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Activity of manogepix against yeast and mold isolates from 2025 in the United States

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Introduction

- Fosmanogepix is the prodrug of manogepix, a novel antifungal agent targeting the fungal Gwt1 enzyme.
 - Gwt1 is an acyltransferase in the glycosylphosphatidylinositol (GPI) biosynthesis pathway, which is required for anchoring of cell wall proteins in fungi.
- Manogepix has activity against both yeasts and molds.
 - It is currently in phase 3 clinical trials for the treatment of invasive candidiasis and mold infections.
- Here, we look at the *in vitro* activity of manogepix against yeast and molds from the United States collected as a part of a surveillance program in 2025.

Methods

- A total of 427 isolates from the United States were collected and tested.
 - 358 yeast and 69 molds.
- Only 1 isolate per patient episode was included.
- All isolates were identified by MALDI-TOF MS and/or DNA sequencing.
- Isolates were tested by CLSI reference broth microdilution method (M27 or M38) for manogepix, micafungin (yeast only), fluconazole (yeast only), itraconazole (molds only), voriconazole, and amphotericin B.
 - Minimum effective concentration (MEC) was read for manogepix against molds; minimum inhibitory concentration (MIC) was read for all comparators against yeast and molds and for manogepix against yeast.
- CLSI breakpoints (M27M44S, M38M51S) or epidemiological cutoff values (ECVs, M57S) were applied for comparator agents as available; no breakpoints or epidemiological cutoff values are available for manogepix.

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Results

- Isolates were from all 9 U.S census divisions (Figure 1).
 - There were no molds from census divisions 4 (West North Central) or 6 (East South Central).
- There were 18 yeast species (Table 1) and 15 mold species represented (Table 2).
- Yeast isolates were from bloodstream infections (244/358, 68.2%), skin and soft tissue infections (39/358, 10.9%), intra-abdominal infections (23/358, 6.4%), respiratory tract infections (22/358, 6.1%), head and neck infections (7/358, 2.0%), urinary tract infections (6/358, 1.7%), or other infection type including aspirate or genital tract (17/358, 4.7%) (Figure 2).
- Mold isolates were from respiratory tract infections (50/69, 72.5%), head and neck infections (11/69, 15.9%), skin and soft tissue infections (5/69, 7.2%), bloodstream infections (1/69, 1.4%), and no listed infection type (2/69, 2.9%) (Figure 2).
- For yeast, manogepix $MIC_{50/90}$ was 1 to 2 doubling dilutions lower than micafungin for all species with the exception of *C. krusei* against which manogepix does not have activity (Table 1). Manogepix $MIC_{50/90}$ was 3–4 doubling dilutions lower than fluconazole for all *Candida* spp. besides *C. krusei*. Manogepix $MIC_{50/90}$ was similar to voriconazole for most *Candida* spp. except for *C. auris* where manogepix was 6 doubling dilutions more active and *C. lusitaniae* where voriconazole was more active by 1 to 3 doubling dilutions. Manogepix $MIC_{50/90}$ was also lower than that of amphotericin B against all species besides *C. krusei*. Manogepix $MIC_{50/90}$ was lower than all comparators besides voriconazole against less common yeast.
 - There were 1 *C. albicans* and 5 *C. glabrata* non-susceptible to micafungin and 2 *C. albicans*, 6 *C. glabrata*, 1 *C. parapsilosis*, and 3 *C. tropicalis* resistant to fluconazole; manogepix MICs among these isolates were 0.004–0.12 mg/L (data not shown).
- For molds, manogepix $MEC_{50/90}$ was lower than $MIC_{50/90}$ for all comparators by 5 to 8 doubling dilutions.
 - There was 1 *Rhizopus oryzae* isolate with a manogepix MEC of 4 mg/L, voriconazole MIC >8 mg/L, itraconazole 4 mg/L, amphotericin B 0.06 mg/L.
 - Among the 3 *A. fumigatus* non-susceptible to voriconazole, manogepix MECs were 0.015 to 0.03 mg/L (data not shown).

Conclusions

- Manogepix is highly active *in vitro* against yeast and mold collected from diverse patient infection types across the United States.
 - These isolates were geographically diverse including yeast from all 9 census divisions and molds from 7/9 census divisions.
- Against most organisms manogepix MICs or MECs were lower than the MICs of comparator antifungal agents.
 - Higher MICs were observed against *C. krusei* among yeast and higher MECs in 1 *Rhizopus oryzae* among molds.
- These data support the continued development of fosmanogepix for the treatment of invasive fungal infections in the United States.

