25th ECCMID 25-28 April 2015, Copenhagen-Denmark

EW03: Optimising Antifungal Therapy- Bridging Laboratory and Clinical Expertise

New Antifungal Drugs in the Pipeline

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Disclosures

- No conflict of interest related to this presentation

- Otherwise, in the last five years:

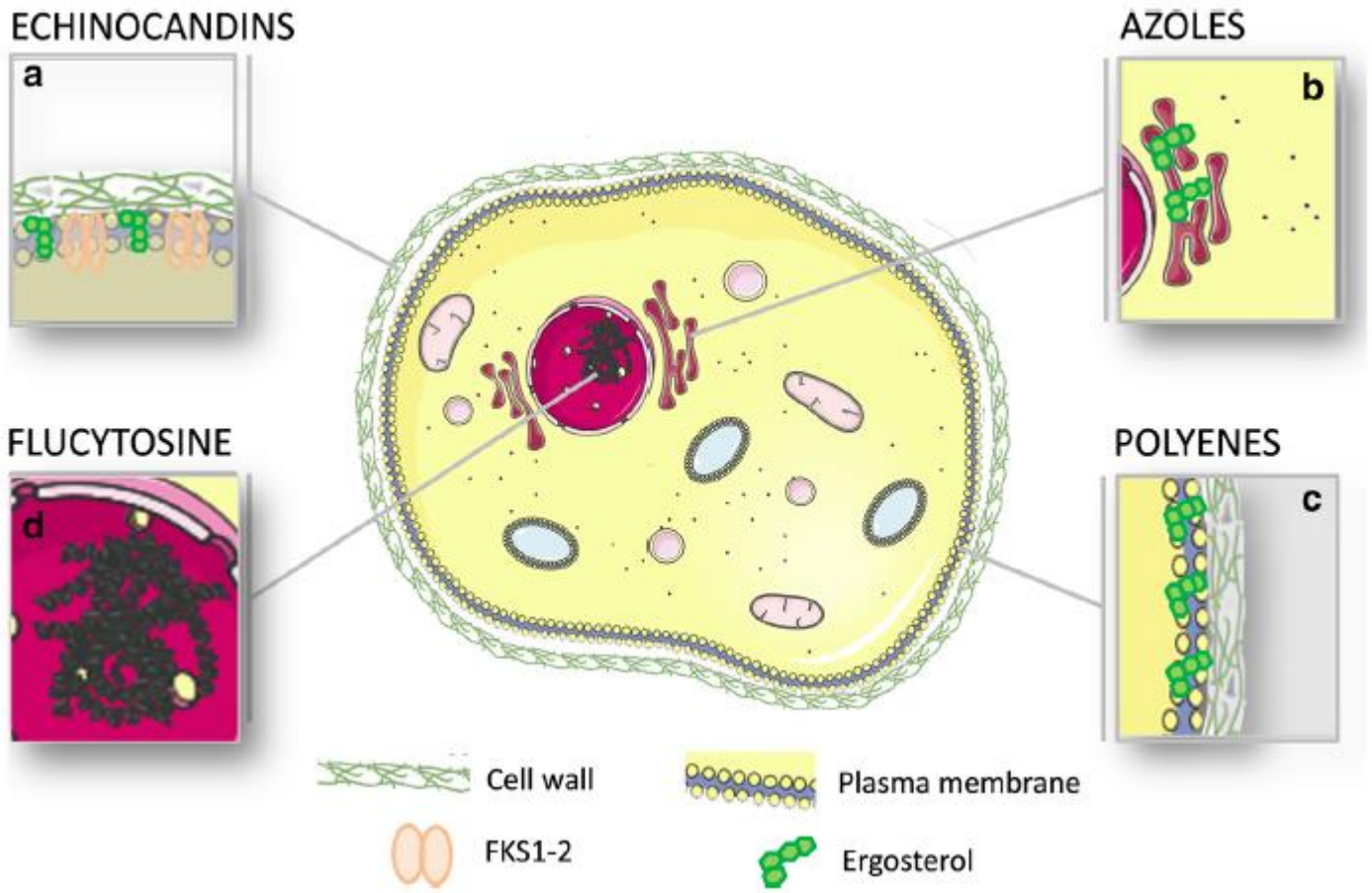
  Investigator Initiated Research Grant from Pfizer

  Lecture honoraria from Astellas, Gilead, Merck, and Pfizer

Agenda

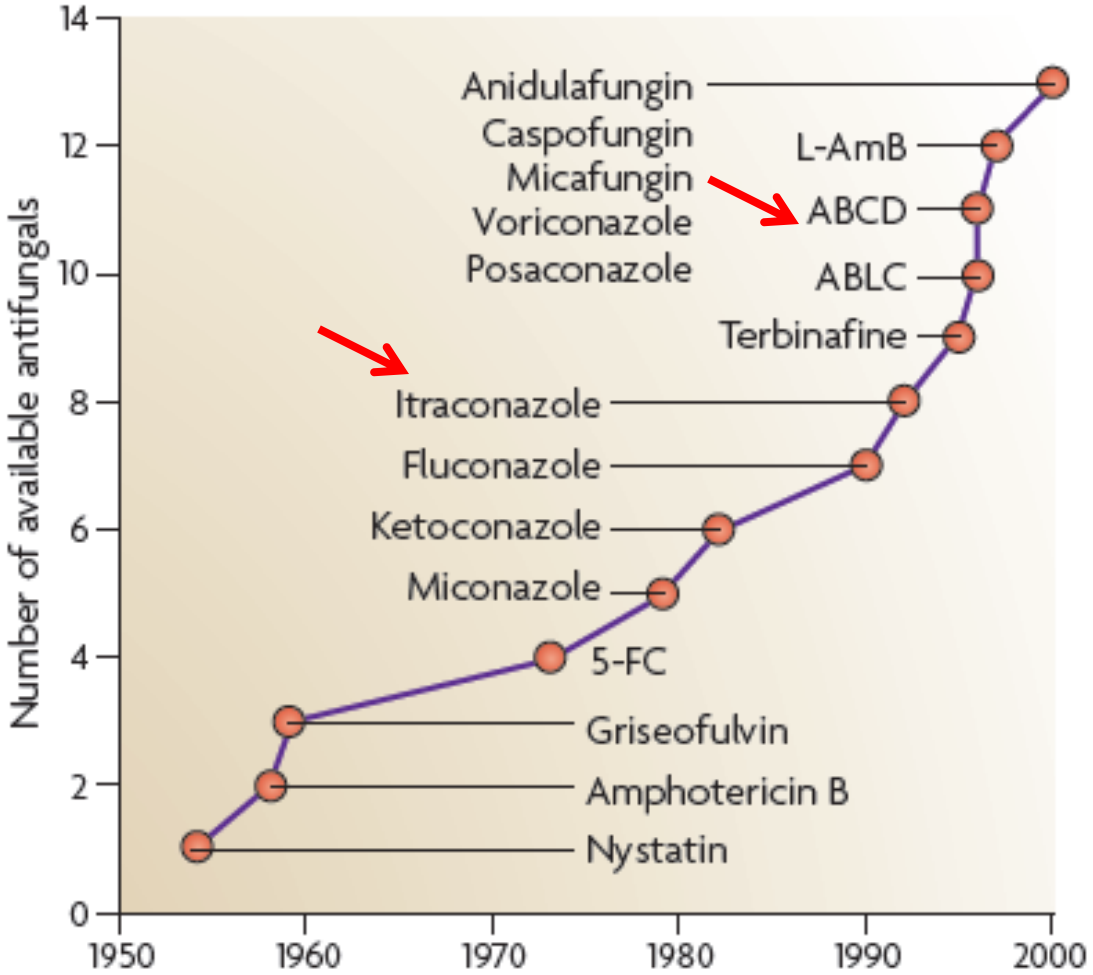
- Drugs recently approved and included in antifungal armamentarium
- Compounds in Phase 2/3 clinical trials
- Selected notes for some investigational compounds that are in Phase 1/2 / preclinical trials

