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Comparison of manogepix activity against 2,659 community-acquired and nosocomial mould isolates from the SENTRY Antimicrobial Surveillance Program (2017–2024)

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Introduction

- Existing antifungal agents are active against common fungal pathogens; however, less frequently encountered isolates tend to exhibit reduced susceptibility to the currently available agents.
- Manogepix is a novel antifungal agent targeting the fungal Gwt1 enzyme that has previously demonstrated potent *in vitro* activity against many species of yeast and mould.
- The manogepix prodrug (fosmanogepix) is being evaluated in a Phase 3 clinical trial for the treatment of invasive mould infections (NCT06925321).
- In this study, we evaluated the *in vitro* activity of manogepix against 2,659 mould isolates (2017–2024) stratified as community-acquired or nosocomial.

Materials and Methods

- Mould isolates were collected from patients in medical centers located in North America (27 sites; 38.2%), Europe (27 sites; 40.8%), Asia-Pacific (11 sites; 19.3%), and Latin America (2 sites; 1.7%).
- Isolates were collected from the following indications: pneumonia in hospitalized patients (PIHP; 63.7%), skin and skin structure infections (SSSI; 9.9%), bloodstream infections (BSI; 1.5%), urinary tract infections (UTI; 0.05%), intra-abdominal infections (IAI; 0.15%), and other infection types (24.7%).
- A total of 2,659 mould isolates were tested; of these, 2,186 (82.2%) were *Aspergillus* spp. and 473 (17.8%) were other moulds including *Fusarium* spp. (4.0%), *Rhizopus* spp. (2.4%), and *Scedosporium* spp. (3.5%).
- 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 followed Clinical and Laboratory Standards Institute (CLSI) M38 (2017) and M38M51S (2022) documents.
- Manogepix MEC endpoints were determined for mould isolates using the same reading criteria as echinocandins.

Acknowledgments

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References

CLSI. *Reference method for broth dilution antifungal susceptibility testing of filamentous fungi*. 3rd ed. CLSI standard M38. Wayne, PA: Clinical and Laboratory Standards Institute: 2017.

CLSI. Performance standards for antifungal susceptibility testing of filamentous fungi. 3rd ed. CLSI supplement M38M51S. Clinical and Laboratory Standards Institute: 2022.

Figure 1. Community-acquired mould isolates by infection type

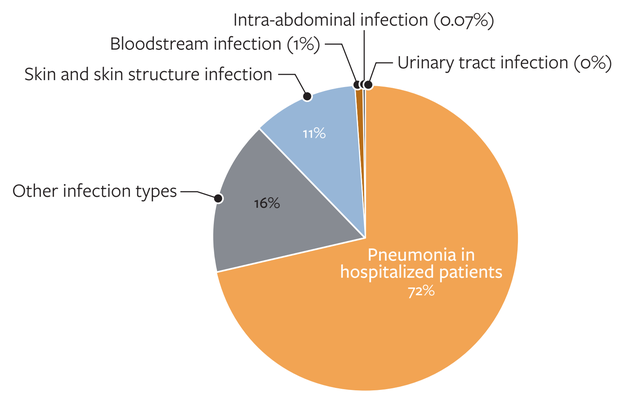
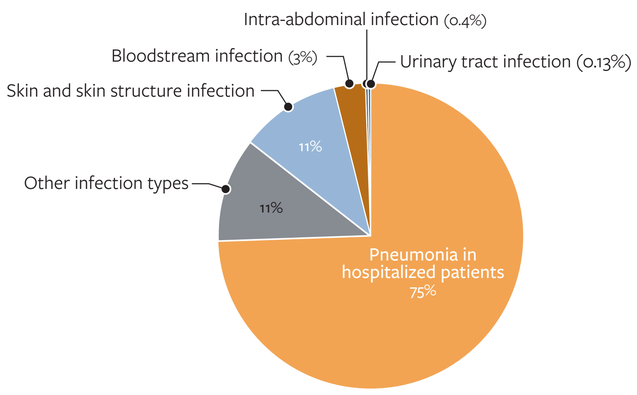


