Prediction of multiple-dose relative bioavailability outcome for an extended release valproic acid formulation

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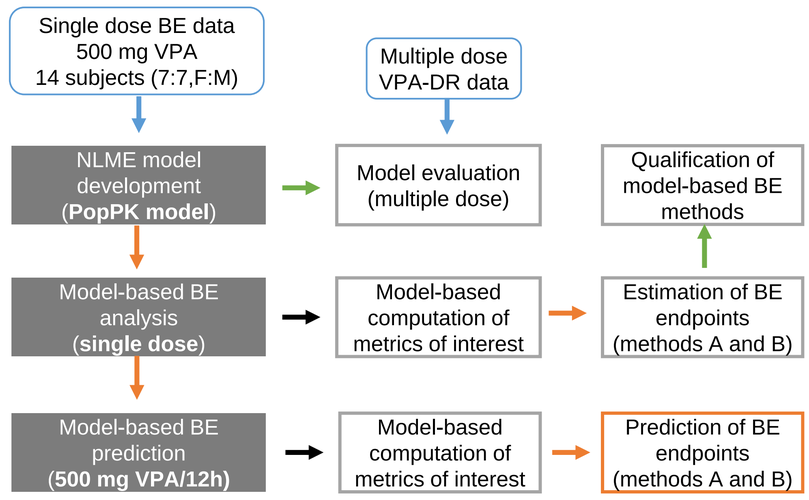
BACKGROUND

A local product (Test) containing valproic acid (VPA) was developed in collaboration between our group and a local laboratory to reduce PTF. It was primarily approved for marketing in Uruguay after showing ER properties in a relative bioavailability study versus a delayed release formulation (Depakote®, Abbot, Reference) under single dose fasting conditions. The regulatory authority has required to further evaluate the Test product in a multiple-dose scenario with healthy subjects. The aim of this work was to: (i) evaluate methods for model-based bioequivalence (BE) assessment using a non-linear mixed effects (NLME) model developed with single dose data; and (ii) predict the Test pharmacokinetic performance in the multiple-dose scenario relative to the IR formulation.

METHODS



METHOD A: 90% nonparametric CI for the T/R ratio obtained from the distribution of medians computed in each simulated study from the individual T/R ratios.

METHOD B: 90% parametric CI for the T/R ratio of geometric means and residual variance derived from the standard average BE analysis applied to each simulated study.

ANALYSIS OF BE ENDPOINTS

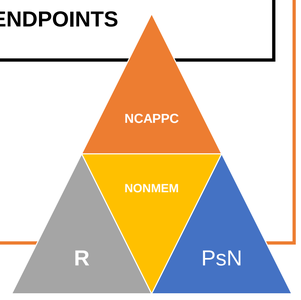


Figure 1: Workflow on the right, methods and software on the left.

MODEL DEVELOPMENT

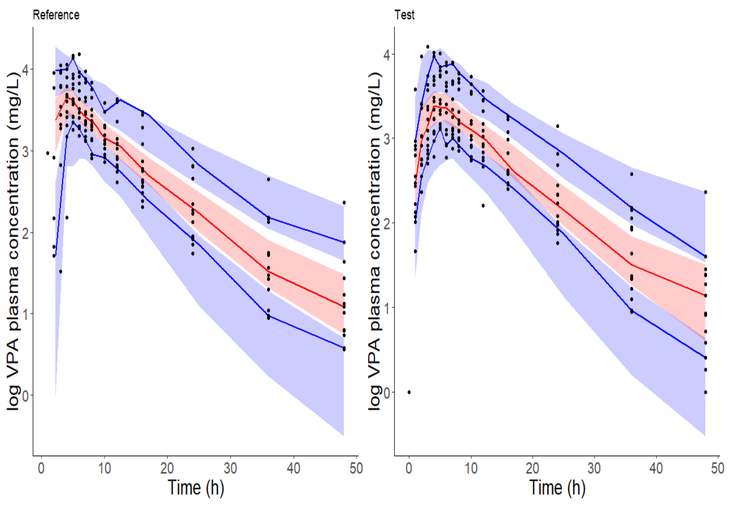


Figure 2: Visual predictive check (VPC) for the two formulations, reference on the left and test on the right side, both for single dose. The 5th, 95th (dotted lines) and 50th (continuous line) percentiles of observed concentrations and the simulated CI 95% for each percentile (shade area). Concentrations are shown in log-scale.

