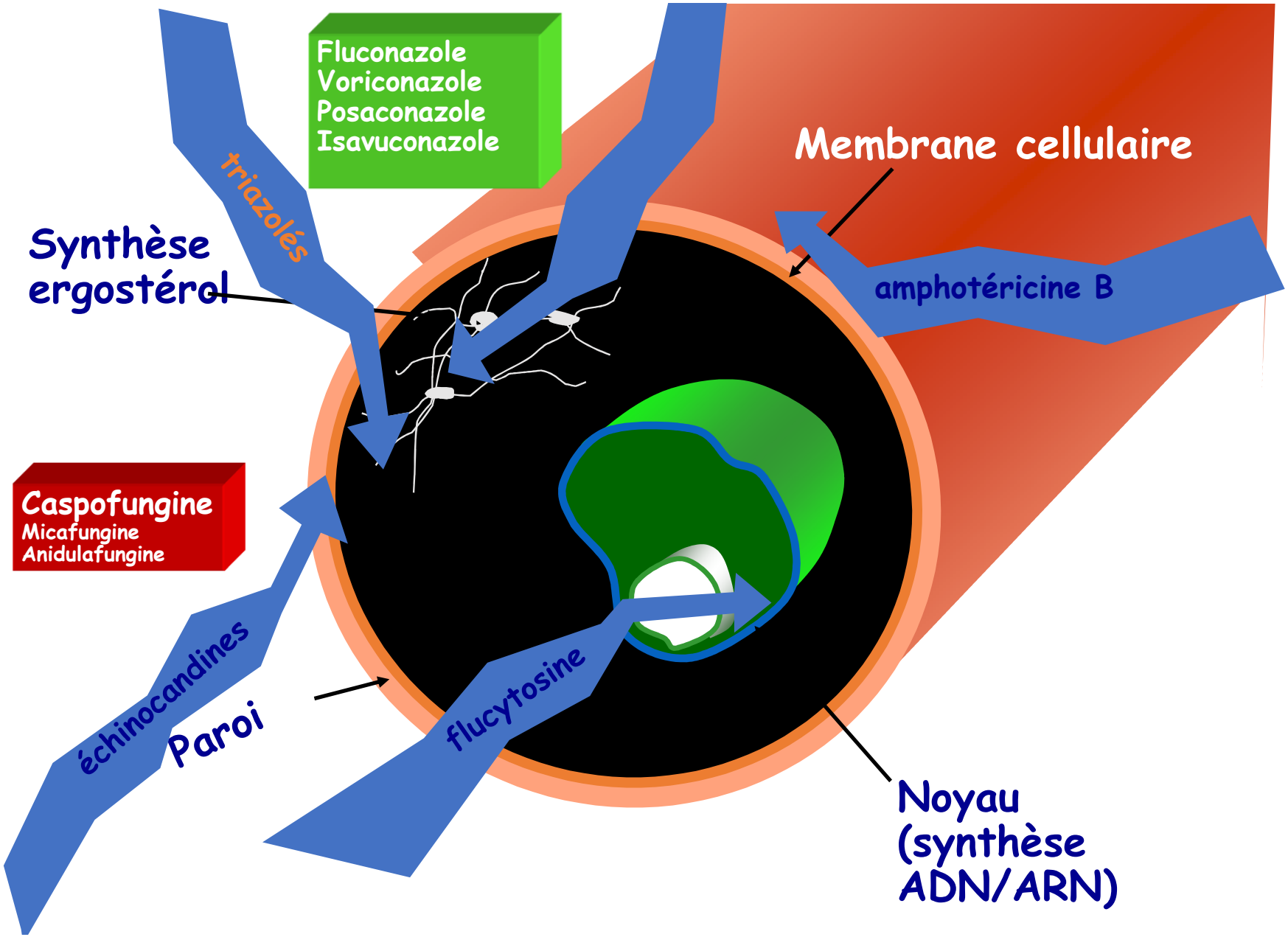
Traitements antifongiques: nouveautés

Fanny Lanternier
Service de maladies infectieuses
Hôpital Necker, Paris
Université Paris Cité

CNR Mycoses invasives et Antifongiques
Institut Pasteur


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

Spectre des différentes molécules

Table 2. Relative *in vitro* and clinical activity of antifungal agents for more common and important invasive fungal pathogens[a]

	Polyenes	Triazoles				Echinocandins		
	Amphotericin B formulations	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Caspofungin	Micafungin	Anidulafungin
Candida spp.								
C. albicans	++	++	++	++	++	++	++	++
C. glabrata	++	+/–	N	+	+	++	++	++
C. tropicalis	++	++	++	++	++	++	++	++
C. parapsilosis	++	++	++	++	++	+	+	+
C. krusei	+	-	+/–	+	+	++	++	++
Cryptococcus neoformans	++	+	+	++	++	–	–	–
Trichosporon spp.	–	++	N	N	N	–	–	–
Aspergillus spp.								
A. fumigatus	++	–	++	++	++	+	+	N
A. flavus	++	–	++	++	++	+	+	N
A. terreus	–	–	++	++	++	+	+	N
A. niger	++	–	++	++	++	+	+	N
A. nidulans	–	–	++	++	++	+	+	N
Scedosporium prolificans	–	–	N	N	N	–	–	–
Scedosporium apiospermum	–	–	+/–	+	N	–	–	–
Fusarium spp.	+	–	-	+	+	–	–	–
Mucorales	+	–	+/–	–	+	–	–	–

Relative activity is indicated as follows: –, no activity; +/–, slight activity; +, modest activity; ++, good activity; N = no data.

[a]Most fungi causing cutaneous and allergic disease have been excluded.

