Isavuconazole Pharmacodynamic Target Determination for Candida species in an In vivo Murine Disseminated Candidiasis Model

Running Title: Isavuconazole Pharmacodynamic Target Candida spp

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ABSTRACT

Pharmacodynamic studies with triazoles in the neutropenic murine disseminated candidiasis model have been extensively studied for *C. albicans*. They have consistently shown the pharmacodynamic index most closely correlated with efficacy is the 24 h area under the concentration-time curve (AUC)/MIC ratio and a target 24 h free drug AUC/MIC near 25 is associated with 50% of maximal microbiologic efficacy. We utilized this model to investigate the pharmacodynamics of isavuconazole. Isavuconazole pharmacokinetics were linear over the dose range studied. Oral-gastric doses of 640, 160, 40, and 10 mg/kg of prodrug produced peak levels of 0.51 to 25.4 mg/L, an elimination half-life of 1 to 5 h; and an AUC\(_{0-\infty}\) of 0.9 to 287 mg*h/L. The pharmacodynamic index AUC/MIC correlated best with efficacy (\(R^2 = 0.84\)). Pharmacodynamic target studies were performed using 4 *C. albicans* isolates in both a 24 h and 96 h treatment duration. The strains were chosen to include previously characterized, fluconazole-resistant strains. The mean ED\(_{50}\) (mg/kg/12 h) and associated 24 h free drug AUC/MIC were: 89.3 ± 46.7 and 67.7 ± 35 for the 24 h duration experiment; 59.6 ± 22 and 33.3 ± 25.5 for the 96 h duration experiment. These differences were not statistically significant. Pharmacodynamic targets were also explored for two non-albicans species. The mean ED\(_{50}\) (mg/kg/12 h) and associated 24 h free drug AUC/MIC were: *C. tropicalis* (n=1) 31.2 and 6.2; *C. glabrata* (n=2) 50.5 and 1.6. These PD targets were significantly different than *C. albicans* targets (p=0.04). Isavuconazole pharmacodynamic PD targets for *C. albicans* are similar to those observed in this model for other triazoles. However, the PD target for non-albicans species was more than 10-fold lower than for *C. albicans* (p=0.04). This difference is similar to the species specific PD relationships for the echinocandins. The lower PD target for these species in this model will be important to consider in analysis of clinical trial data and during the development of susceptibility breakpoints.
INTRODUCTION

*Candida* species are the 4th most common cause of nosocomial bloodstream infection in the United States (1, 2). Unfortunately, despite medical advances morbidity and mortality remain unacceptably high (2-5). One strategy to improve outcomes is to utilize pharmacokinetic/pharmacodynamic (PK/PD) approaches to optimize antifungal therapy.

Mechanistically, PK/PD studies integrate the pharmacokinetic properties of a drug, *in vitro* potency (MIC), and treatment efficacy. The goal of PK/PD studies is to maximize clinical outcome through optimization of dosing design, minimize toxicity, prevent emergence of resistance, and assist with the setting of susceptibility breakpoints (6-8). These investigations have been integral in the rational use of triazoles in mucosal and invasive candidiasis (9).

*Isavuconazole* (BAL4815) is a new triazole compound with broad activity and potency including *Candida* spp. (10-12). Active drug is generated after plasma esterases hydrolyze the prodrug, isavuconazonium sulfate (BAL8557), to the active form isavuconazole (BAL4815) and an inactive cleavage product BAL8728 (13, 14).

In the current study, we [1] characterized the PK/PD properties of isavuconazole including predictive PK/PD index in the neutropenic invasive candidiasis (IC) murine model, [2] and determined the PK/PD target against eight clinical isolates of *Candida* species, including *C. albicans*, *C. glabrata*, and *C. tropicalis*, in order to provide a framework for the development of optimal dosing regimens and *in vitro* susceptibility breakpoints.

