J Antimicrob Chemother 2019; **74**: 3505–3510
doi:10.1093/jac/dkz390 Advance Access publication 20 September 2019

Journal of Antimicrobial Chemotherapy

In vitro activity of rezafungin against common and rare *Candida* species and *Saccharomyces cerevisiae*

Zoltán Tóth[1,2], Lajos Forgács[1,2], Jeffrey B. Locke[3], Gábor Kardos[1], Fruzsina Nagy[1,2], Renátó Kovács[1,4], Adrien Szekely[5], Andrew M. Borman[5] and László Majoros[1]*

[1]Department of Medical Microbiology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [2]Doctoral School of Pharmaceutical Sciences, University of Debrecen, Debrecen, Hungary; [3]Cidara Therapeutics, Inc., 6310 Nancy Ridge Dr., Suite 101, San Diego, CA, 92121, USA; [4]Faculty of Pharmacy, University of Debrecen, Debrecen, Hungary; [5]UK National Mycology Reference Laboratory (MRL), Public Health England South-West, Bristol, UK

*Corresponding author. E-mail: major@med.unideb.hu

Received 14 June 2019; returned 18 July 2019; revised 5 August 2019; accepted 13 August 2019

Background: Rezafungin is a novel echinocandin with excellent activity against common *Candida* species; however, limited data are available regarding rare *Candida* species.

Methods: We determined the *in vitro* susceptibility of 689 clinical isolates of 5 common and 19 rare *Candida* species, as well as *Saccharomyces cerevisiae*. The activity of rezafungin was compared with that of anidulafungin, caspofungin, micafungin, amphotericin B and fluconazole, using CLSI broth microdilution methodology (Fourth Edition: M27).

Results: Rezafungin MIC_{90} values were 0.06 mg/L for *Candida albicans* (*n*=125), *Candida tropicalis* (*n*=51), *Candida dubliniensis* (*n*=22), *Candida inconspicua* (*n*=41), *Candida sojae* (*n*=10), *Candida lipolytica* (*n*=10) and *Candida pulcherrima* (*n*=10), 0.12 mg/L for *Candida glabrata* (*n*=81), *Candida krusei* (*n*=53), *Candida kefyr* (*n*=52) and *Candida fabianii* (*n*=15), 0.25 mg/L for *Candida lusitaniae* (*n*=46) and *Candida auris* (*n*=19), 0.5 mg/L for *Candida metapsilosis* (*n*=15) and *S. cerevisiae* (*n*=21), 1 mg/L for *Candida orthopsilosis* (*n*=15) and *Candida guilliermondii* (*n*=27) and 2 mg/L for *Candida parapsilosis sensu stricto* (*n*=59). Caspofungin MIC_{90} values were 0.25–2 mg/L for all species, while micafungin and anidulafungin MIC_{90} values were similar to those of rezafungin. Fluconazole resistance was found in *C. albicans* (5.6%) and *C. glabrata* (4.9%); rezafungin was effective against these isolates as well. Amphotericin B MIC values did not exceed 2 mg/L.

Conclusions: Rezafungin showed excellent *in vitro* activity against both WT and azole-resistant *Candida* species, as well as against *S. cerevisiae*. Rezafungin had similar activity to other echinocandins (excluding caspofungin) against common *Candida* species and, notably, against clinically relevant uncommon *Candida* species.

Introduction

Rezafungin is a novel, once-weekly echinocandin in development for treatment of candidaemia and invasive candidiasis, with a Phase 3 trial currently under way, and for prophylaxis against invasive fungal infections caused by *Candida*, *Aspergillus* and *Pneumocystis* spp. in patients undergoing blood or marrow transplantation.[1,2] Rezafungin has excellent *in vitro* activity, comparable to that of other echinocandins, against the five most frequently isolated *Candida* species (*Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis sensu stricto* and *Candida krusei*) using either CLSI or EUCAST broth microdilution (BMD) methodologies.[3–5] However, limited data are available regarding activity against less common *Candida* species. Therefore, our study aimed at determining the *in vitro* susceptibility of 668 clinical isolates of 5 common and 19 rare *Candida* species, as well as 21 clinical isolates of *Saccharomyces cerevisiae*. The activity of rezafungin was compared with that of five licensed systemic antifungal agents (anidulafungin, caspofungin, micafungin, fluconazole and amphotericin B).

