BRIVARACETAM

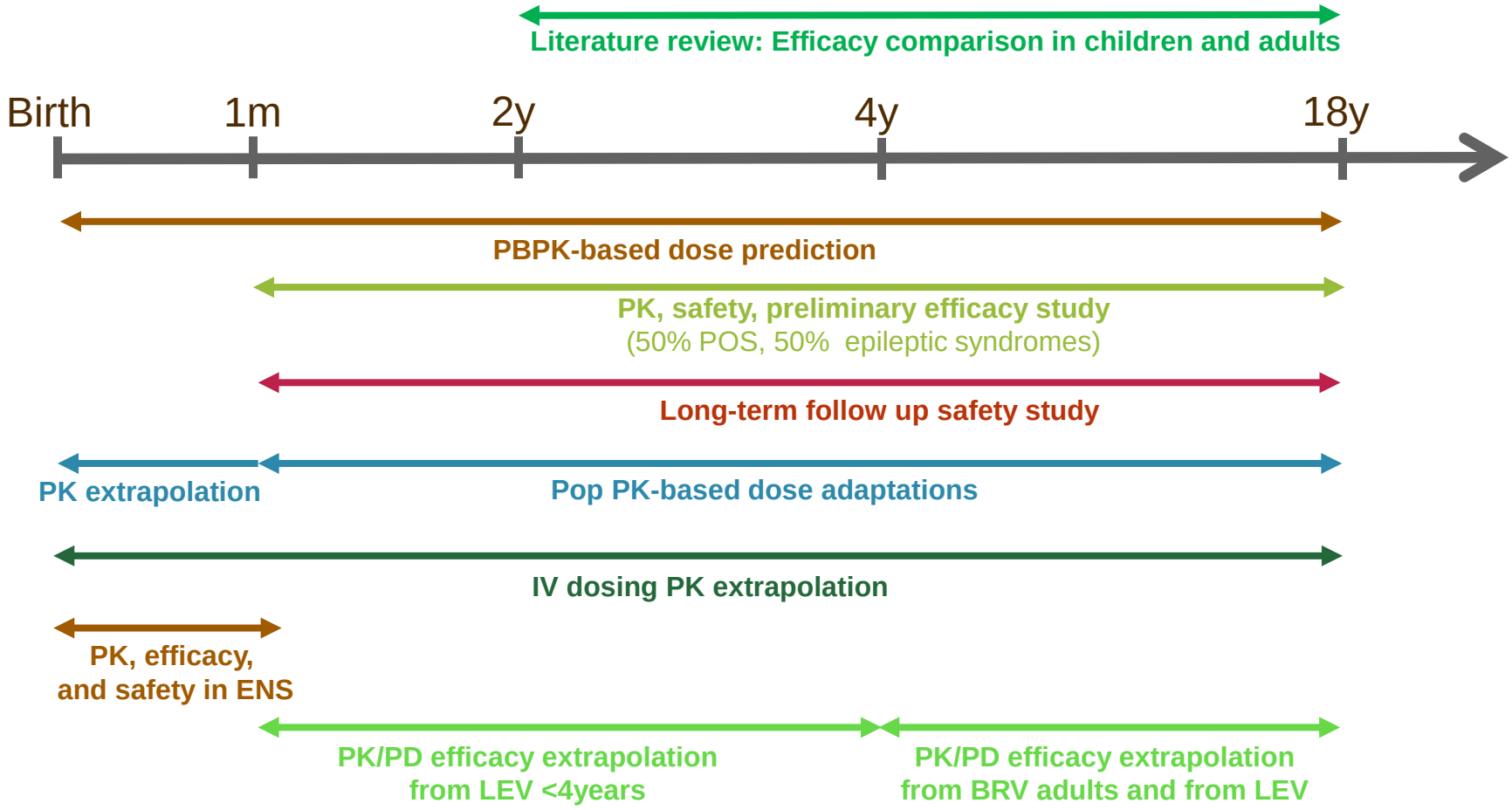
Paediatric Development in Partial Onset Seizures

17 May 2016

Inspired by patients.
Driven by science.

