Traitements antifongiques: nouveautés

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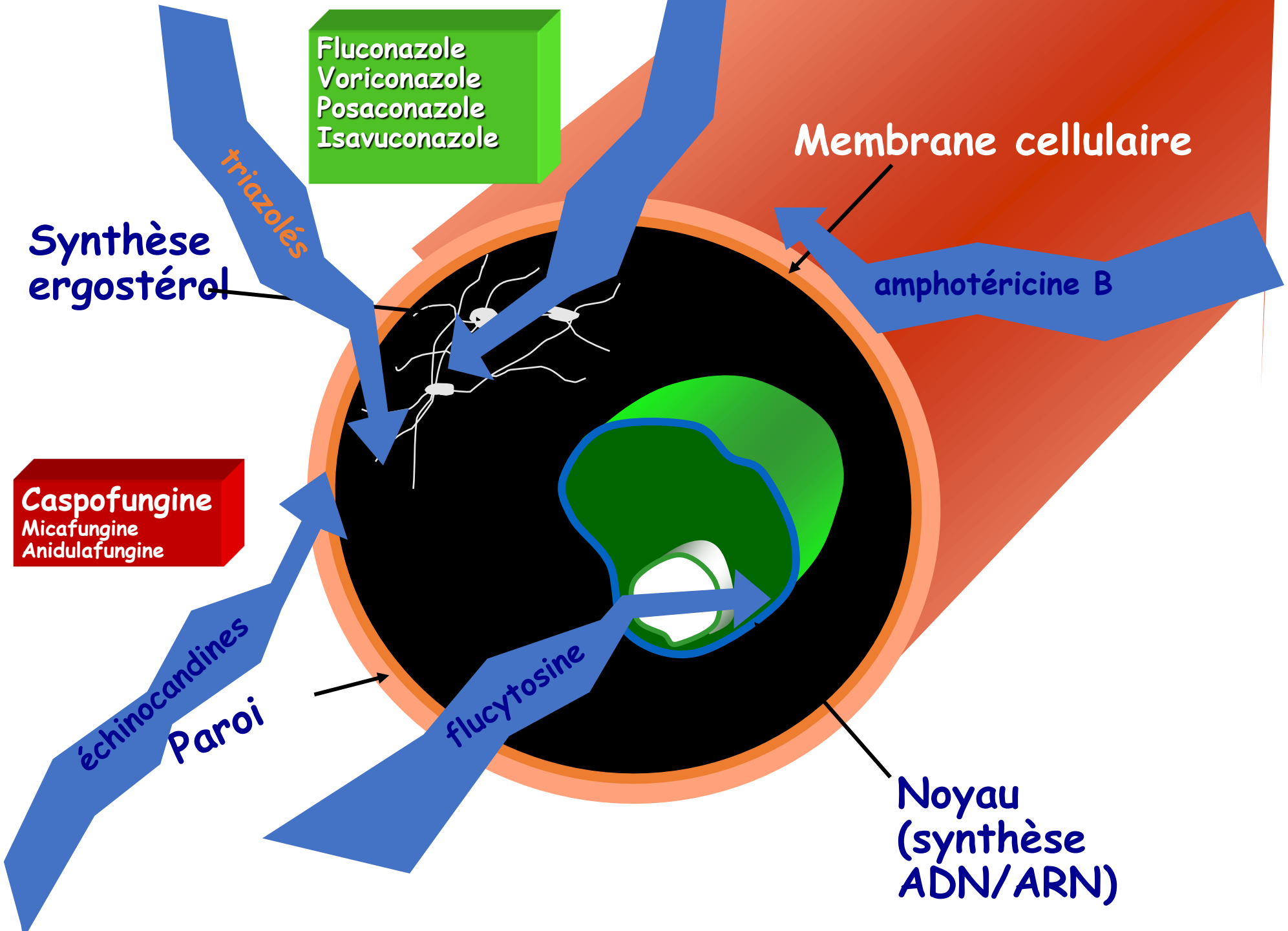

Fluconazole
Voriconazole
Posaconazole
Isavuconazole
triazolés
Synthèse ergostérol
Membrane cellulaire
amphotéricine B
Caspofungine
Micafungine
Anidulafungine
échinocandines
Paroi
flucytosine
Noyau (synthèse ADN/ARN)

Pourquoi de nouvelles molécules

- Emergence d'espèces résistances: *Mucorales, Lomentospora, Rasamsonia, Candida auris*
- Emergence de résistances acquises: *Aspergillus* R azoles

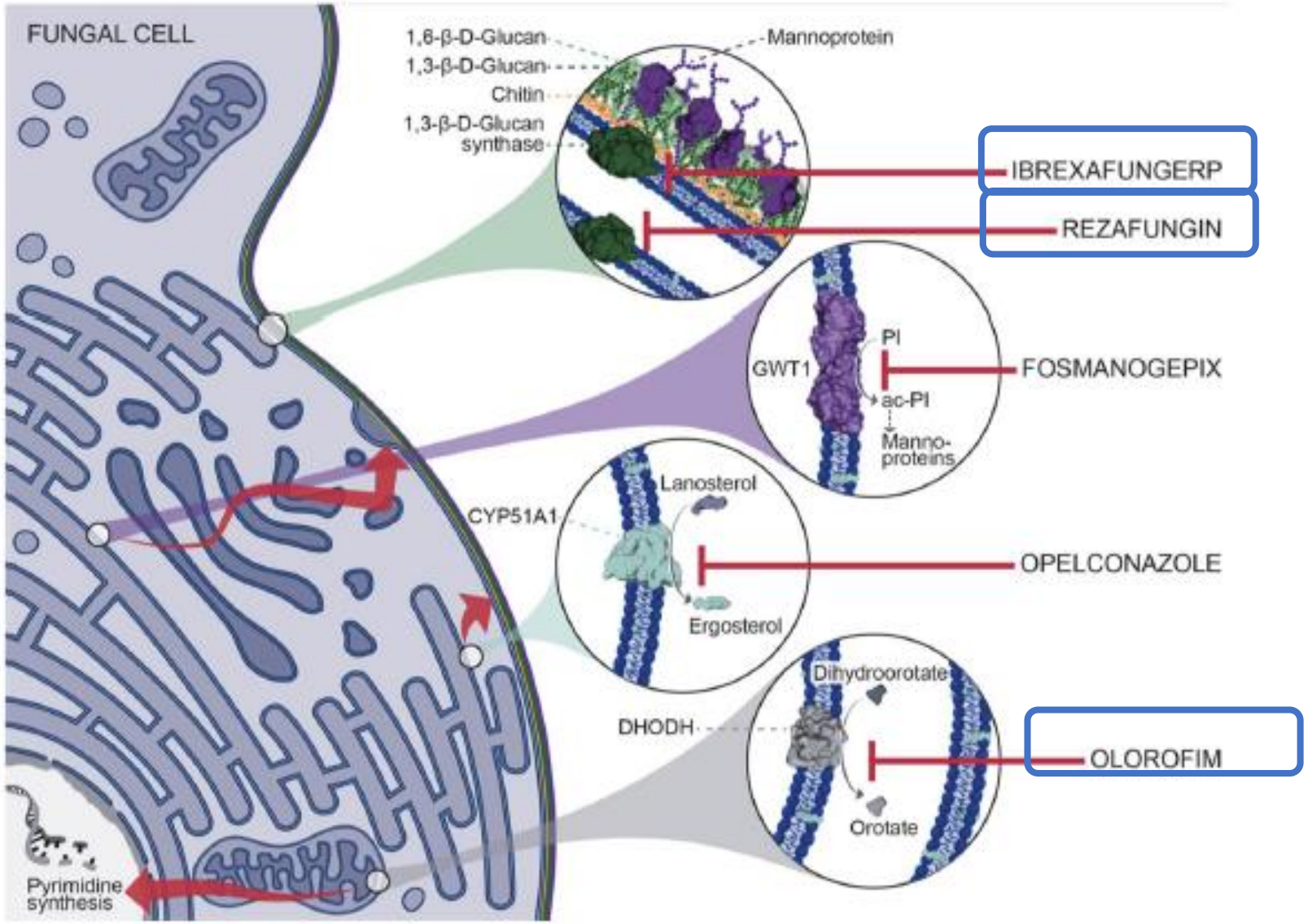
- Toxicité des molécules actuellement disponibles

- Absence de formulation orale des echinocandines et des polyènes

- Diffusion limitée SNC, œil, urines

Nouvelles molécules

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



Hoenigl M, Drugs 2021

Table 1 Antifungals in the pipeline

Antifungal agent	Class	Mechanism of action (novel*)	Target fungi	Stage of development	Advantages	Anticipated place in therapy
Fosmanogepix (APX001)	Gwt1 inhibitor	Inhibits fungal enzyme Gwt1* (mannoproteins)	*Candida* spp. (not *C. krusei*) *C. auris* *Cryptococcus* *Aspergillus* spp. *Fusarium* spp. *Scedosporium* spp. *L. prolificans*	Phase 2	Active against resistant *Candida* spp.; broad mold activity (not *Mucorales*); encouraging CNS penetration	Candidiasis and IA, including treatment of azole- and echinocandin-resistant infections; cryptococcal meningitis; invasive mold infections other than *Mucorales*
Ibrexafungerp	Triterpenoid	Inhibits 1,3-beta-D-glucan synthase	*Candida* spp. *Aspergillus* spp.	FDA-approved (VVC)	Oral formulation; active against resistant *Candida* spp.	Treatment of candidiasis among patients with echinocandin-resistant *Candida* or when oral therapy is preferred for azole-resistant candidiasis; potential role in combination therapy of IA
Olorofim (F901318)	Orotomide	Inhibits dihydroorotate dehydrogenase*	*Aspergillus* spp. *Scedosporium* spp. *L. prolificans* Endemic fungi	Phase 2b	Limited toxicity; IV and oral formulation	IA and other mold infections with limited treatment options
Opelconazole (PC945)	Inhaled triazole	Inhibits 14-alpha demethylase	*Aspergillus* spp.	Phase 2b	Inhaled route avoids systemic toxicity	Antifungal prophylaxis in patients with lung transplant or cystic fibrosis; IA as combination therapy with systemic triazole
Oteseconazole (VT-1161)	Tetrazole	Inhibits 14-alpha demethylase	*Candida* spp.	FDA-approved (VVC)	Improved selectivity for fungal CYP450 (lower potential for toxicity and drug interactions); lower rates of recurrent VVC compared with fluconazole	Treatment of VVC among patients with history of multiple recurrences
Rezafungin (CD101)	Echinocandin	Inhibits 1,3-beta-D-glucan synthase	*Candida* spp. *C. auris* *P. jiroveci* *Aspergillus* spp.	Phase 3	Single or weekly IV dosing; optimized pharmacokinetic-pharmacodynamic profile	Treatment of candidiasis, particularly when single/weekly dosing improves convenience of care; prophylaxis in immunocompromised patients

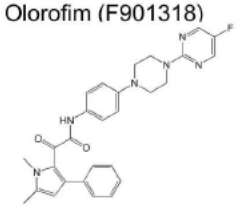
CNS central nervous system, *IA* invasive aspergillosis, *IV* intravenous, *VVC* vulvovaginal candidiasis

Hoenigl M, Drugs 2021

Olorofim

- Orotomide
- Inhibiteur selectif DHODH (Dihydroorotate dehydrogenase) fongique
  - Enzyme impliquée synthèse pyrimidine
- Voie orale
- Interfère synthèse ADN, ARN, synthèse paroi
- Arret du cycle et lyse
- Inhibition de la germination

Olorofim (F901318)

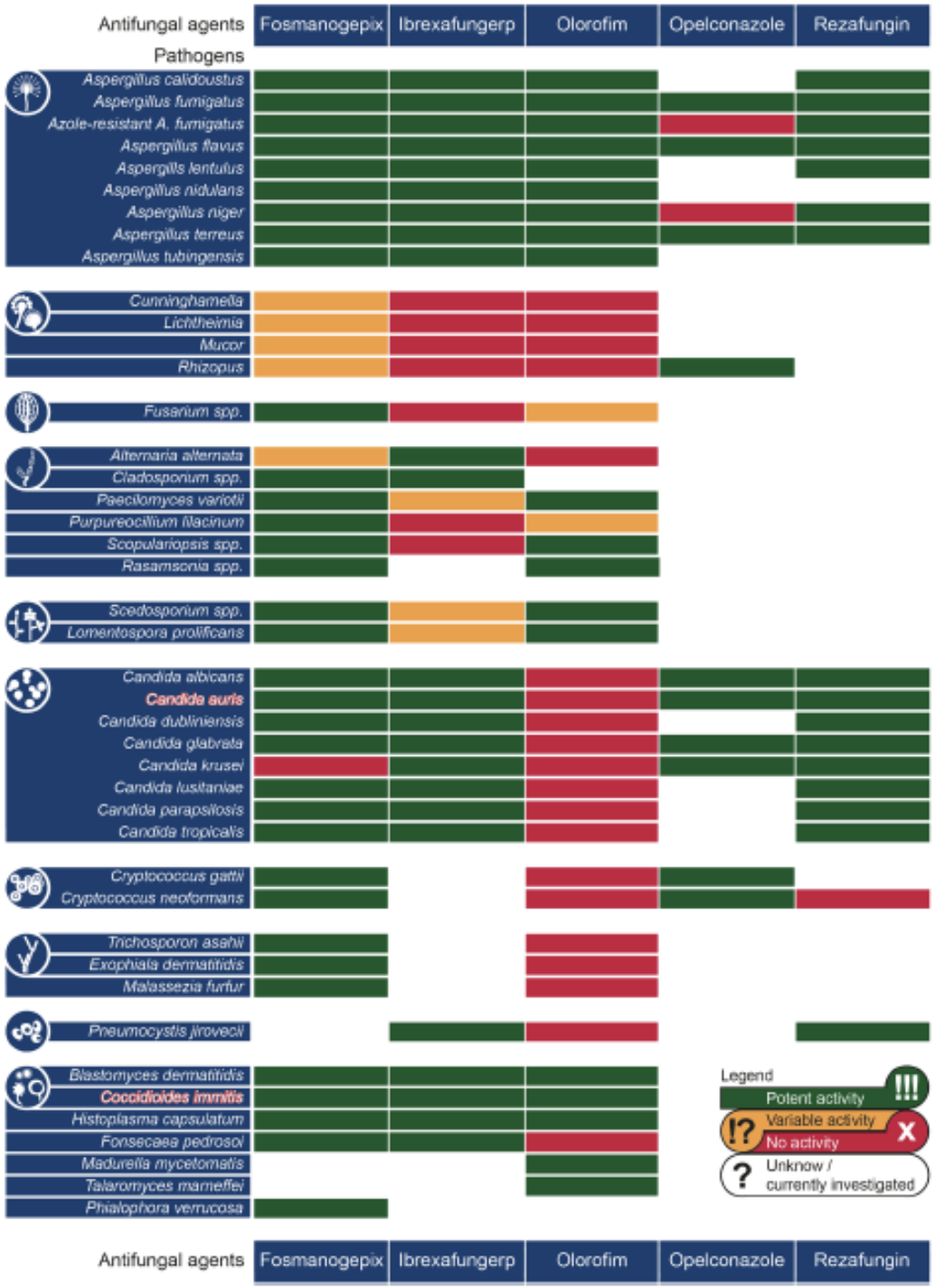


Orotomide - Reversible inhibition of dihydroorotate dehydrogenase, part of pyrimidine biosynthesis (*DHODH*)

Oliver, J., Sibley, G., Beckmann, N., Dobb, K., Slater, M., McEntee, L., Pré, S., Livermore, J., Bromley, M., Wiederhold, N., Hope, W., Kennedy, A., Law, D., Birch, M. (2016). ***F901318 represents a novel class of antifungal drug that inhibits dihydroorotate dehydrogenase*** *Proceedings of the National Academy of Sciences 113(45), 12809-12814.*
https://dx.doi.org/10.1073/pnas.1608304113

Olorofim

- Diffusion including the kidney, liver, lung, and the brain (at lower levels)
- Oral dosing is 45% bioavailable.
- Susceptible fungi exhibit time-dependent killing effect after dosing.
- Metabolized by multiple CYP450 enzymes including CYP3A4 and is thus susceptible to strong CYP3A4 inhibitors and inducers
  - CI rifampicine
  - Dose modification with anticalcineurine
  - Olorofim dose redction with azoles
- Dose:
  - Day 1: 150mg twice a day (12 hours apart) loading dose
  - Day 2 and subsequent doses: 90 mg twice a day (12 hours apart
  - Olorofim may be taken either with or without food.