Targets & Mechanisms of Action of Antifungals



Maubon et al. Inten Care Med 2014; 40: 1241

Early Antifungal Pipeline and the Changing Face of Antifungal Drug Spectrum



Ostrosky-Zeichner et al. Nature Rev 2010; 9: 719

Development of a novel drug

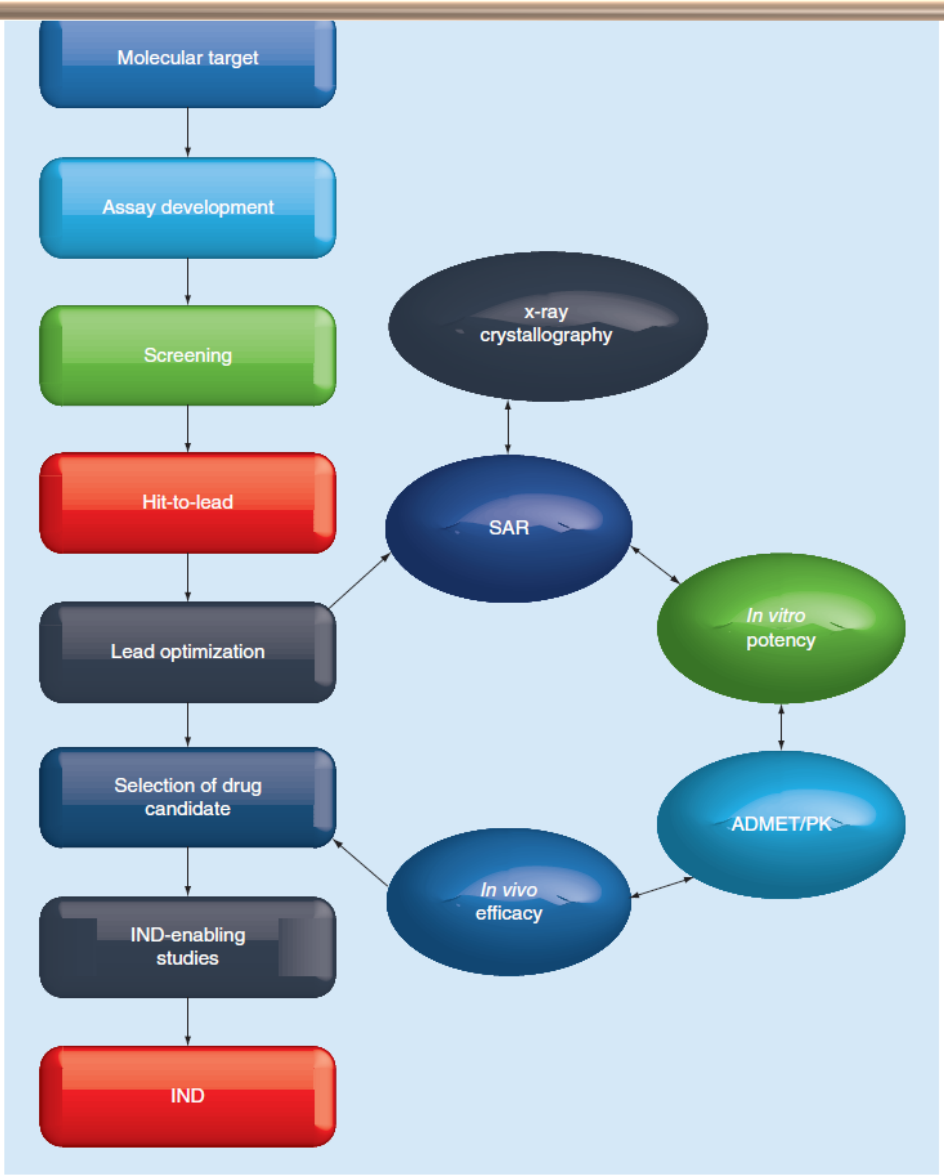


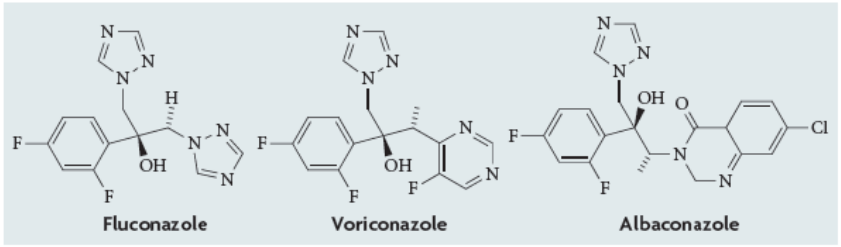
Figure 3. General drug development path and lead optimization components.
ADMET: Absorption, distribution, metabolism, elimination and toxicity; IND: Investigational new drug; PK: Pharmacokinetic; SAR: Structure–activity relationships.

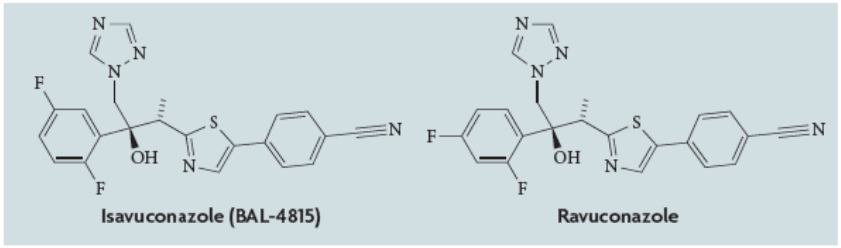
Calderone et al.
Future Microbiol 2014; 9:791

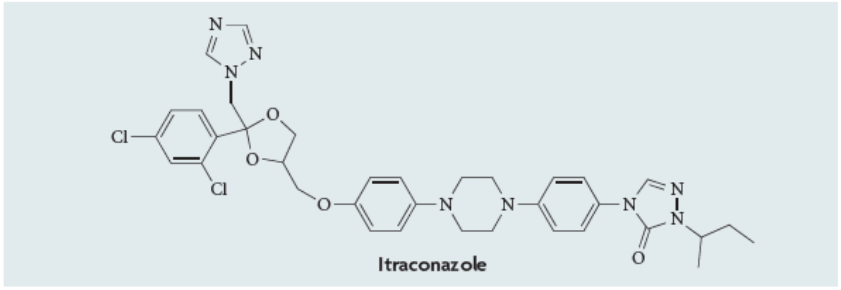
New Drugs: "Expected" Advantages

- Efficacy in difficult-to-treat IFI due to fungi resistant / less susceptible to available drugs (multi-drug-resistant strains, resistant/less susceptible genera including Fusarium, Scedosporium, Lomentospora, those belonging to order Mucorales,…)
- More favorable safety
- PK profile enabling reduced dosing
- Formulation
- More favorable drug–drug interaction profile

Azoles







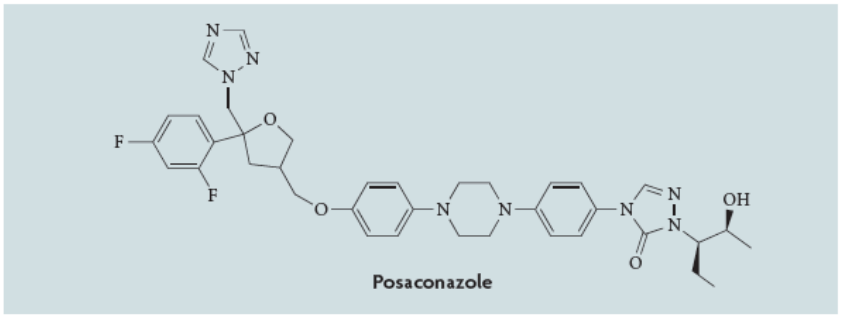


Figure 3 | **Structures of triazoles.** The chemical structures of selected triazoles.

Triazoles

Isavuconazole
Efinaconazole
Albaconazole

Imidazole

Luliconazole

Ostrosky-Zeichner et al. Nature Rev 2010; 9: 719

ISAVUCONAZOLE (BAL-8557)

In Vitro Activities of Isavuconazole and Comparator Antifungal Agents Tested against a Global Collection of Opportunistic Yeasts and Molds

Michael A. Pfaller, Shawn A. Messer, Paul R. Rhomberg, Ronald N. Jones, Mariana Castanheira

Journal of Clinical Microbiology p. 2608–2616 August 2013 Volume 51 Number 8

1358 Candida, 101 Aspergillus, 54 non-Candida yeast, 21 non-Asp mould - - - CLSI

µg/ml **ISV (/POS /VOR) MIC_{90}**	
>8	Non-Aspergillus mould (Penicillium, Paecilomyces, S. apiospermum, Gibberella, Sarocladium)
2 / 1 /1	Aspergillus spp.
1	Non-Candida yeast (Trichosporon)
0.5 / 1 / 0.25	Candida spp.
0.125	Cryptococcus neoformans

Mucorales
(3 strains)
ISV / POS
MIC range: 1-4/1

Percent agreement (± 1, ± 2 two-fold dil.) betw. CLSI & EUCAST methods: 90.1 and 99.1%, respectively (111 strains, Candida)

ISAVUCONAZOLE

Determination of Isavuconazole Susceptibility of *Aspergillus* and *Candida* Species by the EUCAST Method

Susan J. Howard,[a] Cornelia Lass-Flörl,[b] Manuel Cuenca-Estrella,[c] Alicia Gomez-Lopez,[c] Maiken C. Arendrup[d]

Antimicrobial Agents and Chemotherapy p. 5426–5431 November 2013 Volume 57 Number 11

