

Rationale for EUCAST clinical breakpoints

Agent	Rezafungin	
Current version	2.0	26th June 2025
Previous versions	1.0	09 February 2024

Foreword

EUCAST

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is organised by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre for Disease Prevention and Control (ECDC), and the active national antimicrobial breakpoint committees in Europe. EUCAST was established by ESCMID in 1997, was restructured in 2001-2002 and has been in operation in its current form since 2002. The current remit of EUCAST is to harmonise clinical breakpoints for existing drugs in Europe, to determine clinical breakpoints for new drugs, to set epidemiological (microbiological) breakpoints, to revise breakpoints as required, to harmonise methodology for antimicrobial susceptibility testing, to develop a website with MIC and zone diameter distributions of antimicrobial agents for a wide range of organisms and to liaise with European governmental agencies and European networks involved with antimicrobial resistance and resistance surveillance.

Information on EUCAST and EUCAST breakpoints is available on the EUCAST website at <http://www.EUCAST.org>.

EUCAST rationale documents

EUCAST rationale documents summarise the information on which the EUCAST clinical breakpoints are based.

Availability of EUCAST documents

All EUCAST documents are freely available from the EUCAST website at <http://www.EUCAST.org>.

Citation of EUCAST documents

The copyright of all documents and data published on the EUCAST website remains with EUCAST. All are freely available for re-use if reference to the EUCAST website is given and documents and data are not resold. Any secondary publication of the data must be referenced with the declaration that "These data have (or this document has) been produced in part under ECDC service contracts, is made available at no cost by EUCAST and can be accessed freely on the EUCAST website www.eucast.org. EUCAST recommendations are frequently updated and the latest versions are available at www.eucast.org."

This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Rezafungin: Rationale for the clinical breakpoints, version 2.0 2025. <http://www.eucast.org>."

1. Introduction

Rezafungin is a next-generation antifungal agent derived from the echinocandin-class agent, anidulafungin. The compound has a molecular weight of 1226 g/mol for the base compound and 1285 g/mol for the acetate salt, the latter being the formulated drug product. Rezafungin is a cyclic hexapeptide with a lipophilic tail. It displays potency and spectrum of activity *in vitro* typical of the echinocandins but has a distinct structural feature, a choline moiety at the C5 ornithine position, that confers greater metabolic stability (1, 2), resulting in a longer half-life (3, 4). This enables a once-weekly dosing regimen compared with the once-daily regimen required by the currently marketed echinocandins.

The *in vitro* activity of rezafungin against species of *Candida* is not uniform. The species more frequently associated with human infections include *C. albicans*, *C. auris*, *C. dubliniensis*, *C. glabrata*, *C. krusei*, *C. parapsilosis* and *C. tropicalis*, of which all but *C. parapsilosis* exhibit low rezafungin MIC values. The underlying reason for the higher MICs for *C. parapsilosis* (and *C. guilliermondii*) is the presence of a naturally occurring amino-acid substitution at a hot spot region of the target enzyme, known to be involved in resistance in other species. Therefore, species identification is important and every attempt should be made to identify *Candida* to species level (5).

Some isolates have acquired resistance with elevated MICs and mutations in *fks* target genes that conferred echinocandin cross-resistance (6). As with the other echinocandins, rezafungin is not fungicidal against moulds but does show activity *in vitro* and in animal models against *Aspergillus* spp. (including azole-resistant strains) and *Pneumocystis* (7, 8).

The propensity for development of resistance to rezafungin during *in vitro* spontaneous mutation frequency and serial passage assays was consistent with that observed for comparator echinocandins (9). Rezafungin mutants selected *in vitro* had mutations within hot spot regions of *FKS1* and *FKS2*, as expected, and conferred cross-resistance with other echinocandins (9).

Rezafungin is indicated for treatment of candidaemia and invasive candidiasis.

2. Dosage

Standard dose schedule	Treatment of candidaemia and invasive candidiasis: IV infusion: single 400 mg loading dose on Day 1, followed by 200 mg dose on Day 8 and once weekly thereafter
Maximum dose schedule	As above
Available formulations	IV

3a. MIC distributions* (numbers) and epidemiological cut-off (ECOFF) values (mg/L)

Organism	N	0.0002	0.0005	0.001	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	>8	ECOFF
<i>Candida albicans</i>	154	1	9	71	56	13	3			1									0.008
<i>Candida auris</i>	149				2	6	22	44	50	17	5	2		1					0.125
<i>Candida dubliniensis</i>	151	1	2	8	36	81	21	2											0.016
<i>Candida glabrata</i>	153				2	41	100	8	1				1						0.016
<i>Candida krusei</i>	154				1		59	86	6	2									0.03
<i>Candida parapsilosis</i>	203										2	24	60	76	30	10		1	4
<i>Candida tropicalis</i>	153				4	54	62	32	1										0.03

* MIC distribution data presented for each species is the combined data from 6 laboratories (5 in Europe and 1 in the US) (10). Rezafungin MIC values were determined in accordance with EUCAST E.Def 7.4 broth microdilution methodology, which specifies the use of RPMI 1640 assay medium containing 0.002% Tween 20 for rezafungin testing (11).

The table includes minimum inhibitory concentration (MIC) distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-off (ECOFF) values and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms. They should not be used to infer resistance rates. When there is insufficient evidence, no ECOFF has been determined (ND).

3b. MIC distributions (%)# and epidemiological cut-off (ECOFF) values (mg/L)

Organism *	N	0.0002	0.0005	0.001	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	>8	ECOFF
<i>Candida albicans</i>	154	1	6	46	36	8	2			1									0.008
<i>Candida auris</i>	149				1	4	15	30	34	11	3	1		1					0.125
<i>Candida dubliniensis</i>	151	1	1	5	24	54	14	1											0.016
<i>Candida glabrata</i>	153				1	27	65	5	1										0.016
<i>Candida krusei</i>	154				1		38	56	4	1									0.03
<i>Candida parapsilosis</i>	203										1	12	30	37	15	5			4
<i>Candida tropicalis</i>	153				3	35	41	21	1										0.03

Percentage values are rounded to nearest whole number. Consequently, the sum can deviate slightly from 100%.

