Title: Clinical Pharmacodynamic Index Identification for Micafungin in Esophageal Candidiasis: Dosing Strategy Optimization

Running Title: Clinical Micafungin Pharmacodynamics

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Abstract: Echinocandins exhibit concentration dependent effects against *Candida* species and preclinical studies support large, infrequent dosing. The current study examines the pharmacokinetics/pharmacodynamics of two multicenter, randomized trials of micafungin dosing regimens that varied in both dose level and dosing interval. Analysis demonstrates the clinical relevance of the dose level and AUC. Better outcomes were seen, although not statistically significant (0.056), with higher $C_{\text{max}}$ and large, infrequent dosing. The results support further clinical investigation of novel micafungin dosing regimens with large but less than daily administration.
Text: Understanding the pharmacodynamics driver of antimicrobial efficacy provides a means to identify the optimal dosing strategy (1, 2). Ideal dosing of antimicrobials for which Cmax/MIC is most closely linked to effect would involve administration of large doses infrequently. Conversely, when the AUC/MIC index is best predictive of outcome, it is the total amount of compound rather than dosing frequency that impacts the treatment strategy. The clinical utility of this information has long been recognized with the Cmax-linked aminoglycoside drug class for which once daily administration both improves efficacy and reduces toxicity (3, 4). More recently, clinical studies have identified enhanced efficacy for beta-lactam extended and continuous infusion in the critical care setting, an approach to dosing which optimizes % time above MIC, the PK/PD index associated with efficacy (5-7).

The majority of data available to determine the ideal pharmacodynamic dosing strategy is the product of preclinical in vitro and in vivo dose fractionation studies. While clinical studies may vary dose level, the evaluation of more than a single dosing interval is uncommon. The goal of the present analysis was to utilize an existing clinical dataset for the antifungal agent, micafungin, in which both dose and dosing interval were varied in order to identify the optimal dosing strategy.

Experimental infection models have consistently found concentration-dependent killing and prolonged post-antifungal effects for the echinocandin class (8-18). Dose fractionation and pharmacokinetic/pharmacodynamic (PK/PD) index analysis have demonstrated the importance of both the Cmax/MIC and AUC/MIC indices to predict efficacy.

In the present investigation, micafungin PK and efficacy were explored using pooled data from two multicenter, double-blind, randomized clinical trials in which adult patients were treated for esophageal candidiasis. The two studies were completed in 2002 (Sponsor Study #03-7-005/NCT00666185) and 2004 (Astellas Study #03-7-008/ NCT00665639) (19). The study
protocols were identical with regard to disease diagnosis, treatment duration, and study endpoint determination. Both clinical trials, which were approved by the Institutional Review Board or Ethical Review Committee and relevant regulatory approvals in each country, were conducted in accordance with Good Clinical Practice guidelines; written informed consent was obtained from all study participants prior to the start of each trial. The two micafungin treatment regimens compared were 150 mg every day (QD) and 300 mg every other day (QOD) for a minimum of 14 days and up to 21 days. It was hypothesized that use of the higher but less frequently administered regimen would be associated with either superior or equivalent efficacy compared to the standard dose daily regimen based upon achieving a higher $C_{\text{max}}$ and similar AUC, respectively. Both endoscopically obtained microbiologic and histopathologic success at the end of therapy and clinical relapse two weeks after the end of therapy were considered in the current analysis. The per-protocol dataset, which included patients with biopsy-proven disease and who received at least 10 doses of micafungin, were evaluated. The study arms included 189 patients in the 150mg QD group and 132 study participants receiving the QOD regimen. Patient demographics were statistically similar in both studies and treatment arms (Supplemental Table 1S). The majority of patients carried an HIV diagnosis. Pooled data from both studies were used to assess the PK/PD relationships for the two treatment groups. Both binary study outcomes were compared for the two treatment groups using the $\chi^2$ test or the Fisher exact test and statistical significance was defined as a p-value $\leq 0.05$. Plasma samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 h after infusion on day 1 and 11. Samples were analyzed for micafungin by using solid phase extraction and reverse phase high-performance liquid chromatography as previously described (20-24). A previous population PK model was developed for micafungin across multiple studies (n=4), utilizing concentration data from 364 patients, including a subset of 67 patients from the two clinical studies described herein (25). In the above-described population PK model, body weight was a statistically significant predictor of micafungin clearance. Individual post-hoc predicted PK parameters from
the 53 patients who received the two dosing regimens of interest for this analysis and were in the per protocol set were used to simulate plasma micafungin concentrations over a 48-hour period at steady-state for the purposes of calculating $C_{\text{max}}$ and $AUC_{0-48}$. Population mean PK parameters were instead used to estimate $C_{\text{max}}$ and $AUC_{0-48}$ for the 267 patients in the PP who did not have measured plasma PK data available for analysis.

