



Activity of manogepix against *Candida auris*

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Introduction

- Candida auris* is a rising threat worldwide due to high antifungal resistance rates and tolerance to cleaning solutions
- Fosmanogepix (prodrug of manogepix) is a novel antifungal agent in Phase 3 clinical trials for the treatment of invasive yeast and mould infections
- Manogepix targets the fungal Gwt1 enzyme, which is a different mechanism of action relative to currently approved antifungal agents: azoles, echinocandins, and amphotericin B
- There is no cross-resistance among manogepix and other antifungal agents
- The *in vitro* activity of manogepix and comparator antifungal agents was evaluated against *C. auris* isolates

Methods

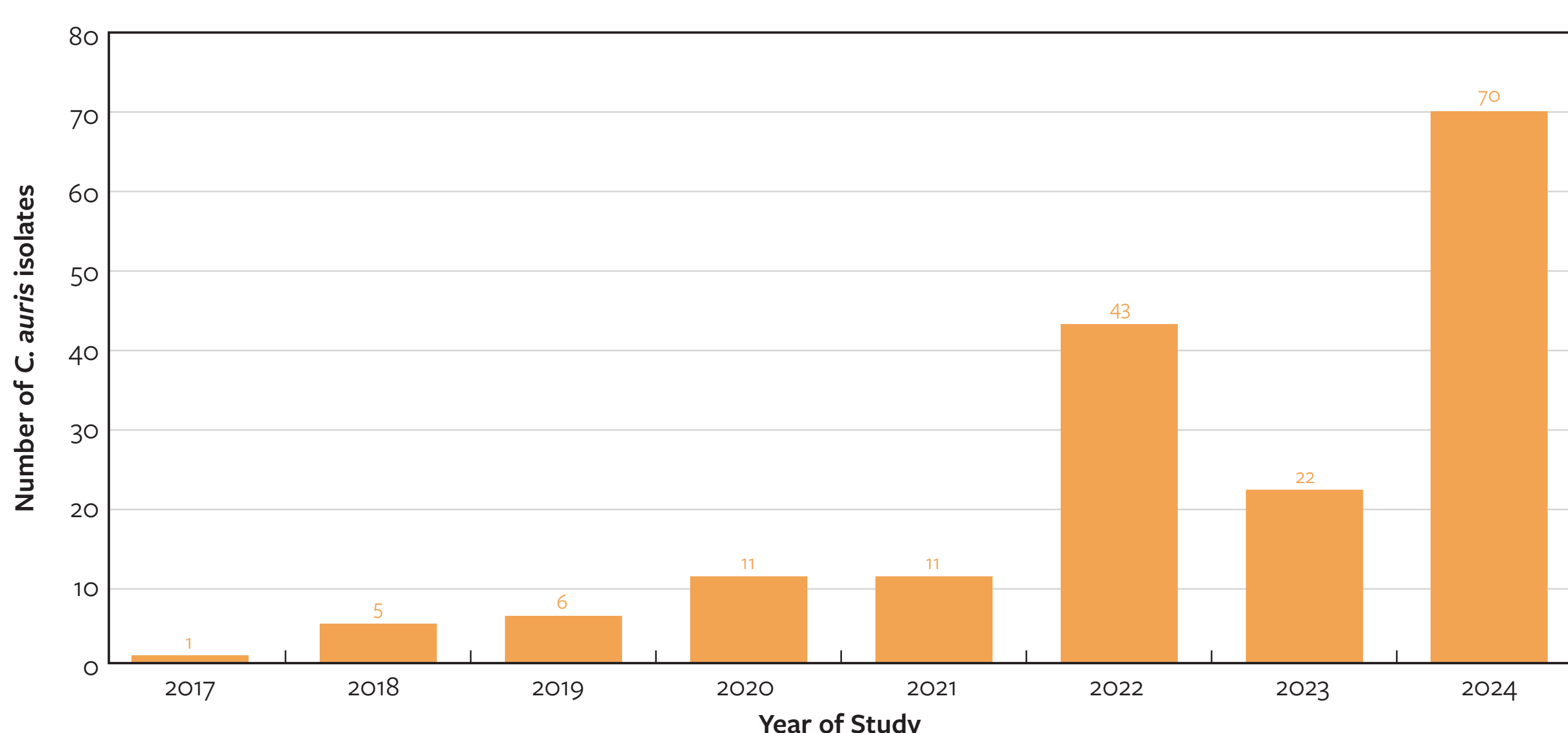
- A total of 169 *C. auris* isolates were collected from 20 different hospitals in 9 different countries over 7 years
- Only 1 isolate per patient episode was included
- All isolates were identified by MALDI-TOF MS and/or DNA sequencing
- Isolates were tested by CLSI reference broth microdilution method (M27) to obtain minimal inhibitory concentration (MIC) measurements
- CDC breakpoints were applied for comparator agents; no breakpoints or epidemiological cutoff values are available for manogepix
- Whole genome sequencing was performed on isolates resistant to one or more echinocandins with analysis of FKS hotspot (HS) regions

