



Abstract

Population Pharmacokinetic Model of Valproic Acid in Adult Patients: an Update.

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Objectives: The main goal of this work was to develop an updated population pharmacokinetic model to identify and quantify the influence of demographics, clinical and treatment factors on the clearance (CL) of valproic acid (VLP) in adult patients.

Methods:

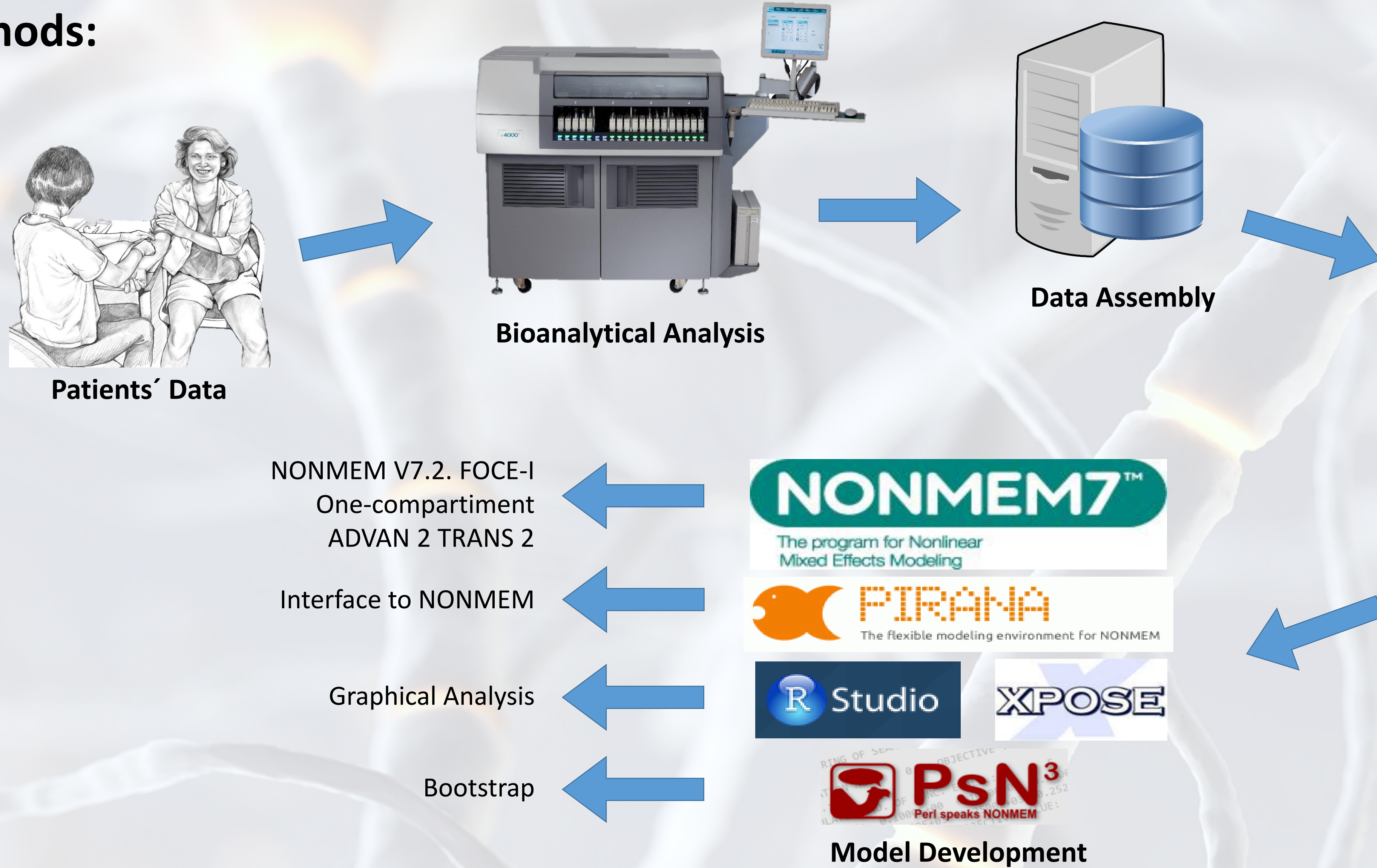


TABLE 1. Demographic and Clinical Characteristic of the Adult Patients Included in the Study.

