Exposure-Response Relationships for Isavuconazole in Patients with Invasive Aspergillosis and Other Filamentous Fungi

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Running Head: Exposure-Response of Isavuconazole

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Abstract: Word count 249

Isavuconazole, the active moiety of the water-soluble prodrug isavuconazonium sulfate, is a triazole antifungal agent for the treatment of invasive fungal infections. The purpose of this analysis was to characterize the isavuconazole exposure-response relationship for measures of efficacy and safety in patients with invasive aspergillosis and other filamentous fungi from the SECURE trial. Two hundred and thirty one patients who received the clinical dosing regimen and had exposure parameters were included in this analysis. The primary drug exposure parameters included were predicted trough steady-state plasma concentrations, predicted trough concentrations after 7 and 14 days of drug administration, and area under the curve estimated at steady state (AUCss). The exposure parameters were analyzed against efficacy endpoints that included: all-cause mortality through Day 42 in the intent-to-treat (ITT) and modified ITT population, data-review committee (DRC)-adjudicated overall response at end of treatment (EOT) and DRC-adjudicated clinical response at EOT. Safety endpoints analyzed were elevated or abnormal alanine aminotransferase, increased aspartate aminotransferase and the combination of both. The endpoints were analyzed using logistic regression models. No statistically significant relationship (P >0.05) was found between isavuconazole exposures and either efficacy or safety endpoints. The lack of association between exposure and efficacy indicates that the isavuconazole exposures achieved by clinical dosing were appropriate for treating the infecting organisms in the SECURE study and that increases in alanine or aspartate aminotransferase were not related to increase in exposures. Without a clear relationship, there is no

current clinical evidence for recommending routine therapeutic drug monitoring for isavuconazole.

INTRODUCTION

The morbidity and mortality from invasive fungal diseases remain substantial (1). Triazole antifungal agents are first-line agents for the prevention and treatment of these infections. Voriconazole is recommended as primary treatment for invasive aspergillosis (IA). Posaconazole is primarily indicated as salvage therapy for patients with IA and prophylaxis for patients with neutropenia and hematopoietic stem-cell transplant recipients (2). Isavuconazole administered as the prodrug isavuconazonium sulfate, is a novel, broad-spectrum, triazole antifungal agent. Recently, isavuconazonium sulfate has been approved by the US Food and Drug Administration for the treatment of adults with IA and invasive mucormycosis (3) and by the European Medicines Agency for the treatment of adults with IA and those with mucormycosis for whom amphotericin B is not appropriate (4). In the SECURE trial, isavuconazole was demonstrated to be non-inferior to voriconazole for the primary treatment of invasive mold disease caused by *Aspergillus* and other filamentous fungi, as determined using all-cause mortality through Day 42 as the primary endpoint (19% vs.20%, respectively) (5). Overall response and clinical response rates were similar for isavuconazole and voriconazole (50% vs 47%, and 62% vs 60%, respectively), and the isavuconazole group had significantly lower rates of hepatobiliary disorders (9% vs 16%), eye disorders (15% vs 27%), skin or subcutaneous tissue disorders (33% vs 42%), and drug-related adverse events (42% vs 60%).

A deep understanding of the relationships between drug exposure and response is required to establish clinically useful threshold values for drug

exposure for both clinical outcomes and adverse events. Exposure-response relationships for efficacy are well established for other currently approved triazoles, such as itraconazole, posaconazole, and voriconazole, which has led to target drug concentrations that are necessary to maintain drug levels within safe and effective ranges (6-10). Exposure-response relationships for safety are also well established for itraconazole and voriconazole (8, 11). Thus, an important question remains as to whether these relationships are also evident for isavuconazole. Establishing clinically relevant exposure-response and exposure-safety relationships will inform guidelines with respect to the potential need for therapeutic drug monitoring (TDM).

In the SECURE trial, isavuconazole plasma concentrations were available for the majority of patients who were enrolled in the isavuconazole arm. Therefore, this *post hoc* analysis was conducted to evaluate the exposure-response relationships in terms of efficacy and safety for isavuconazole using those patient data. Logistic regression modeling was used to explore the potential relationship between various measures of isavuconazole exposure, and both clinical outcomes and adverse events.

MATERIAL AND METHODS

Study design. SECURE (ClinicalTrials.gov identifier: NCT00412893) was a global, phase 3, randomized, multicenter, double-blind, parallel-group, non-inferiority trial (Fig.1). Full details of the SECURE trial have been published previously (5).