Denning, Trends in Microbiology 2010

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

Isavuconazole et aspergillose invasive

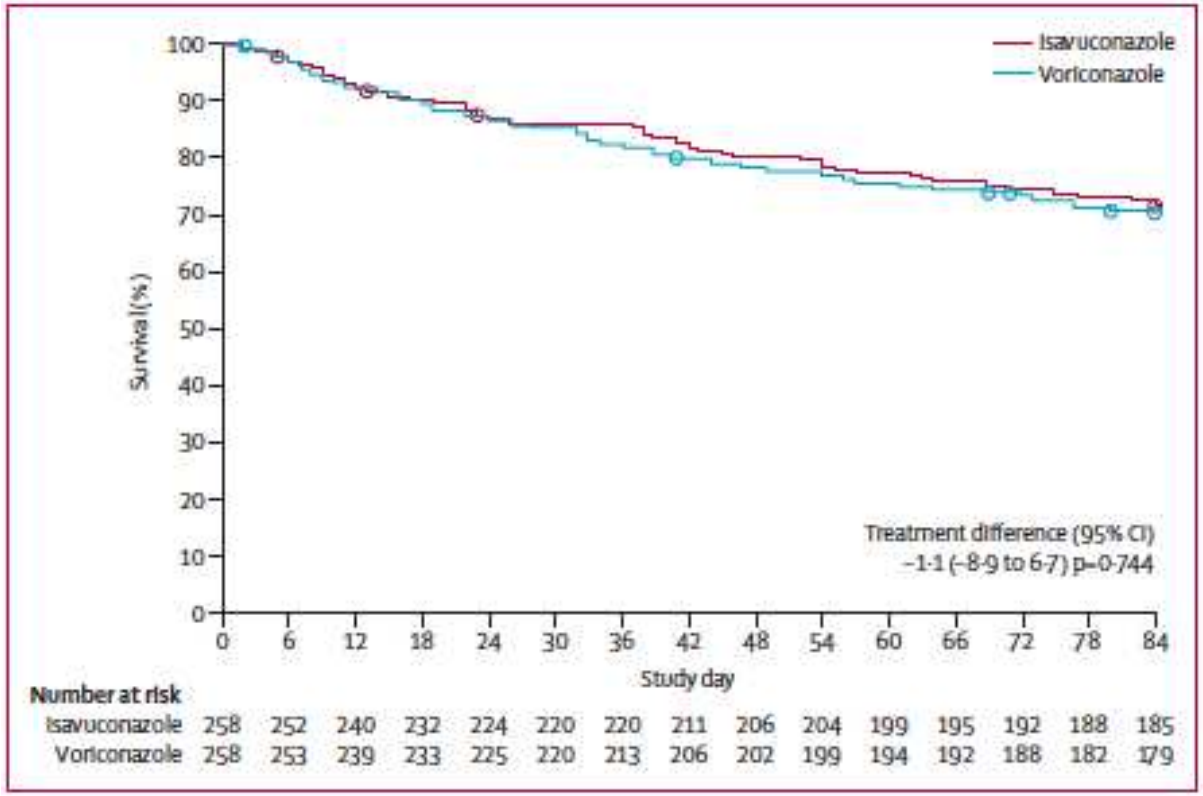


Figure 2: **Survival from first dose of study drug to day 84**
Patients were censored on the day of their last known survival status, represented by the circles. Figure shows data for ITT population. ITT=intention to treat; all randomised patients who received study drug.

Maertens J, Lancet 2016

Isavuconazole: tolérance

	Isavuconazole (n=257)	Voriconazole (n=259)	p value
Overall	247 (96%)	255 (98%)	0·122
Gastrointestinal disorders	174 (68%)	180 (69%)	0·705
Infections and infestations	152 (59%)	158 (61%)	0·719
General disorders and administrative site conditions	148 (58%)	144 (56%)	0·658
Respiratory, thoracic, and mediastinal disorders	143 (56%)	147 (57%)	0·859
Metabolism and nutrition disorders	108 (42%)	121 (47%)	0·289
Nervous system disorders	95 (37%)	89 (34%)	0·582
Skin and subcutaneous tissue disorders*	86 (33%)	110 (42%)	0·037¶
Investigations (abnormal laboratory tests)	85 (33%)	96 (37%)	0·357
Blood and lymphatic system disorders	77 (30%)	82 (32%)	0·703
Psychiatric disorders†	70 (27%)	86 (33%)	0·151
Musculoskeletal and connective tissue disorders	69 (27%)	77 (30%)	0·495
Vascular disorders	67 (26%)	77 (30%)	0·378
Renal and urinary disorders	55 (21%)	58 (22%)	0·832
Cardiac disorders	43 (17%)	57 (22%)	0·148
Eye disorders‡	39 (15%)	69 (27%)	0·002¶
Injury, poisoning, and procedural complications	33 (13%)	39 (15%)	0·526
Hepatobiliary disorders§	23 (9%)	42 (16%)	0·016¶
Immune system disorders	20 (8%)	25 (10%)	0·533
Neoplasms benign, malignant and unspecified	19 (7%)	31 (12%)	0·101
Ear and labyrinth disorders	14 (5%)	13 (5%)	0·846
Reproductive system and breast disorders	8 (3%)	13 (5%)	0·373
Endocrine disorders	5 (2%)	3 (1%)	0·503
Congenital, familial, and genetic disorders	3 (1%)	2 (1%)	0·685
Social circumstances	0	1 (<1%)	>0·999

Maertens J, Lancet 2016

Isavuconazole in mucormycosis treatment: VITAL study

24/37 arrêts de traitement

Décès: 11 (30%)

Effets indésirables: 6 (16%)

Non compliance: 4 (11%)

Non réponse: 3

	Primary treatment group (N=21)	Refractory group (N=11)	Intolerant to other antifungals group (N=5)	Total (N=37)
DRC-assessed overall response at day 42				
Complete response	0	0	0	0
Partial response	3 (14%)	1 (9%)	0	4 (11%)
Stable disease	9 (43%)	4 (36%)	3 (60%)	16 (43%)
Progression of disease	1 (5%)	0	0	1 (3%)
Death	7 (33%)	4 (36%)	2 (40%)	13 (35%)
Missing data	1 (5%)	2 (18%)	0	3 (8%)
DRC-assessed overall response at day 84				
Complete response	1 (5%)	1 (9%)	0	2 (5%)
Partial response	1 (5%)	3 (27%)	1 (20%)	5 (14%)
Stable disease	9 (43%)	0	2 (40%)	11 (30%)
Progression of disease	0	1 (9%)	0	1 (3%)
Death	9 (43%)	4 (36%)	2 (40%)	15 (41%)
Missing	1 (5%)	2 (18%)	0	3 (8%)
DRC-assessed overall response at EOT†				
Complete response	3/19 (16%)	2 (18%)	0	5/35 (14%)
Partial response	3/19 (16%)	2 (18%)	1 (20%)	6/35 (17%)
Stable disease	6/19 (32%)	2 (18%)	2 (40%)	10/35 (29%)
Progression of disease	7/19 (37%)	5 (45%)	2 (40%)	14/35 (40%)
DRC-assessed success rate at EOT				
Clinical response	10/18 (56%)	2/9 (22%)	2/4 (50%)	14/31 (45%)
Mycological response	6/19 (32%)	4/11 (36%)	2/5 (40%)	12/35 (34%)
Radiological response	3/18 (17%)	2/10 (20%)	1/5 (20%)	6/33 (18%)
All-cause mortality through day 42‡	7 (33%)	5 (45%)	2 (40%)	14 (38%)
All-cause mortality through day 84‡	9 (43%)	5 (45%)	2 (40%)	16 (43%)

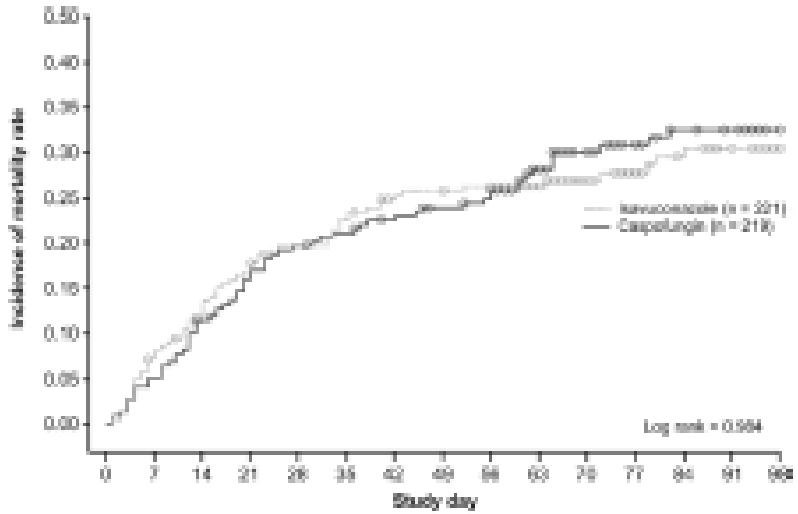
Marty, LID, 2016

Clinical Infectious Diseases
MAJOR ARTICLE

Isavuconazole Versus Caspofungin in the Treatment of Candidemia and Other Invasive *Candida* Infections: The ACTIVE Trial

