In vitro Activity of Manogepix against 1,435 Fungal Isolates Collected Worldwide from the SENTRY Surveillance Program (2020)

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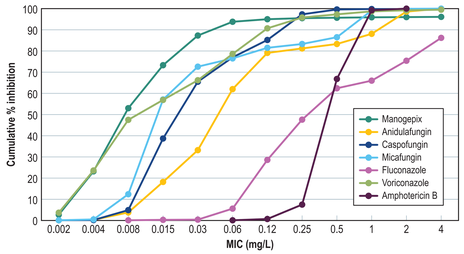
Introduction

- Manogepix has previously demonstrated potent *in vitro* activity against *Candida* spp. (except *C. krusei*), *Cryptococcus* spp., *Aspergillus* spp., as well as rare yeast and mold isolates (including resistant strains).
- Fosmanogepix (manogepix prodrug) is in Phase 2 development for the treatment of invasive mold infections caused by *Aspergillus* spp. and rare molds (NCT04240886) and has completed Phase 2 clinical studies for Candidemia (NCT03604705) and *Candida auris* infections (NCT04148287).
- We evaluated the *in vitro* activity of manogepix and comparator agents against 1,435 fungal isolates collected worldwide during 2020 as part of the SENTRY Antifungal Surveillance Program.

Materials and Methods

- Fungal surveillance isolates were collected from 73 medical centers located in North America (*n*=29), Europe (*n*=28), the Asia-Pacific region (*n*=10), and Latin America (*n*=6).
- Isolates (1 per patient infection episode) were collected from patients with bloodstream infection (48.3%); pneumonia in hospitalized patients (17.6%); skin and skin structure infection (7.0%); urinary tract infection (3.1%); intra-abdominal infection (1.4%); and other infection types (22.6% isolates).
- Of the 1,435 fungal isolates tested, 1,072 (74.7%) were *Candida* spp., 246 (17.1%) were *Aspergillus* spp., 53 (3.7%) were non-*Candida* yeasts (including 27 *Cryptococcus neoformans* var. *grubii*), and 64 (4.5%) were other molds.
- Fungal identifications were confirmed using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (Bruker Daltonics, Billerica, MA) and/or sequencing-based methods.
- Broth microdilution susceptibility testing was conducted according to the following Clinical and Laboratory Standards Institute (CLSI) guidelines: M27 (2017), M38 (2017), M59 (2020), M60 (2020), and M61 (2020).
- Manogepix MIC values were determined for yeast and MEC values for mold using the same reading criteria as echinocandins.

Figure 1. *In vitro* Activity of Manogepix and Comparators against 1,072 *Candida* spp. Isolates

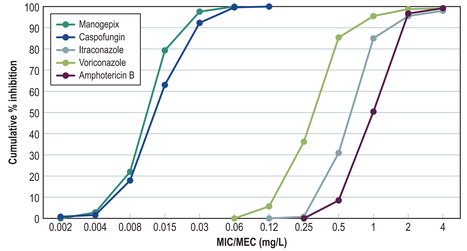


Organisms include: *Candida albicans* (350), *C. auris* (11), *C. dubliniensis* (40), *C. glabrata* (258), *C. kefyr* (10), *C. krusei* (45), *C. lusitaniae* (16), *C. orthopsilosis* (12), *C. parapsilosis* (165), *C. tropicalis* (139), and 26 other *Candida* spp. isolates.