Materials and methods

Isolates

The vast majority of 689 non-duplicate clinical isolates were collected between January 2005 and December 2018 in our diagnostic laboratory. All *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis sensu stricto*, *C. krusei*, *Candida rugosa*, *Candida catenulata*, *Lodderomyces elongisporus*

Table 1. MIC values of rezafungin and comparator antifungal agents for *Candida* ATCC and type strains

	MIC (mg/L)					
ATCC and type strains	RZF	ANF	CAS	MCF	FLC	AMB
C. krusei ATCC 6258	0.03–0.06	0.03–0.06	0.5–1	0.12–0.25	8–32	0.5–1
C. parapsilosis ATCC 22019	0.5–1	0.5–2	0.5–1	1–2	0.5–1	0.25–1
C. albicans ATCC 10231	0.03	0.015	0.25	0.008	0.25	0.25
C. glabrata ATCC 90030	0.06	0.0015	0.5	0.03	>32	0.5
C. tropicalis ATCC 750	0.06	0.015	0.12	0.03	1	1
C. dubliniensis CD36	0.03	0.015	0.06	0.015	0.25	0.25
C. auris ATCC 21092	0.06	0.03	0.25	0.12	0.5	0.5
C. inconspicua ATCC 16783	0.06	0.008	0.12	0.03	32	0.5
C. orthopsilosis ATCC 96139	2	1	1	0.5	0.5	0.5
C. metapsilosis ATCC 96144	0.5	0.5	0.25	0.25	1	0.5
C. africana ATCC 2669	0.03	≤0.004	0.12	0.06	0.12	0.25
C. sojae CBS 7871	0.06	≤0.004	0.25	0.015	0.25	0.12
C. rugosa ATCC 2142	0.03	0.06	0.12	0.12	1	0.25
C. guilliermondii ATCC 6260	1	0.5	0.5	2	1	0.5

RZF, rezafungin; ANF, anidulafungin; CAS, caspofungin; MCF, micafungin; FLC, fluconazole; AMB, amphotericin B.

and *S. cerevisiae* isolates were derived from normally sterile body sites (blood, cerebrospinal, pleural and peritoneal fluids, deep wounds, etc.). At least one-third of the isolates were cultured from normally sterile body sites in the case of the other *Candida* species as well. In addition, 14 ATCC and type strains were also tested (Table 1). Clinical isolates were obtained prior to antifungal administration and identified with MALDI Biotyper (Bruker, Bremen, Germany) and/or PCR ribotyping.[6–9]

Antifungal susceptibility testing

All isolates were tested by BMD according to CLSI in RPMI-1640 (Sigma, Budapest, Hungary).[10] MIC assays were conducted in U-bottom, tissue culture-treated microtitre test plates (TPP Techno Plastic Products AG, Switzerland; cat. no. 92097). Rezafungin pure powder was provided by Cidara Therapeutics, Inc. (San Diego, CA, USA). Caspofungin, micafungin and anidulafungin were obtained from Molcan Corporation (Richmond Hill, Ontario, Canada). Amphotericin B and fluconazole were purchased from Sigma (Budapest, Hungary). The concentration ranges tested were 0.004–2 mg/L for rezafungin, anidulafungin, caspofungin and micafungin, 0.015–8 mg/L for amphotericin B and 0.06–32 mg/L for fluconazole. In cases of the '*psilosis*' group and *Candida guilliermondii*, the ranges for all four echinocandins were 0.015–8 mg/L.

