IDWEEK 2020 | Poster Number: 1260

Activity of Manogepix (APX001A) against 2,669 Fungal Isolates from the SENTRY Surveillance Program (2018–2019) Stratified by Infection Type

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Introduction

- Existing antifungal agents are active against many common fungal pathogens; however, breakthrough fungal infections occur and often involve less frequently encountered yeast and mould isolates.
  - These rarer isolates tend to exhibit reduced susceptibility to current antifungal agents.
- Manogepix (MGX, APX001A) is a novel inhibitor of the fungal Gwt1 enzyme.
- The manogepix prodrug (fosmanogepix) is being evaluated in Phase 2 clinical trials for invasive candidiasis/candidemia (NCT03604705), *Candida auris* infections (NCT04148287), and invasive aspergillosis and rare mould infections (NCT04240886).
- In this study, we evaluated the *in vitro* activity of manogepix and comparator agents against 2,669 clinical fungal isolates collected worldwide during 2018–2019 and stratified by infection type.

Materials and Methods

- Fungal isolates were collected from 82 medical centres located in North America (34 medical centres; 9 US census divisions), Europe (30 medical centres), the Asia-Pacific region (11 medical centres), and Latin America (7 medical centres).
- Fungal isolates were collected consecutively from patients (1 per patient infection episode) with bloodstream infection (BSI; 1,381 isolates); intraabdominal infection (IAI; 50 isolates); skin and skin structure infection (SSSI; 147 isolates); urinary tract infection (UTI; 62 isolates); respiratory tract infection (RTI), including pneumonia in hospitalized patients (PIHP; 562 isolates); and other infection types (467 isolates) (Figure 1).
- A total of 2,669 fungal isolates were tested; of these, 1,887 (70.7%) were *Candida* spp. and 95 (3.5%) were non-Candida yeasts, including 49 *Cryptococcus neoformans* var. *grubii*, 578 (21.7%) were *Aspergillus* spp., and 109 (4.1%) were other moulds.
- Isolate identifications were confirmed using matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Billerica, MA), phenotypic, proteomic, or sequencing based methods.
- All isolates were tested for susceptibility to manogepix and comparator agents using reference broth microdilution methods as described in Clinical and Laboratory Standards Institute (CLSI) documents M27 (2017), M38 (2017), M59 (2020), M60 (2020), and M61 (2020).
- Manogepix MIC values were determined for yeast and MEC values for mould isolates using the same reading criteria as echinocandins ("approximately 50% inhibition" for yeast and "small, rounded, compact, hyphal forms" for mould).

Results

- Manogepix ($MIC_{50/90}$, 0.008/0.06 mg/L) was the most potent antifungal agent tested against 1,887 *Candida* spp. isolates (Table 1 and Figure 2).
  - Anidulafungin, caspofungin, and micafungin MIC_{90} values were 16-, 4-, and 16-fold higher.
- Against common *Candida* spp. isolates, manogepix was highly active against 588 *C. albicans* ($MIC_{50/90}$, 0.004/0.008 mg/L), 460 *C. glabrata* ($MIC_{50/90}$, 0.03/0.06 mg/L), 321 *C. parapsilosis* ($MIC_{50/90}$, 0.008/0.015 mg/L), and 225 *C. tropicalis* ($MIC_{50/90}$, 0.015/0.015 mg/L) isolates.
  - Manogepix was active *in vitro* against *Candida* spp. isolates, regardless of infection type (Table 1).
  - Manogepix activity was unchanged against *Candida* spp. isolates, demonstrating resistance to echinocandins and the azoles (Table 1).
- All *C. auris* isolates were inhibited by ≤0.06 mg/L of manogepix ($MIC_{50/90}$, 0.015/0.03 mg/L) (Table 1).
- Manogepix ($MIC_{50/90}$, 0.5/2 mg/L) was ≥4-fold more active than anidulafungin, caspofungin, and micafungin ($MIC_{50/90}$ values, >4/>4 mg/L) against *C. neoformans* var. *grubii* isolates (Table 1).
  - Similarly, manogepix ($MIC_{50/90}$, 0.03/1 mg/L) was at least ≥8-fold more active than anidulafungin, caspofungin, and micafungin (MIC_{90} values, >4 mg/L) against other (non-Candida) yeasts (Table 1).
- Manogepix (MEC_{90}, 0.03 mg/L) was comparable in activity to the echinocandins and ≥32-fold more active by MIC_{90} than itraconazole, voriconazole, and amphotericin B against *Aspergillus* spp. isolates (Table 2 and Figure 3).
- Manogepix (MEC_{90}, 0.03 mg/L) was ≥256-fold more active by MIC_{50} than the other comparator agents against *Scedosporium* spp. isolates (Table 2).
- Rare mould isolates, including *Coprinopsis cinerea*, *Exophiala dermatitidis*, *Fusarium* spp., *Gibberella fujikuroi* species complex, *Microascus cirrosus*, *Paecilomyces* spp., *Pleurostromophora richardsiae*, *Rasamasonia* spp., *Sarcocladium kiliense*, *Scopulariopsis brevicaulis*/*S. brumptii*, and *Trichoderma longibrachiatum* were inhibited by low concentrations (≤0.002-0.12 mg/L) of manogepix (Table 3).