References

CLSI, *M38M51S Ed4. Performance standards for antifungal susceptibility testing of molds*. 2026, Clinical and Laboratory Standards Institute: Wayne, PA.

CLSI, *M57S Ed4. Epidemiological cutoff values for antifungal susceptibility testing*. 2022, Clinical and Laboratory Standards Institute: Wayne, PA.

CLSI, *M38 Ed3. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi*. 2017, Clinical and Laboratory Standards Institute: Wayne, PA.

CLSI, *M27 Ed4. Reference method for broth dilution antifungal susceptibility testing of yeasts*. 2017, Clinical and Laboratory Standards Institute: Wayne, PA.

Figure 1. Geography of collected isolates

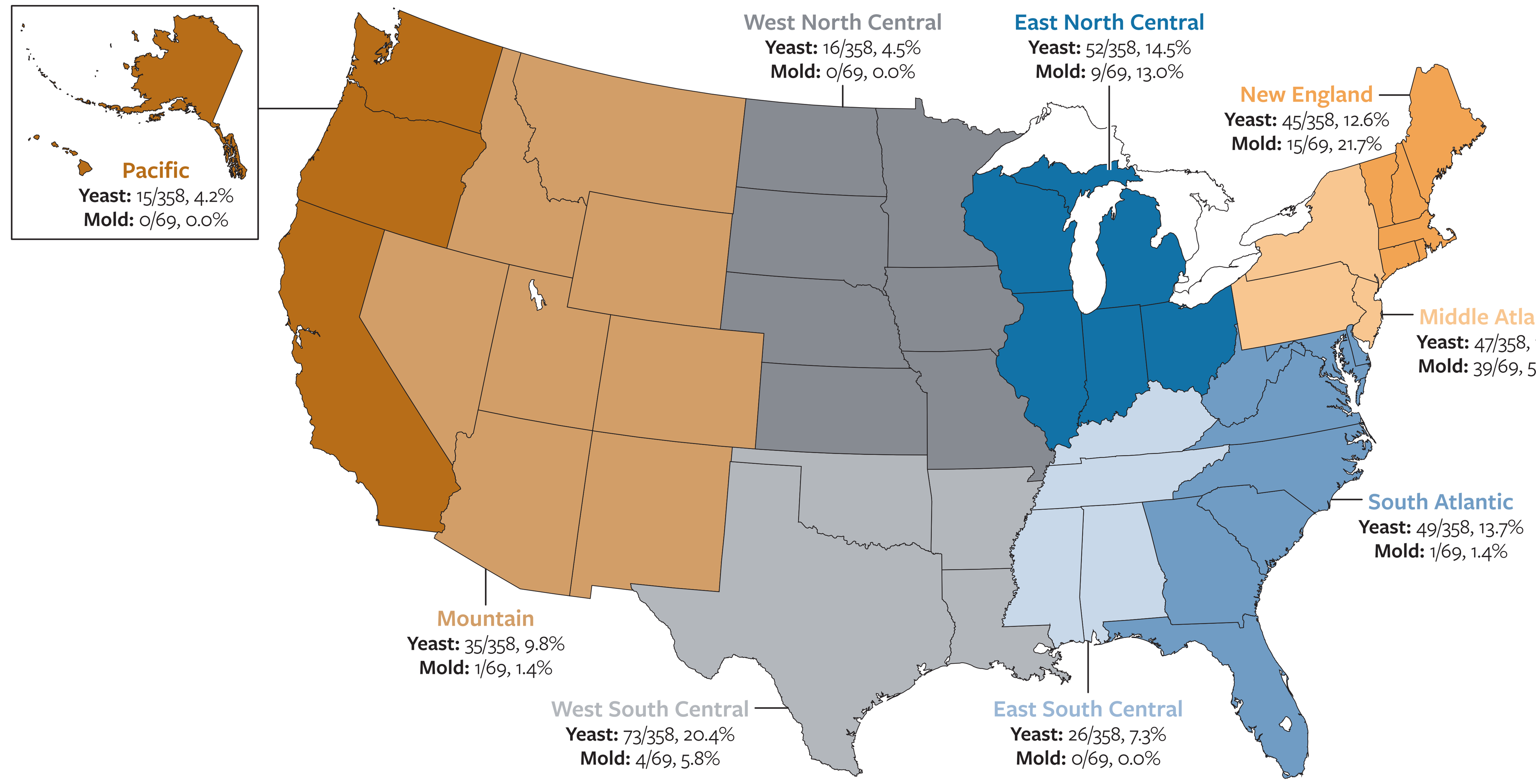

Pacific
Yeast: 15/358, 4.2%
Mold: 0/69, 0.0%
West North Central
Yeast: 16/358, 4.5%
Mold: 0/69, 0.0%
East North Central
Yeast: 52/358, 14.5%
Mold: 9/69, 13.0%
New England
Yeast: 45/358, 12.6%
Mold: 15/69, 21.7%
Middle Atlantic
Yeast: 47/358, 13.1%
Mold: 39/69, 56.5%
South Atlantic
Yeast: 49/358, 13.7%
Mold: 1/69, 1.4%
Mountain
Yeast: 35/358, 9.8%
Mold: 1/69, 1.4%
West South Central
Yeast: 73/358, 20.4%
Mold: 4/69, 5.8%
East South Central
Yeast: 26/358, 7.3%
Mold: 0/69, 0.0%

