

Application of a mixture model to lamotrigine XR bioequivalence study

Jiansong Yang¹, Fan Zhang¹, Peiming Ma¹, Chao Chen²

¹Clinical Pharmacology Modelling and Simulation, GSK, Shanghai, China
²Clinical Pharmacology Modelling and Simulation, GSK, London, UK

Introduction

A single-dose, randomized, parallel-group, open-label study in 126 healthy subjects was conducted to investigate bioequivalence (BE) of 250 mg lamotrigine XR and the combination of 200 and 50 mg lamotrigine XR (Figure 1). The 90% CIs for geometric mean ratio of AUC_{0-∞} and C_{max}, calculated by non-compartmental analysis, were (0.735, 0.956) and (0.894, 1.045), respectively. The failure for AUC_{0-∞} to meet the BE criterion (0.80, 1.25) was suspected to be caused by the difference in clearance (CL) (Figure 2), not absorption (Lovric et al, TDM 2012) .

Objective

To perform *post hoc* analyses using population pharmacokinetic (PK) modelling approach, to identify the source of treatment difference in AUC.

Methods

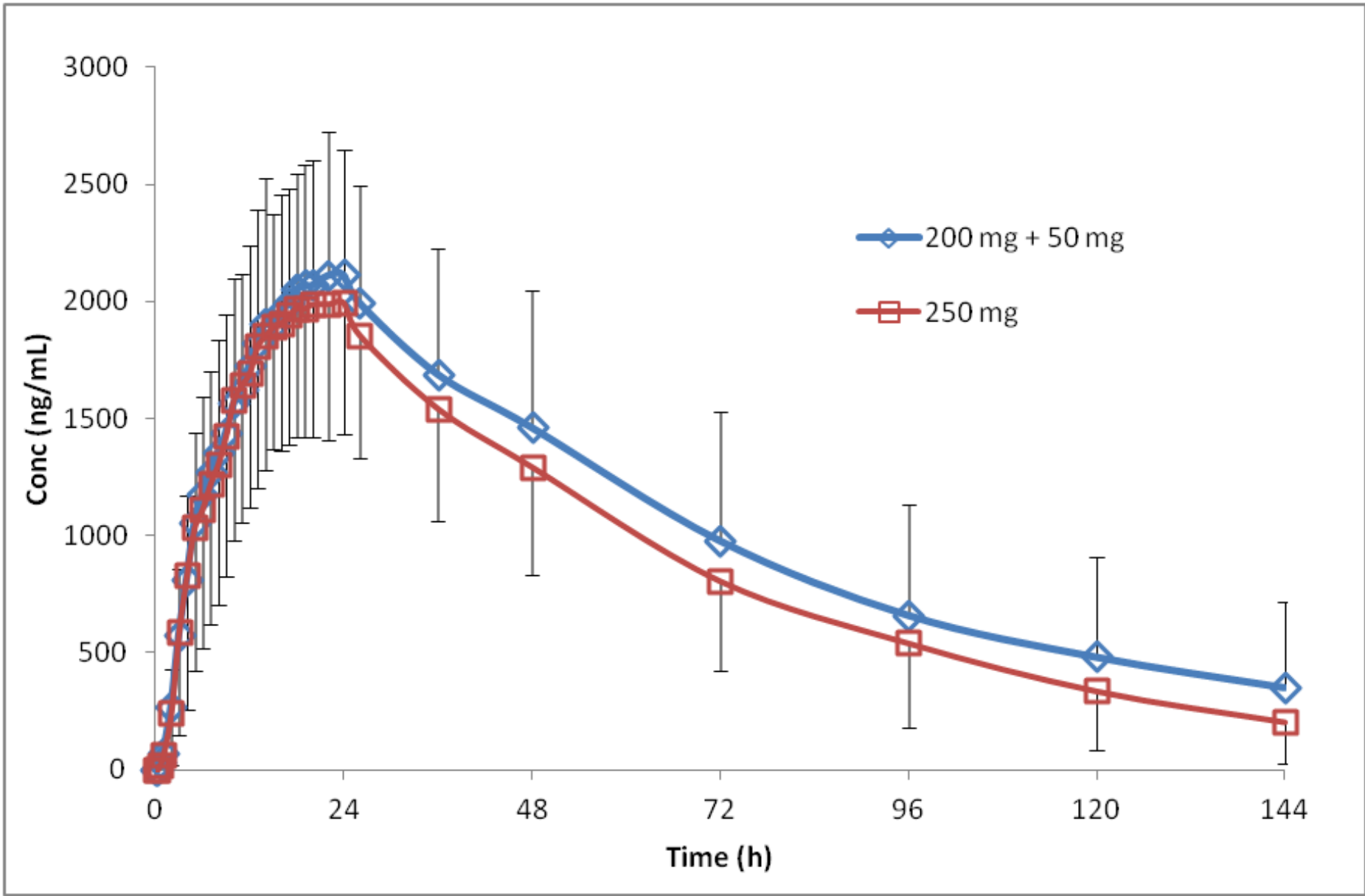
Lamotrigine concentrations from the BE study were analyzed using nonlinear mixed-effect modelling by Monolix version 4.3.3 (<http://www.lixoft.eu/>). The main objective of this exercise was to check if formulation was a significant covariate influencing lamotrigine PK. Parameters were estimated by the stochastic approximation expectation-maximization (SAEM) algorithm with a Markov Chain Monte Carlo (MCMC) procedure.

