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Population Pharmacokinetics of Posaconazole Tablets and Monte Carlo Simulations To Determine whether All Patients Should Receive the Same Dose

Antoine Petitcollin, C. Boggione-Kerrien, C. Tron, S. Nimubona, S. Lalanne, F. Lemaître, E. Bellissant, M. -C. Verdier

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1 **Population pharmacokinetics of posaconazole tablets and Monte-Carlo**
2 **simulations: should all the patients receive the same dose?**

3 Running title: population pharmacokinetics of posaconazole tablets

4

5 Authors

6 Petitcollin A^{1,2,3}, Boglione-Kerrien C¹, Tron C^{1,2,3}, Nimubona S⁴, Lalanne S^{1,2,3}, Lemaitre F^{1,2,3},
7 Bellissant E^{1,2,3}, Verdier M-C^{1,2,3}.

8

9 Authors' affiliations

10 ¹Rennes University Hospital, Department of Clinical and Biological Pharmacology and
11 Pharmacovigilance, Pharmacoepidemiology and Drug Information Center, Rennes, France.

12 ²Rennes 1 University, Faculty of Medicine, Laboratory of Experimental and Clinical
13 Pharmacology, Rennes, France.

14 ³Inserm, CIC-P 1414 Clinical Investigation Center, Rennes, France.

15 ⁴Rennes University Hospital, Department of Clinical Haematology, Rennes, France.

16

17 Corresponding author:
18 Dr Antoine Petitcollin
19 Laboratory of Biological Pharmacology
20 Rennes University Hospital
21 Rue Henri Le Guilloux
22 35033 Rennes
23 FRANCE
24 Tel: +332 99 28 42 80
25 Fax: +332 99 28 41 84
26 Email: antoine.petitcollin@chu-rennes.fr
27

28 **Abstract**

29 Background

30 Posaconazole is extensively used for invasive fungal infection prophylaxis. The gastro-
31 resistant tablet formulation has allowed overcoming bioavailability issues encountered with
32 the oral suspension. However, now overexposure is frequent. This study aimed at (i)
33 describing posaconazole tablets pharmacokinetics in a real-life cohort of patients with
34 haematological malignancies, and (ii) performing Monte-Carlo simulations to assess the
35 possibility to reduce the daily dose while keeping sufficient exposure.

36 Patients and methods

37 Forty-nine consecutive inpatients were prospectively included. Posaconazole trough
38 concentrations (TC) were measured once a week and biological and demographic data were
39 collected. Concentrations were analysed by compartment modelling, and Monte-Carlo
40 simulations were performed using estimated parameters to assess the rate of attainment of
41 target TC after dose reduction.

42 Results

43 Posaconazole pharmacokinetics was well described using a one-compartment model with
44 first-order absorption and elimination. The values of the parameters (interindividual
45 variabilities) were: absorption constant $k_a=0.588h^{-1}$ (fixed), distribution volume $V/F=420L$
46 (28.2%), clearance $CL/F=7.3L/h$ (24.2%) with 31.9% interoccasion variability. Forty-nine
47 percent of the simulated patients had TC at steady-state $\geq 1.5\mu g/mL$ and maintained TC
48 above $1\mu g/mL$ after dose reduction to 200mg daily. A third of these patients eligible to dose
49 reduction had TC $\geq 1.5\mu g/mL$ as soon as 48h of treatment.

50 Conclusion

51 Though less impacted by bioavailability issues than the oral suspension, posaconazole
52 tablets pharmacokinetics remains highly variable. Simulations showed that approximately
53 half of the patients would benefit from a dose reduction from 300mg to 200mg while
54 keeping TC above the minimal recommended target of 0.7µg/mL, resulting in a 33% cost
55 saving of this very expensive drug.

56

57 **Keywords**

58 Posaconazole, Pharmacokinetics, Therapeutic Drug Monitoring, Compartment modelling,
59 Monte-Carlo simulations

60

61 **Manuscript (2917 words)**

62 **Introduction**

63 Posaconazole is a broad spectrum triazole antifungal approved for the prophylaxis of
64 invasive fungal infections (IFI) in severely immunocompromised patients. To overcome the
65 limitations with poor bioavailability of the oral suspension, a delayed-release tablet
66 maximizing systemic absorption was designed. Pharmacokinetic data showed a reduced
67 interpatient variability and a more favourable absorption profile compared with the oral
68 suspension (1-6), and a relative independence to food intake and concomitant medications
69 altering gastric pH (7,8). Optimizing bioavailability appeared as a major challenge as several
70 studies reported the existence of a concentration-effect relationship of posaconazole (9-12).
71 This was confirmed by the analysis of data issued from large clinical trials (13,14), based on
72 which the 6th European Conference on Infections in Leukemia (ECIL-6) and the British Society
73 for Medical Mycology recommended minimal trough concentration (TC) of 0.7µg/mL for
74 prophylaxis of IFI (15). However, it is noticeable that if the goal of avoiding underexposure to
75 posaconazole seems to be reached with the tablet formulation, there are now many patients
76 in whom TC are largely above 0.7µg/mL (16). In a phase 3 pharmacokinetic and safety study
77 in 186 patients, Cornely *et al.* reported that 65% of the measured TC at steady-state were
78 above 1.25µg/mL and 13% above 2.5µg/mL (4). Though no concentration-toxicity
79 relationship has been established to date, it seems reasonable to think that a dose reduction
80 might be considered in those patients, as long as it does not increase the risk of IFI. This is
81 particularly relevant considering the substantial costs associated with the extended use of
82 this highly expensive drug. However, to our knowledge this issue has not been explored to
83 date and dose reduction in routine practice is currently off-label. Thus, we conducted this