Brivaracetam is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy

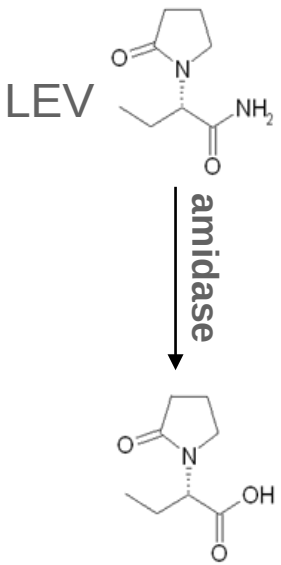
1. Paediatric extrapolation strategy



2. BRV ADME contrasting with LEV

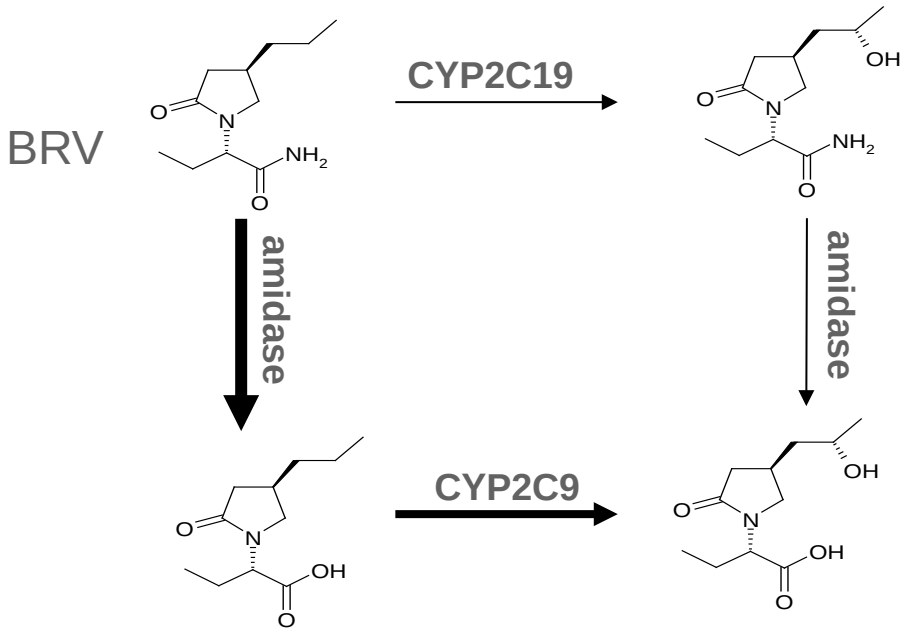
Levetiracetam

Log P= -0.714
fu = 0.95
F = 1
CLr = 0.60 mL/min/kg
CLnr = 0.36 mL/min/kg



Brivaracetam

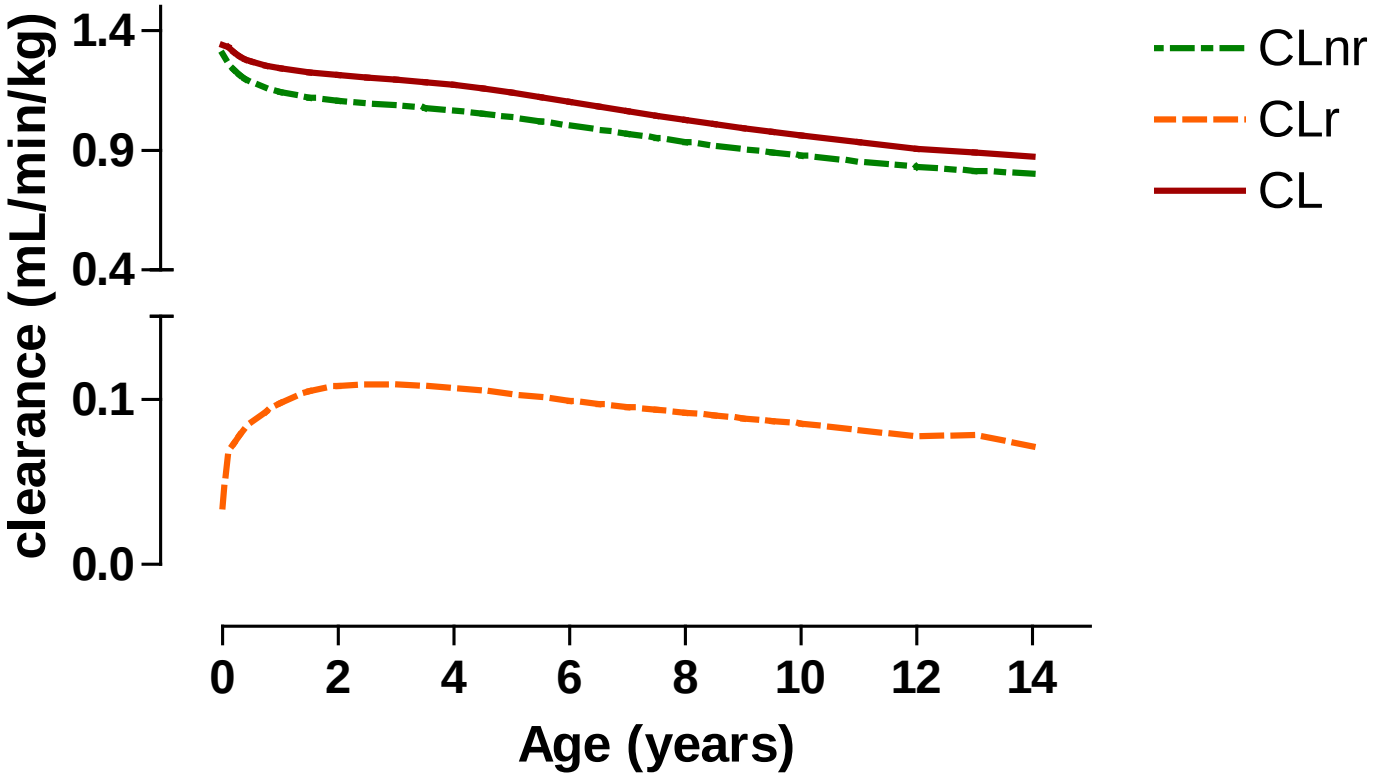
Log P= 1.04
fu = 0.79
F = 1
CLr = 0. 06 mL/min/kg
CLnr = 0.80 mL/min/kg



Binds to synaptic vesicle protein 2A
Approved in children ≥1 month of age

(Stockis A et al., DMD 2016)

