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

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

Running title: population pharmacokinetics of posaconazole tablets

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Abstract

Background

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

Patients and methods

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

Results

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

Conclusion

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

Keywords

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

Manuscript (2917 words)

Introduction

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

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

Patients and methods

Ethics

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

Patients and study design.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Monte-Carlo simulations.

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

Results

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

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

Simulations were performed accordingly to the estimated pharmacokinetic parameters. Following the standard loading dose of 300 mg BID on day 1 and 300 mg QD on day 2, 95.6% and 72.6% of simulated patients reached a TC at 48h ≥0.7µg/mL and ≥1µg/mL, respectively. With the standard regimen at 300 mg QD, rates of TC≥0.7µg/mL and ≥1µg/mL at day 10 were 93.0% and 76.8%, respectively. These rates fall to 74.4% and 50.8% with the lowered dose regimen (200 mg QD from day 3). Rates of patients with TC≥2µg/mL at day 10 were 24.6% and 5.2% with the standard and lowered dose regimens, respectively. According to the simulations, we calculated that 100% of patients with TC at 48h ≥1.5µg/mL would keep TC at day 10 ≥1µg/mL after lowering the dose to 200 mg QD from day 3 (figure 3 and table 4).

214 The additional simulations showed that only 66.8% and 16.0% of simulated patients reached
215 TC ≥0.7µg/mL and ≥1µg/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 ≥0.7µg/mL and ≥1µg/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 0.46µg/mL to 3.44µg/mL and a coefficient of variation of 40.5%. Moreover, we
228 also found an important intrapatient 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

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

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

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

The results of the simulations showed that with the recommended regimen almost all the patients achieve TC≥0.7µg/mL at 48h following the loading dose of 300 mg BID on day 1 followed by 300 mg QD on day 2, thus ensuring the efficacy of the prophylaxis. Conversely, only two thirds of the simulated patients reach TC>0.7µg/mL at 48h with a reduced loading dose of 200 mg BID on day 1 followed by 200 mg QD on day 2. Based on these results, there is no argument in favour of reducing the loading dose.

Nevertheless, regarding the maintenance dose, with the standard regimen of 300 mg QD TC keep increasing slowly in a proportion of patients, bringing to a quarter (24.6%, table 4) the rate of patients with TC≥2µg/mL at day 10. The simulations showed that following a dose reduction to 200 mg QD from day 3, half of the patients would keep TC>1µg/mL thereafter. Additional simulations also showed that up to 11% of patients would maintain TC≥1µg/mL after dose reduction to 100 mg QD.

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

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

Conclusion

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

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Conflicts of interest

None to declare.

Authors' contribution

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

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Figures legends

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

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

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

413 # Tables

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

	Median	Range (min - max)
Demographics		
Age (years)	53	19 - 73
Males (%)	59.2	N/A
Body weight (kg)	72	50 - 125
Body Mass Index (kg/m²)	26.4	17.7 - 40.4
Biologics (baseline)		
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
Study data		
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.

414

Table 2. Results of the final model

Parameter	Value	RSE (%)
Fixed effects		
k_a (h^{-1})	0.588	15
V/F (L)	420	10
CL/F ($L.h^{-1}$)	7.3	5
Random effects		
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
Residual error		
Proportional (%)	14.8	4

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

415

Table 3. Results of model selection

	Model	OFV	ΔOFV	Ref. model	p-value (LRT)
Structural model					
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**
Covariate model					
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. biliribin 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 ; ΔOFV : 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.

416

Table 4. Results of the Monte Carlo simulations

	<0.5µg/mL	≥0.7µg/mL	≥1.0µg/mL	≥1.5µg/mL	≥2.0µg/mL
Standard regimen : 300 mg BID then 300 mg QD					
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
Lowered dose regimen : 300 mg BID. 300 mg at day 2. then 200 mg QD					
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
Lowered dose regimen : 200 mg BID then 200 mg QD					
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
Lowered dose regimen : 300 mg BID. 300 mg at day 2. then 100 mg QD					
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

417

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Manuscript figures

Fig 1.