84 study which aimed at (i) describing posaconazole pharmacokinetics by compartment
85 modelling in a real-life cohort of patients with haematological malignancies and (ii)
86 exploring, using Monte-Carlo simulations, whether a dose reduction might be considered in
87 highly exposed patient while keeping the TC above the recommended threshold of
88 0.7µg/mL.

89

90 **Patients and methods**

91 *Ethics*

92 This was a fully non-interventional, observational study with no modification of patients'
93 management. This study was conducted in accordance with the declaration of Helsinki and
94 national and institutional standards. It was approved by the local Ethics Committee
95 (approval no. 15.114). Patients were informed of their eligibility prior to their inclusion and
96 could refuse to participate.

97 *Patients and study design.*

98 The study prospectively included 49 consecutive inpatients hospitalized between October
99 2015 and October 2016 in our clinical haematology department and treated with
100 posaconazole tablets for prophylaxis of IFI. Posaconazole was administered following
101 recommendations as a loading dose of 300mg twice a day (BID) on the first day of
102 treatment, and a maintenance dose of 300mg once a day (QD) thereafter. Demographics
103 and biologics were recorded at baseline and throughout hospitalization. Patients could be
104 followed during several stays in the department. Blood samples for determination of
105 posaconazole TC were to be drawn 7 days after treatment beginning and once a week
106 thereafter, until discharge or posaconazole discontinuation. As the concentrations used in

107 the pharmacokinetic analysis were part of routine therapeutic drug monitoring of
108 posaconazole, some samples were not drawn precisely 24 hours after posaconazole intake.
109 Therefore, the detail of the doses administered as well as precise intake and sampling times
110 were thoroughly recorded all along the study for the purpose of pharmacokinetic modelling.
111 Concentration values were not included in the dataset for model building in case of digestive
112 disorders (such as diarrhoea, vomiting) that might have altered posaconazole absorption and
113 biased parameters estimation. Posaconazole concentrations were determined using a fully
114 validated tandem mass spectrometry method (17). If needed, additional blood samples
115 could be drawn and posaconazole dose could be adapted at the clinician's discretion. No
116 additional blood sample was drawn for the purpose of the study.

117 *Pharmacokinetic analysis.*

118 Population pharmacokinetic compartmental modelling was performed using Monolix 4.2.3
119 (Lixsoft; Orsay, France).

120 Structural model. One and two-compartment structural models with first order absorption,
121 distribution and elimination were tested, using exponential inter-individual and inter-
122 occasion variability models as follows:

$$\theta_i = \theta_{TV} \cdot e^{\eta_i}, \eta_i \sim \mathcal{N}(0, \omega^2)$$

123 and

$$\theta_{ik} = \theta_i \cdot e^{\kappa_i}, \kappa_i \sim \mathcal{N}(0, \gamma^2)$$

124

125 where θ_i is the estimated individual parameter for the i^{th} patient at the first occasion (i.e.,
126 the first stay), θ_{ik} is the estimated individual parameter for the i^{th} patient at the k^{th} occasion,

127 θ_{TV} is the typical value of the parameter, and η_i and κ_i are the interindividual and
128 interoccasion random effects for the i^{th} patient, respectively. The values of η_i and κ_i are
129 supposed to be normally distributed with mean 0 and variances ω^2 and γ^2 , respectively. For
130 each parameter, variabilities were fixed to 0 if the variances could not be estimated
131 properly.

132 Error model. Additive, proportional and mixed additive-proportional residual error models
133 were tested. The proportional error model was implemented as follows:

$$Y_{O,ij} = Y_{P,ij} \cdot (1 + \varepsilon_{prop,ij}), \varepsilon_{prop,ij} \sim \mathcal{N}(0, \sigma_{prop}^2)$$

134 where $Y_{O,ij}$ and $Y_{P,ij}$ are observed and predicted j^{th} measurements for the i^{th} patient,
135 respectively, and $\varepsilon_{prop,ij}$ is the proportional residual error, with mean 0 and variance σ_{prop}^2 .

136 Covariate model. The influence of relevant demographic and biological covariates on
137 posaconazole pharmacokinetics was tested. Covariates influence was implemented as
138 follows:

139 - continuous covariates: age, body weight (BW), body mass index (BMI), serum creatinine,
140 Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST), Alkaline phosphatase
141 (ALK), and Gamma Glutamyl Transferase (GGT) were tested. Continuous covariates were
142 centred on their median as follows:

$$\theta_{TV} = \theta_0 \cdot (COV/med(COV))^{\beta_{cov}}$$

143 where θ_0 is the value of θ for a median subject, β_{cov} quantifies the influence of the
144 covariate on θ , and $med(COV)$ is the median value of the covariate in the study population.
145 As an initial approach, we tested the influence of the baseline values of the continuous
146 covariates. However, considering the length of the hospital stay, we postulated that

147 biologics values could change over time, especially those reflecting liver function that could
148 be altered by posaconazole. So we also tested ALT, AST, ALK and GGT as time-varying
149 covariates implemented in the model as described above.