Conclusions

- Manogepix is a first-in-class antifungal agent possessing a novel mechanism of action and potent *in vitro* activity.
- Manogepix demonstrated potent antifungal activity similar to or greater than the azoles and echinocandins when read at the same test/end point conditions against *Candida* spp. (except *C. krusei*), *Aspergillus* spp., *C. neoformans*, and many less common non-*Aspergillus* moulds.
  - Notable activity was observed for manogepix against *C. auris*, echinocandin-resistant and azole-resistant yeast and mould isolates, *Scedosporium* spp., and rare mould isolates.
- Further clinical development of the manogepix prodrug (fosmanogepix) in difficult-to-treat resistant fungal infections is warranted.

Acknowledgements

This study and poster presentation were funded by a research grant from Amplyx Pharmaceuticals, Inc.

Figure 1 Occurrence of Fungal Infections by Infection Type (2018–2019)

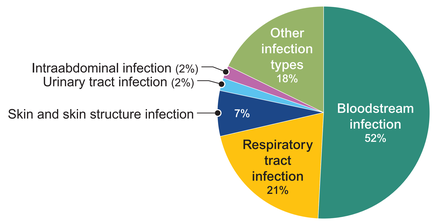


Table 1 *In Vitro* Activity of Manogepix and Comparator Agents against Yeast

Organism (no. tested) Antimicrobial agent	Infection Type[a]	$MIC_{50/90}$	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R	ECV[b] %WT	ECV[b] %NWT
Candida spp. (1,887)[c]							
Manogepix	ALL	0.008 / 0.06					
Manogepix (1,331)	BSI	0.008 / 0.06					
Manogepix (97)	PIHP	0.008 / 0.06					
Manogepix (86)	SSSI	0.008 / 0.03					
Micafungin	ALL	0.03 / 1					
Anidulafungin	ALL	0.03 / 1					
Caspofungin	ALL	0.03 / 0.25					
Fluconazole	ALL	0.25 / 4					
Voriconazole	ALL	0.015 / 0.12					
Amphotericin B	ALL	0.5 / 1					
C. albicans (588)							
Manogepix	ALL	0.004 / 0.008					
Manogepix (410)	BSI	0.004 / 0.008					
Manogepix (33)	PIHP	0.008 / 0.008					
Manogepix (29)	SSSI	0.008 / 0.015					
Micafungin	ALL	0.015 / 0.03	99.7	0.0	0.3	99.7	0.3
Anidulafungin	ALL	0.008 / 0.03	99.8	0.0	0.2	99.7	0.3
Caspofungin	ALL	0.015 / 0.03	99.7	0.0	0.4		
Fluconazole	ALL	0.12 / 0.25	99.5	0.2	0.3	97.3	2.7
Voriconazole	ALL	0.004 / 0.015	100.0	0.0	0.0	98.3	1.7
Amphotericin B	ALL	0.5 / 1				100.0	0.0
C. auris (11)							
Manogepix	ALL	0.015 / 0.03					
Micafungin	ALL	0.25 / 0.25	100.0[d]		0.0		
Anidulafungin	ALL	0.25 / 0.25	100.0[d]		0.0		
Caspofungin	ALL	0.12 / 0.12	100.0[d]		0.0		
Fluconazole	ALL	128 / >128	36.4[d]		63.6[d]		
Voriconazole	ALL	1 / 2					
Amphotericin B	ALL	1 / 1	90.9[d]		9.1		
C. dubliniensis (65)							
Manogepix	ALL	0.004 / 0.008					
Manogepix (37)	BSI	0.004 / 0.008					
Manogepix (10)	PIHP	0.004 / 0.004					
Manogepix (3)	SSSI	0.008 / —					
Micafungin	ALL	0.03 / 0.03				100.0	0.0
Anidulafungin	ALL	0.03 / 0.12				100.0	0.0
Caspofungin	ALL	0.03 / 0.06					
Fluconazole	ALL	0.12 / 0.25				96.9	3.1
Voriconazole	ALL	0.008 / 0.015					
Amphotericin B	ALL	0.25 / 0.5					
C. glabrata (460)							