Bart Jan Kullberg,[1] Claudio Viscoli,[2,3] Peter G. Pappas,[4] Jose Vazquez,[5] Luis Ostrosky-Zeichner,[6] Coleman Rotstein,[7] Jack D. Sobel,[8] Raoul Herbrecht,[9] Calla Rahav,[10] Sutep Jaruratanasirikul,[11] Ploenchan Chetchotisakd,[12] Eric Van Wijngaerden,[13] Jan De Waele,[14] Christopher Lademacher,[15] Marc Engelhardt,[16] Laura Kovanda,[16] Rodney Croos-Dabrera,[16] Christine Fredericks,[16] and George R. Thompson III[17]

- Etude de Phase iii
- Randomisée:
- Isavuconazole
- Caspofungine
- Relais PO à J10
- Succès en fin de traitement IV
- 400 patients m ITT 60% isavu vs 71% caspo
- **Pas de non infériorité**



Number of subjects at risk

Isavuconazole	221	204	191	180	172	168	167	155	153	113	94	84	77	73	68
Caspofungin	219	208	193	182	174	170	165	160	157	114	102	86	78	73	65

Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial

*Johan A Maertens, Galia Rahav, Dong-Gun Lee, Alfredo Ponce-de-León, Isabel Cristina Ramírez Sánchez, Nikolay Klimko, Anne Sonet, Shariq Haider, Juan Diego Vélez, Issam Raad, Liang-Piu Koh, Meinolf Karthaus, Jianying Zhou, Ronen Ben-Ami, Mary R Motyl, Seongah Han, Anjana Grandhi, Hetty Waskin, on behalf of the study investigators**

Summary

Background Voriconazole has been recommended as primary treatment for patients with invasive aspergillosis. *Lancet* 2021; 397: 499–509

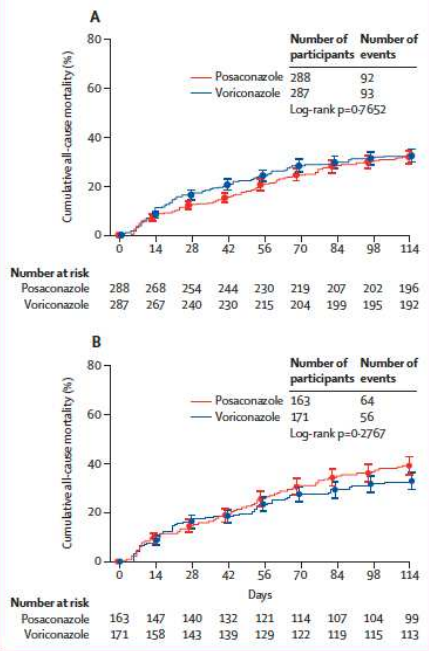
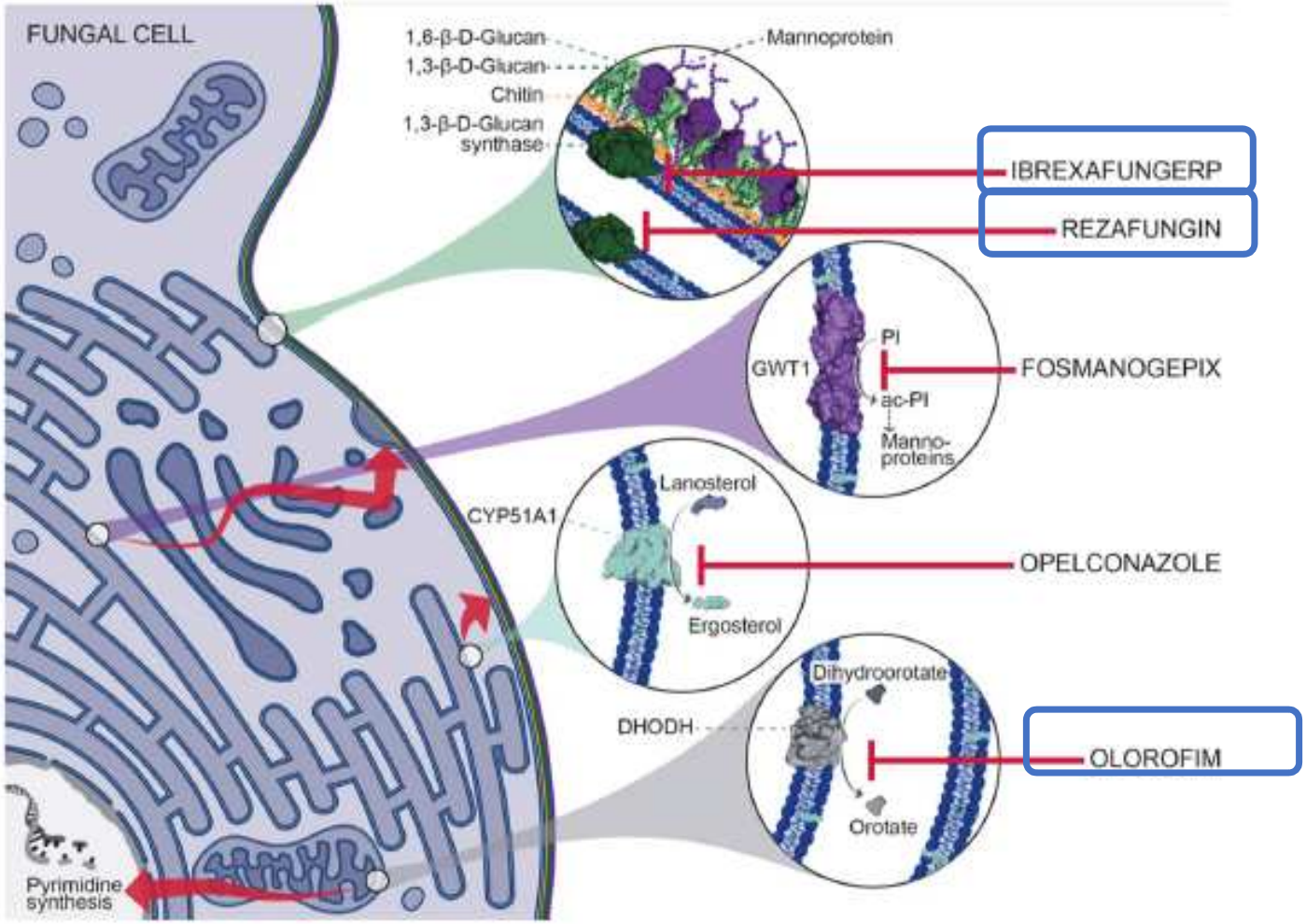


Figure 2: **Kaplan-Meier plot for cumulative all-cause mortality up to and including day 114**
(A) ITT population. (B) Full analysis set population (ITT with proven or probable invasive aspergillosis). The ITT population included all randomly assigned participants who received one or more dose of study drug. ITT=intention-to-treat.

