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Activity of Rezafungin and Comparator Antifungal Agents Tested Against a Worldwide Collection of Contemporaneous Invasive Fungal Isolates (2019–2020)

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INTRODUCTION

- Echinocandins are the mainstay treatment for invasive candidiasis and are currently approved for once-daily administration.
- Rezafungin is a new echinocandin in clinical development, with a long half-life and front-loaded drug exposure that allows for once-weekly intravenous administration.
- Rezafungin is being studied in Phase 3 trials for the treatment of candidemia and invasive candidiasis and the prevention of invasive fungal disease caused by *Candida, Aspergillus*, and *Pneumocystis* spp. in allogeneic blood and marrow transplant recipients.
- Recently, provisional susceptible-only breakpoints and epidemiological cutoff values (ECV) criteria were approved by CLSI Subcommittee on Antifungal Susceptibility Tests (Table 1).
- We evaluated the activity of rezafungin and comparators against invasive fungal isolates from the SENTRY Antimicrobial Surveillance Program.

MATERIALS AND METHODS

- A total of 1,427 *Candida* spp., 38 *Cryptococcus neoformans,* and 214 *Aspergillus* spp. non-duplicate fungal isolates were prospectively collected (1/patient) from 48 medical centers located in Europe (18 sites), North America (16), the Asia-Pacific region (8), and Latin America (6) in 2019–2020 (Figures 1 and 2).
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program.
- Isolates were identified by MALDI-TOF MS using the MALDI Biotyper (Bruker Daltonics, Billerica, Massachusetts USA).
- Isolates that were not identified by proteomic methods were identified using previously described sequencing-based methods.
- CLSI antifungal broth microdilution assays were performed according to standard methods (M27, M38) with the exception that panels were made by dispensing 10 µL of a 20x drug stock solution into wells that contained 90 µL of RPMI and mixing.
- CLSI susceptibility breakpoint and epidemiological cutoff criteria (ECV) were applied, including the recently approved rezafungin provisional breakpoints and ECVs (M59, M60, M61; Table 1).

Table 1. Rezafungin provisional epidemiological cutoff values and clinical breakpoints criteria approved by CLSI Subcommittee on Antifungal Susceptibility Tests

Organism	Rezafungin CLSI criteria [a] (mg/L)	
	Epidemiological cutoff value	Susceptible breakpoint
C. albicans	0.06	≤0.25
C. glabrata	0.12	≤0.5
C. parapsilosis	4	≤2
C. krusei	0.12	≤0.25
C. tropicalis	0.12	≤0.25
C. dubliniensis	0.12	≤0.12
C. auris	0.5	≤0.5

[a] Rezafungin provisional susceptible-only breakpoints and epidemiological cutoff values (ECV) criteria were approved in the CLSI June 2021 meeting.

Figure 1. Distribution of fungal clinical isolates recovered worldwide during 2019–2020

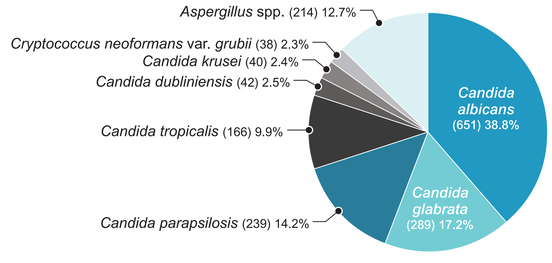


Table 2. Antimicrobial activity of rezafungin and comparator agents tested against *Candida* spp. isolated worldwide during 2019–2020

Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	CLSI [a]			ECV [b]	
			%S	%I	%R	%WT	%NWT
C. albicans (*n*=651)							
Rezafungin [c]	0.03	0.06	100.0	0.0	0.0	97.8	2.2
Anidulafungin	0.03	0.06	100.0	0.0	0.0	100.0	0.0
Caspofungin	0.015	0.03	100.0	0.0	0.0	—	—
Micafungin	0.015	0.03	100.0	0.0	0.0	99.7	0.3
Fluconazole	0.12	0.25	99.2	0.3 [d]	0.5	98.3	1.7
Itraconazole	0.06	0.12	—	—	—	—	—
Posaconazole	0.03	0.06	—	—	—	98.0	2.0
Voriconazole	0.004	0.015	99.8	0.2	0.0	98.5	1.5
Amphotericin B	0.5	1	—	—	—	100.0	0.0
C. glabrata (*n*=289)							
Rezafungin [c]	0.06	0.06	98.3	—	—	97.2	2.8
Anidulafungin	0.06	0.12	96.2	1.4	2.4	97.6	2.4
Caspofungin	0.03	0.06	97.2	1.0	1.7	—	—
Micafungin	0.015	0.03	97.9	0.0	2.1	96.9	3.1
Fluconazole	4	16	—	95.5 [d]	4.5	89.3	10.7
Itraconazole	0.5	1	—	—	—	99.3	0.7
Posaconazole	0.5	1	—	—	—	96.5	3.5
Voriconazole	0.06	0.5	—	—	—	90.0	10.0
Amphotericin B	1	1	—	—	—	100.0	0.0
C. parapsilosis (*n*=239)							
Rezafungin [c]	1	2	99.6	—	—	99.6	0.4
Anidulafungin	2	4	86.2	13.4	0.4	99.6	0.4
Caspofungin	0.25	0.5	100.0	0.0	0.0	100.0	0.0
Micafungin	1	1	100.0	0.0	0.0	100.0	0.0
Fluconazole	0.5	8	87.9	1.7 [d]	10.5	87.9	12.1
Itraconazole	0.12	0.25	—	—	—	100.0	0.0
Posaconazole	0.06	0.12	—	—	—	100.0	0.0
Voriconazole	0.008	0.12	91.6	6.3	2.1	87.0	13.0
Amphotericin B	0.5	1	—	—	—	100.0	0.0
C. tropicalis (*n*=166)							
Rezafungin [c]	0.03	0.06	100.0	—	—	99.4	0.6
Anidulafungin	0.03	0.06	100.0	0.0	0.0	98.8	1.2
Caspofungin	0.03	0.03	100.0	0.0	0.0	—	—
Micafungin	0.03	0.06	100.0	0.0	0.0	100.0	0.0
Fluconazole	0.25	1	98.2	0.6 [d]	1.2	97.0	3.0
Itraconazole	0.12	0.25	—	—	—	98.8	1.2
Posaconazole	0.06	0.12	—	—	—	97.0	3.0
Voriconazole	0.03	0.06	98.8	0.6	0.6	98.8	1.2
Amphotericin B	0.5	1	—	—	—	100.0	0.0
C. krusei (*n*=40)							
Rezafungin [c]	0.03	0.03	100.0	—	—	100.0	0.0
Anidulafungin	0.06	0.06	100.0	0.0	0.0	100.0	0.0
Caspofungin	0.06	0.12	100.0	0.0	0.0	—	—
Micafungin	0.06	0.12	100.0	0.0	0.0	100.0	0.0
Fluconazole	32	32	—	—	—	—	—
Itraconazole	0.25	0.5	—	—	—	100.0	0.0
Posaconazole	0.25	0.5	—	—	—	100.0	0.0
Voriconazole	0.25	0.25	100.0	0.0	0.0	100.0	0.0
Amphotericin B	1	2	—	—	—	100.0	0.0
C. dubliniensis (*n*=42)							
Rezafungin [c]	0.06	0.12	100.0	—	—	100.0	0.0
Anidulafungin	0.06	0.12	—	—	—	100.0	0.0
Caspofungin	0.03	0.06	—	—	—	—	—
Micafungin	0.015	0.03	—	—	—	100.0	0.0
Fluconazole	0.12	0.25	—	—	—	100.0	0.0
Itraconazole	0.06	0.12	—	—	—	100.0	0.0
Posaconazole	0.03	0.06	—	—	—	100.0	0.0
Voriconazole	0.004	0.008	—	—	—	—	—
Amphotericin B	0.25	0.5	—	—	—	100.0	0.0

ECV, epidemiological cutoff value; "—", not available
[a] Criteria published by CLSI M60 (2020).
[b] ECV criteria published in CLSI M59 (2020).
[c] Rezafungin provisional susceptible-only breakpoints and ECV criteria were approved in the CLSI June 2021 meeting.
[d] Intermediate is interpreted as susceptible-dose dependent.

