

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

3

4

5 Amit V. Desai,^a# Laura L. Kovanda,^{a,b} William W. Hope,^b David Andes,^c Johan W.
6 Mouton,^d Donna L. Kowalski,^a Robert W. Townsend,^a Salim Mujais,^a Peter L.
7 Bonate^a

8

9 Astellas Pharma Global Development, Inc., Northbrook, Illinois, USA^a; University
10 of Liverpool, Liverpool, UK^b; University of Wisconsin, Madison, WI, USA^c;
11 Erasmus MC, Rotterdam, The Netherlands^d

12

13 Running Head: Exposure-Response of Isavuconazole

14

15 #Address correspondence to Amit Desai, amit.desai@astellas.com

16

17

18 **Abstract:** Word count 249

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

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

44 **INTRODUCTION**

45 The morbidity and mortality from invasive fungal diseases remain
46 substantial (1). Triazole antifungal agents are first-line agents for the prevention
47 and treatment of these infections. Voriconazole is recommended as primary
48 treatment for invasive aspergillosis (IA). Posaconazole is primarily indicated as
49 salvage therapy for patients with IA and prophylaxis for patients with neutropenia
50 and hematopoietic stem-cell transplant recipients (2). Isavuconazole
51 administered as the prodrug isavuconazonium sulfate, is a novel, broad-
52 spectrum, triazole antifungal agent. Recently, isavuconazonium sulfate has been
53 approved by the US Food and Drug Administration for the treatment of adults
54 with IA and invasive mucormycosis (3) and by the European Medicines Agency
55 for the treatment of adults with IA and those with mucormycosis for whom
56 amphotericin B is not appropriate (4). In the SECURE trial, isavuconazole was
57 demonstrated to be non-inferior to voriconazole for the primary treatment of
58 invasive mold disease caused by *Aspergillus* and other filamentous fungi, as
59 determined using all-cause mortality through Day 42 as the primary endpoint
60 (19% vs.20%, respectively) (5). Overall response and clinical response rates
61 were similar for isavuconazole and voriconazole (50% vs 47%, and 62% vs 60%,
62 respectively), and the isavuconazole group had significantly lower rates of
63 hepatobiliary disorders (9% vs 16%), eye disorders (15% vs 27%), skin or
64 subcutaneous tissue disorders (33% vs 42%), and drug-related adverse events
65 (42% vs 60%).

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

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

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

85 **MATERIAL AND METHODS**

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

90 Patients with proven/probable disease, as assessed by an independent
91 and blinded data-review committee (DRC), were included in the modified ITT
92 (mITT) population. All patients received 372 mg of isavuconazonium sulfate
93 (equivalent to 200 mg isavuconazole) administered by intravenous infusion (IV)
94 every 8 hours for 6 doses (i.e., days 1 and 2), followed by a maintenance dose of
95 372 mg isavuconazonium sulfate administered once daily, either IV or orally (PO),
96 from Day 3 to end of treatment (EOT). Hereafter, only isavuconazole and the
97 dosing equivalent will be used.

98

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

106

107 **Estimation of pharmacokinetic (exposure) parameters.** A population
108 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, $AUC = F \times \text{dose}/CL$, 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 (C_{ss}), trough concentrations after 7 days of dosing (C_7), and trough
118 concentrations after 14 days of dosing (C_{14}).

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 ($<1/\geq 1$); and lower respiratory tract disease (yes/no). Covariates along with

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

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

143 **RESULTS**

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

149

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

155

156 **All-cause mortality at Day 42.** All drug exposure parameters (i.e., AUC_{ss},
157 trough concentrations at C_{ss}, C7 and C14) were examined graphically and were
158 modeled univariately. There was no apparent relationship between drug
159 exposure parameters and mortality at Day 42 for either the ITT population or
160 mITT population (Figure 2a and 2b, respectively). None of the primary
161 parameters were retained in the logistic regression model. Logistic regression
162 analysis did not suggest any positive association between exposure parameters
163 and mortality at Day 42. Since none of the primary exposure parameters were
164 retained in the model, further covariate analysis was not explored.

165

166 **DRC adjudicated overall and clinical response at end of treatment (EOT).**
167 Graphical examination of binary outcomes for AUC₀₋₂₄ and C₂₄ for the ITT and
168 mITT populations against clinical and overall response are shown in Fig. 3a and
169 3b, respectively. Logistic regression models did not demonstrate any relationship
170 of drug exposure with mortality, clinical response and overall response. None of
171 the exposure parameters were significant at a significance level of 0.05 to be
172 retained in the model. Similar results were obtained for C₇ and C₁₄ (data not
173 shown).