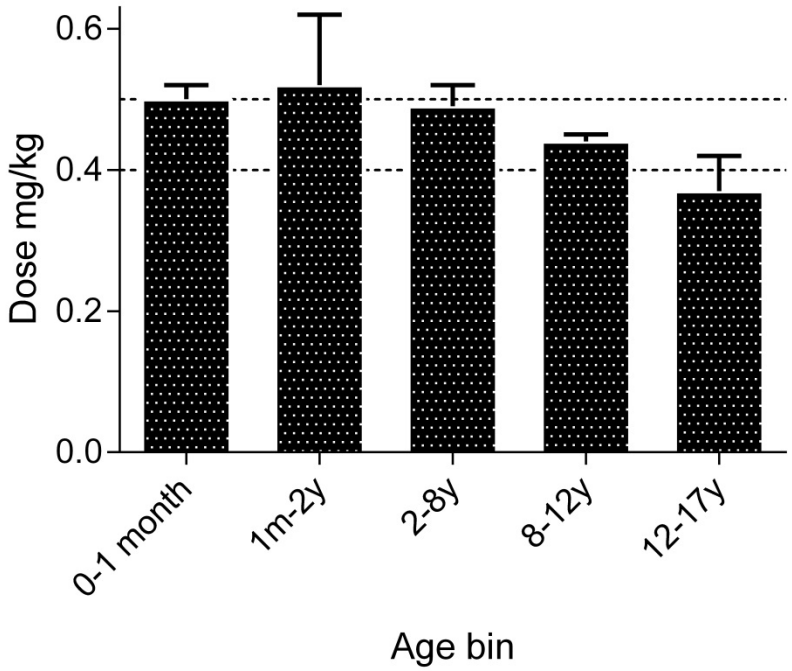
3. PBPK-predicted BRV pediatric clearance



Driving force is non-CYP dependent non-renal disposition

(UCB data on file)

3. PBPK-predicted BRV pediatric dose adaptations



Pediatric dosing at 0.4-0.5 mg/kg BID ensures exposure similar to 25mg BID in adults (lowest efficacious dose)

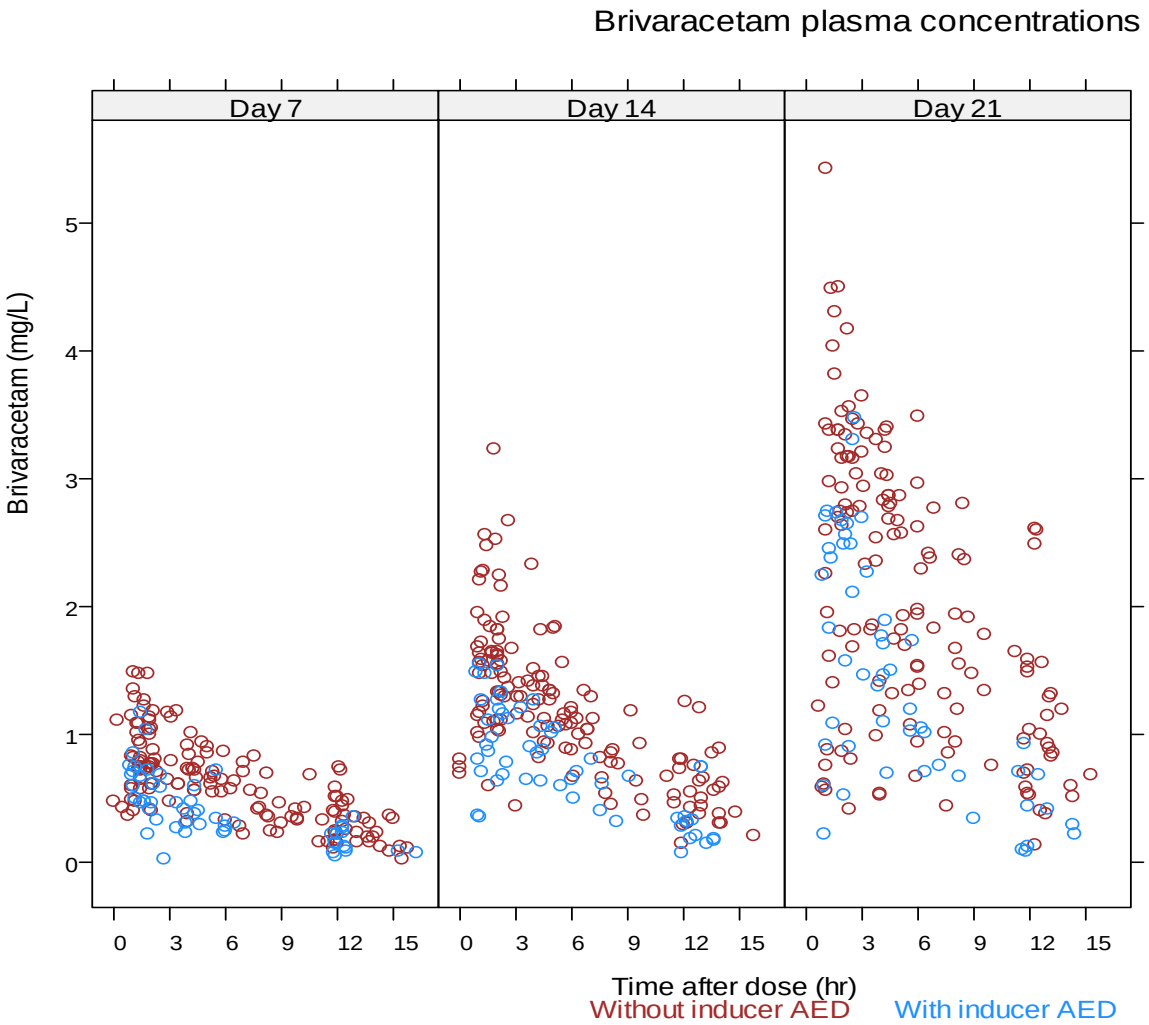
(UCB data on file)

4. First pediatric clinical trial

- Trial population:
  100 children with epilepsy, aged 1 month to 16 years,
  not controlled by 1 to 3 concomitant anti-epilepsy drugs (AEDs)
- 1-week baseline
- Three-step weekly titration with BRV 10 mg/mL oral solution
  - Week 1: 0.4-0.5 mg/kg bid
  - Week 2 0.8-1.0 mg/kg bid
  - Week 3 1.6-2.0 mg/kg bid
- Maximum dose 100 mg bid at BW≥50kg (like in adults)
- 2-3 blood samples (≤0.5mL) on the last day of each week,
  for determinations of BRV and 3 metabolites
- Roll over to long term safety study, or 2-week down titration