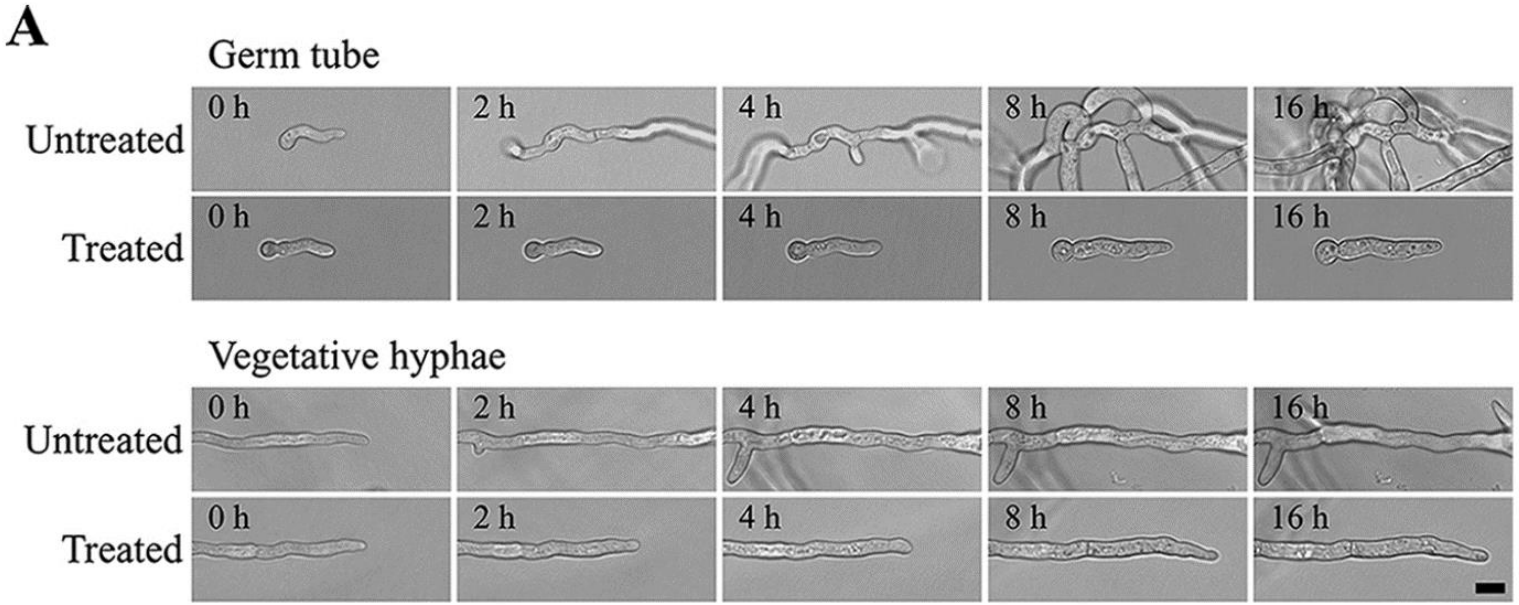


Spectre olorofim

Filamenteux hors Mucorales et Alternaria dont Aspergillus azoles R, Scedosporium, Lomentospora, Scopulariopsis, Rasamsonia

Fusarium: dépend espèces

Dimorphiqus



Olorofim

- Inhibition précoce germination
- Exposition prolongée (24-48 heures)
  - activité fongicide

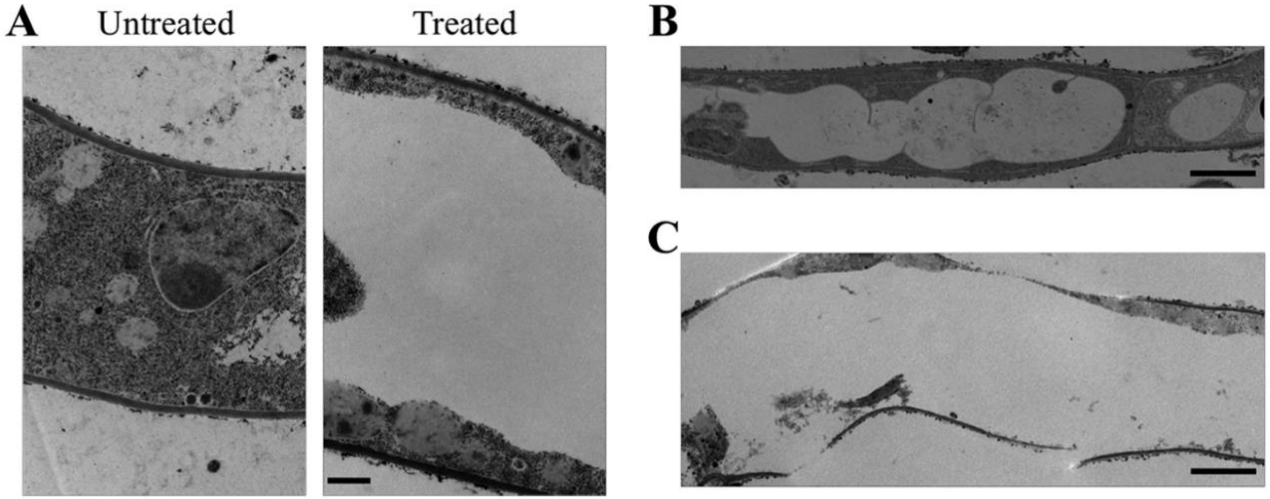


FIG 4 (A) TEM image of an untreated hypha and a hypha treated for 24 h with 0.1 μg/ml F901318. Images show the increased diameter of the treated hypha. Bar = 0.5 μm. (B) TEM image showing enlarged vacuoles in a hypha treated for 24 h with 0.1 μg/ml F901318. Bar = 2 μm. (C) TEM image showing ruptured cell walls in a hypha treated for 24 h with 0.1 μg/ml F901318. Bar = 2 μm.

Pré, S., Beckmann, N., Almeida, M., Sibley, G., Law, D., Brand, A., Birch, M., Read, N., Oliver, J. (2018). Effect of the Novel Antifungal Drug F901318 (Olorofim) on Growth and Viability of *Aspergillus fumigatus* Antimicrobial Agents and Chemotherapy 62(8), e00231-18. https://dx.doi.org/10.1128/aac.00231-18

International Journal of Antimicrobial Agents 56 (2020) 106105

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journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

In vitro activity of olorofim (F901318) against fungi of the genus, *Scedosporium* and *Rasamsonia* as well as against *Lomentospora prolificans*, *Exophiala dermatitidis* and azole-resistant *Aspergillus fumigatus*

Lisa Kirchhoff[a], Silke Dittmer[a], Jan Buer[a], Peter-Michael Rath[a], Joerg Steinmann[a,b,*]

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[b] Institute for Clinical Hygiene, Medical Microbiology and Infectiology, Klinikum Nuernberg, Paracelsus Medical University, Prof.-Ernst-Nathan-Str. 1, 90419 Nuremberg, Germany

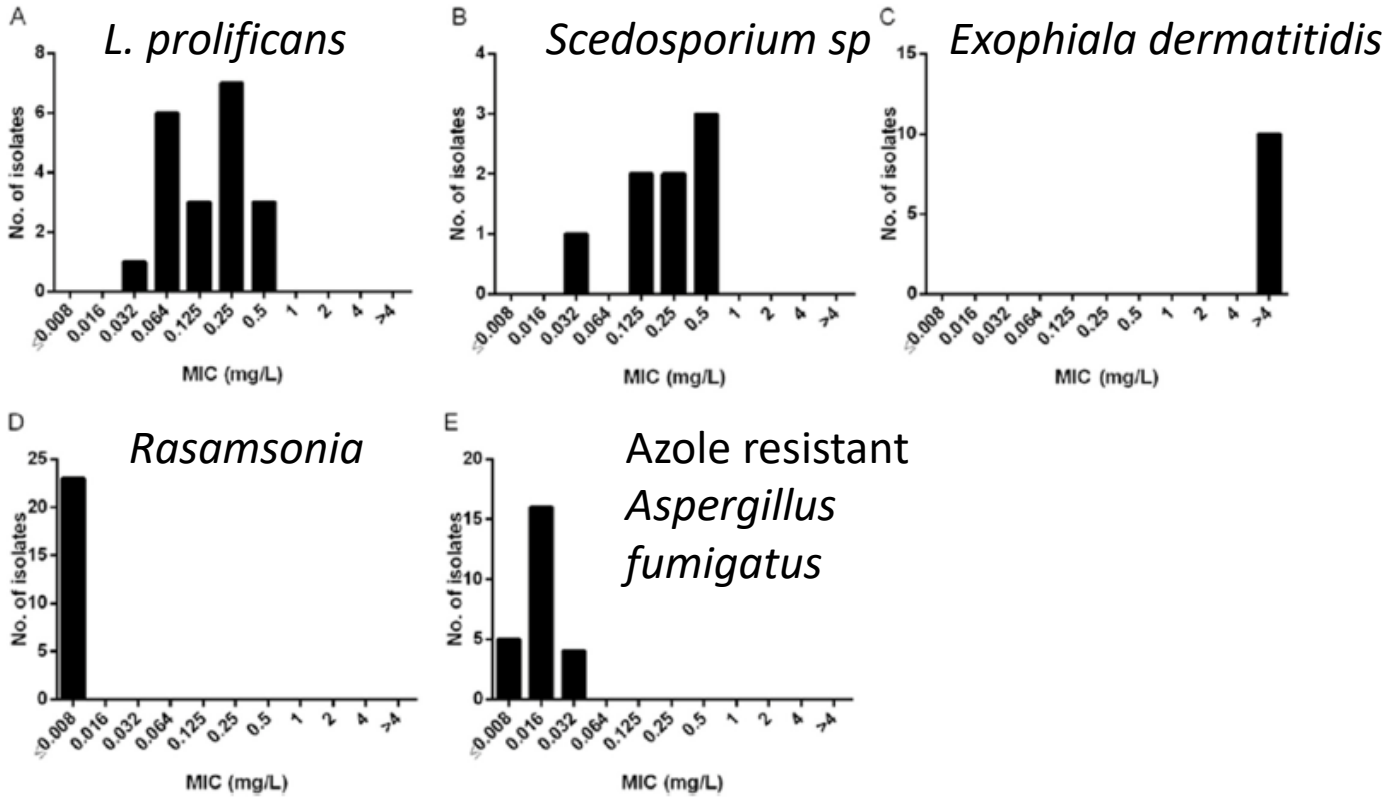

Fig. 1. Minimum inhibitory concentrations (MIC) for olorofim against (A) *Lomentospora prolificans* ($n = 20$), (B) *Scedosporium* spp. ($n = 8$), (C) *Exophiala dermatitidis* ($n = 10$), (D) *Rasamsonia argillacea* species complex ($n = 23$) and (E) azole-resistant *Aspergillus fumigatus* ($n = 25$).

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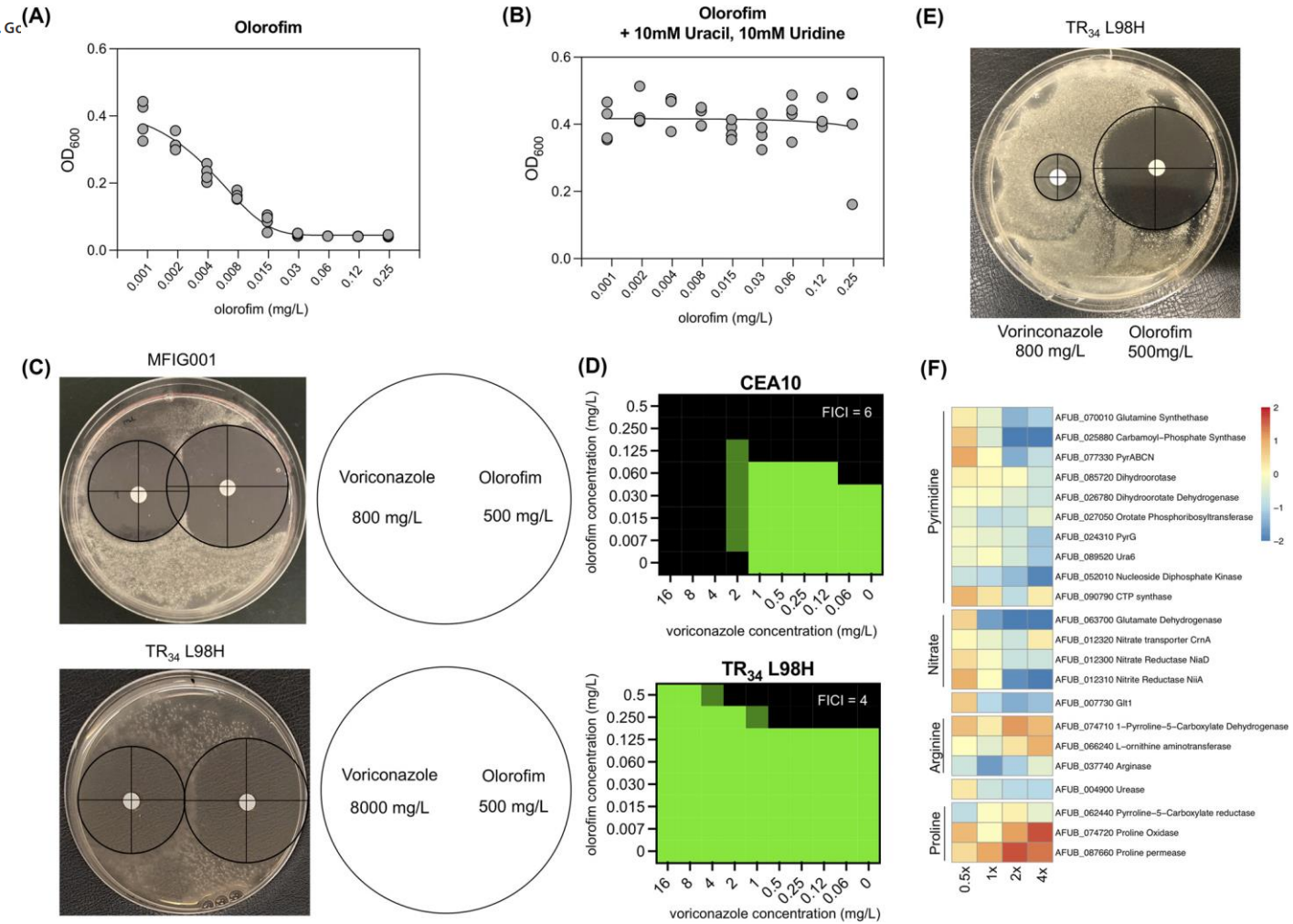
RESEARCH ARTICLE

Antagonism of the Azoles to Olorofim and Cross-Resistance Are Governed by Linked Transcriptional Networks in *Aspergillus fumigatus*

Norman van Rhijn,[a,b] Sam Hemmings,[a] Isabelle S. R. Storer,[a] Clara Valero,[a,c] Hajer Bin Shuraym,[a] Gustavo H. Go
Fabio Gsaller,[a,d] Jorge Amich,[a,e] Michael J. Bromley[a,b]

