Supplementary Material

Table S1. Previously published population pharmacokinetic modeling results for levetiracetam.

Clinical study	Spencer et al., 2011	Karatza et al., 2020	Hernandez-Mitre et al., 2020	Rhee et al., 2017	Sime et al., 2021	Pigeolet et al., 2007	Ito et al., 2016	Chhun et al., 2009	Toublanc et al., 2008
Patient population	Adult ICU	Adults with persistent epilepsy	Epileptic adults	Epileptic adults	Critically ill adult patients with severe traumatic brain injury or aneurysmal subarachnoid hemorrhage without renal dysfunction	86 healthy και 438 epileptic adults	Children - adults - elderly	Children 4 - 16 years	Children with epilepsy, 3 months-18 years
Sample size	12	8	107	425	30	524	225	44	228
Route of administration	IV (ss)	oral (ss)	oral (ss)	oral (ss)	16 patients received oral doses and the remaining 14 received intermittent IV infusion over 15 min	oral	oral	oral (ss)	oral
Software	Boomer	Monolix	NONMEM	NONMEM	Pmetrics	NONMEM	NONMEM	NONMEM	NONMEM

Pharmacokinetic structural model	two-compartment with with first order elimination	one-compartment with first order absorption and elimination	one-compartment with first order absorption and elimination	one-compartment with first order absorption and elimination	two-compartment with first-order order oral absorption	one-compartment with first order absorption and elimination	one-compartment with first order absorption and elimination	one-compartment with first order absorption and elimination	one-compartment with first order absorption and elimination
Residual error model	NA	proportional	proportional	additive	additive	proportional	proportional	proportional	proportional
Pharmacokinetic estimates	V = 17.1 l V_{ss} = 36.8 l Cl = 5.6 l/h	K_a = 0.616 h^{-1} V/F = 34.7 l Cl/F = 3.26 l/h	K_a = 3.63 h^{-1} V/F = 29.7 l Cl/F = 2.74 l/h	K_a = 2.44 h^{-1} (fixed) V/F = 65.3 l Cl/F = 3.9 l/h	K_a = 2.4 h^{-1} V/F = 8.9 L Cl/F = 2.5 l/h Kcp= 1.8 h^{-1} Kpc = 0.7 h^{-1} Tlag = 0.5 h	K_a = 4.80 h^{-1} without food K_a = 2.44 h^{-1} food intake V/F = 52.7 l Cl/F = 4.02 l/h	K_a = 0.464 h^{-1} Cl/F = 4.8 l/h 500 mg bid Cl/F = 5.9 l/h 1500 mg bid V: fixed to 0.753 L/kg	K_a = 3.83 h^{-1} V/F = 21.9 l Cl/F = 2.47 l/h	K_a = 1.46 h^{-1} V/F = 21.5 l Cl/F = 2.17 l/h
Interindividual variability, CV %	NA	IIV for ka = 32.7 IIV for V/F = 27.4 IIV for CL/F = 15.9	IIV for ka = 139.6 IIV for V/F = 30.4 IIV for CL/F = 43.6	IIV for V/F = 19.9 IIV for CL/F = 60.8	IIV for ka = 84.84 IIV for V/F = 33.4 IIV for CL/F = 45.6 IIV for Kcp = 60.2 IIV for Kpc = 40.4 IIV for Tlag = 134.0	IIV for K_a without food = 108 IIV for K_a food intake = 108 IIV for CL/F = 19.5 IIV for V/F = 11.8	IIV for ka = 63.8 IIV for CL/F = 24.4	IIV for ka = 137 IIV for V/F = 2.65 IIV for CL/F = 5.9	IIV for ka = 100 IIV for V/F = 19 IIV for CL/F = 19
Correlations	NA	Between V_d/F and Cl/F	NA	Between V/F και Cl/F	NA	NA	NA	NA	NA