174

175 **AUC/MIC calculations.** There was only a small sample subset of patients with
176 both PK parameters and pathogen susceptibility data available ($n = 36$)
177 compared with the total number of subjects in this study. Details of patients with
178 MIC values are provided in the Supplementary Table S1. No significant
179 relationship ($P > 0.05$) was identified between the AUC/MIC ratio and mortality at
180 Day 42, the overall response at EOT, or the clinical response at EOT. Since only
181 2 of the 36 patients were not included in the mITT population, that analysis would
182 necessarily have yielded almost identical results and so it was not performed. No
183 relationship was observed between MIC values and outcome parameters (15).

184

185 **Exposure-safety analysis.** Patients with PK parameters used in the exposure-
186 response analysis were also included in this analysis. Graphical examination of
187 binary outcomes for AUC₀₋₂₄ and C₂₄ for the ITT and mITT populations against
188 normal/elevated levels of ALT and ALT are shown in Fig. 4. None of the primary
189 exposure parameters were found to be statistically significant for any of the

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

193

194 **DISCUSSION**

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

202 We were unable to demonstrate any statistically significant relationships
203 for any measure of drug exposure (i.e., AUC₀₋₂₄ or C₂₄ or AUC/MIC) and various
204 outcomes (i.e., all-cause mortality at Day 42 or clinical and overall responses at
205 EOT or MIC of fungal isolates). A slight trend was observed for overall responses
206 for both ITT and mITT populations, but this was not statistically significant ($P >$
207 0.05).

208 There could be several reasons for any lack of relationship between drug
209 exposure and clinical outcomes from this analysis. Firstly, even though there
210 were some extremes in predicted exposures, the variability was only 62% in
211 patient population (12). Secondly, it is possible there was a degree of bias in the
212 PPK model. The PPK model was fitted to data from both phase 1 and sparse
213 data from phase 3 data. Even though there were 231 patients in the SECURE
214 study, sparse data may potentially have led to biased estimates of exposure and
215 C₂₄ values. However, there is no evidence of this given concordance with PK
216 models fitted to other isavuconazole datasets (16). Poor compliance to the study
217 drug could also have led to biased estimates of drug exposures, although there is

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

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

240 Even though a threshold value for any drug exposure parameters was not
241 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 $> 0.7 \mu\text{g/mL}$

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

278 In conclusion, no statistically significant relationships were observed for
279 any of the exposure parameters of isavuconazole (AUC₀₋₂₄, C₀, C₇, and C₁₄)
280 with any safety markers (ALT, AST, and combined ALT/AST), either at the EOT
281 or post baseline, nor with any efficacy endpoints (all-cause mortality, overall and
282 clinical response). In some models, duration of therapy was retained in the model.
283 However, this covariate is highly confounded making its relevance in this analysis
284 unclear. Also, experimental PD models were conducted to establish the
285 exposure-response relationship associated with efficacy and to estimate the
286 target exposure associated with the optimal exposure-response relationship. The
287 results showed that the clinical dosing regimen achieved exposures adequate to
288 treat infections. All models were developed on the observed data (12); however,

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

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

294
295

296 **ACKNOWLEDGMENTS**

297 Astellas Pharma, Inc. provided funding for the studies described here. Editorial
298 assistance was provided by John Clarke PhD CMPP, Envision Scientific
299 Solutions, and was funded by Astellas Pharma, Inc. AVD, LLK, DK, RT, SM, and
300 PLB are employees of Astellas Pharma Global Development, Inc. WWH reports
301 personal fees from Basilea and Gilead, and grants and personal fees from
302 Amplyx, Astellas, F2G, and Pfizer, outside the submitted work. DA was a
303 consultant for Astellas, outside the submitted work. JWM reports grants from
304 Astellas, Basilea, Gilead, Merck, and Pfizer, outside the submitted work.