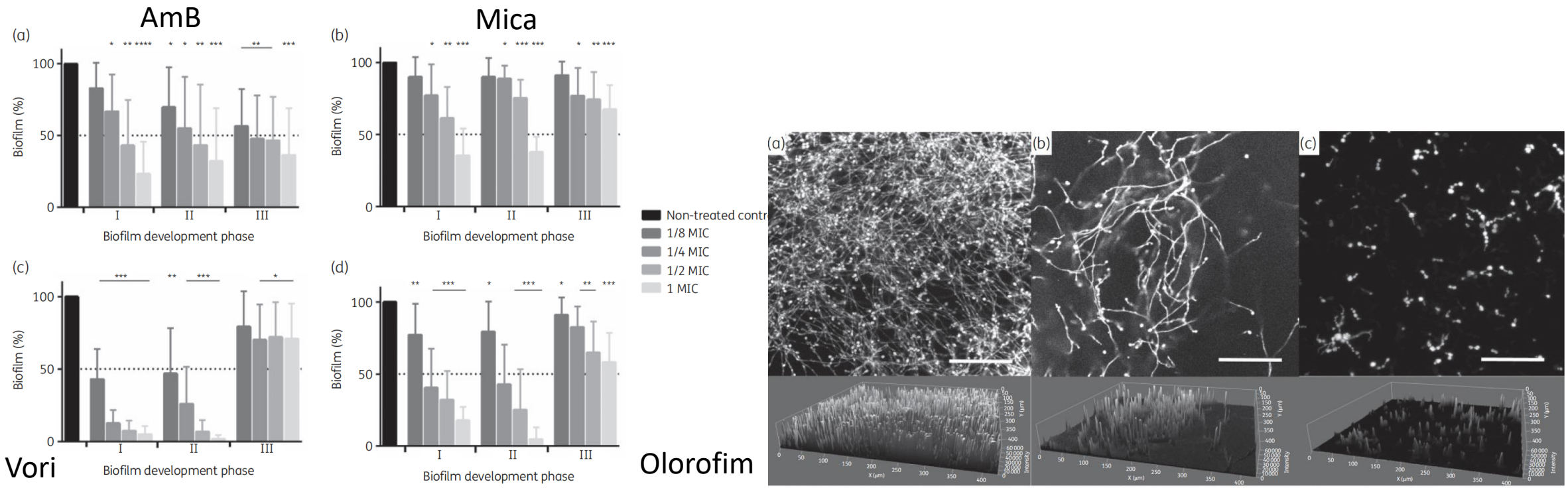


J Antimicrob Chemother 2020; **75**: 2133–2140
doi:10.1093/jac/dkaa157 Advance Access publication 9 May 2020

Journal of Antimicrobial Chemotherapy

Antibiofilm activity of antifungal drugs, including the novel drug olorofim, against *Lomentospora prolificans*

Lisa Kirchhoff [1]*, Silke Dittmer[1], Ann-Kathrin Weisner[1], Jan Buer[1], Peter-Michael Rath[1] and Joerg Steinmann[1,2]



igure 3. Antibiofilm activity of (a) amphotericin B, (b) micafungin, (c) voriconazole and (d) olorofim at 1× MIC, ½× MIC, ¼× MIC and ⅛× MIC gainst *L. prolificans* biofilms at different phases: adhesion (I), biofilm formation (II) and mature biofilm (III). The dotted line represents 50% of the iofilm in the non-treated control. Statistical significance was analysed using Dunnett's multiple comparisons by analysing treated biofilms and the on-treated control biofilm. Significant difference is indicated by asterisks: *$P<0.05$, **$P<0.01$, ***$P<0.001$ and ****$P<0.0001$.

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PHARMACOLOGY

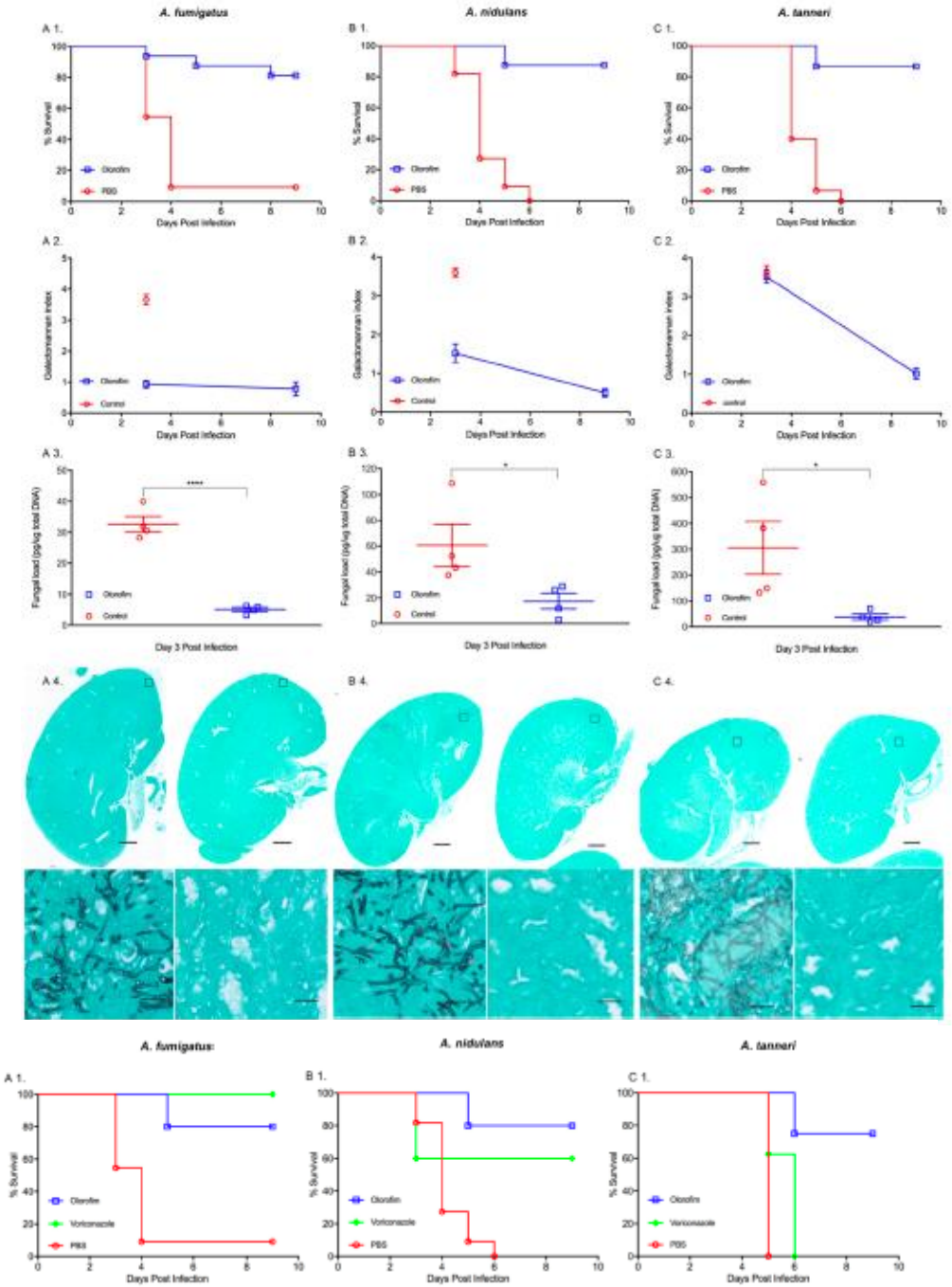
Efficacy of Olorofim (F901318) against *Aspergillus fumigatus*, *A. nidulans*, and *A. tanneri* in Murine Models of Profound Neutropenia and Chronic Granulomatous Disease

S. Seyedmousavi,[a] Y. C. Chang,[a] D. Law,[b] M. Birch,[b] J. H. Rex,[b] K. J. Kwon-Chung[a]

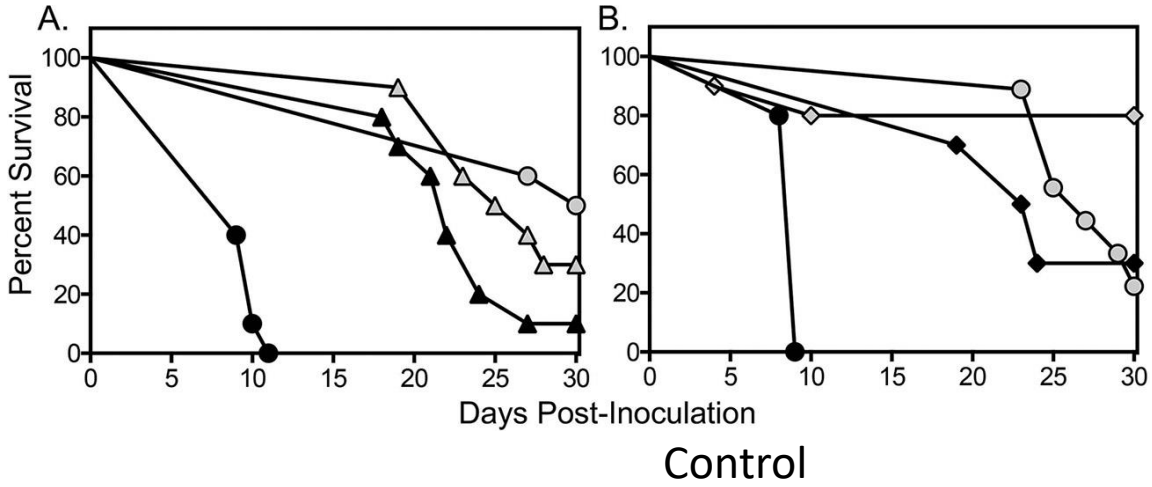
TABLE 1 MICs of six antifungals for *Aspergillus* species

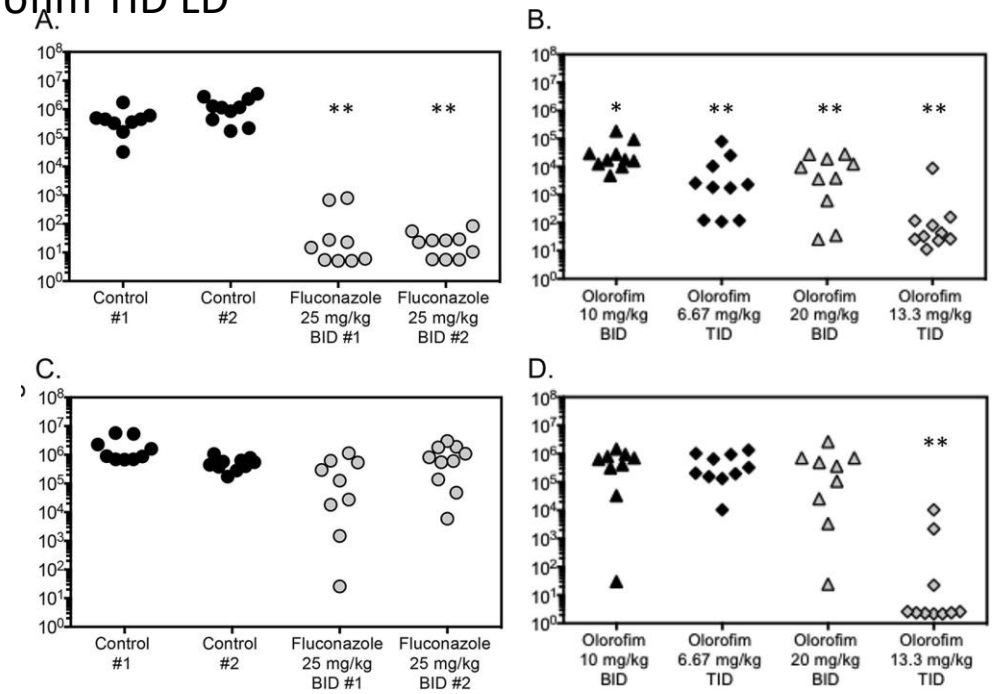
Species (strain)[a]	MIC (μg/ml)[b]					
	AMB	ITC	VRC	POS	TRB	Olorofim
A. fumigatus (B5233)[c]	0.5	0.5	0.5	0.125	4	0.008
A. fumisynnematus (CFN1891)	2	2	2	0.5	1	0.008
A. nidulans (M24)[c]	2	0.5	0.25	0.25	1	0.008
A. pseudoviridinutans (NIHAV1)	2	2	2	0.5	0.5	0.008
A. subramanianii (DI 16-475)	2	0.5	0.25	0.5	0.25	0.016
A. tanneri (NIH1004)[c]	>16	4	4	0.5	0.25	0.062
A. udagawae (F41)	4	1	2	0. 5	1	0.008

[a]All strains are clinical isolates.
[b]The geometric mean MIC from three independent replicates of each strain is reported. AMB, amphotericin B; ITC, itraconazole; VRC, voriconazole; POS, posaconazole; TRB, terbinafine; olorofim, F901318.
[c]Species used for determination of olorofim efficacy in experimental animals.



The Orotomide Olorofim Is Efficacious in an Experimental Model of Central Nervous System Coccidioidomycosis





Wierderhold N, AAC, 2018

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EXPERIMENTAL THERAPEUTICS

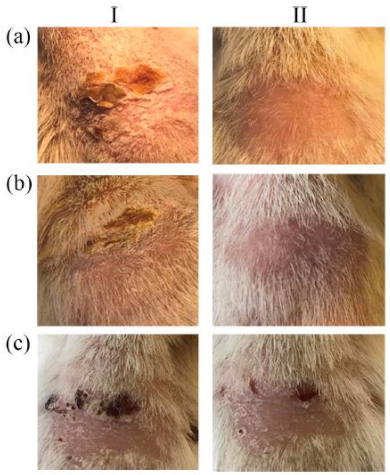
Olorofim Effectively Eradicates Dermatophytes *In Vitro* and *In Vivo*

Esmat Mirbzadeh Ardakani,[a,b] Atefeh Sharifirad,[a] Nasrin Pashootan,[c] Mahsa Nayebhashemi,[a] Mozhgan Zahmatkesh,[a] Somayeh Enayati,[a] Mehdi Razzaghi-Abyaneh,[c] Vahid Khalaj[a]

December 2021 Volume 65 Issue 12 e01386-21 Antimicrobial Agents and Chemotherapy

TABLE 1 *In vitro* susceptibility of aspergilli and dermatophytes to olorofim, posaconazole, voriconazole, and clotrimazole

	MIC (mg/L)							
	Aspergillus		Dermatophytes					
Antifungal compound	*Aspergillus fumigatus* PTCC5009	*Aspergillus flavus* PTCC5004	*Trichophyton mentagrophytes* NBRC5809	*Trichophyton tonsurans* CBS 130814	*Trichophyton rubrum* IR613	*Epidermophyton floccosum* CBS 130793	*Microsporum canis* PTCC5069	*Microsporum gypseum* PTCC5070
Olorofim	0.01	0.01	0.01	0.06	0.01	0.03	0.03	0.03
Posaconazole	0.15	0.3	0.04	0.6	0.08	0.12	0.3	0.6
Voriconazole	0.15	0.15	0.15	0.15	0.15	0.12	0.6	0.6
Clotrimazole	2	4	0.25	1	16	2	4	1



J Antimicrob Chemother 2022; **77**: 1645–1654
https://doi.org/10.1093/jac/dkac062 Advance Access publication 15 March 2022

Journal of Antimicrobial Chemotherapy

Inhibition of azole-resistant *Aspergillus fumigatus* biofilm at various formation stages by antifungal drugs, including olorofim

Lisa Kirchhoff[1]*, Silke Dittmer[1], Dan-Tiberiu Furnica[1], Jan Buer[1], Eike Steinmann[2], Peter-Michael Rath[1] and Joerg Steinmann[1,3]

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID

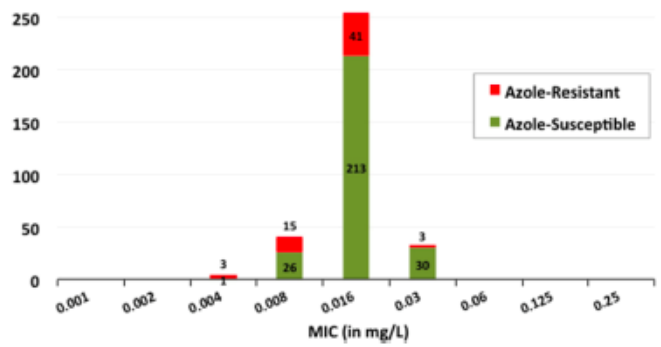
Research note

In vitro activity of olorofim against *Aspergillus fumigatus* sensu lato clinical isolates: activity is retained against isolates showing resistance to azoles and/or amphotericin B

Pilar Escribano [1, 2, **], Ana Gómez [1, 2], Elena Reigadas [1, 2], Patricia Muñoz [1, 2, 3, 4], Jesús Guinea [1, 2, 3, *], on behalf of the ASPEIN Study Group

MIC distributions of olorofim and comparators against the *A. fumigatus* sensu stricto and the cryptic species studied

