New Antifungals In Hematology

SITA

11° CONGRESSO NAZIONALE

FIRENZE | 3 dicembre 2021

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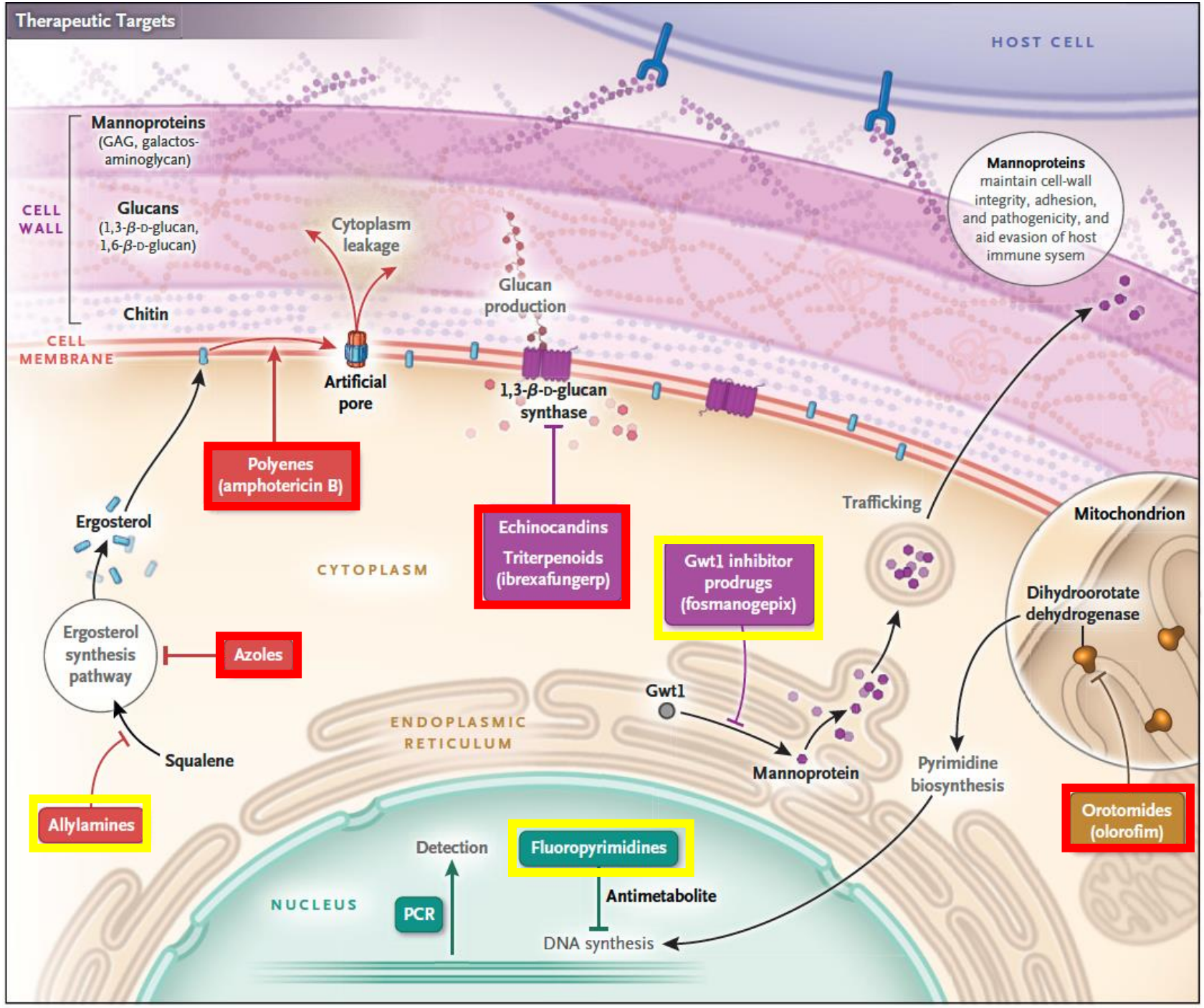
Invited Speaker – Consultant – Research grants

Risk stratification for invasive fungal infections in patients with haematological malignancies: SEIFEM recommendations

HIGH risk	INTERMEDIATE risk	LOW risk
AML undergoing induction CHT with any of the following risk factors: neutropenia at baseline, low CR probability (adverse K, secondary AML), age >65 yrs, significant pulmonary dysfunction AML with prior IA AML undergoing salvage regimens for relapsed/refractory disease	AML not meeting criteria for high- or low-risk groups	AML <45 yrs; undergoing first remission-induction or consolidation CHT and without ANY risk factors for IFI APL treated with ATRA/ATO
Allogeneic stem cell transplantation (from donors other than a matched sibling donor, patients active HM, GvHD requiring high-dose steroids and history of previous IFI)	Allogeneic stem cell transplantation (from matched sibling donors, patients in CR with no evidence of GvHD and no previous IFI)	
MDS/AML receiving AZA as salvage therapy after intensive regimens	MDS with IPSS >1.5 treated with AZA 75 mg/m(2) for 7 days MDS during the first 2–3 cycles of AZA/decitabine	
ALL: Elderly patients (≥55 yrs); intensive pediatric regimens (induction); high-dose dexametazone; previously treated (relapsed/refractory)	ALL: Adults (age 30–54 yrs); standard induction CHT; intensive consolidation treatment; TKI + reduced CHT (Ph+ ALL)	ALL: Younger adults (<30 yrs); maintainance treatment (CR); TKI + steroids (Ph+ ALL)
	ASCT: Previous IFI; >3 lines of therapy (disease burden); prolonged neutropenia (ANC <500/mm^3 for more than 14 days); corticosteroid therapy; colonisation by *Candida* spp; previous fludarabine treatment	MPN (chronic myeloid leukaemia, essential thrombocythemia, idiopathic thrombocytosis, polycythemia vera)
	CLL treated with multiple lines of CTX Multiple myeloma in 3 or more lines or during ASCT HD: if received 'escalating BEACOPP' DLBCL relapsed/refractory	Low- or high-grade NHL, CLL, MM, HD treated with conventional frontline CHT

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; ANC, absolute neutrophil count; APL, acute promyelocytic leukaemia; ASCT, autologous stem cell transplantation; ATO, arsenic trioxide; ATRA, all-trans retinoic acid; AZA, azacitidine; BEACOPP, bleomycin-cyclophosphamide-doxorubicin-etoposide-prednisolone-procarbazine-vincristine; CHT, chemotherapy; CLL, chronic lymphocytic leukaemia; CR, complete remission; CTX, cyclophosphamide; DLBCL, diffuse large B-cell lymphoma; GvHD, graft versus host disease; HD, Hodgkin disease; HM, haematological malignancy; IA, invasive aspergillosis; IFI, invasive fungal infection; IPSS, International Prognostic Scoring System; K, karyotype; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, myeloproliferative neoplasms; NHL, non-Hodgkin lymphoma; Ph+, Philadelphia chromosome-positive; SEIFEM, Sorveglianza Epidemiologica Infezioni nelle Emopatie; TKI, tyrosine kinase inhibitor; yrs, years.

Pagano, et al. Blood Rev. 2017;31:17–29.



Molds infections, mainly Aspergillosis represents the most important IFI in HMS

At present new antifungals can be used for the treatment of Invasive aspergillosis that remains the most important IFI in HMs

Aspergillus Infections

Thompson III & Young, N Engl J Med 2021

Rezafungin

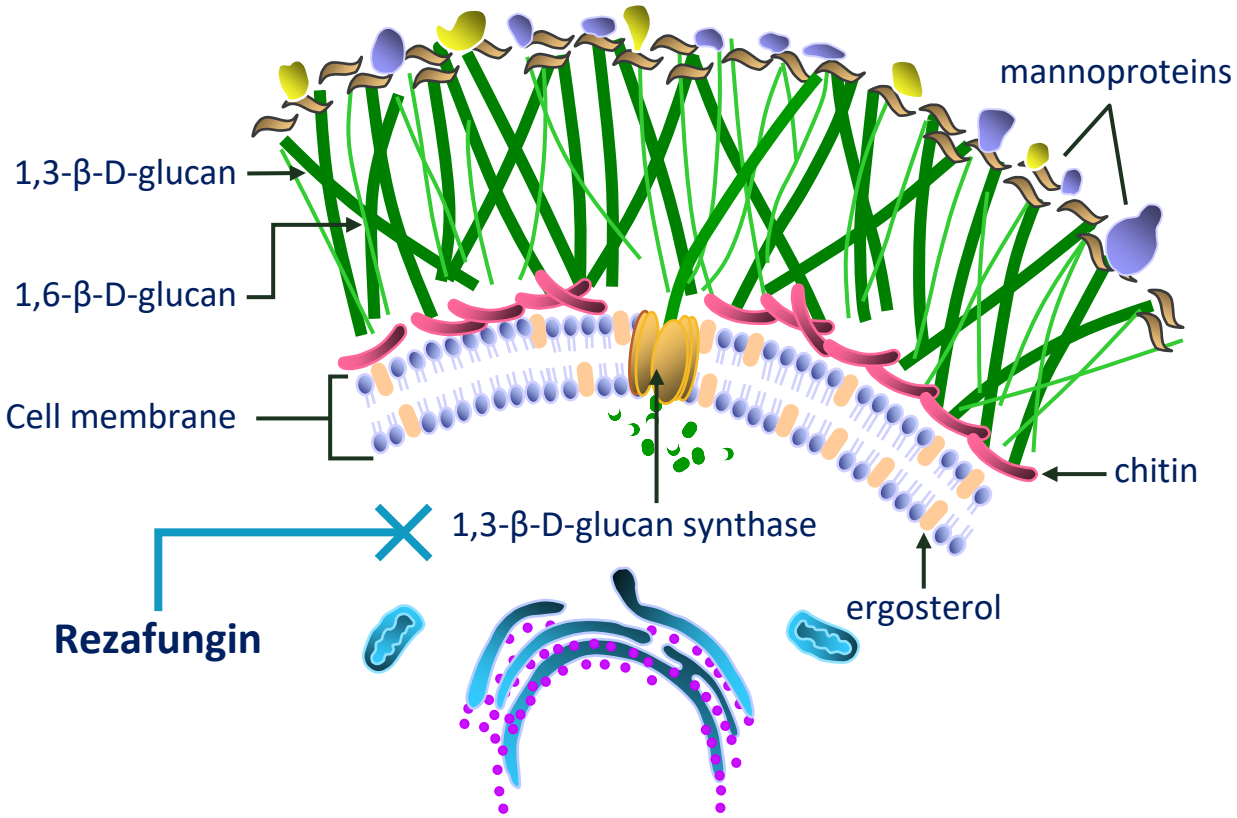


Image adapted from Diamond RD, ed. Atlas of Infectious Diseases: Fungal Infections. Copyright 2000 Springer Science+Business Media New York.

Rezafungin inhibits production of 1,3-β-D-glucan[2]

Increased permeability of the cell wall causes osmotic imbalance[2]

Fungal cell lysis occurs[2]

- **Fungicidal against *Candida* spp.**
- **Fungistatic against *Aspergillus* spp.[2]**
- **Active against *Pneumocystis* spp.[3,4]**

1. Diamond RD, ed. *Atlas of Infectious Diseases: Fungal Infections*. 1st ed. Current Medicine Group; 2000. **2.** Patil, et al. *J Pharm Pharmacol*. 2017 Dec;69(12):1635-1660. **3.** Cushion, et al. ASH 2019; Orlando, Florida. **4.** Sandison, et al. ICHS 2021.