Figure 2. Infection source of collected yeast (A) and mold (B) isolates

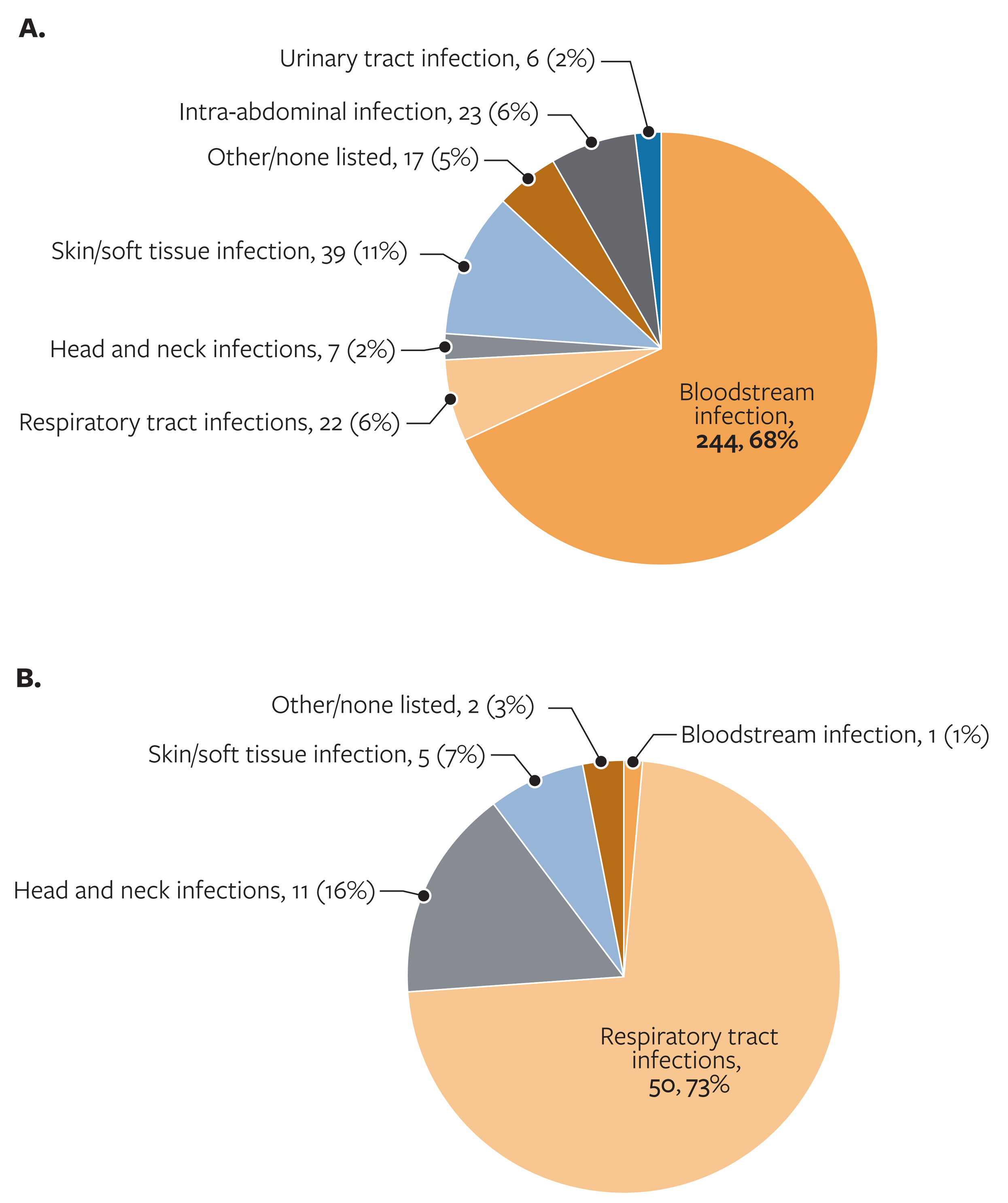

A.
Urinary tract infection, 6 (2%)
Intra-abdominal infection, 23 (6%)
Other/none listed, 17 (5%)
Skin/soft tissue infection, 39 (11%)
Head and neck infections, 7 (2%)
Respiratory tract infections, 22 (6%)
Bloodstream infection, 244, 68%
B.
Other/none listed, 2 (3%)
Bloodstream infection, 1 (1%)
Skin/soft tissue infection, 5 (7%)
Head and neck infections, 11 (16%)
Respiratory tract infections, 50, 73%

Table 1. MIC/MEC range (mg/L) and MIC/$MEC_{50/90}$ (mg/L) for manogepix (MGX), micafungin (MCG), fluconazole (FLC), voriconazole (VRC), and amphotericin B (AmB) in yeast

	MGX		MCG (%S/WT)[1]		FLC (%S/WT)[1]		VRC (%S/WT)[1]		AmB (%S/WT)[1]	
Organism (n)	MIC range	$MIC_{50/90}$	MIC range	$MIC_{50/90}$	MIC range	$MIC_{50/90}$	MIC range	$MIC_{50/90}$	MIC range	$MIC_{50/90}$
All yeast (358)	0.001 – >4	0.015/0.12	0.008 – >4	0.03/1	0.06 – >128	0.5/64	≤0.002 – >8	0.015/0.25	0.12 – 2	1/1
All *Candida* spp. (339)	0.001 – >4	0.015/0.06	0.008 – 4	0.03/1	0.06 – >128	0.5/64	≤0.002 – >8	0.015/0.25	0.12 – 2	1/1
C. albicans (91)	0.002 – 0.03	0.008/0.008	0.008 – 0.5 (98.9/98.9)	0.015/0.03	0.06 – 8 (97.8/96.7)	0.12/0.25	≤0.002 – 0.12 (100.0/96.7)	0.004/0.008	0.12 – 1 (NA/100.0)	0.5/1
C. glabrata (84)	0.008 – 0.12	0.03/0.12	0.008 – 1 (94.0/94.0)	0.015/0.03	0.25 – 128 (92.9/89.3)	4/16	0.008 – 4 (NA/89.3)	0.06/0.5	0.25 – 1 (NA/100.0)	1/1