(Liu E et al, Epilepsy Curr 2014)

4. Observed concentration vs time data



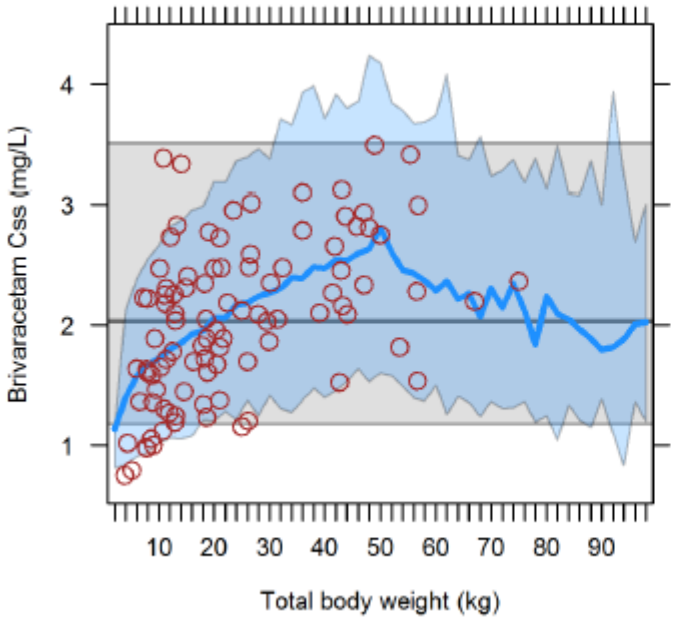
(Schoemaker R et al, Epilepsia 2014)

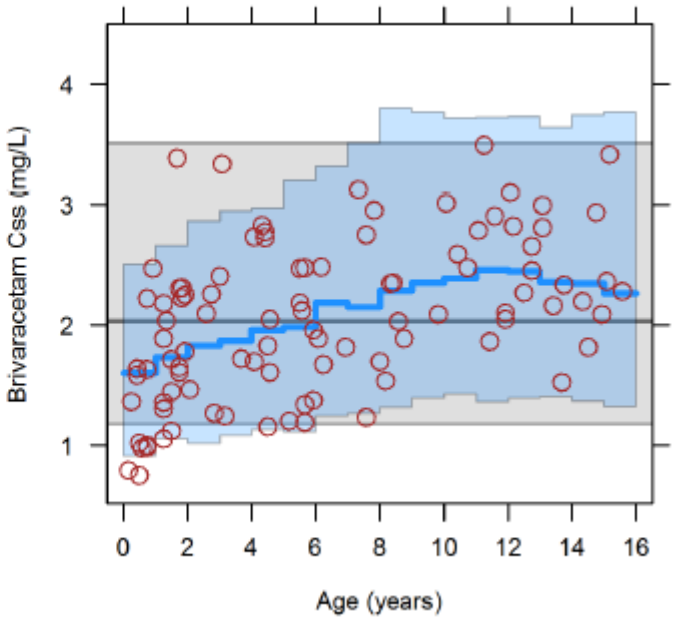
4. Final Population PK model (NONMEM)

- Structural model: single compartment, first order absorption and elimination, and allometric scaling on CL/F and V/F:
  - CL/F (L/h) = $3.63 \times (BW/70)^{0.75}$
  - V/F (L) = $47.8 \times (BW/70)^{1.00}$
  - Ka (1/h) = 1.84
  - Residual error = 23%
- Strong enzyme-inducing AEDs (phenobarbital, carbamazepine) increase BRV clearance (like in adults, no dose adjustment needed)
- No significant effects for race, ethnicity, sex, age, post-conceptional age (PCA), or eGFR (renal function)

(Schoemaker R et al, Epilepsia 2014)