Manogepix	ALL	0.03 / 0.06					
Manogepix (336)	BSI	0.03 / 0.06					
Manogepix (97)	PIHP	0.008 / 0.06					
Manogepix (86)	SSSI	0.008 / 0.03					
Micafungin	ALL	0.015 / 0.03	98.3	0.2	1.5	96.7	3.3
Anidulafungin	ALL	0.06 / 0.12	97.4	1.3	1.3	98.7	1.3
Caspofungin	ALL	0.03 / 0.06	98.5	0.2	1.3		
Fluconazole	ALL	4 / 16		93.7	6.3	88.0	12.0
Voriconazole	ALL	0.06 / 0.5				89.3	10.7
Amphotericin B	ALL	1 / 1				100.0	0.0
C. kefyr (28)							
Manogepix	ALL	0.12 / 0.25					
Manogepix (10)	BSI	0.12 / 0.25					
Manogepix (2)	PIHP	0.12 / —					
Manogepix (1)	SSSI	— / —					
Micafungin	ALL	0.03 / 0.12					
Anidulafungin	ALL	0.03 / 0.12					
Caspofungin	ALL	0.008 / 0.03					
Fluconazole	ALL	0.12 / 0.25					
Voriconazole	ALL	0.008 / 0.015					
Amphotericin B	ALL	1 / 1					
C. lusitaniae (52)							
Manogepix	ALL	0.03 / 0.06					
Manogepix (35)	BSI	0.03 / 0.06					
Manogepix (2)	PIHP	0.03 / —					
Manogepix (4)	SSSI	0.03 / —					
Micafungin	ALL	0.12 / 0.25				100.0	0.0
Anidulafungin	ALL	0.25 / 0.5				100.0	0.0
Caspofungin	ALL	0.25 / 0.25				100.0	0.0
Fluconazole	ALL	0.25 / 2				88.5	11.5
Voriconazole	ALL	0.008 / 0.015					
Amphotericin B	ALL	0.5 / 1					
C. parapsilosis (321)							
Manogepix	ALL	0.008 / 0.015					
Manogepix (249)	BSI	0.008 / 0.015					
Manogepix (6)	PIHP	0.008 / —					
Manogepix (15)	SSSI	0.008 / 0.015					
Micafungin	ALL	1 / 2	100.0	0.0	0.0	100.0	0.0
Anidulafungin	ALL	2 / 2	94.4	5.6	0.0	100.0	0.0
Caspofungin	ALL	0.25 / 0.5	100.0	0.0	0.0		
Fluconazole	ALL	0.5 / 4	89.7	2.8	7.5	87.2	12.8
Voriconazole	ALL	0.008 / 0.06	92.8	5.9	1.2	88.2	11.8
Amphotericin B	ALL	0.5 / 1				100.0	0.0
C. tropicalis (225)							
Manogepix	ALL	0.015 / 0.015					
Manogepix (154)	BSI	0.008 / 0.015					
Manogepix (12)	PIHP	0.008 / 0.015					
Manogepix (8)	SSSI	0.008 / —					
Micafungin	ALL	0.03 / 0.06	100.0	0.0	0.0	97.8	2.2
Anidulafungin	ALL	0.015 / 0.06	100.0	0.0	0.0	99.6	0.4
Caspofungin	ALL	0.03 / 0.06	100.0	0.0	0.0		
Fluconazole	ALL	0.25 / 1	98.7	0.0	1.3	96.0	4.0
Voriconazole	ALL	0.015 / 0.06	98.7	0.9	0.4	98.7	1.3
Amphotericin B	ALL	0.5 / 1				100.0	0.0
Cryptococcus neoformans var. *grubii* (49)							
Manogepix	ALL	0.5 / 2					
Manogepix (27)	BSI	0.5 / 2					
Manogepix (1)	PIHP	— / —					
Manogepix (1)	SSSI	— / —					
Micafungin	ALL	>4 / >4					
Anidulafungin	ALL	>4 / >4					
Caspofungin	ALL	>4 / >4					
Fluconazole	ALL	4 / 8				98.0	2.0
Voriconazole	ALL	0.06 / 0.12				100.0	0.0
Amphotericin B	ALL	0.5 / 1				69.4	30.6
Other Yeast (37)[e]							
Manogepix	ALL	0.03 / 1					
Manogepix (12)	BSI	0.03 / 1					
Manogepix (5)	PIHP	0.06 / —					
Manogepix (8)	SSSI	0.015 / —					
Micafungin	ALL	1 / >4					
Anidulafungin	ALL	2 / >4					
Caspofungin	ALL	2 / >4					
Fluconazole	ALL	8 / >128					
Voriconazole	ALL	0.12 / 0.5					
Amphotericin B	ALL	1 / 1					

