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In Vitro Activity of Manogepix Against 2,810 Fungal Isolates from the SENTRY Surveillance Program (2020–2021) Stratified by Infection Type

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Introduction

- Current antifungal agents are active against most common fungal pathogens; however, breakthrough infections occur and increasingly involve less frequently encountered yeast and mold isolates.
- Manogepix (MGX) is a novel inhibitor of the fungal Gwt1 enzyme and demonstrates potent *in vitro* activity against most common fungal pathogens including rare yeast and mold strains.
- The prodrug of manogepix (fosmanogepix) is in Phase 3 clinical development for invasive candidiasis/candidemia (NCT05421858) and Phase 2 clinical development for invasive aspergillosis and rare mold infections (NCT04240886).
- In this study, we evaluated the activity of manogepix and comparators against 2,810 recent (2020–2021) clinical fungal isolates collected worldwide and stratified according to infection type.

Methods

- Fungal isolates were collected from 77 medical centers located in North America (30 medical centers; 9 US Census Divisions), Europe (30 medical centers), the Asia-Pacific region (11 medical centers), and Latin America (6 medical centers).
- Isolates were collected from patients (1 per infection episode) with bloodstream infection (BSI; 48% of isolates); intra-abdominal infection (IAI; 2% of isolates); skin and skin structure infection (SSSI; 8% of isolates); urinary tract infection (UTI; 3% of isolates); respiratory tract infection (RTI), including pneumonia in hospitalized patients (PIHP; 20% of isolates); and other infection types (19% of isolates) (Figure 1).
- Of the 2,810 fungal isolates tested, 2,075 (73.8%) were *Candida* spp.; 93 (3.3%) were non-*Candida* yeasts, including 53 (1.9%) *Cryptococcus neoformans* var. *grubii*; 534 (19.0%) were *Aspergillus* spp.; and 108 (3.8%) were other molds.
- Fungal identifications were confirmed using matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Billerica, MA, USA) via phenotypic, proteomic, or sequencing-based methods.
- Broth microdilution susceptibility testing was conducted according to Clinical and Laboratory Standards Institute (CLSI) documents M27 (2017), M38 (2017), M59 (2020), M60 (2020), and M61 (2020).
- Manogepix MIC values for yeast isolates and MEC values for mold isolates were determined using the same reading criteria as the echinocandins ("approximately 50% inhibition" for yeasts and "small, rounded, compact, hyphal forms" for molds).

Results

- Manogepix ($MIC_{50/90}$, 0.008/0.06 mg/L) was the most potent antifungal tested against 2,075 *Candida* spp. isolates (Table 1 and Figure 2).
- Manogepix demonstrated potent *in vitro* activity against common *Candida* spp. isolates, including 700 *C. albicans* ($MIC_{50/90}$, 0.004/0.008 mg/L), 471 *C. glabrata* ($MIC_{50/90}$, 0.03/0.06 mg/L), 333 *C. parapsilosis* ($MIC_{50/90}$, 0.008/0.015 mg/L), and 263 *C. tropicalis* ($MIC_{50/90}$, 0.015/0.015 mg/L) isolates (Table 1).
- Manogepix ($MIC_{50/90}$, 0.004/0.03 mg/L) inhibited 100% of *C. auris* isolates at ≤0.06 mg/L (Table 1).
- Manogepix was active against 45 infrequently encountered *Candida* spp. ($MIC_{50/90}$, 0.004/0.03 mg/L) isolates and 53 *C. neoformans* var. *grubii* ($MIC_{50/90}$, 0.25/1 mg/L) isolates (Table 1).
- Against 534 *Aspergillus* spp. isolates, manogepix ($MEC_{50/90}$, 0.015/0.03 mg/L; Table 2) was ≥32-fold more active by MIC_{90} than itraconazole, voriconazole, and amphotericin B (Figure 3).
- Manogepix was active against *Fusarium* spp. ($MEC_{50/90}$, 0.015/0.06 mg/L), *Lomentospora prolificans* ($MEC_{50/90}$, 0.03/0.06 mg/L), *Paecilomyces* spp. ($MEC_{50/90}$, 0.004/0.008 mg/L), and *Scedosporium* spp. ($MEC_{50/90}$, 0.06/0.12 mg/L) isolates (Table 2).
- Rare molds, including *Acremonium* sp., *Corpinellus* sp., *Exophiala attenuata*, *E. dermatitidis*, *Gibberella fujikuroi* species complex, *Microascus ruber*, *Penicillium* spp., *Rasamasonia* spp., *Sarcocladium kiliense*, and *Scopulariopsis brevicaulis*, were inhibited by ≤0.002–0.25 mg/L of manogepix (Table 3).