Covariates	NA	Cl/F: CrCl ($p = 0.004$)	Cl/F: CrCl V/F: BSA	Cl/F: Body weight and eGFR V/F: Body weight	Cl/F: urinary creatinine clearance and body surface V/F: body surface Ka: body surface	V_d/F: Body weight, disease, valproic Cl/F: Body weight, gender, Cl_{Cr}, AEDs inducers P450, valproic	Cl/F: eGFR, dosing regimen, body weight	V_d/F: Body weight Cl/F: Body weight	K_a: Age V_d/F: Body weight Cl/F: Body weight, dosing regimen Cl_{Cr}, AEDs inducers P450

Key: ss, steady-state, IV, intravenous; V, volume of distribution, Cl, clearance; Ka, absorption rate constant; F, bioavailability fraction; Tlag, absorption lag time; IIV: interindividual variability; NA, not available

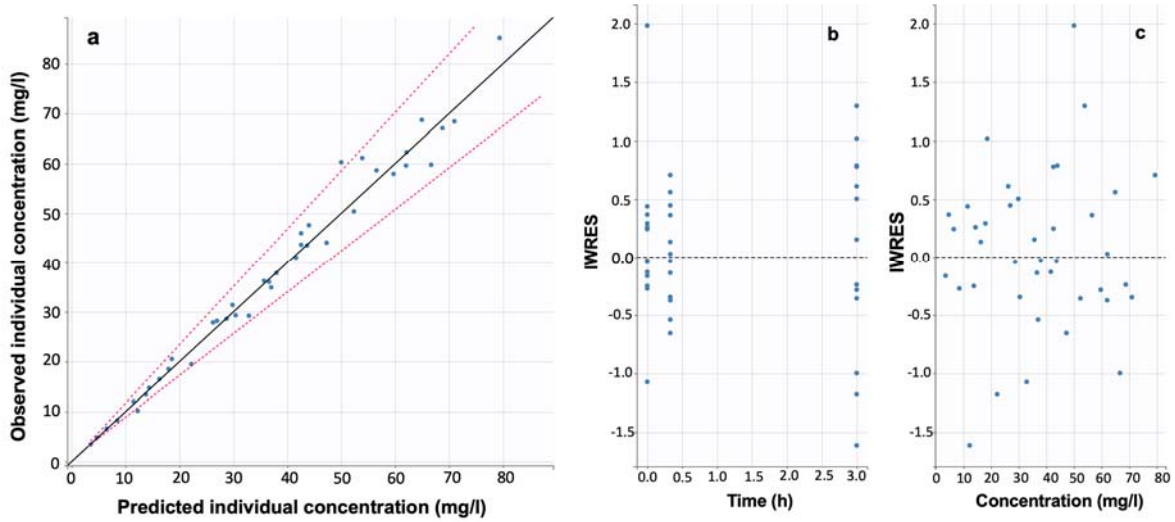

Figure S1. Goodness-of-fit plots for the final best model. a) Observed vs. predicted by the model individual concentrations of levetiracetam. The closed circles refer to the (predicted, observed) pairs, the solid line expresses the ideal situation of unity (i.e., y = x), while the dotted lines show the 90% prediction interval. b) Individual Weighted Residuals (IWRES) *versus* time, and c) Individual Weighted Residuals versus concentration. The dotted line represents the ideal situation of y = 0.

