Population Pharmacokinetic-Pharmacodynamic Analysis of Voriconazole and Anidulafungin in Adult Patients with Invasive Aspergillosis

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Abstract (246/250 words)

To evaluate the exposure-response relationships for efficacy and safety of voriconazole and anidulafungin in adult patients with invasive aspergillosis (IA), a population pharmacokinetic-pharmacodynamic (PK-PD) analysis was performed with data from a phase 3, prospective, double-blind, comparative study evaluating voriconazole and anidulafungin combination therapy versus voriconazole (and placebo) monotherapy. Anidulafungin/placebo treatment duration was 2 to 4 weeks and voriconazole treatment duration was 6 weeks. Efficacy (6-week all-causality mortality and 6-week global response, [n = 176]) and safety (hepatic [n = 238], visual [n = 199], psychiatric [n = 183] adverse events [AEs]) endpoints were analyzed separately using binary logistic regression model. In IA patients receiving voriconazole monotherapy, no positive associations between voriconazole exposure and efficacy or safety were identified. In IA patients receiving combination therapy, no positive associations between voriconazole or anidulafungin exposures and efficacy were identified. The 6-week survival rate tended to increase as anidulafungin treatment duration increased; this finding should be considered with caution. Additionally, in IA patients receiving combination therapy, a positive association between voriconazole and anidulafungin exposures (area under the curve [AUC] and trough concentration [C_min]) and hepatic AEs was established; a weak positive association between voriconazole exposure (AUC and C_min) and psychiatric AEs was also established; but no association between voriconazole exposure and visual AEs was identified. Besides the drug exposures, no other covariates (i.e., CYP2C19 genotype status, age, weight, body mass index, sex, race or neutropenia status) were identified as significant predictors of the efficacy and safety endpoints in IA patients.
Although substantial efforts have been made, the correlations between antifungal agent exposures and clinical outcomes and treatment-related toxicity have not been well established. Among them, voriconazole (a broad-spectrum azole) is one of the most studied agents due to its extensive clinical use and high inter-subject variability in pharmacokinetics (PK). Originally, a retrospective analysis using pooled voriconazole data from 10 phase 2/3 clinical studies showed that patients with elevated voriconazole concentrations may have an increased risk of experiencing liver function test (LFT) abnormalities and visual adverse events (AEs), but individual voriconazole concentrations could not be used to predict subsequent LFT abnormalities (1). In addition, no association between voriconazole concentrations and clinical efficacy was identified (2). Following extensive use of voriconazole in clinical practice, many independently published studies showed positive association between voriconazole concentrations and treatment-related toxicity (e.g., neurotoxicity and hepatotoxicity) and/or clinical efficacy, and different target trough (Cmin) values have been proposed for voriconazole therapeutic drug monitoring (TDM) (3-12). Note that many of these were retrospective analyses of data from a limited number of patients. A brief summary of most of these studies can be found elsewhere (9, 13). It is noteworthy that two recently published retrospective analyses of large-scale voriconazole TDM data from real clinical settings showed no associations between voriconazole concentrations and clinical outcomes or treatment-related toxicity (14, 15). Until now, no formal consensus on the voriconazole exposure-response relationship has been reached due to the complex clinical setting of fungal infections.

A recent phase 3 study evaluated the efficacy, safety and tolerability of voriconazole and anidulafungin (an echinocandin) combination therapy versus voriconazole monotherapy for the...
treatment of invasive aspergillosis (IA) in allogeneic hematopoietic stem cell transplantation
recipients and patients with hematological malignancies (16). Voriconazole and anidulafungin
concentration data were available in a subset of these patients (17). These data were used to
explore the relationships of voriconazole and anidulafungin exposures with clinical outcomes
and commonly reported AEs in these IA patients. This analysis also explored potential covariates
that may be predictive of pharmacodynamic (PD) responses. In addition, the area under the curve
(AUC)/MIC ratio showed a clear relationship to survival rate for both voriconazole and
anidulafungin in murine infection models with disseminated aspergillosis (18, 19). To confirm
this relationship, the correlation between the AUC/MIC ratio and clinical efficacy endpoints was
explored in this analysis.

The safety profiles of voriconazole and anidulafungin as monotherapy are well-known (2,
20). The most commonly reported treatment-related AEs for voriconazole are hepatic and visual
AEs, and for anidulafungin are hepatic AEs. Hence, the main focus for safety endpoints in this
PK-PD analysis was on hepatic and visual AEs. In addition, psychiatric AEs (related to
neurotoxicity) were also of interest for voriconazole treatment and were explored in this analysis.

