The Antifungal Pipeline

Maertens Johan, MD, PhD

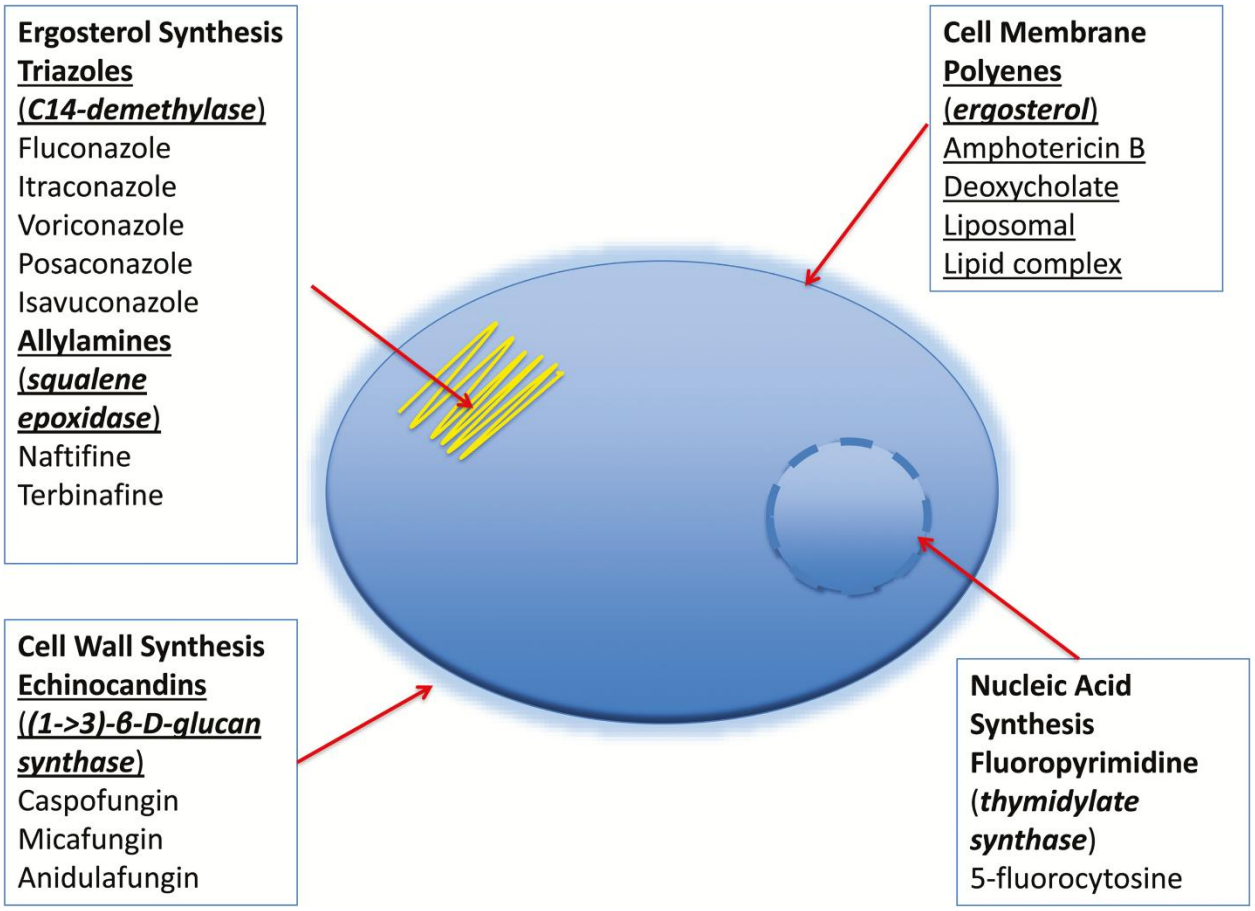
University Hospital Gasthuisberg, Leuven, Belgium

Disclosures

- Received grants, speaker's fee, ad board honoraria and/or travel support from
  - Gilead Sciences
  - Pfizer Inc.
  - MSD
  - Basilea Pharmaceuticals
  - Astellas
  - Bio-Rad laboratories
  - F2G
  - Scynexis
  - Amplyx
  - Cidara
  - Vical

"Yes, I am employee of the month again. And yes, I'm the one who chooses the employee of the month. And no, I don't see a conflict of interest."

The current antifungal armamentarium: cellular and biochemical targets



McCarthy MW et al. J Infect Dis 2017; 216: S474-83

Isavuconazonium sulfate

- ***SECURE-study***
  - Invasive aspergillosis and other filamentous moulds[1]
- ***VITAL-study***
  - Mucormycosis, rare fungal infections and renally impaired patients[2,3]
- ***ACTIVE-study***
  - Candidemia and other invasive *Candida* infections[4]

1. Maertens JA, et al. *Lancet* 2016; 387: 7609
2. Marty FM, et al. *Lancet Infect Dis* 2016; 16: 828-37
3. Thompson GR 3rd, et al. *Clin Infect Dis* 2016; 63: 356-62
4. Kullberg BJ, et al. 26th ECCMID Amsterdam, The Netherlands,9-12 April 2016; abstract #1239

Isavuconazole versus voriconazole

	Voriconazole	Isavuconazole*
Active against Mucorales	No	Active against some
Food effect	Yes	No
β-cyclodextrin	Yes	No
Administration	Twice/d following loading dose	Once/d following loading dose
Predictable PK in adults	No	Yes (up to 600 mg)
Need for TDM	Yes	Not routinely
Drug Interactions	+++	++
Safety (visual)	++	+ (no visual)
Clinical experience	Extensive	Limited

*Miceli MH and Kauffman CA. Clin Infect Dis 2015

Isavuconazole versus voriconazole (SECURE) study: Primary endpoint (ITT population)

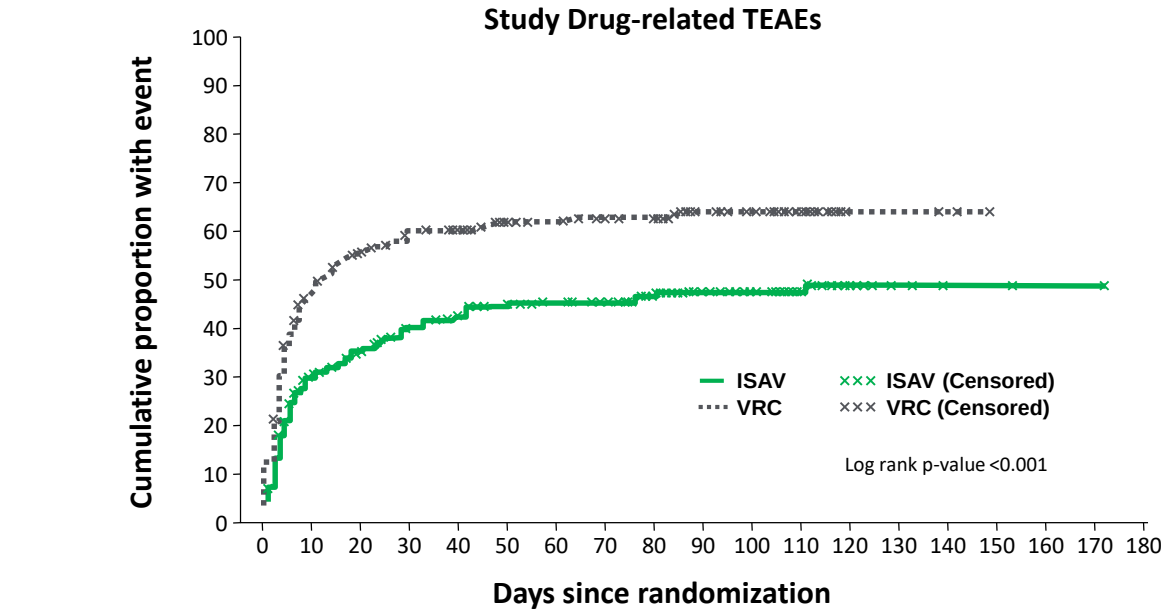
All-cause mortality (ACM) through Day 42

	Isavuconazole N = 258	Voriconazole N = 258
All-cause mortality, n (%)	48 (**18.6**)	52 (**20.2**)
Adjusted treatment difference, % (95% CI)[a]	–1.0 (–7.8, 5.7)	
Deaths, n (%)	45 (17.4)	50 (19.4)
Unknown survival status, n (%)[b]	3 (1.2)	2 (0.8)

[a]Isavuconazole–voriconazole calculated by a stratified Cochran–Mantel–Haenszel method (strata: Geographic region, Allogeneic BMT/HSCT, and uncontrolled malignancy status)
[b]Patients with unknown survival status were counted as deaths

Maertens J. et al. *Lancet* 2016; 387: 760-9

Isavuconazole versus voriconazole (SECURE) study:
Cumulative incidence of TEAEs over time



TEAEs leading to study drug discontinuation: 14.4% (ISA) vs. 22.8% (VOR); p<0.05

Ullmann A. et al. *ECCMID 2015, Copenhagen Denmark, April 25-25, 2015, EPO18*

Maertens J. et al. *Lancet* 2016; 387: 760-9

Isavuconazole versus voriconazole (SECURE) study:
Most frequent Adverse Events (>10%) by SOC

System Organ Class (%)	Isavuconazole (N=257)	Voriconazole (N=259)
Patients with any AE	96.1	98.5
Skin and subcutaneous tissue disorders	33.5[#]	42.5
Eye disorders	15.2[#]	26.6
Hepatobiliary disorders	8.9[#]	16.2

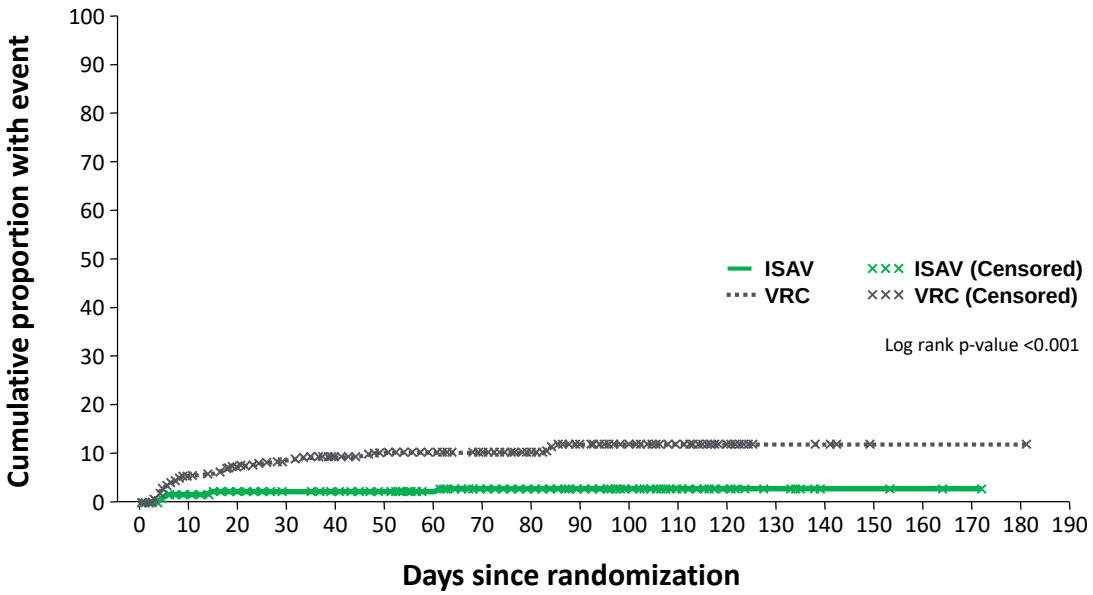
[#]p<0.05

- Other adverse events were not significantly different between isavuconazole and voriconazole