Table 1. MIC range, MIC_{50/90} and % organisms non-resistant for manogepix and comparator agents for *C. auris*

Antifungal agent	MIC range (mg/L)	MIC _{50/90} (mg/L)	% not resistant ¹
Manogepix	≤0.002 to 0.25	0.015/0.03	NA
Micafungin	0.06 to >4	0.25/0.5	97.0
Anidulafungin	0.06 to >4	0.25/0.5	97.6
Caspofungin	0.015 to >4	0.12/0.5	92.3
Fluconazole	2 to >128	128/>128	7.7
Itraconazole	0.06 to >8	0.5/1	NA
Posaconazole	0.03 to >8	0.25/0.5	NA
Voriconazole	0.015 to >8	1/2	NA
Amphotericin B	0.5 to 4	1/2	56.8

MIC, minimal inhibitory concentration; NA, not applicable, no breakpoints defined
¹ As defined in <https://www.cdc.gov/candida-auris/hcp/laboratories/antifungal-susceptibility-testing.html>

Figure 1. Number of *C. auris* isolates collected per year



Results

- The number of isolates increased from 1 in 2017 to 70 in 2024 (Figure 1)
- Isolates were from various infection sources (Figure 2)
- Manogepix MIC_{50/90} values against *Candida auris* were 0.015/0.03 mg/L (Table 1)
 - The highest observed manogepix MIC was 0.25 mg/L
 - Manogepix MIC_{50/90} values were within 2 doubling dilutions across the years of study
 - In 2020, MIC_{50/90} values were 0.004/0.015 mg/L; in 2024 MIC_{50/90} values were 0.015/0.03 mg/L
- There were 156 isolates resistant to fluconazole and 73 isolates resistant to amphotericin B
 - Low manogepix MICs were maintained against all resistant subgroups (Table 2)
- Echinocandin resistance was first observed in 2022
 - 13 isolates were resistant to ≥1 echinocandin
 - From Panama, USA, Israel, Turkey, Greece
 - 1 isolate (2.3%) in 2022, 5 isolates (22.7%) in 2023, and 7 isolates (10.0%) in 2024
 - 9 isolates had FKS1 HS alterations (Table 3)
 - The 4 isolates without FKS1 alterations were only resistant to caspofungin

Conclusions

- Manogepix has potent *in vitro* activity among 169 *C. auris* isolates collected since 2017
- More echinocandin-resistant isolates have been observed since 2022
 - No trend towards increasing manogepix MICs were observed over this time period
- Manogepix also maintained low MICs against isolates with FKS1 alterations
- Manogepix is a promising novel antifungal agent for the treatment of infections due to yeast including organisms of critical concern like *C. auris*