	Posaconazole group (n=288)	Voriconazole group (n=287)	Treatment difference (95% CI)*
At least one treatment-related adverse event	86 (30%)	115 (40%)	−10·2% (−17·9 to −2·4)
Blood and lymphatic system disorders	2 (1%)	6 (2%)	−1·4% (−3·9 to 0·7)
Eye disorders	5 (2%)	28 (10%)	−8·0% (−12·2 to −4·5)
Dyschromatopsia	0	6 (2%)	−2·1% (−4·5 to −0·8)
Photopsia	2 (1%)	6 (2%)	−1·4% (−3·9 to 0·7)
Vision blurred	3 (1%)	10 (3%)	−2·4% (−5·4 to −0·0)
Visual impairment	0	6 (2%)	−2·1% (−4·5 to −0·8)
Gastrointestinal disorders	23 (8%)	25 (9%)	−0·7% (−5·4 to 3·9)
Abdominal pain	2 (1%)	4 (1%)	−0·7% (−2·9 to 1·3)
Diarrhoea	4 (1%)	2 (1%)	0·7% (−1·3 to 2·9)
Nausea	12 (4%)	11 (4%)	0·3% (−3·1 to 3·8)
Vomiting	9 (3%)	5 (2%)	1·4% (−1·3 to 4·3)
General disorders and administration site conditions	7 (2%)	8 (3%)	−0·4% (−3·3 to 2·5)
Hepatobiliary disorders	9 (3%)	10 (3%)	−0·4% (−3·6 to 2·8)
Hepatic function abnormal	5 (2%)	4 (1%)	0·3% (−2·0 to 2·8)
Investigations	43 (15%)	35 (12%)	2·7% (−2·9 to 8·4)
Alanine aminotransferase increased	22 (8%)	18 (6%)	1·4% (−2·9 to 5·7)
Aspartate aminotransferase increased	18 (6%)	16 (6%)	0·7% (−3·3 to 4·7)
Blood alkaline phosphatase increased	7 (2%)	16 (6%)	−3·1% (−6·7 to 0·1)
Blood bilirubin increased	8 (3%)	5 (2%)	1·0% (−1·6 to 3·9)
Blood lactate dehydrogenase increased	4 (1%)	3 (1%)	0·3% (−1·8 to 2·6)
γ-glutamyltransferase peptidase increased	5 (2%)	11 (4%)	−2·1% (−5·2 to 0·7)
Total bile acids increased	0	4 (1%)	−1·4% (−3·5 to −0·1)
Metabolism and nutrition disorders	18 (6%)	7 (2%)	3·8% (0·5 to 7·5)
Decreased appetite	4 (1%)	1 (<1%)	1·0% (−0·7 to 3·2)
Hypokalaemia	11 (4%)	1 (<1%)	3·5% (1·4 to 6·4)
Nervous system disorders	9 (3%)	14 (5%)	−1·8% (−5·3 to 1·6)
Psychiatric disorders	6 (2%)	22 (8%)	−5·6% (−9·5 to −2·2)
Hallucination	4 (1%)	12 (4%)	−2·8% (−5·9 to −0·1)
Hallucination, visual	1 (<1%)	5 (2%)	−1·4% (−3·7 to 0·4)
Renal and urinary disorders	4 (1%)	3 (1%)	0·3% (−1·8 to 2·6)
Respiratory to thoracic and mediastinal disorders	5 (2%)	3 (1%)	0·7% (−1·5 to 3·1)
Skin and subcutaneous tissue disorders	5 (2%)	12 (4%)	−2·4% (−5·6 to 0·4)