	MIC distributions (number of isolates at each MIC, in mg/L)															Resistance (2020 breakpoints)	
	0.001	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	≥16	No. of isolates	%
A. fumigatus sensu stricto (n = 312)																	
Amphotericin B	—	—	—	—	0	0	0	14	141	131	26	0[A,C]	0[A,C]	0[A,C]	0[A,C]	0	0
Itraconazole	—	—	—	—	0	0	0	7	114	151	6	2[A,B,C]	1[A,C]	0[A,C]	31[A,C]	34	109
Voriconazole	—	—	—	—	0	0	0	1	49	192	32	13[A,B,C]	19[A,C]	3[A,C]	3[A,C]	38	122
Posaconazole	—	—	—	—	0	14	168	84	16[B]	20[A,C]	3[A,C]	0[A,C]	1[A,C]	0[A,C]	6[A,C]	33	106
Isavuconazole	—	—	—	—	0	0	0	0	6	168	98	10[B]	10[A,C]	16[A,C]	4[A,C]	35	112
Olorofim	0	0	0	30	249	33	0	0	—	—	—	—	—	—	—	NA	NA
Cryptic species (n = 20)																	
Amphotericin B	—	—	—	—	0	0	0	2	0	1	4	7[A,C]	5[A,C]	1[A,C]	0[A,C]	13	65
Itraconazole	—	—	—	—	0	0	0	0	2	2	6	0[A,B,C]	1[A,C]	1[A,C]	8[A,C]	10	50
Voriconazole	—	—	—	—	0	0	0	0	0	1	1	6[A,B,C]	8[A,C]	4[A,C]	0[A,C]	18	90
Posaconazole	—	—	—	—	0	0	2	1	10[B]	7[A,C]	0[A,C]	0[A,C]	0[A,C]	0[A,C]	0[A,C]	12	60
Isavuconazole	—	—	—	—	0	0	0	0	1	0	6	8[B]	4[A,C]	1[A,C]	0[A,C]	13	65
Olorofim	0	0	4	11	5	0	0	0	—	—	—	—	—	—	—	NA	NA
A. flavus ATCC 204304																	
Olorofim	0	0	0	0	22	2	0	0	—	—	—	—	—	—	—	NA	NA
A. fumigatus ATCC 204305																	
Olorofim	0	0	0	2	19	3	0	0	—	—	—	—	—	—	—	NA	NA



Olorofim, Etude de phase II

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	100 participants
Intervention Model:	Single Group Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	Phase IIb Study of F901318 as Treatment of Invasive Fungal Infections Due to Lomentospora Prolificans, Scedosporium Spp., Aspergillus Spp., and Other Resistant Fungi in Patients Lacking Suitable Alternative Treatment Options
Actual Study Start Date :	June 6, 2018
Estimated Primary Completion Date :	December 2020
Estimated Study Completion Date :	February 2021

Go to

Olorofim, phase III

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	225 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Single (Investigator)
Masking Description:	Adjudicator and sponsor-blinded.
Primary Purpose:	Treatment
Official Title:	Phase III, Adjudicator-blinded, Randomised Study to Evaluate Efficacy and Safety of Treatment With Olorofim Versus Treatment With AmBisome® Followed by Standard of Care in Patients With Invasive Fungal Disease Caused by Aspergillus Species
Actual Study Start Date :	March 31, 2022
Estimated Primary Completion Date :	September 14, 2024
Estimated Study Completion Date :	March 4, 2025

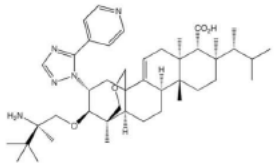
Ibrexafungerp

- Nouvel inhibiteur de ß-1,3-glucan synthase
- Triterpenoides - enfumafungine
- Disponible Oral
- Fongicide sur *Candida*
- 1/2 vie longue (20h)
- Distribution tissulaire importante

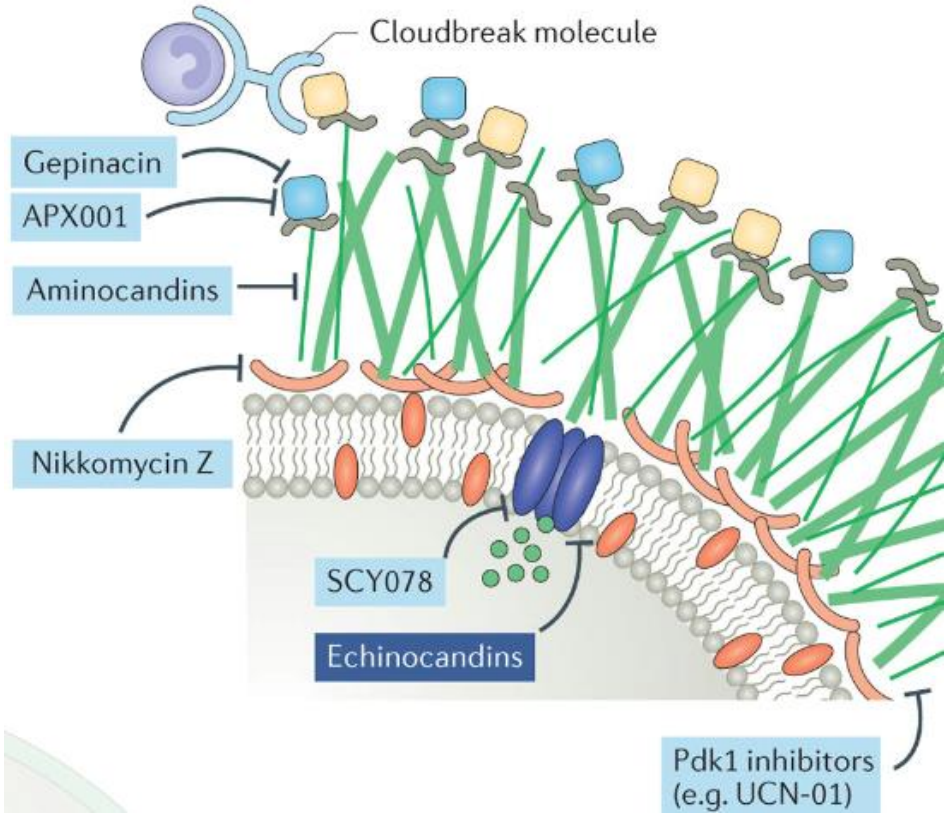
- Bonne diffusion peritoine (modele murin)

- Etudes en cours ou finies:
- -candidose vulvo vaginale récidivante
- -candidose invasive relais
- -aspergillose invasive

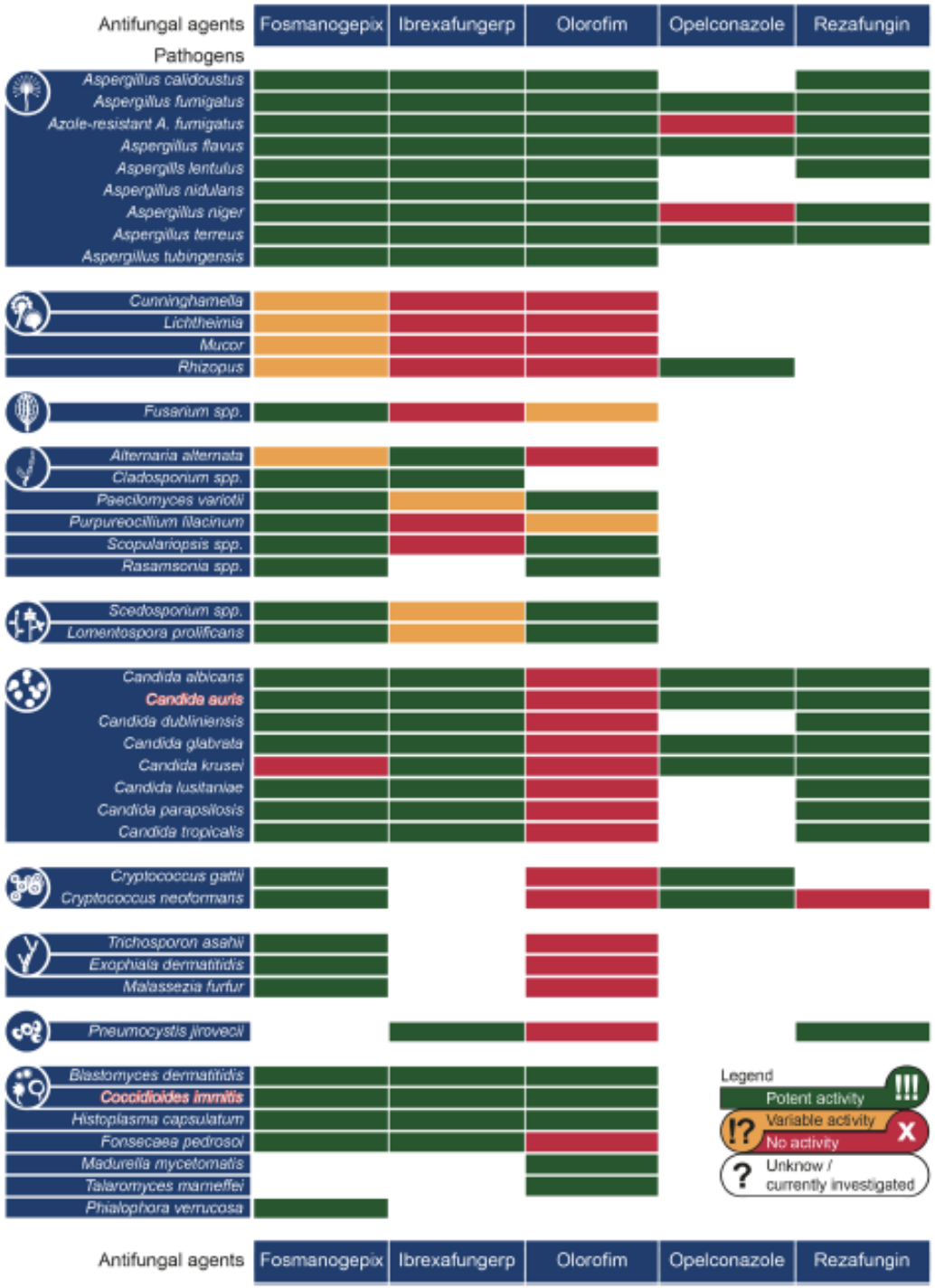
Ibrexafungerp (SCY-078)



Triterpenoid - Non-competitive inhibition of 1,3-β-D-glucan synthase, depleting 1,3-β-D-glucan in cell wall
(*FKS1* and *FKS2*)



Perfect JR, (2017) Nat Rev Drug Discov.



Spectre ibrexafungerp

Levures non basidio: pas d'activité sur crypto, trichosporon

Filamenteux hors Mucorales, Fusarium et Alternaria, Scedosporium, Lomentospora

Dimorphiques

PCP

Ibrexafungerp

- *Human data showed a peak plasma concentration within*
- *4–6 h and a linear decline with a mean half-life of approximately*
- *20–30 hours supporting a once-daily dosing strategy*

- *high-fat meal increased bioavailability, delayed median time to Cmax from 4 h (fasted state) to 6h [*
- *high tissue penetration with the following tissueto- blood AUC ratios:*
  - *spleen 54-fold*
  - *iver 50-fold*
  - *Lung 31-fold*
  - *bone marrow 25-fold*
  - *kidney 20-fold*
  - *skin 12-fold*
  - *vaginal tissue nine-fold; and skeletal muscle fourfold,*
- *minimal distribution to central nervous system tissues*

- *Candida vaginitis using a single-day 600-mg treatment (300 mg twice-daily dosage)*
- *penetration into the lens is poor,*
- *ibrexafungerp shows high concentrations in the uvea*
- *mainly eliminated via feces and is marginally from urine (approximately 1%)*

DONNEES *IN VITRO*

Species and antifungal drug	MIC (μg/ml) Range[a]
C. albicans (*n* = 33)	
SCY-078	0.06–0.25
FLC	≤0.125 to 128
ANF	≤0.015 to 1
MCF	≤0.015 to 1
CAS	≤0.015 to 0.5
VRC	≤0.015 to >16
C. albicans/dubliniensis not further identified (*n* = 5)	
SCY-078	0.12
FLC	≤0.125 to 0.25
ANF	≤0.125 to 0.03
MCF	≤0.015 to 0.03
CAS	≤0.015 to 0.03
VRC	≤0.015
C. glabrata (*n* = 23)	
SCY-078	0.25–1
FLC	2 to >128
ANF	0.03–1
MCF	≤0.015 to 0.5
CAS	≤0.015 to 0.5
VRC	0.03–8
C. krusei (*n* = 6)	
SCY-078	0.5–4
FLC	64–128
ANF	0.03–0.25
MCF	0.03–0.25
CAS	0.06–0.5
VRC	0.5–1
C. parapsilosis (*n* = 18)	
SCY-078	0.25–0.5
FLC	0.25–4
ANF	0.06–2
MCF	0.5–2
CAS	0.06–0.5
VRC	≤0.015 to 0.12
C. tropicalis (*n* = 12)	
SCY-078	0.03–0.5
FLC	0.25–1
ANF	≤0.015
MCF	≤0.015 to 0.06
CAS	≤0.015 to 0.06
VRC	≤0.015

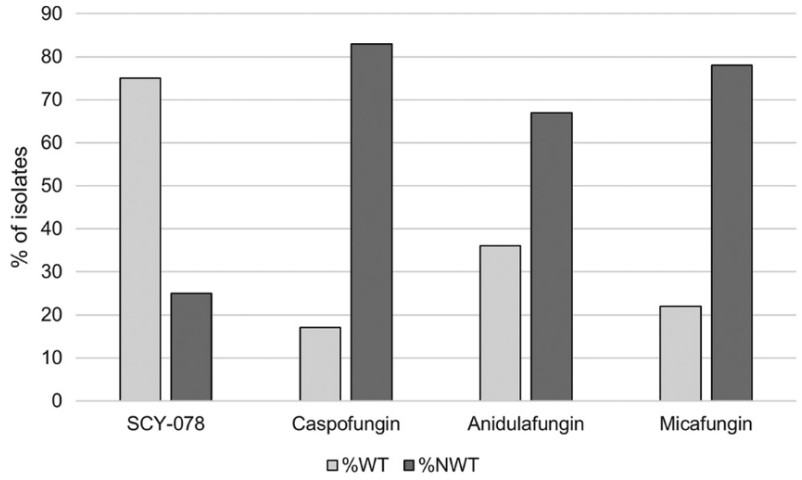


FIG 1 Activity of SCY-078, anidulafungin, caspofungin, and micafungin against strains displaying *FKS* mutations. %WT, percent wild type; %NWT, percent non-wild type (for SCY-078, %NWT is the percent exceeding the wild-type upper-limit value [WT-UL; two 2-fold dilutions higher than the modal MIC value of each WT population]).

Pfaller, M., Messer, S., Rhomberg, P., Borroto-Esoda, K., Castanheira, M. (2017). Differential Activity of the Oral Glucan Synthase Inhibitor SCY-078 against Wild-Type and Echinocandin-Resistant Strains of Candida Species Antimicrobial Agents and Chemotherapy 61(8), e00161-17. https://dx.doi.org/10.1128/aac.00161-17

Schell, W., Jones, A., Borroto-Esoda, K., Alexander, B. (2017). Antifungal Activity of SCY-078 and Standard Antifungal Agents against 178 Clinical Isolates of Resistant and Susceptible Candida Species. Antimicrobial Agents and Chemotherapy 61(11), e01102-17. https://dx.doi.org/10.1128/aac.01102-17

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EXPERIMENTAL THERAPEUTICS

In Vitro Activity of Ibrexafungerp (SCY-078) against *Candida auris* Isolates as Determined by EUCAST Methodology and Comparison with Activity against *C. albicans* and *C. glabrata* and with the Activities of Six Comparator Agents

Maiken Cavling Arendrup,[a,b,c] Karin Meinike Jørgensen,[a] Rasmus Krøger Hare,[a] Anuradha Chowdhary[d]

TABLE 2 *In vitro* activity of ibrexafungerp (IBX) and comparators against *C. auris* and selected *C. albicans* and *C. glabrata* isolates, as determined by EUCAST E.Def 7.3.1[a]

Strain and agent	MIC (mg/liter)															MIC range (mg/liter)	Modal MIC (mg/liter)	MIC_{50} (mg/liter)
	≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	≥64			
C. auris (*n* = 122)																		
IBX					1	3	33	63	20	2						0.06–2	0.5	0.5
ANF*			1	11	35	30	12	12	11	2	1			7		0.016–>32	0.06	0.125
MCF*				5	30	70	9							8		0.03–>32	0.125	0.125
AMB*								14	108							0.5–1	1	1
FLU*								1					2	10	109	0.5–≥64	≥64	≥64
VOR*	1			1	1	16	13	34	38	13	5					≤0.004–4	Bimodal	0.5
ISA*	20	1	1	19	9	19	21	21	6	5						≤0.004–2	Trimodal	0.125
C. albicans (*n* = 16)																		
IBX				5	10	1										0.03–0.125	0.06	0.06
ANF	10	6														≤0.004–0.008	≤0.004	≤0.004
MCF		4	10	2												0.008–0.03	0.016	0.016
AMB					1	6	9									0.06–0.25	0.25	0.25
FLU						10	6									0.125–0.25	0.125	0.125
VOR	12	4														≤0.004–0.008	≤0.004	≤0.004
ISA	14	2														≤0.004–0.008	≤0.004	≤0.004
C. glabrata (*n* = 16)																		
IBX							10	6								0.25–0.5	0.25	0.25
ANF			4	12												0.016–0.03	0.03	0.03
MCF			8	8												0.016-0.03	0.016/0.03	0.016
AMB				1		1	11	3								0.03–0.5	0.25	0.25
FLU										6	10					2–4	4	4
VOR				1	13	2										0.03–0.125	0.06	0.06
ISA			1	3	6	6										0.016–0.125	0.06/0.125	0.06

[a]Gray-shaded areas indicate concentrations not tested for that particular compound. An underlined value indicates a modal MIC for unimodal distributions but the lowest MIC peak for multimodal distributions, thus illustrating the modal MIC of the presumed wild-type distribution. The MIC distributions for comparator antifungals against *C. auris* indicated by an asterisk (*) are compiled from reference 1 except that isolates above the tested MIC range in that publication were retested using extended concentration ranges.