Maertens J. et al. *Lancet* 2016; 387: 760-9

Isavuconazole versus voriconazole (SECURE) study:

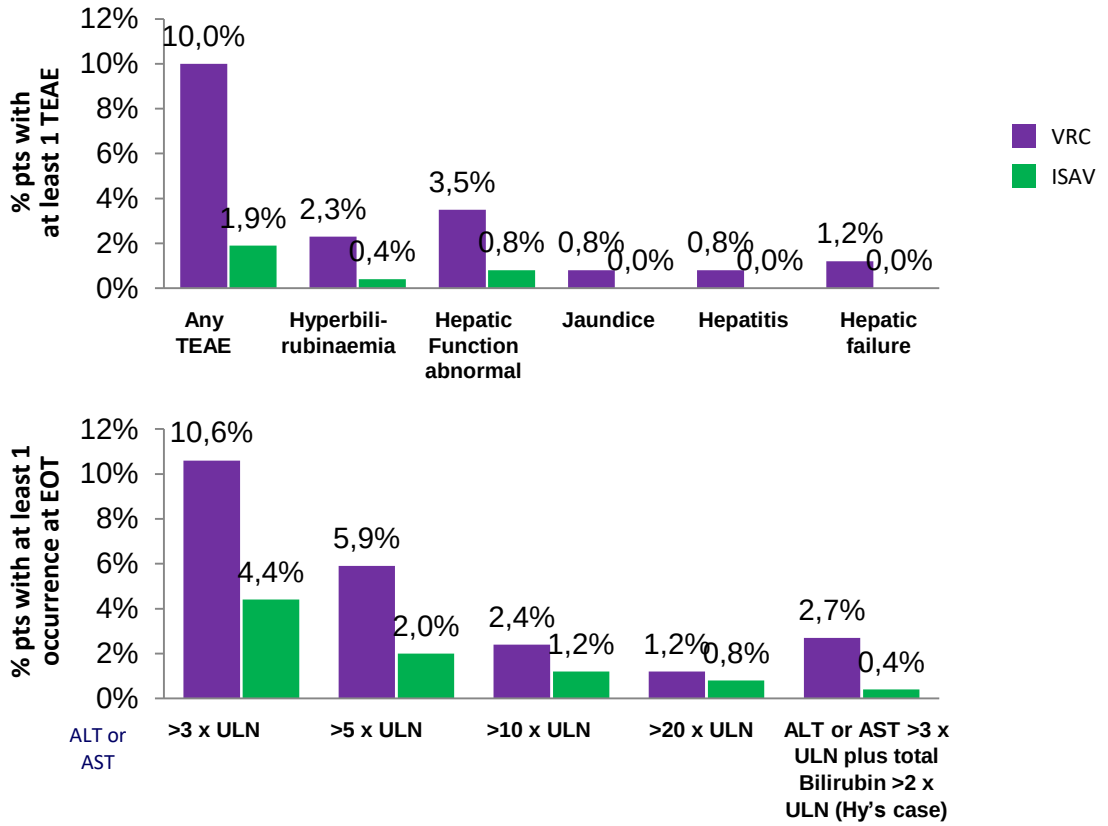
Cumulative incidence of study drug-related hepatobiliary TEAEs



Ullmann A. et al. *ECCMID 2015, Copenhagen Denmark, April 25-25, 2015, EPO18*

Isavuconazole versus voriconazole (SECURE) study:

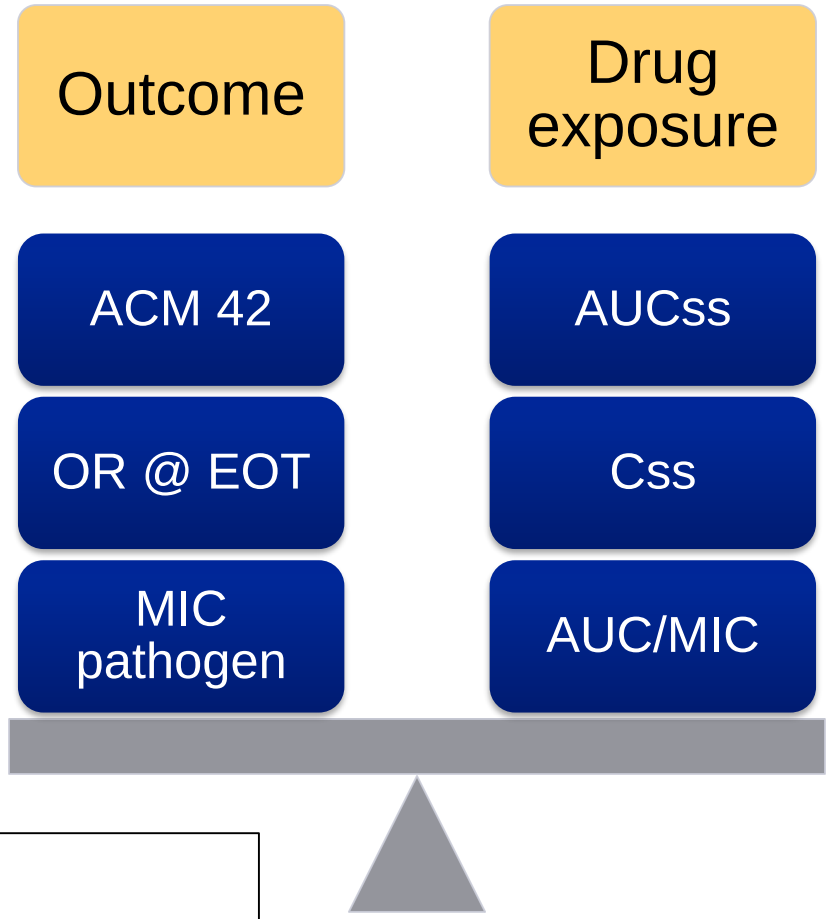
Cumulative incidence of study drug-related hepatobiliary TEAEs and lab values



Ullmann A. et al. *ECCMID 2015, Copenhagen Denmark, April 25-25, 2015, EPO18*

Isavuconazole: exposure-response

Lack of any statistically significant relationship

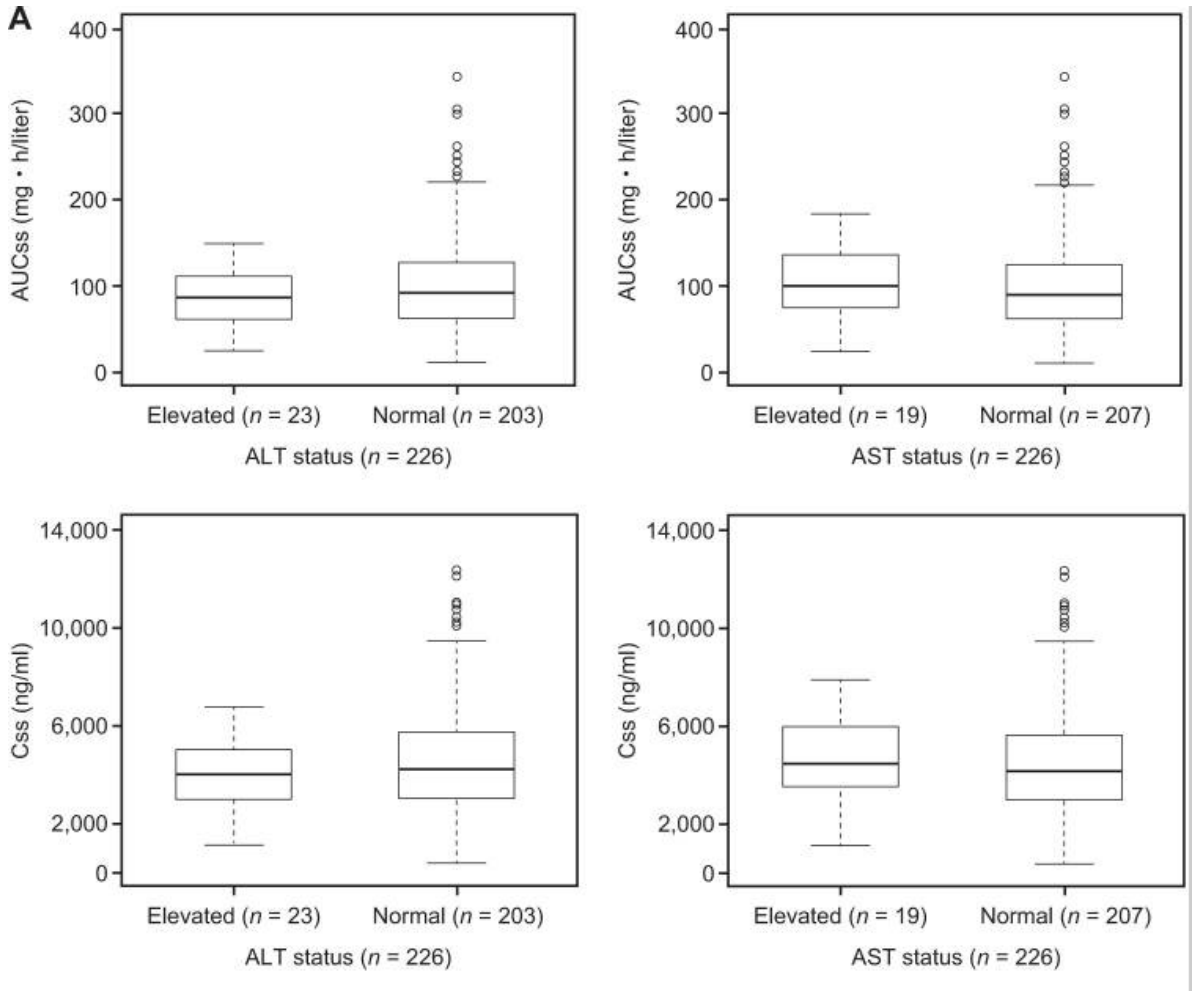


ACM: all cause mortality
OR: overall response
EOT: end of treatment
MIC: minimal inhibitory concentration
AUCss: are under the concentration-time curve at steady state
Css: mean through concentration at steady state