150 - categorical covariates: patients' gender and disease were tested. The influence of
151 categorical covariates on θ_{TV} was implemented as follows:

$$\ln(\theta_{TV}) = \ln(\theta_{CAT=0}) + \beta_{CAT=i}$$

152 where $\theta_{CAT=0}$ is the value of θ_{TV} in an arbitrary reference category and $\beta_{CAT=i}$ quantifies the
153 influence of the i^{th} category on the value of θ_{TV} .

154 Model comparison and covariate selection. Structural, interindividual, interoccasion, residual
155 error and covariate models were compared using the likelihood ratio test (LRT) at a risk α of
156 5% for nested models, or reduction of Akaike's Information Criterion (AIC) value otherwise.

157 Evaluation of the goodness-of-fit and final model selection. The goodness-of-fit was assessed
158 for each model by plotting population-predicted (PRED) and individually predicted (IPRED)
159 concentrations versus observed concentrations (OBS) and by evaluating the residuals by
160 graphical inspection of normalized prediction distribution errors (NPDE) versus time and
161 NPDE distribution. The precision of the parameters estimation as determined by the Relative
162 Standard Errors (RSE) was taken into account for model selection and choice of the final
163 model. Stochastic approximation was used for RSE estimation and correlation matrix of the
164 estimates determination. Individual fits were also inspected. The model offering the greater
165 reduction of OFV (or AIC) together with acceptable precision of the estimations of the
166 parameters and goodness-of-fit was selected. A Visual Predictive Check (VPC) figure was
167 built to ensure the predictive performance of the model.

168

169 *Monte-Carlo simulations.*

170 Monte-Carlo simulations were performed using SimulX 1.0.0 (Lixoft, Orsay, France). The
171 values of the pharmacokinetic parameters previously estimated were used to simulate the
172 concentration profiles of 500 patients following two dosing regimen: (i) 300 mg BID on day 1
173 and then 300 mg QD (standard regimen, used as a reference), and (ii) 300 mg BID on day 1,
174 300 mg QD on day 2, followed by 200 mg QD (lowered dose regimen). The mean
175 concentration and 90% confidence interval were determined for each regimen. Simulations
176 endpoints were the rate of patients achieving $TC \geq 0.7 \mu\text{g/mL}$ (minimal recommended
177 concentration for prophylaxis of IFI) and $TC \geq 1 \mu\text{g/mL}$ (proposal of TC to be targeted in clinical
178 practice to ensure keeping $TC \geq 0.7 \mu\text{g/mL}$ with a safety margin of $0.3 \mu\text{g/mL}$) at 48h and at day
179 10. Additional simulations were performed at a dose of 200 mg BID on day 1 and 200 mg QD
180 thereafter to evaluate the proportion of patients achieving the targeted TC with a reduced
181 loading dose, and at a dose of 300 mg BID on day 1, 300 mg on day 2, and 100 mg QD
182 thereafter to assess the rate of patient attaining sufficient TC with only a third of the
183 recommended daily dose.

184

185 **Results**

186 Patients' characteristics are summarized in table 1. A total of 205 posaconazole
187 concentrations were used to build the pharmacokinetic model, 139 (67.8%) of which were at
188 trough +/-3h. The other concentrations were drawn mostly before trough (60
189 concentrations, range: 9.0 to 20.8 hours after posaconazole intake) or after (6
190 concentrations, range 27.2 to 33.2 hours after intake). A one-compartment model best fitted

191 the data. The pharmacokinetic parameters were accurately estimated, though the
192 interindividual variability of the absorption constant could not be correctly estimated and
193 was then fixed to 0. The addition of an interoccasion variability to account for intra-
194 individual variations of posaconazole clearance from one stay to another greatly improved
195 the predictive performance ($p < 0.0001$, LRT). The typical values (interindividual variability) of
196 the pharmacokinetic parameters were: first order absorption constant $k_a = 0.588 \text{ h}^{-1}$ (fixed),
197 apparent central volume of distribution $V/F = 420 \text{ L}$ (28.2%), apparent elimination clearance
198 $CL/F = 7.3 \text{ L/h}$ (24.2%) with 31.9% interoccasion variability (table 2). Clearance slightly
199 decreased with increasing baseline ALT ($p = 0.022$, LRT), and V/F was lower in women
200 ($p = 0.022$, LRT). However, the addition of these covariates in the model altered the accuracy
201 of the parameters estimation and barely improved the predictive performance, thus we
202 chose to remove them from the final model (table 3). The diagnostic plots inspection did not
203 reveal any obvious model misspecification or bias (figures 1 and 2).