Patients with proven/probable disease, as assessed by an independent and blinded data-review committee (DRC), were included in the modified ITT (mITT) population. All patients received 372 mg of isavuconazonium sulfate (equivalent to 200 mg isavuconazole) administered by intravenous infusion (IV) every 8 hours for 6 doses (i.e., days 1 and 2), followed by a maintenance dose of 372 mg isavuconazonium sulfate administered once daily, either IV or orally (PO), from Day 3 to end of treatment (EOT). Hereafter, only isavuconazole and the dosing equivalent will be used.

Efficacy and safety assessments. In the current analysis, the efficacy endpoints included were (i) all-cause mortality through Day 42 in the ITT population and mITT populations (ii) DRC-adjudicated overall response at EOT in the ITT and mITT populations and (iii) DRC-adjudicated clinical response at EOT in the ITT and mITT populations. Liver function test values (aspartate aminotransferase [AST] and alanine transaminase [ALT]) at the EOT and post baseline (EOT + 10 days) were assessed as safety outcomes.

Estimation of pharmacokinetic (exposure) parameters. A population pharmacokinetic model (PPK) was previously developed for concentration data

109 from the SECURE study in combination with data from healthy subjects, using
110 NONMEM version 7.2 (GloboMax LLC, Hanover, MD, USA) (12). This publication
111 lists values and dispersions associated with parameters that were used for the
112 simulation. Total-drug area under the concentration-time curve at steady state
113 (AUC_{SS}) was calculated using the standard formula, AUC = F × dose/CL, based
114 on the individual parameter estimates from the best PPK model, where F is
115 bioavailability and CL is clearance. Individual parameter estimates obtained from
116 the best model with covariates were used to calculate trough concentrations at
117 steady state (Css), trough concentrations after 7 days of dosing (C7), and trough
118 concentrations after 14 days of dosing (C14).
119
120 **Exposure-response analysis.** All the efficacy and safety data were evaluated
121 as binary and ordinal data using a logistic regression model in SAS® (version 9.3,
122 SAS Institute Inc., Cary, NC, USA). The graphic processing of the data was also
123 performed in SAS or R (Version 2.17, available at: https://www.r-project.org (13)).
124 Each efficacy endpoint and safety endpoint as described above was analyzed
125 separately using isavuconazole exposure parameters.
126 The covariates were identified based on scientific interest or prior
127 knowledge of any possible relationship with exposure parameters. Duration of
128 therapy was the only continuous covariate investigated. Categorical covariates
129 tested for the exposure-efficacy analysis included: race (Caucasian/Asian);
130 hematological malignancy (yes/no); uncontrolled malignancy at baseline
131 (yes/no); neutropenia at baseline (yes/no); serum galactomannan at baseline
132 (<1/≥1); and lower respiratory tract disease (yes/no). Covariates along with

primary exposure parameters were added in an automated stepwise approach with $\alpha = 0.3$ for model inclusion and $\alpha = 0.05$ for model retention.

Exposure-response analyses were also performed for patients in the ITT population who had minimum inhibitory concentration (MIC) values for any *Aspergillus* spp. (including *A. flavus*, *A. fumigatus*, *A. niger*, and *A. terreus*). MIC values were determined using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology (14) by Case Western Reserve University, Cleveland, OH, USA. AUC_{∞}/MIC ratios were calculated based on model-predicted AUC_{ss} values for a patient and the corresponding highest MIC value, irrespective of the fungus that was cultured.

RESULTS

Data for analysis. Two hundred thirty-one patients from a previously developed PPK model provided exposure parameters (12) used in the exposure-response analysis for both clinical outcomes and safety. One hundred twenty-nine patients qualified for the mITT population based on DRC-adjudicated criteria. A summary of the covariates used in this analysis is provided in Table 1.

Exposure-efficacy analysis. Exposure parameters are summarized in Table 2. The mean calculated exposure at steady state (AUCss) was 101 mg*hr/L, with exposures ranging from 10 to 343 mg*hr/L. Mean trough concentrations at Css, C7 and C14 were approximately 3600 ng/mL, 2600 ng/mL, and 3000 ng/mL respectively. Trough concentrations ranged from 174 to 10,000 ng/mL.