Figure 2. Nosocomial mould isolates by infection type



Results

- Manogepix demonstrated potent *in vitro* activity against *Aspergillus* spp. isolates from community-acquired and nosocomial infections including *A. fumigatus*, *A. nidulans* species complex, *A. flavus* species complex, *A. niger* species complex, *A. terreus* species complex, *A. tubingensis*, *A. ustus* species complex, *A. versicolor* species complex, and other *Aspergillus* spp. ($MEC_{50/90}$, ≤0.008–0.016/0.016–0.06 mg/L) (Table 1).
- Similarly, manogepix was active against other mould isolates from community-acquired and nosocomial infections including *Fusarium* spp. ($MEC_{50/90}$, 0.016/0.03–0.12 mg/L), *Lomentospora prolificans* ($MEC_{50/90}$, 0.016/0.06 mg/L), *Paecilomyces variotii* ($MEC_{50/90}$, ≤0.008/≤0.008), *Purpureocillium lilacinum* ($MEC_{50/90}$, ≤0.008/0.016 mg/L), *Rasamsonia argillacea* species complex ($MEC_{50/90}$, ≤0.008/0.016 mg/L), and *Scedosporium* spp. ($MEC_{50/90}$, 0.03/0.06 mg/L) (Table 1).
- Pneumonia in hospitalized patients, skin and skin structure infections, and other infection types accounted for 99% of community-acquired and 97% of nosocomial infections (Figures 1 and 2).
- Manogepix was active with MEC values of ≤0.002–0.12 mg/L against many infrequently encountered mould isolates including strains with elevated MIC values to other drug classes (Table 2).

Conclusions

- Manogepix is a first-in-class antifungal agent possessing a novel mechanism of action and activity against mould isolates including strains demonstrating elevated MIC/MEC values to other drug classes.
- Manogepix showed potent *in vitro* activity against mould isolates from patients with community-acquired and nosocomial infections caused by *Aspergillus* spp., *Fusarium* spp., *L. prolificans*, *P. variotii*, *P. lilacinum*, *R. argillacea* species complex, and *Scedosporium* spp.
- Manogepix was active with low MEC values (≤0.002–0.06 mg/L) against many infrequently encountered mould isolates, including isolates with elevated MIC values to other drug classes.
- Further Phase 3 clinical development of fosmanogepix (manogepix prodrug) in the treatment of invasive mould infections is warranted.

Table 1. Activity of manogepix against community-acquired and nosocomial mould isolates (2017–2024)

Organism	Manogepix $MEC_{50/90}$ (mg/L) (no. tested)			MIC or $MEC_{50/90}$ (mg/L) (% susceptible)		
	All	Community-acquired	Nosocomial	AMB	MFG	VCZ
Aspergillus fumigatus	**0.016/0.03** (1,425)	0.016/0.03 (714)	0.016/0.03 (446)	1/2 (—)	≤0.008/0.016 (—)	0.5/0.5 (90.5%) [a]
A. nidulans species complex	**0.016/0.03** (52)	0.016/0.03 (30)	0.03/— (9)	2/2 (—)	≤0.008/0.03 (—)	0.12/0.25 (—)
A. flavus species complex	**0.016/0.06** (236)	0.016/0.03 (94)	0.016/0.06 (78)	2/2 (—)	≤0.008/0.016 (—)	0.5/1 (—)
A. niger species complex	**≤0.008/0.016** (283)	≤0.008/0.016 (163)	≤0.008/0.016 (61)	0.25/1 (—)	≤0.008/0.016 (—)	1/2 (—)
A. terreus species complex	**0.016/0.03** (94)	0.016/0.03 (47)	0.008/0.03 (29)	2/4 (—)	≤0.008/0.016 (—)	0.5/0.5 (—)
A. tubingensis	**≤0.008/0.03** (23)	0.03/— (7)	≤0.008/— (4)	0.12/0.5 (—)	≤0.008/0.03 (—)	2/4 (—)
A. ustus species complex	**≤0.008/0.016** (15)	≤0.008/— (9)	≤0.008/— (3)	1/4 (—)	0.016/0.03 (—)	4/8 (—)
A. versicolor species complex	**0.016/0.03** (11)	0.016/— (9)	0.008/— (2)	2/2 (—)	0.016/0.03 (—)	0.5/1 (—)
Other *Aspergillus* spp. [b]	**0.016/0.03** (45)	0.016/0.03 (24)	0.016/— (9)	2/4 (—)	0.008/0.03 (—)	0.5/4 (—)
Exophiala spp. [c]	**≤0.008/≤0.008** (16)	≤0.008/≤0.008 (13)	0.008/— (3)	0.5/2 (—)	>4/>4 (—)	0.12/0.25 (—)
Fusarium fujikuroi species complex	**0.016/0.12** (24)	0.016/0.03 (14)	0.008/— (5)	2/>2 (—)	>4/>4 (—)	4/>8 (—)
Fusarium oxysporum species complex	**0.016/0.06** (22)	0.016/0.06 (14)	0.016/— (8)	2/4 (—)	>4/>4 (—)	4/8 (—)
Fusarium solani species complex	**0.016/0.03** (46)	0.016/0.03 (19)	0.016/0.03 (14)	2/2 (—)	>4/>4 (—)	8/>8 (—)
Other *Fusarium* spp. [d]	**0.016/2** (15)	0.016/— (8)	0.008/— (4)	1/2 (—)	>4/>4 (—)	4/>8 (—)
Lomentospora prolificans	**0.016/0.06** (25)	0.016/0.03 (16)	0.03/— (6)	>2/>2 (—)	>4/>4 (—)	>8/>8 (—)
Mucor spp. [e]	**1/>4** (26)	0.25/>4 (13)	>8/— (5)	0.25/0.5 (—)	>4/>4 (—)	>8/>8 (—)
Paecilomyces variotii	**≤0.008/≤0.008** (14)	≤0.008/≤0.008 (11)	0.002/— (2)	0.12/0.5 (—)	≤0.008/≤0.008 (—)	4/8 (—)
Purpureocillium lilacinum	**≤0.008/0.016** (21)	≤0.008/0.016 (13)	0.008/— (5)	>2/>2 (—)	0.03/0.12 (—)	0.25/0.5 (—)
Rasamsonia argillacea species complex	**≤0.008/0.016** (12)	≤0.008/— (9)	0.016/— (3)	1/2 (—)	≤0.008/≤0.008 (—)	>8/>8 (—)
Rhizopus spp. [f]	**4/>4** (65)	>4/>4 (31)	4/>4 (27)	0.5/1 (—)	>4/>4 (—)	8/>8 (—)
Scedosporium spp. [g]	**0.03/0.06** (94)	0.03/0.06 (66)	0.016/0.03 (12)	>2/>2 (—)	0.5/>4 (—)	1/2 (—)