305
306

307 **REFERENCES**

- 308 1. **Perlin DS, Shor E, Zhao Y.** 2015. Update on antifungal drug resistance.
309 Curr Clin Microbiol Rep **2**:84-95.
- 310 2. **Lass-Flori C.** 2011. Triazole antifungal agents in invasive fungal
311 infections: a comparative review. Drugs **71**:2405-2419.
- 312 3. **Astellas US Pharma Inc.** 2015. CRESEMBA[®] (isavuconazonium sulfate)
313 prescribing information, on US FDA.
314 http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207500Orig1s
315 [000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207500Orig1s000lbl.pdf) (accessed 23 February 2016). Accessed
- 316 4. **European Medicines Agency.** 2015. Cresemba (isavuconazole).
317 <http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/m>
318 [edicines/002734/human_med_001907.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002734/human_med_001907.jsp&mid=WC0b01ac058001d124)
319 (Accessed 23 February 2016). Accessed
- 320 5. **Maertens JA, Raad, II, Marr KA, Patterson TF, Kontoyiannis DP,**
321 **Cornely OA, Bow EJ, Rahav G, Neofytos D, Aoun M, Baddley JW,**
322 **Giladi M, Heinz WJ, Herbrecht R, Hope W, Karthaus M, Lee DG,**
323 **Lortholary O, Morrison VA, Oren I, Selleslag D, Shoham S, Thompson**
324 **GR, 3rd, Lee M, Maher RM, Schmitt-Hoffmann AH, Zeiher B, Ullmann**
325 **AJ.** 2016. Isavuconazole versus voriconazole for primary treatment of
326 invasive mould disease caused by *Aspergillus* and other filamentous fungi
327 (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet
328 **387**:760-769.

- 329 6. **Andes D, Pascual A, Marchetti O.** 2009. Antifungal therapeutic drug
330 monitoring: established and emerging indications. *Antimicrob Agents*
331 *Chemother* **53**:24-34.
- 332 7. **Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R,**
333 **Hope WW.** 2014. Therapeutic drug monitoring (TDM) of antifungal agents:
334 guidelines from the British Society for Medical Mycology. *J Antimicrob*
335 *Chemother* **69**:1162-1176.
- 336 8. **Dolton MJ, Ray JE, Chen SC, Ng K, Pont L, McLachlan AJ.** 2012.
337 Multicenter study of posaconazole therapeutic drug monitoring: exposure-
338 response relationship and factors affecting concentration. *Antimicrob*
339 *Agents Chemother* **56**:5503-5510.
- 340 9. **Jang SH, Colangelo PM, Gobburu JV.** 2010. Exposure-response of
341 posaconazole used for prophylaxis against invasive fungal infections:
342 evaluating the need to adjust doses based on drug concentrations in
343 plasma. *Clin Pharmacol Ther* **88**:115-119.
- 344 10. **Troke PF, Hockey HP, Hope WW.** 2011. Observational study of the
345 clinical efficacy of voriconazole and its relationship to plasma
346 concentrations in patients. *Antimicrob Agents Chemother* **55**:4782-4788.
- 347 11. **Lestner JM, Roberts SA, Moore CB, Howard SJ, Denning DW, Hope**
348 **WW.** 2009. Toxicodynamics of itraconazole: implications for therapeutic
349 drug monitoring. *Clin Infect Dis* **49**:928-930.
- 350 12. **Desai A, Kovanda L, Kowalski D, Lu Q, Townsend R, Bonate PL.** 2016.
351 Population pharmacokinetics of isavuconazole from phase 1 and phase 3
352 (SECURE) trials in adults and target attainment in patients with invasive