Neither a clinical breakpoint nor an epidemiological cut-off value (ECV) has been published for rezafungin against *Candida* species. The revised species-specific CLSI clinical breakpoints were used in cases of *C. albicans*, *C. glabrata*, *C. parapsilosis sensu stricto*, *C. tropicalis*, *C. krusei* and *C. guilliermondii* for anidulafungin, caspofungin, micafungin and fluconazole (except *C. guilliermondii* for fluconazole, where an ECV of ≤8 mg/L was used).[11,12] The previously established ECVs were used for anidulafungin, caspofungin, micafungin and fluconazole for *Candida kefyr*, *Candida lusitaniae*, *Candida dubliniensis* and *Candida orthopsilosis*.[12–14] For amphotericin B, an ECV of ≤2 mg/L was used for the previously mentioned *Candida* species.[12,13] In the case of *Candida auris* for anidulafungin, caspofungin, micafungin, amphotericin B and fluconazole, we used the tentative MIC breakpoints as suggested by the CDC.[15] For other *Candida* species and *S. cerevisiae* neither clinical breakpoints nor ECVs exist, thus only $MIC_{50/90}$ values are shown.

Quality control strains *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 were included on each day of testing (25 different days).

Results

MIC values for the 14 ATCC and type strains are shown in Table 1. MIC values of the six antifungal agents for the quality control strains were always within the accepted ranges.[10,11] MIC values of rezafungin also fell always within the 24 h quality control ranges tentatively accepted by CLSI (January 2018 Subcommittee on Antifungal Susceptibility Tests meeting; *C. krusei* ATCC 6258, 0.015–0.12 mg/L; *C. parapsilosis* ATCC 22019, 0.25–1 mg/L).

Activity of echinocandins against Candida species and S. cerevisiae isolates

Rezafungin inhibited all *C. albicans* isolates at ≤0.12 mg/L, similarly to anidulafungin and micafungin, but only 70.4% were susceptible to caspofungin (Table 2). Susceptibility patterns were similar to the closely related *C. dubliniensis* and *Candida africana* isolates, as well as to *C. tropicalis* (Table 2).

Activity of rezafungin ($MIC_{50/90}$, 0.06/0.12 mg/L) against *C. glabrata* was comparable to that of anidulafungin and micafungin. Susceptibility rates were 100%, 100% and 4.9% for anidulafungin, micafungin and caspofungin, respectively (Table 2).

All four echinocandins showed similar activities against the '*psilosis*' group and *C. guilliermondii*; the most susceptible was *Candida metapsilosis* (MIC_{90} was 0.5 mg/L) (Table 2). In the case of 53.3% of *C. orthopsilosis* isolates, MICs were higher than the ECV (0.5 mg/L) for caspofungin (Table 2).

C. krusei isolates were inhibited by ≤0.12 mg/L rezafungin. All isolates were susceptible to anidulafungin and micafungin, but only 11.3% were susceptible to caspofungin (Table 2). Rezafungin, anidulafungin and micafungin, but not caspofungin, were highly active against the other fluconazole-resistant *Candida* species, *Candida inconspicua* (Table 2).

Rezafungin $MIC_{50/90}$ values were 0.06/0.12 and 0.12/0.25 mg/L for *C. kefyr* and *C. lusitaniae*, respectively. Against these two species, anidulafungin was the most active. In the case of *C. kefyr*,

Table 2. Activity of rezafungin and comparator antifungal agents against *Candida* species and *S. cerevisiae* clinical isolates