122 isolats *C. auris*

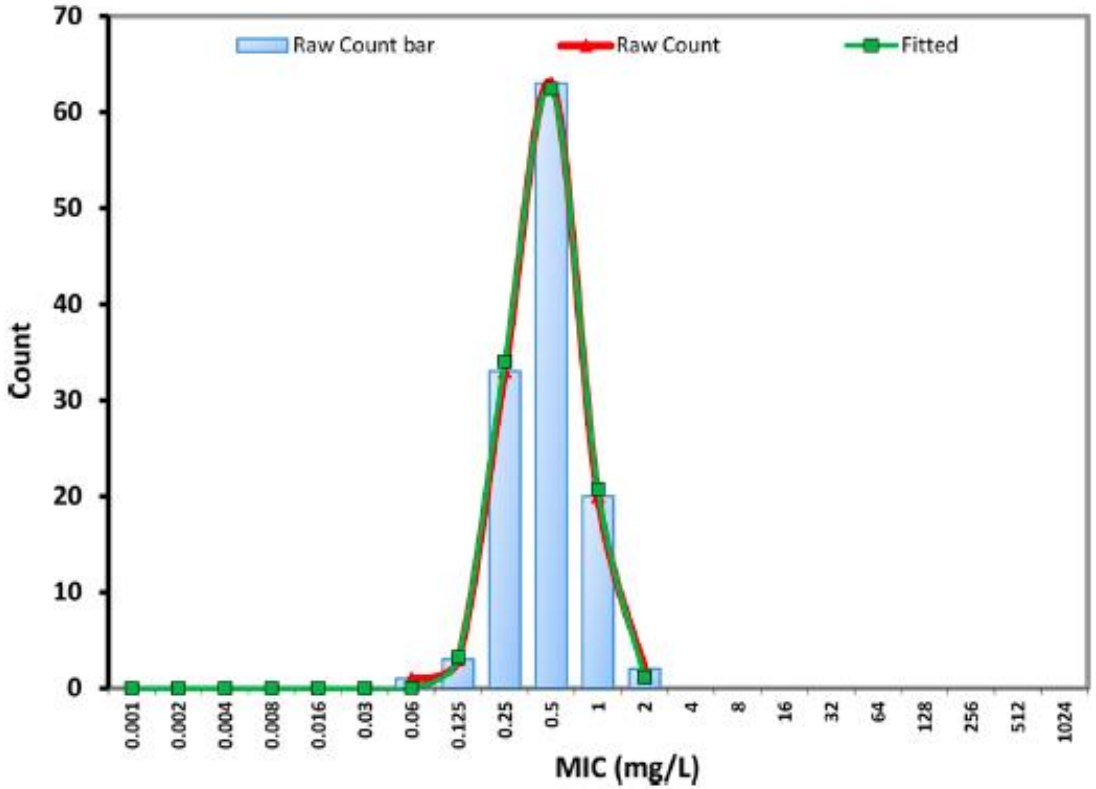


FIG 1 EUCAST MIC distribution for ibrexafungerp against 122 clinical *C. auris* isolates. Raw counts are presented as bars and a red curve, whereas the fitted curve was determined by the ECOFF finder program (v2.0) that iteratively fits each subset of the data from left to right.

March 2020

Efficacité ibrexafungerp sur des souches de Candida R echinocandines

- Souches de *C. glabrata* avec mutations Fks
- CMI plus basses ibrexafungerp vs echinocandines

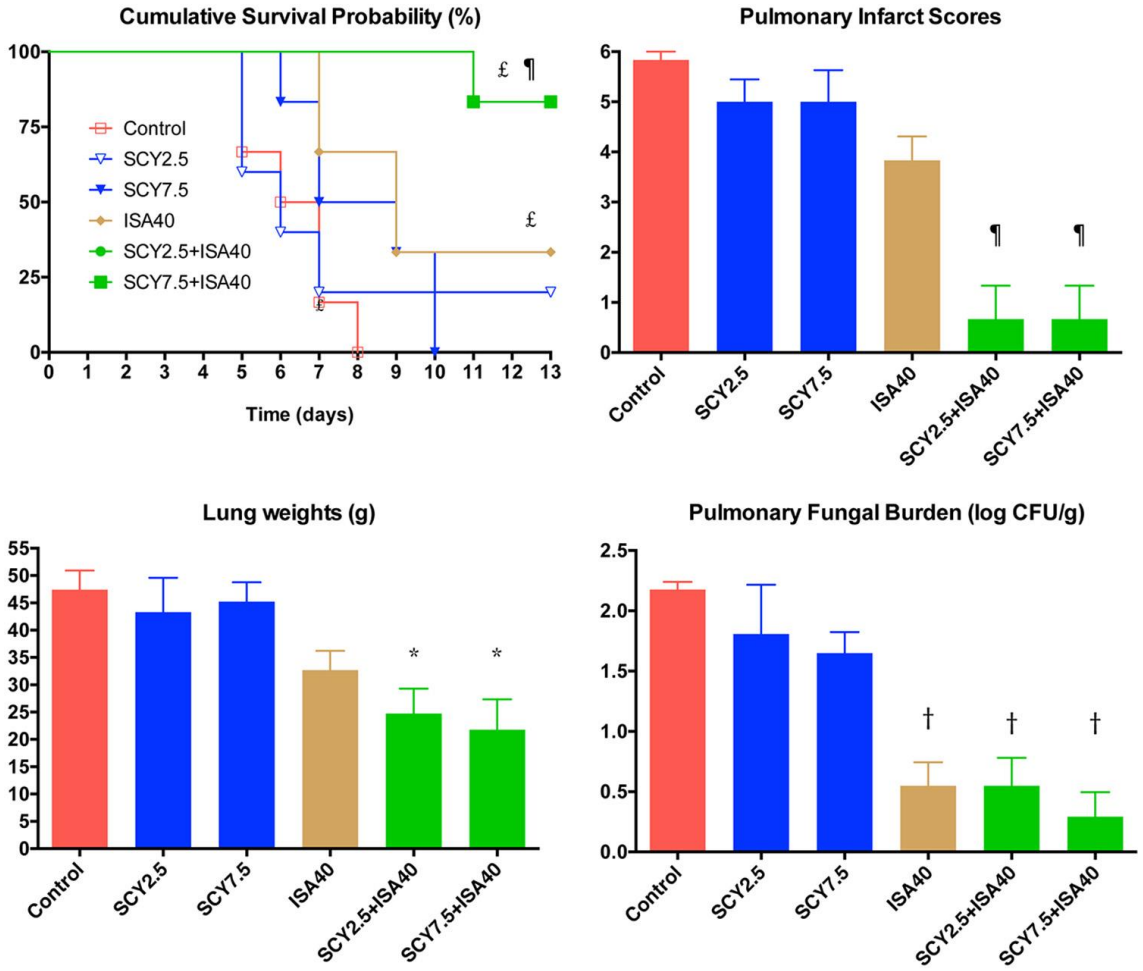
TABLE 2 MIC values for ibrexafungerp and three echinocandins, with *FKS* sequencing results for each isolate

	MIC (μg/ml) of:				Gene and hot spot region(s)[a]			
Isolate ID	Anidulafungin	Caspofungin	Micafungin	Ibrexafungerp	*FKS1* HS1	*FKS1* HS2	*FKS2* HS1	*FKS2* HS2
1	1	0.5	1	1	S629P	WT	WT	WT
24	2	8	1	0.25	S629P	WT	WT	WT
28	0.5	0.5	0.125	0.5	S629P	WT	WT	WT
31	0.5	0.125	0.125	0.5	S629P	WT	WT	WT
32	4	>16	2	0.5	S629P	WT	WT	WT
68	2	2	0.5	1	S629P	WT	WT	WT
72	2	16	4	0.5	S629P	WT	WT	WT
84	4	8	2	0.125	S629P	WT	WT	WT
85	2	>16	2	0.125	S629P	WT	WT	WT
80	1	8	1	0.125	S629P	WT	S663P	WT
38	2	4	1	0.5	S629P	WT	D666V	WT
48	0.125	0.125	0.5	0.25	S629P	WT	D666V	WT
63	1	2	1	0.5	S629P	WT	D666V	WT
50	2	4	0.125	0.25	S629T	WT	F659Y	WT
2	2	4	2	0.25	WT	WT	S663P	WT
3	4	>16	4	0.5	WT	WT	S663P	WT
4	2	8	4	1	WT	WT	S663P	WT
5	0.5	16	4	0.5	WT	WT	S663P	WT
7	2	16	4	1	WT	WT	S663P	WT
8	1	16	4	1	WT	WT	S663P	WT
9	4	>16	4	0.5	WT	WT	S663P	WT
12	2	2	0.5	0.5	WT	WT	S663P	WT
14	0.5	1	2	0.25	WT	WT	S663P	WT
15	4	>16	4	0.5	WT	WT	S663P	WT
18	4	8	2	0.25	WT	WT	S663P	WT
19	2	1	2	0.5	WT	WT	S663P	WT
22	2	>16	2	0.5	WT	WT	S663P	WT
23	2	>16	2	0.25	WT	WT	S663P	WT
30	4	>16	2	0.5	WT	WT	S663P	WT
37	4	16	2	0.5	WT	WT	S663P	WT
40	1	2	1	0.25	WT	WT	S663P	WT
41	4	16	4	0.5	WT	WT	S663P	WT
45	1	16	2	0.25	WT	WT	S663P	WT
46	1	4	1	0.5	WT	WT	S663P	WT
53	4	>16	2	0.5	WT	WT	S663P	WT
55	2	8	2	0.5	WT	WT	S663P	WT
62	2	8	1	0.25	WT	WT	S663P	WT
67	2	8	2	0.25	WT	WT	S663P	WT
69	2	8	1	0.25	WT	WT	S663P	WT
70	2	8	1	0.25	WT	WT	S663P	WT
71	2	>16	4	1	WT	WT	S663P	WT
73	1	8	1	0.5	WT	WT	S663P	WT
74	1	8	1	0.5	WT	WT	S663P	WT
75	4	>16	4	0.125	WT	WT	S663P	WT
76	2	4	2	0.25	WT	WT	S663P	WT
82	2	4	2	0.25	WT	WT	S663P	WT
87	1	4	1	0.125	WT	WT	S663P	WT
88	2	>16	1	1	WT	WT	S663P	WT
89	2	4	2	1	WT	WT	S663P	WT
90	2	4	1	0.125	WT	WT	S663P	WT
36	2	16	4	0.5	R631G	WT	S663P	WT
6	2	2	0.25	0.25	WT	WT	P667H	WT
10	1	0.5	0.25	0.5	WT	WT	F659Y	WT
11	1	2	0.25	0.25	WT	WT	F659Y	WT
57	1	2	0.25	0.25	WT	WT	F659Y	WT
59	0.5	1	0.25	0.5	WT	WT	F659Y	WT
13	0.5	0.25	0.125	0.25	WT	WT	S663F	WT
25	2	2	0.25	0.125	WT	WT	S663F	WT
17	0.25	0.25	0.5	0.0625	R631G	WT	WT	WT
20	0.06	0.125	0.25	0.25	R631G	WT	WT	WT
21	0.25	0.5	1	0.0625	R631G	WT	WT	WT
29	0.06	0.125	0.25	<0.03	R631G	WT	WT	WT
16	0.5	0.25	0.5	0.125	R631G	WT	D666V	WT
33	0.5	0.5	0.25	0.125	WT	WT	del658F	WT

Nunnally N, AAC, 2019

Modèle lapin aspergilllose pulmonaire invasive

- Ibrexafungerp and isavuconazole
- combination demonstrated prolonged survival, decreased pulmonary injury, reduced
- residual fungal burden, and lower GMI and (1¡3)- -D-glucan levels in
- comparison to those of single therapy for treatment of IPA.



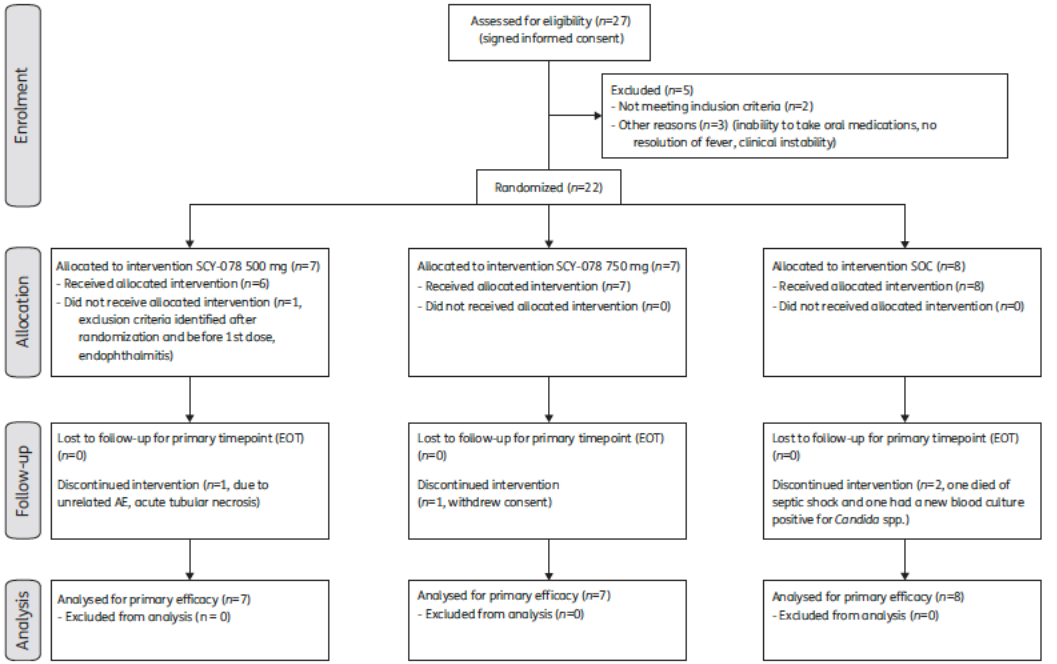
Petraitis, AAC, 2020

Phase 2 oral ibrexafungerp following initial echinocandin therapy in non neutropenic patients with invasive candidiasis

- Meilleure exposition: 1500mg J1 puis 7750mg/j
- Troubles digestifs
- Réponse 6/8 *C. glabrata et C. krusei*

Table 2. Global response in the ITT population of 22 patients with invasive candidiasis