%S, percent susceptible; %I, percent intermediate; %R, percent resistant; ECV, epidemiological cutoff value; WT, wild-type; NWT, non-wild-type.
[a] All includes BSI, PIHP SSSI, IAI, UTI, and other infection types.
[b] Criteria published by CLSI M60 (2020). ECV criteria published in CLSI M59 (2020).
[c] Organisms include: *Candida albicans* (588), *C. auris* (11), *C. bracarensis* (1), *C. dubliniensis* (65), *C. duobushaemulonii* (2), *C. fabianii* (4), *C. fermentati* (13), *C. glabrata* (460), *C. guilliermondii* (6), *C. haemulonii* (2), *C. inconspicua* (3), *C. kefyr* (28), *C. krusei* (44), *C. lipolytica* (1), *C. lusitaniae* (52), *C. metapsilosis* (14), *C. nivariensis* (3), *C. orthopsilosis* (33), *C. parapsilosis* (321), *C. pelliculosa* (5), *C. pseudohaemulonii* (2), *C. sphaerica* (2), *C. tropicalis* (225), and *C. utilis* (1).
[d] CDC tentative breakpoint interpretive criteria for this organism is published at https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html.
[e] Organisms include: *Aureobasidium pullulans* (1), *Geotrichum clavatum* (5), *Lodderomyces elongisporus* (1), *Magnusiomyces capitatus* (1), *Pichia norvegensis* (5), *Rhodotorula minuta* (1), *R. mucilaginosa* (4), *Saccharomyces cerevisiae* (9), *Trichosporon asahii* (5), *T. loubieri* (1), *T. mycotoxinivorans* (1), unspeciated *Pichia* (1), unspeciated *Rhodotorula* (1), and *Yarrowa lipolytica* (1).

Table 2 *In Vitro* Activity of Manogepix and Comparator Agents against *Aspergillus* spp. and *Scedosporium* spp. isolates

Organism (no. tested) Antimicrobial agent	Infection Type[a]	$MIC/MEC_{50/90}$
Aspergillus spp. (578)[c]		
Manogepix	ALL	0.015 / 0.03
Manogepix (4)	BSI	0.008 / —
Manogepix (401)	PIHP	0.015 / 0.03
Manogepix (33)	SSSI	0.015 / 0.03
Micafungin	ALL	0.008 / 0.015
Anidulafungin	ALL	0.008 / 0.015
Caspofungin	ALL	0.015 / 0.03
Itraconazole	ALL	0.5 / 2
Voriconazole	ALL	0.5 / 1
Amphotericin B	ALL	2 / 2
Scedosporium spp. (33)[d]		
Manogepix	ALL	0.03 / 0.03
Manogepix (0)	BSI	— / —
Manogepix (24)	PIHP	0.03 / 0.03
Manogepix (2)	SSSI	0.03 / —
Micafungin	ALL	0.5 / >4
Anidulafungin	ALL	4 / >4
Caspofungin	ALL	1 / >4
Itraconazole	ALL	>8 / >8
Voriconazole	ALL	0.5 / 8
Amphotericin B	ALL	>4 / >4

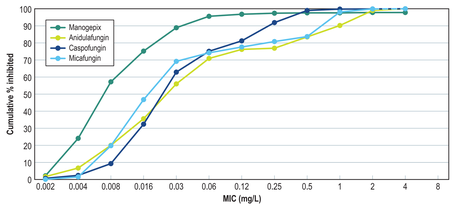
%S, percent susceptible; %I, percent intermediate; %R, percent resistant; ECV, epidemiological cutoff value; WT, wild-type; NWT, non-wild-type.
[a] All includes BSI, PIHP SSSI, IAI, UTI, and other infection types.
[b] Criteria published by CLSI M38 (2017). ECV criteria published in CLSI M59 (2020).
[c] *Aspergillus flavus* species complex (69), *A. fumigatus* (397), *A. lentulus* (2), *A. nidulans* (8), *A. nidulans* species complex (2), *A. niger* (32), *A. niger* species complex (32), *A. nomius* (1), *A. parasiticus* (1), *A. sclerotiorum* (1), *A. tamarii* (2), *A. terreus* (8), *A. terreus* species complex (11), *A. tubingensis* (3), *A. unguis* (1), *A. ustus* species complex (4), *A. versicolor* (3), and *A. versicolor* species complex (1).
[d] *Scedosporium* (*Lomentospora*) *prolificans* (3), *S. apospermum*/*S. boydii* (20), *S. aurantiacum* (3), *S. boydii* (4), *S. minutisporum* (2), and unspeciated *Scedosporium* (1).