Table 1. *In Vitro* Activity of Manogepix against Yeasts

Organism (no. tested) Antimicrobial agent	Infection Type	MIC range (mg/L)	$MIC_{50/90}$ (mg/L)
***Candida* spp. (2,075)[a]**			
Manogepix	ALL	≤0.002–>8	0.008 / 0.06
Manogepix (1,302)	BSI	≤0.002–>8	0.008 / 0.06
Manogepix (134)	PIHP	≤0.002–>8	0.008 / 0.06
Manogepix (145)	SSSI	≤0.002–0.06	0.008 / 0.03
***C. albicans* (700)**			
Manogepix	ALL	≤0.002–0.12	0.004 / 0.008
Manogepix (404)	BSI	≤0.002–0.03	0.004 / 0.008
Manogepix (71)	PIHP	≤0.002–0.12	0.004 / 0.008
Manogepix (57)	SSSI	≤0.002–0.015	0.004 / 0.008
***C. auris* (22)**			
Manogepix	ALL	≤0.002–0.06	0.004 / 0.03
Manogepix (14)	BSI	≤0.002–0.06	0.004 / 0.06
Manogepix (3)	PIHP	0.004–0.03	0.015 / —
Manogepix (2)	SSSI	0.004–0.03	0.004 / —
***C. dubliniensis* (68)**			
Manogepix	ALL	≤0.002–0.008	0.004 / 0.008
Manogepix (33)	BSI	≤0.002–0.008	0.004 / 0.008
Manogepix (11)	PIHP	0.004–0.008	0.004 / 0.008
Manogepix (6)	SSSI	≤0.002–0.008	0.004 / —
***C. glabrata* (471)**			
Manogepix	ALL	0.004–0.12	0.03 / 0.06
Manogepix (321)	BSI	0.004–0.12	0.03 / 0.06
Manogepix (17)	PIHP	0.015–0.06	0.03 / 0.06
Manogepix (29)	SSSI	0.008–0.06	0.03 / 0.06
***C. guilliermondii* (10)**			
Manogepix	ALL	0.004–0.015	0.008 / 0.015
Manogepix (5)	BSI	0.004–0.008	0.008 / —
Manogepix (2)	SSSI	0.015	0.015 / —
***C. kefyr* (30)**			
Manogepix	ALL	0.03–1	0.12 / 0.5
Manogepix (11)	BSI	0.06–0.5	0.25 / 0.5
Manogepix (2)	PIHP	0.12–0.5	0.12 / —
***C. lusitaniae* (38)**			
Manogepix	ALL	0.008–0.25	0.03 / 0.06
Manogepix (27)	BSI	0.008–0.12	0.03 / 0.06
Manogepix (2)	SSSI	0.015–0.03	0.015 / —
***C. orthopsilosis* (18)**			
Manogepix	ALL	0.008–0.03	0.008 / 0.03
Manogepix (16)	BSI	0.008–0.03	0.008 / 0.03
***C. parapsilosis* (333)**			
Manogepix	ALL	0.004–0.06	0.008 / 0.015
Manogepix (234)	BSI	0.004–0.06	0.008 / 0.03
Manogepix (11)	PIHP	0.008–0.015	0.008 / 0.015
Manogepix (25)	SSSI	0.008–0.03	0.008 / 0.015
***C. tropicalis* (263)**			
Manogepix	ALL	≤0.002–0.12	0.015 / 0.015
Manogepix (166)	BSI	≤0.002–0.12	0.015 / 0.015
Manogepix (11)	PIHP	0.004–0.03	0.015 / 0.015
Manogepix (19)	SSSI	≤0.002–0.03	0.015 / 0.03
Other *Candida* spp. (45)[b]			
Manogepix	ALL	≤0.002–2	0.004 / 0.03
Manogepix (31)	BSI	≤0.002–2	0.004 / 0.03
Manogepix (2)	PIHP	0.004–0.03	0.004 / —
Manogepix (3)	SSSI	≤0.002–0.008	≤0.002 / —
***Cryptococcus neoformans* var. *grubii* (53)**			
Manogepix	ALL	0.03–4	0.25 / 1
Manogepix (23)	BSI	0.03–1	0.25 / 1
Manogepix (3)	PIHP	0.25–0.5	0.25 / —