204 Simulations were performed accordingly to the estimated pharmacokinetic parameters.
205 Following the standard loading dose of 300 mg BID on day 1 and 300 mg QD on day 2, 95.6%
206 and 72.6% of simulated patients reached a TC at 48h $\geq 0.7 \mu\text{g/mL}$ and $\geq 1 \mu\text{g/mL}$, respectively.
207 With the standard regimen at 300 mg QD, rates of TC $\geq 0.7 \mu\text{g/mL}$ and $\geq 1 \mu\text{g/mL}$ at day 10
208 were 93.0% and 76.8%, respectively. These rates fall to 74.4% and 50.8% with the lowered
209 dose regimen (200 mg QD from day 3). Rates of patients with TC $\geq 2 \mu\text{g/mL}$ at day 10 were
210 24.6% and 5.2% with the standard and lowered dose regimens, respectively. According to
211 the simulations, we calculated that 100% of patients with TC at 48h $\geq 1.5 \mu\text{g/mL}$ would keep
212 TC at day 10 $\geq 1 \mu\text{g/mL}$ after lowering the dose to 200 mg QD from day 3 (figure 3 and table
213 4).

214 The additional simulations showed that only 66.8% and 16.0% of simulated patients reached
215 $TC \geq 0.7 \mu\text{g/mL}$ and $\geq 1 \mu\text{g/mL}$ at 48h, respectively, following a reduced loading dose of 200 mg
216 BID on day 1 and 200 mg QD on day 2. Twenty-nine percent and 11.0% of the simulated
217 patients had $TC \geq 0.7 \mu\text{g/mL}$ and $\geq 1 \mu\text{g/m}$ at day 10, respectively, after a standard loading
218 dose followed by a dose reduction to 100 mg QD from day 3 (table 4).

219

220 **Discussion**

221 To the best of our knowledge, this study is the first to describe the pharmacokinetics of
222 posaconazole gastro-resistant tablets in a real-life cohort of patients using a population
223 approach, and the first to explore the potential impact of dosing adaptations using
224 pharmacokinetic simulations.

225 The values of the TC in the present study are in accordance with phase 3 data (4) and
226 indicate a still important interpatient variability of posaconazole concentrations, with a
227 range from $0.46 \mu\text{g/mL}$ to $3.44 \mu\text{g/mL}$ and a coefficient of variation of 40.5%. Moreover, we
228 also found an important inpatient variability, which was already reported before with the
229 oral suspension (18) but was never investigated by compartment modelling with the tablet
230 formulation.

231 Posaconazole pharmacokinetics was well described with a one-compartment model, as
232 expected with a dataset including a majority of TC. The lack of data during the absorption
233 phase did neither allow to properly estimate the interindividual variability of the first-order
234 absorption constant, nor to test other absorption models. However, we previously reported
235 that a first-order absorption model described well the absorption of posaconazole tablets
236 (19). The values of V/F and CL/F we estimated are in accordance with those determined in

237 patients by non-compartmental analysis with the tablet formulation (1,4), though they are
238 much smaller than reported with the oral suspension because of the enhanced
239 bioavailability of the tablets (18,20). These parameters were accurately estimated as
240 attested by the values of the RSE ($\leq 10\%$) because the dataset included about a third of
241 concentrations that were not drawn at trough, which allowed to describe the elimination
242 phase much more precisely than with only trough concentrations. Noticeably, the addition
243 of an inter-occasion variability of posaconazole clearance greatly improved the model,
244 indicating that the elimination of posaconazole is susceptible to vary in a same patient from
245 a stay to another, though being relatively stable in the time course of a stay. This further
246 supports the necessity of therapeutic drug monitoring of posaconazole. Posaconazole
247 pharmacokinetics was not influenced by the demographic and biological covariates we
248 tested, or only at a minimal level, probably indicating that the variability of the
249 concentrations mainly results from a variability of the bioavailability. In particular, baseline
250 ALT were found to be negatively correlated to posaconazole clearance, suggesting that
251 impaired liver function could be associated with a lower clearance of posaconazole.
252 However, this effect was modest, with a 5-fold increase of ALT resulting only in a 25%
253 decrease of posaconazole clearance. Moreover, because of lacking data, the effect of this
254 covariate was poorly estimated and was thus not retained in the final model.

255 The results of our simulations are strongly comforted by the fact that they concur very
256 closely with those reported before in patients: we calculated that 63.6% and 10.6% of the
257 simulated patients with the standard regimen had TC at steady-state $>1.25\mu\text{g/mL}$ and
258 $>2.5\mu\text{g/mL}$, respectively, compared with 65% and 13%, respectively, in a phase 3 clinical
259 study in 186 patients with haematological malignancies (4). At a smaller scale, the

260 concentration-time profiles and concentration values of the simulations are also very close
261 to those reported in a phase 1b study in 32 patients with haematological malignancies (3).

262 The results of the simulations showed that with the recommended regimen almost all the
263 patients achieve $TC \geq 0.7 \mu\text{g/mL}$ at 48h following the loading dose of 300 mg BID on day 1
264 followed by 300 mg QD on day 2, thus ensuring the efficacy of the prophylaxis. Conversely,
265 only two thirds of the simulated patients reach $TC > 0.7 \mu\text{g/mL}$ at 48h with a reduced loading
266 dose of 200 mg BID on day 1 followed by 200 mg QD on day 2. Based on these results, there
267 is no argument in favour of reducing the loading dose.