All-cause mortality at Day 42. All drug exposure parameters (i.e., AUCss, trough concentrations at Css, C7 and C14) were examined graphically and were modeled univariately. There was no apparent relationship between drug exposure parameters and mortality at Day 42 for either the ITT population or mITT population (Figure 2a and 2b, respectively). None of the primary parameters were retained in the logistic regression model. Logistic regression analysis did not suggest any positive association between exposure parameters and mortality at Day 42. Since none of the primary exposure parameters were retained in the model, further covariate analysis was not explored.

DRC adjudicated overall and clinical response at end of treatment (EOT). Graphical examination of binary outcomes for AUCss and Css for the ITT and mITT populations against clinical and overall response are shown in Fig. 3a and 3b, respectively. Logistic regression models did not demonstrate any relationship of drug exposure with mortality, clinical response and overall response. None of the exposure parameters were significant at a significance level of 0.05 to be retained in the model. Similar results were obtained for C7 and C14 (data not shown).

AUC/MIC calculations. There was only a small sample subset of patients with both PK parameters and pathogen susceptibility data available (n = 36) compared with the total number of subjects in this study. Details of patients with MIC values are provided in the Supplementary Table S1. No significant relationship (P>0.05) was identified between the AUC/MIC ratio and mortality at Day 42, the overall response at EOT, or the clinical response at EOT. Since only 2 of the 36 patients were not included in the mITT population, that analysis would necessarily have yielded almost identical results and so it was not performed. No relationship was observed between MIC values and outcome parameters (15).

Exposure-safety analysis. Patients with PK parameters used in the exposure-response analysis were also included in this analysis. Graphical examination of binary outcomes for AUCss and Css for the ITT and mITT populations against normal/elevated levels of ALT and ALT are shown in Fig. 4. None of the primary exposure parameters were found to be statistically significant for any of the

safety outcomes (ALT or AST or combined ALT/AST) for either the ITT (*n* = 226) or mITT (*n* = 126) populations. As none of the primary exposure parameters were significant (*P*>0.3), there was no retention of parameters in the logistic model.

DISCUSSION

The primary aim of this analysis was to investigate any potential relationship between various measures of drug exposure of isavuconazole and both efficacy and safety outcomes. Such an understanding is required to further reflect on the potential requirement for TDM as a component of routine clinical care of patients receiving isavuconazole. Conducting an exposure-response/safety analysis provides an understanding of any threshold of exposure that is predictive of efficacy and/or adverse events.

We were unable to demonstrate any statistically significant relationships for any measure of drug exposure (i.e., AUCss or Css or AUC/MIC) and various outcomes (i.e., all-cause mortality at Day 42 or clinical and overall responses at EOT or MIC of fungal isolates). A slight trend was observed for overall responses for both ITT and mITT populations, but this was not statistically significant ($P > 0.05$).

There could be several reasons for any lack of relationship between drug exposure and clinical outcomes from this analysis. Firstly, even though there were some extremes in predicted exposures, the variability was only 62% in patient population (12). Secondly, it is possible there was a degree of bias in the PPK model. The PPK model was fitted to data from both phase 1 and sparse data from phase 3 data. Even though there were 231 patients in the SECURE study, sparse data may potentially have led to biased estimates of exposure and Css values. However, there is no evidence of this given concordance with PK models fitted to other isavuconazole datasets (16). Poor compliance to the study drug could also have led to biased estimates of drug exposures, although there is

no specific evidence to suggest this occurred. Alternatively, assuming the existence of a sigmoidal exposure-response relationship, the lack of a relationship with outcomes might simply reflect that exposures were on the plateau of the curve (suprathreshold). The lack of association between exposure and response is consistent with the proposition that the isavuconazole exposures achieved by the clinical dosage regimen were near maximal for treating the infecting organisms in the SECURE study. In this respect, it is worth noting that the overall cure rate observed for isavuconazole in the SECURE trial was comparable to other trials of triazole antifungals (2, 5, 17, 18).

Although isolates were not obtained from the majority of patients (and therefore MIC values for the invading pathogens were not determined), it is likely that most patients were infected by wild-type organisms. It is possible that the inclusion of more patients infected with non wild-type strains might have enabled exposure-response relationships to be better described. *In vivo* and *ex vivo* models have demonstrated that the MIC values have a clear impact on exposure-response relationships, as proportionally higher drug exposures are required to achieve the same outcomes for strains with higher MICs (19-23). Although there were insufficient numbers of patients in the SECURE study for whom pathogen susceptibility was the only distinction to allow that possibility to be tested, a few patients with MIC values up to 8 mg/L were successfully treated (5). However, ongoing information from the post-license database may eventually enable clinical exposure-response relationships to be better defined.