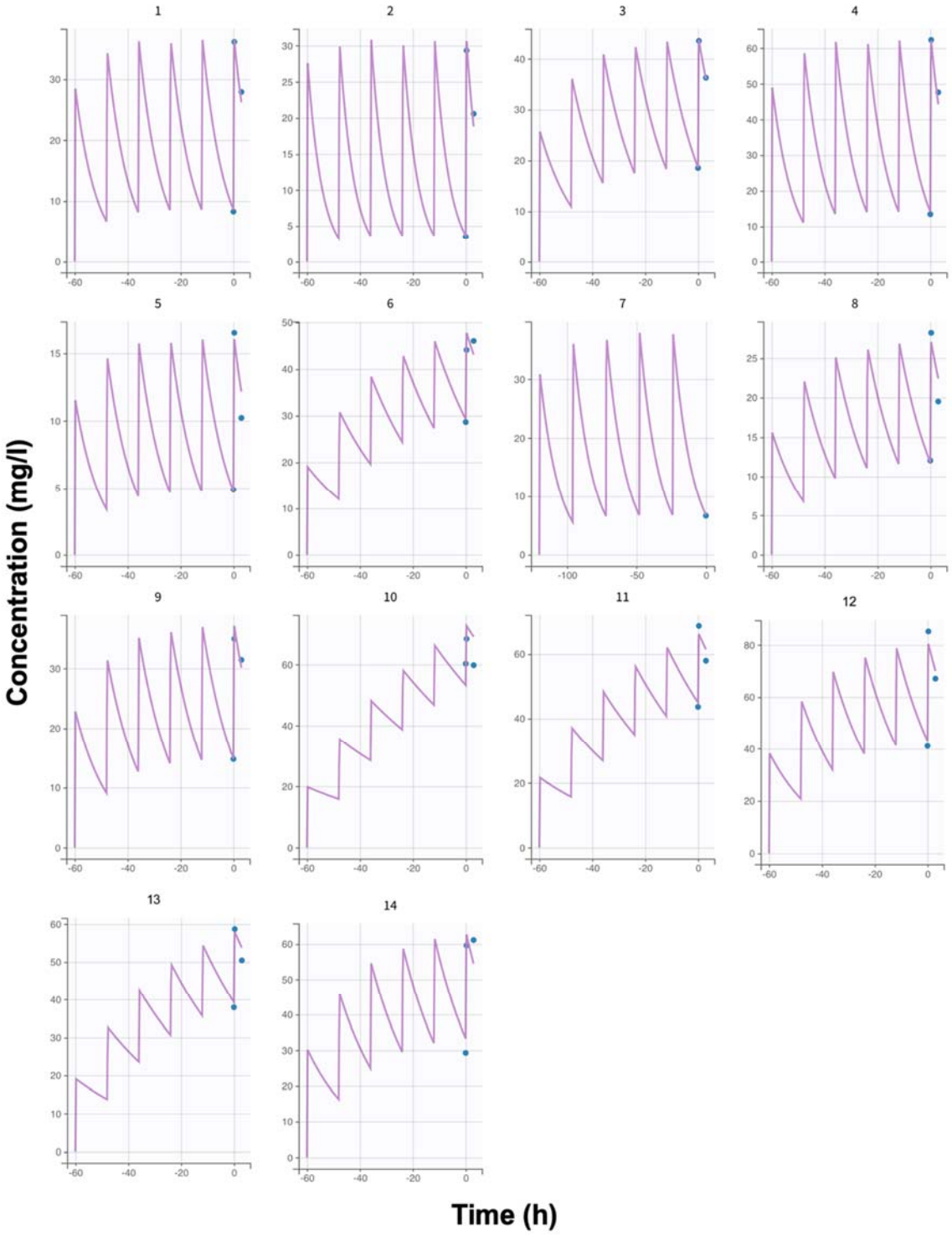

Figure S2. Levetiracetam concentration vs. time plots for the 14 patients of the study. Lines refer to the predicted profile by the pharmacokinetic model, whereas closed circles represent the experimental concentration data. For all subjects blood sampling was done two days after the start of administration to ensure that the serum concentration reached steady state. The duration of time (x-axis) before the sampling points, is automatically created by Monolix® and does not refer to the actual sampling time.