Potent, Broad-Spectrum Activity Against *Candida* Species

In Vitro Activity Comparable With Current Echinocandins

	MIC_{90} (µg/mL)[1-3*]									
	C. albicans (n=835)[2†]	*C. glabrata* (n=374)[2†]	*C. tropicalis* (n=196)[2†]	*C. krusei* (n=77)[2†]	*C. parapsilosis* (n=329)[2†]	*C. kefyr* (n=52)[3‡]	*C. lusitaniae* (n=46)[3‡]	*C. guilliermondii* (n=27)[3‡]	*C. dubliniensis* (n=22)[3‡]	*C. auris* (n=19)[3‡]
Rezafungin	**0.06**	**0.12**	**0.06**	**0.06**	**2**	**0.12**	**0.25**	**1**	**0.06**	**0.25**
Anidulafungin	0.03	0.12	0.06	0.12	2	0.06	0.06	2	0.03	0.25
Caspofungin	0.03	0.06	0.06	0.25	0.5	0.5	1	1	0.25	1
Micafungin	0.03	0.03	0.06	0.12	1	0.12	0.25	2	0.03	0.5

*CLSI broth microdilution methodology was employed for MIC determination (M27-A3).[1-3]

†Clinical isolates collected internationally in the JMI Laboratories SENTRY Antimicrobial Surveillance Program (2016-2018).[2]

‡Clinical isolates collected in Hungary (2005-2018), except for *C. auris* obtained from the National Mycology Reference Laboratory (Bristol, UK), tested as part of a retrospective study.[3]

CLSI, Clinical and Laboratory Standards Institute; MIC, minimal inhibitory concentration.

1. Berkow, et al. *Diagn Microbio Infect Dis*. 2018;90:196-197. **2.** Pfaller, et al. *Antimicrob Agents Chemother*. 2020;pii:AAC.00099-20. **3.** Toth, et al. *J Antimicrob Chemother*. 2019;74:3505-3510.

Potent Activity Against *Aspergillus* Species

In Vitro Activity Includes Azole-Resistant Strains and Cryptic Species

	MEC_{90}/MIC_{90} (µg/mL)*	
	A. fumigatus (n=183)[1†]	*A. flavus* (n=45)[1†]
Rezafungin	**0.03**	**0.015**
Anidulafungin	0.03	0.015
Caspofungin	0.03	0.03
Micafungin	0.015	0.03

	MEC_{90}/MIC_{90} (µg/mL)*		
	Azole-resistant *A. fumigatus* (n=31)[2‡]	*A. lentulus* (n=11)[2‡]	*A. calidoustus* (n=11)[2‡]
Rezafungin	**0.12**	**≤0.015**	**0.06**
Posaconazole	4	0.5	4
Voriconazole	>16	8	4
Micafungin	0.06	≤0.015	0.03

*CLSI broth microdilution methodology was employed for MEC and MIC determination (M38-A2).[2]

†Clinical isolates collected internationally in the JMI Laboratories SENTRY Antimicrobial Surveillance Program (2016-2018).[1]

‡Clinical isolates collected in the US and resistance genotypes confirmed by DNA sequence analysis (CYP51A only, n=13; TR_{34}/L98H, n=2; TR_{46}/Y121F/T289A, n=2; resistant/no CYP51A mutation, n=6; resistant/CYP51A status unknown, n=8).[3]

CLSI, Clinical and Laboratory Standards Institute; CYP, cytochrome P450; MEC, minimal effective concentration; MIC, minimal inhibitory concentration.

1. Pfaller, et al. *Antimicrob Agents Chemother*. 2020;pii: AAC.00099-20. **2.** Wiederhold, et al. *J Antimicrob Chemother*. 2018b;73:3063-3067.

High Probability of PK/PD Target Attainment

Percent Probability Against *Candida albicans* and *C. glabrata* 1 Week After Dose Based on Non-Clinical PK/PD Targets

MIC (µg/mL)	*C. albicans*[1,2]			
	Micafungin	Anidulafungin	Caspofungin	Rezafungin
0.008	99.4	100	100	100
0.015	71.2	99.1	100	100
0.03	10.1	52.7	100	100
0.06	0.1	0.90	97.9	100
0.12	0	0	76.7	100
0.25	0	0	35.7	100
0.5	0	0	12.1	100
1	0	0	4.4	76.5
2	0	0	1.35	1.00
4	0	0	0.25	0
8	0	0	0.05	0

MIC (µg/mL)	*C. glabrata*[1,2]			
	Micafungin	Anidulafungin	Caspofungin	Rezafungin
0.008	100	100	100	100
0.015	100	100	100	100
0.03	97.5	99.2	100	100
0.06	49.9	54.3	100	100
0.12	3.40	0.95	100	100
0.25	0	0	100	100
0.5	0	0	97.0	100
1	0	0	73.2	100
2	0	0	33.9	100
4	0	0	11.3	100
8	0	0	4.35	100

Shading reflects relative probability of PK/PD target attainment 1 week after dose (stasis).

Rezafungin high probability of PK/PD target attainment against *C. albicans* and *C. glabrata* in Monte Carlo simulations

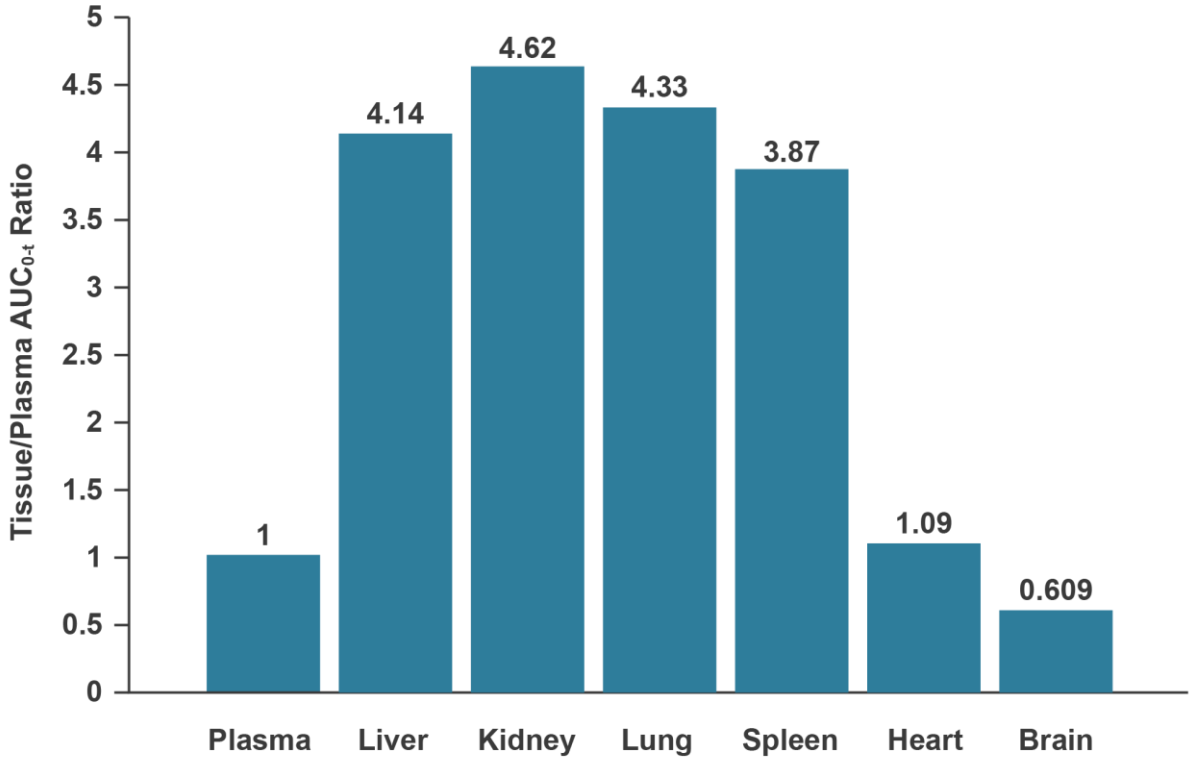
MIC, minimal inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic.

1. Bader, et al. IDWeek 2017; poster 833. **2.** Bader, et al. *Antimicrob Agents Chemother*. 62:e02614-17.

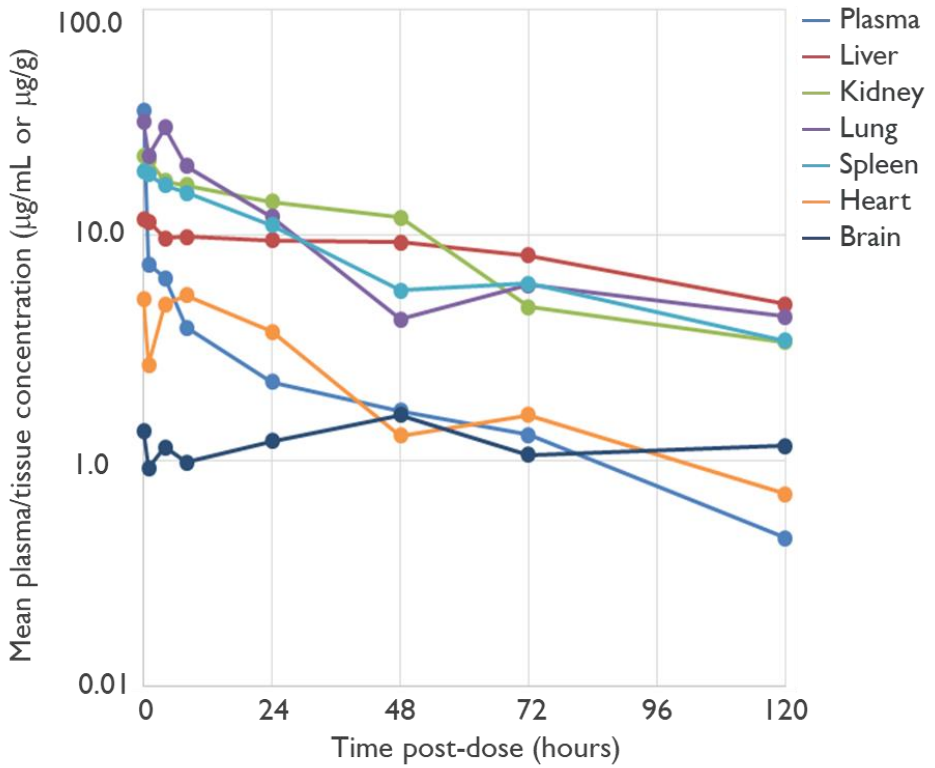
Tissue Distribution *In Vivo*

Rat PK Models

Uniform tissue distribution across liver, kidney, lungs, and spleen[1]



Similar half-life/elimination in organs[2]



AUC, area under the curve.

1. Ong, et al. *Antimicrob Agents Chemother*. 2017;61:e01626-16. **2.** Ong, et al. *Biol Blood Marrow Transplant*. 2018;24:S291–S459.