Desai A. et al. Antimicrob Agents Chemother 2017; 61: e01034-17

Isavuconazole: exposure-hepatic safety

Lack of any statistically significant relationship



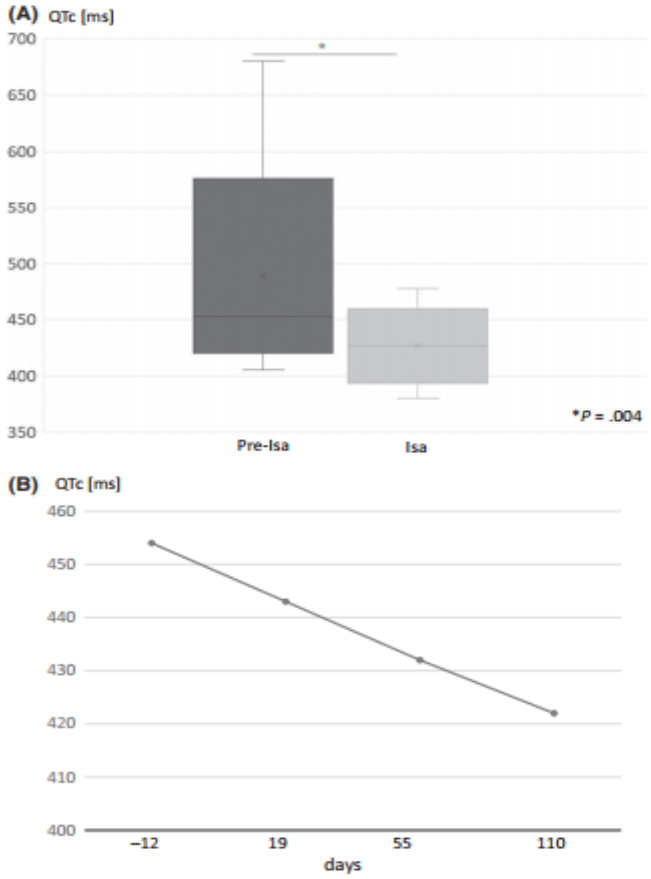
Desai A. et al. Antimicrob Agents Chemother 2017; 61: e01034-17

Isavuconazole shortens the QTc interval

A. QTc changes in 26 patients before (pre-Isa) and under treatment with isavuconazole (Isa): mean decrease of 36.5 ± 38.8 msec. (range 7-202 msec.)

B. QTc intervals in a patient with long-term isavuconazole treatment

C. Contra-indicated in patients with familial short QT syndrome



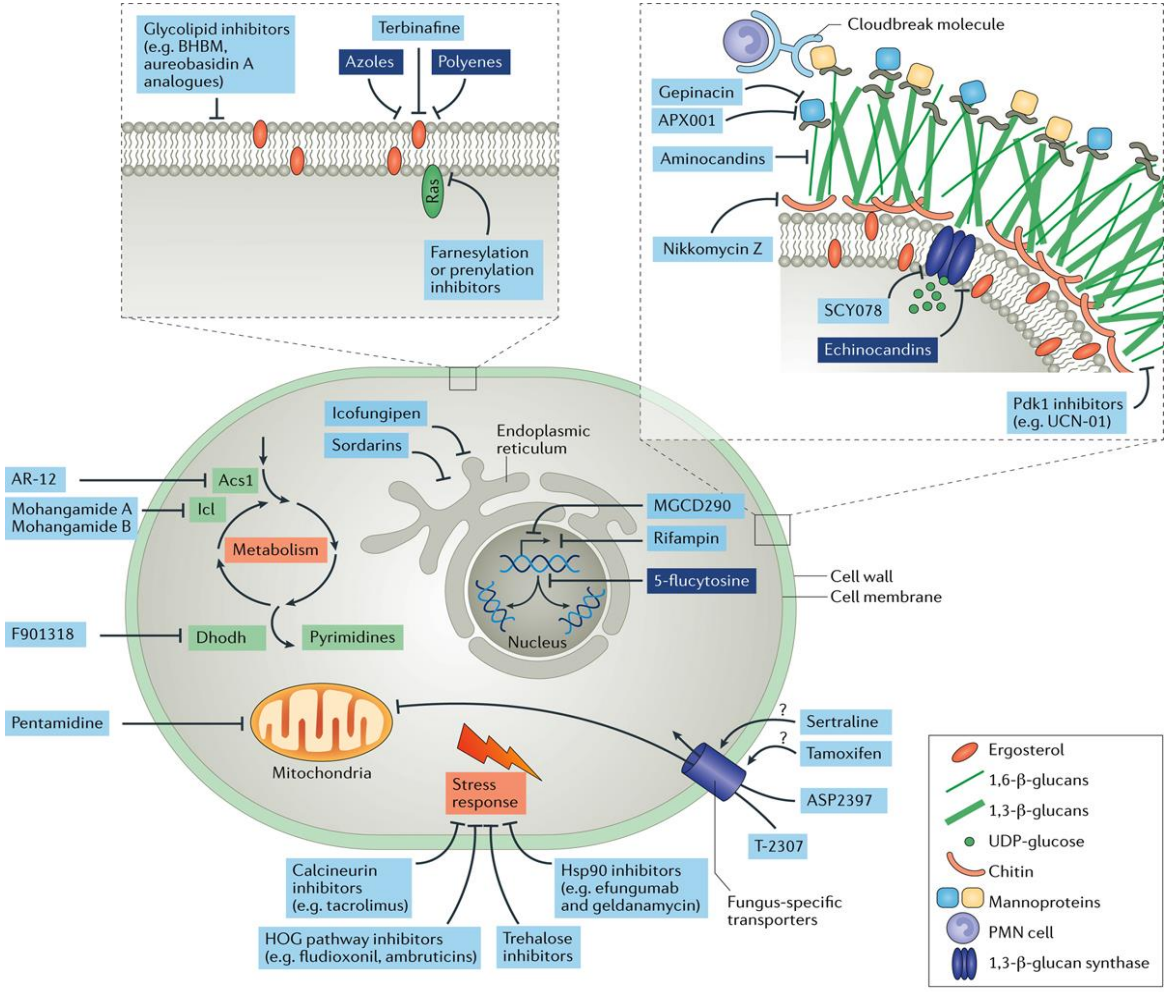
Mellinghoff S. et al. Mycoses, 2018: 1-5

A need for novel antifungal agents (modes of action)

- Gaps in the spectrum of available antifungals
- Emergence of (multi-drug) resistance
- Hazardous drug-drug interactions
- Lack of oral formulations for prolonged (out-patient) therapy
- Acute drug-related toxicities (resulting in early discontinuation) and toxicities associated with prolonged use
- Need for therapeutic drug monitoring due to nonlinear and saturable pharmacokinetics
- Food effects
- Patient complicance

