# Impact of Elevated MIC Values on Echinocandin Pharmacokinetic-Pharmacodynamic *Candida glabrata* Target Attainment

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## INTRODUCTION

- Given the increasing prevalence of non-albicans Candida species [1], including *C. glabrata* and *C. auris*, which have higher predisposition to develop antifungal resistance (e.g., fks mutations conferring reduced susceptibility to echinocandins) [2, 3], re-evaluation of the pharmacokinetic-pharmacodynamic (PK-PD) target attainment of currently approved echinocandins is warranted.
- Rezafungin is a next generation echinocandin in development for treatment of candidemia and invasive candidiasis and for prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp. in blood and marrow transplantation.
- The completed Phase 3 treatment trial (ReSTORE; NCT03667690, [4]) demonstrated non-inferiority of rezafungin once weekly to caspofungin once daily in patients with candidemia and invasive candidiasis.
- Herein, we describe the conduct of PK-PD target attainment analyses performed to evaluate four echinocandins, anidulafungin, micafungin, caspofungin, and rezafungin, against *C. glabrata* in the context of isolates with elevated minimum inhibitory concentration (MIC) values [5, 6] and which build on previous analyses using rezafungin patient pharmacokinetic (PK) data [7].

## METHODS

- Monte Carlo simulations were conducted using published population PK models for anidulafungin, micafungin, caspofungin, and rezafungin [7, 8, 9, 10, 11].
- All simulations were conducted in R, statistical software version 4.0.4.
- A summary of relevant simulation inputs are provided in **Table 1**.
  - Dosing regimens were as per the labels for candidemia for once daily echinocandins [12, 13, 14] and as per the Phase 3 proposed clinical dosing regimen for rezafungin (400 mg Day 1, 200 mg once weekly thereafter).
  - Individual free-drug plasma area under the concentration time curve values from time zero to the end of the dosing interval of 24 or 168 h ($AUC_{0\text{-}tau}$) were calculated for each drug for 2 weeks.
  - MIC values corresponding to observed *C. glabrata* $MIC_{90}$ and $MIC_{100}$ (MICs for 90% and 100% of isolates tested, respectively) values for each drug were derived from 2018-2020 SENTRY Antifungal Surveillance Program *in vitro* data (n = 407) [5, 6].
  - Free-drug plasma $AUC_{0\text{-}tau}$:MIC ratio targets associated with return to baseline colony-forming units (CFU) (net fungal stasis) of *C. glabrata*, derived from neutropenic mouse disseminated candidiasis models, were used [15, 16].
- Percent probabilities of PK-PD attainment by MIC were calculated and evaluated relative to the MIC distributions for each echinocandin.
- Simulated echinocandin free-drug plasma $AUC_{0\text{-}tau}$:MIC ratio distributions relative to the $MIC_{90}$ and $MIC_{100}$ were also generated.

## METHODS

**Table 1.** Summary of drug-specific inputs for PK-PD target attainment simulations for *C. glabrata*

| Drug-specific input | Anidulafungin | Caspofungin | Micafungin | Rezafungin |
|---|---|---|---|---|
| Dosing regimen | 200 mg Day 1, 100 mg daily | 70 mg Day 1, 50 mg daily | 100 mg daily | 400 mg Day 1, 200 mg weekly |
| Free-fraction | 0.01 [12] | 0.03 [13] | 0.0025 [14] | 0.026 [17] |
| $MIC_{90}$ (mg/L) | 0.12 | 0.06 | 0.03 | 0.06 |
| $MIC_{100}$ (mg/L) | 4 | 8 | 4 | 2 |
| MIC references | Pfaller *et al.*, 2020 [5], Carvalhaes *et al.*, 2022 [6] | | | |
| PK-PD model | Neutropenic murine disseminated candidiasis | | | |
| PK-PD index | Free-drug plasma $AUC_{0\text{-}24}$:MIC ratio | | | Free-drug plasma $AUC_{0\text{-}168}$:MIC ratio |
| PK-PD target (net fungal stasis) | 13.7 | 2.9 | 3.9 | 1.4 |
| PK-PD references | Andes *et al.*, 2010 [15] | | | Lepak *et al.*, 2018 [16] |

Abbreviations: $AUC_{0\text{-}24}$ = area under the concentration-time curve from time 0 to 24 hours; $AUC_{0\text{-}168}$ = area under the concentration-time curve from time 0 to 168 hours; MIC = minimum inhibitory concentration; $MIC_{90}$ = minimum inhibitory concentration for ≥90% of isolates; $MIC_{100}$ = minimum inhibitory concentration for 100% of isolates; PK-PD = pharmacokinetic-pharmacodynamic

## RESULTS

- A summary of the PK-PD target attainment results at the $MIC_{90}$ and $MIC_{100}$ values for each drug is provided in **Table 2**.
- The FDA-approved dosing regimens for caspofungin, micafungin and anidulafungin did not achieve adequate percent probabilities of PK-PD target attainment at higher *C. glabrata* MIC values associated with their respective $MIC_{100}$ values (**Figure 1** and **Figure 2**), and anidulafungin also did not achieve adequate percent probabilities of PK-PD target attainment at its $MIC_{90}$ value.
- In contrast, the rezafungin dosing regimen used in the Phase 3 study program achieved percent probabilities of PK-PD target attainment of 100% at both the $MIC_{90}$ and $MIC_{100}$ values (**Figure 1** and **Figure 3**).