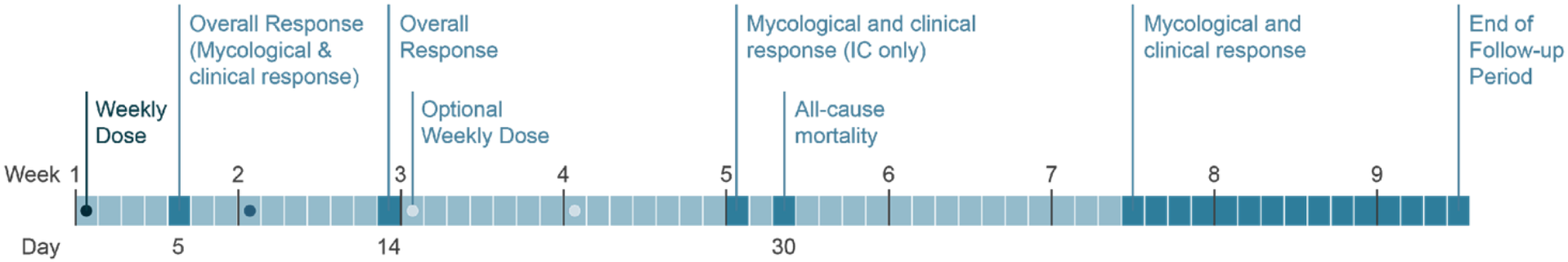
The STRIVE Trial

Phase 2 *Candida* Treatment

Trial Not Powered for Inferential Statistical Analysis

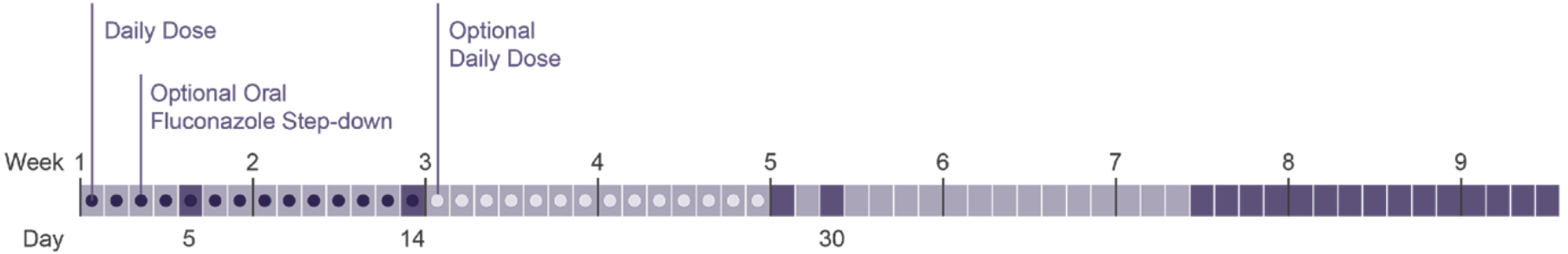
mITT N=183[1]

REZAFUNGIN
(N=122)
400/400 mg N=76
400/200 mg N=46



CASPOFUNGIN
(N=61)
70/50 mg

Optional Oral
Fluconazole Step-down
800/400 mg



ANALYSIS POPULATIONS:

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

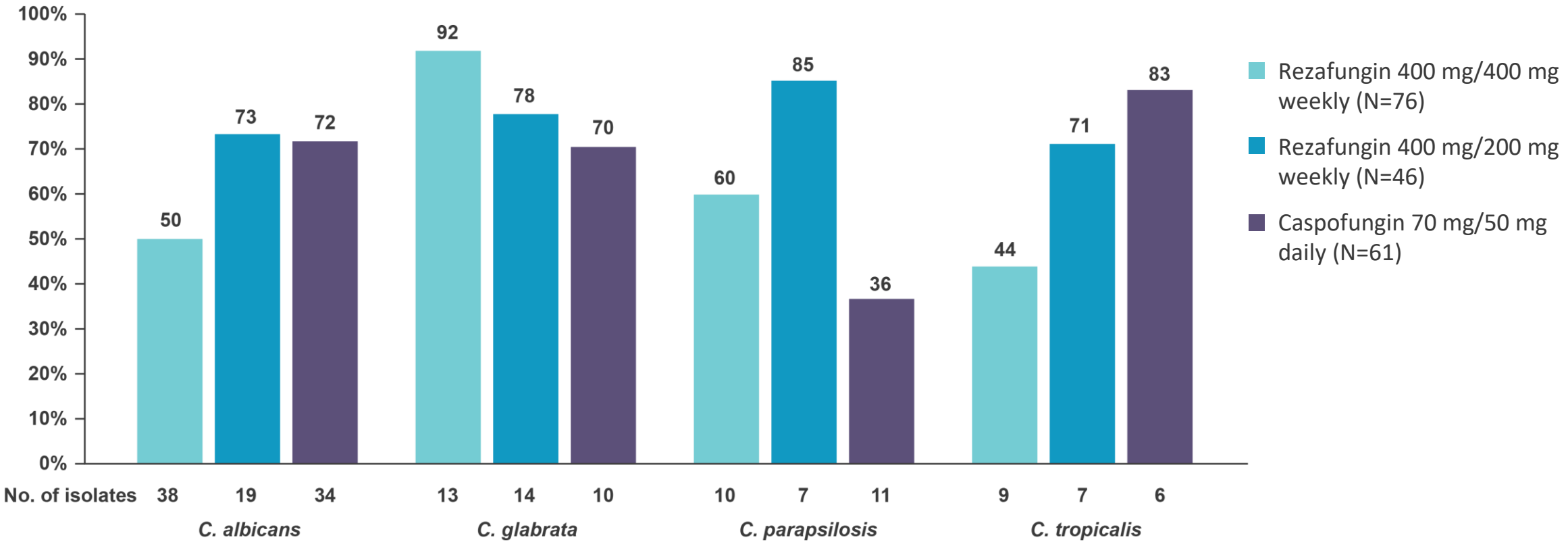
IC, invasive candidiasis.

1. Thompson, et al. *Clin Infect Dis*. 2020, ciaa1380, https://doi.org/10.1093/cid/ciaa1380.

The STRIVE Trial

Phase 2 *Candida* Treatment

Overall Response by *Candida* Species at Day 14 (mITT Population)[1]



Rezafungin efficacy compared with caspofungin consistent in variety of *Candida* species

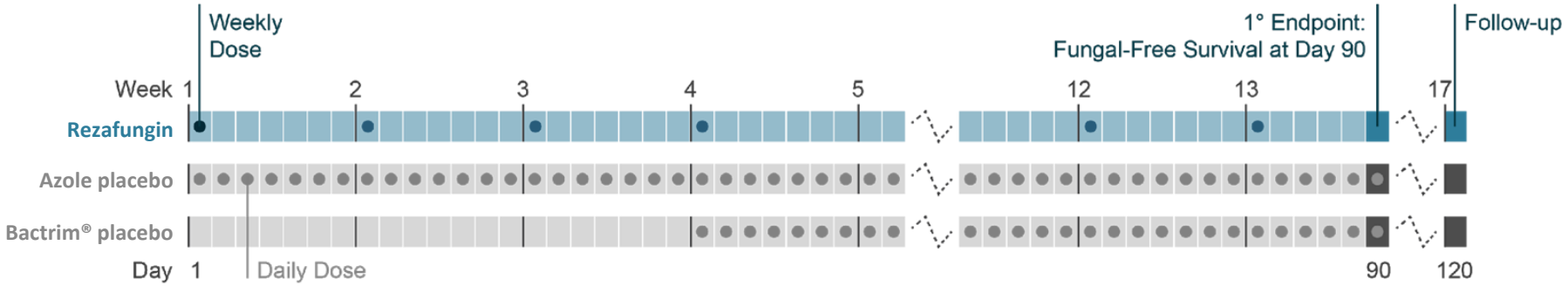
mITT, microbiological intent-to-treat.

1. Thompson, et al. ID week 2020;poster 1284.

The ReSPECT Trial

Prophylaxis in HSCT

REZAFUNGIN
(N≅300)
400/200 mg once weekly

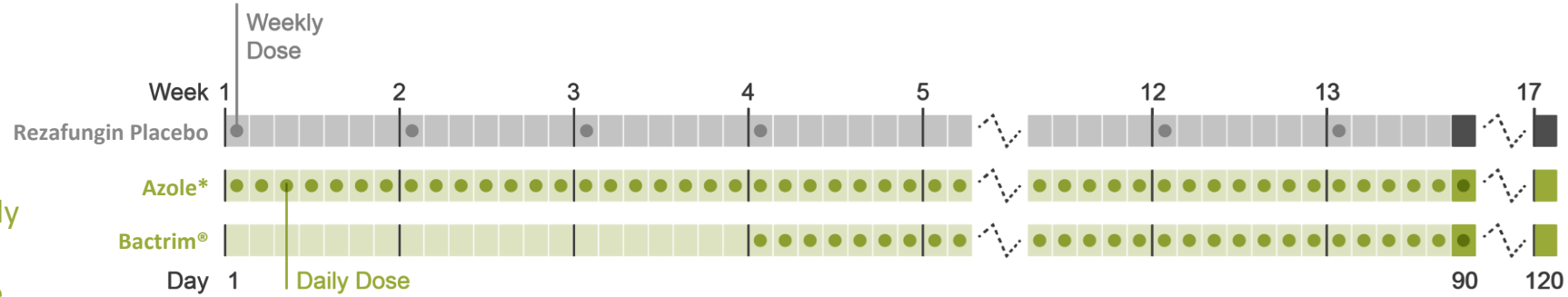


COMPARATOR
(N≅150)

400 mg fluconazole once daily*

80 mg TMP/400 mg SMX once daily

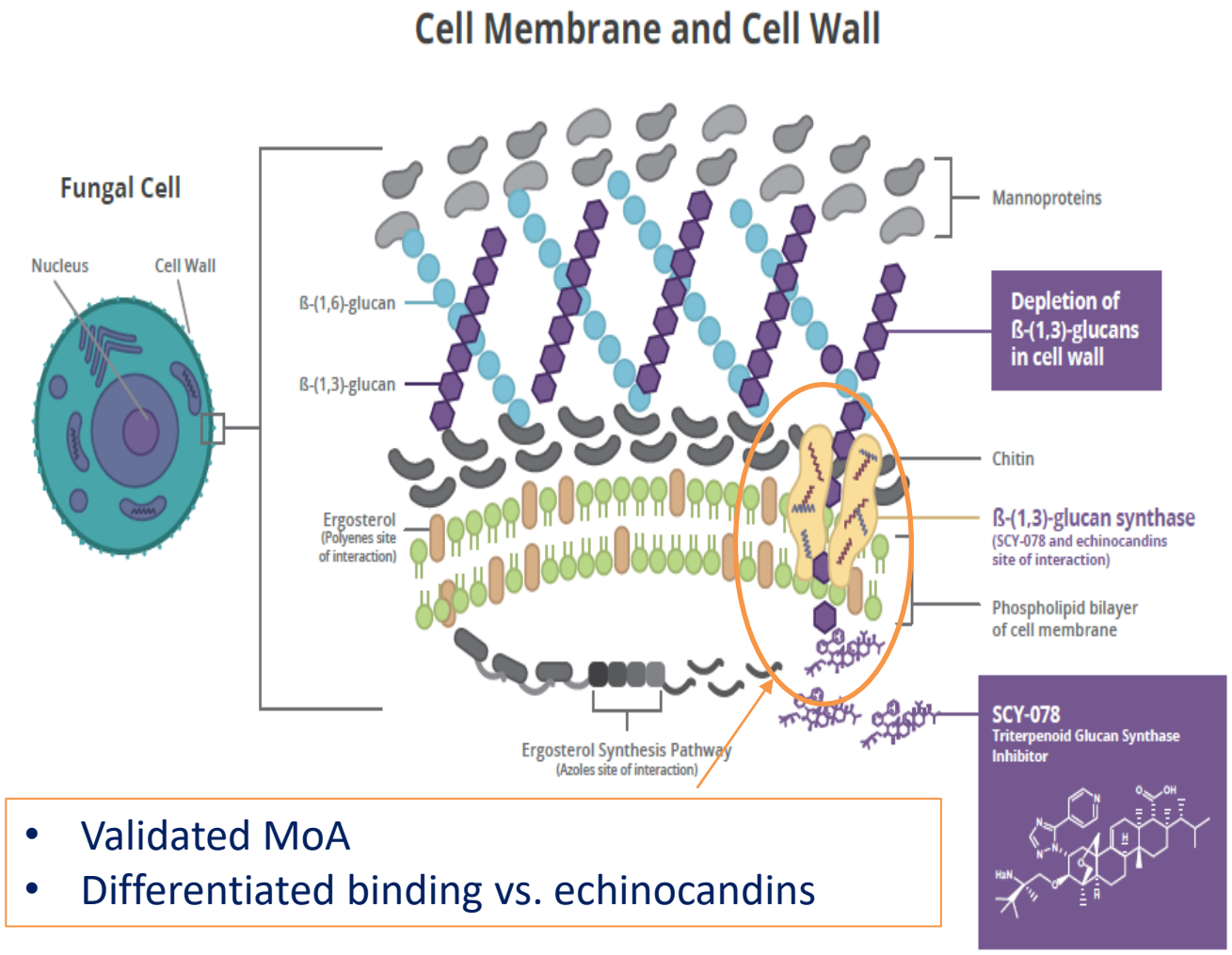
*Patients with acute GVHD can be switched to posaconazole



