Table 1: Demographics of the total modelling population. Carbamazepine-Valproic acid: number of patients receiving the comedication and the range of doses.

Demographic	Mean (SD)	Median (range)
No. of patients	494	-
Gender (M:F)	248:246	-
Age, years	45.3 (24.2)	29 (0.2-91)
Weight, kg	70.3 (27.5)	58 (3-151.9)
LMT dose	255 (190) mg/day	200 (2-1200) mg/day
Comedication	Frequency	Dose range
Carbamazepine	62	300-1200 mg/day
Clobazam	11	2.5-40 mcg/day
Clonazepam	22	0.25-175 mcg/day
Gabapentin	13	100-3600 mg/day
Levetiracetam	67	125-4250 mg/day
Oxcarbazepine	25	150-1500 mg/day
Phenobarbital	33	24-400 mg/day
Phenytoin	81	40-780 mg/day
Topiramate	37	12.5-700 mg/day
Valproic acid	75	250-3000 mg/day

Table 2: Weight (WT) calculation functions per age group, and its coefficient of variance (CV%) used in the simulations.

Population	Age range	WT mean	WT CV%
Infants and toddlers	2 – 23 months	$9.35*(1+0.0587*SEX)*AGE^{0.356}$	18
Children and adolescents	2 – <18 years	3*AGE+7	25
Adults	18 – 65 years	65+10*SEX	16
Older adults	65 – 91 years	65+10*SEX	16

Table 3: The final model parameter estimates and corresponding bootstrap results, including the 95% confidence intervals (CI). θ: population value; ω^2: variance of deviation (η) of individuals from population value θ; σ^2: variance of proportional (prop) and additive (add) residual errors (ε).

Parameter	Value (95% CI)	Bootstrap median (95% CI)
$\theta_{Ka\ IR}$	2.43 (1.425 – 3.435)	2.56 (1.44 – 3.97)
$\theta_{Ka\ XR}$	0.087 (0.073 – 0.101)	0.09 (0.07 – 0.11)
θ_{CL}	2.23 (1.985 – 2.475)	2.28 (2.01 – 2.53)
θ_{V}	1.97 (1.694 – 2.246)	1.92 (1.64 – 2.36)
θ_{CBZ}	0.765 (0.516 – 1.014)	0.75 (0.53 – 1.12)
θ_{PHT}	1.29 (1.041 – 1.539)	1.29 (1.02 – 1.55)
θ_{VPA}	-0.474 (-0.555 – -0.393)	-0.49 (-0.57 – -0.41)
θ_{TM50}	128.5 (76.9-333.3)	125 (100-250)
θ_{Hill}	-5.66 (-10.736 – -0.584)	-15.98 (-152.94 – -2.75)
θ_{Amax}	0.629 (0.196 – 1.062)	0.60 (0.34 – 1.07)
θ_{Older}	0.148 (0.032 – 0.264)	0.16 (0.04 – 0.25)
$\omega^2_{Ka\ IR}$	0.609 (-0.536 – 1.754)	0.53 (0.0001 – 3.09)
$\omega^2_{Ka\ XR}$	0.46 (-0.442 – 0.715)	0.57 (0.27 – 1.18)
ω^2_{CL}	0.274 (-0.263 – 0.811)	0.27 (0.22 – 0.32)
ω^2_{V}	0.626 (0.3516 – 0.9004)	0.63 (0.31 – 1.09)
σ^2_{prop}	0.156 (0.103 – 0.209)	0.16 (0.11 – 0.20)
σ^2_{add}	0.236 (0.045 – 0.427)	0.23 (0.10 – 0.42)

Table 4: Optimised dosing levels and predicted steady state concentrations (Css) per age group. Each column summarises the proportion of patients in each group who are exposed above the absolute toxicity level of 20 mg/L, above the therapeutic maximum of 15 mg/L, and below the therapeutic minimum of 2.5 mg/L.

Population	Age range	Dose	% Css > 20*	% Css > 15*	% Css < 2.5*
Infants	2 – 6 months	70 mg/day	0.49	1.9	10.6
Toddlers	6 – 23 months	100 mg/day	0.89	3.4	6.4
Children and adolescents	≥2 – 18 years	6 mg/kg/day	1.9	6.1	3.7
Adults	18 – 65 years	350 mg/day	2.0	6.6	3.5
Older adults	65 – 91 years	300 mg/day	2.1	6.6	3.5

*mg/L

Table 5: Final model estimates along with previously published pharmacokinetic data in each population.

Population	Parameter	Final model values	Literature values
Adults	Ka IR (h^{-1})	2.43	0.38-3.19 [12,16,17,20,21,33,34,44
	KA XR (h^{-1})	0.087	0.0739 [44]
	V (L/kg)	1.97	0.9-1.9 [12,16,17,19–21,33–35]
	CL (L/h/kg)	0.0319	0.028-0.15 [12,16,17,19–21,33–35]
Older adults 65-91 years	Ka IR (h^{-1})	2.43	2.98-3.5 [14,44]
	KA XR (h^{-1})	0.087	0.0739 [44]
	V (L/kg)	1.97	1.3-1.42 [14,44]
	CL (L/h/kg)	0.0271	0.033-0.039 [14,44]
Children and adolescents 2-18 years	Ka IR (h^{-1})	2.43	1-3.5 [13,18,21]
	KA XR (h^{-1})	0.087	-
	V (L/kg)	1.97	0.6-2.12 [13,18,21]
	CL (L/h/kg)	0.0374	0.036-0.09 [13,18,21]
Infants and toddlers	Ka IR (h^{-1})	2.43	1 [18]
	KA XR (h^{-1})	-	-
	V (L/kg)	1.97	0.6 [18]
	CL (L/h/kg)	0.051-0.10	0.037 [18]