Parameter	Typical Value (RSE%)	BSV (RSE%)
Ka_{F-R}	1.13 h^{-1} (29)	180% (24)
Ka_{M-R}	1.93 h^{-1} (13)	-
Ka_T	0.451 h^{-1} (12)	47% (18)
$Tlag_{F-R}$	0.920 h (5.4)	-
$Tlag_{M-R}$	1.93 h (12)	31% (32)
$Tlag_T$	0.315 h (35)	-
BA_R	1 (FIX)	-
BA_T	0.926 (3.0)	9.0% (31)
Cl_F	0.464 $^L/_h$ (10)	20% (17)
Cl_{M+CT}	0.857 $^L/_h$ (6.4)	20% (17)
Vc	10.5 L (4.7)	20% (24)
Q	0.199 $^L/_h$ (15)	-
Vp	3.44 L (18)	-
Residual Error	0.158 (16)	-

Table 1: Parameters of the bi-compartmental model, typical values and between subject variabilities (BSV) expressed as coefficient of variation: Absorption rate (ka), lag time (Tlag), bioavailability (BA), central clearance (CL), Volume of central compartment (Vcentral), Intercompartmental clearance (Q), Volume of peripheral compartment (Vperipheral) and Residual error (additive model on log scale) F= female, M= male, R= reference formulation, T= test formulation, CT= contraceptive therapy. CL for Female is only for women without CT.

MODEL EVALUATION FOR MULTIPLE DOSE EXTRAPOLATION

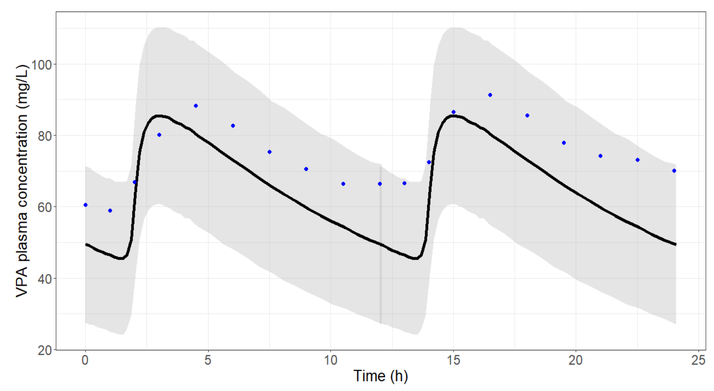


Figure 3: Continuous line and shade: mean and standard deviation of simulated plasma VPA concentration. Dots: observed plasma VPA concentrations reported by Dutta and collaborators in 14 subjects (3:11, F:M)

	AUC_0^{24}	C_{max}
In vivo	1789 ± 332 $\frac{mg*h}{L}$	99.4 ± 15.7 $\frac{mg}{L}$
Simulated	1551 ± 247 $\frac{mg*h}{L}$	110 ± 29.3 $\frac{mg}{L}$
Predictive error	-13.3 %	10.7 %

Table 2: Observed and simulated (mean ± standard deviation) AUC_0^{24} and C_{max}. Predictive errors (%) for the model steady-state mean predictions of AUC_0^{24} and C_{max}.

