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Activity of manogepix against invasive fungal infections from immunocompromised hosts

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Introduction

- Fosmanogepix is the prodrug of manogepix, which is a novel antifungal agent that targets the Gwt1 enzyme
- Fosmanogepix is currently in Phase 3 clinical trials for the treatment of invasive candidiasis and invasive mould infections
- Invasive candidiasis and invasive mould infections often affect immunocompromised hosts
- The *in vitro* activity of manogepix and comparator antifungal agents was evaluated against isolates collected from invasive fungal infections in immunocompromised hosts

Methods

- A total of 827 isolates were collected from hematology-oncology and transplant service lines
  - 196 moulds and 631 yeasts
- Only 1 isolate per patient episode was included
- All isolates were identified by MALDI-TOF MS and/or DNA sequencing
- Isolates were tested by CLSI reference broth microdilution method (M27) to obtain minimal inhibitory concentration (MIC) measurements for yeast
- Isolates were tested by CLSI reference broth microdilution method (M38) to obtain minimum effective concentration (MEC) measurements for moulds for echinocandins and manogepix, and MICs for moulds for azoles and amphotericin B
- CLSI breakpoints or epidemiological cutoff values (ECVs) were applied for comparator agents where available; no breakpoints or ECVs are available for manogepix

Results

- There were 24 genera and 63 species collected from 25 countries (Figure 1)
- Isolates were from various infection sources (Figure 2)
- For 522 *Candida* spp. (*C. krusei* and *C. kefyr* were excluded due to elevated MICs) manogepix $MIC_{50/90}$ was 0.008/0.06 mg/L (Table 1)
  - This was up to 7 doubling dilutions lower than for comparator agents
- In resistant subsets of *C. glabrata* and *C. parapsilosis* low manogepix MICs were maintained while the percentage of isolates non-susceptible or non-wildtype to comparator agents increased
- 137 *Aspergillus* spp. were tested with manogepix $MEC_{50/90}$ 0.015/0.03 mg/L (Table 2)
  - The MEC_{90} was 3-5 doubling dilutions lower than the MIC_{90} for comparator agents
  - 12.0% of *Aspergillus fumigatus* isolates were non-susceptible to voriconazole
    - Among these, manogepix MECs were 0.008 to 0.03 mg/L
- There were 20 *Fusarium* spp. tested with manogepix MECs ≤0.008 to 0.06 mg/L
  - All azole MICs were ≥0.5 mg/L
- 10 *Scedosporium* and *Lomentospora* spp. were tested with manogepix MECs 0.008 to 0.06 mg/L and MEC_{90} 0.06 mg/L
  - Comparator agent MIC_{90}s were 6-7 doubling dilutions higher
- There were 22 Mucorales tested with manogepix MECs 2 to >4 mg/L and MEC_{90} >4 mg/L
  - 14 *Rhizopus* spp., 3 *Mucor* spp., 4 *Lichtheimia* spp., and 1 *Rhizomucor* spp.
  - Amphotericin B MICs were lowest against this organism group with MIC_{90} 0.5 mg/L

Conclusions

- Manogepix has potent *in vitro* activity among isolates collected from invasive fungal infection in immunocompromised hosts as a part of a worldwide surveillance program
- Manogepix has low MIC/MECs against challenging yeast and moulds
  - Low MIC/MECs are maintained against resistant subsets of *C. glabrata*, *C. parapsilosis*, and *Aspergillus fumigatus*
  - Low MECs are also observed against *Fusarium* spp. and *Scedosporium*/*Lomentospora* spp. isolates with limited or no other treatment options
- Manogepix is a promising novel antifungal agent for the treatment of infections due to yeast and moulds in immunocompromised hosts
  - This warrants further investigation in Phase 3 clinical trials

Figure 2. Infection source of collected invasive fungal infections from immunocompromised hosts

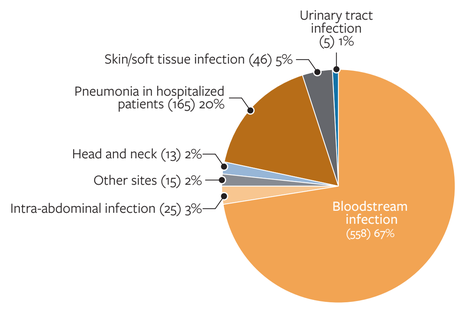

Figure 1. Geographic distribution of fungal isolates collected from immunocompromised hosts