→ **Pressing need for new drugs that inhibit novel *fungus-specific* targets**

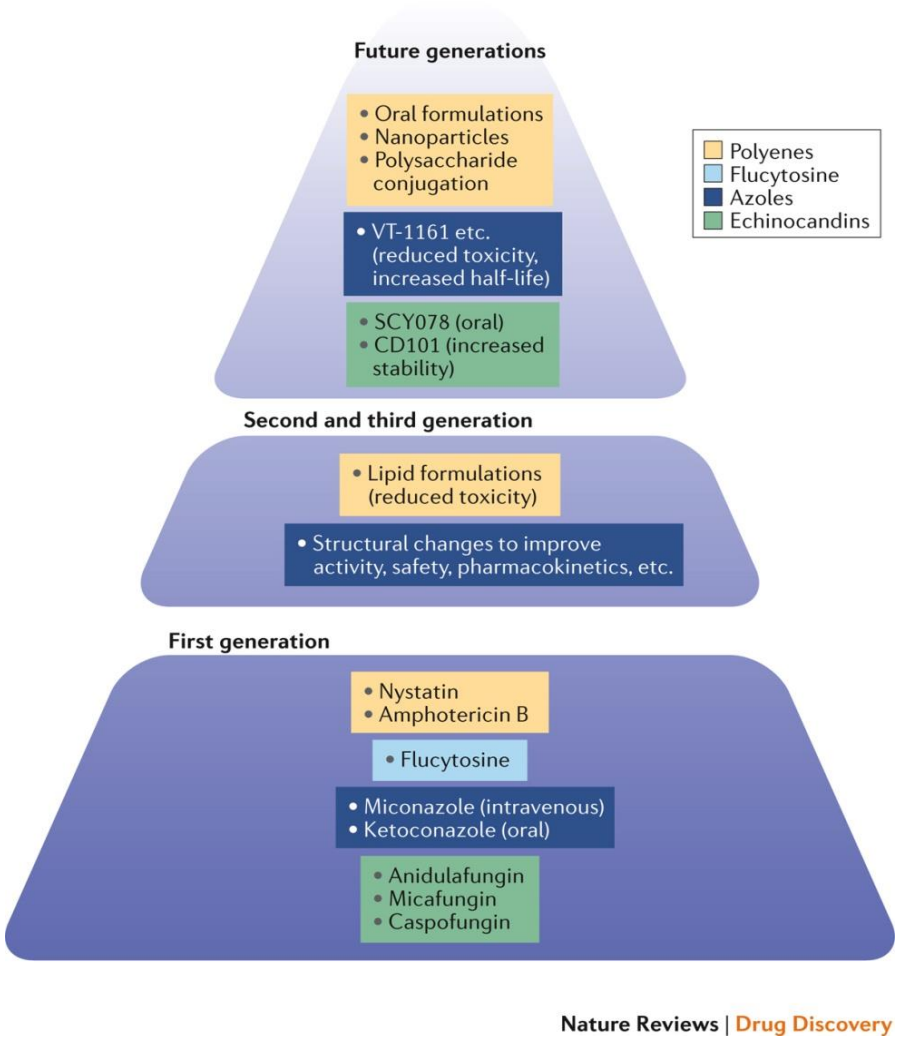
The antifungal pipeline



Nature Reviews | Drug Discovery

Perfect JR. Nat Rev Drug Discov 2017; 16: 603-616

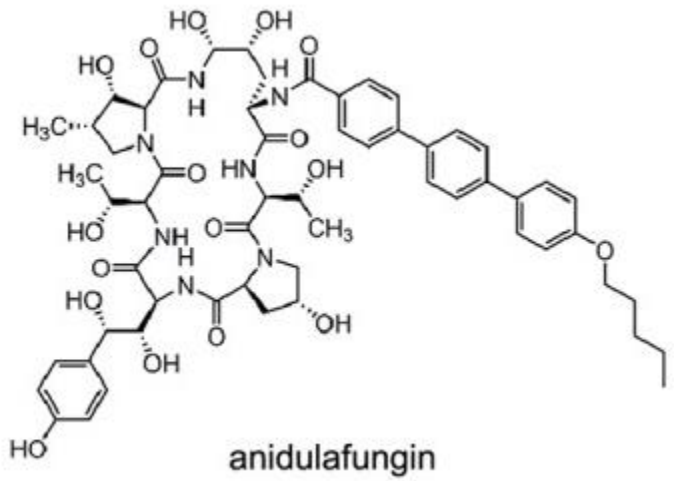
Improving existing antifungals



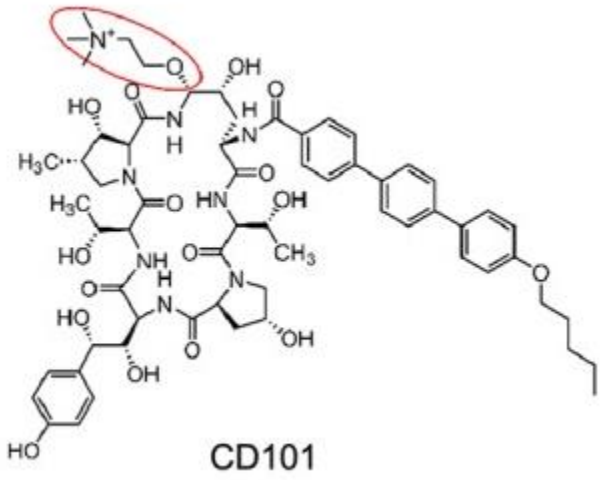
Perfect JR. Nat Rev Drug Discov 2017; 16: 603-616

Rezafungin (CD101): a more stable echinocandin

(Cidara Therapeutics, San Diego, CA, USA)



anidulafungin



CD101

Structural modification yields improved chemical & biological properties

- Prolongs half-life (~133 h) ..... **once weekly dosing**
- Allows high exposures ..... **improved efficacy (less susceptible pathogens)**
- Eliminates toxic degradation products ..... **improved safety**
- Enables multiple formulations ..... **intravenous and subcutaneous; no oral**

Rezafungin: activity against *Candida* and *Aspergillus*

Reza, anidulafungin and caspofungin tested against international clinical surveillance isolates

	Candida MIC_{90} (mg/L)[1]					*Aspergillus* MEC_{90} (mg/L)[2]			
	albicans (n=655)	*glabrata* (n=321)	*tropicalis* (n=206)	*krusei* (n=130)	*parapsilosis* (n=275)	*fumigatus* (n=20)	*terreus* (n=19)	*niger* (n=16)	*flavus* (n=12)
Rezafungin	**0.06**	**0.125**	**0.06**	**0.03**	**2**	**0.015**	**0.015**	**≤0.008**	**≤0.008**
Anidulafungin	0.03	0.125	0.03	0.06	2	0.015	0.015	≤0.008	≤0.008
Caspofungin	0.03	0.25	0.25	0.5	1	0.125	0.125	0.06	0.06

- CLSI broth microdilution methodology was employed for MIC/MEC determination (M27-A3, M38-A2)

[1]*Candida* spp. MIC data were derived from the 2014 and 2015 SENTRY international surveillance program and the 2014 Micromyx US surveillance program (Pfaller, et al, 2017, AAC; Pfaller, et al, 2017, IJAA; Hall, et al, 2017, DMID)

[2]*Aspergillus* spp. isolates were collected internationally between 2007 and 2011 and were tested as part of a retrospective study (Pfaller, et al, 2016, JAC)

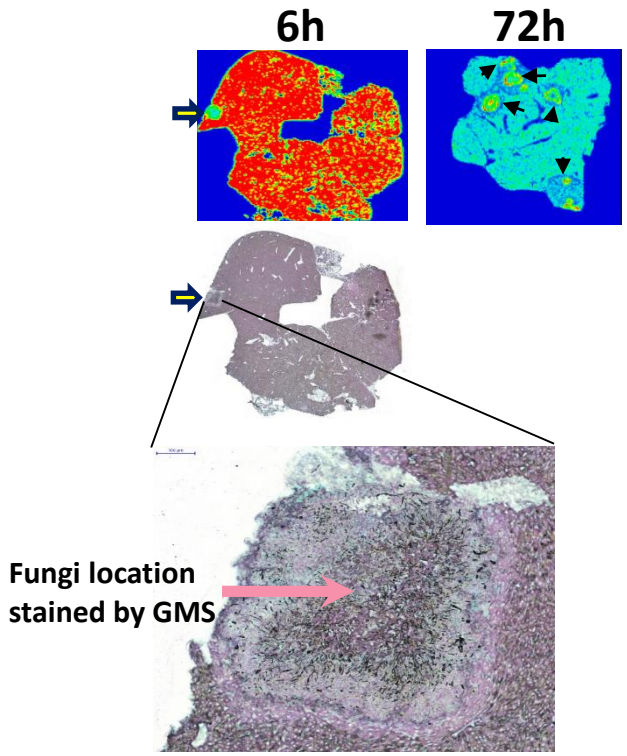
- The activity of CD101 is comparable to that of other members of the echinocandin class
- Similar results for CD101 activity versus Candida and Aspergillus spp. may be obtained with either CLSI or EUCAST BMD methods.

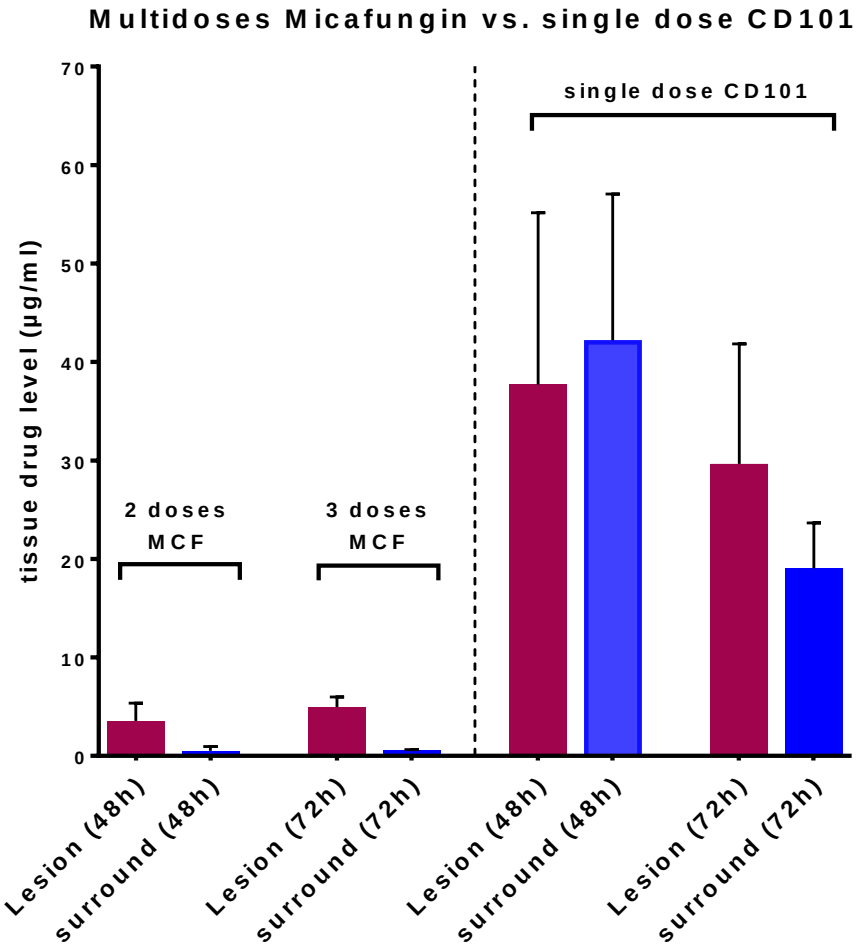
Pfaller M. et al. J Antimicrobial Chemother 2016; 71: 2868-73 and Arendrup M et al. Clin Microbiol Infect 2018 [Epub ahead of print]

Rezafungin: superior penetration and accumulation at at the site of infection versus micafungin (5mg/kg)

Intra-abdominal invasive candidiasis abscess model

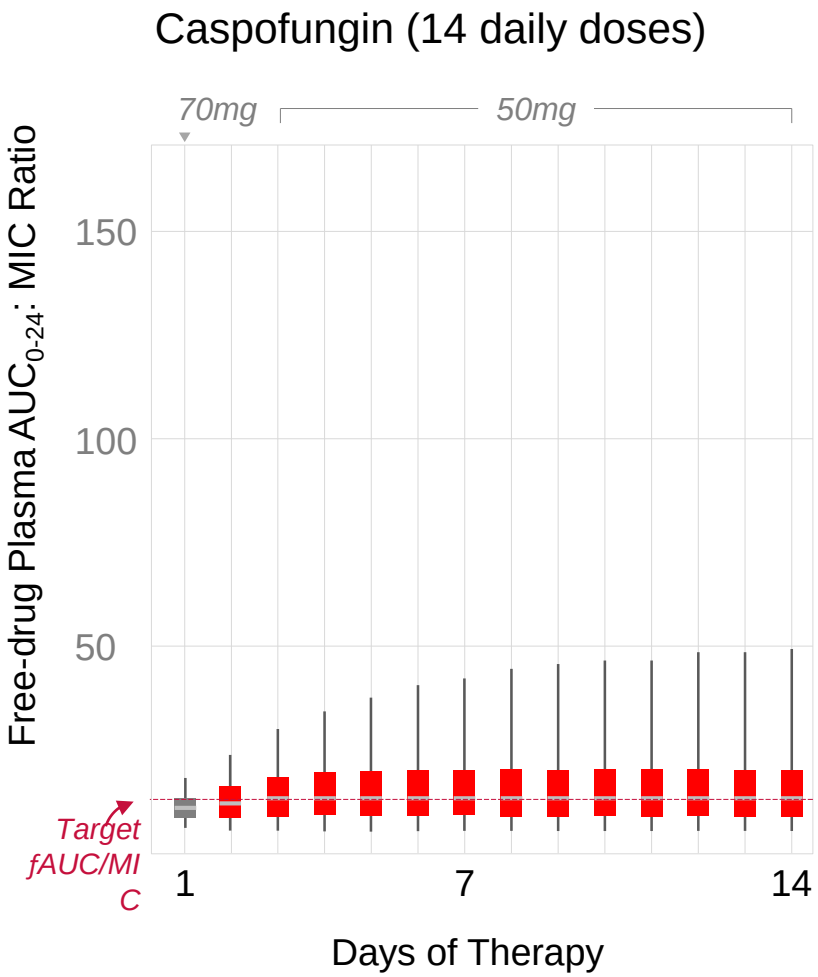
Drug distribution in liver after single dose CD101 at 20 mg/kg determined by MALDI MS Imaging