Even though a threshold value for any drug exposure parameters was not found to be correlated with mortality and clinical response, the duration of

242 therapy did appear to be important and was statistically significant ($P < 0.05$).
243 This finding should be interpreted with some caution. The importance of the
244 duration of therapy may be confounded by other factors that influence outcomes
245 (e.g., nature of the underlying disease). There is currently no definitive evidence
246 that suggests that longer duration of therapy is necessarily associated with a
247 better clinical response. Furthermore, there is no clear clinical evidence of the
248 minimum duration of antifungal therapy that is required for clinical cure.

249 Hepatotoxicity is a class effect for the azole group of antifungal agents
250 with effects ranging from mild increase in liver function tests to possibly fatal
251 hepatic failure being reported (24). The exact mechanism of elevated liver
252 function with azole antifungal agents remains unknown (24). Due to the primary
253 concern of elevated liver function values, exposure-safety analysis was
254 performed on elevated ALT and AST levels. These values were available for all
255 patients. The current analysis did not identify any association between
256 isavuconazole exposure and elevated ALT or AST levels, or for a combination of
257 both ALT/AST levels. One limitation of this analysis is the small proportion of
258 patients who had elevated ALT or AST levels. Only 23/226 and 19/226 patients in
259 this analysis had elevated ALT or AST levels.

260 Voriconazole, posaconazole and itraconazole have target trough
261 concentrations that need to be maintained in order optimize the probability of
262 response. The voriconazole C_{min} target recommended by the British Society of
263 Medical Mycology is between 1.0 and 5.5 mg/L when the drug is used to treat
264 invasive infection (7). The target voriconazole concentrations for prophylaxis is
265 less clear. For posaconazole, the target trough concentrations are > 0.7 µg/mL

for prophylaxis and >1 mg/L for salvage therapy. For itraconazole, the target trough concentrations are similar to voriconazole (7). Fluconazole does not require routine therapeutic drug monitoring. There is no apparent relationship between exposure and efficacy to suggest routine TDM for isavuconazole. However, it is reasonable to continue observing real-world patients who are administered isavuconazole and monitor their exposures when necessary to ensure they do not require TDM. There might be a necessity to confirm isavuconazole exposures in select clinical cases (e.g. severe gut disease from graft-versus-host disease [in which drug absorption through oral route is problematic], in treatment of central nervous system infections, or in infections with non-wild type fungal pathogens). TDM may also be necessary when dosing in children or adolescents due to minimum exposure information (25).

In conclusion, no statistically significant relationships were observed for any of the exposure parameters of isavuconazole (AUCss, Css, C7, and C14) with any safety markers (ALT, AST, and combined ALT/AST), either at the EOT or post baseline, nor with any efficacy endpoints (all-cause mortality, overall and clinical response). In some models, duration of therapy was retained in the model. However, this covariate is highly confounded making its relevance in this analysis unclear. Also, experimental PD models were conducted to establish the exposure-response relationship associated with efficacy and to estimate the target exposure associated with the optimal exposure-response relationship. The results showed that the clinical dosing regimen achieved exposures adequate to treat infections. All models were developed on the observed data (12); however,

the model was not validated against external data from a clinical trial, which would have required performing additional isavuconazole studies.

Finally, TDM may be considered for individual cases as discussed, but, at present, there is no clear evidence that there is a general need for TDM or a clear target in which to recommend.

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Figure legends

Fig 1 Study design

BID, twice daily; EOT, end of treatment; IV, intravenous; QD, once daily; TID, three times daily.

Fig 2 Box and whisker plots of drug exposure (AUCss and Css) vs mortality at Day 42 for ITT population (A) and mITT population (B)

AUCss, total area under the concentration-time curve at steady state; Css, concentration at steady state; ITT, intent-to-treat; mITT, modified intent-to-treat.

Fig 3 Box and whisker plots of drug exposure (AUCss and Css) vs clinical and overall response at EOT for ITT population (A) and mITT population (B)

AUCss, total area under the concentration-time curve at steady state; Css, concentration at steady state; ITT, intent-to-treat; mITT, modified intent-to-treat.