Species	*Preliminary* ECOFFs (mg/l)
A. fumigatus	2
A.flavus	2
A.nidulans	0.25
A.niger	4
A.terreus	2
C. albicans	0.03
C. parapsilosis	0.03
C. tropicalis	0.03

1237 Aspergillus
2010 Candida
4 lab.s

- Elevated ISV MICs for A.fumigatus w TR_{34}/L98H mutants
- Wild-type MICs for G54 and M220 alterations

ISAVUCONAZOLE

Isavuconazole Activity against *Aspergillus lentulus*, *Neosartorya udagawae*, and *Cryptococcus gattii*, Emerging Fungal Pathogens with Reduced Azole Susceptibility

K. Datta,[a] P. Rhee,[a] E. Byrnes III,[a] G. Garcia-Effron,[b] D. S. Perlin,[c] J. F. Staab,[a] K. A. Marr[a]

Journal of Clinical Microbiology p. 3090–3093 September 2013 Volume 51 Number 9

TABLE 1 Summary of drug sensitivities of all *Aspergillus* section *Fumigati* and *C. gattii* VGII isolates[a]

Organism (no. of isolates)	Drug	Mode MIC (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	Geometric mean MIC (μg/ml)
A. lentulus ($n = 15$)	Itraconazole	1	1	2	0.5–2	1.097
	Voriconazole	2	2	2	0.5–2	1.516
	Isavuconazole	0.25	0.25	0.25	0.063–0.5	0.188
N. udagawae ($n = 10$)	Itraconazole	1	1	1	0.25–1	0.660
	Voriconazole	1	1	1	0.25–1	0.812
	Isavuconazole	0.125	0.125	0.25	0.031–0.25	0.100
All *C. gattii* ($n = 90$)	Fluconazole	4	4	8	2–64	4.560
	Itraconazole	0.125	0.125	0.5	0.031–0.5	0.187
	Voriconazole	0.125	0.125	0.125	0.031–0.5	0.093
	Isavuconazole	0.031	0.063	0.125	0.031–0.5	0.057
C. gattii VGIIa ($n = 72$)	Fluconazole	4	4	8	2–16	3.849
	Itraconazole	0.125	0.125	0.5	0.031–0.5	0.177
	Voriconazole	0.125	0.125	0.125	0.031–0.25	0.088
	Isavuconazole	0.031	0.031	0.063	0.031–0.125	0.046
C. gattii VGIIb ($n = 8$)	Fluconazole	8	8	64	4–64	8.724
	Itraconazole	0.125	0.25	0.5	0.125–0.5	0.210
	Voriconazole	0.031	0.063	0.125	0.031–0.125	0.063
	Isavuconazole	0.063	0.125	0.25	0.031–0.25	0.088
C. gattii VGIIc ($n = 10$)	Fluconazole	8	8	32	4–32	9.190
	Itraconazole	0.25	0.25	0.5	0.125–0.5	0.250
	Voriconazole	0.25	0.25	0.5	0.063–0.5	0.189
	Isavuconazole	0.25	0.25	0.5	0.125–0.5	0.203

ISAVUCONAZOLE

Multicenter Study of Isavuconazole MIC Distributions and Epidemiological Cutoff Values for *Aspergillus* spp. for the CLSI M38-A2 Broth Microdilution Method

A. Espinel-Ingroff,[a] A. Chowdhary,[b] G. M. Gonzalez,[c] C. Lass-Flörl,[d] E. Martin-Mazuelos,[e] J. Meis,[f,g] T. Peláez,[h] M. A. Pfaller,[i] J. Turnidge[j]

August 2013 Volume 57 Number 8 Antimicrobial Agents and Chemotherapy p. 3823–3828

Species complex or section[a]	ECV[c]			% observed above ECV		
	95%	97.5%	99%	ECV 95%	ECV 97.5%	ECV 99%
A. fumigatus	1	1	1	5.6	5.6	5.6
A. flavus	1	1	2	3.2	3.2	0.2
A. nidulans[d]	0.25	0.25	0.25	27.4	27.4	27.4
A. niger	4	4	4	1.0	1.0	1.0
A. terreus	1	1	1	0.3	0.3	0.3
A. versicolor[d]	1	1	2	2.7	2.7	1.3
Aspergillus section *Usti*[e]	ND	ND	ND	ND	ND	ND

Isavuconazole –IA - Animal model ECCMID 2015

28 Apr Tuesday 12:30-13:30 Poster area

P1286	**Efficacy of isavuconazole against wild-type and *Cyp*51 mutant isolates of *Aspergillus fumigatus* in a mouse infection model** *S. Seyedmousavi* (Rotterdam, Netherlands), R.J.M. Brüggemann, J.F. Meis, W.J.G. Melchers, P.E. Verweij, J.W. Mouton*

ECCMID 2015 Final Programme
www.eccmid.org/fileadmin/eccmid/2015/media/documents/912604_ECCMID2015_20Final_Programme_WEB.compressed.pdf

ISAVUCONAZOLE

Multicenter Study of Isavuconazole MIC Distributions and Epidemiological Cutoff Values for the *Cryptococcus neoformans-Cryptococcus gattii* Species Complex Using the CLSI M27-A3 Broth Microdilution Method

Antimicrobial Agents and Chemotherapy January 2015 Volume 59 Number 1

A. Espinel-Ingroff,[a] A. Chowdhary,[b] G. M. Gonzalez,[c] J. Guinea,[d] F. Hagen,[e] J. F. Meis,[e,f] G. R. Thompson III,[g] J. Turnidge[h]

TABLE 1 Pooled MIC distributions and ECVs for the *Cryptococcus neoformans-Cryptococcus gattii* species complex and isavuconazole using the CLSI M27-A3-RPMI microdilution method[a]

Species	No. of isolates	No. of isolates with an MIC[b] (μg/ml) of:							MIC range (μg/ml)	Mode (μg/ml)[d]	ECV (μg/ml)[c]	
		0.008	0.016	0.03	0.06	0.12	0.25	0.5			95%	97.5%
C. neoformans VNI[e] (AFLP1)	870	68	270	274	213	37	7	1	0.008–0.5	0.03	0.12	0.12
C. neoformans (nongenotyped)	438	10	135	170	96	19	6	2	0.008–0.5	0.03	0.06	0.12
C. gattii[e]	406	23	78	106	87	87	25	7	0.008–0.5	0.03	0.25	0.25

Isavuconazole and Trichosporon

CLSI M27-A2

		ISAVU	VORI	POSA	FLU	AMB	5-FC
T. asahii (40)	MIC90	0.125	0.06	0.25	2	2	8
	MFC90	2	0.5	4	16	8	>64
T. mucoides (10)	MIC90	0.25	0.06	0.25	1	2	32
	MFC90	4	>16	4	>64	2	>64
T. inkin (4)	MIC range	0.03-0.125	0.03	0.06-0.13	0.25-0.5	0.25-1	8-16
	MFC range	0.06-4	0.03-0.125	0.06-0.5	0.25-4	0.5-2	16-32

Inhibitory activity rank order:
***asahii*: Vori>Isavu>Posa>Flu=AMB>5-FC**
***mucoides*: Vori>Isavu=Posa>Flu>AMB>5-FC**

Cidal activity rank order:
***asahii*: Vori>Isavu>Posa>AMB>Flu>5-FC**
***mucoides*: AMB>Isavu=Posa>Vori>5-FC**

Thompson et al. JAC 2009; 64: 79

ISAVUCONAZOLE

AAC
Journals.ASM.org

Head-to-Head Comparison of Inhibitory and Fungicidal Activities of Fluconazole, Itraconazole, Voriconazole, Posaconazole, and Isavuconazole against Clinical Isolates of *Trichosporon asahii*

Gulsen Hazirolan,[a] Emilia Canton,[b] Selma Sahin,[c] Sevtap Arikan-Akdagli[a]

Hacettepe University Medical School, Department of Medical Microbiology, Ankara, Turkey[a]; Unidad de Microbiología Experimental, Centro de Investigación, Hospital Universitario y Politécnico La Fe, Valencia, Spain[b]; Hacettepe University Faculty of Pharmacy, Ankara, Turkey[c]

October 2013 Volume 57 Number 10 Antimicrobial Agents and Chemotherapy p. 4841–4847

Isavuconazole and Trichosporon: In vitro data [1]

Table1 : MIC (µg/ml) results of 90 *T.asahii* isolates at 24 and 48h of incubation