- 353 infections due to *Aspergillus* and other filamentous fungi. Antimicrob
354 Agents Chemother **60**:5483-5491.
- 355 13. **R project for statistical computing**. 2015. R version 3.17. [https://www.r-](https://www.r-project.org/)
356 [project.org/](https://www.r-project.org/).
- 357 14. **Arundrup MC, Cuenca-Estrella M, Lass-Flörl C, Hope W, Howard SJ,**
358 **and the Subcommittee on Antifungal Susceptibility Testing (AFST) of**
359 **the ESCMID European Committee for Antimicrobial Susceptibility**
360 **Testing (EUCAST)**. 2015. EUCAST DEFINITIVE DOCUMENT EDef 9.2:
361 Method for the determination of broth dilution minimum inhibitory
362 concentrations of antifungal agents for conidia forming moulds.
363 [http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/AFST/Files](http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/AFST/Files/EUCAST-AFST_EDEF_9_2_Mould_testing_20140815.pdf)
364 [EUCAST-AFST_EDEF_9_2_Mould_testing_20140815.pdf](http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/AFST/Files/EUCAST-AFST_EDEF_9_2_Mould_testing_20140815.pdf) Accessed
365 February 23.
- 366 15. **Hope W, Ghannoum M, Kovanda L, Jones M, Kaufhold A, Engelhardt**
367 **M, Santerre Henriksen A**. 2015. Clinical outcomes by minimum inhibitory
368 concentrations of baseline *Aspergillus* pathogens from isavuconazole
369 phase 3 SECURE, abstr 25th European Congress of Clinical Microbiology
370 and Infectious Diseases, Copenhagen, Denmark, 25-28 April 2015.
- 371 16. **Hope WW, Walsh TJ, Goodwin J, Peloquin CA, Howard A, Kurtzberg**
372 **J, Mendizabal A, Confer DL, Bulitta J, Baden LR, Neely MN, Wingard**
373 **JR**. 2016. Voriconazole pharmacokinetics following HSCT: results from
374 the BMT CTN 0101 trial. J Antimicrob Chemother **71**:2234-2240.
- 375 17. **Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE,**
376 **Oestmann JW, Kern WV, Marr KA, Ribaud P, Lortholary O, Sylvester**

377 **R, Rubin RH, Wingard JR, Stark P, Durand C, Caillot D, Thiel E,**
378 **Chandrasekar PH, Hodges MR, Schlamm HT, Troke PF, de Pauw B.**
379 2002. Voriconazole versus amphotericin B for primary therapy of invasive
380 aspergillosis. *N Engl J Med* **347**:408-415.

381 18. **Walsh TJ, Raad I, Patterson TF, Chandrasekar P, Donowitz GR,**
382 **Graybill R, Greene RE, Hachem R, Hadley S, Herbrecht R, Langston A,**
383 **Louie A, Ribaud P, Segal BH, Stevens DA, van Burik JA, White CS,**
384 **Corcoran G, Gogate J, Krishna G, Pedicone L, Hardalo C, Perfect JR.**
385 2007. Treatment of invasive aspergillosis with posaconazole in patients
386 who are refractory to or intolerant of conventional therapy: an externally
387 controlled trial. *Clin Infect Dis* **44**:2-12.

388 19. **Box H, Gregson L, Livermore JL, Felton TW, Whalley S, Goodwin J,**
389 **McEntee L, Johnson A, Hope W.** 2014. Pharmacodynamics (PD) of
390 isavuconazole (ISA) for invasive pulmonary aspergillosis (IPA), abstr 54th
391 Interscience Conference on Antimicrobial Agents and Chemotherapy,
392 Washington, DC, USA,

393 20. **Kovanda LL, Petraitiene R, Petraitis V, Walsh TJ, Desai A, Bonate P,**
394 **Hope WW.** 2016. Pharmacodynamics of isavuconazole in experimental
395 invasive pulmonary aspergillosis: implications for clinical breakpoints. *J*
396 *Antimicrob Chemother* **71**:1885-1891.

397 21. **Lepak AJ, Marchillo K, Vanhecker J, Andes DR.** 2013. Isavuconazole
398 (BAL4815) pharmacodynamic target determination in an in vivo murine
399 model of invasive pulmonary aspergillosis against wild-type and cyp51

- 400 mutant isolates of *Aspergillus fumigatus*. *Antimicrob Agents Chemother*
401 **57**:6284-6289.
- 402 22. **Petraitis V, Petraitiene R, Moradi PW, Strauss GE, Katragkou A,**
403 **Kovanda LL, Hope WW, Walsh TJ.** 2016. Pharmacokinetics and
404 concentration-dependent efficacy of isavuconazole for treatment of
405 experimental invasive pulmonary aspergillosis. *Antimicrob Agents*
406 *Chemother* **60**:2718-2726.
- 407 23. **Seyedmousavi S, Bruggemann RJ, Meis JF, Melchers WJ, Verweij PE,**
408 **Mouton JW.** 2015. Pharmacodynamics of isavuconazole in an *Aspergillus*
409 *fumigatus* mouse infection model. *Antimicrob Agents Chemother* **59**:2855-
410 2866.
- 411 24. **Barr VO, Zdyb EG, Postelnick M.** 2015. The clinical significance of azole
412 antifungals' effects on the liver and transaminase levels. *Curr Fungal*
413 *Infect Rep* **9**:190-195.
- 414 25. **Stott KE, Hope WW.** 2017. Therapeutic drug monitoring for invasive
415 mould infections and disease: pharmacokinetic and pharmacodynamic
416 considerations. *J Antimicrob Chemother* **72(Suppl1)**:i12-i18.
- 417
418
419