Results

- Manogepix ($MIC_{50/90}$, 0.008/0.06 mg/L) was the most potent antifungal agent tested against 1,072 *Candida* spp. isolates, including *C. auris* ($MIC_{50/90}$, 0.004/0.015 mg/L) (Table 1 and Figure 1).
- Manogepix was active against common *Candida* spp. isolates, including *C. albicans* ($MIC_{50/90}$, 0.004/0.008 mg/L), *C. glabrata* ($MIC_{50/90}$, 0.03/0.06 mg/L), *C. parapsilosis* ($MIC_{50/90}$, 0.008/0.015 mg/L), and *C. tropicalis* ($MIC_{50/90}$, 0.015/0.015 mg/L) isolates (Table 1).
  - Manogepix *in vitro* activity was unchanged against *Candida* spp. isolates, demonstrating resistance to echinocandins and azoles.
- Manogepix ($MIC_{50/90}$, 0.5/1 mg/L) was ≥4-fold more active than anidulafungin, caspofungin, and micafungin against *C. neoformans* var. *grubii* isolates (Table 1).
- Manogepix ($MEC_{50/90}$, 0.015/0.03 mg/L) was comparable in activity to the caspofungin and ≥32-fold more active than itraconazole, voriconazole, and amphotericin B against *Aspergillus* spp. isolates (Table 2 and Figure 2).
- Manogepix was the most active compound tested against *Paecilomyces* spp. and *Scedosporium* spp. isolates, with $MEC_{50/90}$ values of 0.004/0.008 and 0.06/0.12 mg/L, respectively (Table 2).
- Rare, non-*Candida* yeasts, including *G. clavatum*, *K. ohmeri*, *M. capitatus*, *R. mucilaginosa*, *S. cerevisiae*, and *Y. lipolytica*, were inhibited by low manogepix concentrations ($MIC_{50/90}$, 0.008/0.06 mg/L) (Table 3).
- Rare molds, including *E. dermatitidis*, *Fusarium* spp., *G. fujikuroi* species complex, *L. prolificans*, *Penicillium* spp., *R. argillacea* species complex, *S. kilíense*, and *S. brevicaulis* were inhibited by low manogepix concentrations ($MEC_{50/90}$, ≤0.002/0.06 mg/L) (Table 3).

Figure 2. *In vitro* Activity of Manogepix and Comparators against 246 *Aspergillus* spp. Isolates



Organisms include: *Aspergillus flavus* species complex (22), *A. fumigatus* (169), *A. hortai* (1), *A. nidulans* (6), *A. nidulans* species complex (2), *A. niger* (13), *A. niger* species complex (14), *A. parasiticus* (2), *A. sclerotorium* (1), *A. terreus* (6), *A. terreus* species complex (7), *A. ustus* (1), *A. ustus* species complex (1), and *A. versicolor* (1).

