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Activity of rezafungin against *Aspergillus* spp. that are non-wild-type to azole antifungal agents

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Introduction

- *Aspergillus* spp. are molds that cause allergic reactions, invasive aspergillosis, and chronic pulmonary aspergillosis (CPA).
- Resistance rates of *Aspergillus* spp. to azoles are rising.
- Rezafungin (RZF) is a long-acting echinocandin with pharmacokinetic and pharmacodynamic properties allowing weekly dosing.
- Rezafungin is in Phase 2 clinical trials for the treatment of CPA.
- Rezafungin was non-inferior to standard antimicrobial regimen in the prophylaxis of invasive fungal diseases in allogeneic hematopoietic stem cell transplant patients in a Phase 3 clinical trial (ReSPECT).
- Our study investigated the *in vitro* activity of RZF against *Aspergillus* spp. isolates that are non-wild-type (NWT) to azole comparators.

Methods

- 1,115 *Aspergillus* spp. isolates were collected from 2014 to 2025 in 25 countries (Figure 1).
 - This included 65 medical centers.
- 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 (M38) for rezafungin, anidulafungin, caspofungin, micafungin, itraconazole, voriconazole, and amphotericin B.
- Minimum inhibitory concentrations (MICs) for azoles and amphotericin B were interpreted by Clinical and Laboratory Standards Institute epidemiological cutoff values (ECVs); minimum effective concentrations (MECs) for echinocandins do not have CLSI interpretations defined.
- Non-wild-type (NWT) ECV criteria were defined as an MIC of >1 mg/L for voriconazole (VRC) and itraconazole (ITR) against *A. fumigatus*; >2 mg/L for voriconazole against *A. niger* species complex, and >4 mg/L for itraconazole against *A. niger* species complex (CLSI M57S 4th edition).
- All isolates that were NWT to ≥1 azole had whole genome sequencing performed with analysis of CYP51A and CYP51B genes.

Results

- Isolate infection sources were respiratory tract (810/1,115, 72.6%), skin and soft tissue infection (108/1,115, 9.7%), head and neck infections (75/1,115, 6.7%), bloodstream infections (12/1,115, 1.1%), and other or not defined (110/1,115, 9.9%).
- There were 4.9% of isolates that were NWT to ITR or VRC (55/1,115) (Table 1).
 - These NWT isolates were from 13 countries (Figure 2).
 - NWT isolates were either *A. fumigatus* (n=45) or *A. niger* species complex (n=10). All *A. flavus* species complex and *A. terreus* species complex isolates were WT for azoles.
- The $MEC_{50/90}$ and MEC range were comparable for rezafungin and anidulafungin against all organism groups in Table 1.
 - The $MEC_{50/90}$ is 6–7 doubling dilutions lower for rezafungin/anidulafungin than the $MIC_{50/90}$ for itraconazole and 5 doubling dilutions lower than for voriconazole among all collected *Aspergillus* spp. isolates.
 - For *A. fumigatus* isolates NWT to azoles, the rezafungin $MEC_{50/90}$ was 7 doubling dilutions and >8 doubling dilutions lower than the $MIC_{50/90}$ for itraconazole and 6 and >8 doubling dilutions lower than the $MIC_{50/90}$ for voriconazole.
 - For *A. niger* isolates NWT to azoles, the rezafungin $MEC_{50/90}$ was >10 doubling dilutions lower than the $MIC_{50/90}$ for itraconazole and 9 doubling dilutions lower than the $MIC_{50/90}$ for voriconazole.
- Among the isolates NWT for ≥1 azole, CYP51 alterations were identified in 23 *A. fumigatus* (23/45, 51.1%) and 4 *A. niger* species complex isolates (4/10, 40%) (Table 2).
 - Isolates with CYP51 alterations were from USA (8/27, 29.6%), Europe (11/27, 40.7%) and the Asia-Pacific region (8/27, 29.6%).
 - 8 of the isolates from Europe had promoter mutations, 2 of the 8 isolates from the Asia-Pacific region had promoter mutations, and none of the USA isolates had promoter mutations.
- Among the isolates with identified CYP51 alterations, rezafungin MECs ranged from 0.002 to 0.12 mg/L with $MEC_{50/90}$ 0.015/0.03 mg/L while voriconazole MICs ranged from 0.5 to >8 mg/L with $MIC_{50/90}$ 2/>8 mg/L.