The PK model development started with a one-compartment model with linear elimination and first-order absorption (Ziad & Posner, BJCP 1997). Other structural PK (one- and two-compartment) and error (additive, proportional and combined) models were evaluated. A variety of more complex absorption models were also explored, including zero- and first-order absorption models with or without a lag time. Between-subject variability in various pharmacokinetic parameters was evaluated using a log-normal distribution, except for Tk0 (duration of 0-order absorption), for which a normal distribution was also evaluated. A mixture model was applied to classify clearance into two subpopulations: high clearance group and low clearance group. In addition, formulation was tested as a covariate for all PK parameters.

Model evaluation and selection were driven by goodness-of-fit criteria, including: (i) visual inspection of diagnostic scatter plots, (ii) successful convergence of the minimization routine with at least 2 significant digits in parameter estimates, (iii) plausibility of parameter estimates, (iv) precision of parameter estimates, (v) log-likelihood ratio test for hierarchical models, and Akaike information criterion (AIC) for non-hierarchical models.

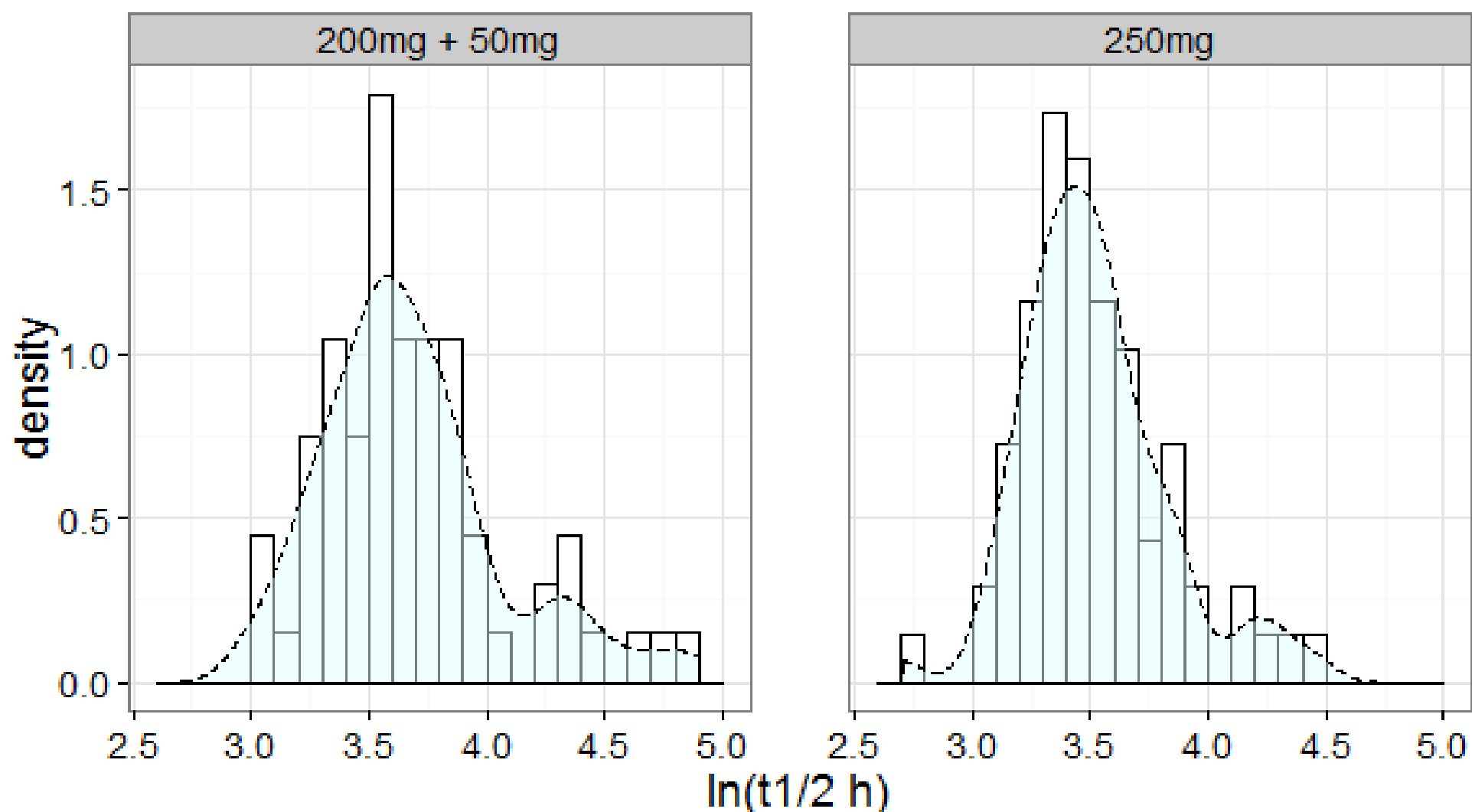
Results

Figure 1: Mean (±SD) lamotrigine serum concentration-time profiles



Lamotrigine XR 250 mg (test, red) or lamotrigine XR (200 mg + 50 mg; reference, blue)

Figure 2: Histogram plots of the log-transformed t1/2 for the two treatment groups



Histogram plots of the log-transformed t1/2 showed a bimodal distribution, suggests there might be two subpopulations in the BE study – one with high clearance and the other with low clearance.