MATERIALS AND METHODS

Organisms. Eight clinical isolates were used for the *in vivo* studies including 5 *C. albicans*, 2 *C. glabrata*, and 1 *C. tropicalis*. The isolates were chosen and screened to have similar fitness in the *in vivo* model but to vary in susceptibility to triazoles (Table 1). The organisms were
maintained, grown, subcultured, and quantified on Sabouraud dextrose agar (SDA; Difco Laboratories, Detroit, MI). Twenty-four hours prior to study the organisms were subcultured at 35°C.

**Drug.** Prodrug isavuconazonium sulfate (BAL8557) and isavuconazole powder (BAL4815) was provided by the sponsor (Astellas, Northbrook, IL) for *in vivo* and *in vitro* studies, respectively. The prodrug was dissolved in sterile water and buffered to a pH of 4.0 with sodium hydroxide prior to oral administration. Isavuconazole powder was dissolved in DMSO per sponsor instructions prior to *in vitro* experiments. A conversion factor was necessary to convert prodrug dose to equivalent *in vivo* isavuconazole dose in the mice. This was determined based on a prodrug:drug equivalency ratio of 1.863 (provided by the sponsor). Additionally, the purity of prodrug powder was 89%. Thus, the resulting conversion factor to convert prodrug to active moiety was 2.07 (i.e. a 100 mg oral prodrug dose was equivalent to 48.3 mg of active isavuconazole drug). The purity of isavuconazole powder for susceptibility testing was >99%.

**In vitro susceptibility testing.** All isolates were tested in accordance with the both CLSI and EUCAST methods (15). MICs were performed on three separate occasions in duplicate. Final results are expressed as the median of these results.

**Animals.** Six-week old ICR/Swiss specific-pathogen-free female mice (Harlan Sprague-Dawley, Indianapolis, IN) weighing 23 to 27 g were used for all studies. Animals were housed in groups of five and allowed access to food and water *ad libitum*. Animals were maintained in accordance with the American Association for Accreditation of Laboratory Care criteria (16).
Infection model. A neutropenic, murine, disseminated candidiasis model was used for treatment studies (17-20). Animals were rendered neutropenic (polymorphonuclear leukocyte count <100 mm$^3$) by cyclophosphamide (Mead Johnson Pharmaceuticals, Evansville, IN) injection intraperitoneally 4 days (150 mg/kg) and 1 day (100 mg/kg) before infection.

Organisms were subcultured on SDA 24 h prior to infection. The inoculum was prepared by placing three to five colonies into 5 ml of sterile 0.15M NaCl warmed to 35°C. The final inoculum was adjusted to 0.6 absorbance at 530 nm. Fungal counts of the inoculum determined by viable counts on SDA were 6.28 ± 0.19 log$_{10}$ CFU/ml.

Disseminated infection was produced by lateral tail vein injection of 0.1 ml of the final inoculum 2 h prior to the start of antifungal therapy. At the end of the study period, animals were euthanized by CO$_2$ asphyxiation. The kidneys of each mouse were immediately removed and placed in sterile 0.15 M NaCl at 4°C. The organs were homogenized and serially diluted 1:10. Aliquots were plated onto SDA for viable fungal colony counts after incubation for 24 h at 35°C. The lower limit of detection was 100 CFU/kidneys. The results were expressed as the mean and standard deviation log$_{10}$ CFU/kidneys from three mice.

Pharmacokinetic studies. Single dose pharmacokinetics of isavuconazole (BAL4815) were determined in individual ICR/Swiss mice following oral administration of the prodrug (BAL8557) at 10, 40, 160, and 640 mg/kg in 0.2 ml volumes by oral-gastric gavage (OG). Plasma from groups of three isoflurane-anesthetized mice was collected at each of 7 time points (0.5, 1, 2, 4, 8, 12, and 24 h). The plasma was stored at -80°C until day of drug assay measurement. Drug concentration measurements were performed by the sponsor using LC-MS/MS. The limit of assay quantification was 10 ng/ml.