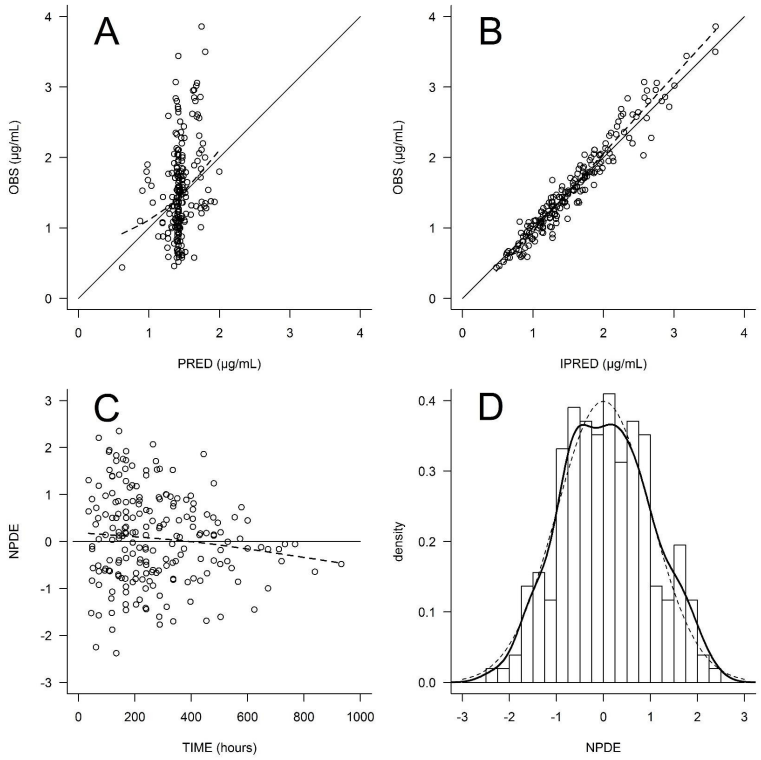


Fig 2.

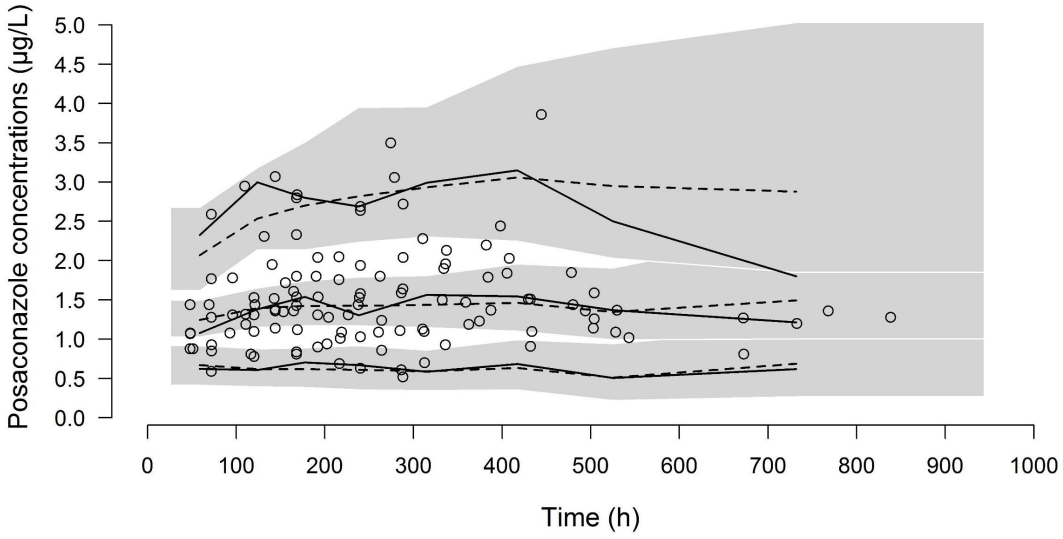
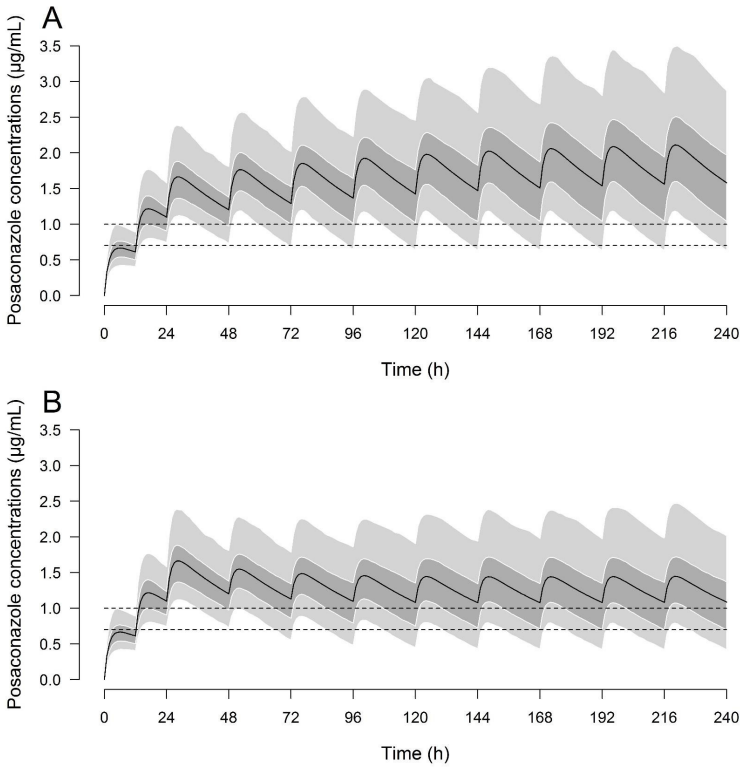

Posaconazole concentrations (µg/L)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
100
200
300
400
500
600
700
800
900
1000
Time (h)

Fig 3.


A
Posaconazole concentrations (µg/mL)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
24
48
72
96
120
144
168
192
216
240
Time (h)
B
Posaconazole concentrations (µg/mL)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
24
48
72
96
120
144
168
192
216
240
Time (h)