Figure 2. Infection source of collected *C. auris* isolates

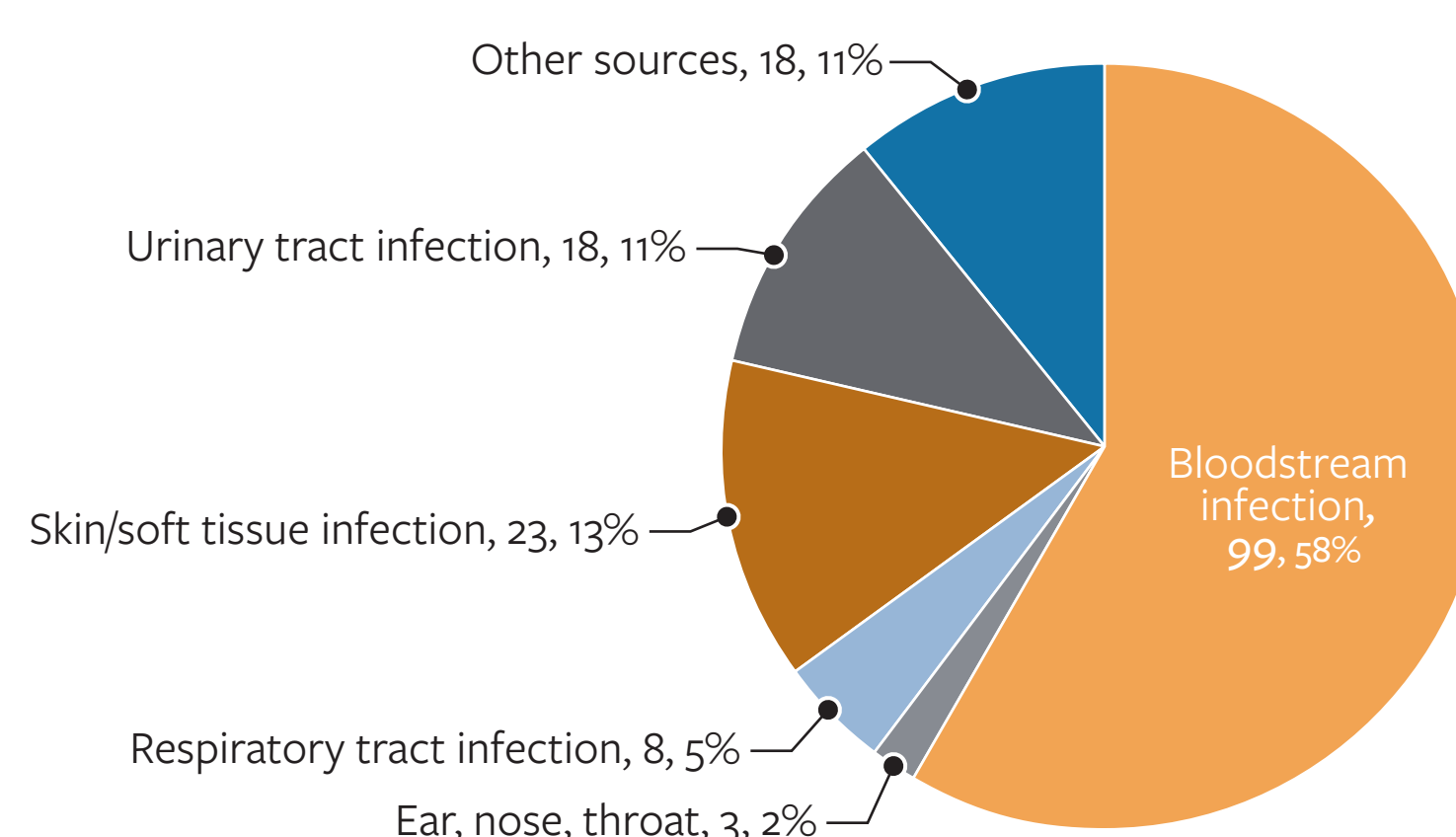


Table 2. MICs for manogepix and comparators against fluconazole-resistant and amphotericin B-resistant *C. auris*

Susceptibility pattern (n)	Manogepix		Anidulafungin		Amphotericin B		Fluconazole	
	MIC range (mg/L)	MIC _{50/90} (mg/L)	MIC range (mg/L)	MIC _{50/90} (mg/L)	MIC range (mg/L)	MIC _{50/90} (mg/L)	MIC range (mg/L)	MIC _{50/90} (mg/L)
FLC-resistant (156)	0.002 – 0.25	0.015/0.03	0.06 – >4	0.25/0.5	0.5 – 4	1/2	32 – >128	>128/>128
AmB-resistant (73)	0.004 – 0.25	0.015/0.06	0.06 – 2	0.25/0.5	2 – 4	2/2	16 – >128	>128/>128
FLC and AmB-resistant (72)	0.004 – 0.25	0.015/0.06	0.06 – 2	0.25/0.5	2 – 4	2/2	32 – >128	>128/>128
Pan-resistant (8) ²	0.008 – 0.25	0.03 ¹	0.5 – 2	1 ¹	2	2 ¹	32 – >128	>128 ¹

¹ Unable to calculate MIC₅₀ if < 10 isolates

² Pan-resistant defined as resistant to amphotericin B, fluconazole, and ≥1 echinocandin

Table 3. Results of FKS sequencing for echinocandin-resistant *C. auris* isolates

Year of collection	Collection site	Manogepix MIC (mg/L)	Anidulafungin MIC (mg/L)	Caspofungin MIC (mg/L)	Micafungin MIC (mg/L)	FKS1 HS1	FKS1 HS2
2022	Panama	0.004	4	>4	4	WT	R1354G
2023	LA, USA	0.008	>4	>4	>4	S639F	WT
2023	LA, USA	0.008	>4	>4	>4	S639F	WT
2023	Turkey	0.008	1	>4	1	WT	R1354H
2023	VA, USA	0.015	1	>4	0.5	D642Y	WT
2023	VA, USA	0.015	2	>4	0.5	D642Y	WT
2024	LA, USA	0.03	>4	>4	>4	S639F	WT
2024	Israel	0.03	1	>4	0.5	WT	WT
2024	VA, USA	0.25	2	>4	1	D642Y	WT
2024	TX, USA	0.015	0.5	>4	1	WT	WT
2024	Greece	0.03	2	>4	>4	F635Y	WT
2024	Greece	0.06	0.5	>4	0.25	WT	WT
2024	Greece	0.12	0.5	>4	0.25	WT	WT

MIC, minimal inhibitory concentration; HS, hotspot; LA, Louisiana; USA, United States of America; VA, Virginia; TX, Texas; WT, wildtype

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