Nouvelles molécules

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



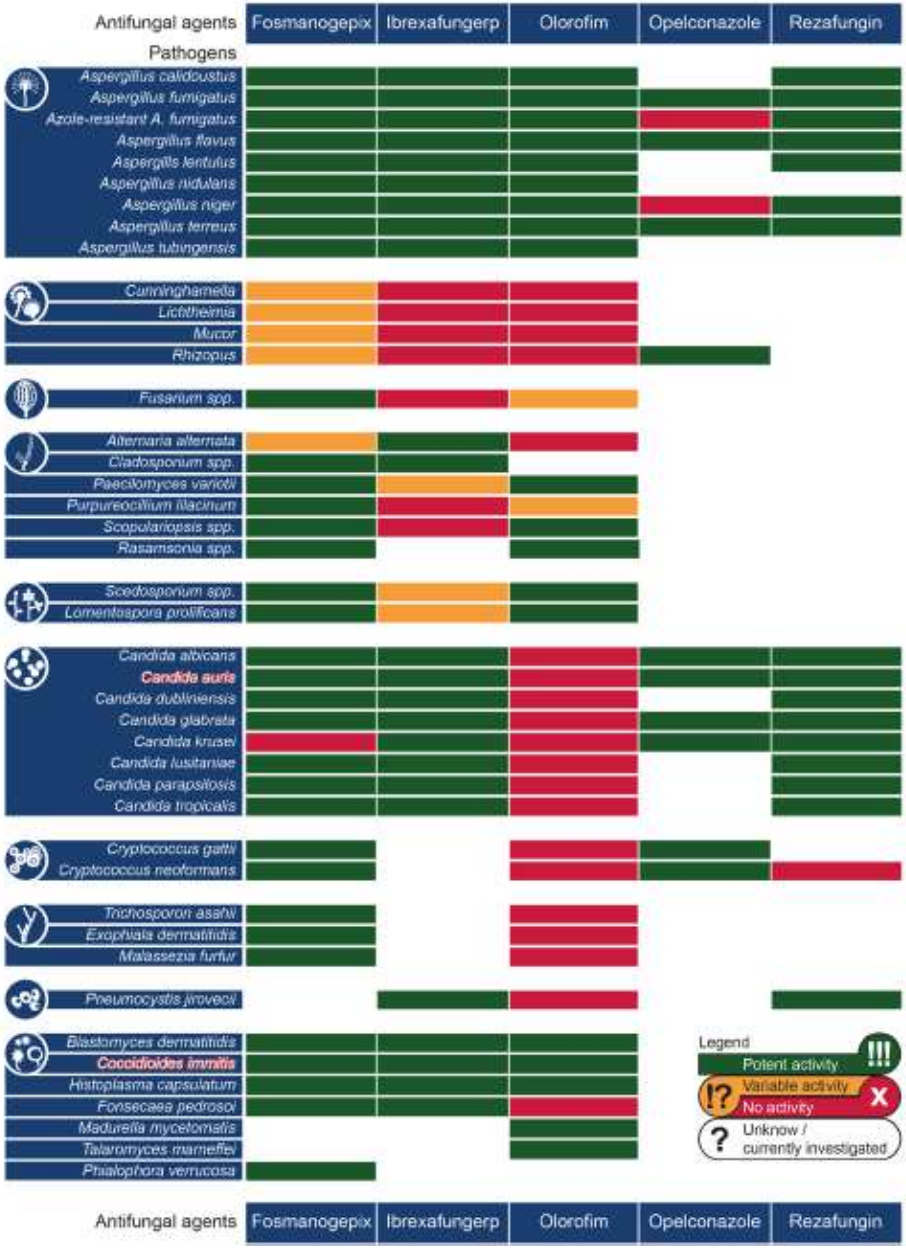
Hoenigl M, Drugs 2021

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

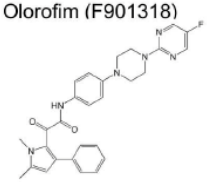

Antifungal agents
Fosmanogepix
Ibrexafungerp
Olorofim
Opelconazole
Rezafungin
Pathogens
Aspergillus calidoustus
Aspergillus fumigatus
Azole-resistant A. fumigatus
Aspergillus flavus
Aspergillus lentulus
Aspergillus nidulans
Aspergillus niger
Aspergillus terreus
Aspergillus tubingensis
Cunninghamella
Lichtheimia
Mucor
Rhizopus
Fusarium spp.
Alternaria alternata
Cladosporium spp.
Paecilomyces variotii
Purpureocillium lilacinum
Scopulariopsis spp.
Rasamsonia spp.
Scedosporium spp.
Lomentospora prolificans
Candida albicans
Candida auris
Candida dubliniensis
Candida glabrata
Candida krusei
Candida lusitaniae
Candida parapsilosis
Candida tropicalis
Cryptococcus gattii
Cryptococcus neoformans
Trichosporon asahii
Exophiala dermatitidis
Malassezia furfur
Pneumocystis jirovecii
Blastomyces dermatitidis
Coccidioides immitis
Histoplasma capsulatum
Fonsecaea pedrosoi
Madurella mycetomatis
Talaromyces marneffei
Phialophora verrucosa
Legend
Potent activity
Variable activity
No activity
Unknow / currently investigated
Antifungal agents
Fosmanogepix
Ibrexafungerp
Olorofim
Opelconazole
Rezafungin

F2G

Olorofim

- Orotomide
- Inhibiteur selectif DHODH (Dihydroorotate dehydrogenase) fongique
  - Enzyme impliquée synthèse pyrimidine
- Voie orale
- Interfère synthèse ADN, ARN, synthèse paroi

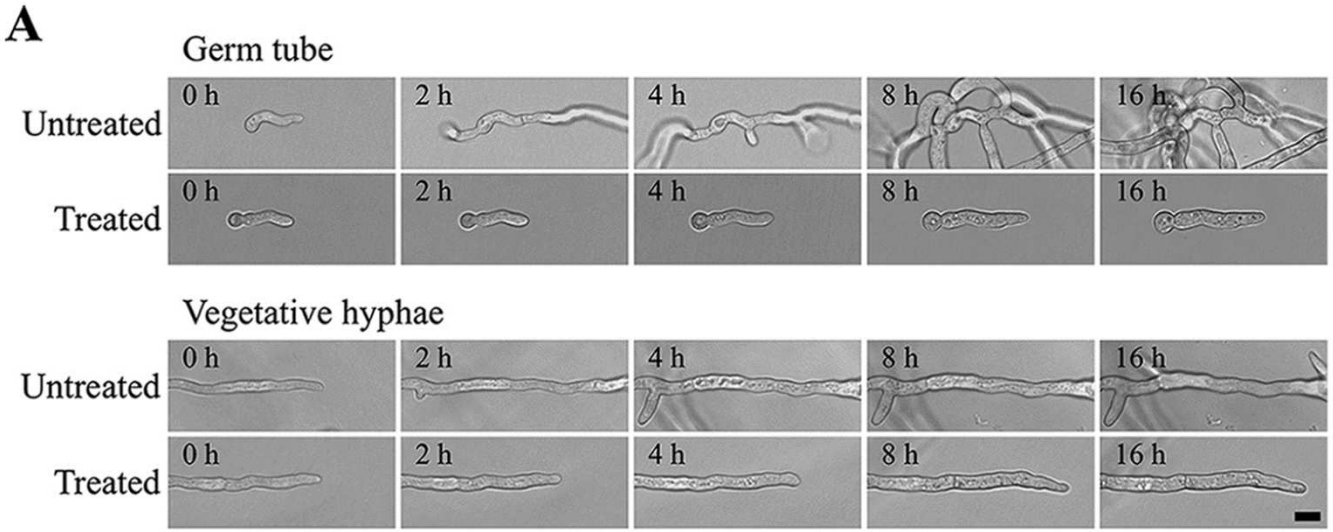
Olorofim (F901318)



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



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

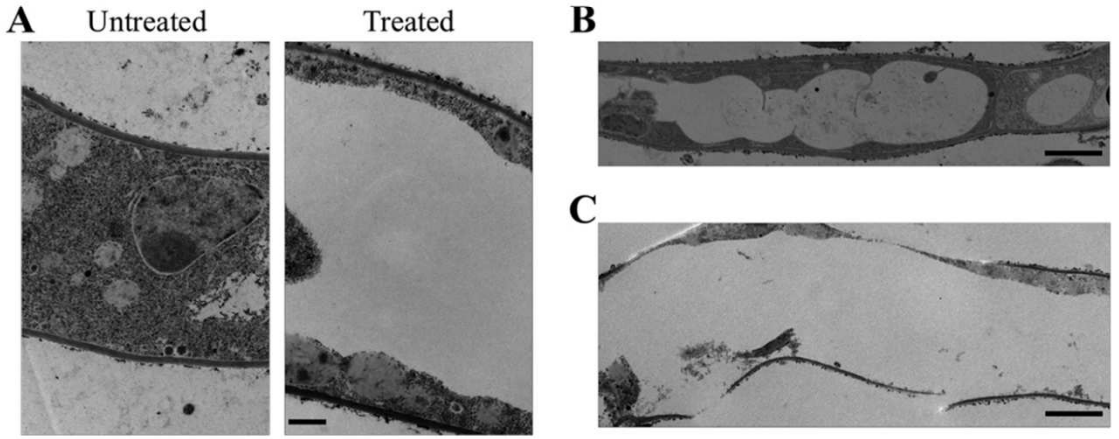


FIG 4 (A) TEM image of an untreated hypha and a hypha treated for 24 h with 0.1 μg/ml F901318. Images show the increased diameter of the treated hypha. Bar = 0.5 μm. (B) TEM image showing enlarged vacuoles in a hypha treated for 24 h with 0.1 μg/ml F901318. Bar = 2 μm. (C) TEM image showing ruptured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

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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,*]

[a] Institute of Medical Microbiology, University Hospital Essen, University of Duisburg-Essen, Hufelandstraße 55, 45147 Essen, Germany
[b] Institute for Clinical Hygiene, Medical Microbiology and Infectiology, Klinikum Nuernberg, Paracelsus Medical University, Prof.-Ernst-Nathan-Str. 1, 90419 Nuremberg, Germany