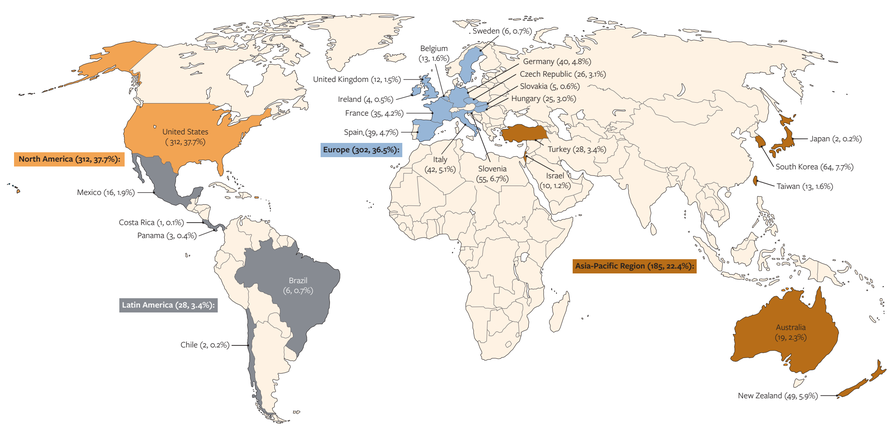

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Table 1. MIC range (mg/L), $MIC_{50/90}$ (mg/L), and % organisms susceptible for manogepix and comparator agents for all yeast with more than 20 organisms per group represented and selected resistant subsets

	MGX		MCF		VRC		FLC		AMB	
Organism (n)	MIC range	$MIC_{50/90}$	MIC range (%S/WT)	$MIC_{50/90}$	MIC range (%S/WT)	$MIC_{50/90}$	MIC range (%S/WT)	$MIC_{50/90}$	MIC range (%S/WT)	$MIC_{50/90}$
Yeast (631)	≤0.002 – >8	0.015/1	≤0.008 – >4	0.03/1	≤0.008 – >8	0.03/0.25	≤0.12 – >128	0.5/32	0.12 – 2	0.5/1
All *Candida* spp. (591)	≤0.002 – >8	0.015/0.5	≤0.008 – >4	0.03/1	≤0.008 – >8	0.015/0.25	≤0.12 – >128	0.5/32	0.12 – 2	0.5/1
Candida spp. (excluding *C. kefyr* and *C. krusei*, 522)	≤0.002 – 0.25	0.008/0.06	≤0.008 – >4	0.015/1	≤0.008 – >8	0.015/0.25	≤0.12 – >128	0.5/8	0.12 – 2	0.5/1
C. albicans (142)	≤0.002 – 0.12	0.004/0.008	≤0.008 – 2 (97.9)[1]	0.015/0.03	≤0.008 – >8 (99.3)[1]	≤0.008/0.015	≤0.12 – >128 (97.9)[1]	≤0.12/0.25	0.25 – 1 (100.0)[2]	0.5/1
C. glabrata (141)	0.008 – 0.25	0.03/0.06	≤0.008 – 1 (96.5)[1]	0.015/0.03	0.015 – 4 (80.1)[2]	0.06/2	1 – 128 (84.4)[1]	4/64	0.12 – 1 (100.0)[2]	1/1
ECH-NS *C. glabrata* (6)	0.015 – 0.12	0.25/NA	0.03 – 1 (33.3)[1]	0.25/NA	0.03 – 4 (33.3)[2]	1/NA	1 – 128 (33.3)[1]	64/NA	0.25 – 1 (100.0)[2]	0.5/NA
FLC-NS *C. glabrata* (22)	0.015 – 0.12	0.06/0.12	0.015 – 1 (77.3)[1]	0.03/0.5	0.06 – 4 (4.5)[2]	2/4	64 – 128 (0.0)[1]	128/128	0.25 – 1 (100.0)[2]	1/1
C. parapsilosis (96)	≤0.002 – 0.12	0.008/0.15	0.015 – 2 (100.0)[1]	1/1	≤0.008 – 2 (95.8)[1]	≤0.008/0.06	≤0.12 – 128 (90.6)[1]	0.5/2	0.25 – 1 (100.0)[2]	0.5/1
FLC-NS *C. parapsilosis* (9)	0.015 – 0.12	0.03/NA	0.5 – 1 (100.0)[1]	1/NA	0.06 – 2 (55.6)[1]	0.12/NA	8 – 128 (0.0)[1]	8/NA	0.5 – 1 (100.0)[2]	1/NA
C. dubliniensis (22)	0.001 – 0.015	0.004/0.008	0.008 – 0.03 (100.0)[2]	0.015/0.03	≤0.008 – 0.015	≤0.008/≤0.008	≤0.12 – 0.25 (100.0)[2]	≤0.12/0.25	0.12 – 0.25 (100.0)[2]	0.25/0.5
Non-*Candida* yeast (40)*	0.004 – >2	0.12/2	0.06 – >4	>4/>4	0.015 – 2	0.06/0.5	1 – >128	4/32	0.25 – 2	0.5/1