420 **Figure legends**

421

422 **Fig 1** Study design

423

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

426

427 **Fig 2** Box and whisker plots of drug exposure (AUC_{ss} and C_{ss}) vs mortality at
428 Day 42 for ITT population (A) and mITT population (B)

429

430 AUC_{ss}, total area under the concentration-time curve at steady state; C_{ss},
431 concentration at steady state; ITT, intent-to-treat; mITT, modified intent-to-treat.

432

433 **Fig 3** Box and whisker plots of drug exposure (AUC_{ss} and C_{ss}) vs clinical and
434 overall response at EOT for ITT population (A) and mITT population (B)

435

436 AUC_{ss}, total area under the concentration-time curve at steady state; C_{ss},
437 concentration at steady state; ITT, intent-to-treat; mITT, modified intent-to-treat.

438

439 **Fig 4** Box and whisker plots of drug exposure (AUC_{ss} and C_{ss}) vs ALT/AST
440 levels at EOT for ITT population (A) and mITT population (B)

441

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

1 **TABLE 1** Summary of patient characteristics

2

Patient characteristics	ITT population (<i>n</i> = 231)		mITT population (<i>n</i> = 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	

3 Yes/No: Had/did not have characteristics at baseline. *n* is number of patients. ^aSome patients (*n* = 27)

4 did not have galactomannan information at baseline.

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

1 **TABLE 2** Summary of exposure parameters

2

	AUC _{ss}	C _{ss}	C ₇	C ₁₄
	(mg*h/L)	(ng/mL)	(ng/mL)	(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

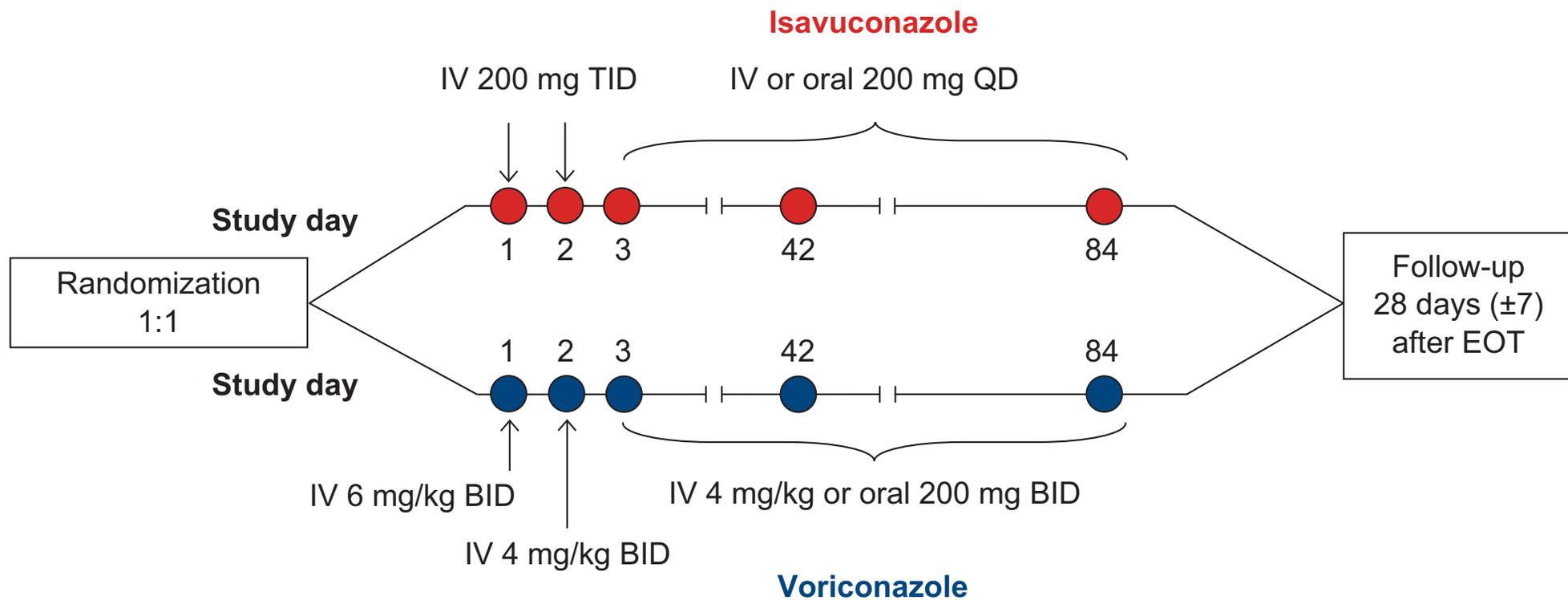
3 Values rounded to nearest whole number.