RESULTS

- Rezafungin demonstrated potent activity against *C. albicans* ($MIC_{50/90}$, 0.03/0.06 mg/L; 100% susceptible), *C. tropicalis* ($MIC_{50/90}$, 0.03/0.06 mg/L; 100% susceptible), *C. glabrata* ($MIC_{50/90}$, 0.06/0.06 mg/L; 98.3% susceptible), *C. krusei* ($MIC_{50/90}$, 0.03/0.03 mg/L; 100% susceptible), and *C. dubliniensis* ($MIC_{50/90}$, 0.06/0.12 mg/L; 100% susceptible).
- Rezafungin inhibited 99.6% of *C. parapsilosis* ($MIC_{50/90}$,1/2 mg/L) at the provisional susceptibility breakpoint of ≤2 mg/L.
- Rezafungin activity was similar to the other echinocandins against these 6 *Candida* spp. (Table 2, Figure 3).
- All *C. albicans, C. tropicalis,* and *C. krusei* isolates, as well as the majority of *C. glabrata* (96.2%-97.9%) and *C. parapsilosis* (86.2%-100%) isolates were susceptible to the comparator echinocandins (Figure 3).
- Fluconazole resistance was detected among 0.5%, 4.5%, 10.5%, and 1.2% of *C. albicans, C. glabrata, C. parapsilosis,* and *C. tropicalis,* respectively (Table 2).
- The azoles were active against *C. neoformans* var. *grubii,* but all echinocandins displayed limited activity against this organism (Table 3).
- Echinocandins were active against *A. fumigatus* (MEC_{50} range, 0.015-0.06 mg/L) and *A.* section *Flavi* (MEC_{90} range, 0.015-0.03 mg/L; Table 3).
  - Rezafungin activity was similar to that of the other echinocandins against *Aspergillus* spp.
- Sixteen (8.6%) *A. fumigatus* isolates were non-susceptible to voriconazole (MIC ≥1 mg/L), while 100% of *A.* section *Flavi* were wild-type to mold-active azoles.

Figure 2. Distribution of fungal isolates by region (2019–2020)

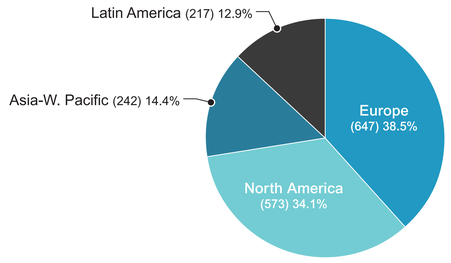
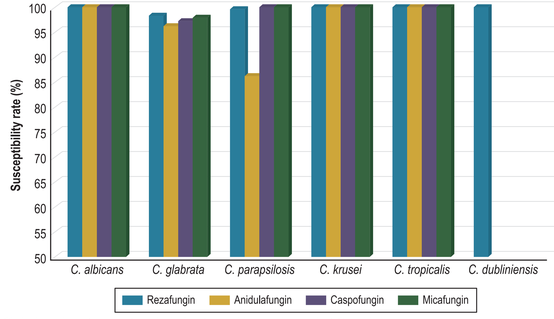


Figure 3. Echinocandin susceptibility rates against *Candida* spp. collected worldwide between 2019 and 2020



Clinical breakpoints are not available for other echinocandins against *C. dubliniensis.*