A non-compartmental model was used in the PK analysis. Pharmacokinetic parameters including elimination half-life and concentration at time zero ($C_0$) were calculated via nonlinear
least-squares techniques. The AUC was calculated by the trapezoidal rule. For treatment doses in which kinetics were not directly determined, pharmacokinetic parameters were estimated by linear interpolation for those doses between two measured doses and by linear extrapolation for doses above or below the highest and lowest measured doses. Protein binding (99%) was based on previous studies in mice by the sponsor (personal communication).

**Pharmacodynamic index determination.** Neutropenic mice were infected with *C. albicans* K1 2 h prior to the start of therapy. Twenty dosing regimens were chosen to determine the impact of dose level and interval on isavuconazole efficacy. These 20 regimens comprised five total 24 h prodrug (BAL8557) dosing levels (640, 320, 160, 80 and 40 mg/kg) divided into one, two, three, or four doses (i.e. drug was administered every 24, 12, 8, or 6 h, respectively). The prodrug was administered by OG route in 0.2 ml volumes. The wide range of dosing levels and intervals were chosen to minimize the interdependence among the three PD indices studied (Cmax/MIC, AUC/MIC, and %T>MIC) and to vary effect from no effect to maximal effect. For each respective dosing regimen, groups of three mice were treated over a 24 h period. Mice were sacrificed at the end of therapy and kidneys removed for CFU determination as described previously. The burden of organisms in kidneys at the end of therapy was the efficacy endpoint.

**Pharmacodynamic index magnitude determination.** Similar to the PD index determination described in the previous section, additional *Candida* isolates including 4 *C. albicans* and 1 *C. tropicalis* strains were studied over a 24 h treatment duration. In a comparable fashion we performed a 96 h treatment experiment with 2 *C. glabrata* isolates as in general this species exhibit a decreased growth rate in the mouse model compared to other *Candida* species (21-23). Finally, we also explored the impact of treatment duration for *C. albicans* with the addition of a 96 h endpoint. Treatment began 2 h after infection. Dosing regimens consisted of 320, 160,
80, 40, and 20 mg/kg of prodrug (BAL8557) administered by OG route every 12 h for the 24 h or 96 h treatment period. For the 96 h treatment duration experiments an additional IP dose of cyclophosphamide (100 mg/kg) was administered at day +2 to ensure neutropenia throughout the study period (24). Groups of three mice were used for each dosing regimen. At the end of the treatment period animals were sacrificed and CFU determined as described above.

**Data analysis.** A sigmoid dose-effect model was used to measure the in vivo potency of isavuconazole. The model was derived from the Hill equation: $E = \frac{E_{\text{max}} \times D^N}{(ED_{50}^N + D^N)}$, where $E$ is the observed effect, $D$ is the total dose, $E_{\text{max}}$ is the maximum effect, $ED_{50}$ is the 50% effective dose, or the dose required to achieve 50% of $E_{\text{max}}$, and $N$ is the slope of the dose-response curve. The correlation between efficacy and each of the three PD indices (AUC/MIC, $C_{\text{max}}$/MIC, and Time above MIC [T>MIC]) was determined by nonlinear least squares regression analysis using Sigma Stat (Systat Software Inc., Chicago, IL). The coefficient of determination ($R^2$) was used to estimate the variance that could be due to regression with each of the three PK/PD indices. Calculations were done using both total and free drug concentrations.

PD target determination was performed by identifying the $ED_{50}$ for each isolate and determining the corresponding AUC/MIC. The $ED_{50}$ was chosen to allow comparison with other triazole PD studies in this model (17-20). Both total and free drug concentrations were again utilized. PD targets including the mean $ED_{50}$ and AUC/MIC results for 24 h and 96 h C. albicans experiments were compared using Students t-test. The mean $ED_{50}$ and AUC/MIC between C. albicans and non-albicans species was compared using Mann-Whitney U Test. A two-tailed $P$ value of <0.05 was considered statistically significant.