4 AUC_{ss}, total area under the curve at steady state; C_{ss}, concentration at steady state; C₇,

5 concentration after 7 days of dosing, C₁₄, concentration after 14 days of dosing; SD, standard

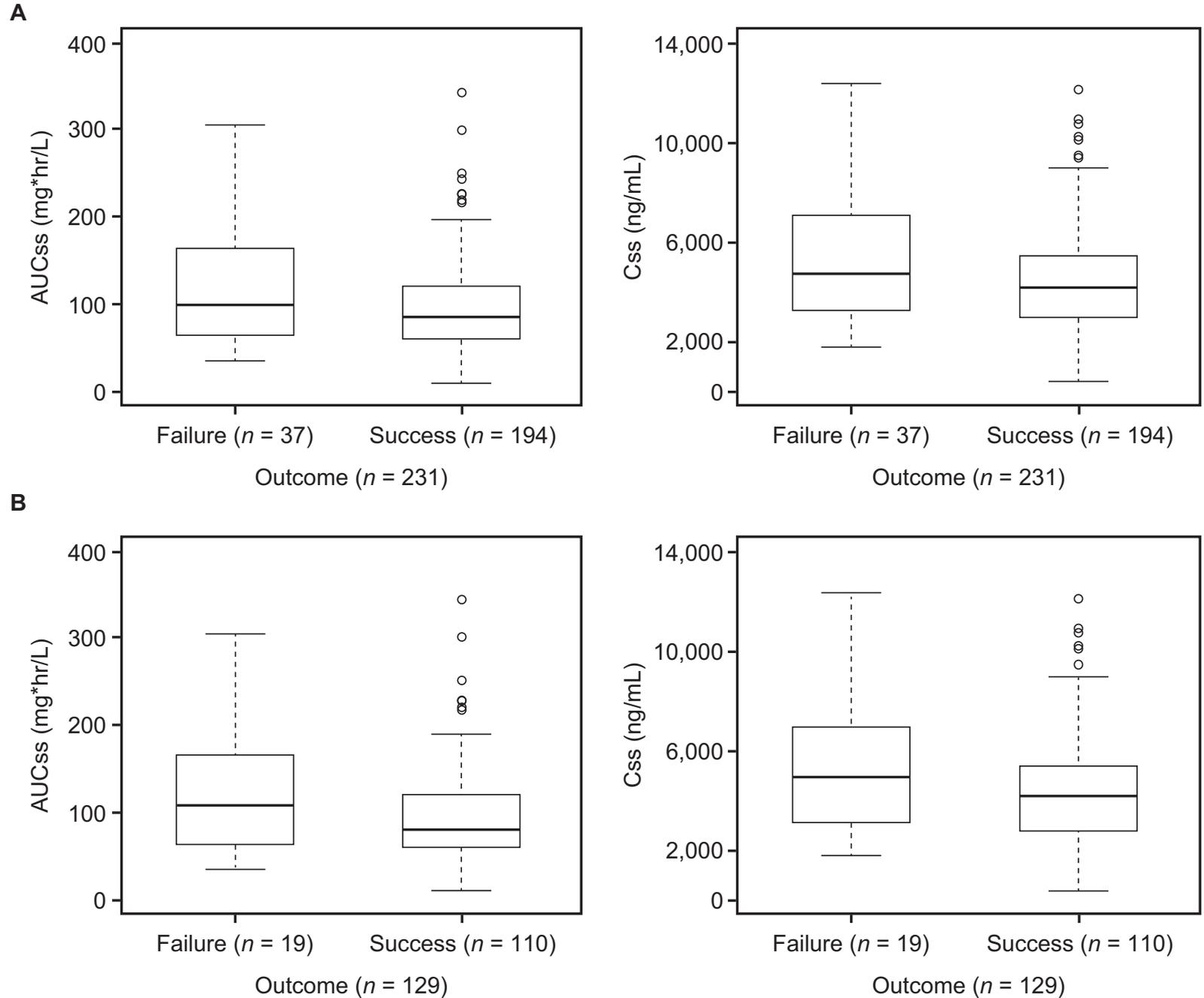
6 deviation.