Table 3. Antimicrobial activity of rezafungin and comparator agents tested against *Aspergillus* spp. and *Cryptococcus* spp. isolated worldwide during 2019–2020

Antimicrobial agent	MIC_{50}/MEC_{50} (mg/L)	MIC_{90}/MEC_{90} (mg/L)	ECV [a]	
			%WT	%NWT
Aspergillus fumigatus (*n*=186)				
Rezafungin	0.015	0.03	—	—
Anidulafungin	0.015	0.06	—	—
Caspofungin	0.015	0.03	100.0	0.0
Micafungin	0.008	0.015	—	—
Itraconazole	1	1	91.4	8.6
Posaconazole	0.25	0.5	—	—
Voriconazole	0.5	0.5	96.8	3.2
Amphotericin B	2	2	98.9	1.1
Aspergillus section *Flavi* (*n*=28)				
Rezafungin	0.015	0.03	—	—
Anidulafungin	0.008	0.015	—	—
Caspofungin	0.015	0.03	100.0	0.0
Micafungin	0.008	0.015	—	—
Itraconazole	0.5	1	100.0	0.0
Posaconazole	0.25	0.5	100.0	0.0
Voriconazole	0.5	1	100.0	0.0
Amphotericin B	2	4	96.4	3.6
C. neoformans var. *grubii* (*n*=38)				
Rezafungin	>2	>2	—	—
Anidulafungin	>4	>4	—	—
Caspofungin	>4	>4	—	—
Micafungin	>4	>4	—	—
Fluconazole	4	8	97.4	2.6
Itraconazole	0.12	0.25	94.7	5.3
Posaconazole	0.12	0.25	97.4	2.6
Voriconazole	0.06	0.12	100.0	0.0
Amphotericin B	1	1	26.3	73.7

ECV, epidemiological cutoff value; "—", not available.
[a] ECV criteria published in CLSI M59 (2020).

CONCLUSIONS

- Rezafungin and other echinocandins displayed similar activity against *Candida, Cryptococcus*, and *Aspergillus* spp. isolates from invasive fungal infections.
- When CLSI provisional breakpoints were applied, rezafungin displayed 98.3%-100% susceptibility against the 6 most frequently isolated *Candida* spp.
- Rezafungin breakpoints and epidemiological cutoff values, although approved by the AFSC, are not yet official and should not be implemented by laboratories until they are officially published in the upcoming CLSI M27M44S and M57S documents, respectively.
- These *in vitro* results support the continued development of rezafungin for the treatment and prevention of invasive fungal disease.

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REFERENCES

1. Garcia-Effron G. Rezafungin-Mechanisms of Action, Susceptibility and Resistance: Similarities and Differences with the Other Echinocandins. J Fungi (Basel). 2020 Nov 1;6(4):262.
2. Ham YY, Lewis JS 2nd, Thompson GR 3rd. Rezafungin: a novel antifungal for the treatment of invasive candidiasis. Future Microbiol. 2021 Jan;16(1):27-36.
3. CLSI Subcommittee on Antifungal Susceptibility Tests. June 2021 meeting minutes. Available at: https://clsi.org/meetings/sub-antifungal/antifungal-susceptibility-testing-files-resources/
4. Pfaller MA, Woosley LN, Messer SA, Jones RN, Castanheira M. Significance of molecular identification and antifungal susceptibility of clinically significant yeasts and moulds in a global antifungal surveillance programme. Mycopathologia. 2012 Oct;174(4):259-71.
5. CLSI (2017). M27Ed4. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi, fourth edition.
6. CLSI (2017). M38Ed3. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi, third edition.
7. CLSI (2020). M60Ed2E. Performance standards for antifungal susceptibility testing of yeasts, second edition.
8. CLSI (2020). M61Ed2E. Performance standards for antifungal susceptibility testing of filamentous fungi, second edition.
9. CLSI (2020). M59Ed3. Epidemiological cutoff values for antifungal susceptibility testing, second edition.