**RESULTS**
**In vitro susceptibility testing and in vivo fitness.** The 24 h isavuconazole (BAL4815) MICs for the isolates studied varied 64-fold and were similar, with exception of *C. albicans* 98-210, using CLSI and EUCAST methodologies (Table 1). Decreased susceptibility to other triazoles did not reliably predict isavuconazole susceptibility. However, a single *C. glabrata* isolate (14378) with an elevated MIC to fluconazole also exhibited a higher isavuconazole MIC. *Candida albicans* and *C. tropicalis* exhibited similar fitness with 2 to 4 log$_{10}$ CFU/kidneys growth over 24 h. *C. glabrata* demonstrated slower growth rates with 0.71 - 1.24 log$_{10}$ CFU/kidneys at the end of a 96 h in vivo growth period. This difference in growth is similar to previous analyses demonstrating slower growth in the animal model for this species (17-22, 25).

**Pharmacokinetics.** The time course for isavuconazole (BAL4815) in the plasma of mice following OG doses of 640, 160, 40, and 10 mg/kg of prodrug (BAL8557) is shown in Figure 1. Peak levels were achieved within 2 h for each dosing regimen and ranged from 0.51 to 25.4 mg/L. The elimination half-life in serum increased in a dose-dependent fashion from 1 to 5 h. The AUC from 0 h to infinity (AUC$_{0-\infty}$), as determined by the trapezoidal rule, ranged from 0.9 to 287 mg*h/L. The AUC was linear over the dose range (R$^2$ 0.98).

**Pharmacodynamic index determination.** The dose-response relationship for *C. albicans* K1 after administration of oral total doses of prodrug (BAL8557) at 640, 320, 160, 80 and 40 mg/kg fractionated into one, two, three, or four doses is shown in Figure 2. At the start of therapy mice had 3.36 ± 0.02 CFU/kidneys after tail vein injection. The dose-response curves are similar for each of the fractionated regimens, suggesting the importance of the AUC/MIC PD index. The relationship between antifungal effect and each of the PD indices (C$_{max}$/MIC, AUC/MIC, and percentage of time free drug concentration exceeds the MIC [T>MIC]) is shown.
in Figure 3. Each PD index fit the data well; however, AUC/MIC index provided the highest correlation ($R^2 = 0.84$).

**Pharmacodynamic index magnitude determination.** The PD index magnitude (PD target) associated with 50% maximal efficacy (ED$_{50}$) was explored for three *Candida* spp. (5 *C. albicans*, 2 *C. glabrata*, and 1 *C. tropicalis*). The AUC/MIC PD index was utilized for magnitude determination and dosing regimens consisted of 2-fold increasing concentrations of prodrug from 20 to 320 mg/kg by OG route q12 h. As noted above, a 96 h treatment duration was utilized for the two *C. glabrata* isolates. This treatment duration was also assessed for *C. albicans* to investigate the impact of treatment duration on the PD target.

The dose-response curves for *C. albicans*, *C. tropicalis*, and *C. glabrata* are shown in panel A-C of Figure 4. At the start of therapy mice had 4.1 ± 0.4 log$_{10}$ CFU/kidneys of *C. albicans* and *C. tropicalis*. For these species growth was rapid and increased to 6.7 ± 0.6 log$_{10}$ CFU/kidneys in untreated controls after only 24h. In general, the dose response curves, including 24 h and 96 h treatment periods, were similar among the *C. albicans* strains. For *C. glabrata*, the mice had 3.5 ± 0.4 log$_{10}$ CFU/kidneys and increased to 4.3 ± 0.2 log$_{10}$ CFU/kidneys in untreated controls. In general, the dose response curves were similar for the two isolates *C. glabrata*.