C. parapsilosis (40)	0.004 – 0.03	0.015/0.015	0.5 – 2 (100.0/100.0)	1/2	0.12 – 16 (97.5/97.5)	0.25/0.5	≤0.002 – 0.25 (97.5/NA)	0.008/0.015	0.25 – 1 (NA/100.0)	0.5/1
C. dubliniensis (29)	0.002 – 0.008	0.004/0.008	0.008 – 0.03 (NA/100.0)	0.03/0.03	0.06 – 0.25 (NA/100.0)	0.12/0.25	≤0.002 – 0.015 (NA/NA)	0.004/0.008	0.12 – 0.5 (NA/100.0)	0.25/0.5
C. auris (25)	0.008 – 0.12	0.015/0.06	0.06 – 1 (100.0/96.0)	0.25/0.5	64 – >128 (0.0/NA)	128/>128	0.25 – >8 (NA/NA)	1/2	0.5 – 2 (44.0/NA)	2/2
C. tropicalis (25)	0.008 – 0.03	0.015/0.03	0.008 – 0.06 (100.0/100.0)	0.03/0.06	0.12 – >128 (88.0/88.0)	0.25/16	0.004 – 2 (88.0/88.0)	0.015/0.25	0.25 – 1 (NA/100.0)	1/1
C. lusitaniae (12)	0.015 – 0.5	0.06/0.25	0.06 – 4 (NA/91.7)	0.25/0.25	0.12 – 128 (NA/83.3)	0.5/128	0.004 – 1 (NA/NA)	0.008/0.5	0.5 – 1 (NA/100.0)	0.5/0.5
Cryptococcus neoformans var. grubii (12)	0.12 – 0.5	0.25/0.25	4 – >4 (NA/NA)	>4/>4	2 – 4 (NA/100.0)	4/4	0.03 – 0.06 (NA/100.0)	0.06/0.06	0.25 – 1 (NA/33.3)	1/1
C. krusei (10)	4 – >4	>4/>4	0.03 – 0.12 (100.0/100.0)	0.12/0.12	16 – 32 (NA/NA)	16/32	0.12/0.25 (100.0/100.0)	0.25/0.25	2 (NA/100.0)	2/2
Other *Candida* spp. (23) [2]	0.001 – 1	0.015/1	0.03 – 1	0.25/0.5	0.25 – 128	1/4	0.004 – 4	0.03/0.12	0.25 – 2	1/2
Other non-*Candida* yeast (7) [3]	0.015 – 0.25	0.03/NA	0.03 – >4	0.25/NA	0.25 – 4	1/NA	0.008 – 0.12	0.03/NA	0.25 – 1	1/NA