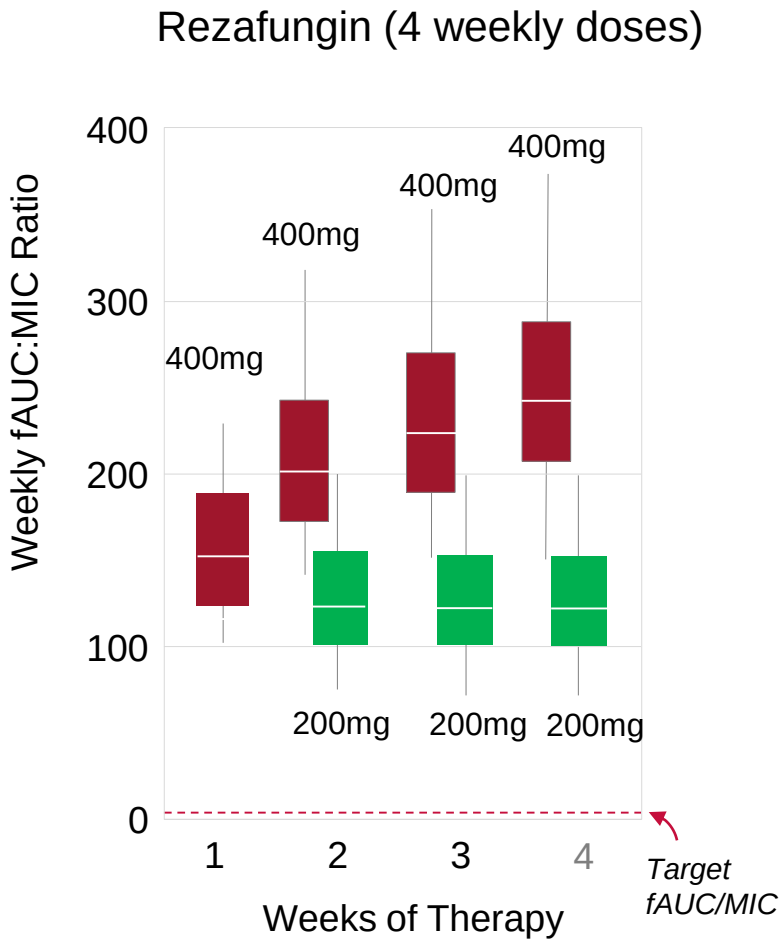




Zhao et al. Antimicrobial Agents Chemother 2017; 61: e01009-17

Rezafungin PK/PD:
Exposure is Key to Improved Efficacy

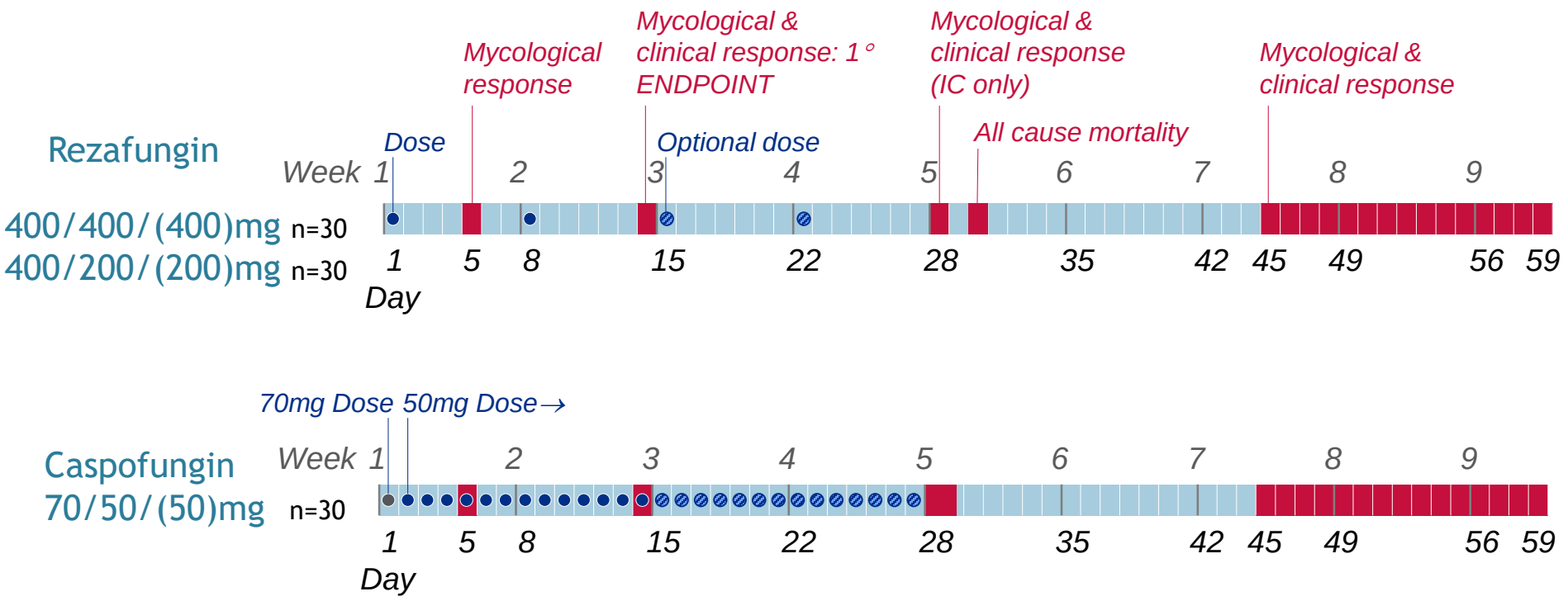




MIC=0.25 for caspofungin. MIC=0.12 for CD101

Bader et al. Emerging Candida glabrata Resistance and Echinocandin Dosing: A Call to Arms! IDWeek 2016
Bader et al. Overcoming the Resistance Hurdle: PK-PD Target Attainment Analyses of Rezafungin (CD101) for Candida albicans and Candida glabrata. Submitted AAC 2018

STRIVE Part A: Candidemia & Invasive Candidiasis



Analysis Populations:

- The Intent-to-treat (ITT) population: all randomized subjects
- The Safety population: all subjects who received any amount of study drug
- The Microbiological Intent-to-treat population (mITT): all subjects in safety population who had documented *Candida* infection

STRIVE Overall Response (Primary Outcome)

Day 14 – mITT Population

Response	Rezafungin 400 mg/400 mg (QWk) N= 33	Rezafungin 400 mg/200 mg (QWk) N= 31	Caspofungin 70 mg/50 mg (QD) N= 28
	n (%)		
Success	19 (57.6)	22 (71.0)	18 (64.3)
Failure	7 (21.2)	6 (19.4)	8 (28.6)
Indeterminate	7 (21.2)	3 (9.7)	2 (7.1)
	Excluding Indeterminate Response*		
Success	19/26 (73.1)	22/28 (78.6)	18/26 (69.2)
Failure	7/26 (26.9)	6/28 (21.4)	8/26 (30.8)

*Indeterminate response indicates inability to assess outcome due to missing data point(s)

Rezafungin shows equivalent efficacy to TMP/SMX in PCP prophylaxis mouse model

Prophylaxis with rezafungin, which blocked cyst/asci formation, offers a new means to prevent PCP