Endoscopically proven mycological response at the end of therapy was observed in 78.8% of patients in the 150mg QD group and 87.1% in the 300mg QOD group (Table 1. $p=0.056$). While these outcomes were not statistically significant, there was a numerically higher efficacy rate in the higher dose, extended interval arm. The treatment outcomes for the two regimens were also similar for the relapse endpoint, with a failure rate of 12.2% in the daily group and 5.6% in the high dose arm (Table 1. $p=0.051$). A comparison of exposure measures for the two dosing regimens at steady state is presented in Table 2. As previously shown in other dose escalation studies, pharmacokinetics increased in a linear manner with dose (26, 27). Steady-state $AUC_{0-48h}$ for the two dosing regimens were comparable. The median $C_{\text{max}}$ was 1.65-fold higher while the median $C_{\text{min}}$ was 0.49-fold lower for the 300mg than for the 150mg group (Wilcoxon rank sum $p<0.0001$ comparisons of $C_{\text{max}}$ and $C_{\text{min}}$).

The present dose escalation and dosing interval clinical study pharmacodynamic analysis is congruent with preclinical studies which demonstrate the importance of the concentration dependent indices, $AUC/MIC$ and $C_{\text{max}}/MIC$. While these outcomes were not statistically significant, there was a numerically higher efficacy rate in the higher dose, extended interval arm. These observations support treatment strategies that optimize both $C_{\text{max}}$ and $AUC$.

Prior safety studies have not identified a clear maximal tolerated dose for micafungin, however, doses as high as 600 mg have been generally well tolerated (28, 29). It is possible that dose levels even higher than the 300 mg used in this study and less frequent administration could offer additional clinical benefits when compared to the currently approved daily regimens.
While this strategy cannot be recommended for clinical use outside of mucosal candidiasis, there may be other situations in which it could be appropriate given more supportive data. In addition, as the inevitable process of resistance emergence becomes a relevant issue for the echinocandin class, these novel dosing strategies may provide useful treatment options. Unfortunately, accurate susceptibility testing was not available to allow us to explore the impact of MIC on outcome in this study. However, as the majority of isolates were *C. albicans*, we do not believe the collection would have included very many "higher" MIC strains or species such as *C. parapsilosis* or *C. guilliermondii*. At a minimum, the results of this evaluation provide an intriguing rationale for future clinical investigation of higher echinocandin doses and extended dosing intervals.
### Table 1. Efficacy of micafungin

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>Success n (%)</th>
<th>Failure n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg QD</td>
<td>145 (78.8)</td>
<td>39 (21.2)</td>
<td>184</td>
</tr>
<tr>
<td>300 mg QOD</td>
<td>115 (87.1)</td>
<td>17 (12.9)</td>
<td>132</td>
</tr>
<tr>
<td>Total</td>
<td>260</td>
<td>56</td>
<td>316</td>
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</tbody>
</table>

<table>
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<tr>
<th>Clinical relapse at 2 weeks post-treatment**</th>
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<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>150 mg QD</td>
</tr>
<tr>
<td>300 mg QOD</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

* p=0.056, ** p=0.051, QD = daily, QOD = every other day
Table 2. Summary statistics of predicted steady state AUC$_{0-48}$ and C$_{\text{max}}$ by micafungin dosing regimen

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th>AUC$_{0-48}$ (µg•h/mL)</th>
<th>C$_{\text{max}}$ (µg/mL)</th>
<th>C$_{\text{min}}$ (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (CV%)</td>
<td>Median (min, max)</td>
<td>Mean (CV%)</td>
</tr>
<tr>
<td>150 mg QD (n=188)$^a$</td>
<td>310 (12.9)</td>
<td>304 (205, 582)</td>
<td>14.4 (9.43)</td>
</tr>
<tr>
<td>300 mg QOD (n=132)</td>
<td>311 (15.6)</td>
<td>303 (244, 616)</td>
<td>23.7 (7.28)</td>
</tr>
</tbody>
</table>

a. Since one patient from this group had no PK data and was missing weight, individual and mean population predicted exposures, respectively, could not be estimated.
Acknowledgements

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References