* MIC distribution data presented for each species is the combined data from 6 laboratories (5 in Europe and 1 in the US) (10). Rezafungin MIC values were determined in accordance with EUCAST E.Def 7.4 broth microdilution methodology which specifies the use of RPMI 1640 assay medium containing 0.002% Tween 20 for rezafungin testing (11).

The table includes minimum inhibitory concentration (MIC) distributions available at the time breakpoints were set. They represent combined distributions from multiple sources and time periods. The distributions are used to define the epidemiological cut-off (ECOFF) values and give an indication of the MICs for organisms with acquired or mutational resistance mechanisms. They should not be used to infer resistance rates. When there is insufficient evidence, no ECOFF has been determined (ND).

4. Pharmacokinetics (PK)

Dosage (mg)	400 mg single dose IV infusion over 1 h (Healthy subjects)	400 mg single dose IV infusion over 1 h (Patients)
C_{max} (mg/L), mean±SD (n)	22.24±4.79 ^a (n=94)	18.76±6.45 ^d (n=167)
C_{min} (mg/L), mean±SD (n)	3.33±0.74 ^a (n=94)	2.29±1.07 ^d (n=167)
CL (mL/min), mean±SD (n)	3.59±0.66 ^b (n=6)	
t_{1/2} (h), mean±SD (n)	132.76±12.25 ^b (n=6)	
AUC₀₋₁₆₈ (mg·h/L), mean±SD (n)	1091.51±215.16 ^a (n=94)	798.61±295.12 ^d (n=167)
Fraction unbound (%)	2.6 ^c (range 2.0-3.6%)	^e
V_{ss} (L), mean±SD (n)	34.43±5.24 ^b (n=6)	
Comments	<p>Abbreviations: C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; Cl, total body clearance, t_{1/2}, terminal half-life; AUC₀₋₁₆₈, area under the plasma concentration time curve from 0 – 168 h post dose; V_{ss}, volume of distribution at steady state.</p> <p>Explanatory footnotes:</p> <p>^a Exposure predicted for healthy subjects derived from a population PK model based upon pooled data from 5 Phase 1 studies, a Phase 2 study (12), and a Phase 3 study (13), consisting of 277 subjects in total, of which 167 were diagnosed with candidaemia and/or invasive candidiasis (Data on File).</p> <p>^b Data from Single Ascending Dose study in healthy subjects receiving rezafungin administered as a single 400 mg dose (IV infusion over 1 hour).</p> <p>^c Protein binding determined in healthy human plasma using the ultrafiltration method (14, 15).</p> <p>^d Exposure predicted for patients derived from the population PK (Data on File).</p> <p>^e The free fraction in patients has been estimated to be approximately 2.7-fold higher than in healthy subjects (Data on File).</p> <p>Cells are left empty when data are not available.</p>	

5. Pharmacodynamics (PD)						
Animal data	Neutropenic Invasive-Candidiasis Mouse Model (3 mice per group)					
PK/PD index	<i>C. albicans</i> ^a (4 strains) (16)	<i>C. dubliniensis</i> ^b (4 strains) (17)	<i>C. glabrata</i> ^c (3 strains) (16)}	<i>C. parapsilosis</i> ^d (3 strains) (16)	<i>C. tropicalis</i> ^e (4 strains) (17)	<i>C. auris</i> ^f (4 strains) (18)
fAUC₀₋₁₆₈/MIC for stasis (min – max)	317 (118-786)	485 (220-1346)	2.8 (0.5-6.7)	23.1 (19.5-26.7) ^g	460 (343-881)	127 (0.6-190)
fAUC₀₋₁₆₈/MIC for 1 log reduction in CFU (min – max)	508 (271-1476)	1954 (462-3314)	16.8 (2.9-20.3)	- ^h	796 (564-1757)	307 (219-849)
Comments	<p>MICs for strains included:</p> <p>^a <i>C. albicans</i> Rezafungin MICs = 0.002, 0.002, 0.004, 0.008 mg/L</p> <p>^b <i>C. dubliniensis</i> Rezafungin MICs = 0.004, 0.004, 0.004, 0.008 mg/L</p> <p>^c <i>C. glabrata</i> Rezafungin MICs = 0.016, 0.5, 0.5 mg/L</p> <p>^d <i>C. parapsilosis</i> Rezafungin MICs = 0.25, 0.5, 1 mg/L</p> <p>^e <i>C. tropicalis</i> Rezafungin MICs = 0.002, 0.004, 0.008, 0.008 mg/L</p> <p>^f <i>C. auris</i> Rezafungin MICs = 0.004, 0.016, 0.03, 16 mg/L</p> <p>^g Stasis was achieved in only 2 isolates</p> <p>^h 1 log reduction was not obtained</p> <p>The fAUC₀₋₁₆₈/MIC targets are calculated using the fAUC₀₋₁₆₈ cited in the relevant reference based on 99.2% protein binding in healthy mice and the median MIC determined using EUCAST E.Def 7.4 broth microdilution methodology containing 0.002% Tween 20.</p> <p>Cells are left empty when data are not available.</p>					

6. Monte Carlo simulations and PK/PD cut-off values

A population PK model was developed based upon data from five Phase 1 studies, a Phase 2 study and a Phase 3 study, and included data from healthy volunteers, hepatically impaired subjects and patients with candidaemia and/or invasive candidiasis (12, 13). Data from both single- and multiple-dose studies, with doses ranging from 50 mg to 1400 mg were included in this analysis. The final rezafungin population PK model was a 3-compartment model with first-order elimination characterised by the PK parameters clearance (CL), central volume of distribution (V1), shared parameter of peripheral volume of distribution for both peripheral compartments (V23), intercompartmental clearance 1 (Q2), and intercompartmental clearance 2 (Q3). Covariate analysis identified the following as statistically significant predictors of PK variability: albumin on peripheral volume (V23), body surface area (BSA) on clearance (CL), and the central and peripheral volumes (V1 and V23); and disease state on clearance and on central volume (CL and V1). Disease state was defined as patients from the Phase 2 and Phase 3 studies and hepatically impaired subjects. (The exact values of CL, VL, V23 have not been disclosed by the company). The variability model included inter-individual variability (IIV) in CL, V1, and V23 and their covariabilities, and a proportional residual variability (RV) model. All fixed and random effect parameters including those of the covariance terms were estimated with reasonable precision (< 39 % relative standard error [RSE]). The magnitudes of the IIV were moderate for all parameters: 30.5 %CV for CL, 37.6 %CV for V1, and 29.3 %CV for V23. Eta (η) shrinkage was low for all parameters (< 11%) and the RV was also low (9.74 %CV). Model evaluation demonstrated that the model, adequately described the PK data of rezafungin.