Fig 4 Box and whisker plots of drug exposure (AUCss and Css) vs ALT/AST levels at EOT for ITT population (A) and mITT population (B)

442 ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUCss, total
443 area under the curve at steady state; Css, concentration at steady state; EOT,
444 end of treatment; ITT, intent-to-treat; mITT, modified intent-to-treat.
445

TABLE 1 Summary of patient characteristics

Patient characteristics	ITT population (*n* = 231)		mITT population (*n* = 129)	
	Yes	No	Yes	No
Hematological malignancy	191	40	100	29
Uncontrolled malignancy	156	75	79	50
Neutropenia	150	81	79	50
Elevated serum galactomannan at baseline[a]	54	150	51	62
Lower respiratory tract disease	182	49	104	25
Duration of therapy (Median)	51 days		59 days	

Yes/No: Had/did not have characteristics at baseline. *n* is number of patients. [a]Some patients (*n* = 27) did not have galactomannan information at baseline.

ITT, intent-to-treat, mITT, modified intent-to-treat.

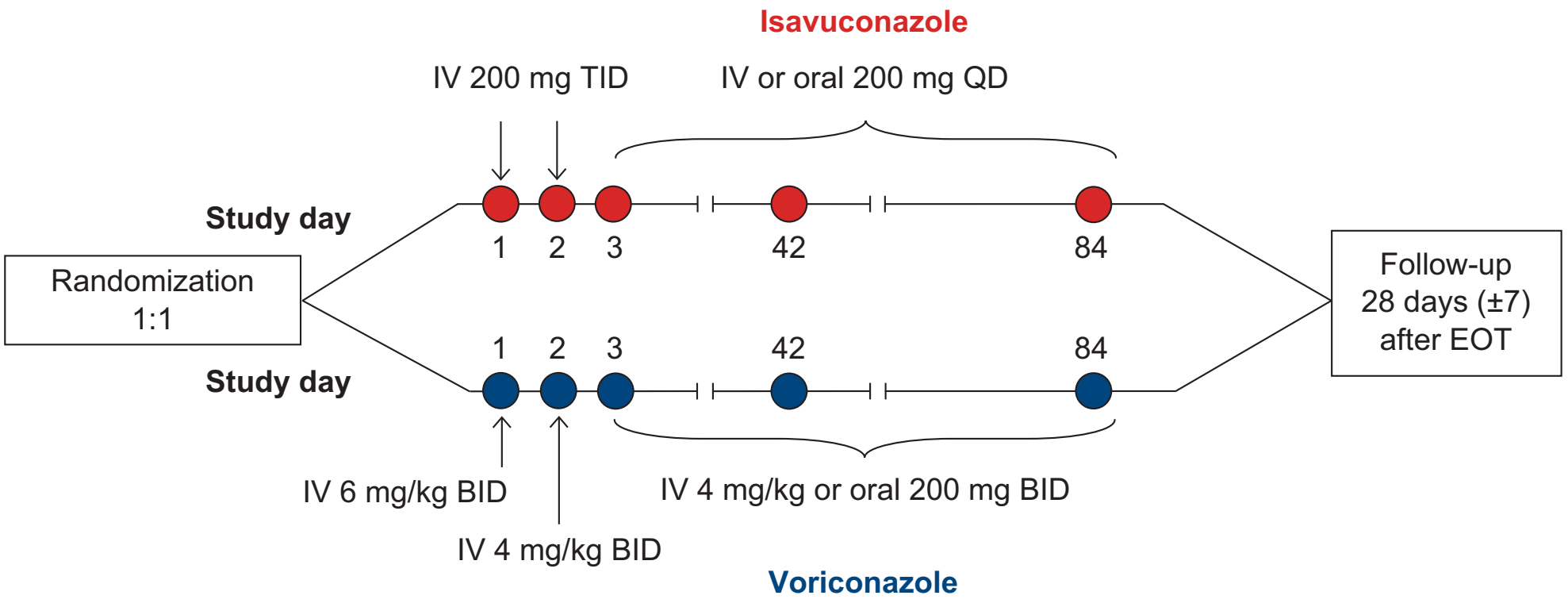
TABLE 2 Summary of exposure parameters

	AUCss (mg*h/L)	Css (ng/mL)	C7 (ng/mL)	C14 (ng/mL)
Mean (SD)	101 (56)	3633 (2023)	2631 (1033)	3049 (1397)
Median	90	3218	2477	2923
Range	10-343	174-10969	189-5627	174-7512

Values rounded to nearest whole number.