STUDY DESIGN

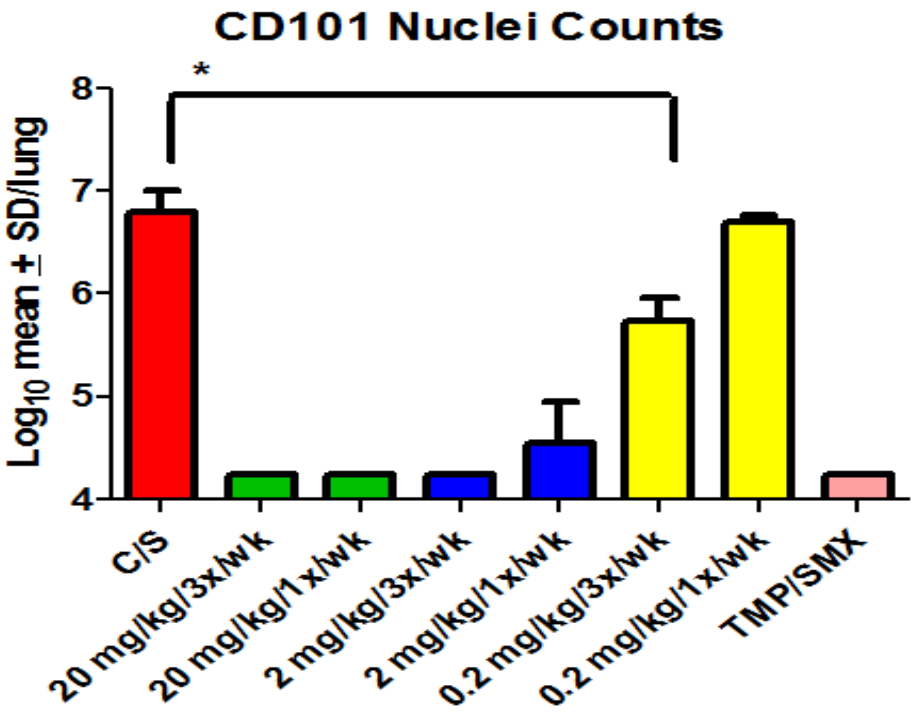
10 mice per arm

Infected with *P. murina* by intranasal inoculation

Immunosuppression with dexamethasone throughout study

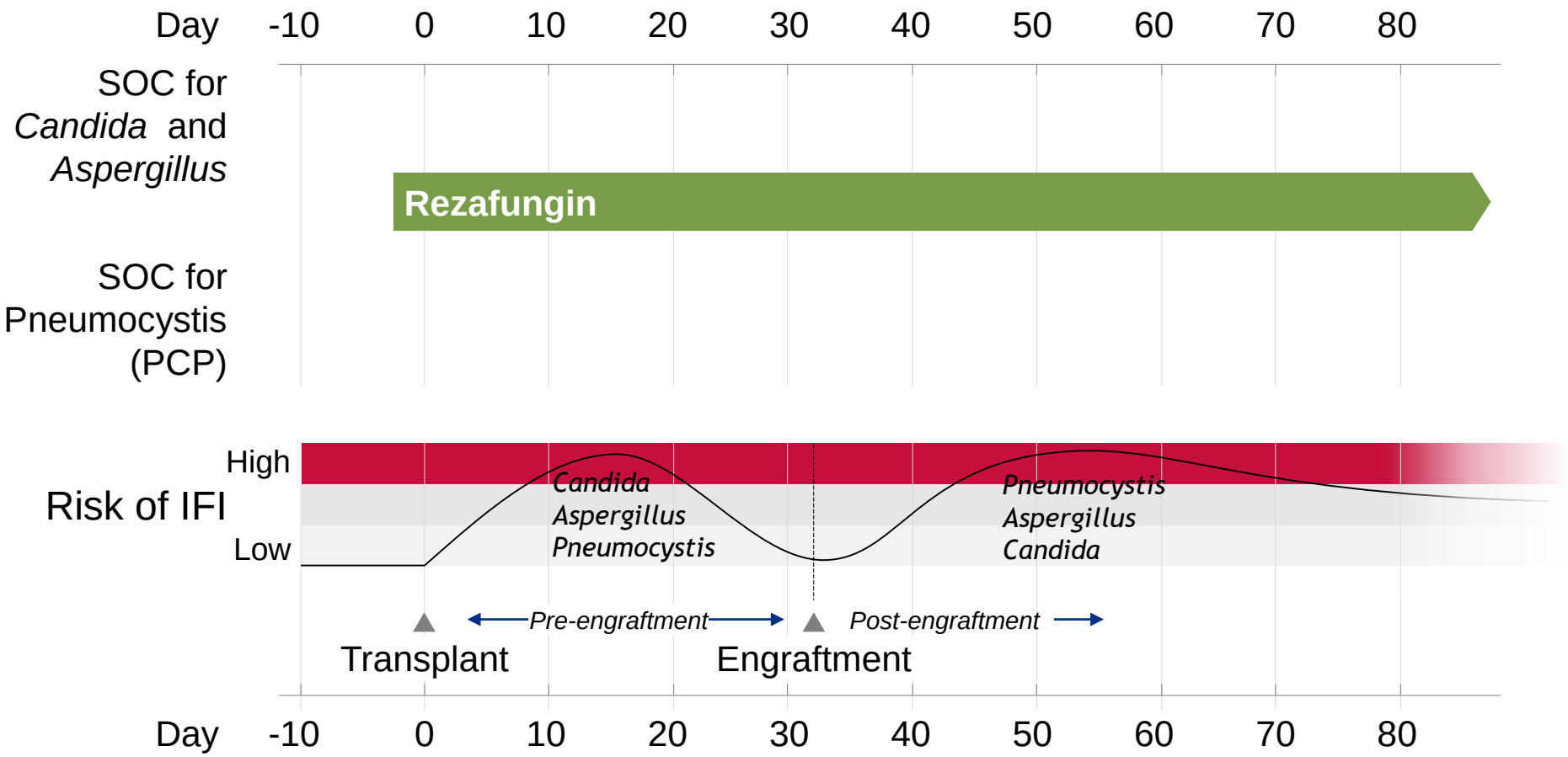
CD101 was administered at the same time the mice were infected

Quantification of PCP from lung



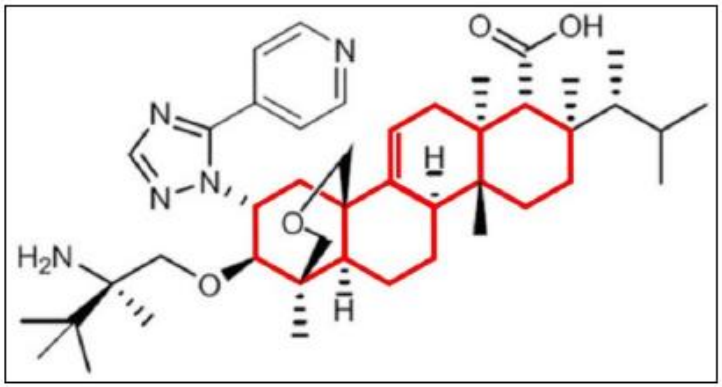
Cushion et al. ASM. 2016

Rezafungin:
Potential for Simplified Single Drug Paradigm



SCY-078: (triterpene) β-(1,3) glucan synthase inhibitor

(Scynexis [spin-off of Sanofi], Jersey City, NJ, USA)



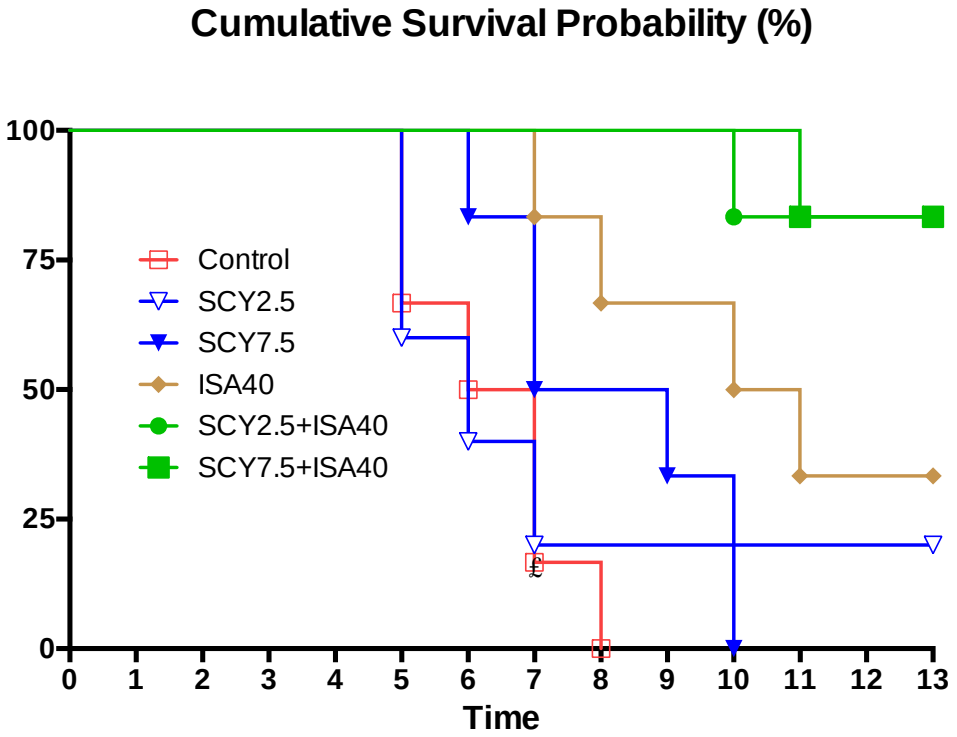
Structurally district from other GSIs (echinocandins)

- IC_{50} against purified glucan synthase from C. albicans is 0.6 ng/mL
- Different enzyme-drug interaction → lower impact of common *fks* mutations
- Oral bioavailability

- Activity against:
  - Cidal against Candida spp (also R and C. *auris*)
  - High activity against *Candida* biofims
  - Aspergillus spp (also azole-R)
  - Pneumocystis spp
  - Paecilomyes variotii
  - No activity Mucorales/*Fusarium*
- ORAL and IV formulations
- Favorable safety profile
- Low risk of drug-drug Interactions (not a CYP substrate nor inhibitor)
- High tissue penetration (Vdss > 8 L/kg) but no CNS penetration
- No QTc effect expected

SCY-078 in combination with azole for invasive pulmonary aspergillosis -Rabbit model

- Neutropenic rabbit model of pulmonary aspergillosis
- Treatment for 12 days
- N=6 / group (QD doses):
  - SCY-078 (IV) at 2.5 or 7.5mg/kg
  - Isavuconazole (PO) 40mg/kg
  - SCY-078 2.5 + Isavuconazole
  - SCY-078 7.5 + Isavuconazole

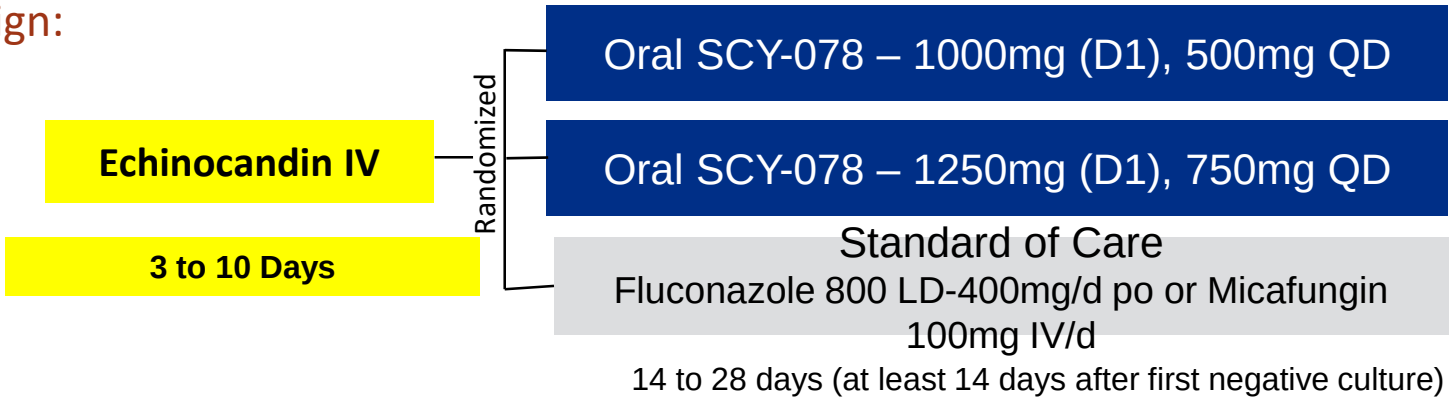


- p<0.05, prolonged survival in SCY2.5+ISA40 and SCY7.5+ISA40 - treated rabbits in comparison to that of single therapy of SCY2.5, SCY7.5, and ISA40

Angulo D. at TIMM 2017

SCY-078 - Phase 2 in Invasive Candidiasis (Step Down) - Completed

Design:



Results:

Pop PK = **SCY-078 PO, 750mg QD achieves target exposure ($AUC_{0\text{-}24hr}$ of 15 µM·hr)**
AEs frequency and severity - comparable for all groups

Global Response at EOT	Favorable	Reasons for Unfavorable
SCY-078 500 mg N = 7 n (%)	5 (71.4)	1. Never received study drug 2. Discontinued due to a non-drug related AE
SCY-078 750 mg N = 7 n (%)	6 (85.7)	1. Withdraw consent after one dose
Fluconazole 400 mg N =7 n (%)	5 (71.4)	1. Died (abdominal sepsis) 2. Discontinued (new + blood culture for *Candida* spp;)

SCY-078 Phase 2 Study in Moderate and Severe Vulvovaginal Candidiasis (VVC): proof-of-concept

70 subjects had cultured-confirmed VVC (per protocol population)