ANTIFUNGAL DRUG, MIC reading endpoint	MIC (µg/ml) – 24h				MIC (µg/ml) – 48h			
	RANGE	MIC_{50}	MIC_{90}	GM	RANGE	MIC_{50}	MIC_{90}	GM
FLU, MIC-0	2-4	8	32	10.66	4-32	8	32	11.31
MIC-2	≤0.125-8	1	4	1.54	0.5-16	4	8	3.24
ITRA, MIC-0	0.5-2	1	2	1.06	0.5-4	2	2	1.44
MIC-2	0.03-1	0.25	0.5	0.23	0.125-1	0.25	1	0.37
VORI, MIC-0	0.06-0.5	0.25	0.5	0.21	0.125-0.5	0.25	0.5	0.25
MIC-2	≤0.015-0.125	0.06	≤0.015	0.04	≤0.015-0.25	0.06	0.125	0.06
POS, MIC-0	0.5-2	1	1	1.06	1-2	1	2	1.12
MIC-2	≤0.015-1	0.125	0.5	0.16	0.06-1	0.25	0.5	0.25
ISAVU, MIC-0	0.125-2	0.5	1	0.53	0.25-2	1	1	0.75
MIC-2	≤0.015-0.5	0.03	0.25	0.07	≤0.015-0. 5	0.125	0.25	0.1

GM: Geometric mean

Hazirolan et al. AAC 2013 Oct 57: 4841

CLSI M27-A3

Isavuconazole and Trichosporon $_2$

Table 2: MFC (µg/ml) results of 90 T.asahii isolates at 24 and 48h of incubation

MFC	FLU		ITRA		VORI		POS		ISAVU	
	24h	48h	24h	48h	24h	48h	24h	48h	24h	48h
MFC $_{50}$	16	32	2	2	0.5	1	2	2	2	2
MFC $_{90}$	64	64	8	8	2	2	2	4	4	4
GM	20.78	23.69	2.43	3.1	0.71	0.83	1.68	1.92	1.79	2.14
MFC RANGE	2-64	4-64	1->8	1->8	0.25-4	0.25-8	0.5-8	0.5-8	0.5-8	0.5-8

GM: geometric mean

CLSI M27-A3

Hazirolan et al. AAC 2013 Oct 57: 4841

Isavuconazole and Trichosporon $_3$ *24h vs. 48h*

Table 3: The percentages of strains which yield 48h MICs that are within ± 1 dilution range of 24h MICs by using MIC-0 and MIC-2 endpoints

ANTIFUNGAL DRUG	% agreement of 48h MICs with 24h MICs at the respective MIC endpoints	
	MIC-0	MIC-2
FLU	98.9	64.4
ITRA	98.9	78.9
VORI	98.9	75.6
POS	100	76.7
ISAVU	97.8	67.8

CLSI M27-A3

Hazirolan et al. AAC 2013 Oct 57: 4841

Isavuconazole and Trichosporon $_4$
Concluding remarks for MICs and MFCs

(1) Against *T.asahii* strains, highest MICs and MFCs are obtained for FLU. In vitro activity of FLU is very limited against *T.asahii*.

(2) VORI is the most active triazole tested against *T.asahii,* with the lowest MICs and MFCs.

(3) VORI, ISAVU, POS, and ITRA appear to have similar and favorable in vitro activities against *T.asahii*. In general, MICs and MFCs of these drugs vary by no more than 3 two-fold dilutions when compared to one another.

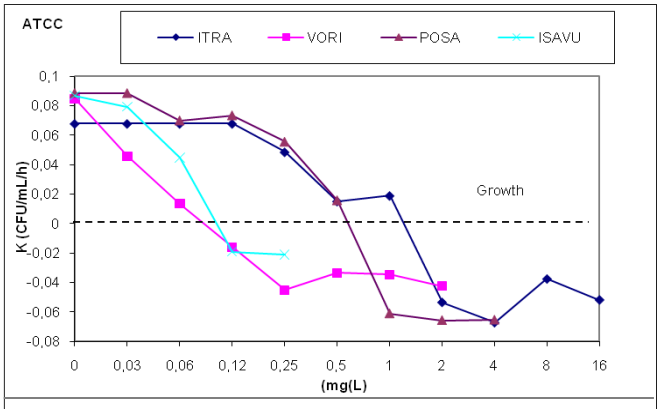
(4) Using MIC-0 endpoint, 48h MICs are within $\pm$ 1 dilution range of 24h MICs for most of the isolates and all drugs tested. When MIC-2 endpoint is used for comparison, the correlation between the two reading time points, 24 and 48h, is less pronounced for all drugs tested. These suggest that using MIC-0 endpoint yields more consistent results which remain mostly unchanged when the incubation period is extended. Furthermore, MIC-0 endpoint MICs are easier to interpret at both reading time points.

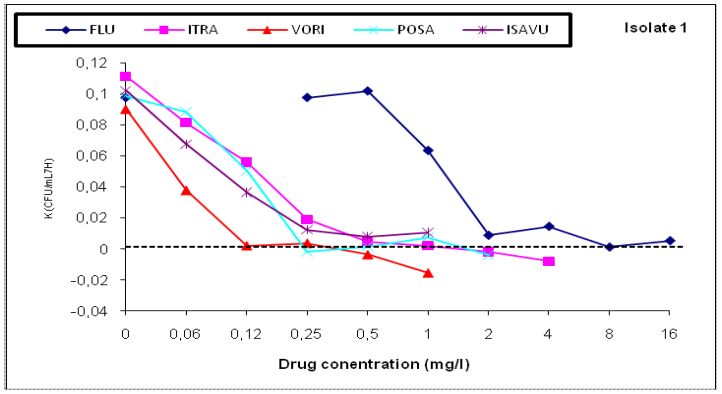
Hazirolan et al. AAC 2013 Oct 57: 4841

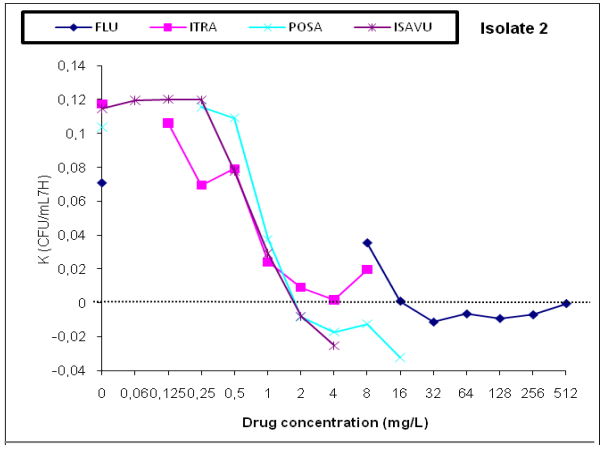
Isavuconazole and Trichosporon $_5$ *Time-kill studies*

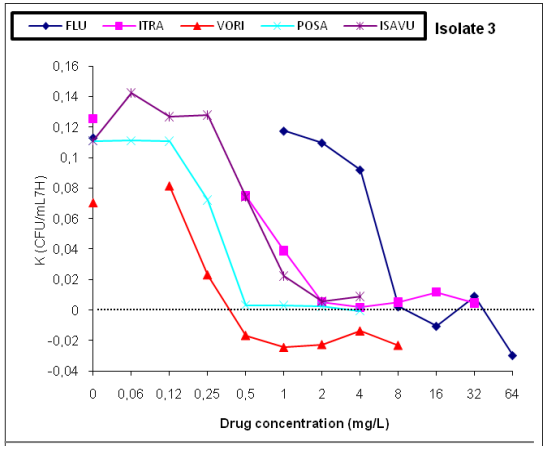
(32xMIC-2xMIC)

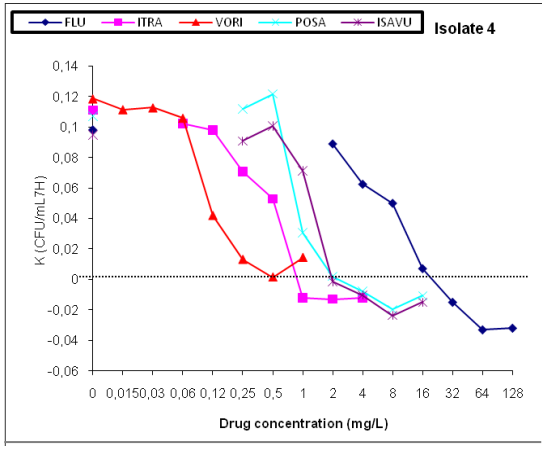
FLU, ITRA, VORI, POSA, ISAVU











Hazirolan et al. AAC 2013 Oct 57: 4841

Isavuconazole and Trichosporon 6
Concluding remarks for time-kill studies

No fungicidal activity with any of the triazoles tested (no decrease of ≥99.9% or 3-$\log_{10}$) - - all are fungistatic

The lowest concentration at which killing activity begins is for voriconazole and the highest is for fluconazole

The number of colonies decreases rapidly at > 2xMIC concentrations for all drugs. Again for all, maximum reduction is observed 48 hours after the incubation.