Species (*n*)	Drug	MIC (mg/L)				Susceptibility (%)			Percentage of MICs above ECV
		range	mode	MIC_{50}	MIC_{90}	S	I/SDD	R	
C. albicans (125)	RZF	0.008–0.12	0.03	0.03	0.06				
	ANF	≤0.004–0.06	≤0.004	0.008	0.03	100			
	CAS	0.06–0.5	0.25	0.25	0.5	70.4	29.6		
	MCF	≤0.004–0.25	0.015	0.015	0.06	100			
	FLC	0.12 to >32	0.12	0.12	0.25	94.4		5.6	
	AMB	0.12–2	0.5	0.5	1				
C. glabrata (81)	RZF	0.06–0.25	0.06	0.06	0.12				
	ANF	0.008–0.12	0.03	0.03	0.06	100			
	CAS	0.12–1	0.5	0.5	0.5	4.9	32.1	63	
	MCF	0.008–0.06	0.015	0.03	0.06	100			
	FLC	0.25 to >32	4	2	16		95.1	4.9	
	AMB	0.25–2	0.5	0.5	1				
C. parapsilosis (59)	RZF	0.5–2	1	1	2				
	ANF	0.25–2	1	1	2	100			
	CAS	0.25–2	1	1	2	100			
	MCF	0.5–2	2	2	2	100			
	FLC	0.12–4	0.5	0.5	1	96.6	3.4		
	AMB	0.12–1	0.5	0.5	1				
C. tropicalis (51)	RZF	0.015–0.12	0.06	0.06	0.06				
	ANF	≤0.004–0.06	0.03	0.015	0.03	100			
	CAS	0.03–0.5	0.25	0.25	0.5	70.6	29.4		
	MCF	0.015–0.12	0.03	0.03	0.06	100			
	FLC	0.06–0–5	0.25	0.25	0.5	100			
	AMB	0.25–1	0.5	0.5	1				
C. krusei (53)	RZF	0.06–0.12	0.06	0.06	0.12				
	ANF	0.015–0.25	0.06	0.06	0.12	100			
	CAS	0.12–1	1	1	1	11.3	22.6	66.1	
	MCF	0.03–0.25	0.25	0.25	0.25	100			
	FLC	8 to >32	32	32	>32				
	AMB	0.5–2	1	1	1				
C. kefyr (52)	RZF	0.015–0.25	0.06	0.06	0.12				
	ANF	0.008–0.12	0.03	0.03	0.06				
	CAS	0.25–1	0.25	0.25	0.5				100
	MCF	0.008–0.12	0.06	0.06	0.12				
	FLC	0.12–4	0.12	0.12	0.5				1.9
	AMB	0.25–1	0.5	0.5	1				
C. lusitaniae (46)	RZF	0.015–0.5	0.12	0.12	0.25				
	ANF	0.008–0.25	0.03	0.03	0.06				
	CAS	0.12–1	0.5–1	0.5	1				
	MCF	0.015–0.5	0.12	0.12	0.25				
	FLC	0.06–32	0.25	0.25	4				10.9
	AMB	0.12–1	0.5	0.5	1				
C. guilliermondii (27)	RZF	0.5–2	1	1	1				
	ANF	0.25–2	1	1	2	100			
	CAS	0.25–1	0.5	0.5	1	100			
	MCF	0.5–2	1	1	2	100			
	FLC	1–32	2	2	4				7.4
	AMB	0.25–1	0.5	0.5	1				
C. dubliniensis (22)	RZF	0.015–0.06	0.06	0.06	0.06				
	ANF	≤0.004–0.03	0.015	0.015	0.03				
	CAS	0.03–0.5	0.25	0.12	0.25				50