ALL includes bloodstream infection (BSI), intra-abdominal infection (IAI), skin and skin structure infection (SSSI), urinary tract infection (UTI), pneumonia in hospitalized patients (PIHP), and other infection types.
[a] Organisms include *Candida albicans* (700), *C. auris* (22), *C. bracarensis* (3), *C. dubliniensis* (68), *C. duobushaemulonil* (2), *C. fabianii* (2), *C. fermentati* (5), *C. glabrata* (471), *C. guilliermondii* (10), *C. haemulonil* (2), *C. inconspicua* (3), *C. kefyr* (30), *C. krusei* (77), *C. lipolytica* (1), *C. lusitaniae* (38), *C. metapsilosis* (9), *C. nivariensis* (2), *C. norvegensis* (1), *C. orthopsilosis* (18), *C. parapsilosis* (333), *C. paranugosa* (1), *C. pelliculosa* (6), *C. rugosa* (3), *C. spencermartiniae* (1), *C. theae* (2), *C. tropicalis* (263), and *C. utilis* (2).
[b] Organisms include *C. bracarensis* (3), *C. duobushaemulonil* (2), *C. fabianii* (2), *C. fermentati* (5), *C. haemulonil* (2), *C. inconspicua* (3), *C. lipolytica* (1), *C. metapsilosis* (9), *C. nivariensis* (2), *C. norvegensis* (1), *C. paranugosa* (1), *C. pelliculosa* (6), *C. rugosa* (3), *C. spencermartiniae* (1), *C. theae* (2), *C. tropicalis* (263), and *C. utilis* (2).

Table 2. *In Vitro* Activity of Manogepix against Molds

Organism (no. tested) Antimicrobial agent	Infection Type	MEC range (mg/L)	$MEC_{50/90}$ (mg/L)
***Aspergillus* spp. (534)[a]**			
Manogepix	ALL	≤0.002–0.25	0.015 / 0.03
Manogepix (6)	BSI	0.008–0.25	0.03 / —
Manogepix (371)	PIHP	≤0.002–0.12	0.015 / 0.03
Manogepix (45)	SSSI	0.008–0.12	0.015 / 0.03
***Fusarium* spp. (19)[b]**			
Manogepix	ALL	≤0.002–0.06	0.015 / 0.06
Manogepix (4)	BSI	0.004–0.06	0.008 / —
Manogepix (3)	PIHP	0.015–0.06	0.015 / —
Manogepix (5)	SSSI	0.015–0.06	0.015 / —
***Lomentospora prolificans* (12)**			
Manogepix	ALL	0.004–0.06	0.03 / 0.06
Manogepix (3)	BSI	0.015–0.03	0.03 / —
Manogepix (7)	PIHP	0.004–0.06	0.03 / —
Manogepix (2)	SSSI	0.015–0.06	0.015 / —
***Paecilomyces* spp. (11)[c]**			
Manogepix	ALL	≤0.002–0.008	0.004 / 0.008
Manogepix (7)	PIHP	0.004–0.008	0.004 / —
***Scedosporium* spp. (17)[d]**			
Manogepix	ALL	0.015–0.5	0.06 / 0.12
Manogepix (8)	PIHP	0.015–0.12	0.03 / —
Manogepix (3)	SSSI	0.03–0.5	0.06 / —

ALL includes bloodstream infection (BSI), intra-abdominal infection (IAI), skin and skin structure infection (SSSI), urinary tract infection (UTI), pneumonia in hospitalized patients (PIHP), and other infection types.
[a] Organisms include *Aspergillus alabamensis* (1), *A. flavus* species complex (44), *A. fumigatus* (366), *A. hortai* (1), *A. lentulus* (2), *A. nidulans* (14), *A. nidulans* species complex (2), *A. niger* (33), *A. niger* species complex (28), *A. parasiticus* (2), *A. sclerotiorum* (1), *A. sydowii* (1), *A. tamarii* (1), *A. terreus* (12), *A. terreus* species complex (15), *A. thermomutatus* (1), *A. tubingensis* (1), *A. udagawae* (1), *A. unguis* (1), *A. ustus* (1), *A. ustus* species complex (3), and *A. versicolor* (3).
[b] Organisms include *Fusarium dimerum* species complex (1), *F. incarnatum-equiseti* species complex (1), *F. oxysporum* species complex (5), *F. solani* (2), and *F. solani* species complex (10).
[c] Organisms include *Paecilomyces lilacinus* (2), *P. variotii* (7), and unspecified *Paecilomyces* (2).
[d] Organisms include *Scedosporium apiospermum*/*S. boydii* (11), *S. aurantiacum* (4), and *S. boydii* (2).