MATERIALS AND METHODS

Study design. A detailed description of the study design for this phase 3, prospective,
double-blind, comparative, multicenter study in IA patients can be found in a separate article
(17). This study was registered on ClinicalTrials.gov (NCT00531479). Briefly, 454 patients were
randomized 1:1 to receive active intravenous (IV) anidulafungin (a 200 mg loading dose,
followed by 100 mg every 24 hours [q24h]) or placebo for at least the first 2 weeks, to a
maximum of 4 weeks per investigator’s discretion; and all patients received open-label
voriconazole for a total of 6 weeks. For the first week, all patients were required to receive IV
voriconazole (6 mg/kg every 12 hours [q12h] for 24 hours, followed by 4 mg/kg q12h), they were then allowed to switch to oral voriconazole (300 mg q12h, or 150 mg q12h for subjects <40 kg), per investigator’s discretion. Note that the use of a 300 mg oral dose would allow an early switch to oral therapy since it was expected to provide voriconazole exposure comparable to the 4 mg/kg IV dose based on the data from healthy subjects (21). In this study, dose adjustment for voriconazole was allowed based on patient’s clinical response, tolerability (AEs) and/or voriconazole concentrations.

Clinical outcomes were assessed after 6 weeks of antifungal therapy (e.g., primary endpoint: all-causality mortality; secondary endpoint: global response). Global response was a composite of clinical and radiological responses, with successful responses requiring clinical improvement and >50% radiographic improvement. The AEs were monitored throughout the study.

**Considerations for AE analysis.** Since there could be multiple AE observations per patient, both single-panel (without counting the frequency of AE occurrence in each subject) and multiple-panel (include all observations) analysis approaches were used. In addition, to avoid any potential bias from the assessment of treatment-relatedness for AEs, both treatment-related and all-causality hepatic and visual AEs were analyzed. Only treatment-related psychiatric AEs were analyzed because of frequent concomitant use of narcotic analgesics (e.g., morphine; also associated with psychiatric AEs) in these IA patients. Note that when a treatment-related AE was reported in the combination group, it was related to either voriconazole alone or the combination therapy (voriconazole and anidulafungin).

In this analysis, both all-causality and treatment-related hepatic AEs included the following: alanine aminotransferase increased or abnormal, aspartate aminotransferase increased,
alkaline phosphatase increased or abnormal, gamma-glutamyltransferase increased or abnormal,
bilirubin increased, hyperbilirubinemia, hepatic function abnormal, transaminases increased,
liver function test abnormal, cholestasis, hepatotoxicity, hepatitis toxic, hepatic vein occlusion,
gallbladder enlargement and hepatic failure. Visual AEs included the following: asthenopia,
chromatopsia, color blindness acquired, glare, photophobia, photopsia, visual impairment, vision
blurred and visual acuity reduced. Psychiatric AEs included the following: hallucination,
nightmare, confusional state, delirium and disorientation.

Estimation of exposure parameters. Population PK models describing anidulafungin
and voriconazole plasma concentration data from this study were reported separately (17).
Individual anidulafungin AUC over a 24-h dosing interval ($AUC_{0-24}$) and $C_{min}$ were
estimated based on individual PK parameters from the anidulafungin population PK model
developed from the data for this study (17), and used for both safety and efficacy analyses.
Specifically, steady-state $AUC_{0-24}$ was calculated as Dose/Clearance and $C_{min}$ was estimated at
24 hours post-dose at steady state. The $AUC_{0-24}$ values were also used for the calculation of the
PK/PD index, AUC/MIC.

Voriconazole doses could vary with time within a patient since dose adjustment was
allowed per protocol. Therefore, individual voriconazole exposures were estimated based on the
actual doses administered in each patient. The AUC over a dosing interval ($AUC_{\tau}$) values were
generated by integrating (in the NONMEM SDES block) individual estimated plasma
concentrations over each dosing interval based on the final voriconazole population PK model
developed from the data for this study (17), and the $C_{min}$ values were the estimated individual
concentrations just prior to the next dose based on the specific doses received. For the efficacy
analysis, average $AUC_{0-12}$ and $C_{min}$ values over the entire treatment period were used. The
average $AUC_{0-12}$ values were also used for the calculation of $AUC/MIC$. For the safety analysis, when patients had no hepatic, visual or psychiatric AEs reported, average $AUC_{0-12}$ and $C_{min}$ values over the entire treatment period were used. When patients experienced an AE, the $AUC_0$ and $C_{min}$ from the onset day of this AE were used. When using the single-panel analysis approach, for patients experiencing multiple AEs, the $AUC_{0-12}$ and $C_{min}$ associated with the first AE occurrence were used. Note that because of the q12h dosing schedule for voriconazole, two $AUC_{0-12}$ and $C_{min}$ values on each day were available. Since most of AEs did not have onset time recorded, average $AUC_{0-12}$ and $C_{min}$ values on the AE onset day were used for analysis.