Continued

Table 2. *Continued*

Species (*n*)	Drug	MIC (mg/L)				Susceptibility (%)			Percentage of MICs above ECV
		range	mode	MIC_{50}	MIC_{90}	S	I/SDD	R	
	MCF	0.008–0.12	0.03	0.03	0.03				
	FLC	0.06–0.25	0.12	0.12	0.25				
	AMB	0.06–0.5	0.12	0.25	0.5				
C. auris (19)	RZF	0.03–0.25	0.12–0.25	0.12	0.25				
	ANF	0.03–0.5	0.03	0.06	0.25				
	CAS	0.25–1	0.5	0.5	1				
	MCF	0.06–2	0.25	0.25	0.5				
	FLC	0.5 to >32	>32	>32	>32				68.4
	AMB	0.12–1	1	0.5	1				
C. orthopsilosis (15)	RZF	0.12–1	1	0.5	1				
	ANF	0.12–1	1	1	1				
	CAS	0.5–1	1	0.5	1				53.3
	MCF	0.25–1	0.5	0.5	1				
	FLC	0.12–0.5	0.25	0.25	0.5				
	AMB	0.12–0.5	0.25	0.25	0.5				
C. metapsilosis (15)	RZF	0.25–0.5	0.5	0.5	0.5				
	ANF	0.12–0.5	0.25	0.25	0.5				
	CAS	0.12–1	0.25	0.25	0.5				
	MCF	0.06–0.5	0.25	0.25	0.5				
	FLC	0.5–16	0.5–1	1	1				
	AMB	0.25–1	0.25–0.5	0.25	0.5				
S. cerevisiae (21)	RZF	0.03–0.5	0.5	0.25	0.5				
	ANF	0.015–0.5	0.12	0.12	0.5				
	CAS	0.5–1	1	1	1				
	MCF	0.12–0.5	0.25	0.25	0.25				
	FLC	2–8	4	4	8				
	AMB	0.25–1	0.5	0.5	1				
C. fabianii (15)	RZF	0.03–0.12	0.06	0.06	0.12				
	ANF	0.015–0.25	0.06	0.06	0.12				
	CAS	0.5–1	1	1	1				
	MCF	0.06–0.5	0.06	0.06	0.12				
	FLC	0.12–2	0.5	0.5	2				
	AMB	0.25–1	0.5	0.5	1				
C. inconspicua (41)	RZF	0.015–0.06	0.06	0.06	0.06				
	ANF	≤0.004–0.015	0.008	0.008	0.015				
	CAS	0.03–0.5	0.25	0.25	0.5				
	MCF	≤0.004–0.12	0.03	0.03	0.06				
	FLC	8 to >32	16	32	>32				
	AMB	0.06–1	0.5	0.5	1				
C. sojae (10)	RZF	0.03–0.06	0.06	0.06	0.06				
	ANF	≤0.004–0.03	0.03	0.015	0.03				
	CAS	0.12–1	0.5	0.25	0.5				
	MCF	0.015–0.12	0.06	0.03	0.06				
	FLC	0.12–0.25	0.25	0.25	0.25				
	AMB	0.12–1	0.5	0.5	0.5				
C. lipolytica (10)	RZF	0.03–0.06	0.06	0.06	0.06				
	ANF	0.03–0.12	0.12	0.06	0.12				
	CAS	0.12–1	0.25	0.25	0.5				
	MCF	0.06–1	1	0.25	1				
	FLC	0.5–2	0.5	0.5	1				
	AMB	0.12–0.5	0.25	0.25	0.5				

Continued

Table 2. *Continued*

Species (*n*)	Drug	MIC (mg/L) range	MIC (mg/L) mode	MIC_{50}	MIC_{90}	Susceptibility (%) S	Susceptibility (%) I/SDD	Susceptibility (%) R	Percentage of MICs above ECV
C. pulcherrima (10)	RZF	0.015–0.06	0.03	0.03	0.06				
	ANF	0.015–0.06	0.015	0.015	0.06				
	CAS	0.12–1	1	0.5	1				
	MCF	0.008–0.5	0.06	0.06	0.25				
	FLC	0.12–0.5	0.25	0.25	0.25				
	AMB	0.12–1	0.5	0.5	1				
Other yeast spp. (17)[a]	RZF	≤0.004–0.5	0.03, 0.06	0.06	0.25				
	ANF	≤0.004–1	0.03	0.03	0.25				
	CAS	0.06–1	0.12	0.25	0.5				
	MCF	≤0.004–0.5	0.03	0.03	0.25				
	FLC	0.06–8	0.12, 0.25	0.25	4				
	AMB	0.06–1	0.25	0.25	1				