Table 1. *In Vitro* Activity of Manogepix and Comparators against Yeast Isolates

Organism (no. tested) Antimicrobial agent	$MIC_{50/90}$	CLSI[a] %S	%I	%R	ECV[a] %WT	%NWT
***Candida* spp. (1,072)[b]**						
Manogepix	0.008 / 0.06					
Anidulafungin	0.06 / 2	97.6		c,d	99.2	0.8
Caspofungin	0.03 / 0.25	99.2		c,d		
Micafungin	0.015 / 1	99.2		c,d	98.9	1.1
Fluconazole	0.5 / 8				94.0	6.0
Voriconazole	0.015 / 0.12				94.7	5.3
Amphotericin B	0.5 / 1				99.9	0.1[d]
***C. albicans* (350)**						
Manogepix	0.004 / 0.008					
Anidulafungin	0.03 / 0.06	100.0	0.0	0.04	99.7	0.3
Caspofungin	0.015 / 0.03	99.7	0.0	0.3		
Micafungin	0.015 / 0.015	99.7	0.0	0.3	99.1	0.9
Fluconazole	0.12 / 0.25	99.1	0.3	0.6[e]	97.1	2.9
Voriconazole	0.004 / 0.015	99.7	0.0	0.3	98.6	1.4
Amphotericin B	0.5 / 0.5				100.0	0.0
***C. auris* (11)**						
Manogepix	0.004 / 0.015					
Anidulafungin	0.25 / 0.25	100.0		0.0[f]		
Caspofungin	0.12 / 0.12	100.0		0.0[f]		
Micafungin	0.12 / 0.12	100.0		0.0[f]		
Fluconazole	32 / >128	36.4		63.6[f]		
Voriconazole	0.12 / 1					
Amphotericin B	1 / 2					
***C. dubliniensis* (40)**						
Manogepix	0.004 / 0.008					
Anidulafungin	0.06 / 0.12				100.0	0.0
Caspofungin	0.03 / 0.06					
Micafungin	0.015 / 0.03				100.0	0.0
Fluconazole	0.12 / 0.25				100.0	0.0
Voriconazole	0.004 / 0.008					
Amphotericin B	0.25 / 0.5				97.5	2.5
***C. glabrata* (258)**						
Manogepix	0.03 / 0.06					
Anidulafungin	0.12 / 0.12	96.5	1.2	2.3	97.7	2.3
Caspofungin	0.03 / 0.06	97.3	1.2	1.6		
Micafungin	0.015 / 0.03	97.3	0.0	2.7	96.9	3.1
Fluconazole	4 / 8		95.0[g]	5.0	88.3	11.7
Itraconazole	0.5 / 1				98.8	1.2
Amphotericin B	1 / 1				100.0	0.0
***C. kefyr* (10)**						
Manogepix	0.25 / 1					
Anidulafungin	0.06 / 0.12				100.0	0.0
Caspofungin	0.015 / 0.015					
Micafungin	0.06 / 0.12				100.0	0.0
Fluconazole	0.5 / 0.5				100.0	0.0
Voriconazole	0.008 / 0.008					
Amphotericin B	1 / 1				100.0	0.0
***C. lusitaniae* (16)**						
Manogepix	0.03 / 0.06					
Anidulafungin	0.5 / 1				100.0	0.0
Caspofungin	0.12 / 0.25				100.0	0.0
Micafungin	0.12 / 0.25				100.0	0.0
Fluconazole	0.5 / 1				93.8	6.2
Voriconazole	0.008 / 0.015					
Amphotericin B	0.5 / 0.5				100.0	0.0[d]
***C. parapsilosis* (165)**						
Manogepix	0.008 / 0.015					
Anidulafungin	2 / 2	92.1	7.9	0.0	100.0	0.0
Caspofungin	0.25 / 0.5	100.0	0.0	0.0	100.0	0.0
Micafungin	1 / 1	100.0	0.0	0.0	100.0	0.0
Fluconazole	0.5 / 2	92.1	0.0	7.9[e]	92.1	7.9
Voriconazole	0.008 / 0.03	94.5	3.6	1.8	91.5	8.5
Amphotericin B	0.5 / 1				100.0	0.0
***C. tropicalis* (139)**						
Manogepix	0.015 / 0.015					
Anidulafungin	0.03 / 0.06	100.0	0.0	0.0	99.3	0.7
Caspofungin	0.015 / 0.03	100.0	0.0	0.0		
Micafungin	0.03 / 0.03	100.0	0.0	0.0	100.0	0.0
Fluconazole	0.5 / 1	95.0	1.4	3.6[e]	94.2	5.8
Voriconazole	0.03 / 0.06	95.7	1.4	2.9	95.7	4.3
Amphotericin B	0.5 / 1				100.0	0.0
***Cryptococcus neoformans* var. *grubii* (27)**						
Manogepix	0.5 / 1					
Anidulafungin	>4 / >4					
Caspofungin	>4 / >4					
Micafungin	>4 / >4					
Fluconazole	4 / 8				100.0	0.0
Voriconazole	0.06 / 0.06				100.0	0.0
Amphotericin B	0.5 / 1				51.9	48.1

%S, percent susceptible; %I, percent intermediate; %R, percent resistant; ECV, epidemiological cutoff value; WT, wild-type; NWT, non-wild-type.
[a] Criteria published by CLSI M60 (2017). ECV criteria published in CLSI M59 (2018).
[b] Organisms include: *Candida albicans* (250), *C. auris* (11), *C. bracarensis* (2), *C. dubliniensis* (40), *C. duobushaemulonil* (1), *C. fermentati* (2), *C. glabrata* (258), *C. guilliermondii* (6), *C. haemulonii* (1), *C. incomspicua* (2), *C. kefyr* (10), *C. krusei* (45), *C. lusitaniae* (16), *C. metapsilosis* (2), *C. nivariensis* (1), *C. orthopsilosis* (12), *C. parapsilosis* (165), *C. pelliculosa* (4), *C. rugosa* (2), *C. spencermartinsiae* (1), *C. tropicalis* (139), and *C. utilis* (2).
[c] Only susceptible values are shown because breakpoints are different among organism species (CLSI 2022).
[d] *C. lusitaniae* is not intrinsically resistant to amphotericin B. However, *C. lusitaniae* may develop resistance to amphotericin B *in vivo* during therapy.
[e] Intermediate is interpreted as susceptible dose-dependent.
[f] Breakpoints from the CDC tentative MIC breakpoints published at https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html.
[g] Non-resistant interpreted as susceptible dose-dependent.