268 Nevertheless, regarding the maintenance dose, with the standard regimen of 300 mg QD TC
269 keep increasing slowly in a proportion of patients, bringing to a quarter (24.6%, table 4) the
270 rate of patients with $TC \geq 2 \mu\text{g/mL}$ at day 10. The simulations showed that following a dose
271 reduction to 200 mg QD from day 3, half of the patients would keep $TC > 1 \mu\text{g/mL}$ thereafter.
272 Additional simulations also showed that up to 11% of patients would maintain $TC \geq 1 \mu\text{g/mL}$
273 after dose reduction to 100 mg QD.

274 However, the extended distribution volume and the low elimination clearance of
275 posaconazole render difficult the identification of patients eligible to maintenance dose
276 reduction, because the pharmacokinetic steady-state is not reached at 48h despite the use
277 of the loading dose. Indeed, the median half-life calculated from the simulated
278 pharmacokinetic parameters was 39.8 h (range 15.4 – 127.8 h), which means that the
279 median time to get 97% of steady-state (i.e., 5 half-lives) is approximately 200 h (8.3 days).
280 We also calculated that at day 7, 95.0% of the simulated patients had no more than 5%
281 variation in their subsequent TC value.

282 Eventually, 16% of the simulated patients have TC $\geq 1.5\mu\text{g/mL}$ at 48h, and all these patients
283 had TC $\geq 1.0\mu\text{g/mL}$ at day 10 after dose reduction to 200 mg QD from day 3. This means that
284 approximately a third of the patients that could benefit from a dose reduction can be
285 identified as soon as the second day of treatment. Thus, dose reduction to 200 mg QD can
286 be considered in patients with TC at 48h $\geq 1.5\mu\text{g/mL}$, but TC monitoring at day 7-8 is also
287 mandatory to identify the other patients eligible to dose reduction once they have reached
288 pharmacokinetic steady-state. Our results are however suitable only if targeting the
289 recommended trough concentration of $0.7\mu\text{g/mL}$ for prophylaxis of IFI and are not suitable
290 in case of curative treatment or in certain particular situations such as suspicion of a lowered
291 susceptibility to triazoles.

292 **Conclusion**

293 Posaconazole tablets show less, but still important pharmacokinetic variability compared
294 with the oral suspension. With the currently recommended dose regimen, trough
295 concentrations are not likely to fall below the recommended target of $0.7\mu\text{g/mL}$, but many
296 patients are overdosed with no evidence of enhanced efficacy. According to the
297 pharmacokinetic simulations, half of the patients could benefit from a dose reduction. Early
298 therapeutic drug monitoring allows identifying a third of them as soon as the second day of
299 treatment. The others can be identified after a week, once they have reached steady-state.
300 Lowering the dose to 200mg QD in patients with TC $\geq 1.5\mu\text{g/mL}$ at 48h or at day 7-8 would
301 allow to keep TC above $1.0\mu\text{g/mL}$, thus ensuring to keep prophylactic efficacy with a security
302 margin, and with a saving of 33% on the daily treatment cost. These findings need however
303 to be confirmed, and prospective clinical trials to assess the safety, the efficacy and the cost-
304 effectiveness of such a dose reduction are warranted.

305

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308 care, as well as the patients themselves.

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311 **Conflicts of interest**

312 None to declare.

313 **Authors' contribution**

314 CBK and AP designed the study. SN provided medical care to the patients and was in charge
315 of their recruitment in the study and blood samples collection. CBK, FL and MCV were in
316 charge of posaconazole concentration measurements. AP performed statistical and
317 pharmacokinetic analysis. AP drafted the manuscript. CT, SL, CBK, FL, EB and MCV revised
318 the draft and participated to the writing of the final manuscript, the interpretation of the
319 data and discussion of the results. All authors revised the manuscript for important
320 intellectual content and approved the manuscript in its submitted form.

321

322 **References**

323

- 324 1. Krishna G, Ma L, Martinho M, Preston RA, O'Mara E. 2012. A new solid oral tablet
325 formulation of posaconazole: a randomized clinical trial to investigate rising single- and
326 multiple-dose pharmacokinetics and safety in healthy volunteers. *J Antimicrob*
327 *Chemother* 67:2725-2730.
- 328 2. Krishna G, Ma L, Martinho M, O'Mara E. 2012. Single-dose phase I study to evaluate the
329 pharmacokinetics of posaconazole in new tablet and capsule formulations relative to
330 oral suspension. *Antimicrob Agents Chemother* 56:4196-4201.
- 331 3. Duarte RF, Lopez-Jimenez J, Cornely OA, Laverdiere M, Helfgott D, Haider S,
332 Chandrasekar P, Langston A, Perfect J, Ma L, van Iersel ML, Connelly N, Kartsonis N,
333 Waskin H. 2014. Phase 1b study of new posaconazole tablet for prevention of invasive
334 fungal infections in high-risk patients with neutropenia. *Antimicrob Agents Chemother*
335 58:5758-5765.
- 336 4. Cornely OA, Duarte RF, Haider S, Chandrasekar P, Helfgott D, Jimenez JL, Candoni A,
337 Raad I, Laverdiere M, Langston A, Kartsonis N, Van Iersel M, Connelly N, Waskin H. 2016.
338 Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in
339 patients at risk for invasive fungal disease. *J Antimicrob Chemother* 71:1747.
- 340 5. Durani U, Tosh PK, Barreto JN, Estes LL, Jannetto PJ, Tande AJ. 2015. Retrospective
341 Comparison of Posaconazole Levels in Patients Taking the Delayed-Release Tablet versus
342 the Oral Suspension. *Antimicrob Agents Chemother* 59:4914-4918.