AMB = Amphotericin B; MFG = Micafungin; VCZ = Voriconazole.
[a] CLSI breakpoints applied.
[b] Organisms include: *Aspergillus alabamensis* (1), *A. brasiliensis* (2), *A. caelatus* (1), *A. clavatus* (2), *A. fumisynnematus* (1), *A. hiratsukae* (1), *A. hortai* (1), *A. lentulus* (9), *A. melleus* (1), *A. nomius* (1), *A. ochraceus* species complex (1), *A. parasiticus* (3), *A. sclerotiorum* (5), *A. sydowii* (5), *A. tamarii* (3), *A. thermomutatus* (2), *A. udagawae* (2), *A. unguis* (3), and *A. welwitschiae* (1).
[c] Organisms include: *Exophiala attenuata* (2), *E. dermatitidis* (13), and unspeciated *Exophiala* (1).
[d] Organisms include: *Fusarium annulatum* (2), *F. dimerum* (1), *F. dimerum* species complex (1), *F. falciforme* (1), *F. incarnatum-equiseti* species complex (6), *F. musae* (1), *F. petroliphilum* (1), and unspeciated *Fusarium* (2).
[e] Organisms include: *Mucor circinelloides* (15), *M. circinelloides/M. ramosissimus* (2), *M. indicus* (1), and unspeciated *Mucor* (8).
[f] Organisms include: *Rhizopus microsporus* (32), *R. oryzae* species complex (27), and unspeciated *Rhizopus* (6).
[g] Organisms include *Scedosporium apiospermum* (10), *S. apiospermum / Scedosporium boydii* (53), *S. aurantiacum* (13), *S. boydii* (12), *S. dehoogii* (3), *S. minutisporum* (2), and unspeciated *Scedosporium* (1).

Table 2. *In vitro* activity of manogepix and comparator agents against infrequently encountered nosocomial and community-acquired mould isolates

Organism (no. tested)	MIC or MEC range (mg/L)			
	Manogepix	AMB	MFG	VCZ
Coprinopsis cinerea (1)	**0.004**	1	>4	0.25
Medicopsis romeroi (2)	**0.03–0.12**	0.5–1	0.06–>4	0.25–>8
Microascus cirrosus (1)	**0.008**	>4	>8	>8
Monascus ruber (1)	**0.03**	0.12	0.016	>8
Penicillium chrysogenum (1)	**0.03**	2	0.008	1
P. citrinum (3)	**0.008–0.03**	1–2	0.004–0.03	>8
P. georgiense (1)	**0.008**	≤0.03	0.016	0.03
P. onobense	**0.008**	1	0.016	0.5
Phaeoacremonium parasiticum (1)	**0.06**	0.5	0.25	0.25
Pleurostromophora richardsiae (1)	**0.06**	1	>4	0.5
Sarocladium kiliense (4)	**0.016–0.12**	2–>4	0.06–>4	2–4
Scopulariopsis brevicaulis/ S. brumptii (3)	**≤0.002–0.008**	4–>4	0.06–1	1–>8
Trichoderma longibrachiatum (3)	**0.008–0.06**	0.25–4	0.016–4	0.5–>8

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