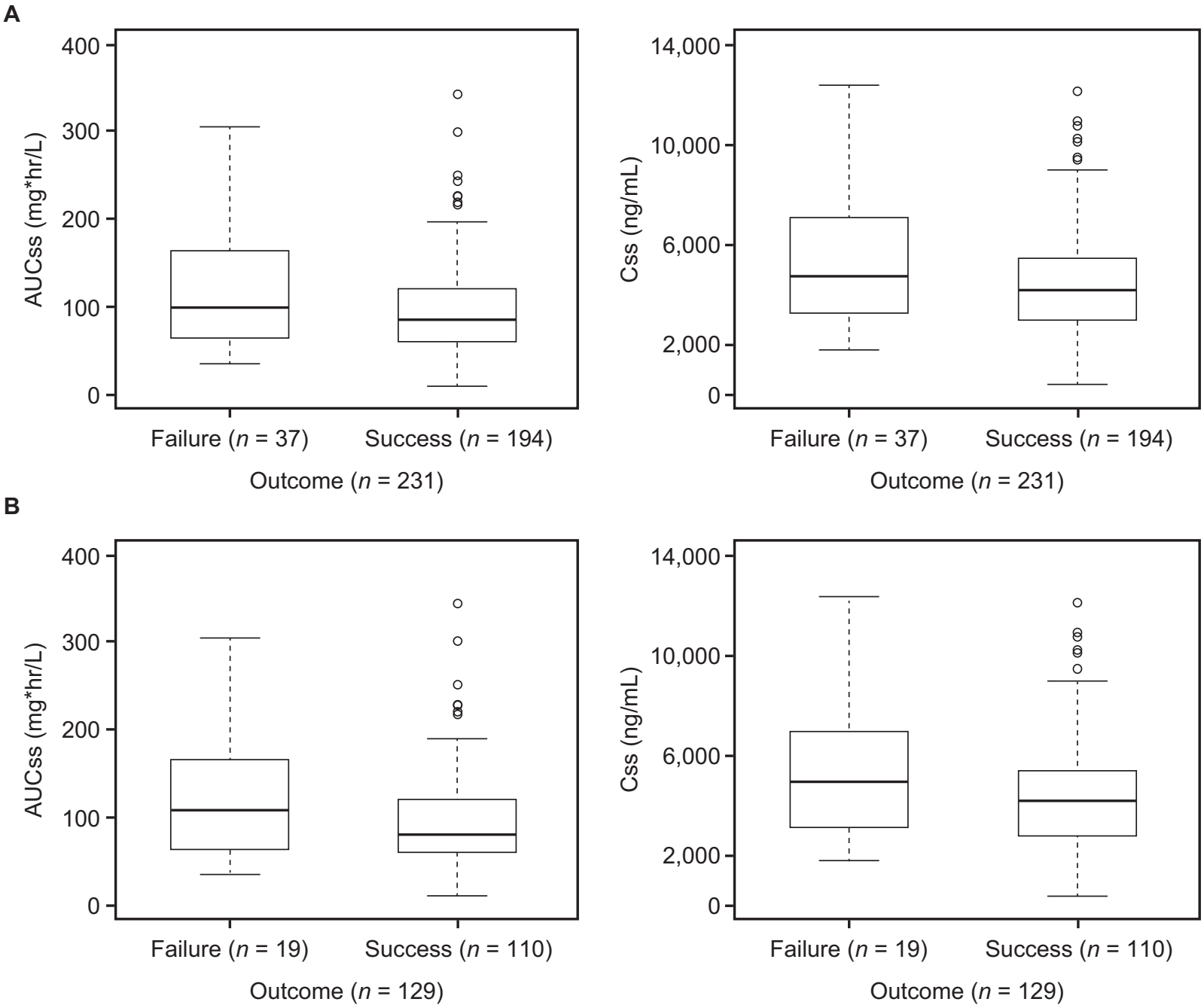
AUCss, total area under the curve at steady state; Css, concentration at steady state; C7, concentration after 7 days of dosing, C14, concentration after 14 days of dosing; SD, standard deviation.