Population PK-PD analysis. All the efficacy and safety data were evaluated as binary data using a logistic regression model in the NONMEM system (Version 7.1.2, Icon Development Solutions, Ellicott City, MD) with the second order conditional (Laplacian) estimation method. The graphic processing of the data and the NONMEM output was performed with R (version 2.12.2).

The efficacy population included the modified intent-to-treat (mITT) patients (with independent Data Review Committee [DRC] confirmed diagnosis of probable or proven IA, and received at least one study dose), who had concentration data available. Note that 5 mITT patients with less than 3 days of study treatment were excluded from the efficacy analysis as they had insufficient exposure to study drug(s). The safety population included all patients (with diagnosis of possible, probable or proven IA) who received at least one study dose and had concentration data available.

Each efficacy endpoint (6-week all-causality mortality and 6-week global response) and safety endpoint (hepatic, visual and psychiatric AEs) was analyzed separately using voriconazole and anidulafungin exposure parameters ($AUC$ and $C_{min}$, assessed separately) as potential
predictors. Other covariates (e.g., CYP2C19 genotype status, age, weight, body mass index [BMI], sex and race) were also examined in each analysis. Furthermore, baseline neutropenia status (as binary data) and AUC/MIC were explored as potential predictors for efficacy. Anidulafungin treatment duration ("Duranid") was also tested as a potential predictor for efficacy. Since anidulafungin treatment may have been stopped at the investigator’s discretion during week 3 and week 4 or because the subject expires, "Duranid" becomes a potential covariate of response. It is acknowledged that caution should be taken when considering "Duranid" as a potential covariate.

The effects of potential covariates on both efficacy and safety endpoints were first explored graphically. If a visual trend was observed, the covariate was selected for further evaluation using logistic regression modeling. The model described the observed trend in the probability of experiencing an AE or meeting an efficacy endpoint (equations below).

$$\lambda_i = \log \left( \frac{p_i}{1 - p_i} \right)$$

where the probability of an event for an individual $i$ is given by $p_i$, $\lambda_i$ is the logit, which is the natural log of the odds ratio, $\theta_1$ is the baseline probability of success/AE occurrence, $\theta_2$ is the log odds contribution of drug exposure (AUC, $C_{min}$ or AUC/MIC), and other covariates ("factor") may be added in with additional adjustments ($\theta_n$) to the baseline probability.
Since each individual contributed only one observation for each endpoint in the single-panel analysis, the individual random effect ($\eta_i$) was fixed at a value of zero. Even with the multiple-panel AE analysis, the majority of the patients still had one response only. The individual random effect ($\eta_i$) was not estimated and also fixed at a value of zero.

Model selection was based on goodness-of-fit criteria including the objective function value (OFV), precision of parameter estimates and diagnostic plots. The acceptance criteria for inclusion of a covariate into the model as a significant predictor included reduction in OFV of at least 7.88 (corresponding to a p-value of 0.005 with one degree of freedom, difference of log-likelihoods from nested models is approximately asymptotically $\chi^2$ distributed), and a reduction (or at least no increase) in the unexplained variability in the model when estimated. Estimates of parameter precision were obtained from the asymptotic standard errors of the estimated parameters and described as percent relative standard error (%RSE).

RESULTS

Data for analysis. There were 176 mITT patients with exposure and efficacy data pairs (80 in the combination group). The data pairs used for exposure-safety analysis are summarized in Table 1. Each AE dataset included 161 patients who had no hepatic, visual, or psychiatric AEs.

Exposure-efficacy analysis. The demographics and exposure parameters tested as potential covariates (predictors) are summarized in Table S1 (supplemental material).

(i) All-causality mortality at week 6 (surviving 6 weeks [SURV6]). Exposure parameters (AUC and $C_{\text{min}}$) and anidulafungin treatment duration were examined graphically as potential predictors (Figure 1). Demographics were also examined graphically as potential
predictors (Figure 2). Only anidulafungin treatment duration was identified as being a significant
predictor for SURV6 in the mITT patients (Table 2). The probability of SURV6 would increase
as anidulafungin treatment duration increased. Caution should be taken for interpretation of this
predictor because of the following caveat: patients expiring prior to week 2 would necessarily
have shorter duration of therapy, which could artificially inflate the effect of this covariate.