- 343 6. Jung DS, Tverdek FP, Kontoyiannis DP. 2014. Switching from posaconazole suspension to
344 tablets increases serum drug levels in leukemia patients without clinically relevant
345 hepatotoxicity. *Antimicrob Agents Chemother* 58:6993-6995.
- 346 7. Kraft WK, Chang PS, van Iersel ML, Waskin H, Krishna G, Kersemaekers WM. 2014.
347 Posaconazole tablet pharmacokinetics: lack of effect of concomitant medications
348 altering gastric pH and gastric motility in healthy subjects. *Antimicrob Agents*
349 *Chemother* 58:4020-4025.
- 350 8. Kersemaekers WM, Dogterom P, Xu J, Marcantonio EE, de Greef R, Waskin H, van Iersel
351 ML. 2015. Effect of a high-fat meal on the pharmacokinetics of 300-milligram
352 posaconazole in a solid oral tablet formulation. *Antimicrob Agents Chemother* 59:3385-
353 3389.
- 354 9. Jang SH, Colangelo PM, Gobburu JV. 2010. Exposure-response of posaconazole used for
355 prophylaxis against invasive fungal infections: evaluating the need to adjust doses based
356 on drug concentrations in plasma. *Clin Pharmacol Ther* 88:115-119.
- 357 10. Dolton MJ, Ray JE, Chen SC, Ng K, Pont L, McLachlan AJ. 2012. Multicenter study of
358 posaconazole therapeutic drug monitoring: exposure-response relationship and factors
359 affecting concentration. *Antimicrob Agents Chemother* 56:5503-5510.
- 360 11. Shields RK, Clancy CJ, Vadnerkar A, Kwak EJ, Silveira FP, Massih RC, Pilewski JM, Crespo
361 M, Toyoda Y, Bhama JK, Bermudez C, Nguyen MH. 2011. Posaconazole serum
362 concentrations among cardiothoracic transplant recipients: factors impacting trough
363 levels and correlation with clinical response to therapy. *Antimicrob Agents Chemother*
364 55:1308-1311.

- 365 12. Cattaneo C, Panzali A, Passi A, Borlenghi E, Lamorgese C, Petulla M, Re A, Caimi L, Rossi
366 G. 2015. Serum posaconazole levels during acute myeloid leukaemia induction therapy:
367 correlations with breakthrough invasive fungal infections. *Mycoses* 58:362-367.
- 368 13. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D,
369 Holowiecki J, Stockelberg D, Goh YT, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D.
370 2007. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with
371 neutropenia. *N Engl J Med* 356:348-359.
- 372 14. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, Greinix H,
373 Morais de Azevedo W, Reddy V, Boparai N, Pedicone L, Patino H, Durrant S. 2007.
374 Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J*
375 *Med* 356:335-347.
- 376 15. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. 2014.
377 Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British
378 Society for Medical Mycology. *J Antimicrob Chemother* 69:1162-1176.
- 379 16. Dekkers BG, Bakker M, van der Elst KC, Sturkenboom MG, Veringa A, Span LF, Alffenaar
380 JC. 2016. Therapeutic Drug Monitoring of Posaconazole: an Update. *Curr Fungal Infect*
381 *Rep* 10:51-61.
- 382 17. Verdier MC, Bentue-Ferrer D, Tribut O, Bellissant E. 2010. Liquid chromatography-
383 tandem mass spectrometry method for simultaneous quantification of four triazole
384 antifungal agents in human plasma. *Clin Chem Lab Med* 48:1515-1522.
- 385 18. Dolton MJ, Bruggemann RJ, Burger DM, McLachlan AJ. 2014. Understanding variability in
386 posaconazole exposure using an integrated population pharmacokinetic analysis.
387 *Antimicrob Agents Chemother* 58:6879-6885.

- 388 19. Petitcollin A, Crochette R, Tron C, Verdier MC, Bogleione-Kerrien C, Vigneau C, Bellissant
389 E, Lemaitre F. 2016. Increased inhibition of cytochrome P450 3A4 with the tablet
390 formulation of posaconazole. *Drug Metab Pharmacokinet* 31:389-393.
- 391 20. AbuTarif MA, Krishna G, Statkevich P. 2010. Population pharmacokinetics of
392 posaconazole in neutropenic patients receiving chemotherapy for acute myelogenous
393 leukemia or myelodysplastic syndrome. *Curr Med Res Opin* 26:397-405.
- 394

395 **Figures legends**

396 **Figure 1. Diagnostic plots.** A. Observed (OBS) versus population-predicted (PRED)
397 concentrations. B. Observed versus individual-predicted (IPRED) concentrations. C.
398 Normalized Prediction Distribution Error (NPDE) versus time. D. Distribution of the NPDE.