	Killing activity starts above (µg/ml)				
Strain no.	FLU	ITRA	VORI	POSA	ISAVU
T.asahii ATCC 201110	*	2	0.125	1	0.125
Clinical strain no. 1	*	2	0.5	2	1
2	32	*	*	2	2
3	64	*	0.5	*	*
4	32	1	*	4	2

*killing activity was not observed at tested concentrations

Hazirolan et al. AAC 2013 Oct 57: 4841

Isavuconazole (isavuconazonium sulfate)

Astellas Pharma, US, Inc. – License holder
Basilea Pharmaceu., Switzerland – outside USA and Canada

- **FDA approves new antifungal drug Cresemba (Oral/IV)**

  March 6, 2015

Invasive Aspergillosis
Invasive Mucormycosis

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm437106.htm

Efficacy of Isavuconazole in (proven/probable) IA

SECURE Study

Phase 3 randomized double-blind active control study adult pat.s - IFI

516 pat.s

- Noninferiority to voriconazole

Overall Success

ISV 35%

VOR 39%

All cause mortality (day 42)

ISV 18.6%

VOR 20.2%

Safety of Isavuconazole in IA

SECURE Study

Phase 3 randomized double-blind active control study adult pat.s - IFI

516 pat.s

- Similar rates of mortality and nonfatal adverse events as voriconazole

- Statistically fewer AE and tx-emergent adverse events (hepatobiliary, skin, eye) compared to voriconazole

Isavuconazole – SECURE Study ECCMID 2015

25 Apr Saturday 15:30-16:30 ePoster area 3

EP016 16:06 Clinical outcomes by minimum inhibitory concentrations of baseline *Aspergillus* pathogens from isavuconazole phase 3 SECURE and VITAL studies

W. Hope (Liverpool, United Kingdom), M. Ghannoum, L. Kovanda, M. Jones, A. Kaufhold, M. Engelhardt, A. Santerre Henriksen*

EP018 16:18 A comparison of the safety profiles of isavuconazole vs voriconazole in the phase 3 SECURE study in patients with invasive mould infections

A.J. Ullmann (Würzburg, Germany), D. Selleslag, W.J. Heinz, R. Herbrecht, G. Rahav, M. Giladi, M. Aoun, O.A. Cornely, N. Azie, K. Achim, E. Marc, J. Maertens*

ECCMID 2015 Final Programme
www.eccmid.org/fileadmin/eccmid/2015/media/documents/912604_ECCMID2015_20Final_Programme_WEB.compressed.pdf

Isavuconazole – SECURE Study ECCMID 2015

25 Apr Saturday 15:30-16:30 Poster area

P0233 **Safety and outcomes in obese patients with invasive fungal disease treated with isavuconazole in the phase 3 randomized double-blind SECURE trial**

D. Goff (Columbus, OH, United States), D. Andes, W. Hope, N. Azie, F. Shi, L. Kim, L. Kovanda, A. Schmitt-Hoffmann, T. Gumbo*

ECCMID 2015 Final Programme
www.eccmid.org/fileadmin/eccmid/2015/media/documents/912604_ECCMID2015_20Final_Programme_WEB.compressed.pdf

Safety and Efficacy of Isavuconazole in IA / IFI

VITAL Study

Phase 3 open-label non-comparative

- Pat.s w. IA and renal impairm. or w. IFI due to other fungi, including Mucorales

Data for mucormycoses

37 cases
All-cause mortality 38%
Survival at 180 days 53%
8% (of 76%) serious AE attributed to ISV

Marty et al. ID Week 2014 Annual Meeting Philadelphia, PA, USA; October 8–12, 2014; Abst. No. 824

Isavuconazole – VITAL Study ECCMID 2015

25 Apr Saturday 15:30-16:30 Poster area

P0230 **An open-label phase 3 study of isavuconazole (VITAL): focus on patients with mixed fungal infections**

G. Rahav (Ramat Gan, Israel), I. Oren, K. Mullane, R. Maher, M. Lee, B. Zeiher, A. Schmitt-Hoffmann, M. Giladi*

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www.eccmid.org/fileadmin/eccmid/2015/media/documents/912604_ECCMID2015_20Final_Programme_WEB.compressed.pdf

ISAVUCONAZOLE

Safety and Pharmacokinetics of Isavuconazole as Antifungal Prophylaxis in Acute Myeloid Leukemia Patients with Neutropenia: Results of a Phase 2, Dose Escalation Study

Oliver A. Cornely,[a] Angelika Böhme,[b] Anne Schmitt-Hoffmann,[c] Andrew J. Ullmann[d*]

Antimicrobial Agents and Chemotherapy
April 2015 Volume 59 Number 4

- Safety and tolerability of ISV at 200 mg/day and 400 mg/day for prophylaxis

LOW DOSE COHORT	
Loading doses	Day 1 400/200/200 mg 6h apart
	Day 2: 200/200 mg 12h apart
Maintenance doses	Days 3-28 200 mg once daily
HIGH DOSE COHORT	X2

20 pat.s completed the study; 18/20 classified as tx. success

Most common adverse event: Headache and rash
2pat.s in each cohort discontinued due to ISV-related AE (Hypersensitivity Rx, infusion related Rx., nausea, dizziness, skin inf. / petechiae

Isavuconazole
ACTIVE Phase III Study

- Safety & efficacy - Invasive candidiasis
- Isavuconazole vs. caspofungin followed by oral voriconazole
- Results expected in second half of 2015

Efinaconazole (KP-103)

(JUBLIA® Valeant Pharmaceu., Canada)

- Topical 10% sln. – mild to moderate distal lateral subungual onychomycosis
- Low keratin affinity
- Early tx. prevents disease progression to other toenails
- Two Phase 3 trials - published
- FDA approval: September 2014

Sugiura et al. AAC 2014; 58: 3837; Elsayed J Control Release 2015; 199: 132

EFINACONAZOLE

Antimicrobial Agents and Chemotherapy p. 1610–1616 April 2013 Volume 57 Number 4

Comparison of *In Vitro* Antifungal Activities of Efinaconazole and Currently Available Antifungal Agents against a Variety of Pathogenic Fungi Associated with Onychomycosis

William J. Jo Siu,[a] Yoshiyuki Tatsumi,[b] Hisato Senda,[b] Radhakrishnan Pillai,[a] Takashi Nakamura,[b] Daisuke Sone,[b] Annette Fothergill[c]

M38-A2, M27-A3

MIC90 (µg/ml)	
0.125	
0.06	C. albicans
0.03	
0.015	T. mentagrophytes
0.008	T. rubrum

MICs similar or lower compared to terbinafine, itraconazole, amorolfine, ciclopirox

Active also against Microsporum, Epidermophyton, Acremonium, Fusarium, Paecilomyces, Pseudallescheria, Scopulariopsis, Aspergillus

EFINACONAZOLE

Efinaconazole 10% solution in the treatment of toenail onychomycosis: Two phase III multicenter, randomized, double-blind studies

Elewski et al. J Am Acad Dermatol 2013; 68: 600

- Vehicle-controlled
- n= 870 and n=785
- 48 wk. tx., 4 wk. posttx. follow-up
- Primary endpoint: Complete cure (clinical and mycological) at wk. 52
- Complete cure rate significantly higher for efinaconazole (study 1: 17.8% vs 3.3%, study 2: 15.2% vs 5.5%, P < .001)

Luliconazole (NND-502)

- Imidazole
- Cream 1%, solution 10%
- High concentration - nail plate
- Phase 3 (Tinea pedis) - Published
- Phase 2b/3 (Distal subungual onychomycosis of the toenails) Randomized, double-blind, vehicle-controlled, 10% solution
- Approved, Japan, 2005 (T.pedis, T.corporis, T.cruris, T.versicolor, candidiasis)
- Approved, USA, Nov 15, 2013 (T.pedis, T.corporis & T.cruris)

Elsayed J Control Release 2015; 199: 132

LULICONAZOLE

Luliconazole Demonstrates Potent *In Vitro* Activity against Dermatophytes Recovered from Patients with Onychomycosis

June 2014 Volume 58 Number 6 Antimicrobial Agents and Chemotherapy p. 3553–3555

Nathan P. Wiederhold,[a] Annette W. Fothergill,[a] Dora I. McCarthy,[a] Amir Tavakkol[b]

M38-A2, MIC-1

TABLE 2 MICs of amorolfine, ciclopirox, terbinafine, and luliconazole against *Trichophyton rubrum* and *Trichophyton mentagrophytes* isolates

Organism (no. of isolates) and antifungal	MIC (μg/ml)[a]			
	Range	50%	90%	GM
Trichophyton rubrum (308)				
Amorolfine	0.008–0.5	0.125	0.25	0.0883
Ciclopirox	0.03–1	0.25	0.5	0.3156
Terbinafine	0.004–0.25	0.015	0.03	0.0195
Luliconazole	0.00012–0.0025	0.00025	0.0005	0.00022
Trichophyton mentagrophytes (10)				
Amorolfine	0.03–0.125	0.03	0.125	0.051
Ciclopirox	0.06–0.5	0.25	0.5	0.2095
Terbinafine	0.008–0.03	0.015	0.03	0.0161
Luliconazole	0.00012–0.001	0.000125	0.001	0.000265