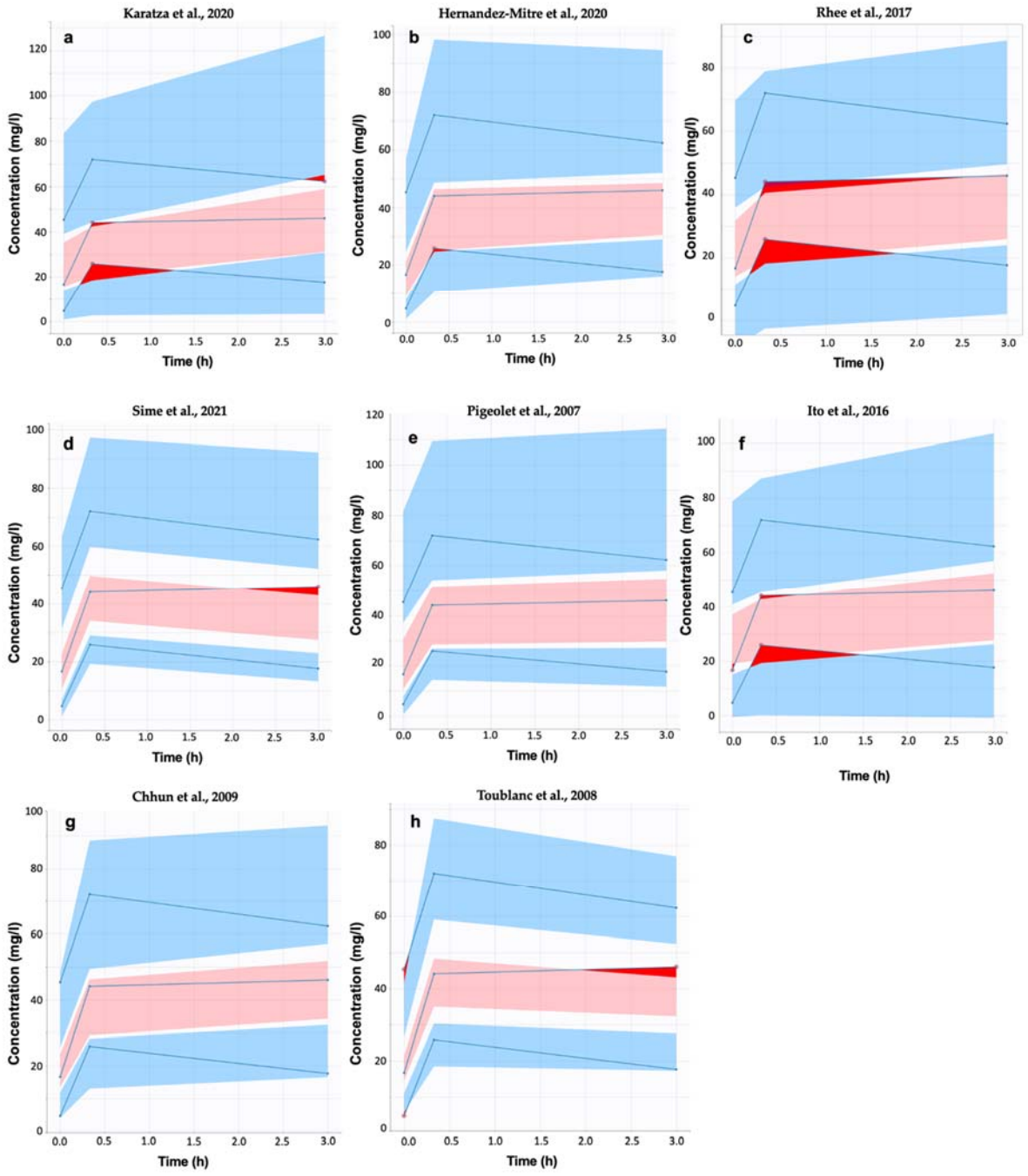

Figure S3. Visual predictive check plots for the literature models. The model estimates (structural model, mean model parameter, between-subject variabilities, error model) were those reported in the literature (summarized in Table S1) and were kept fixed, while the covariates were related to our study patients. Blue lines refer to the 10th, 50th, and 90th percentiles of the empirical data, and shaded areas refer to the predicted 90% confidence intervals around each zone (10th, 50th, and 90th percentiles). Observed data are shown as dots. Outliers are highlighted by red dots and areas. A number of 1,000 Monte Carlo simulations were used.