The final rezafungin population PK model and the distributions of the demographic covariates (determined to be significant predictors of rezafungin PK) of candidaemia and/or invasive candidiasis patients enrolled in the Phase 2 (STRIVE) and Phase 3 (ReSTORE) studies were used to simulate a total of 100 trials of 1,000 virtual patients each (100,000 patients total). Vectors of covariates were randomly resampled from the observed Phase 2 and Phase 3 distributions and assigned to the 100,000 virtual patients. The virtual patients were assigned the dosing regimen of interest (IV rezafungin: 400 mg for Week 1 followed by 200 mg weekly for 3 weeks). All fixed and random effect parameters were fixed to the final estimates and individual Bayesian estimates of PK parameters were simulated for each patient. Using each simulated patient's Bayesian PK parameters and dose amounts, simulations were performed to predict rezafungin concentration-time profiles for 168 hours after each weekly dose and R software was used to integrate the predicted concentration-time profiles to obtain weekly estimates of AUC₀₋₁₆₈. For the purpose of target attainment analyses, AUC₀₋₁₆₈ after the first dose was used (Day 1). A plasma protein binding value of 97.4% (free fraction 2.6%) was used to adjust for unbound "free" drug AUC₀₋₁₆₈, and to calculate separate *f*AUC₀₋₁₆₈/MIC ratios for the range of MIC values from *Candida* species collected in patients with candidaemia and/or invasive candidiasis enrolled in the STRIVE and ReSTORE studies. The plasma protein binding of 97.4% was determined in healthy human plasma using the ultrafiltration method (Data on File) (15) and is a conservative assessment of the free fraction as the free fraction in patients has been estimated to be approximately 2.7-fold higher than in healthy subjects (Data on File). Therefore, PK/PD targets may be overestimated by at least one dilution. The exposures outputs from the population PK simulations are shown below in Table 1.

Table 1 Exposure Outputs from the Monte Carlo Simulation using the Population PK model for Rezafungin

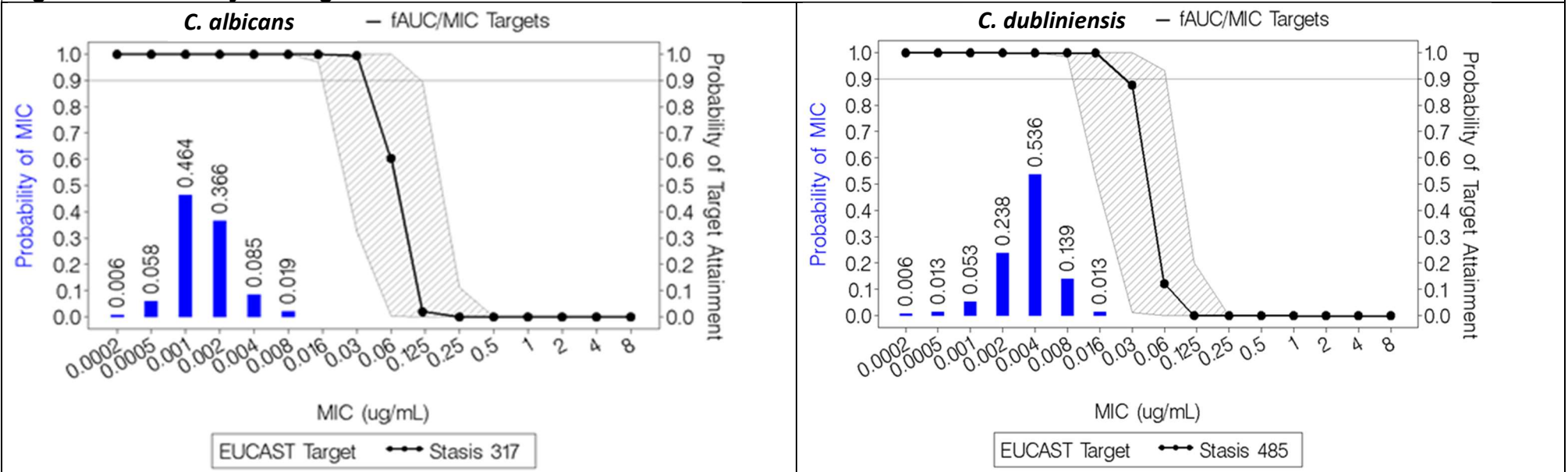
Exposure Measures Week 1, n = 100000	Mean±SD (10 th , 90 th percentile)
Rezafungin AUC ₀₋₁₆₈ (mg·h/L)	826.68±252.23 (539.69, 1157.94)
Rezafungin C _{max} (mg/L)	19.20±5.92 (11.94, 27.05)
Rezafungin C _{min} (mg/L)	2.35±0.89 (1.37, 3.51)
Rezafungin <i>f</i> AUC ₀₋₁₆₈ (mg·h/L)	21.49±6.56 (14.03, 30.11)

Abbreviations: AUC₀₋₁₆₈, area under the concentration-time curve from time 0 to 168 hours; C_{max}, maximum drug concentration; C_{min}, minimum drug concentration; *f*, free; n, number of virtual patients; SD, standard deviation.

As stasis has been shown to best correlate with clinical outcome for invasive candidiasis for other echinocandins (19), percent probabilities of achieving the nonclinical PK/PD targets associated with net fungal stasis for *C. albicans*, *C. dubliniensis*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. auris* were calculated and compared to the frequency distribution of MIC values provided in Section 3.