FIG 1 Study design



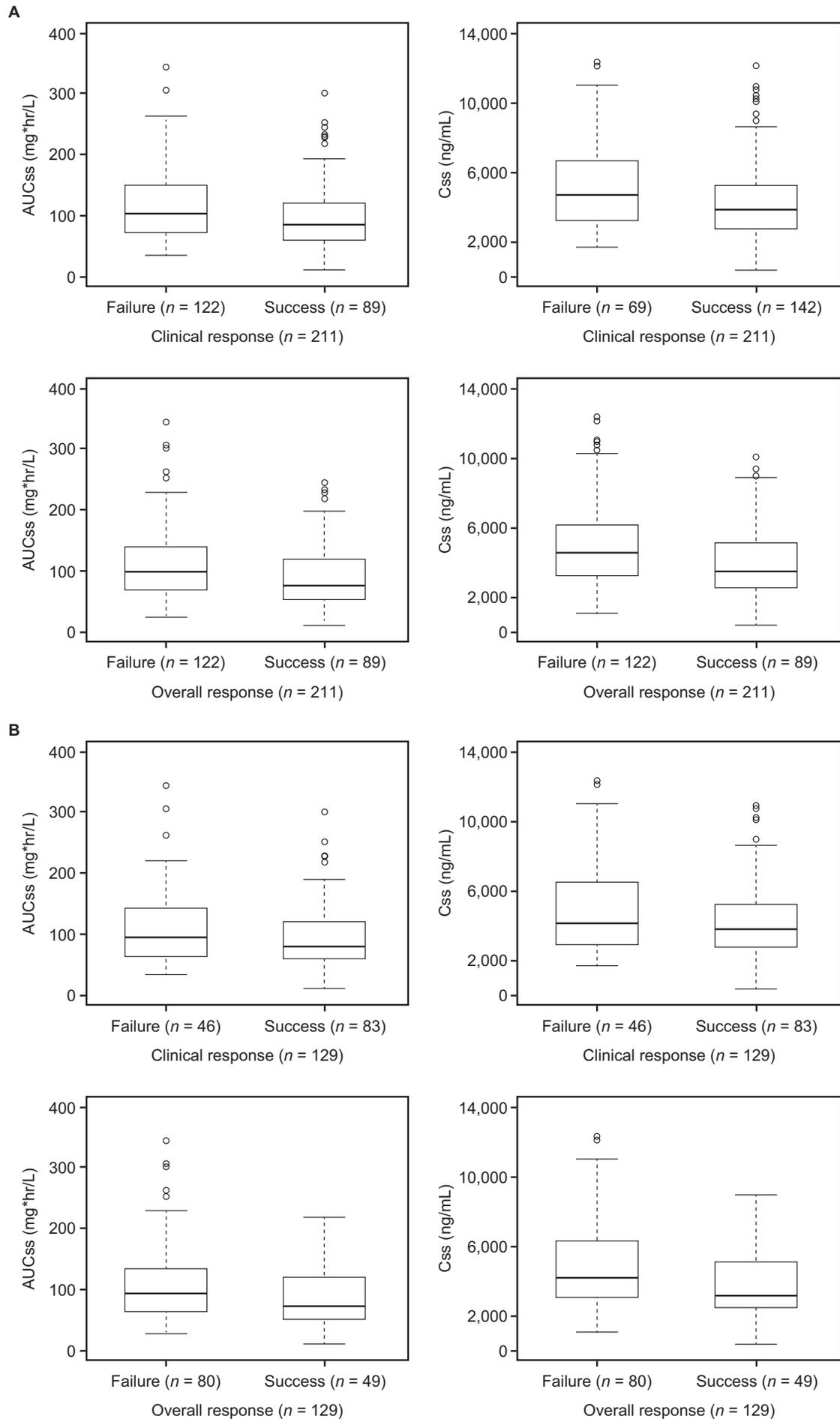
Maximum therapy duration was 84 days.