The ED$_{50}$ was determined for each *Candida* strain is shown in Table 2. The mean 96 h treatment period ED$_{50}$ for 4 *C. albicans* isolates was 59.6 ± 22 mg/kg/12 h. In comparison, the mean 24 h ED$_{50}$ for 4 *C. albicans* isolates was numerically higher at 89.3 ± 46.7 mg/kg/12 h in the 24 h treatment period. This difference was not statistically significant ($p = 0.30$). The corresponding total and free drug AUC/MICs are shown in Table 2 for each group. The mean free drug AUC/MIC that corresponded with the ED$_{50}$ endpoint for *C. albicans* was 33.3 ± 25.5 and 67.7 ± 35.0 for the 96h and 24h treatment durations, respectively. The difference observed
between 96 h and 24 h C. albicans experimental groups was not statistically significant ($p = 0.16$). The relationship between treatment efficacy and the corresponding AUC/MIC for each dosing regimen and for each C. albicans isolate is shown in panel A of Figure 5. The 24 h and 96 h treatment period studies for C. albicans exhibited a similar AUC/MIC regression. Regression with the PD index AUC/MIC resulted in a good fit based upon the coefficient of determination ($R^2 = 0.71$).

The isavuconazole ED$_{50}$ for C. tropicalis was 31.2 mg/kg/12 h and the ED$_{50}$ against 2 C. glabrata isolates was 52.6 and 48.4 mg/kg/12 h. The mean free drug AUC/MIC associated with this endpoint for these non-albicans isolates was 3.1 ±2.7. The ED$_{50}$ and corresponding free drug AUC/MIC PD targets for the C. albicans treatment duration and for the C. albicans and non-albicans isolates were compared by Mann-Whitney U Test. The AUC/MIC target for the non-albicans strains was more than 10-fold lower than for C. albicans ($p=0.04$).

**DISCUSSION**

Pharmacodynamic evaluation of antimicrobial agents has led to the optimization of dosing design, improved clinical outcome, decreased toxicity, prevention of emergence of drug resistance, and appropriate application susceptibility breakpoints (6-8, 26, 27). The goal of the current study was to characterize the pharmacokinetics and pharmacodynamics of isavuconazole (BAL4815) in a neutropenic murine disseminated candidiasis model against multiple Candida species. This infection model and study approach has been undertaken with each of the other FDA approval triazoles (7). Previous studies by several other groups have demonstrated potent in vitro activity of isavuconazole against Candida species (11, 12), which was confirmed in the current study that utilized a select collection of clinical isolates of C. albicans, C. glabrata, and C. tropicalis. Minimum inhibitory concentrations were lowest and similar for C. albicans and C. tropicalis; however, were 32 to 64-fold higher for C. glabrata. This
trend in decreased in vitro potency observed against *C. glabrata* in our current study is 
congruent with previous larger *in vitro* studies (11, 12).

The pharmacokinetics and pharmacodynamics studies of isavuconazole are limited. 
One previous study has examined drug exposure and efficacy of isavuconazole in a murine 
model of invasive candidiasis (28). Similar to the findings in our study, the PK of isavuconazole 
was linear over the dose range studied and in general consistent PK parameters were 
observed. Treatment results were also relatively congruent in comparison of the two 
investigations.

Dose fractionation studies are critical in defining the PD index that is predictive of 
therapeutic efficacy. Studies with four other triazoles in this model have demonstrated 
treatment outcome is dependent on the total amount of drug (AUC), independent of the dosing 
interval (17-20, 29, 30). In the current study we similarly found AUC/MIC to be the PD index 
most closely predictive of efficacy ($R^2 = 0.84$). This is also consistent with a study of 
isavuconazole by Warn and colleagues (28).