The probability of target attainment against *Candida* species using the median (solid black line), minimum and maximum (shaded region) stasis targets shown in Section 6 is displayed in Figures 1 to 3, and the line plots of mean $fAUC_{0-168}/MIC$ ratios versus MIC by species is shown in Figure 4.

Figure 1 Probability of Target Attainment for *C. albicans* and *C. dubliniensis*



A $fAUC_{0-168}/MIC$ target of 317 and a $\geq 95\%$ target attainment rate for *C. albicans* results in a PK/PD susceptible cut-off value of 0.03 mg/L for a rezafungin dose of 400 mg IV, which is the loading dose for the clinical dosing regimen (400 mg Day 1 followed by 200 mg on Day 8 and 200 mg weekly thereafter). There is no higher dose, so the PK/PD resistant cut-off value is >0.03 mg/L.

A $fAUC_{0-168}/MIC$ target of 485 and a $\geq 95\%$ target attainment rate for *C. dubliniensis* results in a PK/PD susceptible cut-off value of 0.016 mg/L for a rezafungin dose of 400 mg IV, which is the loading dose for the clinical dosing regimen (400 mg Day 1 followed by 200 mg on Day 8 and 200 mg weekly thereafter). There is no higher dose, so the PK/PD resistant cut-off value is >0.016 mg/L.

Figure 2 Probability of Target Attainment for *C. glabrata* and *C. parapsilosis*

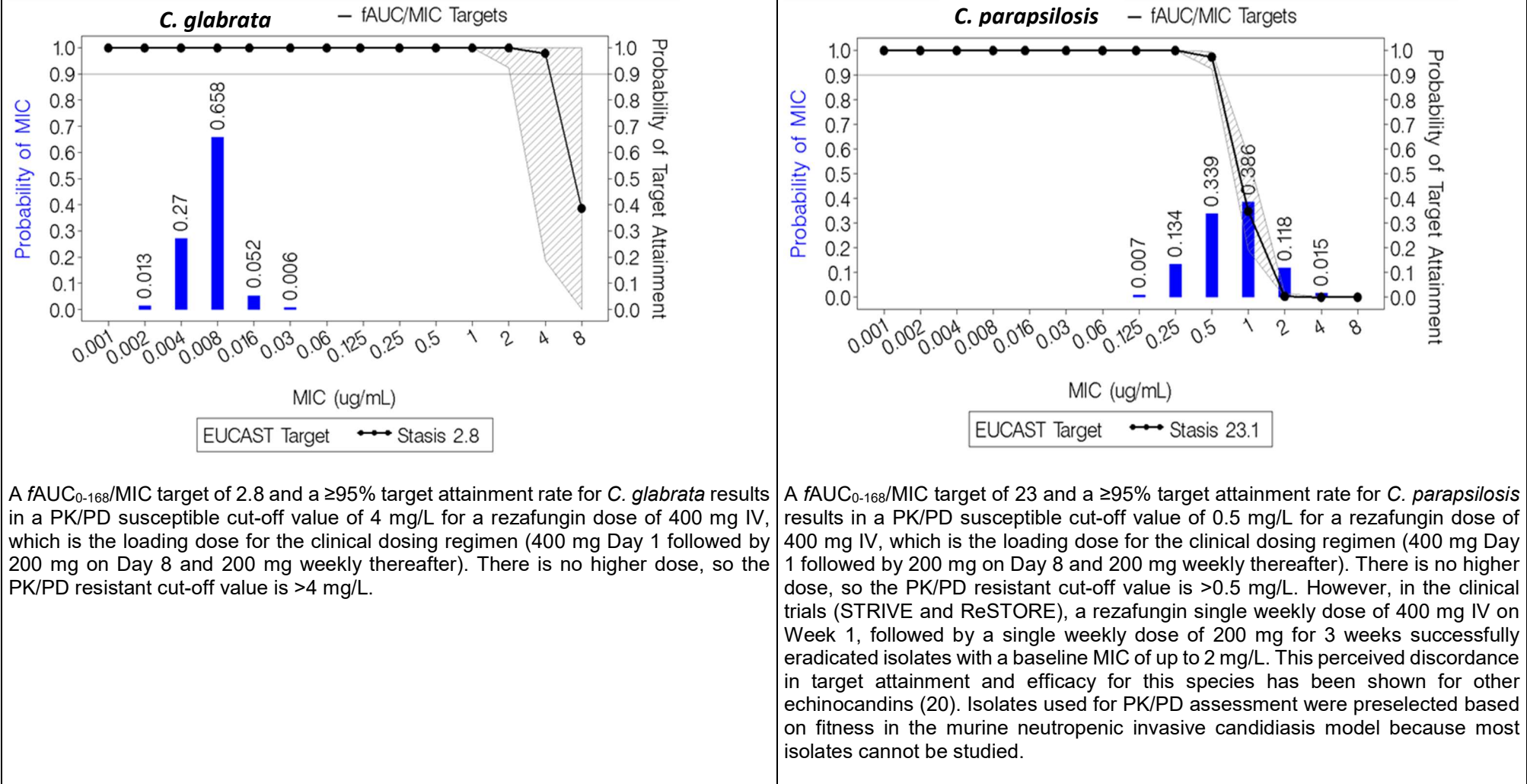
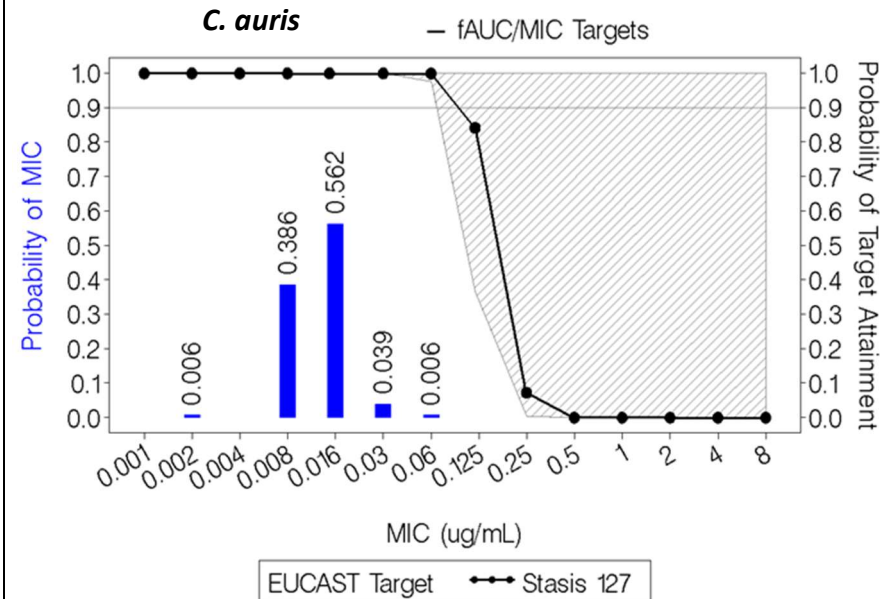
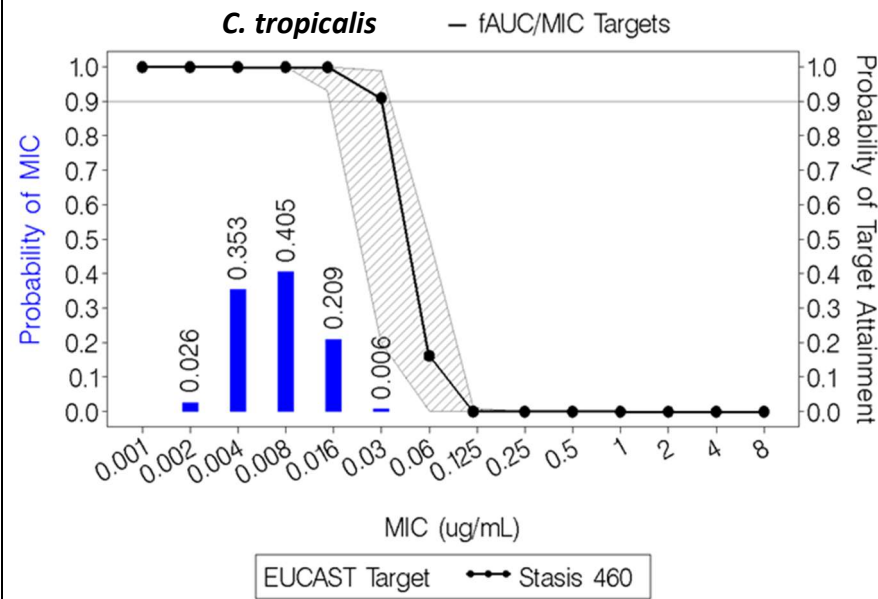