Table 3. *In Vitro* Activity of Manogepix against Infrequently Encountered Mold Isolates

Organism (no. tested)	Manogepix MEC range (mg/L)
Acremonium sp. (1)	0.25
Corpinellus sp. (1)	0.008
Exophiala attenuata (1)	0.008
Exophiala dermatitidis (2)	≤0.002–0.008
Gibberella fujikuroi species complex (8)	0.008–0.12
Monascus ruber (1)	0.03
Penicillium spp. (2)[a]	0.008
Rasamasonia spp. (5)[b]	≤0.002–0.008
Sarocladium kiliense (1)	0.015
Scopulariopsis brevicaulis (1)	0.008

[a] *Penicillium citrinum* (1) and *P. onobense* (1).
[b] *Rasamasonia argillacea* (2) and *R. argillacea* species complex (3).

Conclusions

- Manogepix is a first-in-class antifungal agent that possesses a novel mechanism of action and potent *in vitro* activity.
- Manogepix demonstrated potent *in vitro* activity equal to or greater than the azoles and echinocandins against *Candida* spp. (except *C. krusei*), *Aspergillus* spp., *C. neoformans*, and many infrequently encountered yeast and non-*Aspergillus* molds.
- Notable manogepix activity was observed against *C. auris*, *Fusarium* spp., *Lomentospora prolificans*, *Scedosporium* spp., and rare mold isolates.
- Additional clinical development of the manogepix prodrug (fosmanogepix) in difficult-to-treat/resistant fungal infections is warranted.

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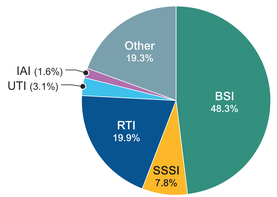
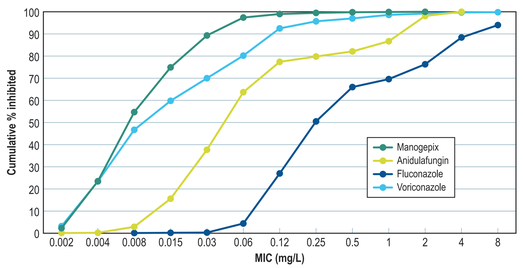
SCAN ME

Figure 1. Occurrence of Fungal Infections by Infection Type (2020–2021)



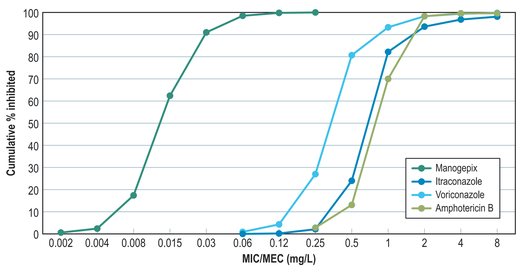
BSI, bloodstream infection; SSSI, skin and skin structure infection; RTI, respiratory tract infection, including pneumonia in hospitalized patients; UTI, urinary tract infection; IAI, intra-abdominal infection; Other, other infection types.

Figure 2. Cumulative % Inhibition MIC Distributions for Manogepix and Comparator Agents against 1,998 *Candida* spp. Isolates (except *C. krusei*) (2020–2021)



Organisms include *Candida albicans* (700), *C. auris* (22), *C. bracarensis* (3), *C. dubliniensis* (68), *C. duobushaemulonil* (2), *C. fabianii* (2), *C. fermentati* (5), *C. glabrata* (471), *C. guilliermondii* (10), *C. haemulonil* (2), *C. inconspicua* (3), *C. kefyr* (30), *C. lipolytica* (1), *C. lusitaniae* (38), *C. metapsilosis* (9), *C. nivariensis* (2), *C. norvegensis* (1), *C. orthopsilosis* (18), *C. parapsilosis* (333), *C. paranugosa* (1), *C. pelliculosa* (6), *C. rugosa* (3), *C. spencermartiniae* (1), *C. theae* (2), *C. tropicalis* (263), and *C. utilis* (2).

Figure 3. Cumulative % Inhibition MIC Distributions for Manogepix and Comparator Agents against 534 *Aspergillus* spp. Isolates (2020–2021)



Organisms include *Aspergillus alabamensis* (1), *A. flavus* species complex (44), *A. fumigatus* (366), *A. hortai* (1), *A. lentulus* (2), *A. nidulans* (14), *A. nidulans* species complex (2), *A. niger* (33), *A. niger* species complex (28), *A. parasiticus* (2), *A. sclerotiorum* (1), *A. sydowii* (1), *A. tamarii* (1), *A. terreus* (12), *A. terreus* species complex (15), *A. thermomutatus* (1), *A. tubingensis* (1), *A. udagawae* (1), *A. unguis* (1), *A. ustus* (1), *A. ustus* species complex (3), and *A. versicolor* (3).