399 **Figure 2. Visual Predictive Check (VPC) Figure.** The figure shows the empirical median, 5th
400 and 95th empirical percentiles (full line), the theoretical median, 5th and 95th theoretical
401 percentiles (dashed line), the 95% confidence interval of the theoretical median and
402 percentiles (shaded areas) and the observed concentrations (open circles). The 95%
403 confidence interval of the theoretical 95th percentile is very large and theoretical and
404 empirical 95th percentiles separate from each other above 500 hours because there is no
405 observed high concentration after this point.

406 **Figure 3. Results of the Monte-Carlo simulations.** A. Standard regimen (300 mg BID on day
407 1, 300 mg thereafter). B. Lowered dose regimen (300 mg BID on day 1, 300 mg QD on day 2,
408 and 200 mg QD thereafter). Full line represents the mean concentration, dark grey area is
409 from the 25th to the 75th percentile, and light grey areas are from the 5th to the 25th
410 percentile and from the 75th to the 95th percentile. Dotted lines denote concentrations at
411 0.7µg/mL and 1µg/mL.

412

Table 1. Patients characteristics and study data(n=49)

	Median	Range (min - max)
<i>Demographics</i>		
Age (years)	53	19 - 73
Males (%)	59.2	N/A
Body weight (kg)	72	50 - 125
Body Mass Index (kg/m ²)	26.4	17.7 - 40.4
<i>Biologics (baseline)</i>		
AST (UI/L)	25	4 - 64
ALT (UI/L)	33	12 - 287
Conjugated bilirubin (mmol/L)	4	2 - 37
Total bilirubin (mmol/L)	8	3 - 40
ALK (UI/L)	68	22 - 279
GGT (UI/L)	37	9 - 602
Serum creatinine (µmol/L)	69	41 - 155
<i>Study data</i>		
Total number of stays (n)	91	N/A
Stays per patient (n)	2	1 - 5
Follow up length per stay (days)	13	3 - 39
Posaconazole concentrations (n)	205	N/A
Number of concentrations per patient (n)	3	1 - 14
Number of concentrations per stay (n)	2	1 - 5
Concentration value (µg/mL)	1.43	0.44 - 3.86
TC (%)	67.8	N/A
TC value (µg/mL)	1.36	0.46 - 3.44

AST : Asparagine Amino Transferase ; ALT Alanine Amino Transferase ; ALK : Alkaline Phosphatase ; GGT : Gamma Glutamyl Transferase ; TC: Trough Concentration, defined as a concentration measured 24+/-3h after posaconazole intake ; N/A: Not Applicable.

Table 2. Results of the final model

Parameter	Value	RSE (%)
<i>Fixed effects</i>		
k_a (h^{-1})	0.588	15
V/F (L)	420	10
CL/F ($L \cdot h^{-1}$)	7.3	5
<i>Random effects</i>		
IIV on k_a (%)	0	fixed
IIV on V/F (%)	28.2	32
IIV on CL/F (%)	24.2	30
IOV on CL/F (%)	31.9	14
<i>Residual error</i>		
Proportional (%)	14.8	4

RSE: Relative Standard Error; IIV: Inter Individual Variability; IOV: Inter Occasion Variability

Table 3. Results of model selection

	Model	OFV	Δ OFV	Ref. model	p-value (LRT)
<i>Structural model</i>					
Base model (no IOV) 1 compartments	1	281.6	-	-	
1-compartment model with IOV on CL	2	195.43	86.17	1	p<0.0001
<i>Covariate model</i>					
BMI on CL	4	195.79	0.36	2	0.55
Sex on V	5	190.22	5.21	2	0.022
Disease on CL	7	191.59	3.84	2	0.050
Baseline ALT on CL	8	190.23	5.20	2	0.023
Baseline AST on CL	9	195.5	0.07	2	0.79
Baseline total bilirubin on CL	10	195.01	0.42	2	0.52
Baseline conj. bilirubin on CL	11	194.00	1.43	2	0.23
Baseline ALK on CL	12	195.82	0.39	2	0.53
Baseline GGT on CL	13	196.16	0.73	2	0.39
Longitudinal ALT on CL	14	193.19	2.24	2	0.13
Longitudinal AST on CL	15	195.24	0.19	2	0.66
Longitudinal total bilirubin on CL	16	195.37	0.06	2	0.81
Longitudinal conj. bilirubin on CL	17	195.26	0.17	2	0.68
Longitudinal ALK on CL	18	191.82	3.61	2	0.057
Longitudinal GGT on CL	19	193.92	1.51	2	0.22

OFV: Objective function value ; Δ OFV : difference in OFV ; LRT : Likelihood Ratio Test ; IOV: Inter Occasion Variability ; "longitudinal" refers to the use of dynamic values changing within the same period of observation.