MGX, manogepix; MCF, micafungin; VRC, voriconazole; FLC, fluconazole; AMB, amphotericin B; MIC, minimum inhibitory concentration; S, susceptible; WT, wildtype; ECH, echinocandin; NS, non-susceptible; NA, not applicable for groups with < 10 isolates
[1] Breakpoint as published in CLSI M27M44S, current edition
[2] ECV as published in CLSI M57S, current edition
*Includes *Cryptococcus neoformans* (18), *Geotrichum clavatum* (8), *Kodamaea ohmeri* (1), *Magnusiomyces capitatus* (2), *Pichia cactophila* (1), *Rhodotorula mucilaginosa* (4), *Saccharomyces cerevisiae* (2), *Trichosporon asahii* (2), *T. mucoides* (1), and unspeciated *Rhodotorula* (1)

Table 2. MEC range (mg/L), MIC/$MEC_{50/90}$ (mg/L), and % organisms susceptible to manogepix and comparator agents for all moulds with more than 10 organisms represented and select resistant subsets

	MGX		VRC		POS		AMB	
Organism (n)	MEC range	$MEC_{50/90}$	MIC range (%S/WT)	$MIC_{50/90}$	MIC range (%S/WT)	$MIC_{50/90}$	MIC range (%S/WT)	$MIC_{50/90}$
Moulds (196)	≤0.008 – >4	0.015/2	0.06 – >8	0.5/>8	0.03 – >8	0.25/>8	0.06 – >2	1/2
Aspergillus spp. (137)	≤0.008 – 0.06	0.015/0.03	0.06 – >8	0.5/1	0.03 – >8	0.25/0.5	0.12 – 4	1/2
Aspergillus fumigatus (100)	≤0.008 – 0.03	0.015/0.03	0.12 – >8 (88.0)[1]	0.5/1	0.06 – 2	0.25/0.5	0.5 – 4 (99.0)[2]	1/2
VRC-NS *A. fumigatus* (12)	0.008 – 0.03	0.015/0.015	1 – >8 (0.0)	1/4	0.12 – 2	0.5/1	0.5 – 2 (100.0)[2]	1/2
Aspergillus flavus species complex (15)	≤0.008 – 0.06	0.015/0.06	0.25 – 1 (100.0)[2]	0.5/1	0.12 – 0.5 (100.0)[2]	0.25/0.5	0.5 – 4 (100.0)[2]	2/2
Fusarium spp. (20)*	≤0.008 – 0.06	0.015/0.03	2 – >8	8/>8	0.5 – >8	>8/>8	0.5 – >2	2/2
Scedosporium/Lomentospora spp. (10)	0.008 – 0.06	0.015/0.06	0.5 – >8	1/>8	2 – >8	>8/>8	2 – >4	>4/>4
Mucorales (22) #	2 – >4	4/>4	4 – >8	>8/>8	0.12 – >8	0.5/2	0.06 – 1	0.25/0.5

MGX, manogepix; VRC, voriconazole; POS, posaconazole; AMB, amphotericin B; MEC, minimum effective concentration; MIC, minimum inhibitory concentration; S, susceptible; WT, wildtype; NS, non-susceptible
[1] Use of breakpoint by CLSI M38M51S, current edition
[2] Use of ECV by CLSI M57S, current edition
* Includes *Fusarium dimerum* species complex (1), *F. oxysporum* species complex (4), *F. solani* species complex (7), unspeciated *Fusarium* (2), and *Gibberella fujikuroi* (6)
# Includes *Lichtheimia corymbifera* (1), *Mucor circinelloides* (2), *M. circinelloides*/ *Mucor ramosissimus* (1), *Rhizomucor pusillus* (1), *Rhizopus microsporus* (10), *R. oryzae* (3), unspeciated *Lichtheimia* (3), and unspeciated *Rhizopus* (1)

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