Table 1. Antimicrobial activity of rezafungin and select comparator agents in mg/L tested against *Aspergillus* spp.

Organism (no. isolates)	Rezafungin		Anidulafungin		Itraconazole		Voriconazole		Amphotericin B	
	$MEC_{50/90}$	MEC Range	$MEC_{50/90}$	MEC Range	$MIC_{50/90}$ (%WT) [c]	MIC Range	$MIC_{50/90}$ (%WT) [c]	MIC Range	$MIC_{50/90}$ (%WT) [c]	MIC Range
Aspergillus spp. (1,115) [a]	0.015/0.03	≤0.002 to 0.12	0.015/0.03	≤0.002 to 0.12	1/1	0.06 to >8	0.5/1	0.06 to >8	1/2	≤0.03 to >2
Aspergillus spp. NWT azoles (55) [b]	0.015/0.03	≤0.002 to 0.12	0.015/0.06	0.004 to 0.12	4/>8	0.5 to >8	2/>8	0.5 to >8	1/2	0.12 to 2
All *A. fumigatus* (874)	0.015/0.03	≤0.002 to 0.12	0.015/0.03	≤0.002 to 0.12	1/1 (95.1)	0.12 to >8	0.5/0.5 (97.9)	0.12 to >8	1/2 (99.8)	0.06 to 4
Aspergillus fumigatus NWT azoles (45)	0.015/0.03	≤0.002 to 0.12	0.015/0.06	0.004 to 0.12	2/>8 (4.4)	0.5 to >8	1/>8 (60.0)	0.5 to >8	1/2 (100.0)	0.25 to 2
All *A. niger* species complex (49)	0.004/0.008	≤0.002 to 0.03	0.004/0.008	≤0.002 to 0.06	2/>8 (79.6)	0.12 to >8	1/2 (91.8)	0.12 to >8	0.12/0.25 (100.0)	≤0.03 to 0.5
A. niger species complex NWT azoles (10)	0.004/0.008	≤0.002 to 0.008	0.004/0.004	0.004	>8/>8 (0.0)	8 to >8	2/4 (60.0)	2 to >8	0.25/0.25 (100.0)	0.12 to 0.25

MEC, minimum effective concentration; MIC, minimum inhibitory concentration; WT, wild-type; NWT, non-wild-type
[a] Organisms include *A. flavus* species complex (164), *A. fumigatus* (874), *A. hiratsukae* (1), *A. lentulus* (1), *A. nidulans* species complex (5), *A. niger* species complex (49), *A. nomius* (2), *A. parasiticus* (2), *A. tamarii* (1), *A. terreus* species complex (13), *A. thermomutatus* (1), *A. unguis* (1), and unspeciated *Aspergillus* (1).
[b] Includes *A. fumigatus* (45) and *A. niger* species complex (10).
[c] ECV criteria published in CLSI M57S (2022), only applied to single species or species complex.

Conclusions

- Rezafungin has potent activity against *Aspergillus* spp. isolates over a 12-year period from diverse geographic areas.
- Rezafungin maintained low MECs against *Aspergillus* spp. isolates that were NWT to ≥1 azole antifungal agent.
 - Low MECs were also maintained against isolates with identified azole resistance mechanisms in CYP51 genes.
- Continued clinical development of rezafungin for the prevention and treatment of invasive aspergillosis infections is warranted based on this *in vitro* data.