Table 2. *In Vitro* Activity of Manogepix and Comparators against Mold Isolates

Organism (no. tested) Antimicrobial agent	$MIC/MEC_{50/90}$	ECV[a] %WT	%NWT
***Aspergillus* spp. (246)[b]**			
Manogepix	0.015 / 0.03		
Anidulafungin	0.015 / 0.06		
Caspofungin	0.015 / 0.03	100.0	0.0
Micafungin	0.008 / 0.015		
Itraconazole	1 / 2	90.2	9.8
Voriconazole	0.5 / 1	97.4	2.6
Amphotericin B	1 / 2	98.7	1.3
***Paecilomyces* spp. (10)[c]**			
Manogepix	0.004 / 0.008		
Anidulafungin	0.008 / 0.03		
Caspofungin	0.03 / 1		
Micafungin	0.004 / 0.015		
Itraconazole	0.5 / 0.5		
Voriconazole	4 / 8		
Amphotericin B	0.25 / 2		
***Scedosporium* spp. (12)[d]**			
Manogepix	0.06 / 0.12		
Anidulafungin	4 / >4		
Caspofungin	>4 / >4		
Micafungin	0.5 / >4		
Itraconazole	>8 / >8		
Voriconazole	1 / 1		
Amphotericin B	>4 / >4		

ECV, epidemiological cutoff value; WT, wild-type; NWT, non-wild-type.
[a] ECV criteria published in CLSI M59 (2020).
[b] *Aspergillus flavus* species complex (22), *A. fumigatus* (169), *A. hortai* (1), *A. nidulans* (6), *A. nidulans* species complex (2), *A. niger* (13), *A. niger* species complex (14), *A. parasiticus* (2), *A. sclerotorium* (1), *A. terreus* (6), *A. terreus* species complex (7), *A. ustus* (1), *A. ustus* species complex (1), and *A. versicolor* (1).
[c] *Paecilomyces lilacinus* (2), *P. variotii* (7), and unspeciated *Paecilomyces* (1).
[d] *Scedosporium apiospermum*/*Scedosporium boydii* (9) and *S. aurantiacum* (3).

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

Organism	MIC/MEC range (mg/L) Manogepix	Caspofungin	Voriconazole	Amphotericin B
Geotrichum clavatum (3)	0.03-0.06	>4	0.12–0.5	1
Kodamaea ohmeri (1)	0.008	0.25	0.03	0.5
Magnusiomyces capitatus (1)	0.015	4	0.06	1
Rhodotorula mucilaginosa (5)	0.03-0.06	>4	0.12-4	0.5
Saccharomyces cerevisiae (7)	0.008-0.03	0.06-0.25	0.03-0.25	0.5-1
Yarrowia lipolytica (1)	0.03	0.12	0.03	1
Exophiala dermatitidis (1)	≤0.002	0.06	0.12	1
Fusarium spp. (8)	≤0.002-0.015	0.008->4	2->8	1-4
Gibberella fujikuroi species complex (6)	0.008-0.015	0.008->4	2->8	2-4
Lichtheimia spp. (2)[a]	4	>4	>8	0.5
Lomentospora prolificans (4)	0.03-0.06	>4	>8	4->4
Mucor spp. (3)[b]	0.25-1	>4	>8	0.5
Penicillium spp. (2)[c]	0.008	0.008-0.015	0.5->8	1
Rasamsonia argillacea species complex (4)	≤0.002-0.004	0.008-0.015	8->8	0.5-2
Rhizopus spp. (6)[d]	2->8	>4	8->8	0.5-1
Sarocladium kilíense (1)	0.015	0.25	2	2
Scopulariopsis brevicaulis (1)	0.008	0.06	>8	4

[a] *Lichtheimia corymbifera* (1) and unspeciated *Lichtheimia* (1).
[b] *Mucor circinelloides* (2) and *M. indicus* (1).
[c] *Penicillium citrinum* (1) and *P. oxoberese* (1).
[d] *Rhizopus microsporus* group (4) and *R. oryzae* species complex (2).

Conclusions

- Manogepix demonstrated potent *in vitro* activity equal to or greater than azole and echinocandin comparators against *Candida* spp. (except *C. krusei*), *Aspergillus* spp., *C. neoformans*, and non-*Candida* yeasts.
- Manogepix was the most active antifungal agent tested against *C. auris*, *Paecilomyces* spp., *Scedosporium* spp., and many rare yeast and mold isolates.
- Further development of fosmanogepix in difficult-to-treat resistant fungal infections is indicated.

Acknowledgements

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