FIG 2 Box and whisker plots of drug exposure (AUC_{Css} and C_{ss}) vs mortality at Day 42 for ITT population (A) and mITT population (B)



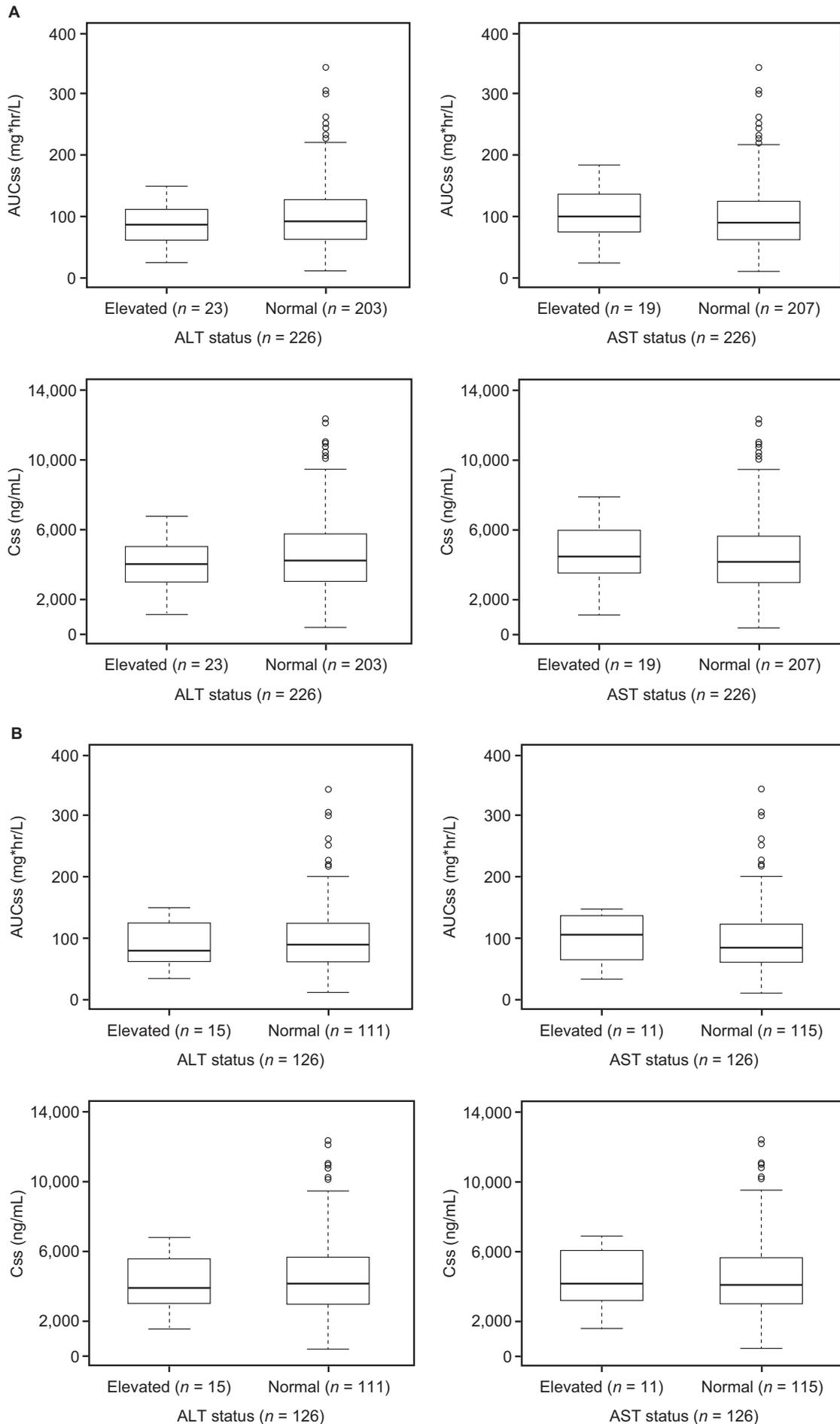
Boxes represent median, 25th and 75th percentiles; whiskers represent range of maximum and minimum values within 1.5 × the interquartile range; outliers are shown as circles.

FIG 3 Box and whisker plots of drug exposure (AUC_{ss} and C_{ss}) 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 C_{ss}) 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 $1.5 \times$ the interquartile range; outliers are shown as circles.