FIG 1 Study design



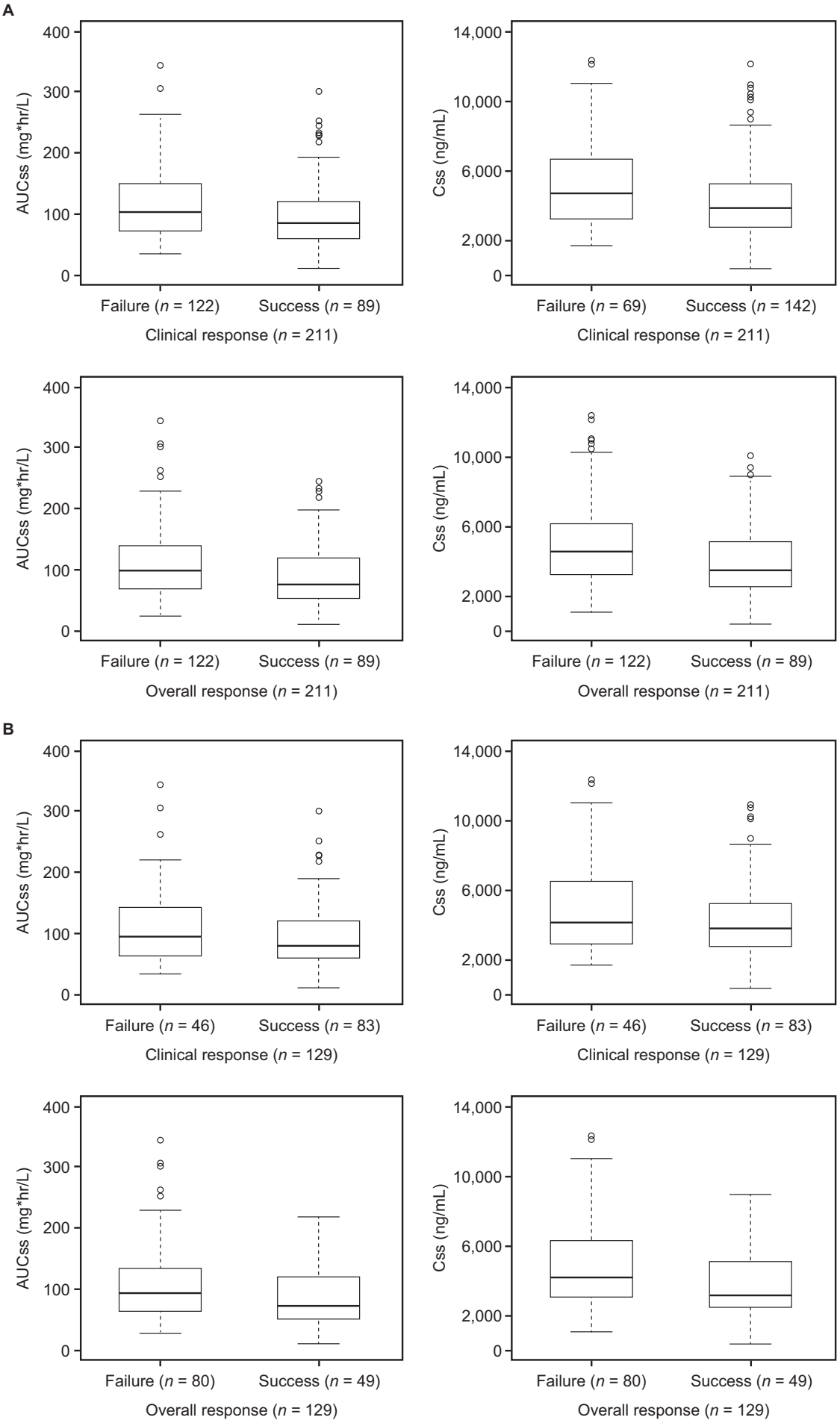
Maximum therapy duration was 84 days.