RZF, rezafungin; ANF, anidulafungin; CAS, caspofungin; MCF, micafungin; FLC, fluconazole; AMB, amphotericin B; S, susceptible; I, intermediate; SDD, susceptible-dose dependent; R, resistant.
[a]Includes *C. pararugosa* (*n*=6), *C. africana* (*n*=3), *C. catenulata* (*n*=2), *C. rugosa* (*n*=2), *L. elongisporus* (*n*=2), *C. intermedia* (*n*=1) and *C. carpophila* (*n*=1).

MICs for all isolates were higher than the ECV (0.03 mg/L) for caspofungin (Table 2).

No MICs for *C. auris* exceeded the tentative MIC breakpoints against the three licensed echinocandins (Table 2). Rezafungin inhibited all isolates at ≤0.25 mg/L ($MIC_{50/90}$, 0.12/0.25 mg/L). Activity of rezafungin ($MIC_{50/90}$, 0.25/0.5 mg/L) against *S. cerevisiae* was comparable to anidulafungin, micafungin and caspofungin (Table 2).

Rezafungin MIC_{90} values for *Candida fabianii*, *Candida sojae*, *Candida lipolytica* and *Candida pulcherrima* were 0.12, 0.06, 0.06 and 0.06 mg/L, respectively. Anidulafungin and micafungin MIC_{90} values for *C. fabianii*, *C. sojae* and *C. pulcherrima* were similar to those of rezafungin. Micafungin MICs for *C. lipolytica* were higher compared with rezafungin and anidulafungin; MICs for 5 of 10 isolates were 0.5–1 mg/L (Table 2).

Against other yeast species represented by <10 isolates (*Candida pararugosa*, *C. africana*, *C. catenulata*, *C. rugosa*, *L. elongisporus*, *Candida intermedia* and *Candida carpophila*), rezafungin was active at ≤0.25 mg/L with the exception of *C. carpophila* (Table 2).

Activity of fluconazole and amphotericin B against Candida species and S. cerevisiae isolates

Fluconazole resistance was found in *C. albicans* (5.6%) and *C. glabrata* (4.9%). Two (3.4%) *C. parapsilosis sensu stricto* isolates showed dose-dependent susceptibility to fluconazole. In cases of *C. guilliermondii*, *C. kefyr*, *C. lusitaniae* and *C. auris* isolates, 7.4%, 1.9%, 10.9% and 68.4% of isolate MICs, respectively, were higher than their ECVs (Table 2).

Amphotericin B MICs with the exception of two, three and three *C. albicans*, *C. glabrata* and *C. krusei* isolates, respectively, (with 2 mg/L MICs for all cases) were ≤1 mg/L for all tested isolates (Table 2).

Discussion

Results of this study, consistent with other published data, demonstrate that rezafungin MIC values for the five most common *Candida* species, including fluconazole-resistant isolates, were comparable to those of anidulafungin and micafungin.[2–5] Activity of rezafungin was comparable to anidulafungin and micafungin against *C. kefyr*, *C. lusitaniae* and *C. dubliniensis*, as well as against the emerging fluconazole-resistant *C. auris* and *C. inconspicua*. As expected, against *C. guilliermondii*, *C. orthopsilosis*, *C. metapsilosis* and *C. carpophila* all echinocandins including rezafungin showed higher MIC values, similarly to *C. parapsilosis sensu stricto*.[16]

Rezafungin at ≤0.12 mg/L was active against very rare *Candida* species (*C. lipolytica*, *C. fabianii*, *C. sojae*, *C. pulcherrima*, *C. pararugosa* and *C. rugosa*) and showed activity against *S. cerevisiae* comparable to anidulafungin or micafungin. *C. sojae* has not been isolated from clinical specimens previously; our 10 isolates, including 1 bloodstream isolate, draw attention to this primarily plant pathogen frequently misidentified as *Candida sake* using traditional identification methods.[9]

