

Manogepix, the Active Moiety of the Investigational Agent Fosmanogepix, Demonstrates *In vitro* Activity Against Members of the *Fusarium oxysporum* and *Fusarium solani* Species Complexes

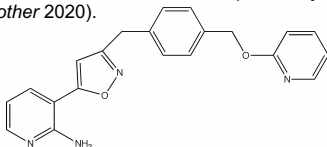
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BACKGROUND

- Invasive fusariosis is associated with marked morbidity and mortality in immunocompromised hosts, and treatment options are limited (Nucci et al. *Clin Microbiol Infect* 2014).
- Common etiologic agents include members of the *Fusarium oxysporum* and *F. solani* species complexes (FOSC and FSSC, respectively).
- Manogepix (MGX; Figure 1), the active moiety of fosmanogepix, is a novel GWT1 inhibitor with broad antifungal activity (Miyazaki, et al. *Antimicrob Agents Chemother* 2011; Pfaller, et al. *Antimicrob Agents Chemother* 2019; Rivero-Menendez et al. *J Antimicrob Chemther* 2019).
- Fosmanogepix has previously shown *in vivo* efficacy in an immunocompromised murine model of invasive fusariosis (Alkhozraji, et al. *Antimicrob Agents Chemother* 2020).

Figure 1. Structure of manogepix.



OBJECTIVE

Our objective was to evaluate the *in vitro* activity of manogepix (MGX) against clinical isolates of the *F. oxysporum* and *F. solani* species complexes (FOSC and FSSC, respectively).

CONCLUSIONS

- MGX demonstrated good *in vitro* activity against FOSC and FSSC clinical isolates.
- Both changes in fungal morphology (MEC) and reductions in growth (MIC 50% inhibition) were observed. The MEC endpoint is now considered the standard endpoint for MGX against filamentous fungi.
- Clinical studies are ongoing to determine the efficacy and safety of fosmanogepix in patients with invasive fungal infections.

MATERIALS AND METHODS

- Clinical isolates of FOSC (n=49) and FSSC (n=19) were identified by phenotypic characteristics and DNA sequence analysis of the translation elongation factor 1-alpha (*TEF1α*) and RNA polymerase II second largest subunit (*RPB2*).
- Susceptibility testing was performed by CLSI M38 broth microdilution. Minimum effective concentrations (MEC) and minimum inhibitory concentrations (MIC) were read after 48 hours of incubation at 50% and 100% inhibition of growth for MGX. MEC is now standard endpoint used for manogepix activity vs. filamentous fungi.
- MIC values were read for amphotericin B (AMB), posaconazole (PSC), isavuconazole (ISC), and voriconazole (VRC) at 100% inhibition of growth.

RESULTS

- MGX demonstrated potent *in vitro* activity against both FOSC and FSSC isolates (Figure 2).
- Against FOSC isolates, MGX MECs ranged from ≤ 0.015 -0.03 $\mu\text{g/mL}$, and MICs at the 50% inhibition of growth endpoint ranged from ≤ 0.015 -0.12 $\mu\text{g/mL}$ (Table). MIC values were higher when read at 100% inhibition of growth.
- Similar results were observed against FSSC isolates (MEC and MIC ranges ≤ 0.015 and ≤ 0.015 -0.25 $\mu\text{g/mL}$, respectively).
- MGX MEC and MIC 50% inhibition values were in close agreement for both FOSC and FSSC isolates.
- AMB demonstrated *in vitro* good activity (MIC ranges 1-4 and 0.25-4 $\mu\text{g/mL}$ against FOSC and FSSC, respectively). In contrast, the azoles demonstrated reduced susceptibility (MIC range 1->16 $\mu\text{g/mL}$).

RESULTS (continued)

Figure 2. MIC/MEC distributions of MGX, AMB, PSC, ISC, and VRC against FOSC & FSSC.

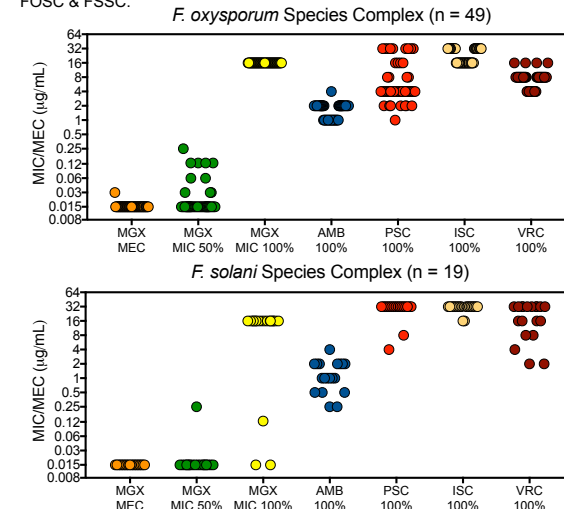


Table 1. MIC/MEC ranges, 50 and 90% inhibition values, and geometric mean (GM) values for MGX, AMB, PSC, ISC, and VRC against FOSC & FSSC.

Antifungal	Manogepix (MGX)			AMB	PSC	ISC	VRC
Endpoint	MEC	MIC 50%	MIC 100%	MIC 100%	MIC 100%	MIC 100%	MIC 100%
<i>Fusarium oxysporum</i> species complex (n = 49)							
Range	≤ 0.015 -0.03	≤ 0.015 -0.12	>8	1-4	1->16	≥ 16	4-16
MEC/MIC ₅₀	≤ 0.015	≤ 0.015	>8	2	4	16	8
MEC/MIC ₉₀	≤ 0.015	≤ 0.015	>8	2	>16	>16	8
GM MEC/MIC	≤ 0.015	0.021	>8	1.59	6.11	>16	6.94
<i>Fusarium solani</i> species complex (n = 19)							
Range	≤ 0.015	≤ 0.015 -0.25	≤ 0.015 ->8	0.25-4	4->16	>16	2->16
MEC/MIC ₅₀	≤ 0.015	≤ 0.015	>8	1	>16	>16	>16
MEC/MIC ₉₀	≤ 0.015	≤ 0.015	>8	2	>16	>16	>16
GM MEC/MIC	≤ 0.015	0.017	5.95	1.08	>16	>16	16