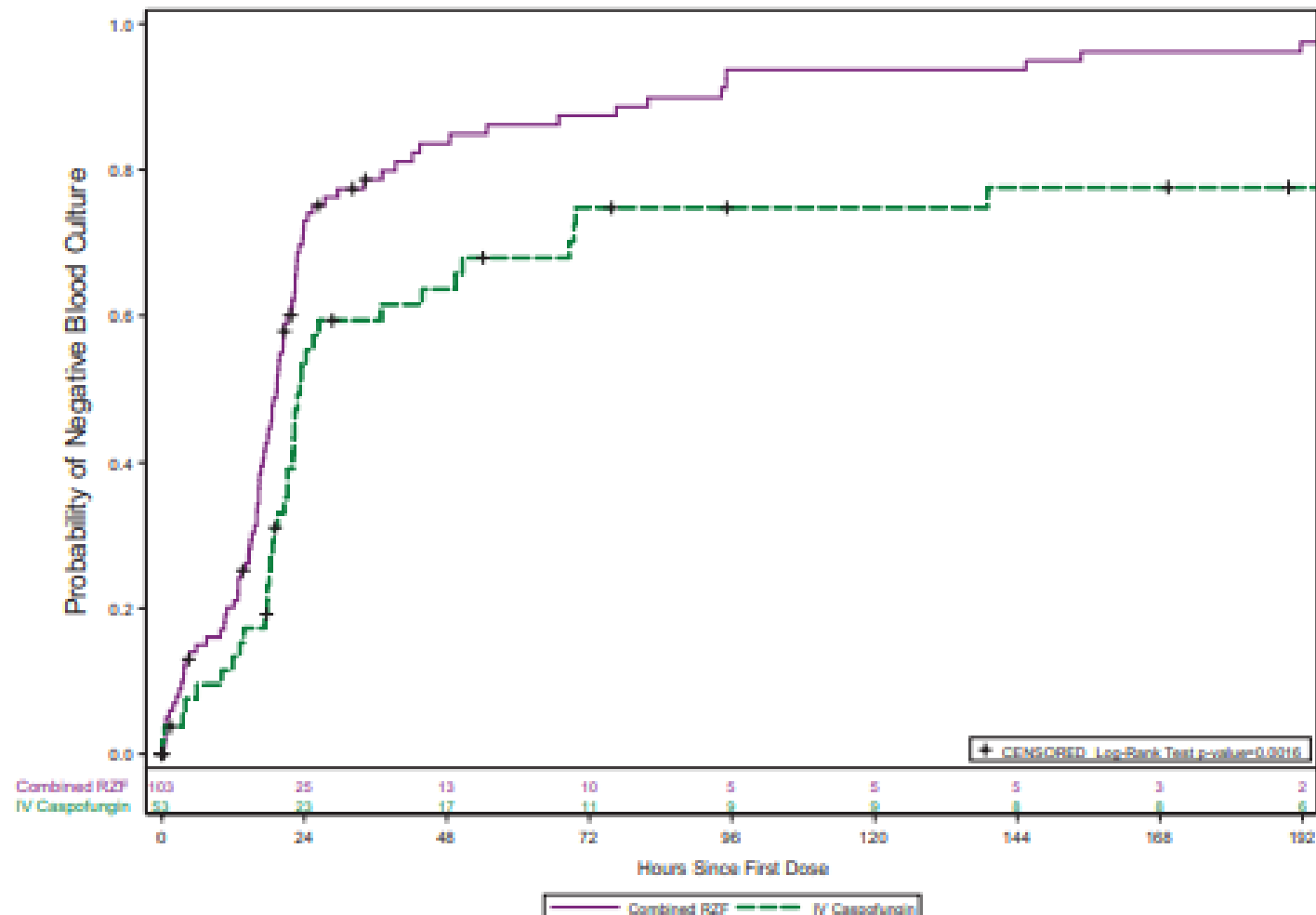
Rezafungin Treatment Asci



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



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



Ongoing Studies (Phase III)

ReSTORE, NCT03667690:

- multicenter, randomized, double blind study
- RZF 400-mg/200-mg once-weekly regimen for the treatment of candidemia and IC
- active comparator is IV CAS followed by optional FLU step-down.
- Primary endpoint is day 30 all-cause mortality and day 14 global cure measured by clinical, radiological, and mycological

ReSPECT, NCT04368559:

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

Take-home messages: RZF

- Earlier hospital discharge and extended outpatient access to the treatment of IC
- As a prophylactic agent for preventing invasive fungal disease caused by *Candida* spp., *Aspergillus* spp., and *P. jirovecii* could overcome current multidrug regimens
- Once weekly dosing with limited drug–drug interactions may be attractive also for prophylaxis during the early phase after SOT (e.g., liver)
- Although in vitro susceptibility results are encouraging, further studies are needed to determine its efficacy in the treatment of IA

Grazie per l'attenzione