Final lamotrigine pharmacokinetic model

The disposition of lamotrigine was adequately described by a one-compartment model, and the oral absorption of lamotrigine XR was best described by a 0-order process after a lag time. Model parameters included an absorption delay (Tlag, h), the duration of zero-order absorption process (Tk0, h), apparent volume of distribution (V/F, L), and apparent clearance (CL/F, L/h). The inter-subject variability was modelled through an exponential model for all parameters except for Tk0, for which a proportional model was better performed. The residual variability was best explained by the proportional error model.

A mixture model was applied to the apparent clearance to classify clearance into higher clearance or lower clearance subpopulations (Figure 3). Adding the mixture model significantly decreased the objective function value and the inter-subject variability of the PK parameters (p< 0.01). The mean pharmacokinetic parameter estimates obtained from the final model are shown in Table 1. Mean CL values for subjects with low and high clearance were 0.64 L/h and 1.99 L/h, respectively. The mixing fraction indicated that 12% of the population had low clearance, while the rest had high clearance. *Post hoc* subpopulation classification indicated there were 13% (n=9) and 4% (n=3) subjects with low clearance in lamotrigine (200 mg + 50 mg) and 250 mg treatment groups, respectively.

Formulation was tested as a covariate for all PK parameters. It was a significant covariate (p<0.01) for ALAG (0.372 and 0.486 for Reference and Test, respectively), but not a significant covariate (p>0.05) for oral bioavailability. The latter suggests the two formulations were likely to be bioequivalent.