	Ibrexafungerp 500 mg (*N*=7), *n* (%)	Ibrexafungerp 750 mg (*N*=7), *n* (%)	SOC	
			fluconazole (*N*=7), *n* (%)	micafungin (*N*=1), *n* (%)
EOT				
global response	5 (71)	6 (86)	5 (71)	1 (100)
clinical response	5 (71)	6 (86)	5 (71)	1 (100)
microbiological response	6 (86)	6 (86)	6 (86)	1 (100)
missing	1 (14)	1 (14)	0 (0)	0 (0)
Week 2 post-treatment				
global response	4 (57)	4 (57)	5 (71)	0 (0)
clinical response	4 (57)	4 (57)	5 (71)	0 (0)
microbiological response	4 (57)	4 (57)	5 (71)	0 (0)
missing	2 (29)	3 (43)	2 (29)	1 (100)
Week 6 post-treatment				
global response	3 (43)	2 (29)	4 (57)	0 (0)
clinical response	3 (43)	2 (29)	4 (57)	0 (0)
microbiological response	3 (43)	2 (29)	4 (57)	0 (0)
missing	3 (43)	5 (71)	3 (43)	1 (100)



Spec A, JAC 2019

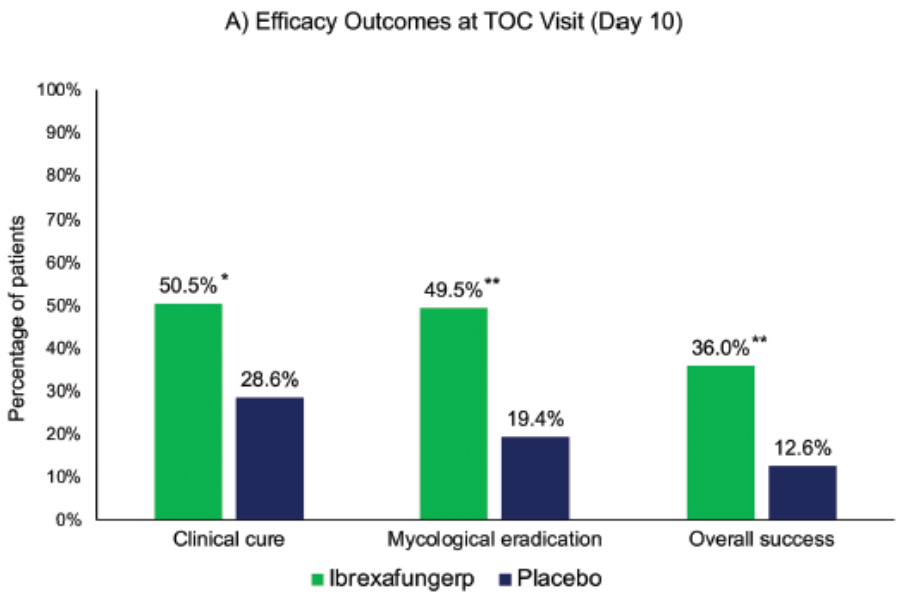
Clinical Infectious Diseases

MAJOR ARTICLE

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

Jane R. Schwebke,[1] Ryan Sobel,[2] Janet K. Gersten,[3] Steven A. Sussman,[4] Samuel N. Lederman,[5] Mark A. Ja
Alfred H. Moffett Jr,[9] Nkechi E. Azie,[10] David A. Angulo,[10] Itzel A. Harriott,[10] Katyna Borroto-Esoda,[11] Mahmo

- CVV aigue
- 2:1 ibrexafungerp (300mg BID J1) vs placebo



	Ibrexafungerp (n = 188)	Placebo (n = 98)
Age, y		
Mean ± SD	33.5 ± 10.36	36.0 ± 12.46
Median (min, max)	32.5 (18, 67)	34.0 (17, 66)
Race, n (%)		
White	103 (54.8)	53 (54.1)
Black	73 (38.8)	43 (43.9)
Asian	4 (2.1)	0
American Indian or Alaska Native	2 (1.1)	0
Other	6 (3.2)	2 (2.0)
Ethnicity, n (%)		
Hispanic or Latino	54 (28.7)	18 (18.4)
Non-Hispanic or Latino	134 (71.3)	80 (81.6)
BMI (kg/m^2)[a], n (%)		
≤35	144 (76.6)	76 (77.6)
>35	44 (23.4)	22 (22.4)
Diabetes mellitus		
Yes	18 (9.6)	8 (8.2)
No	170 (90.4)	90 (91.8)
Composite VSS score		
Median (min, max)	9.0 (5, 18)	9.0 (4, 17)
Candida species		
Candida albicans	173 (92.0)	90 (91.8)
Candida glabrata	11 (5.9)	11 (11.2)
Candida tropicalis	4 (2.1)	1 (1.0)
Candida dubliniensis	2 (1.1)	0
Candida lusitaniae	1 (0.5)	1 (1.0)
Candida parapsilosis	1 (0.5)	0
Candida krusei	0	1 (1.0)
Saccharomyces species	1 (0.5)	0

Table 3. Summary of Treatment-Related Treatment-Emergent Adverse Events (TEAEs) Reported in >2% of Patients

	Ibrexafungerp (n = 247)	Placebo (n = 124)
Patients with ≥1 TEAE	98 (39.7)	21 (16.9)
Mild	78 (31.6)	17 (13.7)
Moderate	24 (9.7)	4 (3.2)
Severe	1 (0.4)	0
Diarrhea	55 (22.3)	5 (4.0)
Mild	38 (15.4)	4 (3.2)
Moderate	17 (6.9)	1 (0.8)
Nausea	27 (10.9)	5 (4.0)
Mild	24 (9.7)	5 (4.0)
Moderate	2 (0.8)	0
Severe	1 (0.4)	0
Abdominal pain	13 (5.3)	0
Mild	12 (4.9)	0
Moderate	1 (0.4)	0
Abdominal discomfort	11 (4.5)	2 (1.6)
Mild	6 (2.4)	2 (1.6)
Moderate	5 (2.0)	0
Dizziness	9 (3.6)	2 (1.6)
Mild	7 (2.8)	2 (1.6)
Moderate	2 (0.8)	0
Abdominal pain upper	7 (2.8)	1 (0.8)
Mild	6 (2.4)	1 (0.8)
Moderate	1 (0.4)	0
Flatulence	6 (2.4)	1 (0.8)
Mild	5 (2.0)	1 (0.8)
Moderate	1 (0.4)	0
Headache	6 (2.4)	3 (2.4)
Mild	5 (2.0)	3 (2.4)
Moderate	1 (0.4)	0

A Phase 3, Randomized, Double-blind Study for Patients With Invasive Candidiasis Treated With IV Echinocandin Followed by Either Oral Ibrexafungerp or Oral Fluconazole (MARIO)

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	220 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Phase 3, Multicenter, Prospective, Randomized, Double-blind Study of Two Treatment Regimens for Candidemia and/or Invasive Candidiasis: Intravenous Echinocandin Followed by Oral Ibrexafungerp Versus Intravenous Echinocandin Followed by Oral Fluconazole (MARIO)
Actual Study Start Date :	August 3, 2022
Estimated Primary Completion Date :	January 2024
Estimated Study Completion Date :	February 2024

Rezafungine

- *Analogue anidulafungin with a similar alkoxytriphenyl moiety but a distinct structural modification*
- *results in a considerably longer half-life*
- *Mean half-life:*
  - *80 hours after the first dose*
  - *150 hours after the second or third dose*

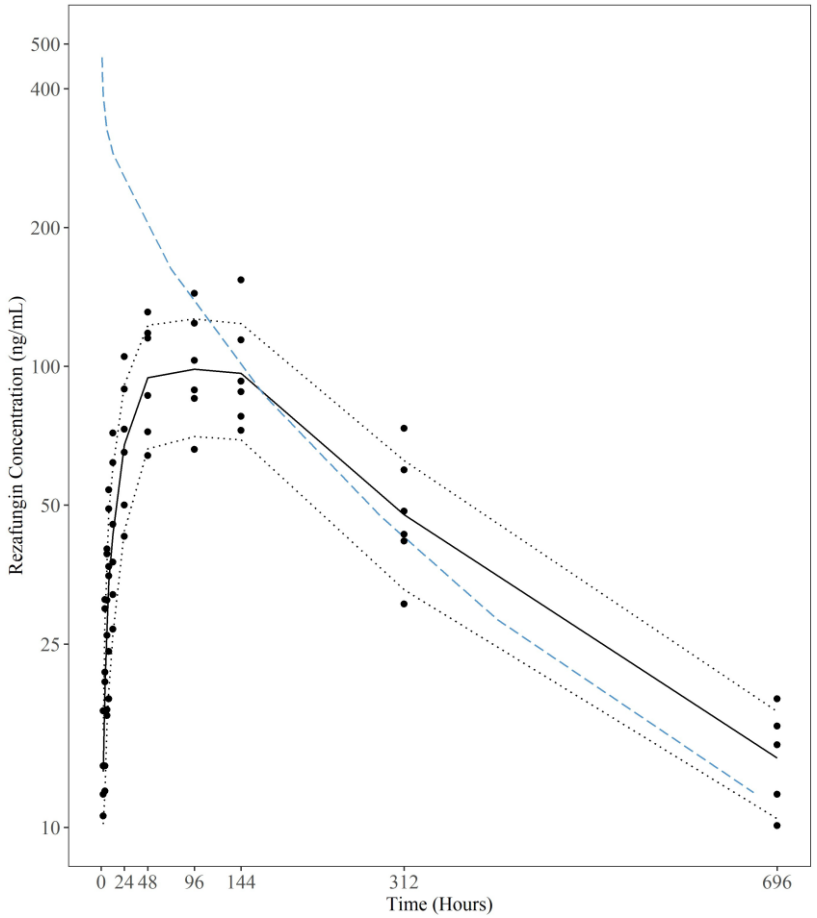
Rezafungine sous cutanée phase I

TABLE 1 Number and percentage of subjects experiencing solicited reactogenicity symptoms by symptom and dose group

	Any dose ($N = 9$)			1 mg ($N = 3$)			10 mg ($N = 6$)			Placebo ($N = 3$)		
Symptom	***n***	**%**	**95% CI**	***n***	**%**	**95% CI**	***n***	**%**	**95% CI**	***n***	**%**	**95% CI**
Any symptom	7	78	45, 94	1	33	6, 79	6	100	61, 100	–	–	–
Pain	3	33	12, 65	1	33	6, 79	2	33	10, 70	–	–	–
Tenderness	4	44	19, 73	–	–	–	4	67	30, 90	–	–	–
Pruritus (itching)	1	11	2, 43	–	–	–	1	17	3, 56	–	–	–
Ecchymosis (bruising), functional grade	2	22	6, 55	–	–	–	2	33	10, 70	–	–	–
Ecchymosis (bruising), measurement grade	1	11	2, 43	–	–	–	1	17	3, 56	–	–	–
Induration (hardness)/swelling, functional grade	1	11	2, 43	–	–	–	1	17	3, 56	–	–	–
Induration (hardness)/swelling, measurement grade	1	11	2, 43	–	–	–	1	17	3, 56	–	–	–
Erythema (redness), functional grade	6	67	35, 88	–	–	–	6	100	61, 100	–	–	–
Erythema (redness), measurement grade	6	67	35, 88	–	–	–	6	100	61, 100	–	–	–
Nodule, functional grade	5	56	27, 81	–	–	–	5	83	44, 97	–	–	–
Nodule, measurement grade	4	44	19, 73	–	–	–	4	67	30, 90	–	–	–
Ulceration, functional grade	–	–	–	–	–	–	–	–	–	–	–	–
Ulceration, measurement grade	–	–	–	–	–	–	–	–	–	–	–	–

Note: N = Number of subjects in safety population.

Abbreviation: CI, confidence interval.



Gu K, Clin Tyranslat Sci, 2022

CMI Rezafungin

TABLE 3 (Continued)

Antimicrobial agent	MIC (μg/ml) 50%	MIC (μg/ml) 90%	CLSI[b] % S	CLSI[b] % R	ECV[b] % WT	ECV[b] % NWT
Cryptococcus neoformans var. *grubii* (*n* = 73)						
Rezafungin	>4	>4				
Anidulafungin	>4	>4				
Caspofungin	>4	>4				
Micafungin	>4	>4				
Fluconazole	2	4			100.0	0.0
Itraconazole	0.25	0.25			93.5	6.5
Posaconazole	0.12	0.25			97.3	2.7
Voriconazole	0.03	0.12			100.0	0.0
Amphotericin B	0.5	1			52.1	47.9
Aspergillus fumigatus (*n* = 183)						
Rezafungin	0.015	0.03			100.0	0.0
Anidulafungin	0.015	0.03				
Caspofungin	0.015	0.03			100.0	0.0
Micafungin	≤0.008	0.015				
Itraconazole	0.5	1			98.4	1.6
Posaconazole	0.25	0.5				
Voriconazole	0.25	0.5			98.9	1.1
Amphotericin B	1	2			100.0	0.0
Aspergillus section *Flavi* (*n* = 45)						
Rezafungin	≤0.008	0.015				
Anidulafungin	≤0.008	0.015				
Caspofungin	0.015	0.03			100.0	0.0
Micafungin	0.015	0.03				
Itraconazole	0.5	1			100.0	0.0
Posaconazole	0.25	0.5			100.0	0.0
Voriconazole	0.5	1			100.0	0.0
Amphotericin B	2	2			100.0	0.0

[a]Abbreviations: S, susceptible; R, resistant; WT, wild type; NWT, non-wild type.
[b]Criteria were published in the CLSI M60 document (40). Epidemiological cutoff value (ECV) criteria were published in the CLSI M59 document (41). The ECVs for rezafungin and each species were determined from data in the present study.
[c]Nonresistant is interpreted as susceptible-dose dependent.

TABLE 3 Antimicrobial activity of rezafungin and comparator agents tested against fungal isolates from the worldwide 2016 to 2018 rezafungin surveillance program[a]

Antimicrobial agent	MIC (μg/ml) 50%	MIC (μg/ml) 90%	CLSI[b] % S	CLSI[b] % R	ECV[b] % WT	ECV[b] % NWT
Candida albicans (*n* = 835)						
Rezafungin	0.03	0.06			99.8	0.2
Anidulafungin	0.015	0.03	100.0	0.0	100.0	0.0
Caspofungin	0.015	0.03	99.9	0.1		
Micafungin	0.015	0.03	99.9	0.1	99.6	0.4
Fluconazole	≤0.12	0.25	99.5	0.4	98.1	1.9
Itraconazole	≤0.06	0.12				
Posaconazole	0.03	0.06			96.5	3.5
Voriconazole	≤0.008	0.015	99.9	0.0	99.0	1.0
Amphotericin B	0.5	1			100.0	0.0
Candida glabrata (*n* = 374)						
Rezafungin	0.06	0.12			95.7	4.3
Anidulafungin	0.06	0.12	94.4	3.2	96.8	3.2
Caspofungin	0.03	0.06	97.1	2.1		
Micafungin	0.015	0.03	96.0	2.4	93.3	6.7
Fluconazole	2	32	91.4[c]	8.6	85.6	14.4
Itraconazole	0.5	2			98.7	1.3
Posaconazole	0.25	1			93.0	7.0
Voriconazole	0.06	1			87.2	12.8
Amphotericin B	1	1			100.0	0.0
Candida parapsilosis (*n* = 329)						
Rezafungin	1	2			100.0	0.0
Anidulafungin	2	2	93.9	0.0	100.0	0.0
Caspofungin	0.25	0.5	100.0	0.0		
Micafungin	1	1	100.0	0.0	100.0	0.0
Fluconazole	0.5	32	86.0	12.5	83.6	16.4
Itraconazole	0.12	0.25				
Posaconazole	0.06	0.12			100.0	0.0
Voriconazole	≤0.008	0.25	88.4	0.9	84.5	15.5
Amphotericin B	0.5	1			100.0	0.0
Candida tropicalis (*n* = 196)						
Rezafungin	0.03	0.06			100.0	0.0
Anidulafungin	0.03	0.06	99.0	1.0	98.0	2.0
Caspofungin	0.015	0.06	99.0	1.0		
Micafungin	0.03	0.06	99.0	1.0	96.4	3.6
Fluconazole	0.25	1	96.9	2.6	94.9	5.1
Itraconazole	0.12	0.5			100.0	0.0
Posaconazole	0.06	0.12			92.9	7.1
Voriconazole	0.015	0.06	96.9	0.0	96.9	3.1
Amphotericin B	0.5	1			100.0	0.0
Candida krusei (*n* = 77)						
Rezafungin	0.03	0.06			100.0	0.0
Anidulafungin	0.06	0.12	100.0	0.0	100.0	0.0
Caspofungin	0.12	0.25	98.7	0.0		
Micafungin	0.06	0.12	100.0	0.0	100.0	0.0
Fluconazole	32	64				
Itraconazole	0.5	1			100.0	0.0
Posaconazole	0.5	0.5			100.0	0.0
Voriconazole	0.25	0.5	96.1	1.3	96.1	3.9
Amphotericin B	1	2			100.0	0.0
Candida dubliniensis (*n* = 93)						
Rezafungin	0.06	0.12			100.0	0.0
Anidulafungin	0.03	0.12			100.0	0.0
Caspofungin	0.03	0.03				
Micafungin	0.03	0.03			100.0	0.0
Fluconazole	≤0.12	0.25			96.8	3.2
Itraconazole	≤0.06	0.25				
Posaconazole	0.03	0.06				
Voriconazole	≤0.008	0.015				
Amphotericin B	0.5	0.5				