*In vivo* experimental and clinical pharmacodynamic studies with triazoles have 
demonstrated the $ED_{50}$ and associated free drug AUC/MIC to be a clinically relevant endpoint 
for this model that is associated with treatment outcome for mucosal and invasive *C. albicans* 
infections in patients (17-20, 31-37). These studies have consistently demonstrated a free drug 
AUC/MIC of between 25 and 50 is associated with the $ED_{50}$ endpoint for both drug-susceptible 
and drug-resistant organisms. The mean free drug AUC/MIC in the current study for *C. albicans* 
isolates was approximately 50.

The majority of previous triazole PK/PD investigations have been limited to *C. albicans*. 
Recent PK/PD investigation with drugs from the echinocandin class suggest species specific 
relationships (21, 23, 38). Specifically, the AUC/MIC target associated with efficacy against *C. 
albicans* was higher than that observed with non-albicans species. In the current studies we
explored the impact of Candida species for two additional species, C. tropicalis and C. glabrata. The PD target for the single C. tropicalis isolate studies was approximately 8-fold lower than the C. albicans isolates, with a free drug AUC/MIC target of approximately 6. The two C. glabrata isolates demonstrated an even lower PD target with free drug AUC/MIC of 1.6 associated with the ED50 endpoint. To our knowledge, this is the first in vivo triazole PD target study utilizing C. glabrata isolates, and interestingly the results are similar to those of the echinocandin class in which C. glabrata isolates had a significantly lower PD target in comparison to other Candida species (21). It will be intriguing to explore the relevance of these observations in clinical datasets.

An additional area of investigation in the current studies was the effect of treatment duration on PD targets. Previous animal model PD studies with triazoles for therapy of invasive candidiasis have been limited predominantly to 24 h of therapy. In the current investigations we found that a longer experimental duration (96 h) resulted in slightly lower PD targets than the more commonly studied 24 h experimental duration (although this was not statistically significant). The longer duration experiment resulted in a steeper exposure-effect curve and particularly identified greater differences in organism burden for animals on the extremes of the drug exposures. This finding may not be unexpected if one considers the impact of effective and ineffective therapy over time. In mice receiving low and suboptimal doses one may anticipate growth of organism to increase over time. Conversely, effective therapy may further reduce organism burden with a longer duration experiment. The clinical relevance of this observation is not clear. However, one might hypothesize the potential for resistance emergence with the marginally effective therapy. Further studies should test for the presence of resistant subpopulations among viable organisms.

Human PK characterization of isavuconazole has been recently reported (13, 14, 39). A current Phase III trial is examining the efficacy of a 200 mg loading dose three times daily for
two days followed by 200 mg oral maintenance dosing once daily thereafter (http://clinicaltrials.gov; NCT00413218). The steady state 24 h AUC for this regimen is approximately 90 mg*h/L (free drug AUC of approximately 1.8 mg*h/L) (13). If one divides the free drug AUC by the PD target identified for each species, an MIC threshold (i.e. ceiling) can be estimated. This would result in a tentative PD centered, species-specific breakpoint of 0.04 mg/L for *C. albicans*, 1.125 mg/L for *C. glabrata*, and 0.3 mg/L for *C. tropicalis* based on the current animal model study. The *in vitro* potency of isavuconazole against various fungal pathogens including *Candida* species has also been examined in relatively large and geographically diverse surveillance series (11, 12, 40). If one integrates the animal model ED$_{50}$ AUC/MIC target, human PK, and surveillance MIC data, the isavuconazole dosing regimen in use for clinical trials would be predicted to achieve the PD target for 99% of *Candida* isolates (10). When population PK data are available a more robust Monte Carlo simulation should be more informative.

In summary, we have shown isavuconazole has PK/PD characteristics that are similar to those described for other triazoles, including the predictive PD index and PD target in the neutropenic murine disseminated candidiasis model. Specifically, AUC/MIC correlated best with therapeutic efficacy and the *C. albicans* PD target was a free drug AUC/MIC of approximately 50. A novel finding was a numerically lower PD targets for two non-albicans *Candida* species. It will be important to explore the clinical relevance of these findings in clinical studies.