Remarkably lower MICs as compared to comparators

LULICONAZOLE

Efficacy and Safety of Once-Daily Luliconazole 1% Cream in Patients ≥12 Years of Age With Interdigital Tinea Pedis: A Phase 3, Randomized, Double-Blind, Vehicle-Controlled Study Jarratt et al. J Drugs Dermatol ; 2014; 13: 838

321 pat.s 14 days tx. Complete clearance at day 42: 26.4% (luli) vs. 1.9% (control)

Efficacy and tolerability of luliconazole cream 1% for dermatophytoses: a meta-analysis Feng et al. J Dermatol 2014;41:779

'……. more effective than control drugs (1% terbinafine, 1% bifonazole) or vehicle (week 4: odds ratio = 1.46, 95% confidence interval = 1.12-1.91)……'

Albaconazole (UR-9825)

Actavis, Ireland

- Orally active
- PK - capsule & tablet (Phase I randomized study; tb. Cmax 10-22% lower than that of capsule)
- Efficacy in animal models (Aspergillus, Candida, Cryptococcus, Scedosporium) – no further development
- Phase II – vulvovaginal candidiasis study terminated
- Phase II onychomycosis study published

van Rossem et al. Clin Pharmacol 2013; 5: 23; Ostrosky-Zeichner et al. Nature Rev 2010; 9: 7; Miller et al. AAC 2004; 48: 384

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2001, p. 2635–2637 Vol. 45, No. 9

In Vitro Antifungal Activities of the New Triazole UR-9825 against Clinically Important Filamentous Fungi

JAVIER CAPILLA, MONTSERRAT ORTONEDA, FRANCISCO JAVIER PASTOR, AND JOSEP GUARRO*

M38-P

Species (no. of isolates) and antifungal agent	MIC (μg/ml)		
	Range	50%	90%
Aspergillus fumigatus (10)			
UR-9825	0.06–0.125	0.06	0.125
Amphotericin B	1–2	1	2
Aspergillus flavus (11)			
UR-9825	0.06–0.25	0.125	0.25
Amphotericin B	0.25–4	1	2
Aspergillus niger (11)			
UR-9825	0.06–0.5	0.25	0.5
Amphotericin B	0.06–1	0.125	1
Fusarium solani (10)			
UR-9825	4–>16	16	>16
Amphotericin B	1–2	2	2
Paecilomyces variotii (10)			
UR-9825	0.03–>16	0.06	0.125
Amphotericin B	0.125–1	0.25	0.5
Paecilomyces lilacinus (10)			
UR-9825	0.06–0.5	0.125	0.125
Amphotericin B	>16	>16	>16
Chaetomium globosum (10)			
UR-9825	1–2	2	2
Amphotericin B	1–16	4	16
Scytalidium lignicola (2)			
UR-9825	>16		
Amphotericin B	2		
Scytalidium dimidiatum (3)			
UR-9825	2–>16		
Amphotericin B	2–4		

Comparator:AMB
Lower MIC_{90}s
than AMB against
all except F.solani
and Scytalidium

ALBACONAZOLE

Sigurgeirsson et al. J Am Acad Dermatol. 2013 Sep;69:416

A phase II, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study to investigate the efficacy and safety of 4 dose regimens of oral albaconazole in patients with distal subungual onychomycosis

- 584 pat.s
- Once weekly 100 to 400 mg ALB vs. placebo
- 24-36 wk. tx. Follow-up period: wk. 52
- Effective tx. rates (all groups):21-54%vs.1%(placebo)
- Effective tx. observed at wk. 24 in $\geq$5% of pat.s
- Tx.-related AE: $\leq$ 3%; no serious AE
- No comparison to other available tx.s

Selected notes on some investigational compounds in Phase 1-2 / preclinical trials

Compound (Notes)	Company	Development Status	Model/Study	Related Ref.s
SCY078 (formerly MK-3118) Enfumafungin derivative IV / Oral	Scynexis, Durham, NC, USA	Phase 2	IC, nonneutr. (oral, vs. Standard-of-Care –MFG or FLU following initial IV MFG) Safety, PK, efficacy	Onishi AAC 2000; Pelaez Syst Appl Microbiol 2000; Pfaller JAC 2013; Jimenez-Ortigosa AAC 2014, Lepak AAC 2015

Clinical trial: clinicaltrials.gov

SCY078 (MK-3118)

J Antimicrob Chemother 2013; **68**: 858–863

Activity of MK-3118, a new oral glucan synthase inhibitor, tested against *Candida* spp. by two international methods (CLSI and EUCAST)

Michael A. Pfaller[1]*, Shawn A. Messer[1], Mary R. Motyl[2], Ronald N. Jones[1] and Mariana Castanheira[1]

Conclusions: MK-3118 was documented to have potent *in vitro* activity against *Candida* spp. when tested by both CLSI and EUCAST BMD methods, with the highest overall EA (99.1%) obtained when MK-3118 MIC results were read after 24 h of incubation using a partial inhibition EC (50%).

Species (no. of strains tested)	Antifungal agent	90%
C. albicans (29)	MK-3118	1
	caspofungin	2
	fluconazole	≥128
C. glabrata (29)	MK-3118	2
	caspofungin	16
	fluconazole	≥128
C. parapsilosis (15)	MK-3118	0.5
	caspofungin	0.5
	fluconazole	64
C. tropicalis (21)	MK-3118	1
	caspofungin	1
	fluconazole	≥128
C. krusei (19)	MK-3118	2
	caspofungin	1
	fluconazole	≥128

3 two-fold lower MICs for C. glabrata as compared to CAS

Low MICs against Flu-R isolates & fks mutants

SCY078 (MK-3118)

Cristina Jiménez-Ortigosa,[a] Padmaja Paderu,[a] Mary R. Motyl,[b] David S. Perlin[a]

Enfumafungin Derivative MK-3118 Shows Increased *In Vitro* Potency against Clinical Echinocandin-Resistant *Candida* Species and *Aspergillus* Species Isolates

Antimicrobial Agents and Chemotherapy p. 1248–1251 February 2014 Volume 58 Number 2

TABLE 3 MEC distributions of CAS and MK-3118 for the *Aspergillus* isolates included in this study

Species	Phenotype (no. of isolates)	Mode value and MEC_{50} range (mg/liter)[a]	
		Caspofungin	MK-3118
A. flavus	WT (10)	0.12 (0.06–2)	8 (2.0–16)
A. fumigatus	WT (1)	0.12	0.12
	ER (1)	>16	0.12
	WT (6 [ITR^s])[c]	0.12 (0.12–0.25)	8 (0.12–8)
	WT (8 [ITR^r])[b]	0.12 (0.06–0.25)	0.25 (≤0.03–8)
A. niger	WT (10)	0.12 (0.06–0.12)	0.12 (≤0.03–0.25)
A. terreus	WT (6)	0.06 (0.06–0.25)	0.12 (0.06–0.12)

[a] Data represent mode values and MEC ranges after 48h of growth at 35°C. All values represent averages of the results of triplicate experiments with less than 15% variance.
[b] Isolates with a WT *FKS1* gene and sensitive to azoles. ITR, itraconazole.
[c] Isolates with a WT *FKS1* gene but resistant to azoles.

Compound (Notes)	Company	Development Status	Model/Study	Related Ref.s
Arasertaconazole nitrate (pessary) Activity against Flu-R	Ferrer Intern. S.A., Spain	Phase 2	VVC (vs. FLU) Efficacy, safety, tolerability, dose finding	
Nikkomycin Z Chitin synthase inhibitor	Univ of Arizona-Valley Fever Center for Excellence	Preparatory to Phase 2	Pulmonary Cocci – Animal model Dosing and pharmacology	Shubitz J Infect Dis 2014
VT-1161 Highly selective fungal CYP51 inhibitor Oral	Viamet Pharmaceu., Durham, NC, USA	Phase 2 Phase 2 Phase 2	VVC (vs. FLU) completed T. pedis (vs. placebo) completed Onychomycosis, RVVC	Hoekstra Bioorg Med Chem Lett 2014; Garvey AAC 2015 (dermatophyt.-guinea pig; once daily/once wk.ly)

Clinical trials: clinicaltrials.gov

VT-1161
ECCMID 2015

25 Apr Saturday 15:30-16:30 Poster area

P0228 **Efficacy and safety of oral VT-1161, a novel inhibitor of fungal CYP51, in a randomized phase 2 study in patients with acute vulvovaginal candidiasis**

S. Brand (Durham, NC, United States), T. Degenhardt, P. Nyirjesy, M. Augenbraun, R. Schotzinger*

25 Apr Saturday 15:30-16:30 ePoster area 3

EP014 **15:54** **VT-1161p protects immunosuppressed mice from *Rhizopus oryzae* infection**