(Continued on next page)

Pfaller, AAC, 2020

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)				
	Fks1	Fks2	RZF	ANF	MCF	AMB	FLU
C. albicans	S645P	NT	**1**	**0.25**	**2**	0.25	0.25
	D648Y	NT	**0.5**	**0.06**	**0.125**	0.25	0.125
	P1354S	NT	**0.5**	**0.06**	**0.125**	0.5	**>64**
	P1354S	NT	**0.25**	0.016	**0.06**	0.5	**>32**
	P1354S	NT	**0.25**	0.016	**0.06**	0.5	**64**
	P1354S	NT	**0.25**	0.016	**0.06**	0.5	**64**
	P1354P/S	NT	**0.25**	0.03	**0.06**	0.5	**>64**
	P1354P/S	NT	**0.25**	**0.06**	**0.06**	0.5	**>64**
	R1361R/S	NT	**0.25**	**0.06**	**0.125**	0.125	0.125
	R1361G	NT	**0.25**	**0.06**	**0.125**	0.125	0.25
	R1361G	NT	**0.25**	0.016	**0.06**	0.5	**64**
C. glabrata	L630Q	S663F	**2**	**1**	**0.5**	0.5	1
	L630Q	S663F	**2**	**1**	**0.5**	0.5	32
	WT	S663F	**2**	**1**	**0.5**	0.5	2
	WT	S663F	**1**	**0.25**	**0.125**	0.125	2
	WT	S663F	**0.5**	**0.25**	**0.125**	0.5	2
	WT	S663F	**0.5**	0.06	**0.06**	0.5	2
	WT	S663P	**2**	**1**	**0.5**	0.125	2
	WT	S663P	**0.5**	**0.125**	**0.125**	0.25	4
	Y1429X	Y658N/L664Q	**0.5**	**0.125**	**0.06**	0.125	**>32**
	WT	F659del	**0.5**	0.06	**0.06**	0.25	**>64**
C. tropicalis	F650S	NT	**1**	**0.25**	**1**	0.25	0.5
	S654P	NT	**2**	**2**	**2**	0.5	0.5
C. dubliniensis	S645P	NT	**2**	**0.25**	**2**	0.03	0.125
	S645P	NT	**1**	**0.25**	**2**	0.03	0.125
C. krusei	S659F	NT	**1**	**0.25**	**4**	0.5	32
C. auris	S639F	NT	**16**	**4**	**>32**	1	**>256**
	S639F	NT	**16**	**>32**	**>32**	1	**>256**
	S639F	NT	**8**	**>32**	**>32**	1	**>256**
	S639F	NT	**8**	**>32**	**>32**	1	**>256**
	S639F	NT	**8**	**>32**	**>32**	1	**>256**
	S639F	NT	**8**	**>32**	**>32**	1	**>256**
	S639F	NT	**8**	**>32**	**>32**	1	**>256**
	S639F	NT	**8**	**>32**	**>32**	1	**>256**
	WT	NT	**2**	**2**	0.25	1	**>256**
	WT	NT	**2**	**1**	0.25	1	**256**
	WT	NT	**2**	0.03	0.03	0.5	**256**

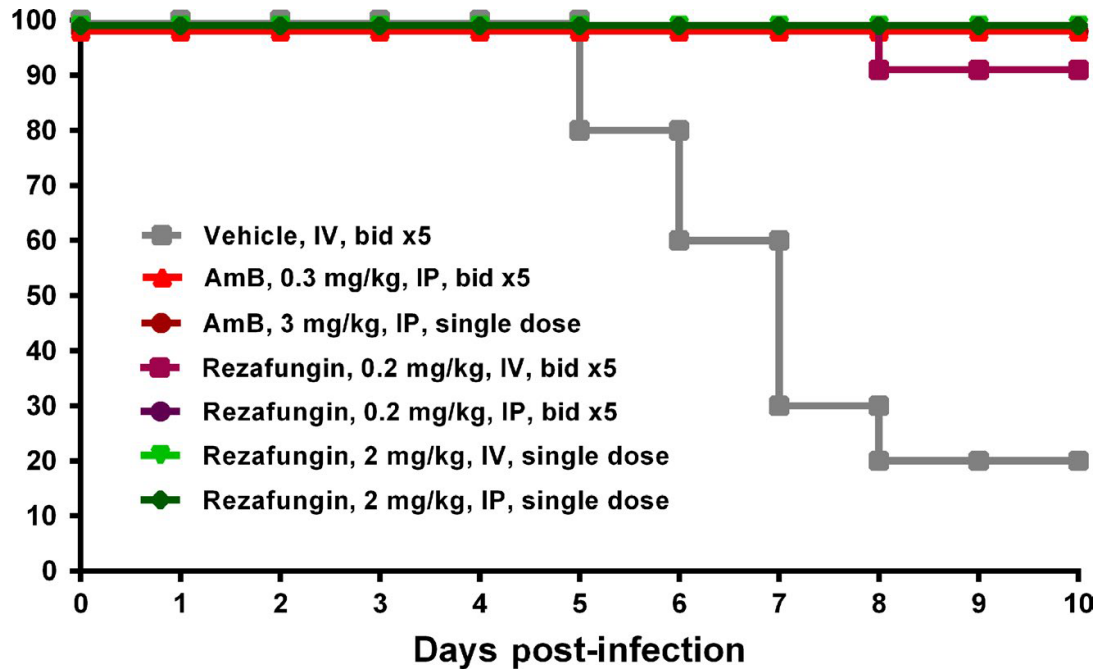
- CMI *C. auris fks1 CMI moins élevées Reza vs autres echino*

Marie Helleberg, AAC 2020

ORIGINAL ARTICLE

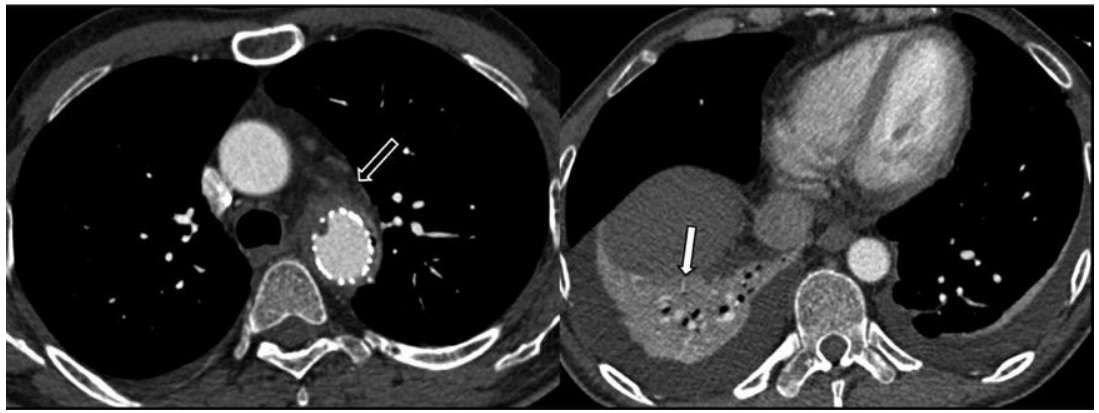
Rezafungin treatment in mouse models of invasive candidiasis and aspergillosis: Insights on the PK/PD pharmacometrics of rezafungin efficacy

Lynn Miesel[1] | Kun-Yuan Lin[1] | Voon Ong[2]



Modèle murin d’infection à Aspergillus

- *We report on the successful ongoing*
- *compassionate use of rezafungin obtained through expanded*
- *access for over 1 year in a patient with a multidrug-resistant*
- *Candida glabrata mediastinal infection from a vascular graft infection*
- *and retained foreign material*



Clinical Infectious Diseases
MAJOR ARTICLE

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 III,[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] and Peter G. Pappas[12]; The STRIVE Trial Investigators

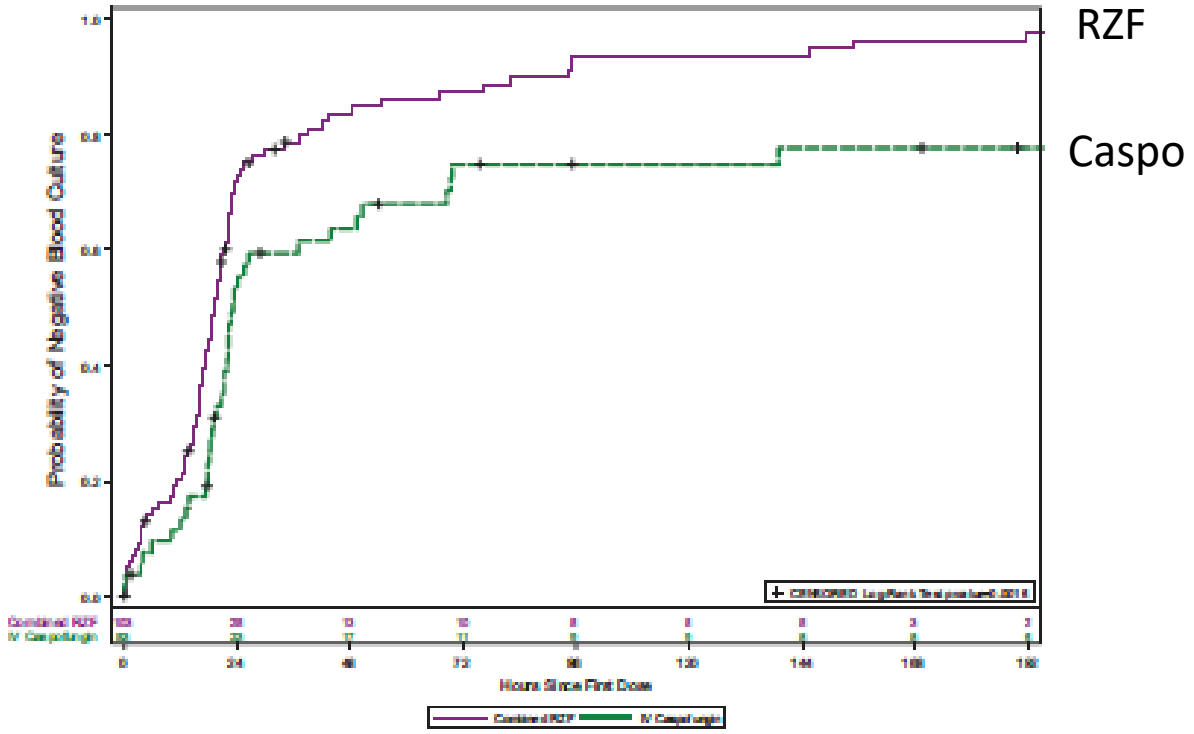
- Rezafungin: demi vie 133h
- Essai de phase 2 randomisé
- Candidémie et candidoses invasives
- RZF 400mg/sem S1 puis 200mg/sem vs 400mg/sem vs Caspo 70mg puis 50mg puis fluco
- Guerison à S2, mortalité à J30
- 207 patients
- Guerison 60%

Table 3. Primary Efficacy Endpoint: Overall Response at Day 14 (Microbiological Intent-to-Treat [mITT] Population)—Part A, Part B, and Combined

Overall Response, n (%)	Rezafungin Once Weekly 400 mg	Rezafungin Once Weekly 400 mg/200 mg	Caspofungin Once Daily 70 mg/50 mg
	N = 76	N = 46	N = 61
Overall cure	46 (60.5)	35 (76.1)	41 (67.2)
95% CI*]	[48.6–71.6]	[61.2–87.4]	[54.0–78.7]
Failure/indeterminate	30 (39.5)	11 (23.9)	20 (32.8)
Failure	20 (26.3)	8 (17.4)	17 (27.9)
Indeterminate	10 (13.2)	3 (6.5)	3 (4.9)

Table 5. Secondary Efficacy Outcomes at Day 5 (Microbiological Intent-to-Treat [mITT] Population)—Parts A and B Combined

Endpoint at Day 5, n (%)	Rezafungin Once Weekly 400 mg N = 76	Rezafungin Once Weekly 400 mg/200 mg N = 46	Rezafungin Once Weekly Pooled N = 122	Caspofungin Once Daily 70 mg/50 mg N = 61
Overall cure	42 (55.3)	34 (73.9)	76 (62.3)	34 (55.7)
Mycological success	50 (65.8)	35 (76.1)	85 (69.7)	38 (62.3)



Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE)

- Multicentre, double-blind, double-dummy, randomised phase 3 trial
- Adults (≥18 years) with systemic signs and mycological confirmation of candidaemia or invasive candidiasis
- Rezafungin once a week (400 mg in week 1, followed by 200 mg weekly, for a total of two to four doses) or intravenous caspofungin (70 mg loading dose on day 1, followed by 50 mg daily) for no more than 4 weeks.
- The primary endpoints were global cure (consisting of clinical cure, radiological cure, and mycological eradication) at day 14
- 2018-2021, 199 patients randomized
- Seven (13%) of 56 patients in the rezafungin group and 14 (28%) of 51 patients in the caspofungin group with candidaemia and a catheter present at screening had catheter removal within 48 h of diagnosis.

	Rezafungin group (n=100)	Caspofungin group (n=99)
Age	59·5 (15·8)	62·0 (14·6)
<65 years	60 (60%)	58 (59%)
≥65 years	40 (40%)	41 (41%)
Sex		
Male	67 (67%)	56 (57%)
Female	33 (33%)	43 (43%)
Race		
Asian	27 (27%)	31 (31%)
Black or African American	5 (5%)	4 (4%)
White	61 (61%)	60 (61%)
Other or not reported	7 (7%)	4 (4%)
Diagnosis		
Candidaemia only	70 (70%)	68 (69%)
Invasive candidiasis*	30 (30%)	31 (31%)
Mean modified APACHE II score†	12·5 (8·0)	13·1 (7·1)
≥20	15 (15%)	18 (18%)
<20	84 (84%)	81 (83%)
Body-mass index mean, kg/m²	25·4 (7·0)	24·5 (6·5)
Absolute neutrophil count, <500 cells per µL†	9 (9%)	6 (6%)

Data are n (%) or mean (SD). APACHE=Acute Physiology and Chronic Health Evaluation. *Includes patients who progressed from candidaemia to invasive candidiasis based on radiological or tissue or fluid culture assessment up to day 14. †Reported for patients with data available.

Table 1: **Demographics and baseline characteristics in the intention-to-treat population**

Thompson, Lancet, 2023

	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)
All-cause mortality at day 30 (US FDA primary outcome)			
Died	22 (24%)	20 (21%)	2·4 (−9·7 to 14·4)*
Known to have died	19 (20%)	17 (18%)	..
Unknown survival	3 (3%)	3 (3%)	..
All-cause mortality at day 30 by diagnosis			
Candidaemia only	18/64 (28%)	17/67 (25%)	2·8 (−12·5 to 18·0)*
Invasive candidiasis	4/29 (14%)	3/27 (11%)	2·7 (−16·7 to 21·7)*
Global response at day 14 as assessed by DRC (EMA primary outcome)			
Cure	55 (59%)	57 (61%)	−1·1 (−14·9 to 12·7)†
Failure	28 (30%)	29 (31%)	..
Indeterminate	10 (11%)	8 (9%)	..
Global response at day 14 as assessed by DRC by diagnosis			
Candidaemia only			
Cure	39/64 (61%)	43/67 (64%)	−3·2 (−19·6 to 13·3)*
Failure	21/64 (33%)	19/67 (28%)	..
Indeterminate	4/64 (6%)	5/67 (7%	..
Invasive candidiasis			
Cure	16/29 (55%)	14/27 (52%)	3·3 (−22·4 to 28·6)*
Failure	7/29 (24%)	10/27 (37%)	..
Indeterminate	6/29 (21%)	3/27 (11%)	..