A significant positive association between anidulafungin exposure (AUC0-24 and Cmin)
and SURV6 could not be established although a slightly positive trend was observed.

The relationship between voriconazole exposure and SURV6 is noteworthy (Figure 1,
lower panel). No clear trend was observed in the combination group. In the monotherapy group,
however, the rate of SURV6 appeared to be lower in patients with higher voriconazole exposure
(e.g., Cmin >5 μg/mL) although the number of patients in this category was low (n = 12). This
might be explained by that patients with poor prognosis may have significantly compromised
body function (e.g., multi-organ failure, decreased hepatic function, etc.), leading to inadequate
elimination of voriconazole from the body. In addition, the rate of SURV6 in patients with
voriconazole Cmin ≤2 μg/mL was similar to or even higher than that in patients with higher Cmin.
The rate of SURV6 tended to decrease slightly as age increased; however, age was not
identified as a significant predictor. The CYP2C19 genotype status, neutropenic status, body
weight, BMI, sex and race had no apparent association with SURV6.

(ii) Global response at week 6. Graphical examinations of potential covariates are
presented in Figure S1 (supplemental material). A slightly positive trend was observed for
anidulafungin treatment duration (with the same caveats mentioned previously), sex, race,
CYP2C19 genotyping status and baseline neutropenic status (male, Asian, CYP2C19 PMs and
neutropenic patients appeared to have lower success rate). However, none of the potential
covariates were identified as significant predictors for global response. Similar to 6-week survival rate, the success rate of global response appeared to be lower in patients with higher voriconazole exposure, and this was observed in both treatment groups (Figure S1). The explanation for SURV6 may also be applicable here.

(iii) The PK-PD index (AUC/MIC). Due to technical challenges, the fungal isolates were obtained in a very small subset of IA patients, which is not unexpected. A total of 23 patients had AUC/MIC values available and 11 of them were from the combination group. Likely due to limited data on MIC values against *Aspergillus spp.*, no apparent association was identified between AUC/MIC and efficacy endpoints (data on file).

Exposure-safety analysis. (i) Hepatic AEs. The demographics and exposure parameters tested as potential covariates for treatment-related hepatic AEs are summarized in Table S2 (supplemental material). The route of administration of voriconazole was not tested as a potential covariate in relation to hepatic AEs. Since a few cases (e.g., hepatic failure, hepatotoxicity and hepatitis toxic) were considered relatively severe and different from other typical hepatic AEs, they were examined separately to ensure no specific trend was present (Table S3, supplemental material). Five out of 6 events were reported from the combination group, and 4 of them (all from combination group) had voriconazole \( C_{\text{min}} \) exceeding 4.5 \( \mu \text{g/mL} \). Note that a total of 54 patients had voriconazole \( C_{\text{min}} \) exceeding 4.5 \( \mu \text{g/mL} \) in the dataset.

Graphical examinations of exposure parameters as potential predictors for treatment-related hepatic AE occurrence with single-panel data are presented in Figure 3. Both voriconazole and anidulafungin \( C_{\text{min}} \) as well as corresponding AUC were identified as being significant predictors for treatment-related hepatic AE occurrence in the combination group (Table 2). However, in the voriconazole monotherapy group, the positive association between
voriconazole exposure and hepatic AE occurrence diminished (Figure 3, bottom panel). This suggests there may be an additive or synergistic effect on the risk of experiencing at least one treatment-related hepatic AE when voriconazole and anidulafungin were used in combination. Moreover, in the monotherapy group, the rate of hepatic AEs appeared to be lower in patients with higher voriconazole exposure (e.g., $C_{\text{min}} > 5 \, \mu\text{g/mL}$) although the number of patients in this category was low ($n = 16$).

For the multiple-panel analysis of treatment-related hepatic AEs, the difference in observed trends from the single-panel data was the higher AE rate in the anidulafungin low exposure category ($C_{\text{min}} \leq 2 \, \mu\text{g/mL}$). Nonetheless, similar results were obtained (data on file). Similar results were also obtained for all-causality hepatic AEs from both single-panel and multiple-panel analyses (data on file).

