

Evaluation of Rezafungin on the Thermo Scientific Sensititre YeastOne Plate

K.L Hajek¹, D.T. Staats¹, M.M Hendrix¹, S.B. Killian¹, D. Paisey², K. Knight² James Bovill², B. Willinger³, M. Redell⁴, M. Ghannoum⁵, Y. Li⁵ P. Rhomberg⁶, A. Klauer⁶

¹Thermo Fisher Scientific, Cleveland, OH; ²Thermo Fisher Scientific, East Grinstead, UK; ³University Hospital AKH Vienna, Austria; ⁴Melinta Therapeutics, Parsippany, NJ; ⁵Case Western Reserve University, Cleveland, OH; ⁶JMI Laboratories, Coralville, IA

Abstract

Background

Rezafungin (RZF) is a novel echinocandin approved for treatment of candidemia and invasive candidiasis in patients with limited treatment options. RZF inhibits the 1,3-β-D-glucan synthase enzyme complex, which is present in fungal cell walls, but not in mammalian cells. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall of many fungi, including *Candida* species. An equivalency study was conducted to evaluate the performance of RZF on the Thermo Scientific™ Sensititre™ YeastOne™ system (East Grinstead, UK) in comparison to frozen broth microdilution (BMD) reference Plates prepared according to CLSI M27 methodology (Thermo Fisher Scientific, Oakwood Village, OH).

Methods

Five hundred and sixty four clinical and challenge *Candida* isolates were tested against RZF on frozen reference Plates and Sensititre YeastOne Plates. 15 isolates were tested in triplicate over three consecutive days at three sites on the Sensititre Plate to assess reproducibility of results. Isolates tested included: *C. glabrata*, *C. tropicalis*, *C. albicans*, *C. parapsilosis*, *C. lusitanae*, *C. krusei*, *C. guilliermondii*, *C. auris*. Quality control organisms included *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 using ranges provided in the CLSI M27M44S document. All isolates were tested in accordance with CLSI M27M44. Sensititre plates were read manually using the Thermo Scientific™ Sensititre™ Vizion™ System. Reference Plates were read using a manual mirror box.

Results

An essential agreement of 97.9% was achieved when comparing Sensititre YeastOne plates to CLSI frozen reference Plates when read on a manual mirror box. Reproducibility results showed 99.8% agreement compared to the modal value of the combined results. QC results met acceptance criteria throughout the study with 96.8% of QC results in range for *C. parapsilosis* ATCC 22019 and 99.2% of QC results in range for *C. krusei* ATCC 6258.

Conclusions

The Sensititre YeastOne Plate demonstrated equivalent performance compared to the reference method when testing RZF against *Candida* strains. With essential agreement of 97.9% and the high categorical agreement of 92.1% obtained in this study indicates that YeastOne plates are an acceptable method for susceptibility testing of isolates of *Candida* species against RZF.

Introduction

Rezafungin (RZF) is a novel echinocandin approved for treatment of candidemia and invasive candidiasis in patients with limited treatment options. RZF inhibits the 1,3-β-D-glucan synthase enzyme complex, which is present in fungal cell walls, but not in mammalian cells. This results in inhibition of the formation of 1,3-β-D-glucan, an essential component of the fungal cell wall of many fungi, including *Candida* species.

A 3-site trial was conducted to evaluate the performance of RZF on the commercially prepared dried Sensititre YeastOne susceptibility plate compared to the CLSI broth microdilution (BMD) frozen reference method (CLSI M27). The evaluation consisted of 564 clinical and challenge strains of indicated *Candida* species. Additionally, a selection of fifteen isolates were tested on the dried plates in triplicate over three days to assess the reproducibility of results on the Sensititre System (Table 4). CLSI recommended quality control organisms were run concurrently (Table 2).

Materials and methods

- Sensititre dried MIC susceptibility plates (Thermo Fisher Scientific, East Grinstead, UK) (Fig. 1)
- CLSI M27 reference broth microdilution method (BMD) plates (Thermo Fisher Scientific, Cleveland, OH)
- 564 clinical and challenge isolates (Table 1)
- 2 quality control strains (Table 2)
- 15 reproducibility isolates (Table 4).

Materials and Methods (cont.)

Table 1. Organisms Tested

Species	Quantity
<i>Candida auris</i>	20
<i>Candida albicans</i>	128
<i>Candida glabrata</i>	122
<i>Candida guilliermondii</i>	19
<i>Candida krusei</i>	68
<i>Candida lusitanae</i>	41
<i>Candida parapsilosis</i>	84
<i>Candida tropicalis</i>	82
Total	564

All 564 isolates were tested against RZF (0.008-8µg/mL) on both the Sensititre dried plates and the frozen reference BMD plates. Dried plates were tested according to manufacturer's instructions. Frozen reference plates were tested according to CLSI M27. Dried plates were read manually using the Sensititre Vizion and frozen plates were read using a manual mirror box.