BMT, blood and marrow transplantation; GVHD, graft-versus-host disease; IFD, invasive fungal disease; SMX, sulfamethoxazole; TMP, trimethoprim.

1. Clinicaltrials.gov NCT04368559 accessed 4 Feb 2021.

Ibrexafungerp: Glucan Synthase Inhibitor



- Validated MoA
- Differentiated binding vs. echinocandins

Key Attributes

- Activity against:
  - *Candida* spp.
  - *Aspergillus* spp.
  - *Pneumocystis* spp.
- Active against azole-resistant and most echinocandin-resistant strains
- Oral and IV formulations
- Favorable safety profile > 500 exposed
  - **Low risk of drug-drug Interactions (IBX does not induce CYP3A)**
- Extensive tissue distribution
  - (V_{dss} > 8 L/kg)

Larkin E., et al. AAC . May 2017

Interactions of mold-active azoles with coadministered chemotherapic agents and target therapies

	COADMINISTERED AGENT	INTERACTION MECHANISM	EFFECT	RECOMMENDATIONS AND ACTIONS
ALL	**Vincristine**	Inhibition CYP3A4	Increased neurotoxicity	**Avoid combo**
ALL	**Cyclophosphamide**	Inhibition CYP3A4/2C9	↑ hepatotoxicity ↓ activation to hydroxy-CTX	Monitor **Avoid combo**
ALL	**Imatinib**	Inhibition CYP3A4	↑ Imatinib exposure	**Avoid combo**
ALL	**Dasatinib**	Inhibition CYP3A4	↑ D. exposure, **↑ QT interval**	**Avoid combo, monitor ECG**
ALL	**Nilotinib**	Inhibition CYP3A4	↑ N. exposure, **↑ QT interval**	**Avoid combo, monitor ECG**
ALL	**Ponatinib**	Substrate CYP3A4	↓ TKI dosage	**Avoid combo**
AML	**Sorafenib**	Inhibition CYP3A4	No effect	**Monitor QTc**
AML	**Midostaurin**	Inhibition CYP3A4	↑ adverse reaction	**Avoid combo, monitor QTc**
AML	**Quirzatinib**	Inhibition CYP3A4	↑ Quirzatinib exposure	**↓ dose (induc 40 mg ->20 mg)**
AML	**Venetoclax**	Inhibition CYP3A4	↑ Venetoclax exposure	**↓ dose** 50% if moderate; 75% if potent

Adapted from Busca & Pagano. Exp Rev Anti-Infect Ther 2018

Ibrexafungerp: *in vitro* Activity against *Candida* spp.

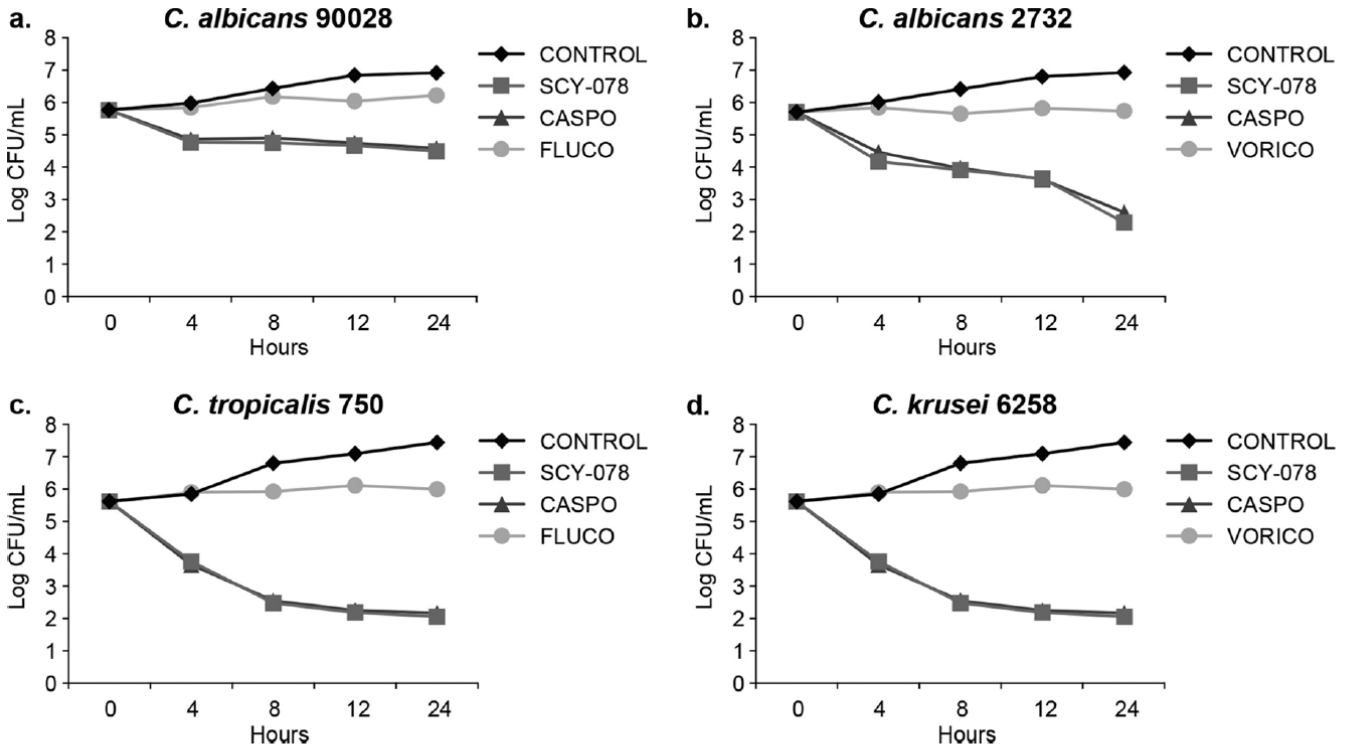


FIG 2 Time-kill curves for SCY-078, caspofungin (CASPO), fluconazole (FLUCO), and voriconazole (VORICO) at 4 times the MIC_{80} against the indicated *Candida* species and a control. 2732, MYA-2732.

Ibrexafungerp has fungicidal activity against *Candida* spp

Scorneaux B, et al. AAC, March 2017

Ibrexafungerp *In vitro* Activity against *Aspergillus* spp.

	Ibrexafungerp		
	MEC		
	Range	MEC_{50}	MEC_{90}
A. fumigatus (n=134)	<0.06 – 4	<0.06	0.125
A. flavus (n=54)	<0.06 – 0.25	<0.06	<0.06
A. niger (n=27)	<0.06 – 0.5	<0.06	<0.06
A. terreus (n=72)	<0.06 – 0.125	<0.06	0.125
Other spp. (n=24)	<0.06 – 0.25	<0.06	<0.06
All isolates (n=311)	<0.06 – 4	<0.06	0.125

Ghannoum M., et al. AAC June 2018

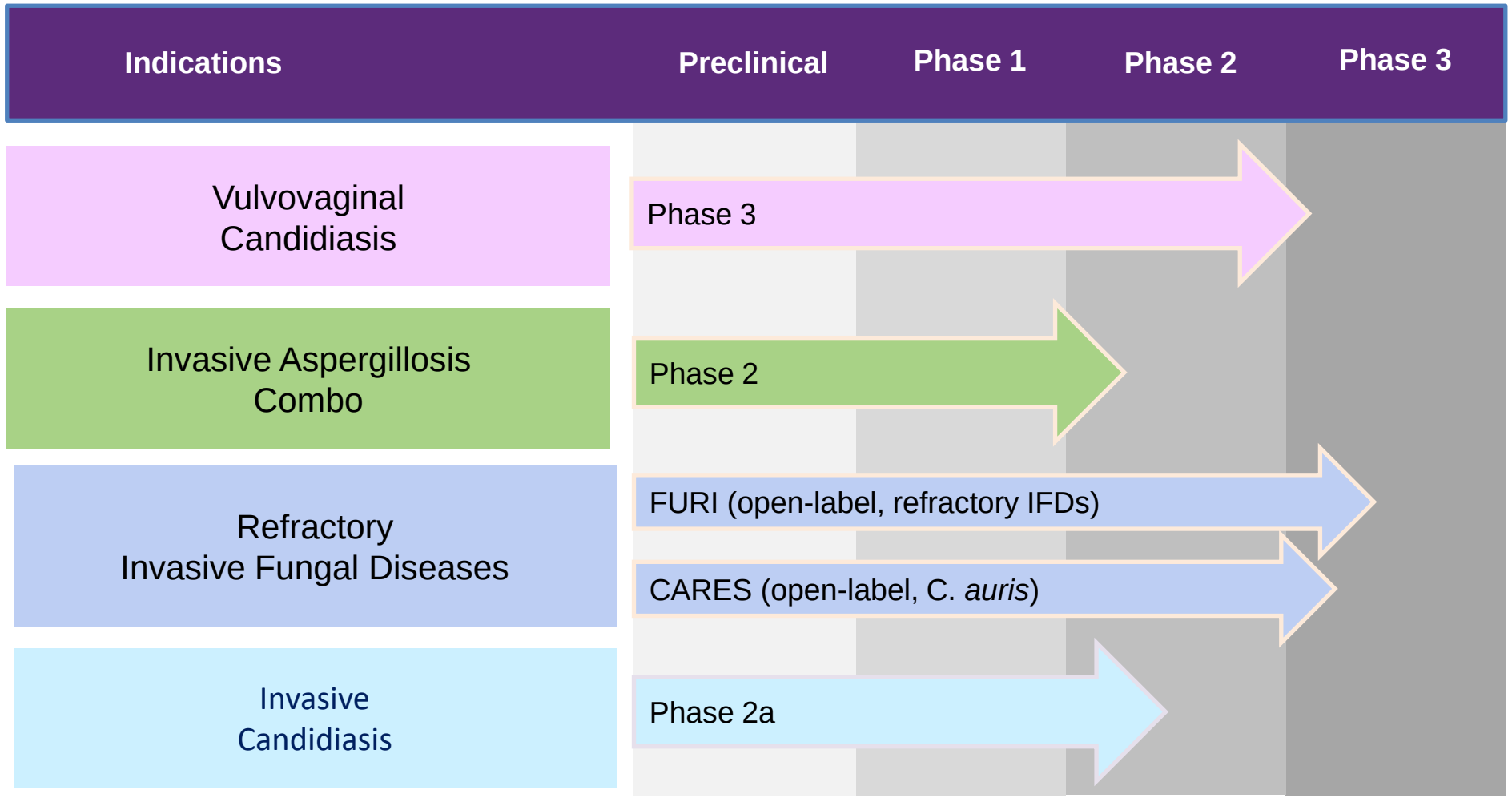
Ibrexafungerp *In vitro* Activity against *Aspergillus fumigatus* in Combination with other Antifungals