Figure 4 presents the observed and model predicted probabilities of experiencing at least one hepatic AE as a function of drug exposures ($C_{\text{min}}$) when voriconazole and anidulafungin were used in combination (based on single-panel data). The predicted mean % increase in the probability of experiencing at least one hepatic AE by drug exposures ($C_{\text{min}}$) from 4 different analyses are summarized in Table 3. For instance, with single-panel data, when voriconazole $C_{\text{min}}$ was increased by 1 µg/mL steps (range: 1 – 9 µg/mL) in the presence of anidulafungin (e.g., median $C_{\text{min}} = 2.6 \, \mu\text{g/mL}$), on average, the risk of experiencing at least one treatment-related hepatic AE would be increased by 5-8%. Similarly, when anidulafungin $C_{\text{min}}$ was increased by 1 µg/mL steps (range: 1 – 8 µg/mL) in the presence of voriconazole (e.g., median $C_{\text{min}} = 3 \, \mu\text{g/mL}$), on average, the risk of experiencing at least one treatment-related hepatic AE would be increased by 6-9%.
(ii) Visual AEs. None of the potential covariates were identified as significant predictors for treatment-related and all-causality visual AEs (both single-panel and multiple-panel analyses). Thus, a summary of demographics and exposure parameters tested as potential covariates is not shown (data on file). Nonetheless, a slightly positive trend between voriconazole exposure and treatment-related visual AEs was observed in the combination group (Figure S2, supplemental material). However, in the monotherapy group, patients with higher voriconazole exposure appeared to have less treatment-related visual AEs (Figure S2). The positive trend between voriconazole exposure and all-causality visual AEs in the combination group was less obvious than that for treatment-related visual AEs (data on file).

(iii) Psychiatric AEs. The demographics and exposure parameters tested as potential covariates are summarized in Table S4 (supplemental material).

For the single-panel data, a positive trend between voriconazole exposure and treatment-related psychiatric AE occurrence was observed in the combination group, but this trend was not identified in the monotherapy group (Figure S3, supplemental material). Again, none of the potential covariates were identified as significant predictors, including voriconazole exposure, which marginally missed the inclusion criteria.

For the multiple-panel data, both voriconazole $C_{\text{min}}$ and AUC$_{0-12}$ were identified as being significant predictors for treatment-related psychiatric AE occurrence only in the combination group (Table 2). A wide 95% confidence interval (CI) around the population prediction on probability of psychiatric AE occurrence was observed when voriconazole $C_{\text{min}}$ exceeded 4 $\mu$g/mL or AUC$_{0-12}$ exceeded 60 $\mu$g.h/mL, indicating low precision on the probability prediction (Figure 5). This is not unexpected given the low incidence of this AE and the small number of patients with high voriconazole exposures in this dataset. Based on the model prediction, when
voriconazole $C_{\text{min}}$ was increased by 1 µg/mL steps (range: 1 – 9 µg/mL) in the presence of anidulafungin, on average, the risk of experiencing at least one treatment-related psychiatric AE would be increased by 3-9% with very large uncertainty.

**DISCUSSION**

**Efficacy.** The primary analysis of the 277 mITT patients from this study showed that the combination of anidulafungin and voriconazole was associated with a trend towards improved survival compared to voriconazole monotherapy although this difference did not meet the pre-specified criteria for superiority (6-week all-causality mortality: 26/135 [19.3%] for combination, 39/142 [27.5%] for monotherapy, $p=0.0868$) (16). In contrast, successful global response at week 6 was lower for combination therapy compared to monotherapy (44/135 [32.6%] vs. 61/142 [43.0%], 95% CI: -21.6% to 1.2% [data on file]) (16). Interpretation of global response between treatment groups was confounded by a large proportion of patients (~40%) who were categorized by the DRC as ‘not evaluable’. The exposure-efficacy analysis of the subset mITT patients ($n = 176$) showed lack of positive association between drug exposures and 6-week global response (GR6), which confirmed that failure of global response was not due to low drug exposures in this study.

Moreover, the exposure-efficacy analysis could not identify a significant positive association between anidulafungin and voriconazole exposures ($AUC$ and $C_{\text{min}}$) and the 6-week survival rate (SURV6), but a slightly positive trend was observed for anidulafungin exposure in the combination group based on graphical examination (Figure 1). The dips in SURV6 and GR6 in the anidulafungin middle exposure category (e.g., $AUC_{0-24}$: >80-120 µg.h/mL) were noted, which could reflect a random observation (Figure 1 and Figure S1). No conclusion can be drawn from this observation.
Note that in the monotherapy group, the 6-week survival rate and successful global response rate appeared to be lower in patients with higher voriconazole exposure (i.e., $C_{\text{min}} > 5 \mu\text{g/mL}$, $n = 12$) (Figure 1 and Figure S1). This possibly is a reflection of the complex clinical situation. Treatment effect is just one of the contributing factors leading to successful clinical outcomes for life-threatening fungal infections (22). Patient’s underlying conditions and ability to respond to the treatment are also important factors influencing the clinical outcomes. The assessment of the relationship between voriconazole or anidulafungin exposure and clinical outcomes could be confounded by these factors. To rule out the possibility of reductions in survival and global response being due to toxicities related to elevated voriconazole exposures, the 9 patients in the monotherapy group, who died before day 42 with voriconazole $C_{\text{min}} > 5 \mu\text{g/mL}$, were assessed thoroughly (Table S5, supplemental material). Five patients stopped the voriconazole treatment at least 6 days before the death occurred, and the other 4 patients died within 2 days after the last dose of voriconazole (2 of them had very short treatment duration). Based on the cause of death, none of them were considered treatment related. Among them, one patient had a successful 6-week global response (others died before the week 6 assessment could be made). Taken together, it is unlikely that these deaths were related to voriconazole-related toxicities due to exposure to high voriconazole concentrations.