ESTIMATION OF BE ENDPOINTS IN SINGLE AND MULTIPLE DOSE SCENARIOS

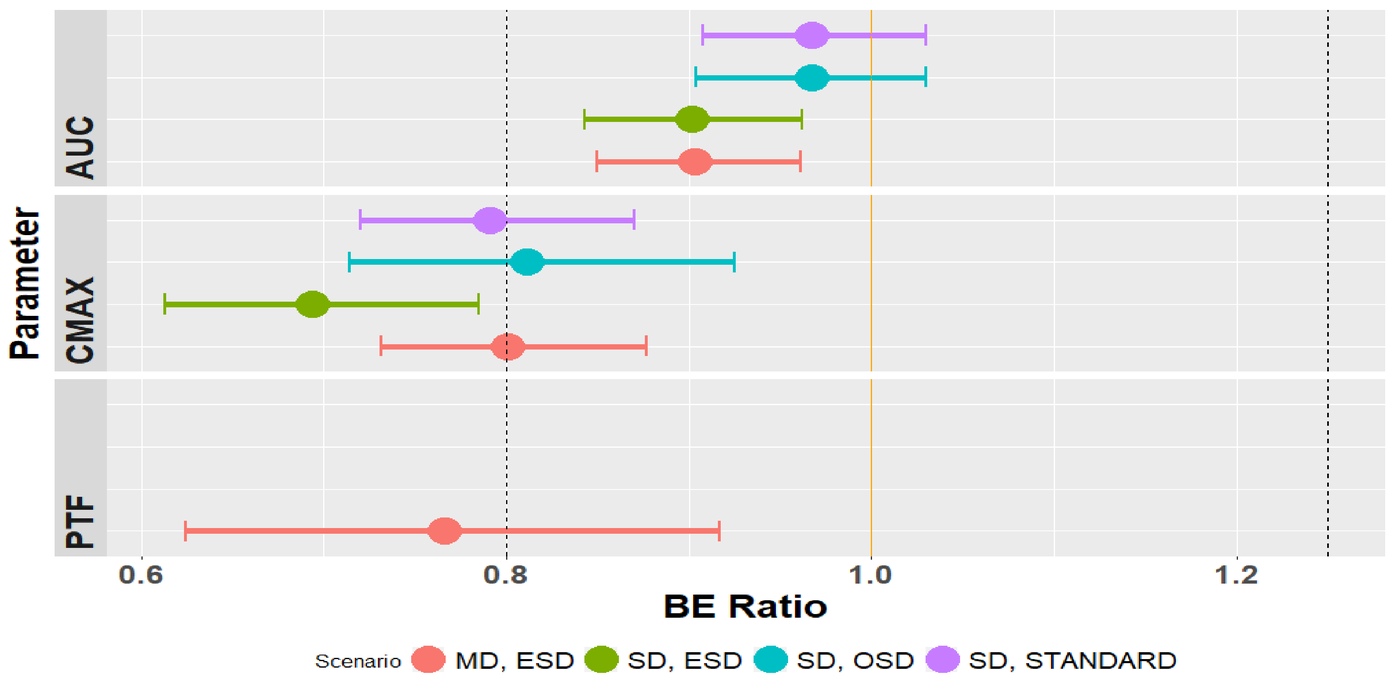


Figure 4: Forest plot of CI of metrics of interest, obtained by method B, in single and multiple dose to simulated results of the original and an extensive sampling time design. Vertical dotted lines represent the accepted BE Ratio. Single dose, standard NCA CI 90%: violet; Single dose and original sampling time design: blue; Single dose and extensive sampling time design: green; Multiple dose and extensive sampling time design: pink. AUC is from 0 to 48 in single dose scenarios and from 0 to 12 in multiple dose scenarios.

CONCLUSION

A 2-compartment pharmacokinetic NLME model with first-order lagged absorption and linear elimination was developed from the single dose bioequivalence data. We present two alternative ways of assessing bioequivalence from a model-based approach. Results of both methods indicate that BE conclusions obtained in the single-dose in vivo study would hold under multiple-dose administration of 500 mg twice daily. Model-based approach with an extensive sample time scheme allows to appreciate bigger differences in VPA exposure between reference and test formulations, due to the better characterization of C_{max}.

REFERENCES

[1] Acharya C et al. 2016. A diagnostic tool for population models using non-compartmental analysis: the ncappc package for R. Comput. Methods Programs. Biomed. 127: 83-93.

[2] Dutta S, Zhang Y. 2004. Bioavailability of divalproex extended-release formulation relative to the divalproex delayed-release formulation. Biopharm. Drug. Dispos. 25:345-352.