T. Gebremariam, N. Wiederhold, A. Fothergill, E. Garvey, W. Hoekstra, R. Schotzinger, T. Patterson, S. Filler, A. Ibrahim (Torrance, CA, United States)*

ECCMID 2015 Final Programme
www.eccmid.org/fileadmin/eccmid/2015/media/documents/912604_ECCMID2015_20Final_Programme_WEB.compressed.pdf

VT-1161
ECCMID 2015

28 Apr Tuesday 12:30-13:30 Poster area

P1274	**High *in vitro* potency of the clinical investigational agent VT-1161 against clinical isolates of *Candida* spp.** *L. Long, N. Isham, M. Ghannoun, E. Garvey* (Cleveland, OH, United States), W. Hoekstra, R. Schotzinger, A. Fothergill, N. Wiederhold*

ECCMID 2015 Final Programme
www.eccmid.org/fileadmin/eccmid/2015/media/documents/912604_ECCMID2015_20Final_Programme_WEB.compressed.pdf

VT-1129 – fungal cyp51 inhibitor ECCMID 2015

25 Apr Saturday 15:30-16:30 Poster area

P0232	**The novel fungal Cyp51 inhibitor VT-1129 demonstrates potent *in vivo* activity in mice against cryptococcal meningitis with a loading/maintenance dosing regimen** *N. Wiederhold* (San Antonio, TX, United States), L. Najvar, A. Alimardanov, J. Cradock, X. Xu, M. Behnke, E. Ottinger, W. Hoekstra, E. Garvey, S. Brand, R. Schotzinger, R. Bocanegra, W. Kirkpatrick, T. Patterson*

ECCMID 2015 Final Programme
www.eccmid.org/fileadmin/eccmid/2015/media/documents/912604_ECCMID2015_20Final_Programme_WEB.compressed.pdf

MGCD290

Compound (Notes)	Company	Development Status	Model/Study	Related Ref.s
MGCD290 Oral histone deacetylase inhibitor Potential for combination tx.	Mirati Therapeu., CA, USA	Phase 2	VVC (FLU+MGCD290 po vs. FLU; mod. to severe VVC	Pfaller DMID 2015; Pfaller JCM 2009; ICAAC 2009 M-1029; ID Week 2012; 1619 (Phase 1)

Clinical trial: clinicaltrials.gov

Diagnostic Microbiology and Infectious Disease 81 (2015) 259–263

In vitro activity of a Hos2 deacetylase inhibitor, MGCD290, in combination with echinocandins against echinocandin-resistant *Candida* species

M.A. Pfaller [a,b,*], P.R. Rhomberg [b], S.A. Messer [b], M. Castanheira [b]

A B S T R A C T

MGCD290, a Hos2 fungal histone deacetylase inhibitor, showed modest activity when tested alone (MIC range, 0.12–4 μg/mL; $MIC_{50/90}$, 0.5/4 μg/mL) against *Candida glabrata* (n = 15; 14 *fks* mutants; 5 also fluconazole resistant), *Candida albicans* (8 *fks* mutants; 2 also fluconazole resistant), *Candida tropicalis* (4 *fks* mutants), and *Candida krusei* (3 *fks* mutants). However, MGCD290 showed synergy or partial synergy for 33.3%, 30.1%, 36.7%, and 80.0% of the isolates when tested with anidulafungin, caspofungin, micafungin, and fluconazole, respectively. Favorable interactions were achieved with low concentrations of MGCD290 (0.015–0.25 μg/mL), and categorical shifts were observed in 2 of 8 (25.0%) isolates of *C. albicans* and 2 of 3 (66.7%) isolates of *C. krusei* and in 4 of the 5 (80.0%) fluconazole-resistant isolates of *C. glabrata*. MGCD290 exerts a distinctly favorable influence on the MICs of fluconazole and the echinocandins, resulting in conversion from resistance to susceptibility regardless of *fks* mutations.

MGCD290

JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2009, p. 3797–3804 Vol. 47, No. 12

Activity of MGCD290, a Hos2 Histone Deacetylase Inhibitor, in Combination with Azole Antifungals against Opportunistic Fungal Pathogens[▽]

M. A. Pfaller,[1,2*] S. A. Messer,[1] N. Georgopapadakou,[3] L. A. Martell,[3] J. M. Besterman,[3] and D. J. Diekema[1,4]

FLU, POS, VOR, MGCD290

Candida , Aspergillus, Mucorales, C. neoformans, Rhodotorula, Fusarium, Trichosporon, Scedosporium

showed modest activity when it was used alone (MICs, 1 to 8 μg/ml) and was mostly active against azole-resistant yeasts, but the MICs against molds were high (16 to >32 μg/ml). MGCD290 was synergistic with fluconazole against 55 (60%) of the 91 isolates, with posaconazole against 46 (51%) of the 91 isolates, and with voriconazole against 48 (53%) of the 91 isolates. Synergy between fluconazole and MGCD290 was observed against 26/30 (87%) *Candida* isolates. All 23 of the 91 *Candida* isolates that were not fluconazole susceptible demonstrated a reduced fluconazole MIC that crossed an interpretive breakpoint (e.g., resistant [MIC, ≥64 μg/ml] to susceptible [MIC, ≤8 μg/ml]) when fluconazole was combined with MGCD290 at 0.12 to 4 μg/ml. The activity of fluconazole plus MGCD290 was also synergistic against 6/10 *Aspergillus* isolates. Posaconazole plus MGCD290 demonstrated synergy against 14/15 Zygomycetes (9 *Rhizopus* isolates and 5 *Mucor* isolates). Voriconazole plus MGCD290 demonstrated synergy against six of eight *Fusarium* isolates.

Compound (Notes)	Company	Development Status	Model/Study	Related Ref.s
E1210 Inositol acyltransferase inhibitor Oral	Eisai Co., Japan	Preclinical	IC (candin-R), IA, Fusariosis - Animal models	Hata AAC 2011; Miyazaki AAC 2011; Pfaller DMID 2011; Pfaller AAC 2011; Castanheira AAC 2012; Wiederhold AAC 2015

E-1210

Antimicrobial Agents and Chemotherapy p. 352–357 Volume 56 Number 1

Activities of E1210 and Comparator Agents Tested by CLSI and EUCAST Broth Microdilution Methods against *Fusarium* and *Scedosporium* Species Identified Using Molecular Methods

Mariana Castanheira,[a] Frederick P. Duncanson,[b] Daniel J. Diekema,[c] Josep Guarro,[d] Ronald N. Jones,[a,e] and Michael A. Pfaller[a,c]

Species (no. tested)	Antifungal agent	Test method	No. of isolates at MIC/MEC (μg/ml) of: 0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
F. solani SC (15)	E1210	EUCAST			3	4	8							
		CLSI		2	8	5								
F. oxysporum SC (15)	E1210	EUCAST			2	8	4	1						
		CLSI		2	3	5	1	3	1					
Fusarium spp. (67)[c]	E1210	EUCAST	2	1	16	21	17	10						
		CLSI		11	19	26	5	5	1					
S. apiospermum (28)	E1210	EUCAST			1	21	6							
		CLSI			1	15	11	1						
S. prolificans (28)	E1210	EUCAST			1	13	12	2						
		CLSI			3	20	5							
Scedosporium spp. (63)[d]	E1210	EUCAST			3	38	19	3						
		CLSI			5	40	17	1						