Strain	IBX with Isavuconazole (ISA)						IBX with Voriconazole (VRC)						IBX with Amphotericin B (AmB)					
	MIC Alone		MIC Combo		FICI	Interpretation*	MIC Alone		MIC Combo		FICI	Interpretation*	MIC Alone		MIC Combo		FICI	Interpretation*
	IBX	ISA	SCY-078	ISA	IBX + ISA		IBX	VRC	SCY-078	VRC	IBX + VRC		IBX	AmB	SCY-078	AmB	IBX + AmB	
WT	4	1	0.016	0.5	0.50	SY	4	1	0.125	0.25	0.27	SY	4	4	0.016	0.5	0.13	SY
WT	4	1	0.125	0.25	0.28	SY	4	0.25	0.5	0.16	0.19	SY	4	2	0.016	0.5	0.25	SY
WT	4	1	0.063	0.25	0.27	SY	8	0.5	0.5	0.125	0.31	SY	4	4	0.016	1	0.25	SY
WT	4	1	0.25	0.25	0.31	SY	8	2	0.25	0.5	0.28	SY	4	4	0.016	1	0.25	SY
Azole-R	4	>8	0.063	>8	1.02	AD	8	>16	0.031	>16	1.00	AD	4	2	0.125	2	1.03	AD
Azole-R	4	>8	0.125	>8	1.03	AD	4	>16	1	>16	1.25	AD	4	4	0.016	1	0.25	SY

IBX in combination with Voriconazole, Isavuconazole and Amphotericin B demonstrated synergistic activity against the majority of *A. fumigatus* isolates tested

Ghannoum M., et al. AAC June 2018

Ibrexafungerp: Platform of Indications



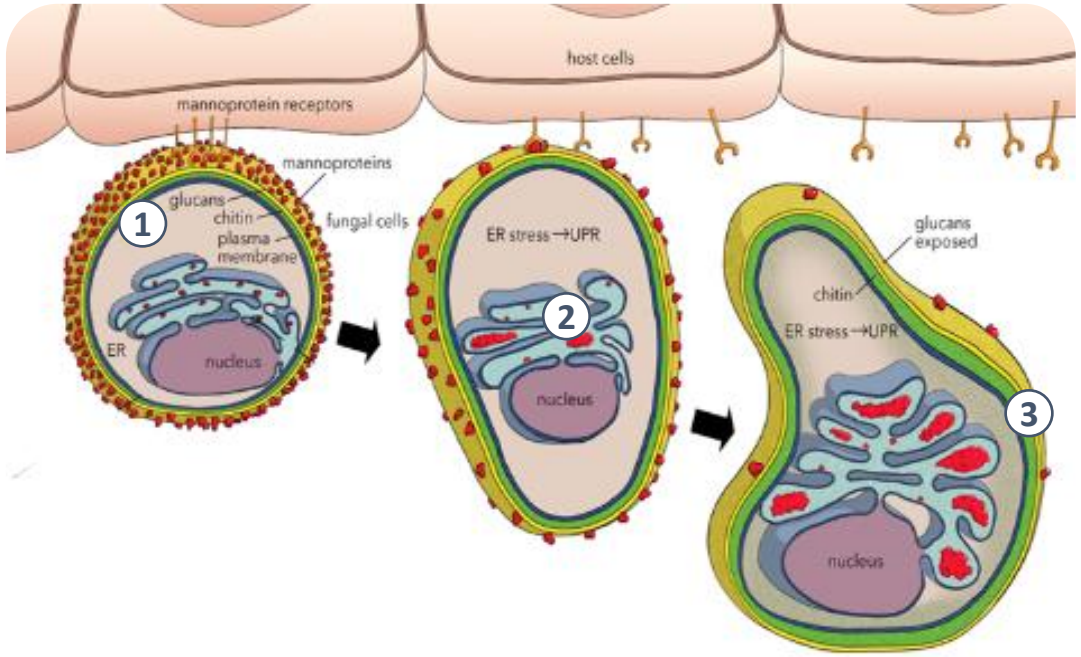
Additional indications under consideration: Chronic Fungal Infections, Prophylaxis

Fosmanogepix: First-in-Class, Potent and Selective Gwt1 Inhibitor

- ✓ **Novel Targeted Mechanism:** Inhibits Gwt1, a target specific to fungal cells that triggers two distinct cell vulnerabilities
- ✓ **Broad Spectrum:** Preclinical antifungal efficacy in yeasts and molds, including rare and resistant strains
- ✓ **Wide Tissue Distribution:** Reaches important compartments in brain, lung, kidney, and eye
- ✓ **Favorable Safety Profile:** Minimizes additional toxicity burden for seriously ill patients
- ✓ **Favorable DDI Profile:** Low potential for CYP3A4 inhibition, simplifies co-administration
- ✓ **IV and Oral Formulations:** Supports continuation of care outside of the hospital

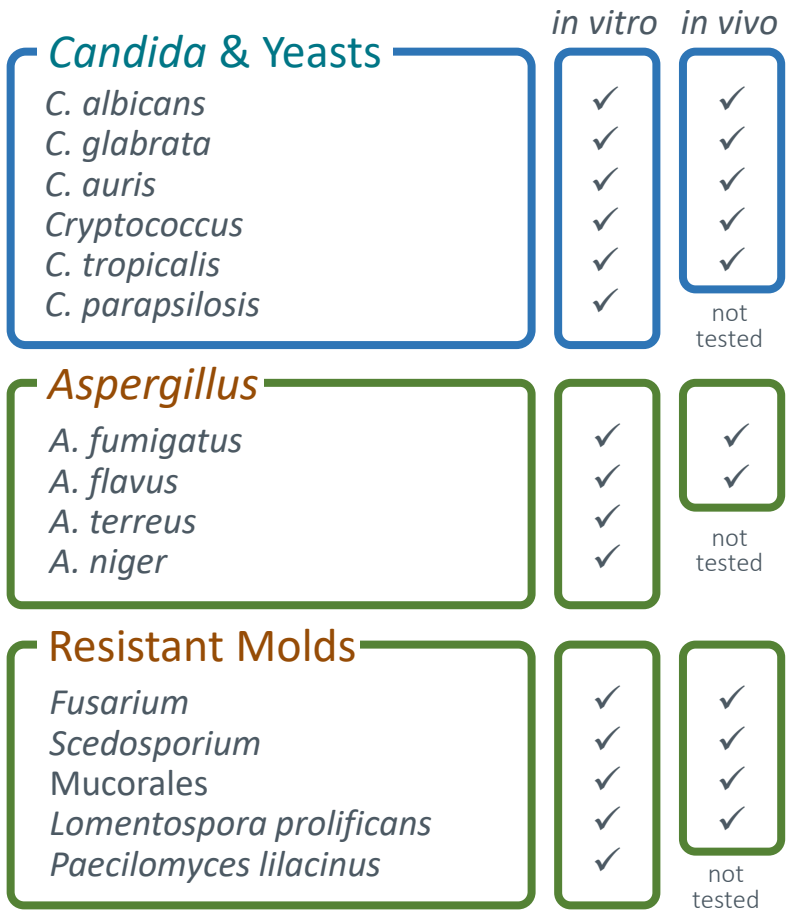
Fosmanogepix Inhibits Gwt1

1. Gwt1 protein exists only in fungal cells
2. Gwt1 inhibition blocks mannoprotein transport
3. Lack of mannoproteins on cell wall and stress response lead to fungal cell death



Fosmanogepix: current available and emerging data

Preclinical Proof-of-Concept



Additional preclinical activity against pathogens that cause endemic mycoses (e.g. Cocci, Blasto, Histo) diamorphic fungi (e.g. Talormyces and Sporothrix) and Phaeohyphomycetes black molds and Hyalohyphomycetes

Phase 2 Clinical Trials

201: Complete
Candidemia

203: Complete
Resistant *C. auris*

202: Enrolling
Invasive Mold Infections

Expanded Access
(available only in USA)

Miyazaki, AAC 2011; Viriyakasol, AAC 2019; Pfaller, AAC 2019

OLOROFIM

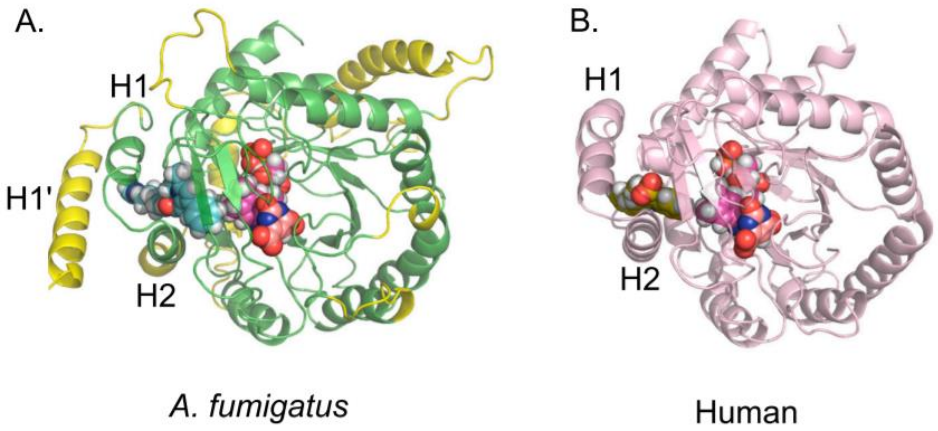
Is a novel mechanism candidate antifungal drug[1]

- It is an **inhibitor of fungal dihydroorotate dehydrogenase** (pyrimidine biosynthesis pathway)
- It shows broad microbiologic **activity vs. mold fungi**
- Low MICs vs. ***Aspergillus spp., Lomentospora prolificans, Scedosporium spp., Fusarium spp., Coccidioides spp.,*** and others
- Fungicidal effects in vitro (*Aspergillus*) and in vivo (*Coccidioides*) [2,3]
- Dosed by mouth (**30-mg tablet**), it has FDA Breakthrough Therapy Designation based on
    - "preliminary clinical evidence indicating that it may …
    - demonstrate substantial improvement over existing therapies …
    - on one or more clinically significant endpoints."