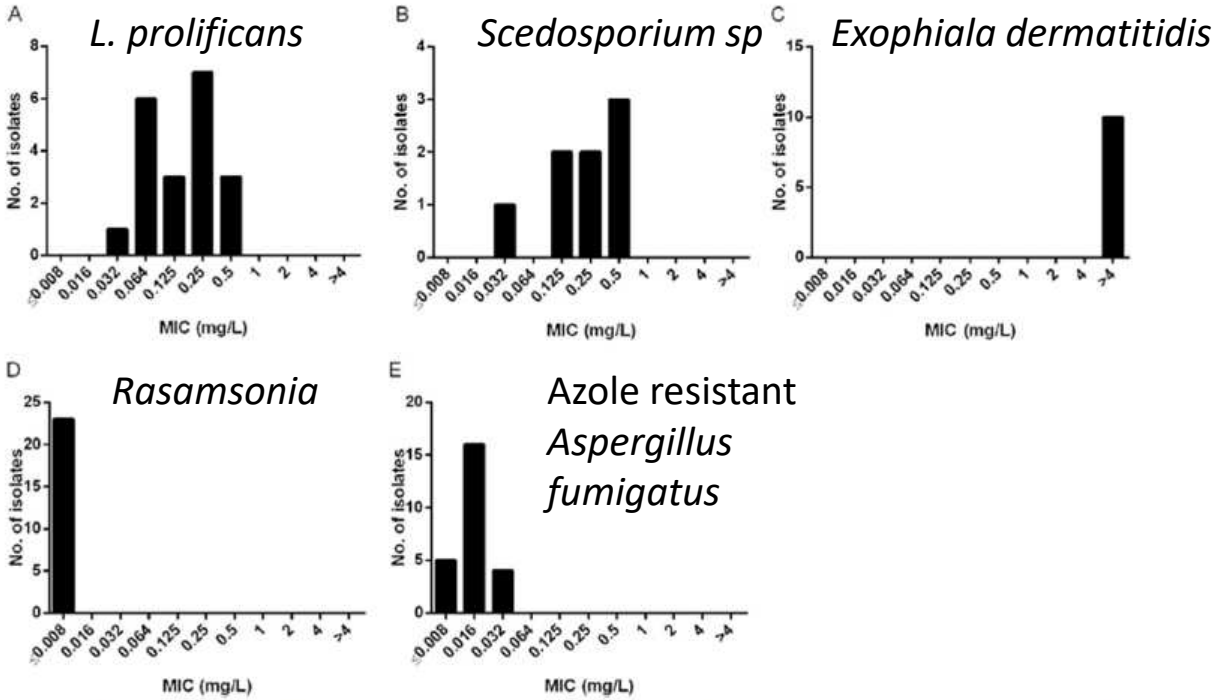

Fig. 1. Minimum inhibitory concentrations (MIC) for olorofim against (A) *Lomentospora prolificans* ($n = 20$), (B) *Scedosporium* spp. ($n = 8$), (C) *Exophiala dermatitidis* ($n = 10$), (D) *Rasamsonia argillacea* species complex ($n = 23$) and (E) azole-resistant *Aspergillus fumigatus* ($n = 25$).

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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]

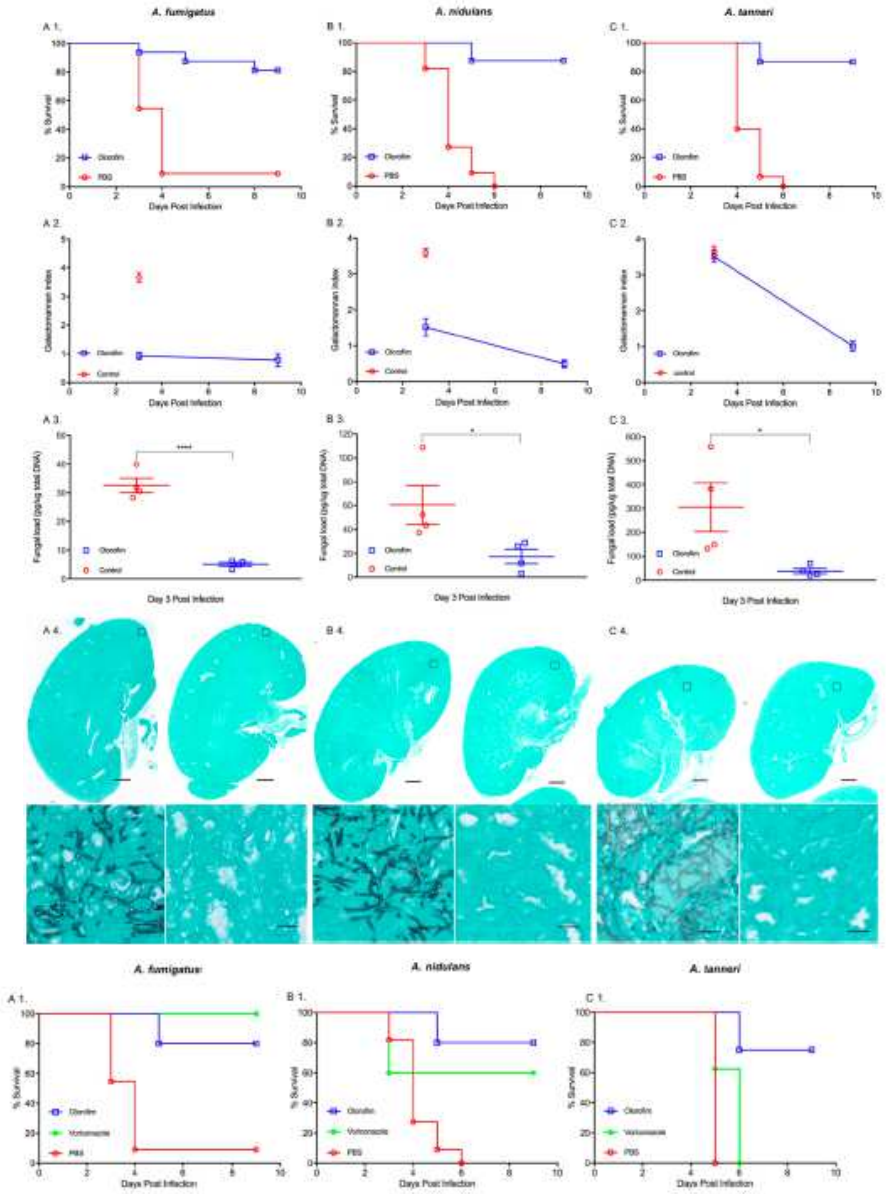
TABLE 1 MICs of six antifungals for *Aspergillus* species

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.