4. Simulated age-independent dosing
4 mg/kg/day (2 mg/kg bid)
max 200 mg/day for BW ≥50kg

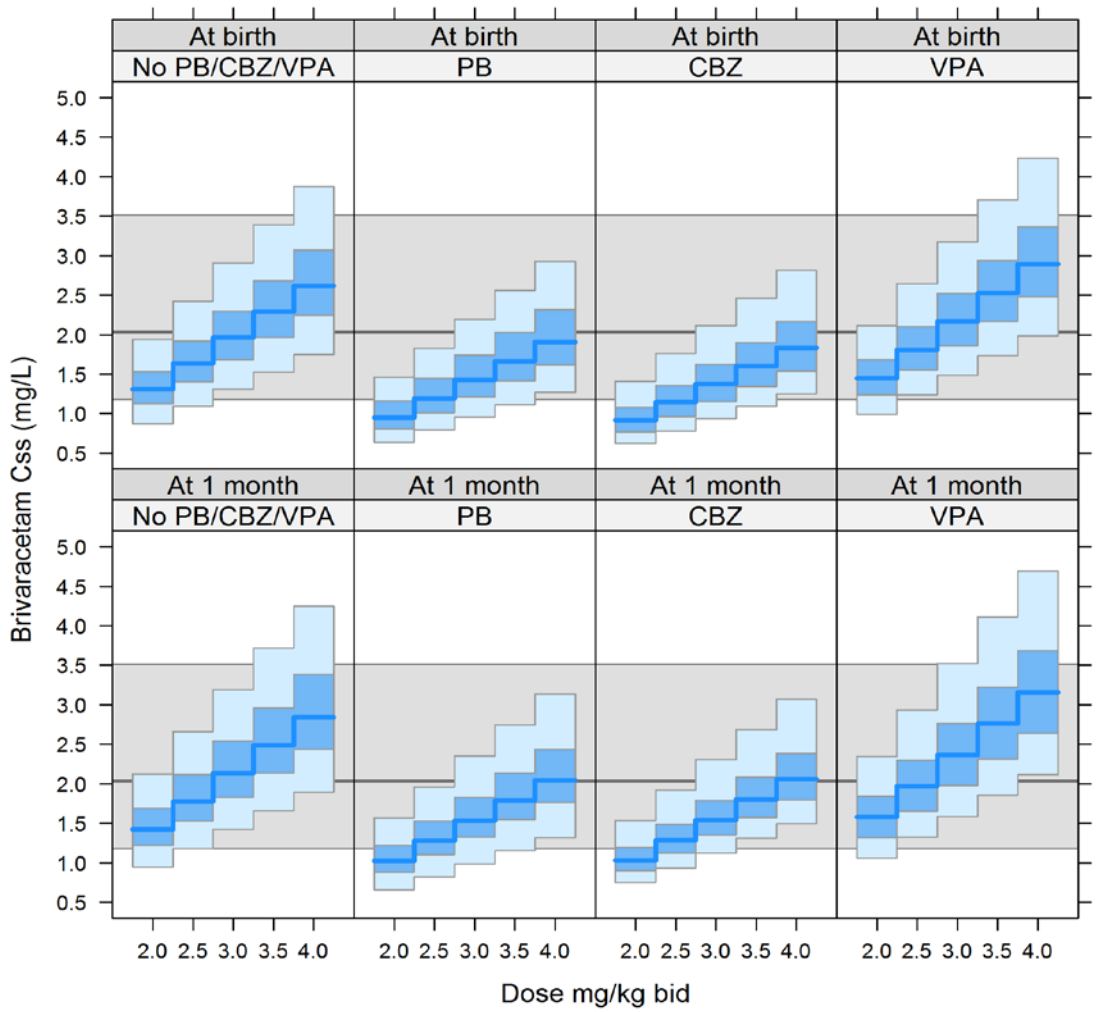




Gray band: adults 90%PI
Red circles: children
Blue line: model median
Blue band: model 90%PI

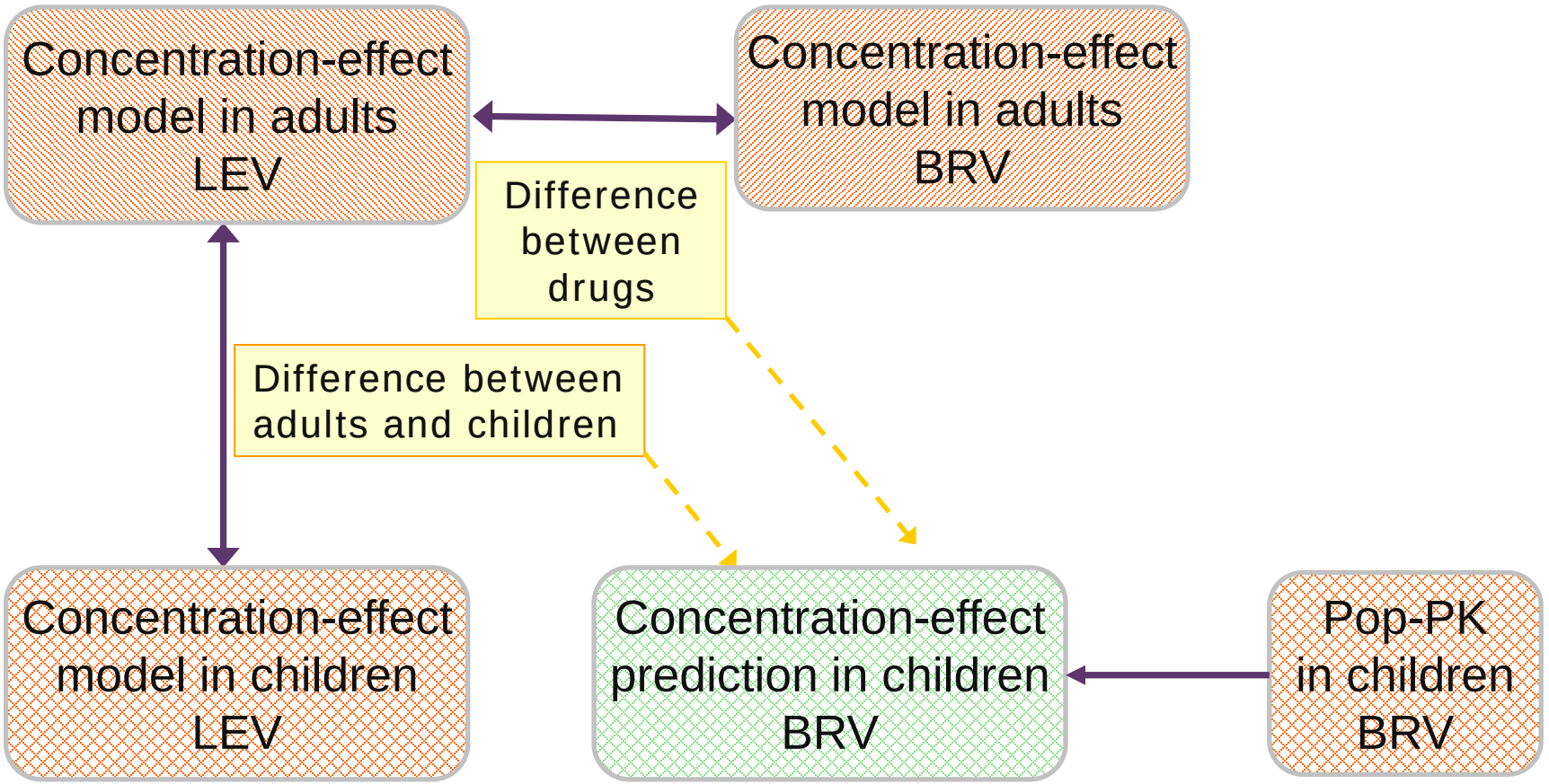
(Schoemaker R et al, Epilepsia 2014)