Although rezafungin MIC values were similar to those of micafungin and of anidulafungin, as might be expected given the latter's structural similarities to rezafungin,[17] MIC values of caspofungin were markedly higher for almost all *Candida* species studied. Our caspofungin MIC distributions were in line with the previously well-documented limitation that caspofungin susceptibility testing suffers from significant interlaboratory variability and is therefore not recommended.[18] As all three echinocandin comparators (anidulafungin, caspofungin and micafungin) originated from the same supplier, drug source does not explain this difference in antifungal efficacy. However, the quality of the microtitre plate (treated versus untreated polystyrene trays) may have influenced differentially our MIC values obtained with the different echinocandins, as previously demonstrated by Fothergill *et al.*[19] This may also be a factor in MIC differences found between

laboratories testing rezafungin susceptibility.[5] Although our MIC data derived from a single centre and we used tissue culture-treated microtitre test plates from the same batch, their impact on rezafungin MIC distribution could not be entirely ruled out.

We have provided a 'head-to-head' comparison between the three clinically available echinocandins and rezafungin using CLSI reference BMD methodology. Although the vast majority of clinical strains were isolated from a single centre, our anidulafungin, micafungin, fluconazole and amphotericin B MIC data for the tested *Candida* species were comparable to data reported by others.[20] The investigational echinocandin rezafungin showed excellent *in vitro* activity against *Candida* species, including the emerging potentially MDR *C. auris*, as well as against *S. cerevisiae*. Rezafungin had similar activity to other echinocandins (excluding caspofungin) against common and, notably, against clinically relevant uncommon *Candida* species.

Acknowledgements

This work was presented at the Twenty-Ninth European Congress of Clinical Microbiology and Infectious Diseases, Amsterdam, The Netherlands, 2019 (P2161).

We thank Lorant Hatvani and Guillermo Quindós for kindly supplying 10 *C. fabianii* and 2 *C. africana* isolates, respectively. Cidara Therapeutics, Inc. provided rezafungin and purchased the comparator echinocandins (but did not provide any direct financial support for the study).

Funding

Z. T. and F. N. were supported by the EFOP-3.6.3-VEKOP-16–2017-00009 Program. R. K. was supported by the TÁMOP 4.2.4.A/2–11-1–2012-0001 National Excellence Program (Elaborating and operating an inland student and researcher personal support system). The project was subsidized by the European Union and co-financed by the European Social Fund. Z. T. and F. N. were supported by the ÚNKP-18–3 New National Excellence Program of the Ministry of Human Capacities.

Transparency declarations

J. B. L. is an employee and shareholder of Cidara Therapeutics, Inc. L. M. has received conference travel grants from MSD, Astellas and Pfizer. All other authors: none to declare.

References

1 Zhao Y, Perez WB, Jiménez-Ortigosa C *et al*. CD101: a novel long-acting echinocandin. *Cell Microbiol* 2016; **18**: 1308–16.

2 Sofjan AK, Mitchell A, Shah DN *et al*. Rezafungin (CD101), a next-generation echinocandin: a systematic literature review and assessment of possible place in therapy. *J Glob Antimicrob Resist* 2018; **14**: 58–64.

3 Pfaller MA, Messer SA, Rhomberg PR *et al*. Activity of long-acting echinocandin (CD101) and seven comparator antifungal agents tested against a global collection of contemporary invasive fungal isolates in the SENTRY 2014 Antifungal Surveillance Program. *Antimicrob Agents Chemother* 2017; **61**: e02045-16.

4 Pfaller MA, Messer SA, Rhomberg PR *et al*. CD101, a long-acting echinocandin, and comparator antifungal agents tested against a global collection of invasive fungal isolates in the SENTRY 2015 Antifungal Surveillance Program. *Int J Antimicrob Agents* 2017; **50**: 352–8.