FIG 2 Box and whisker plots of drug exposure (AUCss and Css) vs mortality at Day 42 for ITT population (A) and mITT population (B)



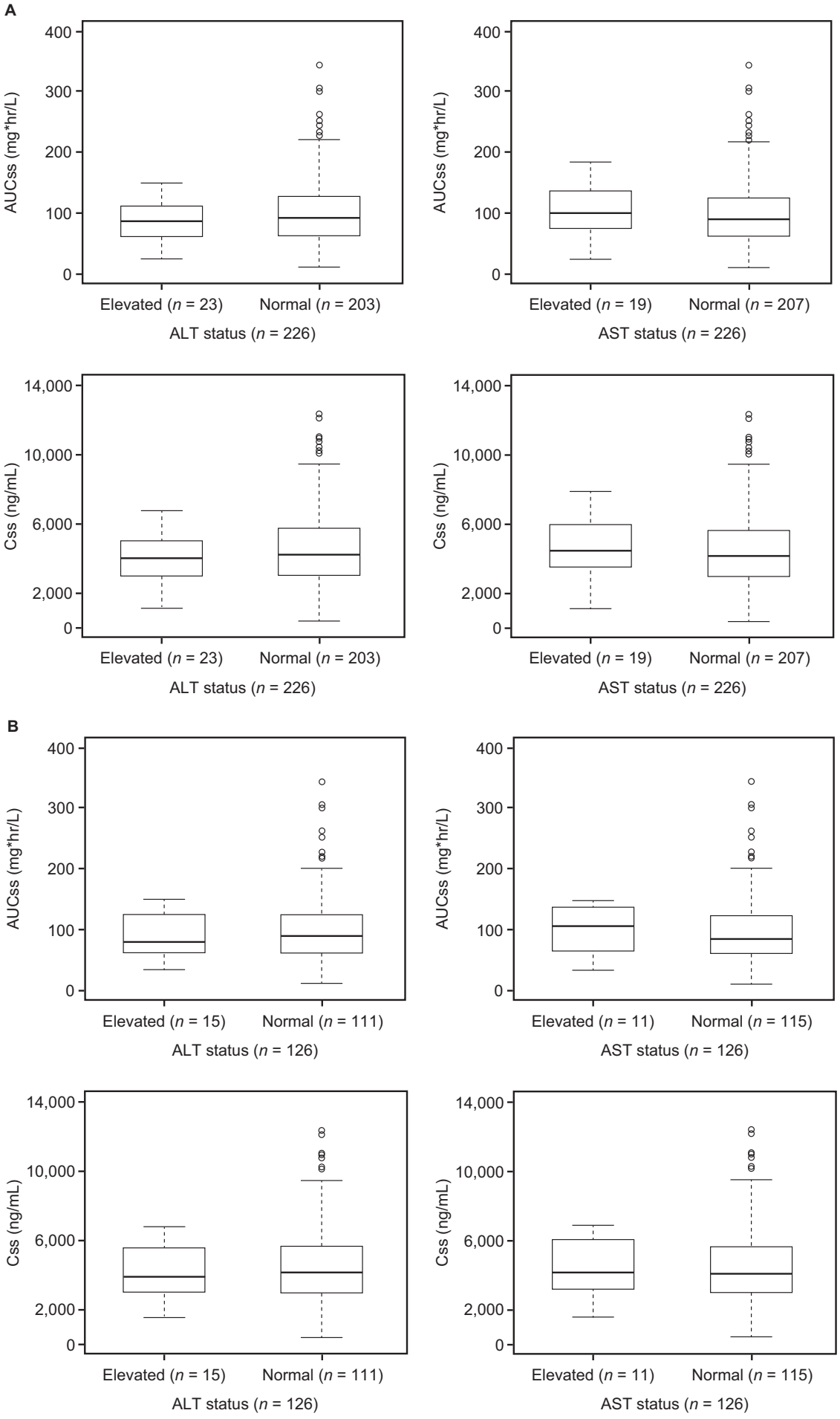
Boxes represent median, 25th and 75th percentiles; whiskers represent range of maximum and minimum values within 1.5 × the interquartile range; outliers are shown as circles.

FIG 3 Box and whisker plots of drug exposure (AUCss and Css) vs clinical and overall response at EOT for ITT population (A) and mITT population (B)



Boxes represent median, 25th and 75th percentiles; whiskers represent range of maximum and minimum values within 1.5 × the interquartile range; outliers are shown as circles.

FIG 4 Box and whisker plots of drug exposure (AUCss and Css) vs ALT/AST levels at EOT for ITT population (A) and mITT population (B)



Boxes represent median, 25th and 75th percentiles; whiskers represent range of maximum and minimum values within 1.5 × the interquartile range; outliers are shown as circles.