5. Dose predictions for upcoming neonatal trial

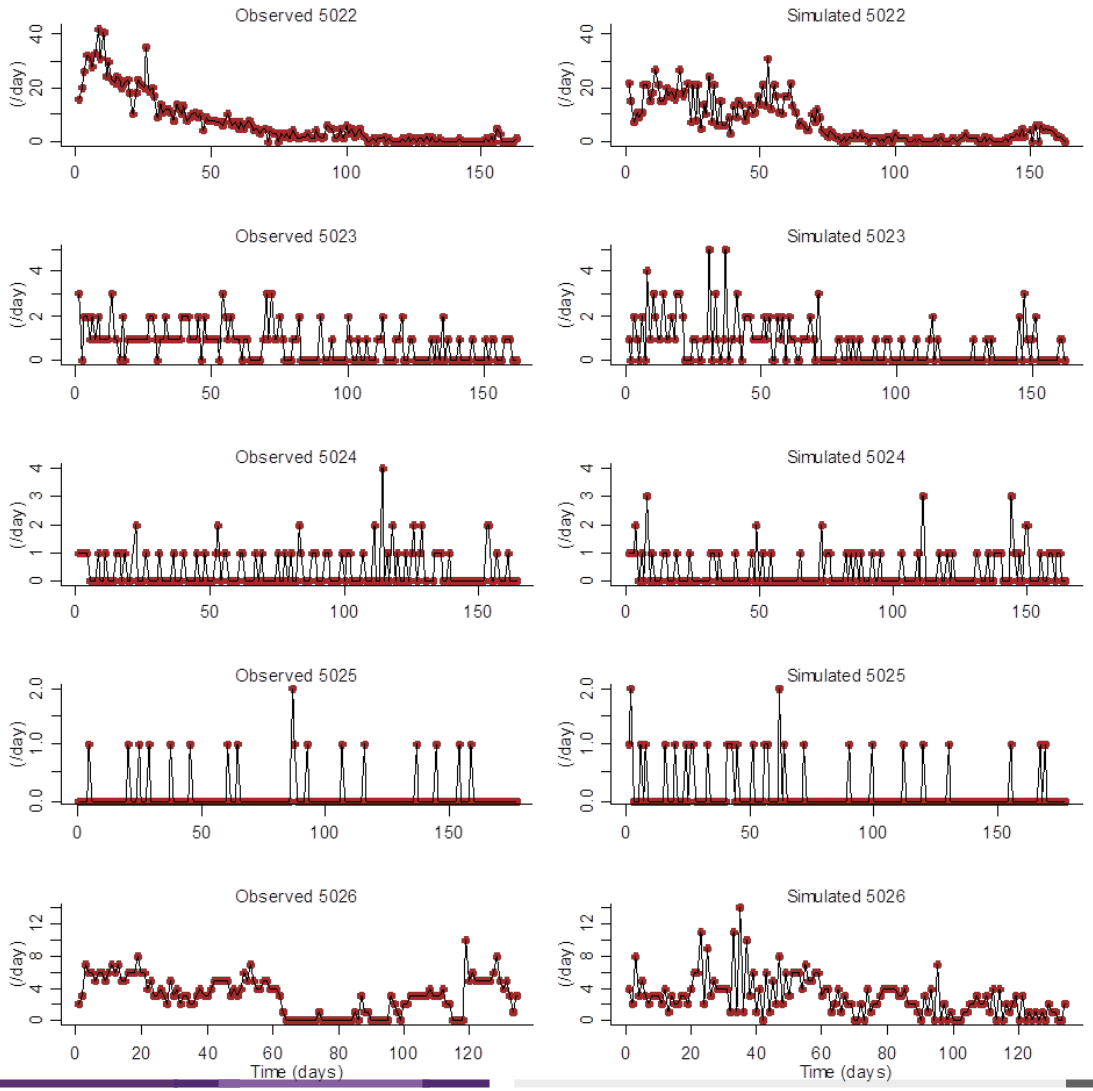


(UCB data on file)