Figure 3 Probability of Target Attainment for *C. tropicalis* and *C. auris*



A $fAUC_{0-168}/MIC$ target of 460 and a $\geq 95\%$ target attainment rate for *C. tropicalis* results in a PK/PD susceptible cut-off value of 0.016 mg/L for a rezafungin dose of 400 mg IV, which is the loading dose for the clinical dosing regimen (400 mg Day 1 followed by 200 mg on Day 8 and 200 mg weekly thereafter). There is no higher dose, so the PK/PD resistant cut-off value is >0.016 mg/L.

A $fAUC_{0-168}/MIC$ target of 127 and a $\geq 95\%$ target attainment rate for *C. auris* results in a PK/PD susceptible cut-off value of 0.06 mg/L for a rezafungin dose of 400 mg IV, which is the loading dose for the clinical dosing regimen (400 mg Day 1 followed by 200 mg on Day 8 and 200 mg weekly thereafter). There is no higher dose, so the PK/PD resistant cut-off value is >0.06 mg/L.

Figure 4 Lineplots of mean $fAUC_{0-168}/MIC$ ratios vs. MIC, by species

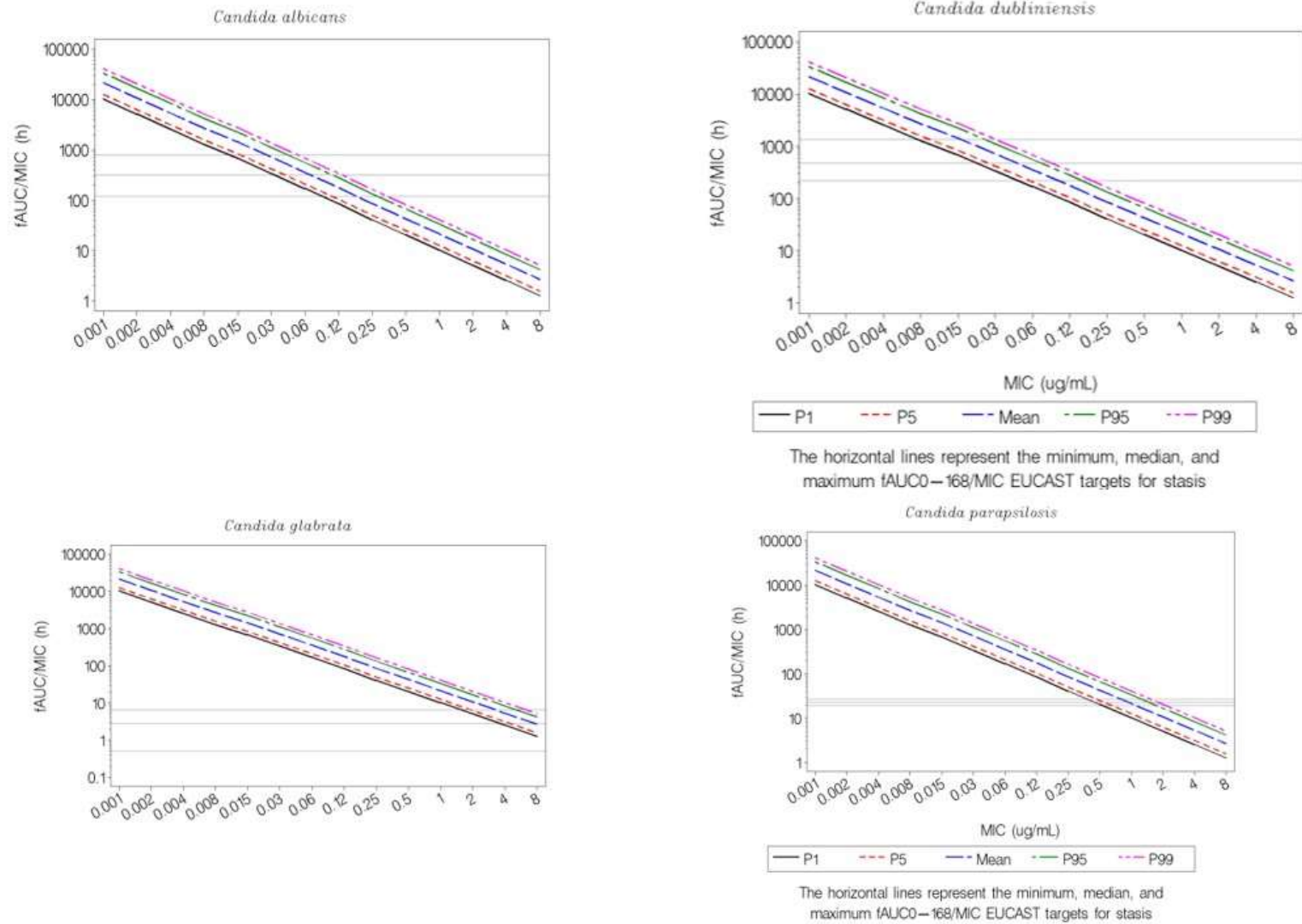
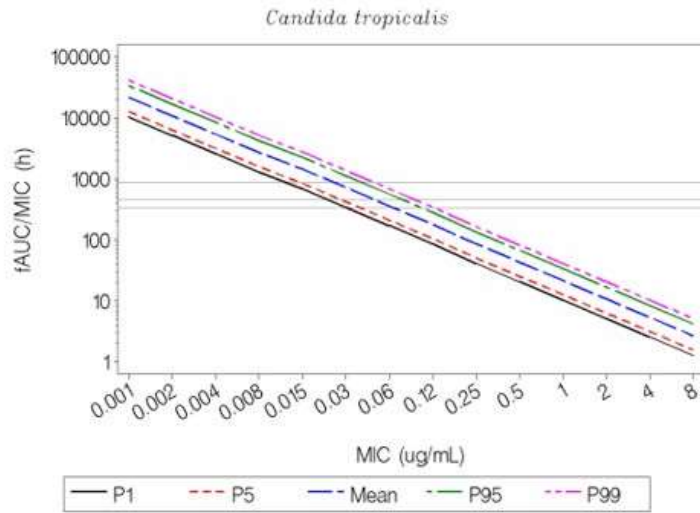
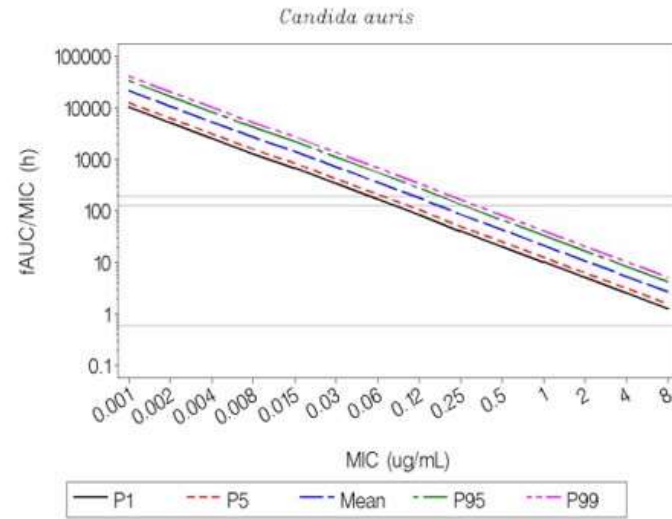


Figure 4 cont. Lineplots of mean $fAUC_{0-168}/MIC$ ratios vs. MIC, by species



The horizontal lines represent the minimum, median, and maximum $fAUC_{0-168}/MIC$ EUCAST targets for stasis



The horizontal lines represent the minimum, median, and maximum $fAUC_{0-168}/MIC$ EUCAST targets for stasis

7. Clinical data

The efficacy and safety of rezafungin in subjects with candidaemia (C) or invasive candidiasis (IC) have been assessed in two clinical studies:

STRIVE, a Phase 2, multicentre, prospective randomised, double-blind study of rezafungin (IV) or caspofungin (IV) with optional oral step-down therapy (12). The primary efficacy outcome of overall response at Day 14 was 60.5% and 76.1% for rezafungin Group 1 and Group 2, respectively, versus 67.2% for caspofungin with oral step-down therapy. The indeterminate rate was high in rezafungin Group 1 (13.2%) compared with Group 2 (6.5%) and caspofungin (4.9%). The all-cause mortality (ACM) rate at Day 30 in the microbiological intent to treat (mITT) population was 15.8% (12/76) in Group 1, 4.3% (2/46) in Group 2, and 13.1% (8/61) in the caspofungin group.

ReSTORE, a Phase 3, multicentre, prospective, randomised double-blind, double-dummy, efficacy, and safety study of rezafungin (IV) versus caspofungin (IV) followed by optional oral fluconazole step-down therapy (in qualifying subjects) in cases with C/IC (13). Non-inferiority was demonstrated for the EMA primary efficacy outcome of global response at Day 14 for rezafungin compared with caspofungin. The percentage of subjects with a global cure at the Day 14 visit was comparable between treatment groups (59.1% rezafungin vs. 60.6% caspofungin, treatment difference = -1.1 [95% CI: -14.9 to 12.7]). The primary reason for failure in both treatment groups was death (10 and 9, rezafungin and caspofungin subjects, respectively) and new or prolonged antifungal therapy (12 and 9 rezafungin and caspofungin subjects, respectively). The number of subjects with an indeterminate response was 10.8% and 8.5% for rezafungin and caspofungin subjects, respectively.