Figure 1. Sensititre Dried MIC Susceptibility Plates

Table 2. Quality Control Strains

Quality Control Strain	CLSI QC Ranges (µg/ml) Rezafungin
<i>Candida krusei</i> ATCC 6258	0.015 – 0.12
<i>Candida parapsilosis</i> ATCC 22019	0.25 – 2

Recommended CLSI quality control organisms were tested daily. Colony counts were performed daily for each QC strain.

Results

Essential agreement

Essential agreement for RZF on the Sensititre YeastOne susceptibility plate compared to the frozen reference microdilution plate was calculated using the ±2 log₂ dilution standard applied to antifungal agents.

The essential agreement of RZF was 97.9% (Table 3).

Table 3. Essential Agreement of Indicated *Candida* Strains

Organism Group	Rezafungin						Total Bias
	Total of all Isolates	Total Evaluable Isolates	Essential Agreement of Total	Essential Agreement of Evaluable	% Essential Agreement of Total	% Essential Agreement of Evaluable	
<i>C. auris</i>	20	20	19	19	95.0%	95.0%	-75.0%
<i>C. albicans</i>	128	105	125	102	97.7%	97.1%	50.3%
<i>C. glabrata</i>	122	122	122	122	100.0%	100.0%	-41.0%
<i>C. guilliermondii</i>	19	19	19	19	100.0%	100.0%	-26.3%
<i>C. krusei</i>	68	68	68	68	100.0%	100.0%	19.1%
<i>C. lusitanae</i>	41	41	40	40	97.6%	97.6%	12.2%
<i>C. parapsilosis</i>	84	84	84	84	100.0%	100.0%	-26.2%
<i>C. tropicalis</i>	82	81	75	74	91.5%	91.4%	79.3%
Total	564	540	552	528	97.9%	97.8%	18.1%

Results (cont.)

Reproducibility

Reproducibility for RZF on the Sensititre susceptibility was 96.8% within ±1 log₂ dilution and 99.8% within ±2 log₂ dilution of the modal MIC (Table 4).

Table 4. Reproducibility of RZF on the Sensititre YeastOne Susceptibility Plate

RZF	Difference in the number of wells between test result and test mode								
	OFF-Scale	≤-3	-2	-1	0	+1	+2	≥+3	OFF-Scale
<i>C. parapsilosis</i>					27				
<i>C. guilliermondii</i>				11	16				
<i>C. krusei</i>			3	8	16				
<i>C. tropicalis</i>				7	20				
<i>C. glabrata</i>				4	23				
<i>C. Glabrata</i>				1	20	6			
<i>C. lusitanae</i>					13	8	6		
<i>C. albicans</i>	13				13	1			
<i>C. auris</i>				3	19	5			
<i>C. krusei</i>				2	19	6			
<i>C. parapsilosis</i>				1	26				
<i>C. krusei</i>					20	6	1		
<i>C. tropicalis</i>				1	26				
<i>C. albicans</i>					14	10	3		
<i>C. auris</i>					27				
TOTAL	13	3	38	299	42	9	1		
Reproducibility Essential Agreement	404/405 = 99.8%								

Table 5. Summary of MIC₅₀ and MIC₉₀ Values Obtained on the Sensititre YeastOne Susceptibility Plate Using Clinical Specimens

Species	MIC Range (µg/ml)	MIC ₅₀	MIC ₉₀
	RZF	RZF	RZF
<i>C. auris</i>	0.06-8	0.25	0.25
<i>C. albicans</i>	≤0.008 – 1	0.06	0.12
<i>C. glabrata</i>	0.015 – 0.5	0.03	0.12
<i>C. guilliermondii</i>	0.25 – 1	1	1
<i>C. krusei</i>	0.015 – 0.12	0.06	0.12
<i>C. lusitanae</i>	0.06 – 0.25	0.25	0.25
<i>C. parapsilosis</i>	0.5 – 1	1	1
<i>C. tropicalis</i>	0.015 – 1	0.12	0.25
Combined	≤0.008 – 1	0.12	1

Conclusions

This study validates that the Sensititre susceptibility system demonstrates an equivalent level of performance compared to the CLSI M27 reference broth microdilution plate when testing RZF against clinically relevant *Candida* isolates. This study suggests that the Sensititre System is an acceptable method for susceptibility testing of RZF according to the CLSI testing methodology.

References

1. CLSI. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. 4th ed. CLSI standard M27. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.
2. CLSI. Performance Standards for Antifungal Susceptibility Testing of Yeasts. 3rd ed. CLSI supplement M27M44S. Clinical and Laboratory Standards Institute; 2022.

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