Table 2. Summary of *Aspergillus* spp. isolates with CYP51A/B alterations, voriconazole MICs, and rezafungin MECs

Organism	Country	CYP51A	CYP51B	Voriconazole MIC (mg/L)	Rezafungin MEC (mg/L)
Aspergillus fumigatus	USA	I242V	wild-type	1	0.015
Aspergillus fumigatus	Belgium	TR34/L98H	wild-type	2	0.03
Aspergillus fumigatus	USA	I242V	wild-type	0.5	0.03
Aspergillus fumigatus	UK	TR34/L98H	wild-type	2	0.004
Aspergillus fumigatus	USA	G448S	wild-type	4	0.004
Aspergillus fumigatus	Belgium	Y121F, M172I, T289A, G448S, TR46	wild-type	≥8	0.004
Aspergillus fumigatus	USA	F46Y, M172V, N248T, D255E, E427K	wild-type	0.5	0.03
Aspergillus fumigatus	New Zealand	G138C	wild-type	8	0.004
Aspergillus fumigatus	UK	TR34/L98H	wild-type	2	0.015
Aspergillus fumigatus	USA	I242V	wild-type	0.5	0.03
Aspergillus fumigatus	France	H147Y	wild-type	≥8	0.015
Aspergillus fumigatus	USA	I242V	wild-type	0.5	0.015
Aspergillus fumigatus	USA	I242V	wild-type	1	0.015
Aspergillus fumigatus	Belgium	TR34/L98H	wild-type	4	0.03
Aspergillus fumigatus	Belgium	TR34/L98H	wild-type	8	0.12
Aspergillus fumigatus	France	TR34/L98H	wild-type	4	0.015
Aspergillus fumigatus	USA	G448S	wild-type	≥8	0.015
Aspergillus fumigatus	New Zealand	TR46, Y121F, T289A	wild-type	≥8	0.015
Aspergillus fumigatus	New Zealand	F46Y, M172V, E427K, G448S	wild-type	4	0.008
Aspergillus fumigatus	New Zealand	TR46, Y121F, T289A	wild-type	≥8	0.004
Aspergillus fumigatus	Czech Republic	G448S	wild-type	4	0.002
Aspergillus fumigatus	Czech Republic	TR46, Y121F, T289A, S363P, I364V, G448S	wild-type	≥8	0.008
Aspergillus fumigatus	Australia	wild-type	P383L	1	0.015
Aspergillus niger species complex	Thailand	A140V, T321A, P413S, L492M, I503F, Q504P	wild-type	2	0.002
Aspergillus niger species complex	Thailand	L383V	wild-type	≥8	0.002
Aspergillus niger species complex	Italy	A9V, L21F, T321A, I503V	wild-type	2	0.004
Aspergillus niger species complex	Australia	A9V, L21F, G52E, T321A, I503V	wild-type	2	0.002