Table 4. Results of the Monte Carlo simulations

	<u><0.5µg/mL</u>	<u>≥0.7µg/mL</u>	<u>≥1.0µg/mL</u>	<u>≥1.5µg/mL</u>	<u>≥2.0µg/mL</u>
<i>Standard regimen : 300 mg BID then 300 mg QD</i>					
At 48h (% of patients)	1.0	95.6	72.6	16.0	2.6
At day 10 (% of patients)	2.6	93.0	76.8	49.2	24.6
<i>Lowered dose regimen : 300 mg BID. 300 mg at day 2. then 200 mg QD</i>					
At 48h (% of patients)	1.0	95.6	72.6	16.0	2.6
At day 10 (% of patients)	9.2	74.4	50.8	18.4	5.2
<i>Lowered dose regimen : 200 mg BID then 200 mg QD</i>					
At 48h (% of patients)	6.2	66.8	16.0	0.6	0.0
At day 10 (% of patients)	9.4	74.4	49.2	15.4	4.4
<i>Lowered dose regimen : 300 mg BID. 300 mg at day 2. then 100 mg QD</i>					
At 48h (% of patients)	1.0	95.6	72.6	16.0	2.6
At day 10 (% of patients)	44.4	29.0	11.0	1.0	0.2

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Manuscript figures

Fig 1.

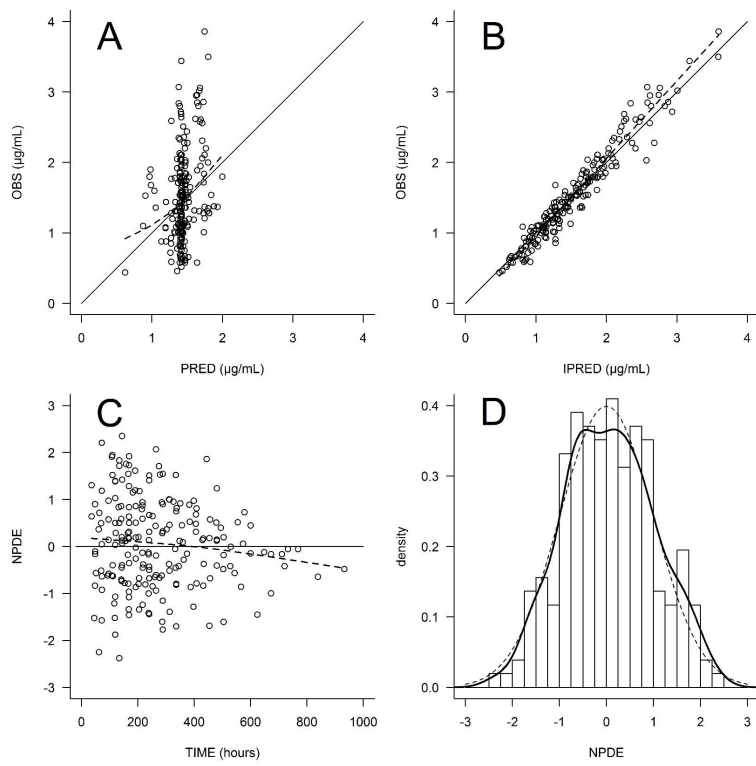


Fig 2.

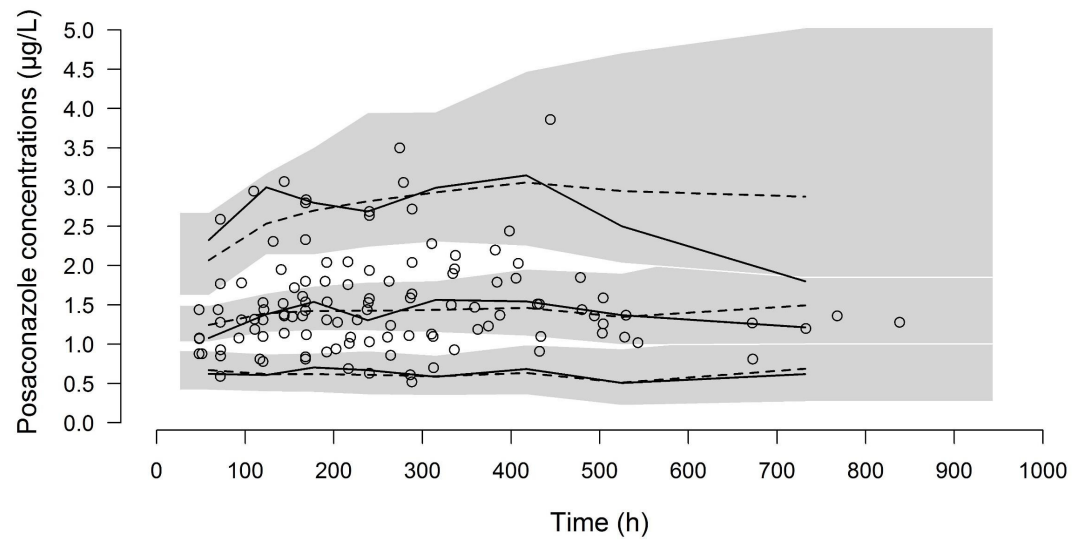


Fig 3.