Nouvelles molécules: olorofim

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EXPERIMENTAL THERAPEUTICS

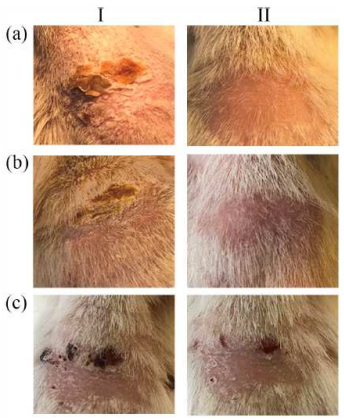
Olorofim Effectively Eradicates Dermatophytes *In Vitro* and *In Vivo*

Esmat Mirbzadeh Ardakani,[a,b] Atefeh Sharifirad,[a] Nasrin Pashootan,[c] Mahs 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

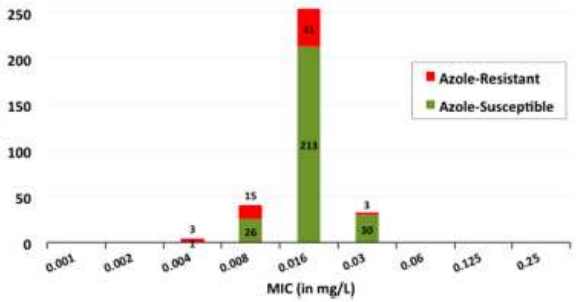
Research note

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[B,C]	19[A,C]	3[A,C]	3[A,C]	38	122
Posaconazole	—	—	—	—	0	14	168	84	16[C]	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[C]	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[C]	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[C]	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

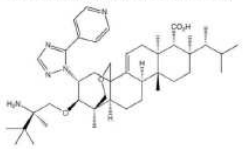
SCYNEXIS

Ibrexafungerp (formerly SCY-078)

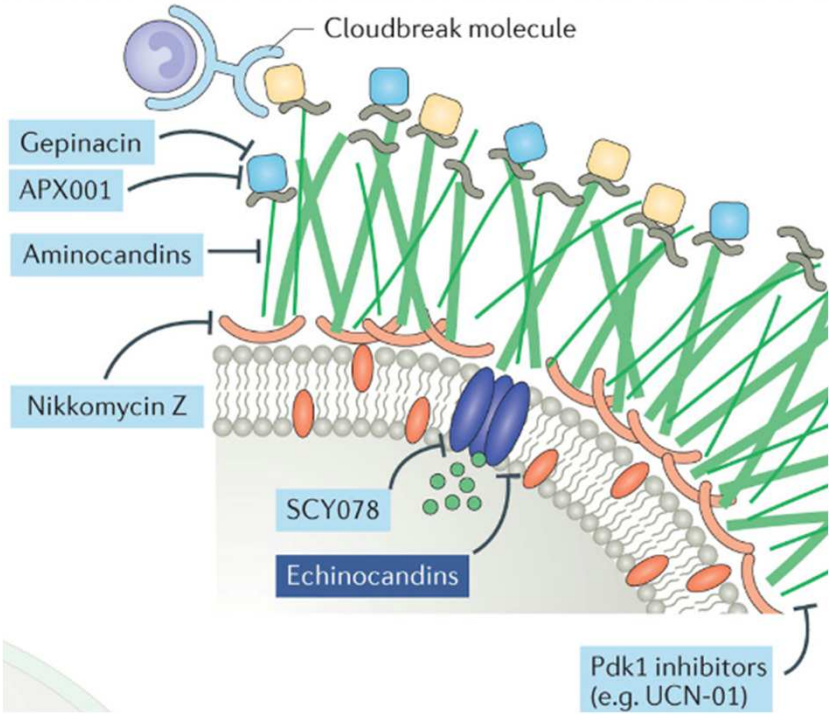
Nouvel inhibiteur de ß-1,3-glucan synthase
Triterpenoides - enfumafungine
Disponible IV et Oral
Fongicide sur *Candida*
1/2 vie longue (20h)
Distribution tissulaire importante

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.

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

Species and antifungal drug	MIC (μg/ml) Range[a]
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

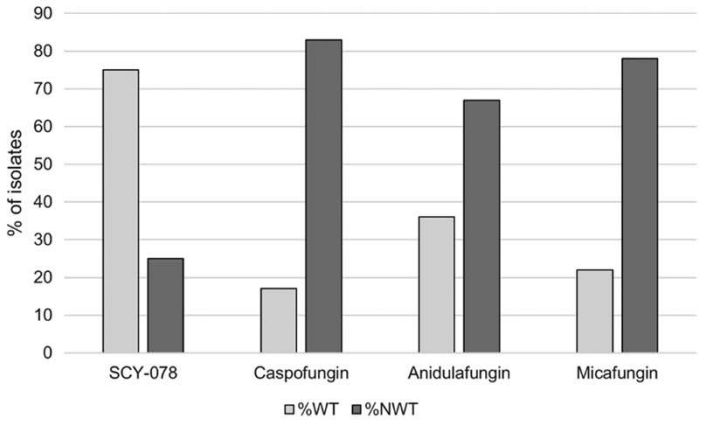


FIG 1 Activity of SCY-078, anidulafungin, caspofungin, and micafungin against strains displaying *FKS* mutations. %WT, percent wild type; %NWT, percent non-wild type (for SCY-078, %NWT is the percent exceeding the wild-type upper-limit value [WT-UL; two 2-fold dilutions higher than the modal MIC value 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) ≤0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	≥64	MIC range (mg/liter)	Modal MIC (mg/liter)	MIC_{50} (mg/liter)
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*

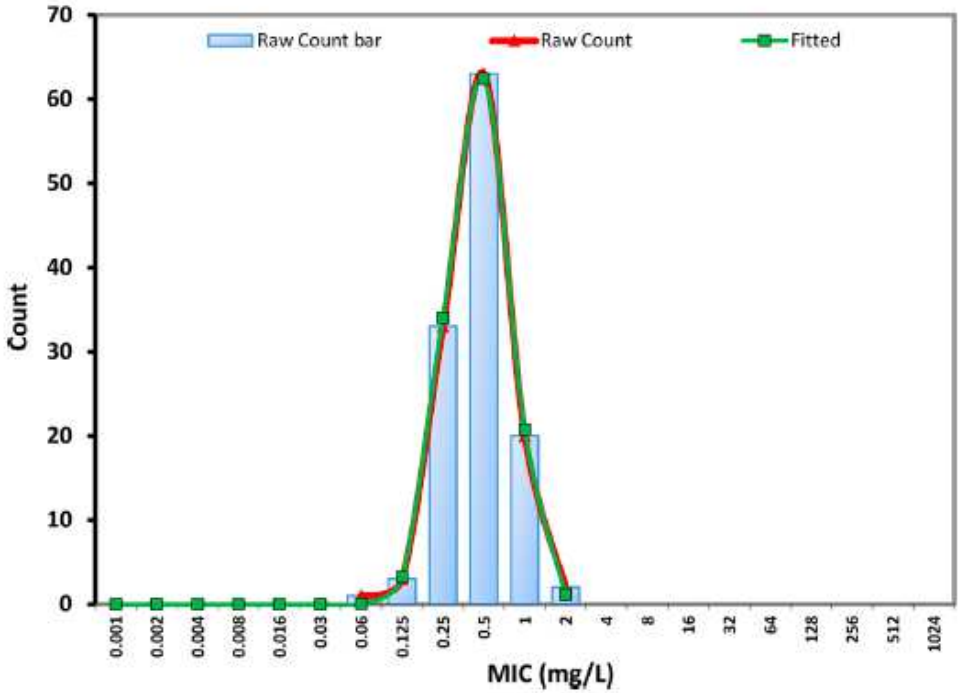


FIG 1 EUCAST MIC distribution for ibrexafungerp against 122 clinical *C. auris* isolates. Raw counts are presented as bars and a red curve, whereas the fitted curve was determined by the ECOFF finder program (v2.0) that iteratively fits each subset of the data from left to right.