MGX, manogepix; MCG, micafungin; S, susceptible; WT, wildtype; VRC, voriconazole; ITR, itraconazole; AmB, amphotericin B; NA, not applicable
[1] CLSI M27M44S, CLSI M57S, or for *C. auris* https://www.cdc.gov/candida-auris/hcp/laboratories/antifungal-susceptibility-testing.html
[2] Includes *C. fermentati* (2), *C. guilliermondii* (5), *C. kefyr* (6), *C. metapsilosis* (5), *C. orthopsilosis* (3), *C. pelliculosa* (2)
[3] Includes *Lodderomyces elongisporus* (1), *Saccharomyces cerevisiae* (5), and *Trichosporon asahii* (1)

Table 2. MIC/MEC range (mg/L) and MIC/$MEC_{50/90}$ (mg/L) for manogepix (MGX), voriconazole (VRC), itraconazole (ITR), and amphotericin B (AmB) in molds

	MGX		VRC		ITR		AmB	
Organism (n)	MEC range	$MEC_{50/90}$	MIC range (%S/WT)[1]	$MIC_{50/90}$	MIC range (%S/WT)[1]	$MIC_{50/90}$	MIC range (%S/WT)[1]	$MIC_{50/90}$
All molds (69)	≤0.0005 – 4	0.008/0.03	0.06 – >8	0.5/2	0.008 – >8	1/8	≤0.03 – >4	1/2
All *Aspergillus* spp. (59)	0.002 – 0.06	0.008/0.03	0.12 – 2	0.5/1	0.008 – >8	1/2	0.12 – 2	1/2
Aspergillus fumigatus (42)	0.008 – 0.03	0.015/0.03	0.25 – 2 (92.9/97.6)	0.5/0.5	0.5 – 4 (NA/97.6)	1/1	0.25 – 2 (NA/100.0)	1/2
Aspergillus niger species complex (11)	0.002 – 0.008	0.004/0.008	0.5 – 2 (NA/100.0)	1/2	1 – >8 (NA/81.8)	2/8	0.12 – 0.25 (NA/100.0)	0.12/0.25
Other *Aspergillus* spp. (6) [2]	0.008 – 0.06	0.008/*	0.12 – 1	0.5/*	0.008 – 0.05	0.5/*	0.5 – 2	1/*
Other molds (10) [3]	≤0.0005 – 4	0.004/0.015	0.06 – >8	1/>8	0.12 – >8	4/>8	≤0.03 – >4	1/>4

*MIC_{50} only as < 10 organisms represented
MGX, manogepix; VRC, voriconazole; ITR, itraconazole; AmB, amphotericin B
[1] CLSI M38M51S, CLSI M57S
[2] Includes *Aspergillus flavus* species complex (3), *A. sclerotiorum* (1), *A. thermomutatus* (1), and *A. versicolor* species complex (1)
[3] Genera include *Exophiala dermatitidis* (1), *Exophiala phaeomuriformis* (1), *Paecilomyces variotii* (1), *Penicillium chrysogenum* (1), *Phialemonum obovatum* (1), *Rhizopus oryzae* (1), *Scedosporium boydii* (1), *Scopulariopsis brevicaulis* (1), *Scedosporium* spp. (2)

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