The pooled mycological response rates by baseline species in the STRIVE and ReSTORE studies for rezafungin at the recommended dose (400 mg week 1 followed by 200 mg weekly) and caspofungin are shown in the table below.

Organism	5-Day Mycological Response (Pooled - n/N [%])		14-Day Mycological Response (Pooled - n/N [%])	
	Rezafungin 400/200 mg (N=139)	Caspofungin 70/50 mg (N=155)	Rezafungin 400/200 mg (N=139)	Caspofungin 70/50 mg (N=155)
<i>C. albicans</i>	42/59 (71.2)	46/69 (66.7)	40/59 (67.8)	46/69 (66.7)
<i>C. dubliniensis</i>	3/3	2/2	3/3	2/2
<i>C. glabrata</i>	29/38 (76.3)	21/35 (60.0)	32/38 (84.2)	22/35 (62.9)
<i>C. krusei</i>	2/5	2/3	2/5	3/3
<i>C. parapsilosis</i>	11/14 (78.6)	18/27 (66.7)	11/14 (78.6)	19/27 (70.4)
<i>C. tropicalis</i>	22/27 (81.5)	12/22 (54.5)	20/27 (74.1)	14/22 (63.6)
<i>C. guilliermondii</i>	1/2	-	1/2	-
<i>C. lusitaniae</i>	1/1	1/1	1/1	1/1
<i>C. metapsilosis</i>	2/2	-	2/2	-
<i>C. intermedia</i>	-	1/1	-	1/1
<i>C. kefyr</i>	-	1/1	-	1/1
<i>C. nivariensis</i>	-	1/1	-	1/1

The pooled mycological response rates by *Candida* species and MIC values from the STRIVE and ReSTORE studies for rezafungin at the recommended dose (400 mg week 1 followed by 200 mg weekly) are shown in the table below.

Organism	Mycological response at:	Subjects with favourable outcome n/N (Total no. of subjects) at indicated baseline MIC [mg/L] (%)														
		0.0002	0.0005	0.001	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4
<i>C. albicans</i>	Day 5		2/4	21/25 (84.0)	14/22 (63.6)	4/7										
	Day 14		3/4	18/26 (69.2%)	13/22 (59.1)	4/7										
<i>C. dubliniensis</i>	Day 5					2/2 ^a										
	Day 14					2/2 ^a										
<i>C. glabrata</i>	Day 5					6/7	22/27 (81.5)	1/3					0/1			
	Day 14					5/7	25/27 (92.6)	1/3					1/1			
<i>C. krusei</i>	Day 5						0/1	2/4								
	Day 14						1/1	1/4								
<i>C. parapsilosis^b</i>	Day 5											0/1	1/2	9/9	1/1	
	Day 14											1/1	1/2	8/9	1/1	
<i>C. tropicalis</i>	Day 5				1/1	7/7	14/18 (77.8)	0/1								
	Day 14				1/1	6/7	13/18 (72.2)	0/1								

a. Of the 3 isolates obtained at baseline, a baseline MIC for 1 isolate is not available (failed to grow).

b. Treatment groups are based on the actual treatment subjects received. Two subjects randomized to rezafungin treatment group received caspofungin.

In vivo effect of rezafungin against *C. auris* specifically has been demonstrated in animal models and found at least comparable to that of the other echinocandins (17, 21). So far, human clinical data is lacking.

8. Clinical breakpoints

Non-species-related breakpoints	There is insufficient evidence to set non-species-related breakpoints.			
Species-related breakpoints	Organism group	MIC breakpoints (mg/L)		Notes
		S ≤	R >	
	<i>C. albicans</i>	0.008	0.008	
	<i>C. auris</i>	IE	IE	
	<i>C. dubliniensis</i>	0.016	0.016	
	<i>C. glabrata</i>	0.016	0.016	
	<i>C. krusei</i>	0.03	0.03	
	<i>C. parapsilosis</i>	4	4	
	<i>C. tropicalis</i>	0.03	0.03	
	<p>Breakpoints were based on microbiological data and clinical experience from the STRIVE and ReSTORE clinical trials. Animal PK/PD studies suggest higher PK/PD cut-off values than the corresponding ECOFFs yet within 2 two-fold dilutions for <i>C. albicans</i>, <i>C. dubliniensis</i> and <i>C. tropicalis</i>, and 8 two-fold dilutions for <i>C. glabrata</i> whereas the PK/PD cut-off value for <i>C. parapsilosis</i> is 3 two-fold dilutions lower than the ECOFF.</p> <p>In the clinical trials, all but one case involved infections due to wild-type isolates. One expanded access case described successful suppression with rezafungin over 13 months of an infection involving foreign body and mediastinitis due to a multidrug resistant <i>C. glabrata</i> with a D666Y alteration in <i>Fks2</i> (22).</p> <p>As the clinical experience with infections due to non-wild-type strains is so far very limited, EUCAST has set clinical breakpoints at the ECOFFs. These will be reviewed and revised as needed when more data become available.</p>			
Species without breakpoints	Clinical breakpoint setting requires information on species-specific clinical outcome data, which are generally non-existent for species other than the common pathogens. For interpretation of MICs for species for which clinical breakpoints have not been set, please consult the document “EUCAST guidance on Interpretation of MICs for rare yeast without breakpoints in breakpoint tables” found on the EUCAST website (What to do when there are no breakpoints - guidance for rare yeasts).			
Clinical qualifications	Rezafungin is indicated for the treatment of both candidemia (a bloodstream infection caused by <i>Candida</i> species) and invasive candidiasis (a severe, deep-seated <i>Candida</i> infection) in adult patients, particularly those who have limited or no alternative treatment options.			
Dosage	Breakpoints apply to the standard dose of rezafungin of a single IV infusion of 400 mg on Day 1, followed by a single IV infusion of 200 mg weekly thereafter for at least 14 days.			
Additional comment	The majority of isolates tested resistant to anidulafungin or micafungin are also resistant to rezafungin.			