Although the best predictor for the 6-week survival rate was anidulafungin treatment duration, as stated earlier, caution in interpretation of this predictor is warranted because of the caveat that patients expiring prior to week 2 would necessarily have shorter duration of therapy, which could artificially inflate the effect of this covariate.

As described earlier, several published articles have proposed target minimum values for voriconazole $C_{\text{min}}$ to improve clinical outcomes, such as 1 or 2 $\mu\text{g/mL}$ (3, 9, 11-13, 23).
However, the results from our analysis do not support these cutoffs. As shown in Figure 1 (lower panel), the 6-week survival rate in IA patients with voriconazole $C_{\text{min}} \leq 2 \mu g/mL$ was similar to or even higher than that in patients with higher $C_{\text{min}}$. A further dissemination of the lower range of voriconazole $C_{\text{min}}$ is presented in Figure S4. Even in patients with voriconazole $C_{\text{min}} \leq 1 \mu g/mL$, the survival rate was still comparable to other exposure categories although the number of patients in this category was small (n = 17 in total). This suggests that voriconazole $C_{\text{min}}$ does not necessarily need to exceed 1 or 2 $\mu g/mL$ to achieve successful clinical outcomes in IA patients.

Our findings on the relationship between voriconazole exposure and clinical outcomes in IA patients (lack of positive association) are consistent with recently published retrospective analyses of large-scale TDM data (in 108 patients) by Chu et al. (14) and that (in 264 patients) by Racil et al. (15).

**Safety.** Our analysis did not identify any positive association between voriconazole exposure and hepatic, visual or psychiatric AEs in IA patients receiving voriconazole monotherapy. It is also noted that in the monotherapy group, the rate of hepatic and visual AEs appeared to be lower in patients with higher voriconazole exposure (e.g., $C_{\text{min}} > 5 \mu g/mL$) although the number of patients in this category was low (Figure 3 and Figure S2).

While in IA patients receiving combination therapy, a positive association between voriconazole and anidulafungin exposures and hepatic AEs was established, and a weak positive association between voriconazole exposure and psychiatric AEs was also established. Although no positive association between voriconazole exposure and visual AEs was established, a slightly positive trend was observed. This suggests an additive/or synergistic effect of combination use on the risk of experiencing hepatic, psychiatric or visual AEs. This effect might potentially be
extrapolated to the combination use of voriconazole with other antifungal agents that have identified risk of hepatotoxicity.

Similarly, several published articles have proposed target maximum values for voriconazole $C_{\text{min}}$ to minimize treatment-related toxicity, such as 6 or 5 or even 4 $\mu$g/mL (3, 9, 11-13, 23), and most of them were based on the identification of the association between elevated concentrations and neurologic AEs, but not hepatic AEs. These proposals were recommended based on voriconazole monotherapy regimens. Again, the results from our analysis do not support these cutoffs. Even in the combination group (where the positive association between exposures and hepatic AEs was established), there was no steep increase in the risk of having a hepatic AE as voriconazole $C_{\text{min}}$ increased in the presence of anidulafungin (e.g., mean increase of 5-8% by 1 $\mu$g/mL increment) (Figure 4). Hepatic AEs can be monitored through routine laboratory tests and visual AEs and neurotoxicity can be observed in clinical practice. Hence, it may not be essential to set up the upper threshold to a lower value if voriconazole $C_{\text{min}}$ is used to minimize the risks of treatment related toxicity, which could lead to unnecessary dose adjustments.

It is possible that the lack of association between voriconazole exposure and efficacy and safety in the voriconazole monotherapy group may be due to the sample size not being large enough to detect the signal. In addition, a positive association between voriconazole exposure and efficacy may be blurred by the absence of information on the pathogen as well as the disease status.