5 Arendrup MC, Meletiadis J, Zaragoza O *et al*. Multicentre determination of rezafungin (CD101) susceptibility of *Candida* species by the EUCAST method. *Clin Microbiol Infect* 2018; **24**: 1200–4.

6 Majoros L, Kardos G, Belák Á *et al*. Restriction enzyme analysis of ribosomal DNA shows that *Candida inconspicua* clinical isolates can be misidentified as *Candida norvegensis* with traditional diagnostic procedures. *J Clin Microbiol* 2003; **41**: 5250–3.

7 Varga I, Sóczó G, Kardos G *et al*. Comparison of killing activity of caspofungin against *Candida parapsilosis*, *C. orthopsilosis* and *C. metapsilosis*. *J Antimicrob Chemother* 2008; **62**: 1466–8.

8 Mlinarić-Missoni E, Hatvani L, Kocsubé S *et al*. *Cyberlindnera fabianii* in the neonatal and paediatric intensive care unit: case reports. *JMM Case Reports* 2015; **2**: doi:10.1099/jmmcr.0.000032.

9 Szabó Z, Tóth B, Kovács M *et al*. Evaluation of the new Micronaut-*Candida* system compared to the API ID32C method for yeast identification. *J Clin Microbiol* 2008; **46**: 1824–5.

10 Clinical and Laboratory Standards Institute. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts—Fourth Edition: M27*. CLSI, Wayne, PA, USA, 2017.

11 Clinical and Laboratory Standards Institute. *Performance Standards for Antifungal Susceptibility Testing of Yeasts—First Edition: M60*. CLSI, Wayne, PA, USA, 2017.

12 Clinical and Laboratory Standards Institute. *Epidemiological Cutoff Values for Antifungal Susceptibility Testing—Second Edition: M59*. CLSI, Wayne, PA, USA, 2018.

13 Pfaller MA, Espinel-Ingroff A, Canton E *et al*. Wild-type MIC distributions and epidemiological cutoff values for amphotericin B, flucytosine, and itraconazole and *Candida* spp. as determined by CLSI broth microdilution. *J Clin Microbiol* 2012; **50**: 2040–6.

14 Pfaller MA, Castanheira M, Diekema DJ *et al*. Triazole and echinocandin MIC distributions with epidemiological cutoff values for differentiation of wild-type strains from non-wild-type strains of six uncommon species of *Candida*. *J Clin Microbiol* 2011; **49**: 3800–4.

15 CDC. *Antifungal Susceptibility Testing and Interpretation/Candida auris/Fungal Diseases/*. 2019. https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html.

16 Perlin DS. Echinocandin resistance, susceptibility testing and prophylaxis: implications for patient management. *Drugs* 2014; **74**: 1573–85.

17 James KD, Laudeman CP, Malkar NB *et al*. Structure-activity relationships of a series of echinocandins and the discovery of CD101, a highly stable and soluble echinocandin with distinctive pharmacokinetic properties. *Antimicrob Agents Chemother* 2017; **61**: e01541-16.

18 Espinel-Ingroff A, Arendrup MC, Pfaller MA *et al*. Interlaboratory variability of caspofungin MICs for *Candida* spp. using CLSI and EUCAST methods: should the clinical laboratory be testing this agent? *Antimicrob Agents Chemother* 2013; **57**: 5836–42.

19 Fothergill AW, McCarthy DI, Albataineh MT *et al*. Effects of treated versus untreated polystyrene on caspofungin *in vitro* activity against *Candida* species. *J Clin Microbiol* 2016; **54**: 734–8.

20 Pfaller MA, Diekema DJ, Turnidge JD *et al*. Twenty years of the SENTRY Antifungal Surveillance Program: results for *Candida* species from 1997-2016. *Open Forum Infect Dis* 2019; **6** Suppl 1: S79–94.