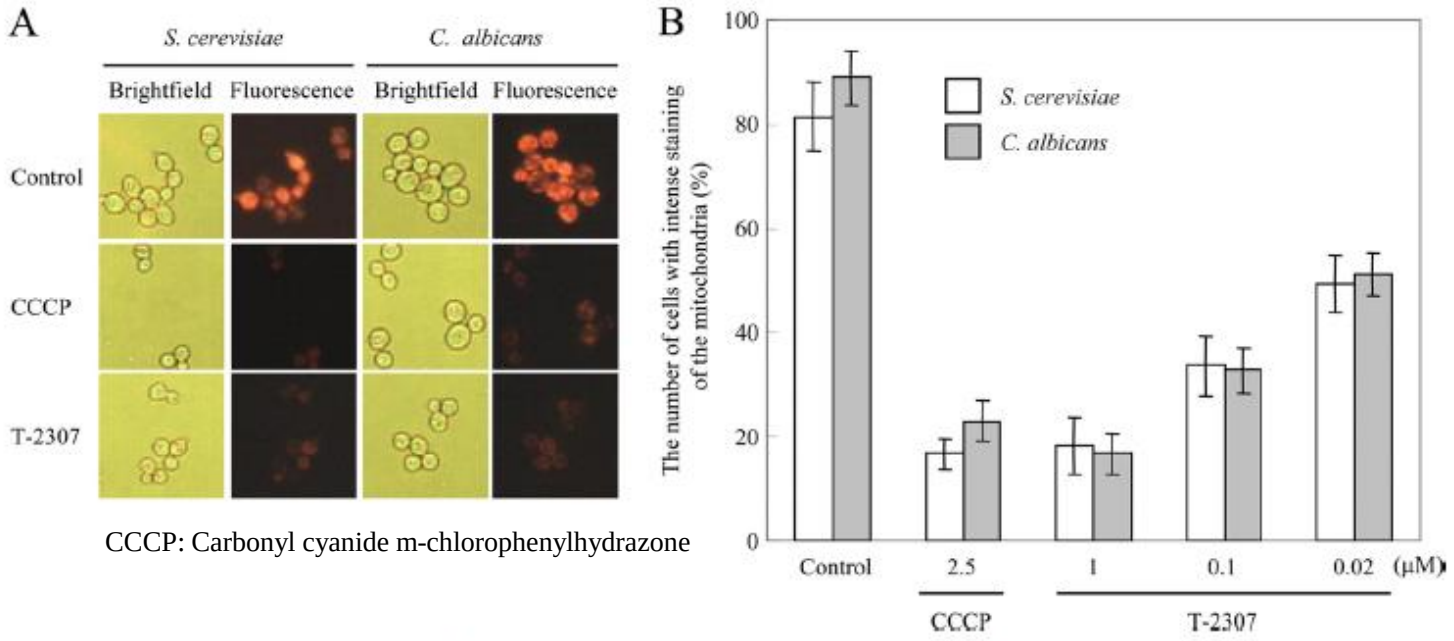
Compound (Notes)	Company	Development Status	Model/Study	Related Ref.s
T-2307 Arylamidine	Toyama, Japan	Preclinical	IC, IA, Cryptococcosis -Animal models Subcut.	Mitsuyama AAC 2008; Wiederhold AAC 2015

Antimicrobial Agents and Chemotherapy p. 5892–5897 November 2012 Volume 56 Number 11

T-2307 Causes Collapse of Mitochondrial Membrane Potential in Yeast

Tatsuya Shibata, Toshinari Takahashi, Eio Yamada, Akiko Kimura, Hiroshi Nishikawa, Hiroyoshi Hayakawa, Nobuhiko Nomura, and Junichi Mitsuyama

Research Laboratories, Toyama Chemical Co., Ltd., Toyama, Japan



CCCP: Carbonyl cyanide m-chlorophenylhydrazone

FIG 2 Effect of T-2307 on mitochondrial function within live yeast cells. Cells of *S. cerevisiae* and *C. albicans* were incubated in the presence or absence of T-2307 for 24 h prior to mitochondrial staining with MTR. CCCP at 2.5 μM was used as a positive control for disruption of mitochondrial membrane potential. Cells were observed by bright-field and fluorescence microscopy and photographed. (A) The concentration of T-2307 was 1 μM. (B) The concentrations of T-2307 were 0.02, 0.1, and 1 μM. Cells with intense staining of the mitochondria were counted. The values are the average for three independent experiments. Error bars represent SD ($n = 3$).

T-2307

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2008, p. 1318–1324 Vol. 52, No. 4

In Vitro and In Vivo Antifungal Activities of T-2307, a Novel Arylamidine▽

Junichi Mitsuyama,* Nobuhiko Nomura, Kyoko Hashimoto, Eio Yamada, Hiroshi Nishikawa, Makoto Kaeriyama, Akiko Kimura, Yozo Todo, and Hirokazu Narita

Active against Candida spp. (including flu-R), C. neoformans, and Aspergillus spp.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2010, p. 3630–3634 Vol. 54, No. 9

T-2307 Shows Efficacy in a Murine Model of *Candida glabrata* Infection despite *In Vitro* Trailing Growth Phenomena▽

Eio Yamada,* Hiroshi Nishikawa, Nobuhiko Nomura, and Junichi Mitsuyama

'Susc. of glabrata strongly influenced by the carbon source conc. in the medium. Trailing decreased as the glu conc. in the medium was decreased to ≤ 0.1% and completely inh.ed when glycerol was used. Using alamar blue (10%) facilitated MIC reading (24h, MIC-2). Efficacious against trailing isolates in murine models.'

T-2307

February 2015 Volume 59 Number 2 Antimicrobial Agents and Chemotherapy

The Novel Arylamidine T-2307 Maintains *In Vitro* and *In Vivo* Activity against Echinocandin-Resistant *Candida albicans*

Nathan P. Wiederhold,[a] Laura K. Najvar,[a,b] Annette W. Fothergill,[a] Rosie Bocanegra,[a,b] Marcos Olivo,[a,b] Dora I. McCarthy,[a] William R. Kirkpatrick,[a,b] Yoshiko Fukuda,[c] Junichi Mitsuyama,[c] Thomas F. Patterson[a,b]

Isolate type (no. of isolates)	MIC data (μg/ml) for indicated antifungal agent		
	T-2307 (50% inhibition)	T-2307 (100% inhibition)	Caspofungin
All *Candida albicans* (37)			
MIC range	≤0.008	0.008 to >4	0.06 to >8
MIC_{50}	≤0.008	>4	0.5
MIC_{90}	≤0.008	>4	>8
GM MIC[a]	0.008	>4	0.4548
Echinocandin susceptible (17)			
MIC range	≤0.008	0.008 to >4	0.06 to 0.125
MIC_{50}	≤0.008	>4	0.125
MIC_{90}	≤0.008	>4	0.125
GM MIC	0.008	3.836	0.1197
Echinocandin resistant (18)			
MIC range	≤0.008	0.008 to >4	1 to >8
MIC_{50}	≤0.008	>4	1
MIC_{90}	≤0.008	>4	8
GM MIC	0.008	3.996	1.587

[a] GM MIC, geometric mean MIC.

- FKS mutant C. albicans
- Improved survival and reduced fungal burden in murine model
- MIC-2 (no complete inh. using MIC-0)

Compound (Notes)	Company	Development Status	Model / Study	Related Ref.s
ASP9726 Novel second generation echinocandin Improved activity	Astellas Pharmaceu., Japan	Preclinical	IPA Animal models (guinea pig, rabbit) Efficacy & PK Subcut. inj.	Wiederhold AAC Accept 2015 March 9; Morikawa Bioorg Med Chem Lett 2014; Petraitis ICAAC 2012 M-981; Paderu ICAAC 2012 F-822

ASP9726

AAC Accepted Manuscript Posted Online 9 March 2015
Antimicrob. Agents Chemother. doi:10.1128/AAC.04857-14

Efficacy of the Investigational Echinocandin ASP9726 in a Guinea Pig Model of Invasive Pulmonary Aspergillosis

Nathan P. Wiederhold,[1] Laura K. Najvar,[1,2] Satoru Matsumoto,[3] Rosie A. Bocanegra,[1,2] Monica L. Herrera,[1] Brian L. Wickes,[1] William R. Kirkpatrick,[1,2] Thomas F. Patterson[1,2]

ASP9726 5 mg/kg (but not 10 mg/kg) increased survival
Paradoxical effect?

- (Decreased MIC) against **echino-R Candida**
- Glucan synthase more sensitive (2-165 fold) to ASP9726 compared to CAS and MCF (comparable or better than MCF, better than CAS)

Morikawa et al. Bioorg Med Chem Lett. 2014 ; 24:1172, Paderu et al. ICAAC 2012; M-981

Compound (Notes)	Company	Development Status	Model/Study	Related Ref.s
Biafungin (CD101) Echinocandin IV	Cidara Therapeutics, CA, USA	Preclinical (Phase 1 to be started in second half of 2015)	PK – animal data IC, animal model (Tx & prevention of systemic Cand inf.)	ICAAC 2014 A-693, A-694, F-1592, M-1082

•Prolonged half-life - -PK expected to allow once weekly IV tx.

•Spectrum of activity & potency comparable to available echinocandins (ANID) (activity against echino-R Cand & Itra-R Asp)

Compound (Notes)	Development Status	Model/Study	Related Ref.s
AMB cochleates	Preclinical	Cand.& Asp.- Animal models (oral), Leishmania chagasi (Macrophage model)	Santangelo AAC 2000; Delmas AAC 2002; Sesana Mem Inst Oswaldo Cruz 2011
Nanoparticle formulations of AMB	Preclinical	Asp., nebulizer-based prophylaxis - Animal model	Shirkhani Nanomedicine 2015 March16; Tang Int J Nanomedicine 2014
Nanoparticle formulations of itraconazole	Preclinical	Cand.- Animal model	Qiu Int J Nanomedicine 2015

Conclusions

- Discovery and development of new antifungal agents are challenging.
- Few molecules are in clinical development. Antifungal drug spectrum offers rather limited choices.
- While the development of new drugs is promising for a number of unmet needs, the efficacy of therapy particularly in immunosuppressed individuals is strongly affected by the host factors as well.


Thank you...