It is acknowledged that it would be beneficial to set up a reference range of voriconazole $C_{\text{min}}$ for prescribers if they have the capacity and prefer to do TDM for voriconazole management. For this purpose, a wide range of 1-6 $\mu$g/mL is deemed acceptable as the ‘typical’
voriconazole $C_{\text{min}}$ range. Given the lack of clear positive association between voriconazole exposure and clinical outcomes and toxicity (with voriconazole monotherapy), the primary consideration for dose adjustment should be based on patient’s clinical response and tolerability, and voriconazole $C_{\text{min}}$ (if available) should be considered as a secondary marker for purpose of dose adjustment. The results from our study have shown that this approach was appropriate: among the 55/277 (20%) mITT patients with voriconazole dose adjustment, only 13 patients used the fast-turnaround voriconazole concentrations for decision making. Detailed information is presented elsewhere (17). It is also be noted that approximately 80% of IA patients in this study had voriconazole $C_{\text{min}}$ ranging from 1 to 6 $\mu$g/mL at 4 mg/kg IV q12h, and approximately 85% of patients had $C_{\text{min}}$ within this range at 300 mg oral q12h (17).

A few scenarios are described to elaborate how to adjust voriconazole dose if voriconazole $C_{\text{min}}$ is taken into consideration. If a patient had a voriconazole $C_{\text{min}}$ of 0.5 $\mu$g/mL and responded well, it is not necessary to increase the dose. If a patient had a voriconazole $C_{\text{min}}$ of 2 $\mu$g/mL and was able to tolerate this dose, but the response seemed less than ideal, voriconazole dose could be increased with caution in the hope of improving the chance of clinical success. If a patient had a voriconazole $C_{\text{min}}$ of 4 $\mu$g/mL and responded well, but treatment-related toxicity was shown (e.g., moderate to severe hepatic AEs), voriconazole dose could be reduced with caution. If a patient had a voriconazole $C_{\text{min}}$ of 6.5 $\mu$g/mL, had responded well and was able to tolerate this dose (e.g., no hepatic, visual or psychiatric AEs), it is not necessary to reduce the dose.

In summary, given the complex clinical situation for patients with serious fungal infections, it is difficult to establish definitive exposure-response relationships for voriconazole. Thus, management of voriconazole treatment (e.g., dose adjustment) requires physicians to take
into consideration the individual patient’s clinical response, tolerability profile and voriconazole concentration (if available).

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REFERENCES


### Table 1. Summary of PK-PD data pairs for safety analysis

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<th>PK-PD data pairs&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
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<td><strong>Subjects without AEs (hepatic, visual or psychiatric)</strong></td>
<td></td>
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<td>Single-panel data</td>
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<td>Multiple-panel data</td>
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<td><strong>Hepatic AEs (Treatment-Related)</strong></td>
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</tr>
<tr>
<td>Multiple-panel data</td>
<td>293 (132)</td>
</tr>
<tr>
<td><strong>Hepatic AEs (All-Causality)</strong></td>
<td></td>
</tr>
<tr>
<td>Single-panel data</td>
<td>238 (77)</td>
</tr>
<tr>
<td>Multiple-panel data</td>
<td>328 (167)</td>
</tr>
<tr>
<td><strong>Visual AEs (Treatment-Related)</strong></td>
<td></td>
</tr>
<tr>
<td>Single-panel data</td>
<td>183 (22)</td>
</tr>
<tr>
<td>Multiple-panel data</td>
<td>189 (28)</td>
</tr>
<tr>
<td><strong>Visual AEs (All-Causality)</strong></td>
<td></td>
</tr>
<tr>
<td>Single-panel data</td>
<td>199 (38)</td>
</tr>
<tr>
<td>Multiple-panel data</td>
<td>208 (47)</td>
</tr>
<tr>
<td><strong>Psychiatric AEs (Treatment-Related)</strong></td>
<td></td>
</tr>
<tr>
<td>Single-panel data</td>
<td>183 (22)</td>
</tr>
<tr>
<td>Multiple-panel data</td>
<td>186 (25)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Number of data pairs (number of AE occurrence).

<sup>b</sup> Multiple events could be reported in one subject and all events were included for analysis.
Table 2. Summary of parameter estimates in the final PK-PD models

