

Scaling brivaracetam pharmacokinetic parameters from adult to pediatric epilepsy patients

Rik Schoemaker¹, Armel Stockis²

¹SGS Exprimio, Mechelen, Belgium; ²UCB Pharma, Braine l'Alleud, Belgium

Introduction

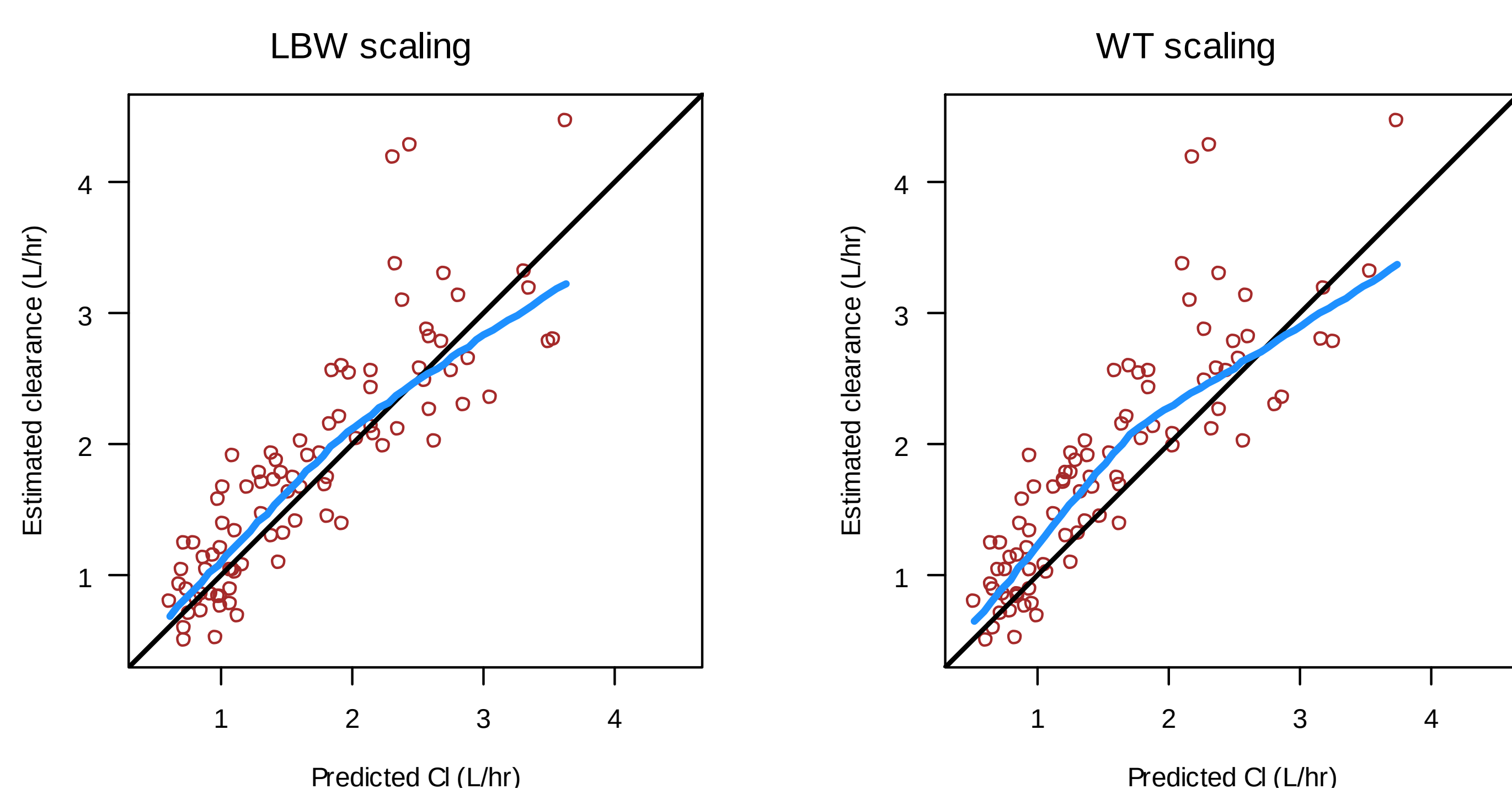
- Brivaracetam is a synaptic vesicle protein ligand (SV2A) that is currently in Phase III development for epilepsy.
- A population pharmacokinetic model (single-compartment, first order absorption and elimination, volume (V) and clearance (Cl) allometrically scaled using body weight (WT) or lean body weight (LBW) with theoretical exponents) was previously developed using data from 1188 adult patients with epilepsy having received adjunctive brivaracetam in five Phase II/III clinical trials.
- A recently completed Phase II trial in pediatric patients (1 month – <2 years, n=30; 2 – 11 years, n=52; 12 – <16 years, n=15) allows comparison of clearance and volume predictions based on allometric scaling of the adult population parameters with those obtained in the actual pediatric patient population, using the adult structural model applied to the pediatric patient data.
- The objective was to investigate the adequacy of allometric scaling of adult brivaracetam population pharmacokinetic parameters to a pediatric patient population using either WT or LBW.