Data are n (%) or n/N (%). ANC=absolute neutrophil count. APACHE II=Acute Physiology and Chronic Health Evaluation II score. DRC=data review committee. EMA=European Medical Agency. FDA=Food and Drug Administration. *Two-sided 95% CI for the observed difference (%), rezafungin group minus caspofungin group. †Two-sided 95% CI for the weighted difference (%), rezafungin group minus caspofungin group adjusted for the two randomisation strata of diagnosis (candidaemia *vs* invasive candidiasis) and high risk (APACHE II score ≥20 or ANC <500 cells per μL) versus low risk (APACHE II score <20 and ANC ≥500 cells per μL).

Table 2: **All-cause mortality at day 30 and global response at day 14 in the modified intention-to-treat population**

	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)*
Patients with negative blood culture†			
24 h	36/67 (54%)	30/65 (46%)	..
48 h	49/66 (74%)	41/64 (64%)	..
Outcomes at the day 5 visit			
Global cure as assessed by DRC	52 (56%)	49 (52%)	3·8 (−10·5 to 17·9)
Mycological eradication‡	64 (69%)	58 (62%)	7·1 (−6·6 to 20·6)
Patients with candidaemia only	50/64 (78%)	46/67 (69%)	9·5 (−5·8 to 24·4)
Investigator assessment of clinical cure	59 (63%)	70 (74%)	−11·0 (−24·0 to 2·3)
Outcomes at the day 14 visit			
Global cure as assessed by DRC§	55 (59%)	57 (61%)	−1·1 (−14·9 to 12·7)¶
Mycological eradication	63 (68%)	62 (66%)	1·8 (−11·7 to 15·2)
Patients with candidaemia only	46/64 (72%)	47/67 (70%)	1·7 (−13·9 to 17·2)
Investigator assessment of	62 (67%)	63 (67%)	−0·4 (−13·8 to 13·1)

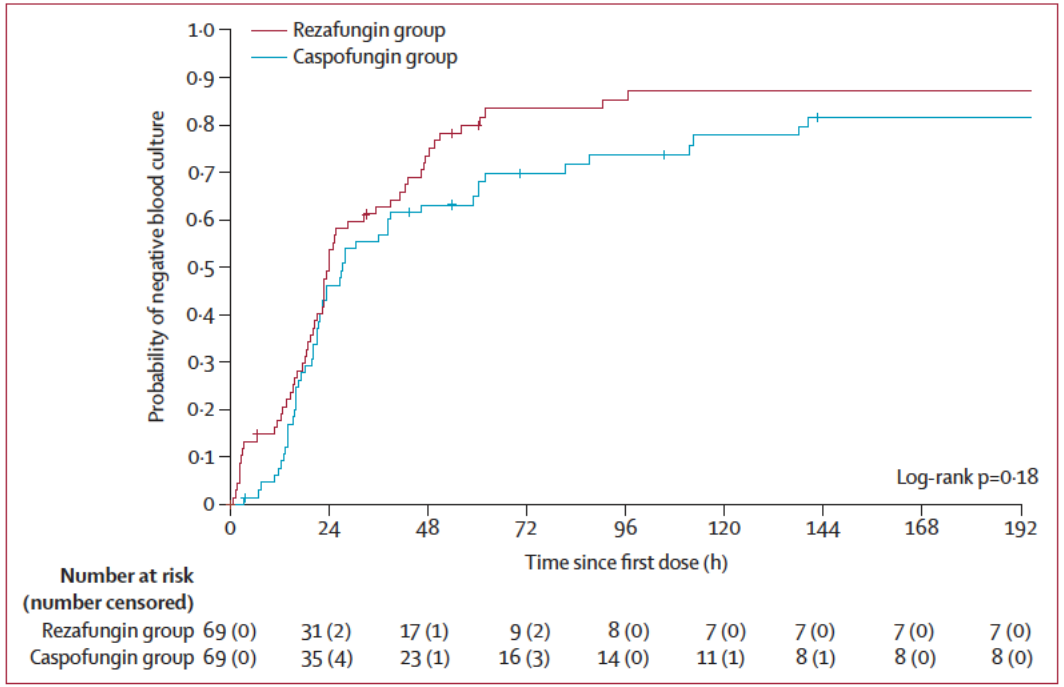
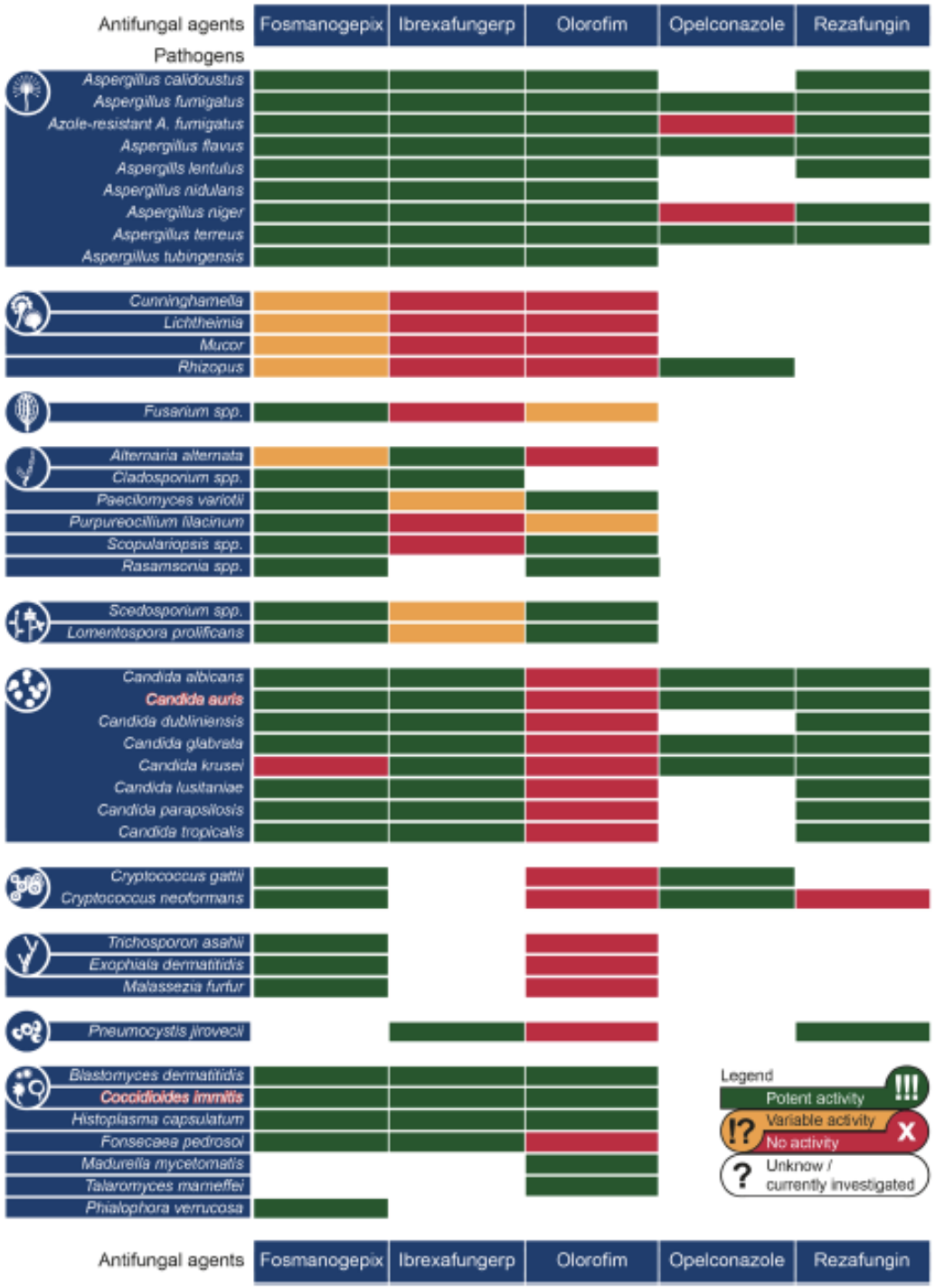


Figure 2: **Time to negative blood culture after treatment with rezafungin versus caspofungin in the modified intention-to-treat population**

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

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	462 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Prevention
Official Title:	A Phase 3, Multicenter, Randomized, Double-Blind Study of the Efficacy and Safety of Rezafungin for Injection Versus the Standard Antimicrobial Regimen to Prevent Invasive Fungal Diseases in Adults Undergoing Allogeneic Blood and Marrow Transplantation (The ReSPECT Study)
Actual Study Start Date :	May 11, 2020
Estimated Primary Completion Date :	August 2024
Estimated Study Completion Date :	August 2024

Reza 400/200 vs fluco et TMP/SMX



Spectre opelconazole

Opelconazole

- *Triazole inhalé*
- *inhalation via commonly available nebulizers*
- *high local concentrations, prolonged lung retention, slow absorption form the lung, and as a consequence, low plasma concentrations*

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

Thomas Colley,[a] Alexandre Alanio,[b,c,d] Steven L. Kelly,[e] Gurpreet Sehra,[a] Yasuo Kizawa,[f] Andrew G. S. Warrilow,[e] Josie E. Parker,[e] Diane E. Kelly,[e] Genki Kimura,[f] Lauren Anderson-Dring,[a] Takahiro Nakaoki,[f] Mihiro Sunose,[g] Stuart Onions,[g] Damien Crepin,[g] Franz Lagasse,[g] Matthew Crittall,[g] Jonathan Shannon,[g] Michael Cooke,[g] Stéphane Bretagne,[b,c,d] John King-Underwood,[h] John Murray,[a] Kazuhiro Ito,[a] Pete Strong,[a] Garth Rapeport[a]

gal effects of PC945 and posaconazole on other fungal species

	No. of strains tested	Culture method	MIC (μg/ml)[a]		
			PC945	Voriconazole	Posaconazole
arius (ATCC 8740)	1	CLSI	4	0.5	0.063
ATCC 204304)	1	CLSI	>8	2	0.13
Aspergillus flavus (AFL8, NRRC3357)	2	EUCAST	6	0.63	0.16
Aspergillus niger (ATCC 1015)	1	EUCAST	>8	1	0.20
Aspergillus terreus (AT49, AT7130)	2	EUCAST	0.078	1	0.093
Penicillium chrysogenum (ATCC 9480)	1	CLSI	>8	2	0.13
Penicillium citrinum (ATCC 9849)	1	CLSI	>8	>8	0.5
Trichophyton rubrum (ATCC 10218)	1	CLSI	0.031	0.063	0.031
Aureobasidium pullulans (ATCC 9348)	1	CLSI	>8	>8	1
Cladosporium argillaceum (ATCC 38013)	1	CLSI	>8	0.5	0.25
Candida albicans[b] (20240.047, ATCC 10231)	2	CLSI	0.081	0.14	0.081
AR *Candida albicans*[b,c] (20183.073, 20186.025)	2	CLSI	8.25	10	8.13
Candida glabrata[b] (ATCC 36583, R363)	2	CLSI	0.5	8.13	0.5
Candida krusei (ATCC 6258)	1	CLSI	0.125	0.25	0.125
Chaetomium globosum (ATCC 44699)	1	CLSI	>8	1	0.25
Gibberella zeae (*Fusarium graminearum*) (ATCC 16106)	1	CLSI	>8	>8	>8
Cryptococcus gattii (clinical isolate)	1	EUCAST	0.25	0.125	0.5
Cryptococcus neoformans (ATCC 24067)	1	CLSI	0.008	0.016	0.016
Lichtheimia corymbifera (ATCC 7909)	1	CLSI	>8	>8	>8
Mucor circinelloides (ATCC 8542)	1	CLSI	>8	>8	>8
Rhizomucor pusillus (ATCC 16458)	1	CLSI	>8	>8	>8
			2	>8	>8

TABLE 3 Antifungal effects of PC945 and known antifungal agents in azole-susceptible and azole-resistant strains of *A. fumigatus*[a]

		IC_{50} (IC_{90}) (μg/ml) of indicated agent					
Strain	Resistance mechanism	PC945	Voriconazole	Posaconazole	Itraconazole	Amphotericin B	Caspofungin
NCPF2010	None	0.0084 (0.010)	0.16 (0.20)	0.0086 (0.014)	0.057 (0.085)	0.23 (0.48)	0.11 (>1)
AF294	None	0.0020 (0.0043)	0.082 (0.27)	0.0056 (0.011)	0.041 (0.052)	0.21 (0.79)	>1 (>1)
AF293	None	0.0012 (0.0041)	0.25 (0.74)	0.010 (0.028)	0.032 (0.23)	0.24 (0.85)	>1 (>1)
AF72	G54E mutation	0.0061 (0.029)	0.019 (0.062)	0.032 (0.19)	0.43 (>1)	0.18 (0.64)	0.10 (>1)
AF91	M220V mutation	0.0081 (0.059)	0.12 (0.38)	0.024 (0.12)	0.26 (>1)	0.42 (>1)	0.072 (>1)
TR34/L98H	TR34/L98H mutation	0.034 (>1)	>1 (>1)	0.086 (0.13)	0.22 (>1)	0.14 (0.29)	0.082 (>1)

[a]IC_{50} and IC_{90} values were determined from optical density measurements.

AAC, 2017

- *Among temporarily neutropenic immunocompromised mice infected with A. fumigatus intranasally,*
  - *50% of the animals survived until day 7 when treated intranasally with*
- *PC945 at 0.56 g/mouse, while posaconazole showed similar effects (44%) at 14 g/mouse.*

AAC, 2017

The Effect of PC945 on Aspergillus or Candida Lung Infections in Patients With Asthma or Chronic Respiratory Diseases

Study Type :	Interventional (Clinical Trial)
Actual Enrollment :	13 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Masking Description:	This is a double-blind study.
Primary Purpose:	Treatment
Official Title:	A Double-blind, Placebo-controlled Study to Assess the Effects of Inhaled PC945 in the Treatment of Culture-positive Aspergillus or Candida Fungal Bronchitis in Subjects With Moderate to Severe Asthma or Other Chronic Respiratory Diseases.
Actual Study Start Date :	November 15, 2018
Actual Primary Completion Date :	June 1, 2020
Actual Study Completion Date :	June 1, 2020

PC945 Prophylaxis or Pre-emptive Therapy Against Pulmonary Aspergillosis in Lung Transplant Recipients

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	100 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Open-label, randomized, active-controlled, parallel-group multi-center study
Masking:	Single (Outcomes Assessor)
Masking Description:	The study will be an open-label study. For the purposes of the exploratory efficacy assessments, however, the Data Review Committee determining the presence of pulmonary fungal disease will be blinded as to treatment assignment. The Sponsor will limit knowledge of treatment assignment to as few sponsor personnel as possible to reduce bias.
Primary Purpose:	Prevention
Official Title:	A Randomized Controlled Open-label Study to Assess the Safety and Tolerability of Nebulized PC945 for Prophylaxis or Pre-emptive Therapy Against Pulmonary Aspergillosis in Lung Transplant Recipients
Actual Study Start Date :	November 19, 2021
Estimated Primary Completion Date :	November 2023
Estimated Study Completion Date :	November 2023

Safety and Efficacy of PC945 in Combination With Other Antifungal Therapy for the Treatment of Refractory Invasive Pulmonary Aspergillosis

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	123 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Masking Description:	Double Blind
Primary Purpose:	Treatment
Official Title:	A Double-blind, Randomized, Placebo-controlled Study to Assess the Safety and Efficacy of Nebulized PC945 When Added to Systemic Antifungal Therapy for the Treatment of Refractory Invasive Pulmonary Aspergillosis
Actual Study Start Date :	June 14, 2022
Estimated Primary Completion Date :	October 31, 2023
Estimated Study Completion Date :	November 30, 2023

Des innovations

- Olorofim: Nouvelle classe+++
  - disponibilité orale, efficace sur des espèces sans autre ressources thérapeutiques ou molécules toxique ou IV
- Ibrexafungerp: potentiel intérêt dans les candidoses invasives et superficielles
- Rezafungin: 1 injection par semaine. Intérêt pour les traitements prolongés
- Opelconazole: ineteret dans la propylaxie? Traitement? Différentes formes d’aspergillose pulmonaire