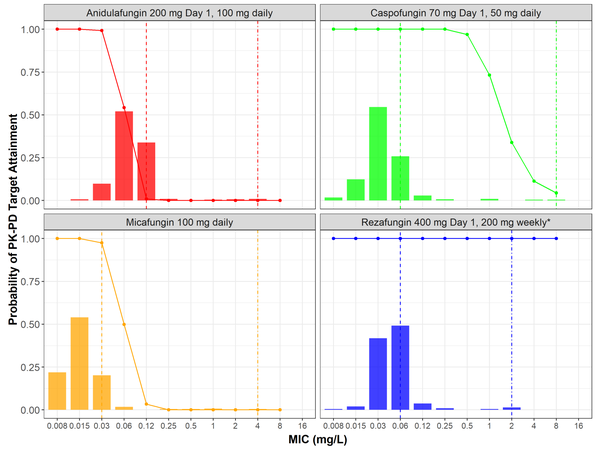
**Table 2.** Summary of percent probabilities of PK-PD target attainment for *C. glabrata* at $MIC_{90}$ and $MIC_{100}$ values by echinocandin

| Echinocandin | Percent probabilities of PK-PD target attainment by week and MIC value | | | |
|---|---|---|---|---|
| | Week 1[a] | | Week 2[b] | |
| | $MIC_{90}$ | $MIC_{100}$ | $MIC_{90}$ | $MIC_{100}$ |
| Anidulafungin | 0.85 | 0 | 0.95 | 0 |
| Caspofungin | 100 | 1.5 | 100 | 4.35 |
| Micafungin | 97.5 | 0 | 97.5 | 0 |
| Rezafungin | 100 | 100 | 100 | 100 |

Abbreviations: $MIC_{90}$ = minimum inhibitory concentration for ≥90% of isolates; $MIC_{100}$ = minimum inhibitory concentration for 100% of isolates; PK-PD = pharmacokinetic-pharmacodynamic
a. $AUC_{0\text{-}24}$ on Day 7 for anidulafungin, caspofungin, and micafungin, $AUC_{0\text{-}168}$ from Day 1 to Day 7 for rezafungin.
b. $AUC_{0\text{-}24}$ on Day 14 for anidulafungin, caspofungin, and micafungin, $AUC_{0\text{-}168}$ from Day 8 to Day 14 for rezafungin.

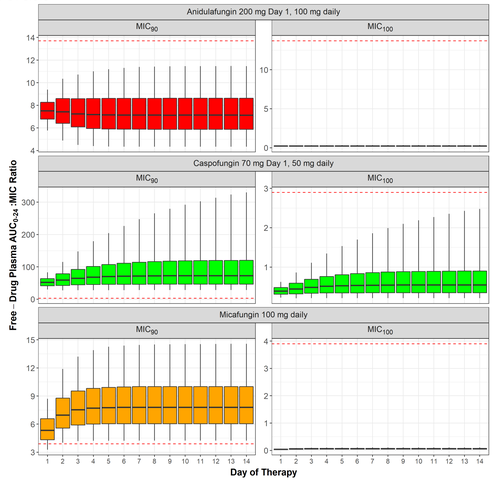
## RESULTS

**Figure 1.** Probabilities of PK-PD target attainment by MIC during Week 2 of therapy for echinocandins using *C. glabrata* PK-PD targets for net fungal stasis




Solid circles and lines show probabilities of PK-PD target attainment by MIC value during Week 2. Barplots show the MIC distributions for each echinocandin. Vertical dashed lines show $MIC_{90}$ value and vertical dot-dashed lines show the $MIC_{100}$ value for each echinocandin.

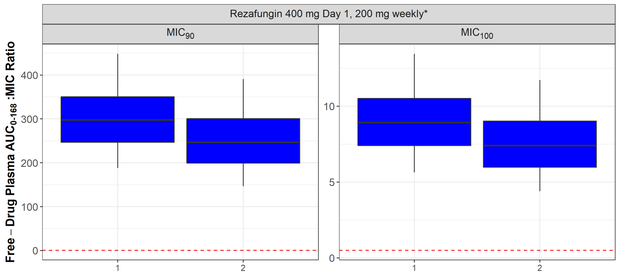
**Figure 2.** Comparison of simulated caspofungin, micafungin, and anidulafungin free-drug plasma AUC:MIC ratio distributions at the *C. glabrata* $MIC_{90}$ and $MIC_{100}$ values relative to PK-PD targets for net fungal stasis




Dashed red lines represent the free-drug AUC:MIC target value at the indicated MIC value.

## RESULTS

**Figure 3.** Comparison of simulated rezafungin free-drug plasma AUC:MIC ratio distributions at the *C. glabrata* $MIC_{90}$ and $MIC_{100}$ values relative to the PK-PD target for net fungal stasis




Dashed red lines represent the free-drug AUC:MIC target value at the indicated MIC.
*Rezafungin PK-PD target attainment is based on weekly free-drug plasma AUC:MIC ratio.

## CONCLUSIONS

- Relative to currently-available echinocandins, rezafungin given once weekly is predicted to have enhanced PK-PD target attainment for *C. glabrata* with higher MIC values, which may result in clinical efficacy in patients infected with less susceptible isolates.

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