Table 3 *In Vitro* Activity of Manogepix and Comparator Agents against Infrequently Encountered Mould Isolates

Organism (no. tested)	MIC/MEC range (mg/L) Manogepix	Caspofungin	Voriconazole	Amphotericin B
Coprinopsis cinerea (1)	0.004	>4	0.25	1
Exophiala dermatitidis (3)	0.008	>4	0.06-0.12	0.5-1
Fusarium spp. (10)[a]	0.008-0.03	>4	4-8	1-4
Gibberella fujikuroi species complex (5)	0.004-0.03	>4	2-8	2-4
Microascus cirrosus (1)	0.008	>4	>8	>4
Mucor spp. (6)[b]	2-8	>4	>8	0.25-0.5
Paecilomyces spp. (6)[c]	0.008-0.015	0.004->4	0.25-8	0.5->4
Pleurostromophora richardsiae (1)	0.06	>4	0.5	1
Rasamasonia spp. (5)[d]	0.004-0.015	0.004-0.015	8->8	1-4
Rhizopus spp. (13)[e]	4->8	>4	4->8	0.5-2
Sarcocladium kiliense (3)	0.03-0.12	0.06->4	2-4	4->4
Scopulariopsis brevicaulis/ *Scopulariopsis brumptii* (2)	≤0.002-0.008	0.25-1	1->8	>4
Trichoderma longibrachiatum (1)	0.06	0.008	1	4

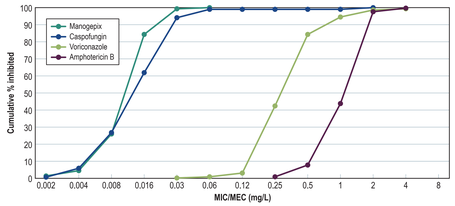
[a] *Fusarium oxysporum* species complex (2), *F. solani* species complex (8).
[b] *Mucor circinelloides* (2), *M. circinelloides*/*M. ramosissimus* (2), and unspeciated *Mucor* (2).
[c] *Paecilomyces lilacinus* (3), *P. variotii* (2), and unspeciated *Paecilomyces*.
[d] *Rasamasonia argillacea* (4), *R. argillacea* species complex (1).
[e] *Rhizopus microsporus* group (7), *R. oryzae* (5), and unspeciated *Rhizopus* (1).

Figure 2 Cumulative % Inhibition MIC Distributions for Manogepix and Echinocandin Comparator Agents against 1,887 *Candida* spp. Isolates (2018–2019)



Organisms include: *Candida albicans* (588), *C. auris* (11), *C. bracarensis* (1), *C. dubliniensis* (65), *C. duobushaemulonii* (2), *C. fabianii* (4), *C. fermentati* (13), *C. glabrata* (460), *C. guilliermondii* (6), *C. haemulonii* (2), *C. inconspicua* (3), *C. kefyr* (28), *C. krusei* (44), *C. lipolytica* (1), *C. lusitaniae* (52), *C. metapsilosis* (14), *C. nivariensis* (3), *C. orthopsilosis* (33), *C. parapsilosis* (321), *C. pelliculosa* (5), *C. pseudohaemulonii* (2), *C. sphaerica* (2), *C. tropicalis* (225), and *C. utilis* (1).

Figure 3 Cumulative % Inhibition MIC Distributions for Manogepix and Comparator Agents against 578 *Aspergillus* spp. Isolates (2018–2019)



Organisms include: *Aspergillus flavus* species complex (69), *A. fumigatus* (397), *A lentulus* (2), *A. nidulans* (8), *A. nidulans* species complex (2), *A. niger* (32), *A. niger* species complex (32), *A. nomius* (1), *A. parasiticus* (1), *A. sclerotiorum* (1), *A tamarii* (2), *A. terreus* (8), *A. terreus* species complex (11), *A. tubingensis* (3), *A. unguis* (1), *A ustus* species complex (4), *A. versicolor* (3), and *A versicolor* species complex (1).

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