Figure 3: Visual predictive checks by subpopulations

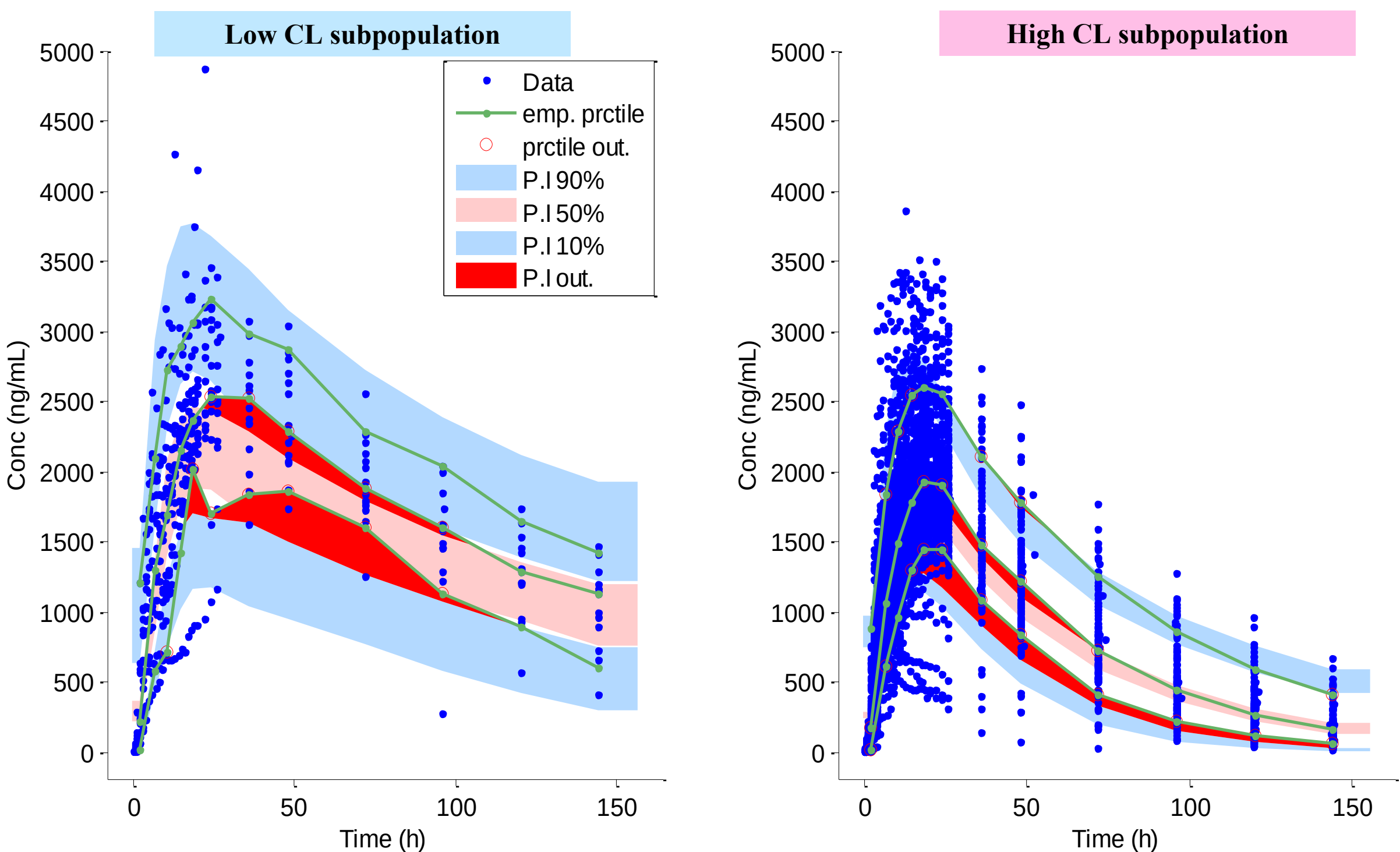


Table 1: Population pharmacokinetic parameters of lamotrigine XR in the final model

Parameter	Final estimate	%RSE	Additional note
ALAG_R (hr)	0.372	7	ALAG for Reference formulation
ALAG_T (hr)	0.486	7	ALAG for Test formulation
Tk0 (hr)	13.2	3	
V (L)	103	2	
Low CL (L/hr)	0.64	18	
High CL (L/hr)	1.99	4	
Mixing fraction	0.12	33	12% of population had low CL
ω (ALAG)	0.56	8	CV= 56%
ω (Tk0)	5.1*	7	SD=5.1 hr
ω (V)	0.26	6	CV=26%
ω (CL)	0.40	8	CV=40%
σ (proportional)	0.19	2	CV=19%
σ (additive) (ng/mL)	5 (fixed)	-	SD = 5 ng/mL (set as half of LLQ)

%RSE: percent relative standard error; ALAG: absorption lag time; Tk0: the duration of a 0-order absorption process; CV: coefficient of variation; SD: standard deviation; LLQ: lower limit of quantification
* A normal distribution described Tk0 distribution better than a log-normal distribution

Conclusion

Using a mixture model, this analysis revealed that the non-BE in this parallel study was likely due to the presence of a small number of subjects with low clearance in one of the two treatment groups, rather than any formulation difference. This finding was supported by literature data of polymorphism of the metabolic pathway responsible for lamotrigine clearance.