DEMOGRAPHICS	
Number of samples/patients	868/411
Gender (SEX) (male/female)	209/202
Age, median (range) (years)	36.1 (15-84)
Body Weight (WGT), median (range) (kg)	68.2 (40-115)
DOSING AND PHARMACOKINETICS	
Observations per patients, median	2.1
VLP plasma concentrations, median (range) (mg/L)	65.0 (11.0-129.6)
COMEDICATION (samples/patients)	
carbamazepine (CBZ)	256/92
phenytoin (PHT)	95/43
phenobarbital (PHB)	117/47
lamotrigine (LTG)	44/26
topiramate (TOP)	37/20
clonazepam (CLO)	35/21
vigabatrin (VIG)	22/7
olanzapine (OLA)	12/11
clobazam (CLB)	6/5
risperidone (RIS)	19/16

Results:

TABLE 2. Summary of Covariates Analyses.

Covariates on the CL/F	Forward Inclusion Method		Backward Elimination Method		Inclusion on the Final Model
	Δ OFV ^a	P Value	Δ OFV ^b	P Value	
WGT	73.434	< 0.05	63.752	< 0.01	YES
SEX	28.940	< 0.05	30.242	< 0.01	NO ^d
COMEDICATION					
VIG	17.161	< 0.05	20.649	< 0.01	YES
TOP	0.985	NS	----	----	NO
CLO	0.001	NS	----	----	NO
CLB	0.066	NS	----	----	NO
LTG	8.035	< 0.05	5.615	NS	NO ^c
PHB	30.448	< 0.05	36.627	< 0.01	YES
PHT	43.572	< 0.05	87.828	< 0.01	YES
CBZ	164.934	< 0.05	159.095	< 0.01	YES

^a Reduction in the objective function value (OFV) between consecutive models.

^b Increase in the OFV between consecutive models.

^c LTG was excluded in the backward elimination process ($p < 0.01$).

^d SEX was also eliminated in the final model because of the low clinical significance (< 15 %).

NS, non-significant.