References

1. Ong V, Hough G, Schlosser M, Bartizal K, Balkovec JM, James KD, Krishnan BR. Preclinical evaluation of the stability, safety, and efficacy of CD101, a novel echinocandin. *Antimicrob Agents Chemother.* 2016;60(11):6872-9.
2. Sofjan AK, Mitchell A, Shah DN, Nguyen T, Sim M, Trojcek A, 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. Ong V, James KD, Smith S, Krishnan BR. Pharmacokinetics of the novel echinocandin CD101 in multiple animal species. *Antimicrob Agents Chemother.* 2017;61(4):01626-16.
4. Sandison T, Ong V, Lee J, Thye D. Safety and pharmacokinetics of CD101 IV, a novel echinocandin, in healthy adults. *Antimicrob Agents Chemother.* 2017;61(2):e01627-16.
5. Hall D, Bonifas R, Stapert L, Thwaites M, Shinabarger DL, Pillar CM. In vitro potency and fungicidal activity of CD101, a novel echinocandin, against recent clinical isolates of *Candida* spp. *Diagn Microbiol Infect Dis.* 2017;89(3):205-11.
6. Helleberg M, Jorgensen KM, Hare RK, Datcu R, Chowdhary A, Arendrup MC. Rezafungin in vitro activity against contemporary nordic clinical candida isolates and candida auris determined by the EUCAST reference method. *Antimicrob Agents Chemother.* 2020;64(4):e02438-19.
7. Cushion MT, Ashbaugh A. The long-acting echinocandin, rezafungin, prevents *Pneumocystis* pneumonia and eliminates *Pneumocystis* from the lungs in prophylaxis and murine treatment models. *J Fungi (Basel).* 2021;7(9):747.
8. Wiederhold NP, Locke JB, Daruwala P, Bartizal K. Rezafungin (CD101) demonstrates potent in vitro activity against *Aspergillus*, including azole-resistant *Aspergillus fumigatus* isolates and cryptic species. *J Antimicrob Chemother.* 2018;73(11):3063-7.
9. Locke JB, Almaguer AL, Zuill DE, Bartizal K. Characterization of in vitro resistance development to the novel echinocandin CD101 in *Candida* species. *Antimicrob Agents Chemother.* 2016;60(10):6100-7.
10. Arendrup MC, Arikian-Akdagli S, Castanheira M, Guinea J, Locke JB, Meletiadis J, Zaragoza O. Multicentre validation of a modified EUCAST MIC testing method and development of associated epidemiologic cut-off (ECOFF) values for rezafungin. *J Antimicrob Chemother.* 2022;78(1):185-95.
11. Zuill DE, Almaguer AL, Donatelli J, Arendrup MC, Locke JB. Development and preliminary validation of a modified EUCAST yeast broth microdilution MIC method with Tween 20-supplemented medium for rezafungin. *J Antimicrob Chemother.* 2023;78(4):1102-10.
12. Thompson GR, Soriano A, Skoutelis A, Vazquez JA, Honore PM, Horcajada JP, et al. Rezafungin versus caspofungin in a phase 2, randomized, double-blind study for the treatment of candidemia and invasive candidiasis: the STRIVE trial. *Clin Infect Dis.* 2021;73(11):e3647-e55.
13. Thompson GR, 3rd, Soriano A, Cornely OA, Kullberg BJ, Kollef M, Vazquez J, et al. Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. *Lancet.* 2023;401(10370):49-59.
14. Bader JC, Lakota EA, Flanagan S, Ong V, Sandison T, Rubino CM, et al. Overcoming the resistance hurdle: pharmacokinetic-pharmacodynamic target attainment analyses for rezafungin (CD101) against *Candida albicans* and *Candida glabrata*. *Antimicrob Agents Chemother.* 2018;62(6):e02614-17.
15. Flanagan S, Sandison T, Locke JB, Ong V, Ye G, Bartizal K, Daruwala P. CD101 prophylactic dose rationale for prevention of *Aspergillus*, *Candida*, and *Pneumocystis* infections. *Biology of Blood and Marrow Transplantation.* 2018;24(3):S389-S90.
16. Lepak AJ, Zhao M, VanScoy B, Ambrose PG, Andes DR. Pharmacodynamics of a long-acting echinocandin, CD101, in a neutropenic invasive-candidiasis murine model using an extended-interval dosing design. *Antimicrob Agents Chemother.* 2018;62(2):e02154-17.
17. Lepak AJ, Zhao M, Andes DR. Determination of pharmacodynamic target exposures for rezafungin against *Candida tropicalis* and *Candida dubliniensis* in the neutropenic mouse disseminated candidiasis model. *Antimicrob Agents Chemother.* 2019;63(11):e01556-19.
18. Lepak AJ, Zhao M, Andes DR. Pharmacodynamic evaluation of rezafungin (CD101) against *Candida auris* in the neutropenic mouse invasive candidiasis model. *Antimicrob Agents Chemother.* 2018;62(11):e01572-18.
19. Lepak AJ, Andes DR. Antifungal pharmacokinetics and pharmacodynamics. *Cold Spring Harb Perspect Med.* 2014;5(5):a019653.
20. Andes D, Ambrose PG, Hammel JP, Van Wart SA, Iyer V, Reynolds DK, et al. Use of pharmacokinetic-pharmacodynamic analyses to optimize therapy with the systemic antifungal micafungin for invasive candidiasis or candidemia. *Antimicrob Agents Chemother.* 2011;55(5):2113-21.

21. Balazsi D, Toth Z, Locke JB, Borman AM, Forgacs L, Balla N, et al. In vivo efficacy of rezafungin, anidulafungin, caspofungin, and micafungin against four *Candida auris* clades in a neutropenic mouse bloodstream infection model. *J Fungi (Basel)*. 2024;10(9):617.
22. Adeel A, Qu MD, Siddiqui E, Levitz SM, Ellison RT, 3rd. Expanded access use of rezafungin for salvage therapy of invasive *Candida glabrata* infection: A case report. *Open Forum Infect Dis*. 2021;8(11):ofab431.