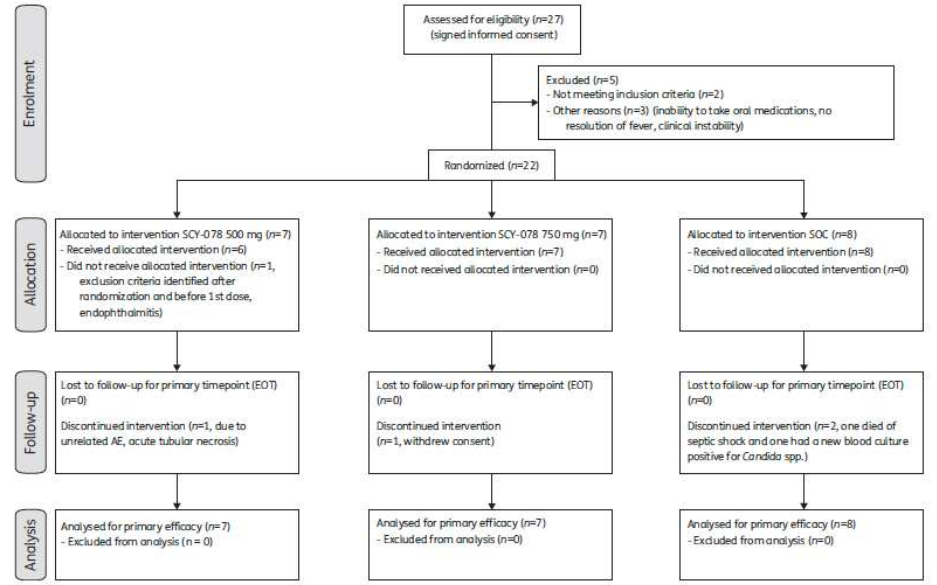
March 2020

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

- Meilleure exposition: 1500mg J1 puis 7
- 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

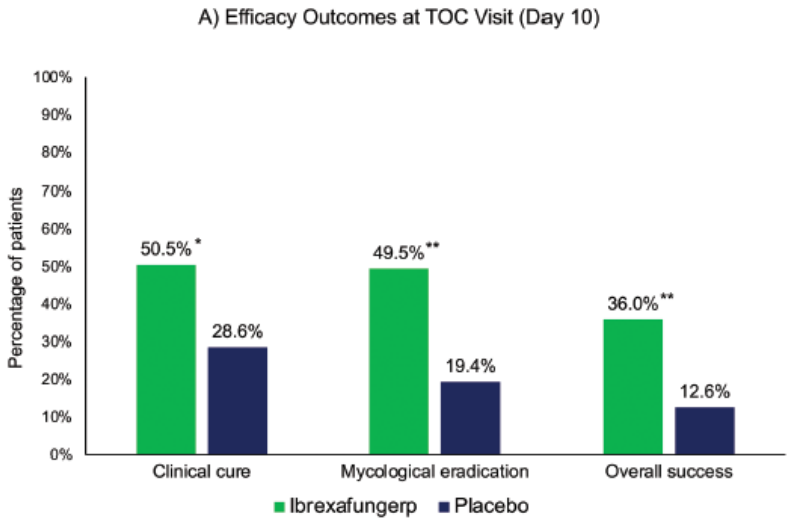
Clinical Infectious Diseases

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



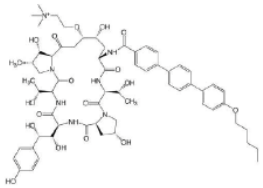
	Ibrexafungerp (n = 188)	Placebo (n = 98)
Age, y		
Mean ± SD	33.5 ± 10.36	36.0 ± 12.46
Median (min, max)	32.5 (18, 67)	34.0 (17, 66)
Race, n (%)		
White	103 (54.8)	53 (54.1)
Black	73 (38.8)	43 (43.9)
Asian	4 (2.1)	0
American Indian or Alaska Native	2 (1.1)	0
Other	6 (3.2)	2 (2.0)
Ethnicity, n (%)		
Hispanic 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

Rezafungin / Cidara

Rezafungin (CD101)



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

- Echinocandine action prolongé
- 1 injection IV par semaine
- Activité *C. auris*

Detailed Description:

A Phase 3, multicenter, prospective, randomized, double-blind, efficacy and safety study of Rezafungin for Injection versus an active comparator regimen of caspofungin followed by optional oral fluconazole step-down therapy in subjects with candidemia and/or invasive candidiasis.

tudy Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	218 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Phase 3, Multicenter, Randomized, Double-blind Study of the Efficacy and Safety of **Rezafungin** for Injection vs. Intravenous Caspofungin Followed by Oral Fluconazole Step Down in the Treatment of Subjects With Candidemia and/or Invasive Candidiasis
Actual Study Start Date :	October 12, 2018
Estimated Primary Completion Date :	September 2020
Estimated Study Completion Date :	September 2020

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

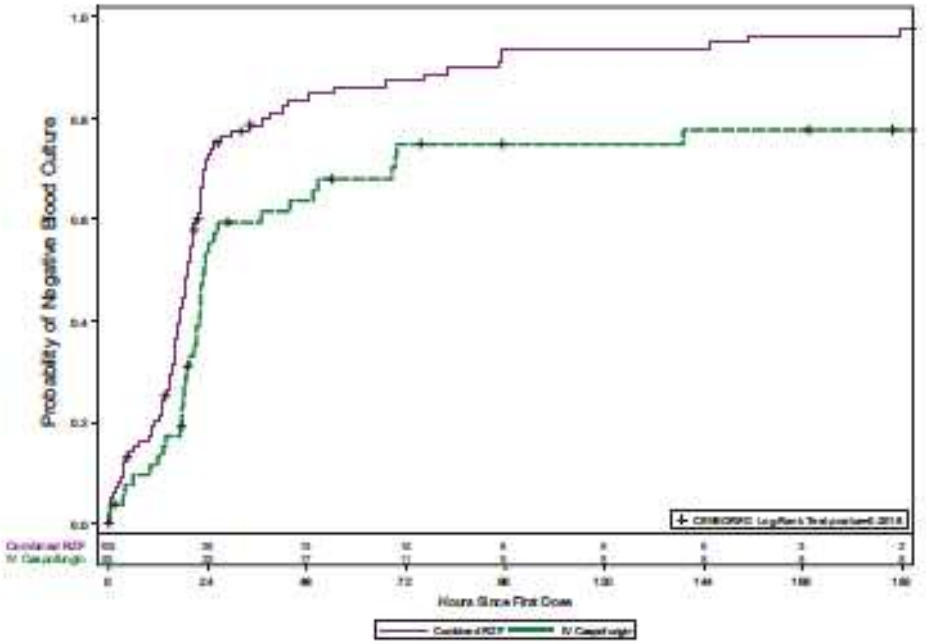
- Rezafungin: demi vie 133h
- Essai de phase 2 randomisé
- Candidémie et candidoses invasives
- RZF 400mg/sem S1 puis 200mg/sem vs 400mg/sem vs Caspo 70mg puis 50mg puis fluco
- Guerison à S2, mortalité à J30
- 207 patients
- Guerison 60%

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)



RZF

Caspo

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