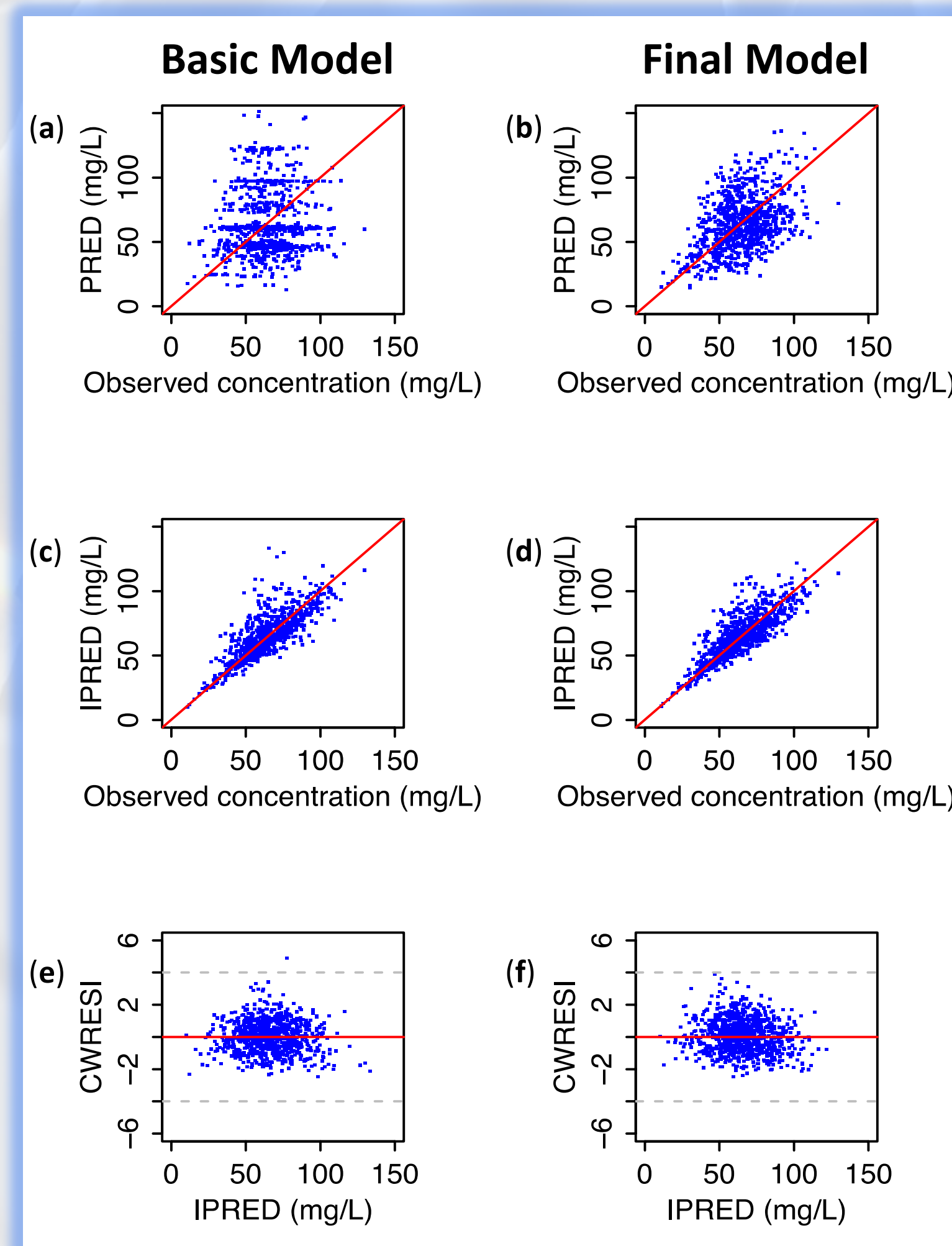


Figure 1. Goodness of fit plots: Basic and Final Model.

a, b: Observed concentrations vs. Populational predicted concentrations (PRED).
c, d: Observed concentrations vs. Individual predicted concentrations (IPRED).
e, f: IPRED vs. Conditional Weighted Residuals with Interaction (CWRESI).

TABLE 3. The Final Parameter Estimates from NONMEM and the Bootstrap Analysis.

Parameter	NONMEM		Bootstrap Analysis	
	Estimate	RSE (%)	Median	95 % CI
Ka (h ⁻¹)	4.1	Fixed [1]	----	----
V/F (L/kg)	0.2	Fixed [2]	----	----
CL (L/h)	0.58	2	0.579	0.560 – 0.602
WGT*	0.584	11	0.583	0.456 – 0.714
VIG*	1.44	8	1.435	1.119 – 1.655
PBT*	1.23	6	1.227	1.103 – 1.376
PHT*	1.39	5	1.396	1.269 – 1.547
CBZ*	1.44	4	1.446	1.346 – 1.552
ω^2	0.055	5	0.054	0.044 – 0.066
σ^2	0.033	4	0.033	0.028 – 0.038

1000 Bootstrap runs.

RSE (%), percentage of relative standard error.

95 % CI, 95 % confidence interval.

* Effect of the covariates on the CL of VLP.

Previous Model [3]:

$$CL_{VLP}/F (L/h) = 0.004 \cdot WGT \cdot (Dose^{0.304}) \cdot (1.363 \cdot CBZ) \cdot (1.397 \cdot PHB) \cdot (1.541 \cdot PHT)$$

$\omega^2 = 23.4 \%$
 $\sigma^2 = 11.4 \text{ mg/L}$

Updated Model:

$$CL_{VLP}/F (L/h) = 0.58 \cdot (WGT/70)^{0.58} \cdot (1.44 \cdot CBZ) \cdot (1.23 \cdot PHB) \cdot (1.39 \cdot PHT) \cdot (1.44 \cdot VIG)$$

$\omega^2 = 0.055$ (shrinkage: 16 %)
 $\sigma^2 = 0.033$ (shrinkage: 21 %)

The standard estimation error was lower than 11 % for all parameters.

Conclusion: The population pharmacokinetic model developed for VLP in adult patients includes WGT and the concomitant administration of CBZ, PHB, PHT and VIG. More studies are required to verify the causes and the true extent of the interaction discovered between VIG and VLP.

References:

- [1] Dutta S, Reed RC. Distinct absorption characteristics of oral formulations of valproic acid/divalproex available in the United States. *Epilepsy Res.* 2007; 73:275-83.
- [2] Patsalos PN. Antiepileptic drug interactions. A clinical guide. 2nd ed. London: Springer; 2013.
- [3] Blanco-Serrano B, Otero MJ, Buelga DS, Garcia Sanchez MJ, Serrano J, Dominguez-Gil A. Population estimation of valproic acid clearance in adult patients using routine clinical pharmacokinetic data. *Biopharm. Drug Dispos.* 1999; 20:233-40.