6. BRV concentration-effect prediction in children



6. Modelling the probability of daily seizures



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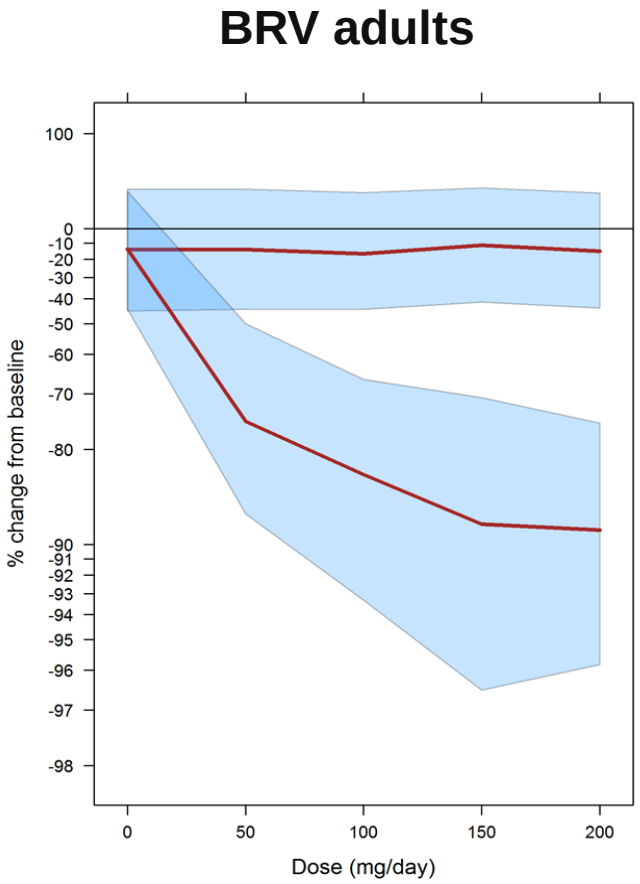
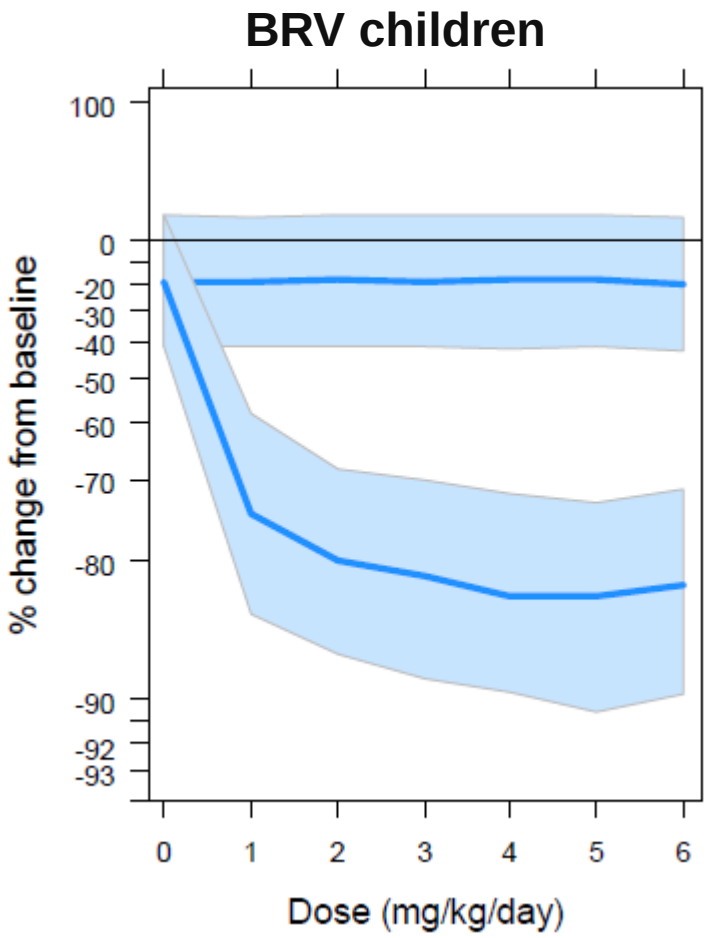
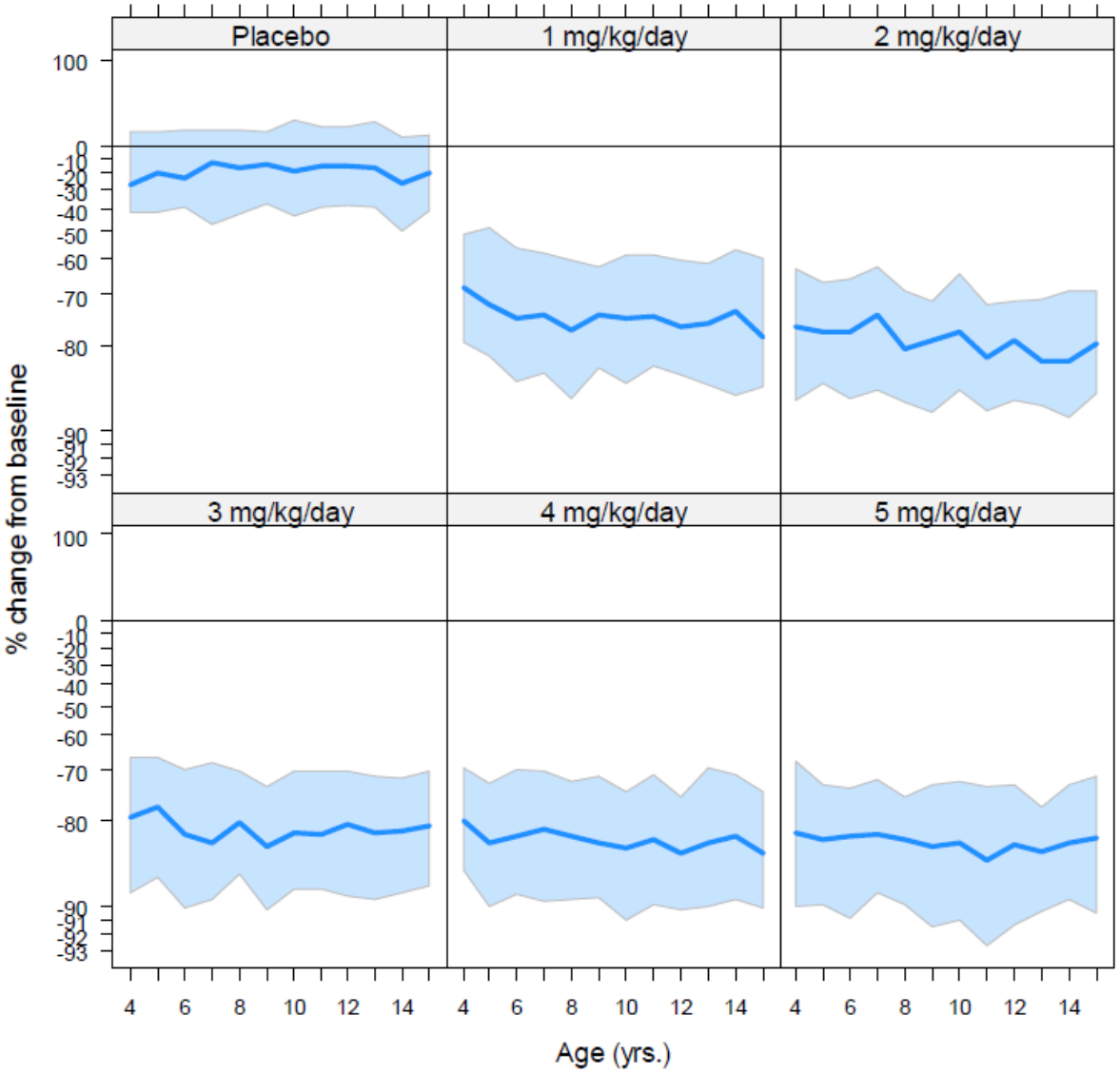
6. Concentration-effect relationship in adults and extrapolation to children