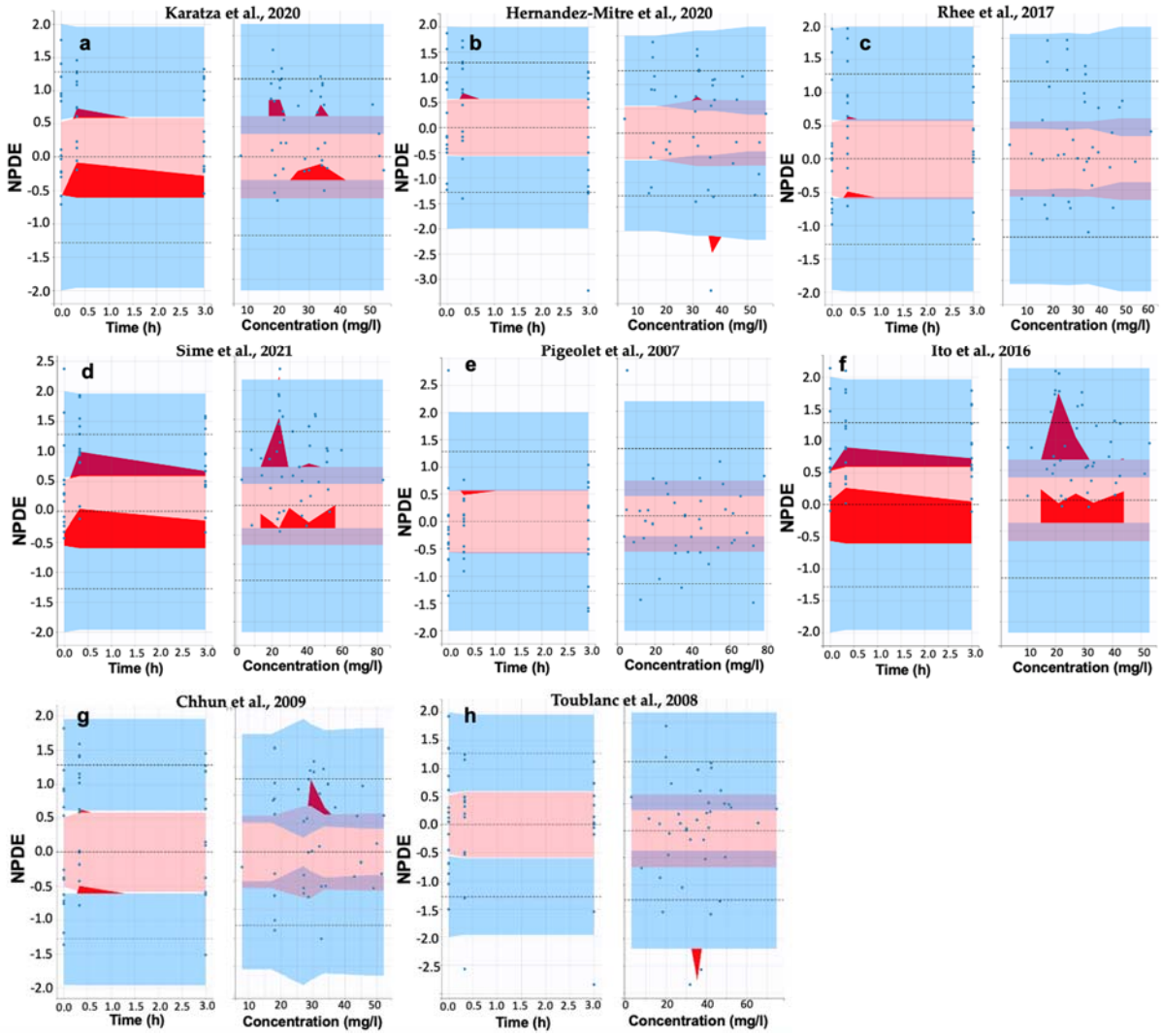

Figure S4. Normalized prediction distribution errors (NPDE) vs. time and concentration for the literature models. The model estimates (structural model, mean model parameter, between-subject variabilities, error model) were those reported in the literature (summarized in Table S1) and were kept fixed, while the covariates were related to our study patients. The dotted lines refer to the predicted median (at y = 0) and the 90% predicted percentiles, while the band indicates the 90% prediction interval.