1. Oliver JD et al. (2016). "F901318 represents a novel class of antifungal drug that inhibits dihydroorotate dehydrogenase." PNAS USA 113: 12809-14.
2. du Pre, S., et al. (2018). "Effect of the Novel Antifungal Drug F901318 (Olorofim) on Growth and Viability of Aspergillus fumigatus." AAC 62(8): e00231-18.
3. Wiederhold, N. P., et al. (2018). "The Orotomide Olorofim Is Efficacious in an Experimental Model of Central Nervous System Coccidioidomycosis." AAC 62(9): e00999-18.

Mechanism of Action

- Olorofim is the first of the orotomides
- Olorofim is a potent selective inhibitor of fungal dihydroorotate dehydrogenase (DHODH) Type 2
  - DHODH is a key enzyme involved in pyrimidine biosynthesis
- Humans also have this enzyme
  - But > 2000-fold difference in IC_{50} between human and fungal enzymes
- Pyrimidine inhibition has profound effects as it interferes with
  - DNA synthesis and cell cycle regulation
  - RNA synthesis and protein production
  - Cell wall synthesis
  - Phospholipid synthesis



Inhibitor binding to DHODH

Oliver et al. PNAS 113:12809-14, 2016.

In vitro activity

- Olorofim *Aspergillus* MICs are tightly clustered
  - MIC_{90}s are 0.03-0.06 mg/L (CLSI and EUCAST)
  - MICs are of the same order for all *Aspergillus* spp. tested
    - 5408 isolates from 63 species including:
    - 4880 isolates of *A. fumigatus, flavus, niger, and terreus*
    - >300 isolates of cryptic *Aspergillus* species
- **No induction of resistance** with serial passage
- Spontaneous resistance rarely seen; **no cross resistance**
- *Scedosporium* spp. and *L. prolificans* plus other moulds and endemic fungi have MICs similar to IA
- **No activity against yeasts or mucorales as these have a structurally different DHODH enzyme**

Beckmann et al. ICAAC 2015; Fothergill et al. ICAAC 2015; Buil et al.JAC 2017; Rivero-Menéndez et al ECCMID 2017; Oliver et al PNAS 2016; Jorgensen et al. TIMM 2017

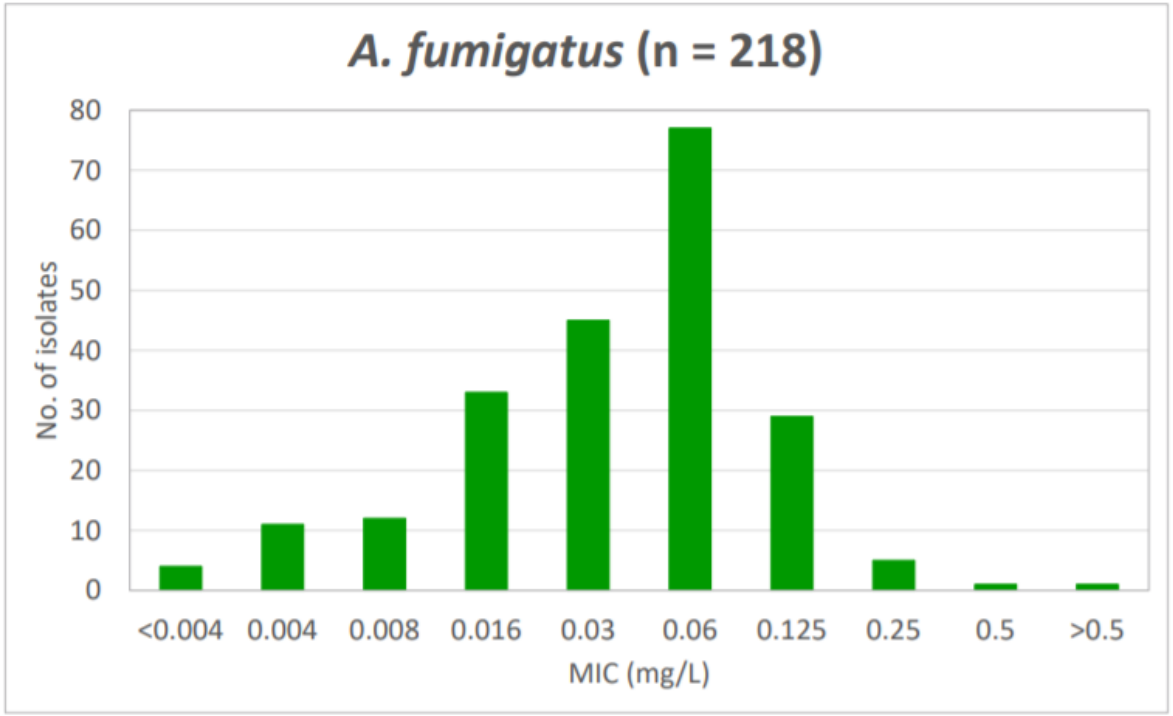
Breakthrough Therapy Designation (BTD) Granted by FDA

- Olorofim is the first antifungal agent to be granted BTD
- BTD designation is granted by FDA based on "preliminary clinical evidence indicating that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints."
- BTD #1 (Nov 2019): Based on data from the first 28 patients:

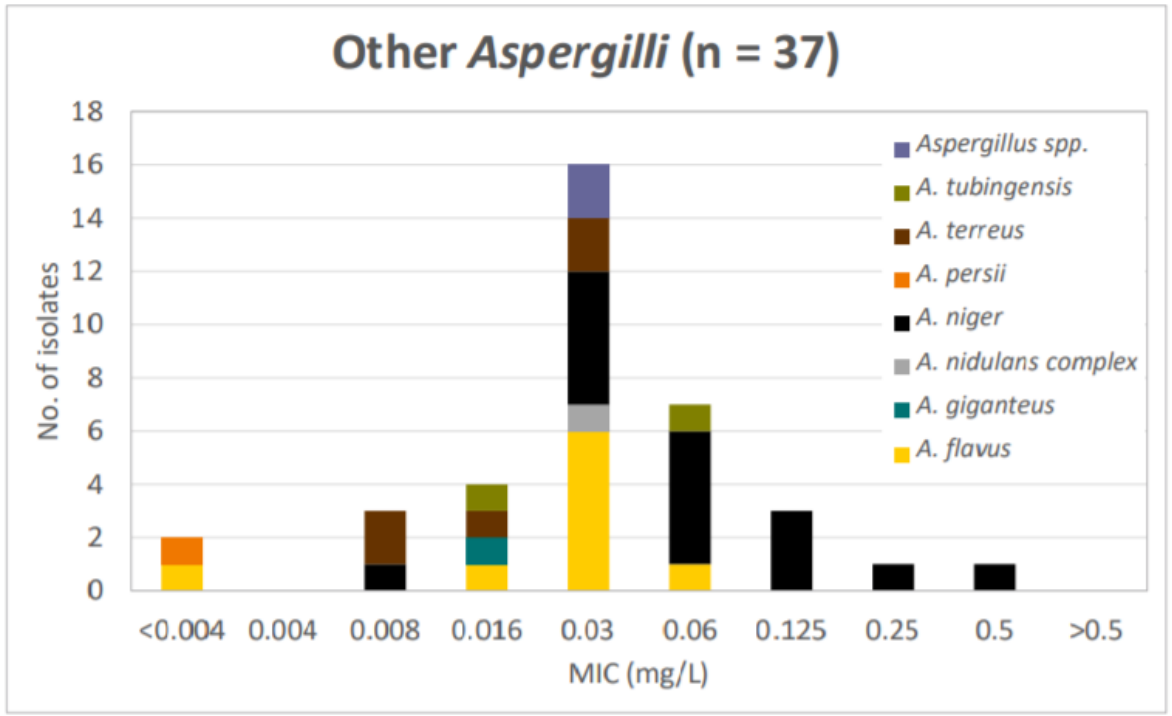
  "Treatment of invasive mold infections in patients with limited or no treatment options, including aspergillosis refractory or intolerant to currently available therapy, and infections due to *Lomentospora prolificans*, *Scedosporium*, and *Scopulariopsis* species"
- BTD #2 (Oct 2020): Based on data from the first 7 cocci patients:

  "Treatment of Central Nervous System (CNS) coccidioidomycosis refractory or otherwise unable to be treated with standard of care therapy"

EUCAST Determination of Olorofim Susceptibility of *Aspergillus spp*



MIC-distribution of F901318 for 216 tested *A. fumigatus* isolates



MIC-distribution of F901318 for 39 other *Aspergilli* tested

Jørgensen KM, et al. EUCAST Susceptibility Testing of F901318: MIC Data for Contemporary Clinical Mould Isolates. P321_TIMM 2017