MIC, minimum inhibitory concentration; MEC, minimum effective concentration

Figure 1. Map of geography of all collected *Aspergillus* spp. isolates

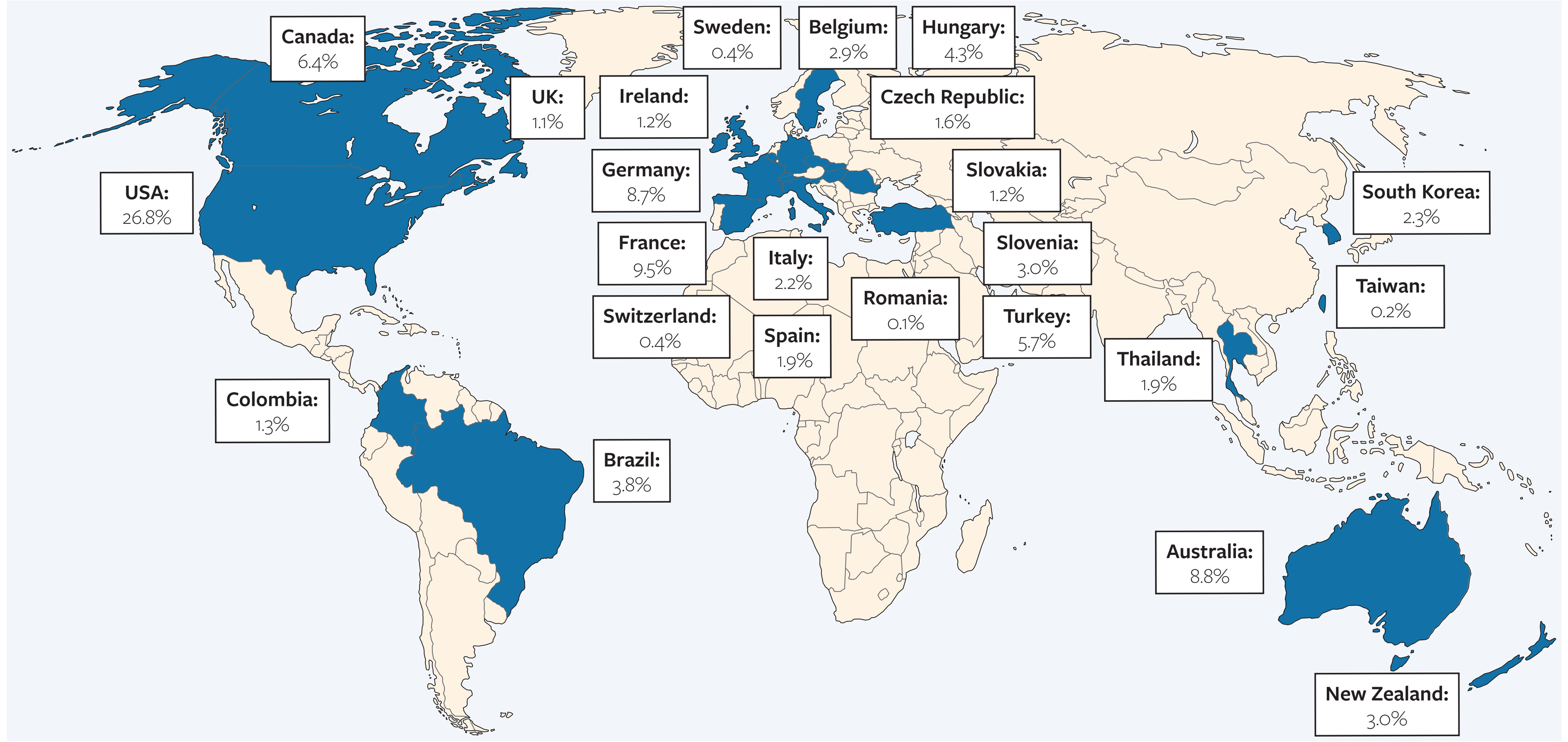
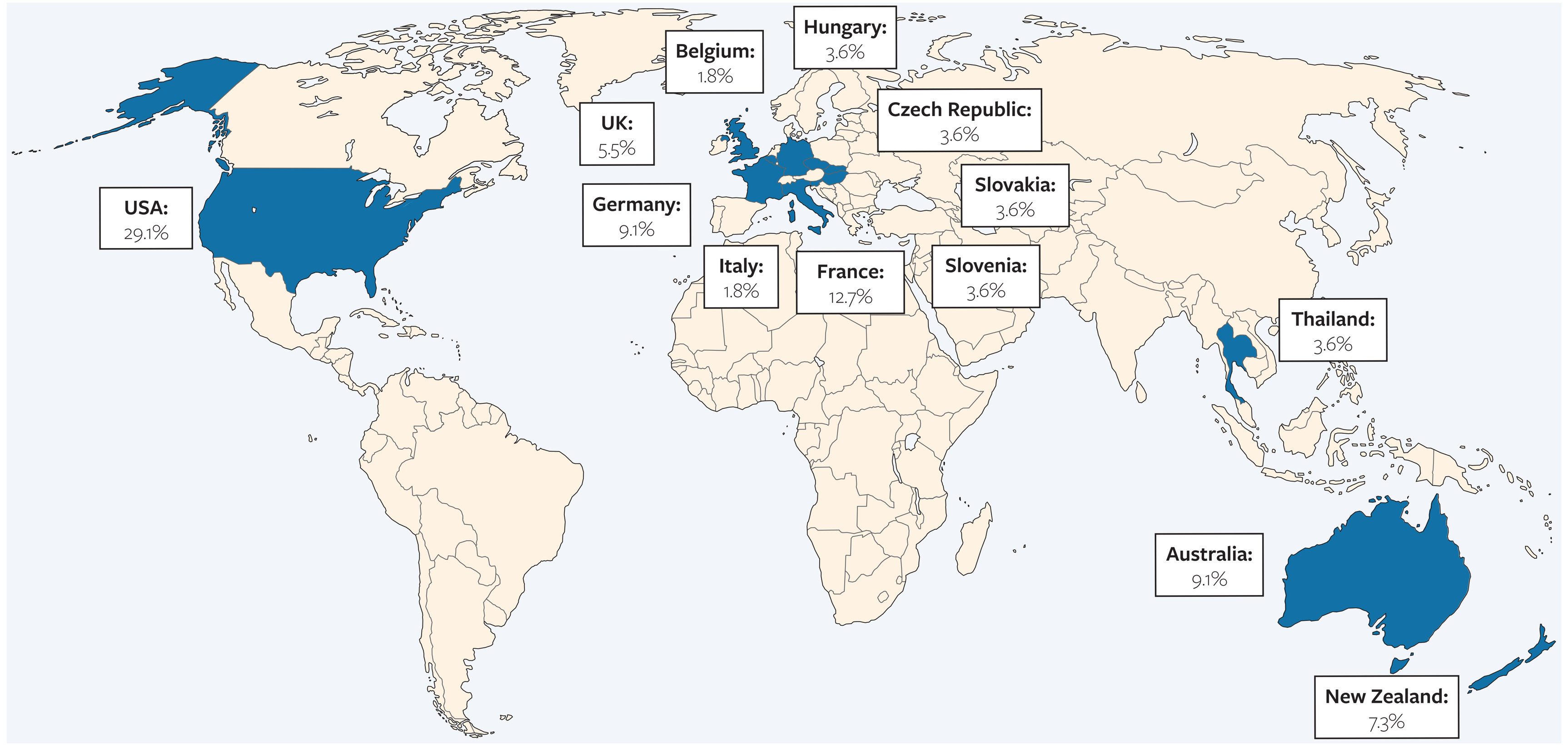

Canada: 6.4%
Sweden: 0.4%
Belgium: 2.9%
Hungary: 4.3%
UK: 1.1%
Ireland: 1.2%
Czech Republic: 1.6%
USA: 26.8%
Germany: 8.7%
Slovakia: 1.2%
South Korea: 2.3%
France: 9.5%
Italy: 2.2%
Slovenia: 3.0%
Taiwan: 0.2%
Romania: 0.1%
Switzerland: 0.4%
Spain: 1.9%
Turkey: 5.7%
Thailand: 1.9%
Colombia: 1.3%
Brazil: 3.8%
Australia: 8.8%
New Zealand: 3.0%

Figure 2. Map of geography of NWT *Aspergillus* spp. isolates


Hungary: 3.6%
Belgium: 1.8%
Czech Republic: 3.6%
UK: 5.5%
USA: 29.1%
Germany: 9.1%
Slovakia: 3.6%
Italy: 1.8%
France: 12.7%
Slovenia: 3.6%
Thailand: 3.6%
Australia: 9.1%
New Zealand: 7.3%

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