Efficacy Evaluation at Day 24 (per protocol population)					
N Rates %	SCY-078 1250mg (D1), 750mg (D2-3) (n= 24)	SCY-078 1250mg (D1), 750mg (D2-5) (n= 26)	SCY-078 (Combined) (n= 50)	Fluconazole 150mg (D1) (n= 20)	% Δ SCY-078 (combined) vs. Fluconazole
Clinical Cure	19 *79.2%*	19 *73.1%*	38 ***76%***	13 ***65%***	**+11%**
Efficacy Evaluation at Month 4					
Recurrences Requiring Antifungal Therapy	1 *4.2%*	1 *3.8%*	2 ***4%***	3 ***15%***	**-11%**

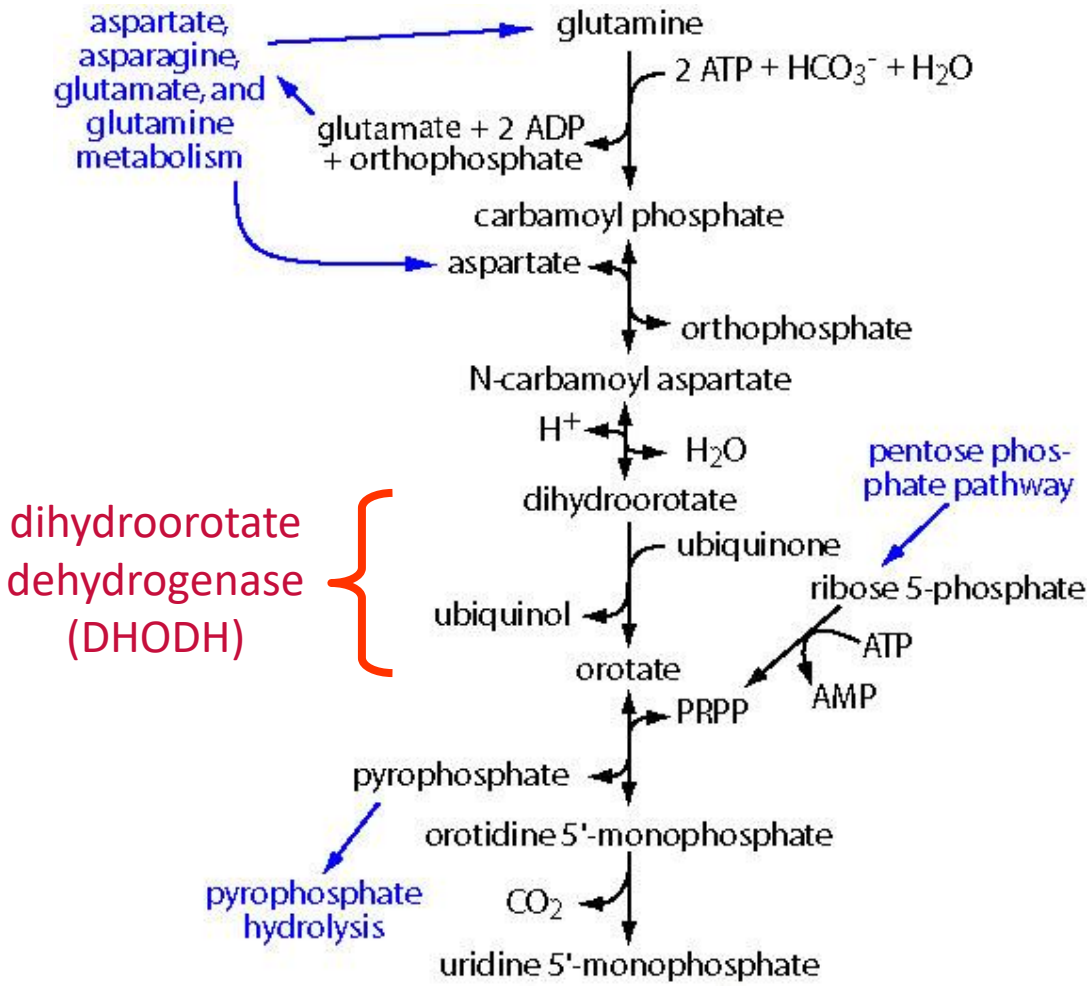
- The rate of mycological eradication at Day 24 and Month 4 was 70% and 74% for the SCY-078 combined arms vs. 65% and 60% for the fluconazole arm
- There were no severe or serious adverse events in any treatment groups. A higher rate of GI adverse events (e.g., nausea, diarrhea) were reported in the SCY-078 treatment arms, which were mild to moderate in severity and transient in nature

Roman M at ECCMID 2017

SCY-078: ongoing clinical trials

- FURI: Phase 3, open-label study in patients that are refractory to or intolerant of approved antifungal agents
  - Intended population includes:
    - Invasive candidiasis, including *C.auris*
    - Chronic disseminated candidiasis
    - Severe mucocutaneous candidiasis
  - Sites opened in the US and in EU
- DOVE: Phase 2, randomized, double blind, dose-finding study in patients with acute VVC
  - Exploring 5 dose regimens of oral SCY-078 vs. Fluconazole
  - Sites opened in the US

Orotomides: inhibitors of pyrimidine biosynthesis
(F901318, F2G Ltd, Manchester, UK)



Oliver JD et al. PNAS 2016; 113: 12809-12814

F901318: In vitro active against all major *Aspergillus* spp., including *A. terreus*

MICs (mg/L) for F901318 against *Aspergillus* spp.

		F901318	Voriconazole	Posaconazole
A. fumigatus	GeoMean	0.037	0.700	0.590
(n=44)	MIC50	0.040	0.630	0.630
	MIC90	0.040	5.0	1.250
A. terreus	GeoMean	0.013	0.112	0.290
(n=17)	MIC50	0.020	0.630	0.310
	MIC90	0.040	0.630	0.630
A. niger	GeoMean	0.048	0.274	0.368
(n=15)	MIC50	0.04	0.31	0.63
	MIC90	0.08	1.25	1.25
A. flavus	GeoMean	0.031	0.466	0.582
(n=17)	MIC50	0.04	0.63	0.31
	MIC90	0.04	1.25	0.63

MIC50 (MIC90) = MIC (mg/L inhibiting 50% (90%) of strains. VORI = voriconazole, POSA = posaconazole

Intrinsic resistance to Amphotericin B

F901318: In vitro active against azole-resistant *A. fumigatus* with defined *cyp51A* mutations

Isolate	cyp51A amino acid substitutions	Itraconazole	Posaconazole	Voriconazole	F901318
F6919	M220K	>8	>8	1	0.08
F7075	G54E	>8	>8	0.5	0.08
F11628	G138C	>8	2	8	0.04
F12219	G54R	>8	2	0.12	0.08
F12636	G54E	>8	2	0.25	0.04
F12776	Y431C	>8	2	2	0.08
F13619	H147Y G448S	8	1	>8	0.04
F13747	G434C	>8	1	2	0.08
F14403	G54R	>8	2	0.12	0.08
F16134	M220K	>8	>8	2	0.04
F16157	G54V	>8	2	0.5	0.04
F16216	L98H+TR	>8	1	4	0.04
F17294	L98H+TR	>8	1	4	0.04

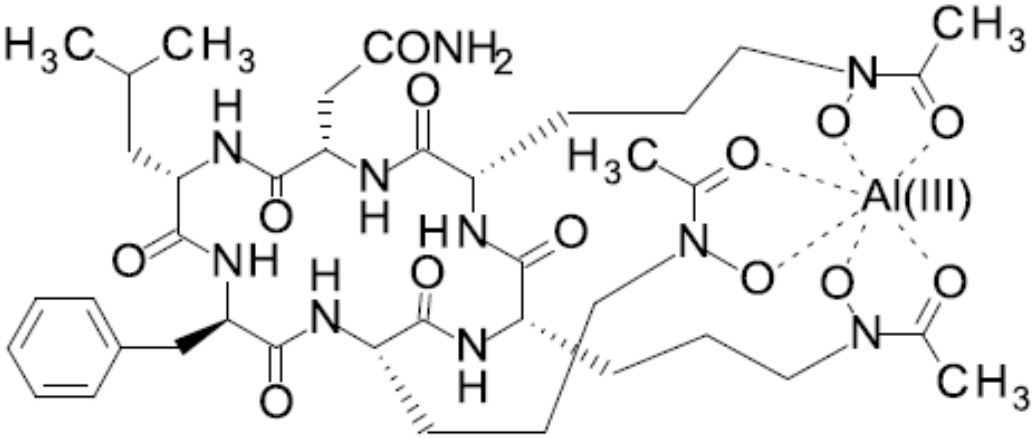
F901318 has the potential to address some of the unmet medical needs

- Novel mechanism of action – inhibitor of pyrimidine biosynthesis
  - Potent dihydroorotate dehydrogenase (DHODH) inhibitor
  - Highly selective for fungal enzyme relative to the human equivalent (900-fold difference)
- Active against all major species of *Aspergillus*
  - Activity includes strains resistant to azoles and amphotericin
  - Unrelated mechanism of action and no cross-resistance with existing drugs
- Active against *Scedosporium* spp. as well as a number of other rare and resistant moulds
- No activity against Zygomycetes, *Candida* spp., and *Cryptococcus* spp.
- [Intravenous and] oral routes of administration
- Animal PK-PD and initial human PK data suggest therapeutic exposures can be achieved in man; efficacy based on C_{min}
- Toxicology studies to date have not revealed major safety concerns
- No safety concerns in initial IV SAD & MAD studies in healthy volunteers
- Weak interaction with CYP 3A4