<table>
<thead>
<tr>
<th>Analysis endpoint</th>
<th>Description of Logit Function ($\lambda_i$)</th>
<th>OFV</th>
<th>Parameter estimate (%RSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$\theta_1$</td>
</tr>
<tr>
<td>SURV6</td>
<td>$0_1 + 0_2 * \text{Duranid}$</td>
<td>171.541</td>
<td>0.828 (26)</td>
</tr>
<tr>
<td></td>
<td>Treatment-related hepatic AEs (single-panel data)</td>
<td>228.061</td>
<td>-1.63 (13)</td>
</tr>
<tr>
<td></td>
<td>$0_1 + 0_2 * C_{\text{min}} * C_{\text{max}}$</td>
<td>228.181</td>
<td>-1.67 (14)</td>
</tr>
<tr>
<td></td>
<td>All-causality hepatic AEs (single-panel data)</td>
<td>280.316</td>
<td>-1.2 (16)</td>
</tr>
<tr>
<td></td>
<td>$0_1 + 0_2 * C_{\text{min}} * C_{\text{max}}$</td>
<td>280.864</td>
<td>-1.23 (16)</td>
</tr>
<tr>
<td></td>
<td>Treatment-related psychiatric AEs (multiple-panel data)</td>
<td>132.822</td>
<td>-2.58 (14)</td>
</tr>
<tr>
<td></td>
<td>$0_1 + 0_2 * C_{\text{min}} * \text{TRTG}$</td>
<td>133.206</td>
<td>-2.63 (14)</td>
</tr>
</tbody>
</table>

OFV = objective function value, %RSE = percent relative standard error, SURV6 = surviving 6 weeks, AUCa = anidulafungin AUC0-24, AUCv = voriconazole AUC0-12, Cmina = anidulafungin Cmin, Cminv = voriconazole Cmin, Duranid = anidulafungin treatment duration, TRTG = treatment group (1 = combination, 0 = monotherapy).

Table 3. Model-based predicted probability change by voriconazole and anidulafungin exposures

<table>
<thead>
<tr>
<th>Analysis type for hepatic AEs</th>
<th>% mean increase in probability by 1 µg/mL increment of voriconazole $C_{\text{min}}$ in the presence of anidulafungin (median $C_{\text{min}}$ of 2.6 µg/mL), Range (%)</th>
<th>% mean change in probability by 1 µg/mL increment of anidulafungin $C_{\text{min}}$ in the presence of voriconazole (median $C_{\text{min}}$ of 3 µg/mL), Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-panel data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related</td>
<td>5 – 8</td>
<td>6 – 9</td>
</tr>
<tr>
<td>All-causality</td>
<td>5 – 6</td>
<td>6 – 7</td>
</tr>
<tr>
<td>Multiple-panel data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related</td>
<td>4 – 10</td>
<td>3 – 11</td>
</tr>
<tr>
<td>All-causality</td>
<td>3 – 9</td>
<td>3 – 10</td>
</tr>
</tbody>
</table>
Figure 1. Observed probabilities of SURV6 vs. voriconazole and anidulafungin exposure parameters and treatment duration.

Anid = anidulafungin, AUC = area under the concentration-time curve, Bin Counts = total number of patients in each exposure category, Cmin = trough concentration, Combo = combination therapy, Mono = monotherapy, Trt = treatment, Vori = voriconazole.

Stacked bar plot showing the probability of the efficacy endpoint, calculated as the ratio of the number of successful outcomes in a particular bin to the total number in that bin and presented as a percentage. An attempt was made to balance the number of observations in each bin.
Figure 2. Observed probabilities of SURV6 vs. demographics

Bin Counts = total number of patients in each demographic category, EM = CYP2C19 extensive metabolizer, HEM = heterozygous extensive metabolizer, PM = poor metabolizer, UNK = unknown.
Figure 3. Observed probabilities of treatment-related hepatic AE occurrence vs.
anidulafungin and voriconazole exposure parameters (single-panel data)

Anid = anidulafungin, Bin Counts = total number of patients in each exposure category, Combo = combination therapy group, Mono = voriconazole monotherapy group, Vori = voriconazole.
Figure 4. Observed and model predicted probability of hepatic AE occurrence vs. voriconazole and anidulafungin $C_{\text{min}}$ (single-panel data)

(a) Treatment-related hepatic AEs

Key – symbols are observed individual data in the combination group (AE present = 1, AE absent = 0), solid circles are observed probability of AE at each concentration level (note: observed probabilities were derived by bucketing concentration data to the nearest integer for summary purpose). The line and the corresponding band represent the population predicted probability and its 95% confidence interval (computed with 1000 bootstrap).

(b) All-causality hepatic AEs
Figure 5. Observed and model predicted probability of treatment-related psychiatric AE occurrence vs. voriconazole exposure parameters (multiple-panel data).

Key – ‘|’ symbols are observed individual data in the combination group (AE present = 1, AE absent = 0), solid circles are observed probability of AE at each concentration level (note: observed probabilities were derived by bucking concentration data to the nearest integer for summary purpose). The solid line and the corresponding band represent the population predicted probability and its 95% confidence interval (computed with 1000 bootstrap).