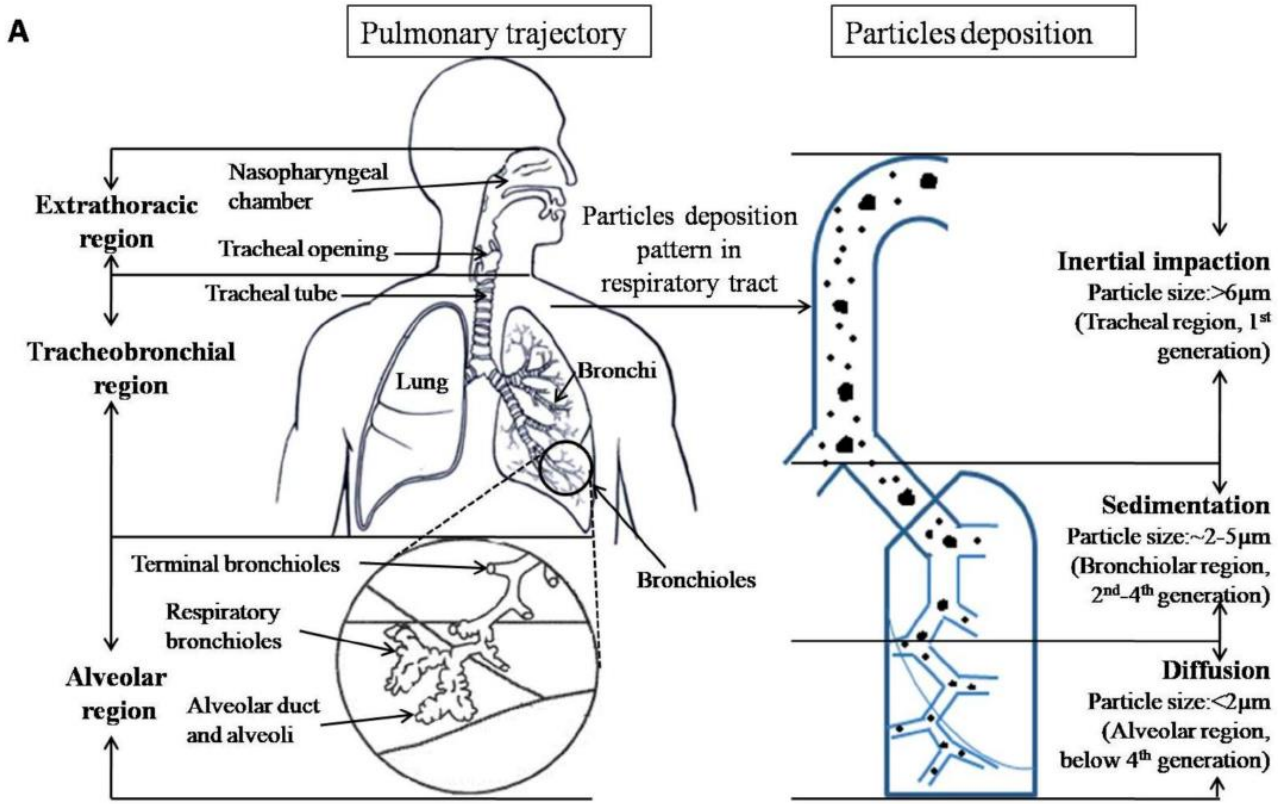
Phase 2 Open-Label Study

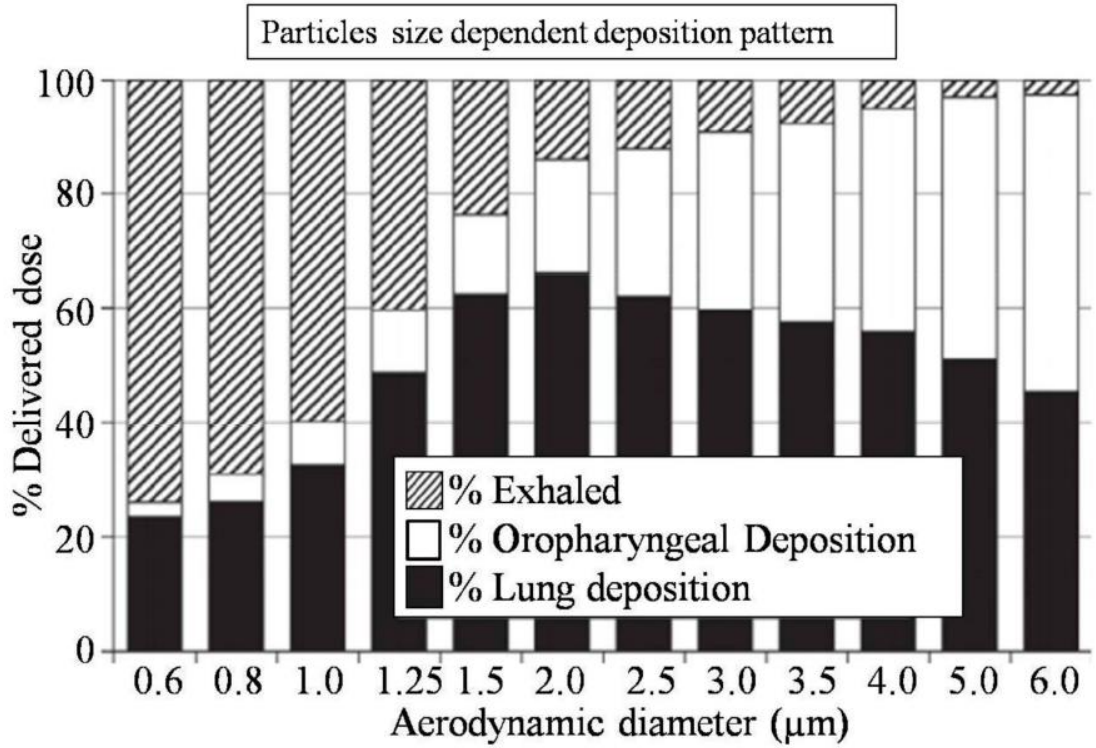
- ClinicalTrials.gov Identifier: NCT03583164
- Key entry criteria
  - Any proven IFI or probable IA (EORTC-MSG 2008 criteria)
  - Limited treatment options e.g.
    - refractory to prior antifungals;
    - intrinsic resistance to existing antifungals
- Design
  - Open-Label olorofim for up to 90 days (plus extension study for those needing longer term therapy)
  - Data-Review Committee to adjudicate at 6 and 12 weeks
  - Regular DSMB review

Limited and Predicted drug-drug interactions

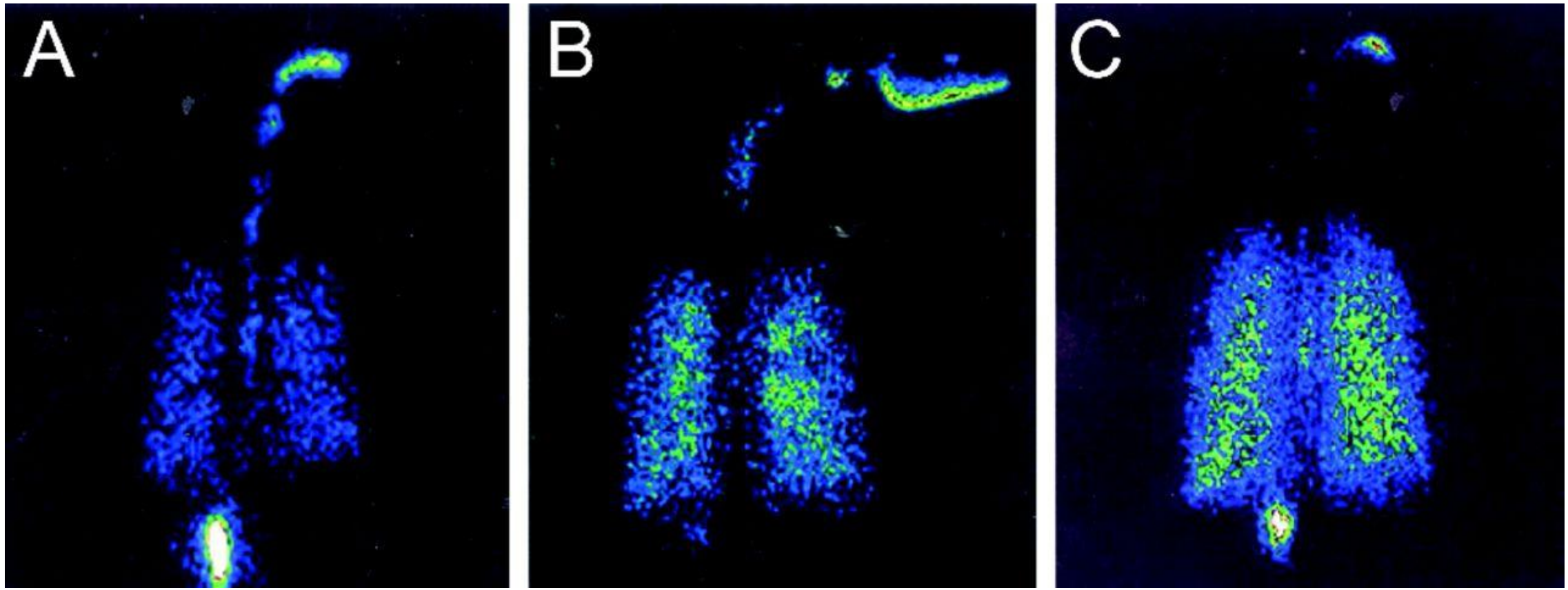
- Olorofim is a weak inhibitor of CYP3A4.
  - When administered in combination with drugs which are metabolized by CYP3A4, a reduction in dose of the substrate may be required.
- Olorofim dose may be affected by co-administration of strong inhibitors of CYP3A4.
  - If co-administering olorofim with any of the triazole antifungals, a reduction in olorofim dose of 30% is recommended.
- Olorofim dose may be affected by strong inducers of CYP3A4 and CYP2C9.
  - If co-administering olorofim with such drugs e.g. rifampicin, the dose of olorofim should be increased by 30%

Dry Powder Inhaler





Aerosol deposition with a pressurized metered-dose inhaler without a spacer (A), and with a spacer (B), compared to the soft mist inhaler (C) using radio scintigraphy.

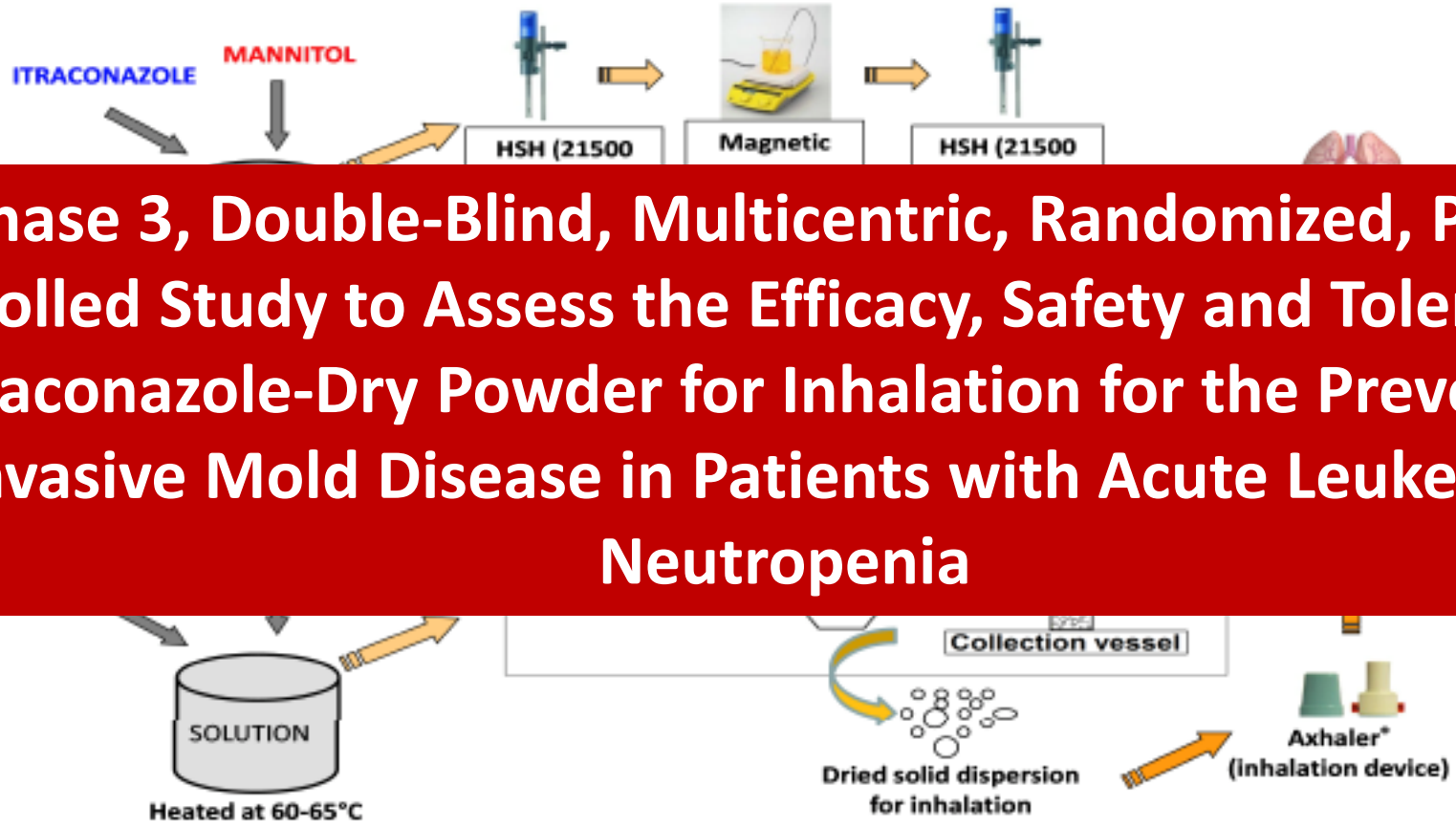


Pleasants & Hess Respir Care 2018

New inhalation-optimized itraconazole nanoparticle-based dry powders for the treatment of invasive pulmonary aspergillosis