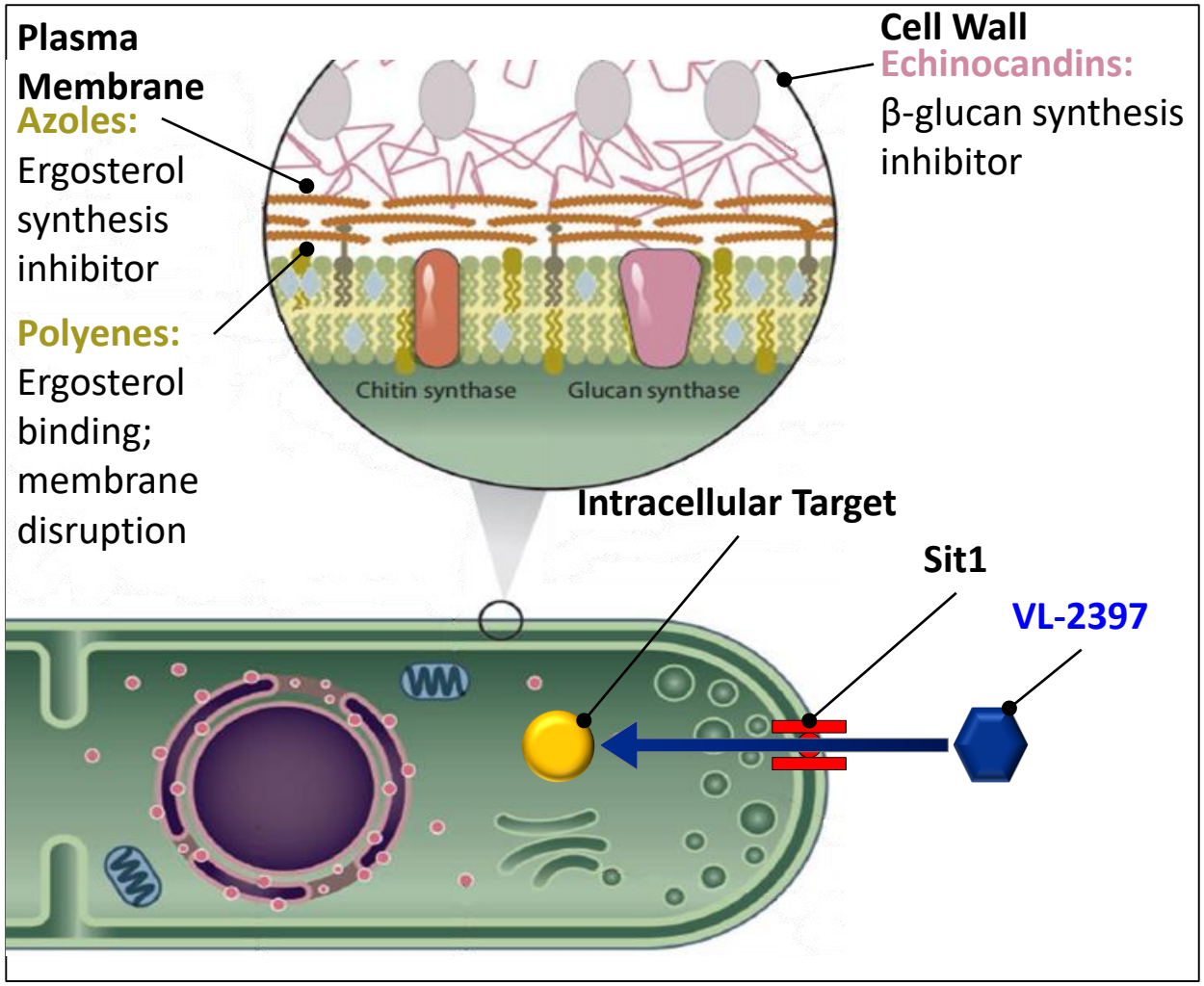
VL-2397 (ASP2397)

(Vical Inc, San Diego, CA, USA)

- Discovered by Astellas Pharma from leaf litter fungus in Malaysia in 2007
  - Extensive nonclinical development studies were conducted
  - Vical in-licensed in March 2015
- Naturally-occurring siderophore isolated from *Acremonium* species
- Cyclic hexapeptide resembling the siderophore ferrichrome, able to chelate aluminum
- IV formulation only



VL-2397 Novel Mechanism of Action



- Active transport into *A. fumigatus* occurs via Sit1
  - Mammalian cells lack Sit1 transporter
- Activity results from effect on an (unknown) intracellular target
- Low propensity for clinically significant DDIs
- Low risk for nephrotoxicity or hepatotoxicity
- Predictable PK and no apparent accumulation

Adapted from Denning *Science* 2015

VL-2397: *In Vitro* Antifungal Activity

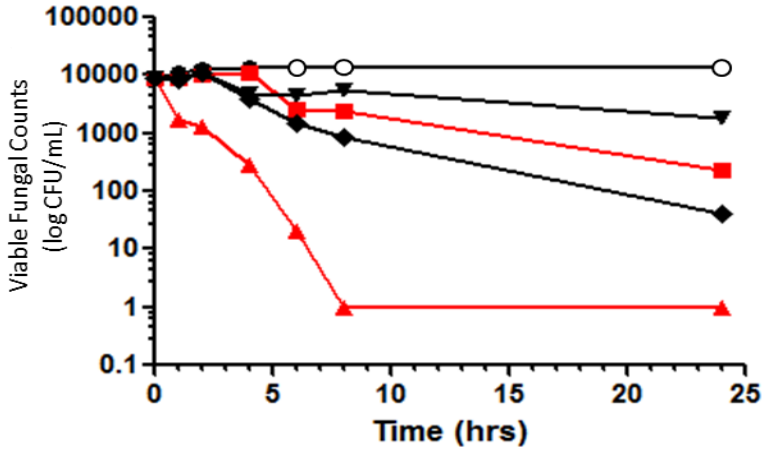
Susceptible fungal pathogens (MIC ≤ 2)

Fungal Species	
***Aspergillus* species**	*A. fumigatus*, *A. terreus*, *A. flavus*, *A. nidulans*, *including azole-R species*
***Candida* species**	*C. glabrata*, *C. kefyr*
Other yeast species	*Cryptococcus neoformans*
	Trichosporon asahii

Assayed in inactivated human serum-containing media
MIC, minimal inhibitory concentration

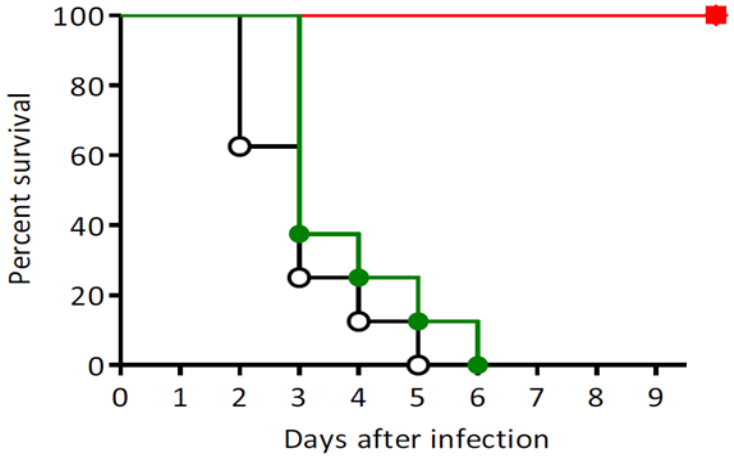
VL-2397 Rapid Activity Against *Aspergillus* Including Drug-Resistant Isolates

Rapid Onset of Antifungal Activity *in Vitro*



MIC: minimal inhibitory concentration
VRCZ: Voriconazole

Activity vs. Azole-Resistant *Aspergillus* *in Vivo*



N = 10 mice /group
PSCZ: Posaconazole

Nakamura, ICAAC, 2014

VL-2397 Phase 2 Design: Invasive Aspergillosis

- Global, multicenter, randomized, open-label study
- N= 200 adults with AML, ALL or allo-HCT recipients
- 2:1 randomization VL-2397 to active comparator
  - Comparator: Physician's choice of voriconazole, isavuconazole or liposomal amphotericin B
- 6 weeks of antifungal treatment
  - 4 weeks of VL-2397 followed by 2 weeks of comparator
- Primary endpoint: All-cause mortality at 4 weeks
  - Key secondary endpoint: ACM at 6 weeks
- Non-inferiority design
- If successful: FDA can grant limited use indication approval

APX001 (E1210) Glycosylphosphatidylinositol biosynthesis (Amplyx, San Diego, CA, USA)

- First in class novel mechanism of action – inhibition of Gwt1[1]
- Broad spectrum yeasts and moulds – including resistant isolates (e.g., *Candida auris*, Mucorales fungi) but maybe not *Candida krusei* (?)
- Oral & IV formulations – 1 hour infusions with ~90% oral bioavailability
- Excellent Phase 1 PK profile – once day dosing with low variability and no food effect
- Safe and well tolerated in Phase 1 up to 14-days in healthy volunteers
  - Target AUCs achieved with no clinically significant safety signals
- Favorable Drug-Drug Interaction potential
- Wide tissue distribution including lung, renal and brain

[1] Gwt1 GPI-anchored wall transfer protein 1

Antifungal agents in clinical phase of development: summary

Agent	Action mechanism	Advantage	Use
VT-1161	Inhibitor of lanosterol demethylase	Tetrazole moiety with high affinity to the fungal CYP51	Candida infections
VT-1129	Inhibitor of lanosterol demethylase	Tetrazole moiety with high affinity to the fungal CYP51	Cryptococcal meningoencephalitis
SCY-078	Glucan synthase inhibitor	Oral bioavailability Activity despite resistance mutations	Invasive Candida infections
CD101	Glucan synthase inhibitor	Increased half-life Reduced toxicity	Invasive Candida infections, Aspergillus infections
CAmB	Ergosterol binding, pore formation in the fungal membrane, K and Mg efflux resulting in cell death	Oral bioavailability Reduced toxicity Broad spectrum activity	Candida and Aspergillus infections, cryptococcal meningoencephalitis
MAT2203	Ergosterol binding, formation of pores in the fungal membrane, K and Mg efflux resulting in cell death.	Oral bioavailability Reduced toxicity Broad spectrum activity	Invasive Candidiasis, Aspergillosis
Nikkomycin Z	Inhibits fungal wall synthesis through inhibition of chitin synthases	Fungal specific target	Coccidioidomycosis, histoplasmosis and blastomycosis
APX001	Inhibits Gwt1, GPI-anchor protein synthesis	Fungal specific target Affects multiple virulence factors	Candida spp Aspergillus spp Scedosporium
F901318	Inhibits DHODH, pyrimidine synthesis pathway.	Fungal specific target Broad spectrum antifungal	Aspergillus spp Dimorphic fungi Scedosporium, Fusarium spp

Invasive aspergillosis: First line therapy recommendations

Drugs	IDSA[1]	ECIL[2]	ESCMID-ECMM-ERS[3]	Australia[4]
AmB DC		A against	DI	Alternative
AmB-LS	Strong Moderate quality	BI	BII	Alternative
ABLC	Weak Low quality	BII	CIII	
ABCD	Weak Low quality	CI	DI	
Itraconazole		CIII	CIII	
Posaconazole				
Voriconazole	**Strong High quality**	**AI**	**AI**	**Recommended**
Caspofungin	Not recommended	CII	CII	
Micafungin	Weak recommendation; moderate-quality evidence		CIII	
Combination	Weak Moderate quality	Discouraged	CI	No supportive evidence

[1]Patterson TF, et al. *Clin Infect Dis* 2016;63(4):433–42; [2]Tissot F, et al. *Haematologica* 2017;102(3):433–444;
[3]Ullmann A, et al. Accepted by Clin Microbiol Infect ; [4]Thursky KA, et al. *Intern Med J* 2008;38:496–520

Thanks for listening….