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**Figure Legends:**

Figure 1. Plasma concentrations of isavuconazole (BAL4815) after administration of oral prodrug (BAL8557) at 640, 160, 40, and 10 mg/kg. Each symbol represents the geometric mean ± standard deviation from three mice. The peak concentration (Cmax), 24 h AUC∞, and elimination half life (t1/2) are shown for each dose.

Figure 2. Impact of dose fractionation on the *in vivo* efficacy of isavuconazole prodrug (BAL8557) against *C. albicans* K1. Groups of three mice were treated with one of a five two-fold increasing total doses of oral prodrug. The doses were fractionated into one, two, three, or four doses over a 24 h treatment period. Each symbol represents the mean ± standard deviation organism burden in the kidneys of three mice.

Figure 3. Relationship between isavuconazole (BAL4815) PD indices 24 h AUC/MIC (panel A), Cmax/MIC (panel B), and percentage of time free-drug concentrations exceed the MIC (T>MIC) (panel C) and *in vivo* efficacy against *C. albicans* K1. Each symbol represents the mean organism burden in the kidneys of three mice. The line through the data points represent the best-fit curves based on the Hill equation. The PD parameters Emax, ED50, slope (N), and the coefficient of determination (R²) are shown for each PD index.

Figure 4. *In vivo* dose-response curves for multiple *C. albicans* (5) (panel A), *C. tropicalis* (1) (panel B), and *C. glabrata* (2) (panel C) isolates. Each symbol represents the geometric mean ± standard deviation of organism burden in the kidneys of three mice.

Figure 5. Relationship between PD index AUC/MIC and treatment efficacy for isavuconazole against five *C. albicans* isolates. Treatment durations are representing by closed symbols (24
h) and open symbols (96 h). Each data point represents the geometric mean of organism burden in three mice. A best-fit line based on the Hill equation is included. The PD parameters $E_{\text{max}}$, $ED_{50}$, slope ($N$), and coefficient of determination ($R^2$) are shown in the figure legend.

REFERENCES


Table 1. *In vitro* susceptibility of select *C. albicans*, *C. glabrata*, and *C. tropicalis* isolates to isavuconazole (BAL4815), fluconazole, voriconazole, and posaconazole.

<table>
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<th>Isolate</th>
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<th>Isavuconazole MIC (mg/L)</th>
<th>Fluconazole MIC (mg/L)</th>
<th>Voriconazole MIC (mg/L)</th>
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CLSI and EUCAST refer to MIC method used for susceptibility testing.
Table 2. *In vivo* activity of isavuconazole against *C. albicans* (24 h and 96 h treatment periods) *C. tropicalis* (24 h treatment period), and *C. glabrata* (96 h treatment period) in a neutropenic disseminated candidiasis model.

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<td>98-17</td>
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<td>0.03</td>
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<td>K1</td>
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<td>27.5</td>
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<tr>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>6773 ± 3499</strong></td>
<td><strong>67.7 ± 34.9</strong></td>
</tr>
<tr>
<td><strong>Mean ± SD</strong> All <em>C. albicans</em></td>
<td></td>
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<td></td>
<td><strong>5053 ± 3377</strong></td>
<td><strong>50.5 ± 33.7</strong></td>
</tr>
<tr>
<td><em>C. tropicalis</em> (24 h)</td>
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<td>31.2</td>
<td>0.016</td>
<td>624</td>
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<tr>
<td><em>C. glabrata</em> (96 h)</td>
<td>14378</td>
<td>52.6</td>
<td>0.25</td>
<td>119</td>
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<td>35315</td>
<td>48.4</td>
<td>0.125</td>
<td>193</td>
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<tr>
<td><strong>Mean ± SD non-albicans</strong></td>
<td></td>
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<td></td>
<td><strong>312 ± 273</strong></td>
<td><strong>3.1 ± 2.7</strong></td>
</tr>
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* p<0.04