Duret et al, Int J Nanomed 2012

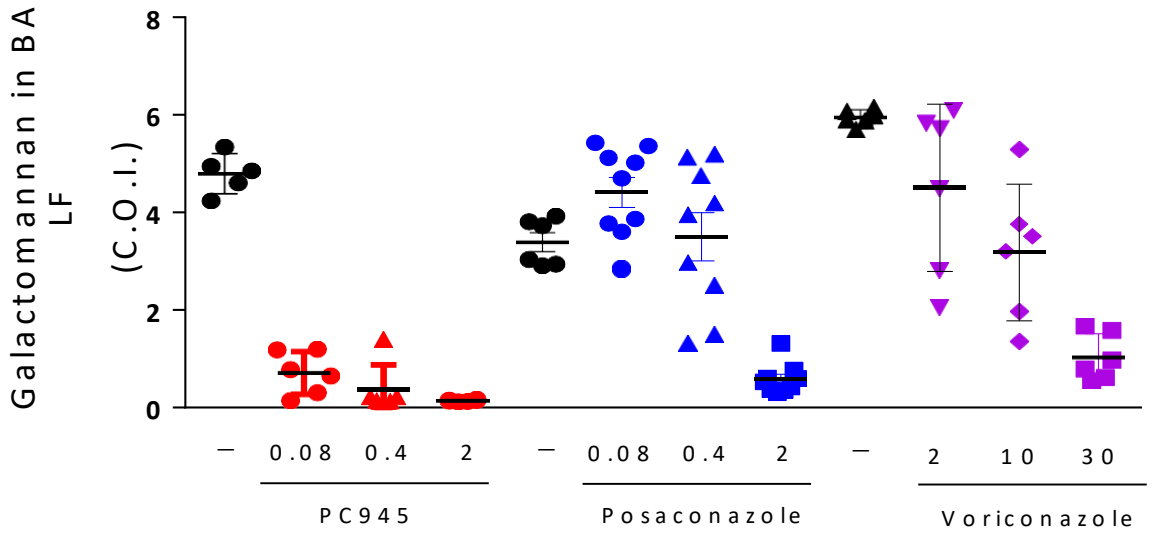
Production of ITZ / Mannitol solid dispersion



A Phase 3, Double-Blind, Multicentric, Randomized, Placebo-Controlled Study to Assess the Efficacy, Safety and Tolerability of Itraconazole-Dry Powder for Inhalation for the Prevention of Invasive Mold Disease in Patients with Acute Leukemia and Neutropenia

Opelconazole

First in class, novel inhaled drug for Aspergillus infections



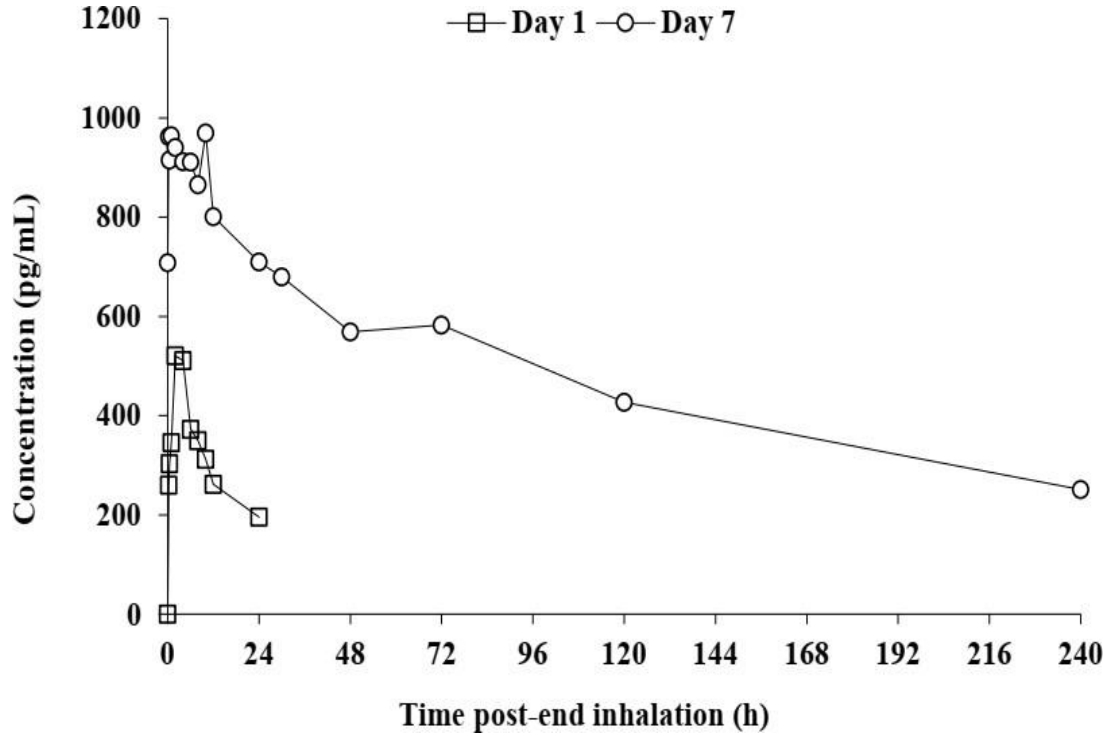
Compounds were treated intranasally on Day 0, 1, 2 and 3 post A.fumigatus conidia inoculation, and GM were measured on Day3.

ID_{50}: µg/kg, in	PC945	Voriconazole	Posaconazole
GM (serum)	<67	3235	393
GM(BALF)	<67	9627	1026
CFU (Lung)	71	5887	205

- Novel compound (granted US patent).
- Broad antifungal activity (*Candida, Rhizopus* spp. and pan-azole resistant *Aspergillus*; L98H; Colley et al., 2017).
- Bespoke profile: nanomolar potency; low dose, prolonged lung half-life.
  - Negligible oral absorption.
- **Excellent activity in immuno-suppressed mice in vivo** (Kimura et al., 2017)

Clinical Stage

- Phase I complete in HVT and asthmatics – excellent safety with low plasma concentrations (1-2 ng/ml).
- Potential for 3 presentations; nebulised, dry-powder and intra-nasal (chronic rhino-sinusitis).



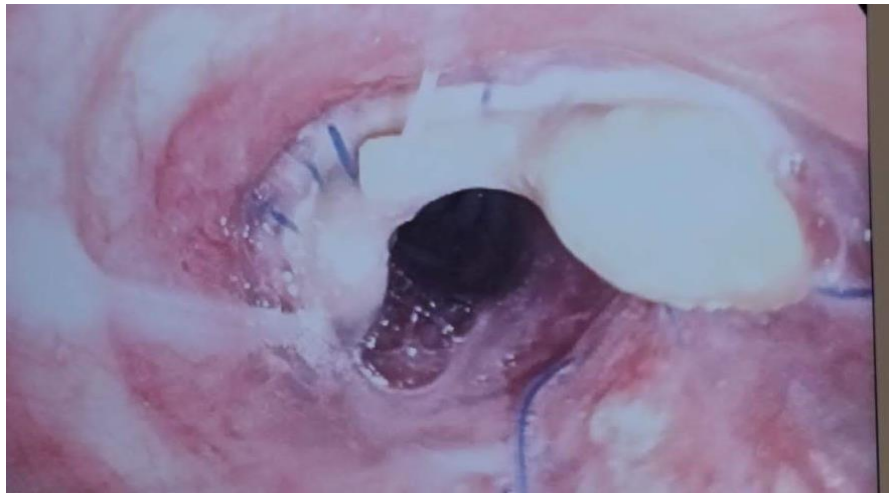
Mean plasma concentrations (pg/ml) of PC945 following single and repeated daily inhaled 5mg doses for 7 days in healthy subjects

Following single doses, absorption into the systemic circulation is slow and sustained, consistent with prolonged lung retention.

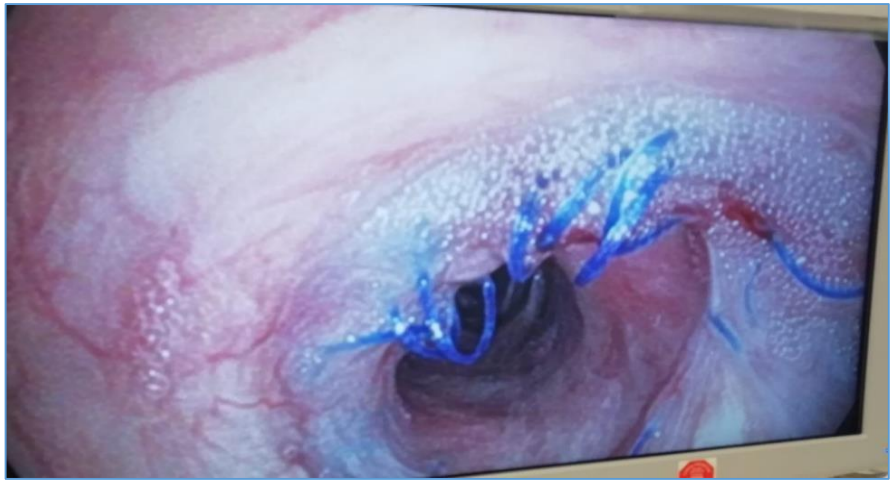
Systemic exposure gradually accumulates with a 2-3 fold increase in AUC 0-24h observed following 7 days of daily dosing.

Case report

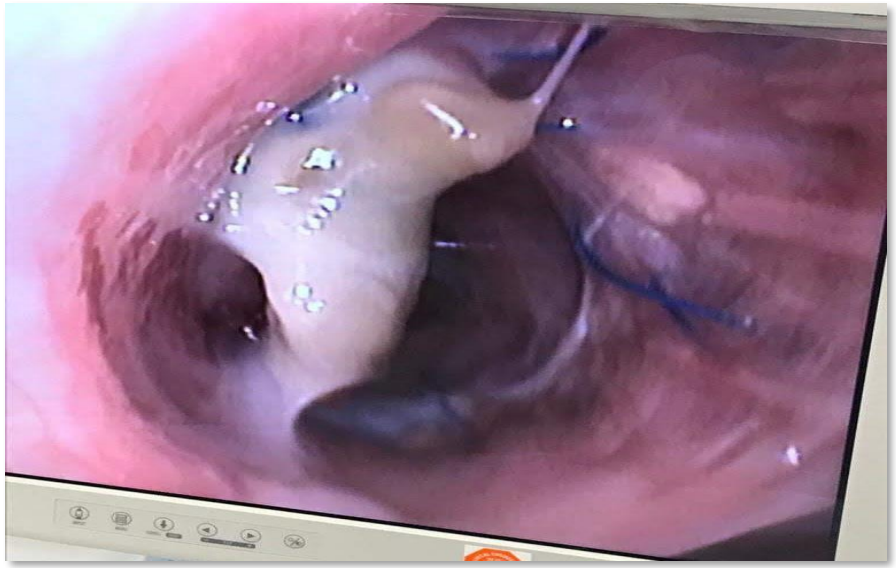
29 y.o. female Lung transplant. Aspergillus tracheobronchitis



December 18th:
Initiate 5mg
OZL daily



February 12th review:
Dramatic response evident



Jan 2nd review:
Patient tolerating
drug well

Pagani *et al.,* PC945, a novel inhaled azole for treatment of fungal tracheobronchitis post-lung transplantation: a case report. 2019, *Journal of Fungi,* Fungal Update 2019 abstract 15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