Methods

- Separate population pharmacokinetic models for brivaracetam were estimated (using NONMEM V7.2.0 with FOCE-I) for the adult and pediatric population using WT or LBW scaling (using the James formula for LBW [1]) with standard allometric exponents of $\frac{3}{4}$ for clearance and 1 for volume. Additionally, the co-administration of enzyme-inducing antiepileptic drugs (AED: carbamazepine, phenytoin, phenobarbital, or primidone) was included as a covariate on clearance.
- The adult population parameters were applied to the recorded WT and LBW values and AED status (inducers present or absent) of the pediatric patients in the trial to arrive at *predicted* clearance estimates, which were compared with the *estimated* empirical Bayes estimates (EBEs) for the pediatric patients.
- The adult population parameters were applied to the WT and LBW values (James estimates) in a NHANES database of 11,364 children from 0 – 17 years [2]. Resulting clearance values were used to predict steady state concentrations (C_{ss} : AUC divided by dosing interval) for the highest dose level administered in the pediatric study: 2.0 mg/kg bid for patients <8 years and 1.6 mg/kg bid for patients ≥ 8 years. Median and 95% of the data were calculated for each 1-year age step and graphically compared with the predictions using pediatric EBEs.

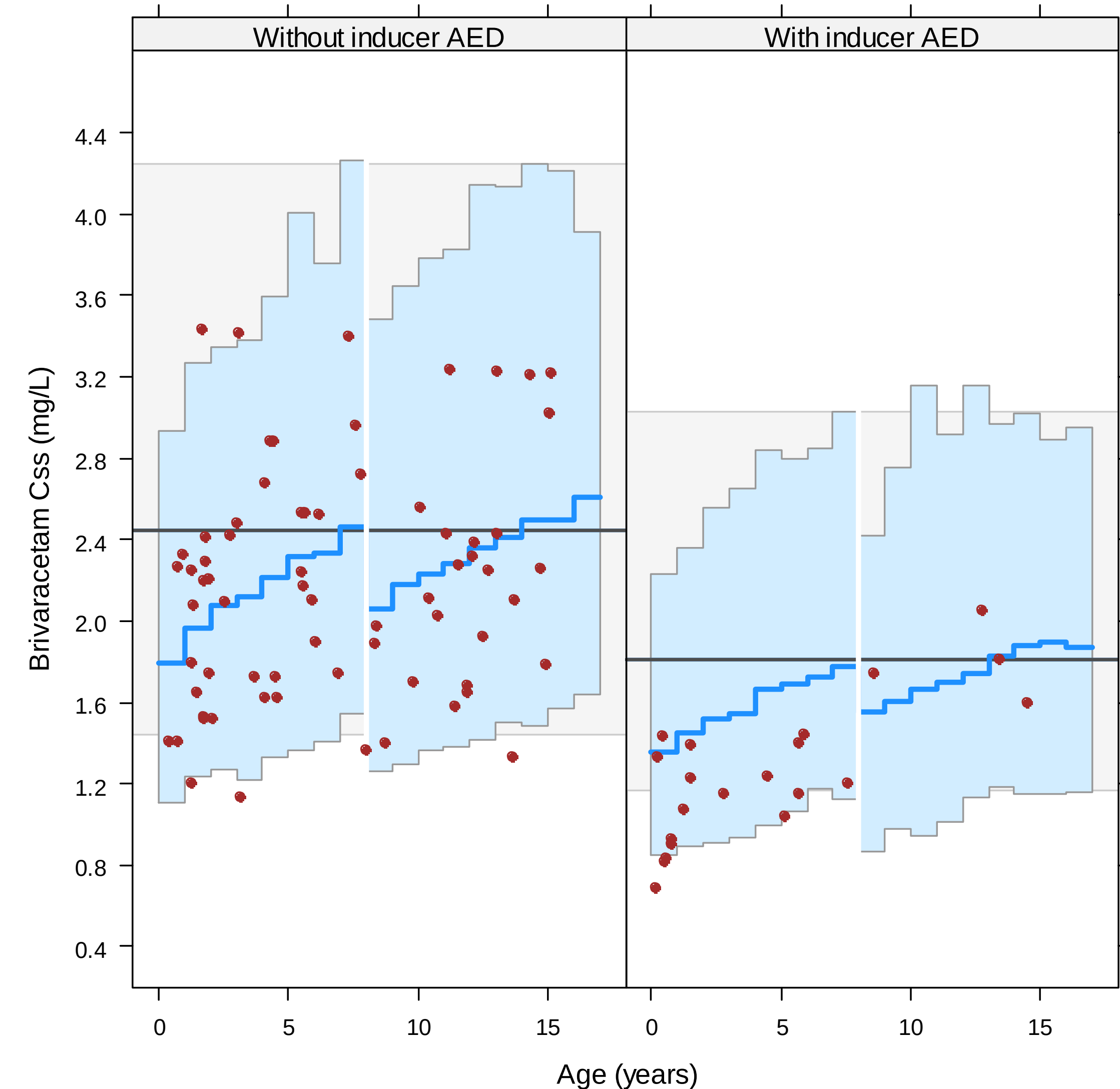
Results

- For the adult data, the LBW-scaled model had a highly significant 101.4 point lower objective function value than the WT-scaled model ($P < 0.0001$).
- Predicted and estimated clearance were strongly correlated, where predictions based on LBW tended to be less biased:

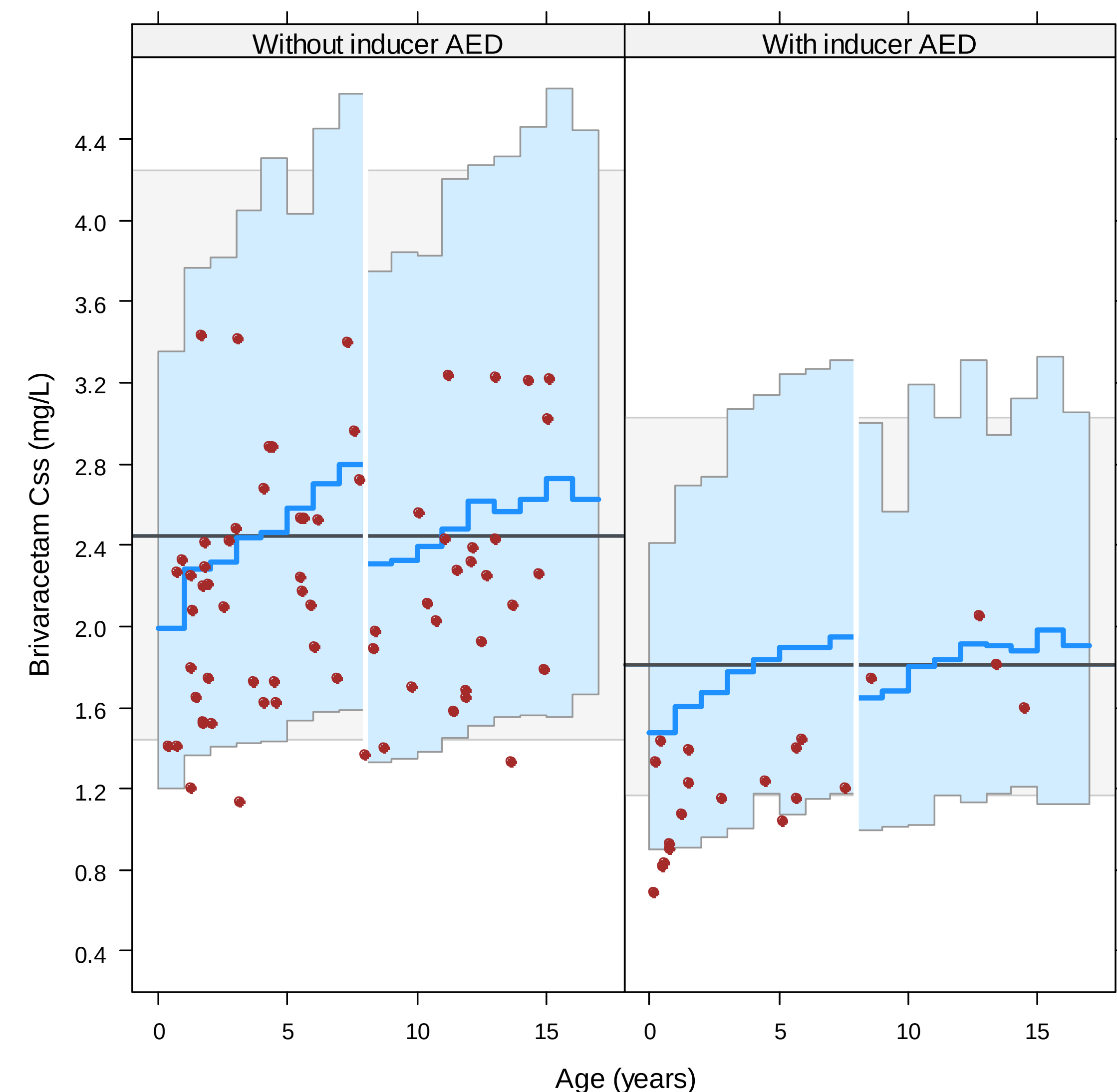


- In the predicted C_{ss} graphs, the black horizontal line and the gray band correspond to the median and 95% of the C_{ss} predictions for the adult patients receiving 100 mg bid, in the subgroups without and with inducer-AEDs. The blue line and the light-blue band correspond to the median and 95% of the C_{ss} predictions for the pediatric population in the NHANES database (with WT restricted to <80kg because 75 kg was the maximum observed WT for pediatric patients) receiving the top pediatric trial dose. Finally, the red dots correspond to the C_{ss} predictions for the pediatric patients.

- For predictions scaled using LBW, the patients are reasonably well distributed across the predicted concentration range in absence of inducer AEDs, while in the presence of inducers, they are restricted to the lower half of the concentration range:



- The predicted concentration range using WT scaling is higher than for LBW scaling:



- The predicted concentration range using the trial-dosing schedule (2.0 mg/kg bid <8 years and 1.6 mg/kg bid ≥ 8 years) corresponds well with the adult schedule of 100 mg bid.
- Hepatic enzyme-inducing AEDs appear to have a more pronounced effect on clearance in pediatric patients than expected from adult data.

Conclusions

- Allometric principles can be used to scale brivaracetam pharmacokinetics from adults to children, where use of LBW provides superior predictions of pediatric clearance than WT, but pediatric patients can be adequately dosed using a WT-based dosing regime.

References

1. James W. Research on Obesity. London: Her Majesty's Stationery Office, 1976
2. The 1999 – 2004 Dual Energy X-ray Absorptiometry (DXA) Multiple Imputation Data Files and Technical Documentation <http://www.cdc.gov/nchs/nhanes/dxx/dxa.htm>