(Schoemaker R et al, J Clin Pharmacol 2016, PAGE 2016)

6. Treatment effect vs age, by dose



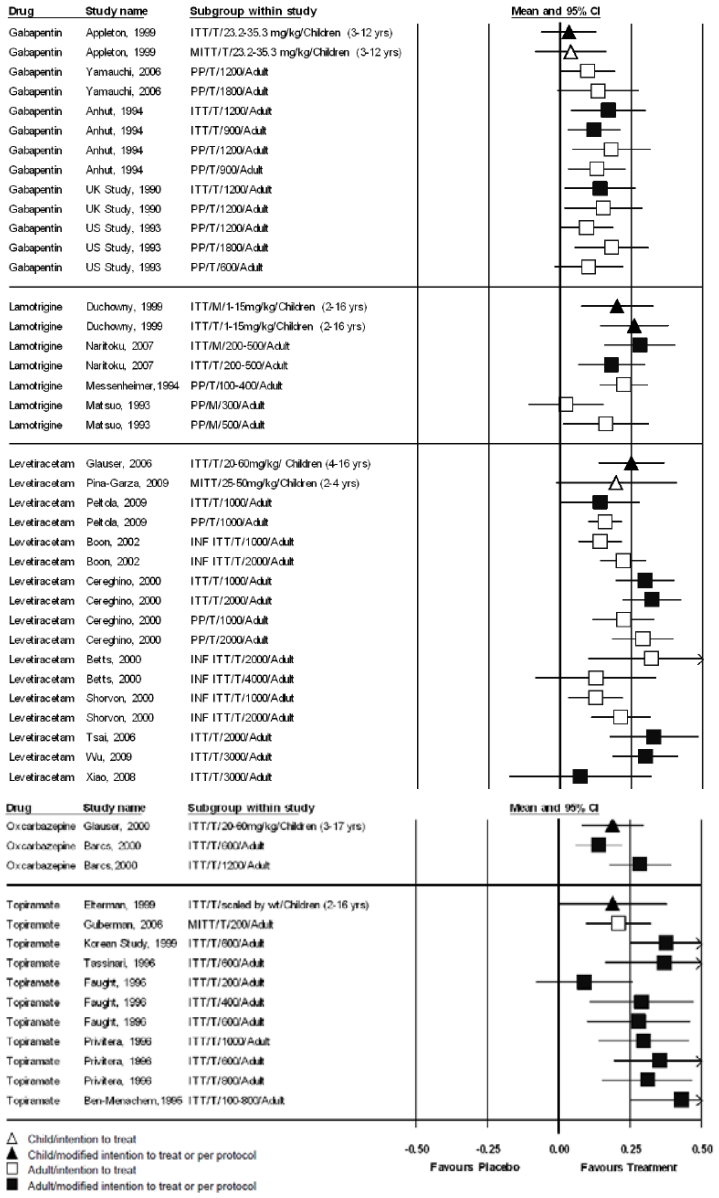
(UCB data on file)

7. Efficacy of antiepileptic drugs in adults predicts efficacy in children: A systematic review

- From over 3,250 publications initially reviewed:
  - 27 studies in adults
  - 8 in children ages 2 to 18 years
  - 3 in children < 2 years
- Randomized, double blind, placebo-controlled, and N≥50
- 2 effect measures calculated from 2 reported efficacy measures:
  - ≥50% responder rate
  - median percent reduction in seizure frequency from baseline
- Quantitative analyses:
  - 6 adjunctive trials in children
  - 24 comparable adjunctive clinical trials in adults
  - 5 different AEDs

(Pellock JM et al., Neurology 2012)

7. Efficacy comparison of differences in >50% reduction in seizure frequency from baseline by drug for children and adults



- The effect measure for placebo-subtracted >50% SF reduction was significantly greater than zero for 37 of 43 regimens in adults and 5 of 8 regimens in children.
- Effect measures were reasonably consistent trial-to-trial, ranging from 2% to 43% in adults and from 3% to 26% in children.
- **Conclusions:** This systematic review supports the extrapolation of efficacy results in adults to predict a similar adjunctive treatment response in 2- to 18-year-old children with POS.

(Pellock JM et al., Neurology 2012)

Impact on the paediatric development program

- PK modelling:
  - No dose-finding study in children
  - No intravenous PK study in children
  - Paediatric dose adaptations to support application for new indications
- 1 PK and safety study in children 1 month – 16 years
  - No placebo group
  - Long-term safety follow-up
- PK/PD modelling:
  - Extrapolation of efficacy from adults and LEV: no pivotal efficacy study

Back up slides

4. Characteristics of the PK study population

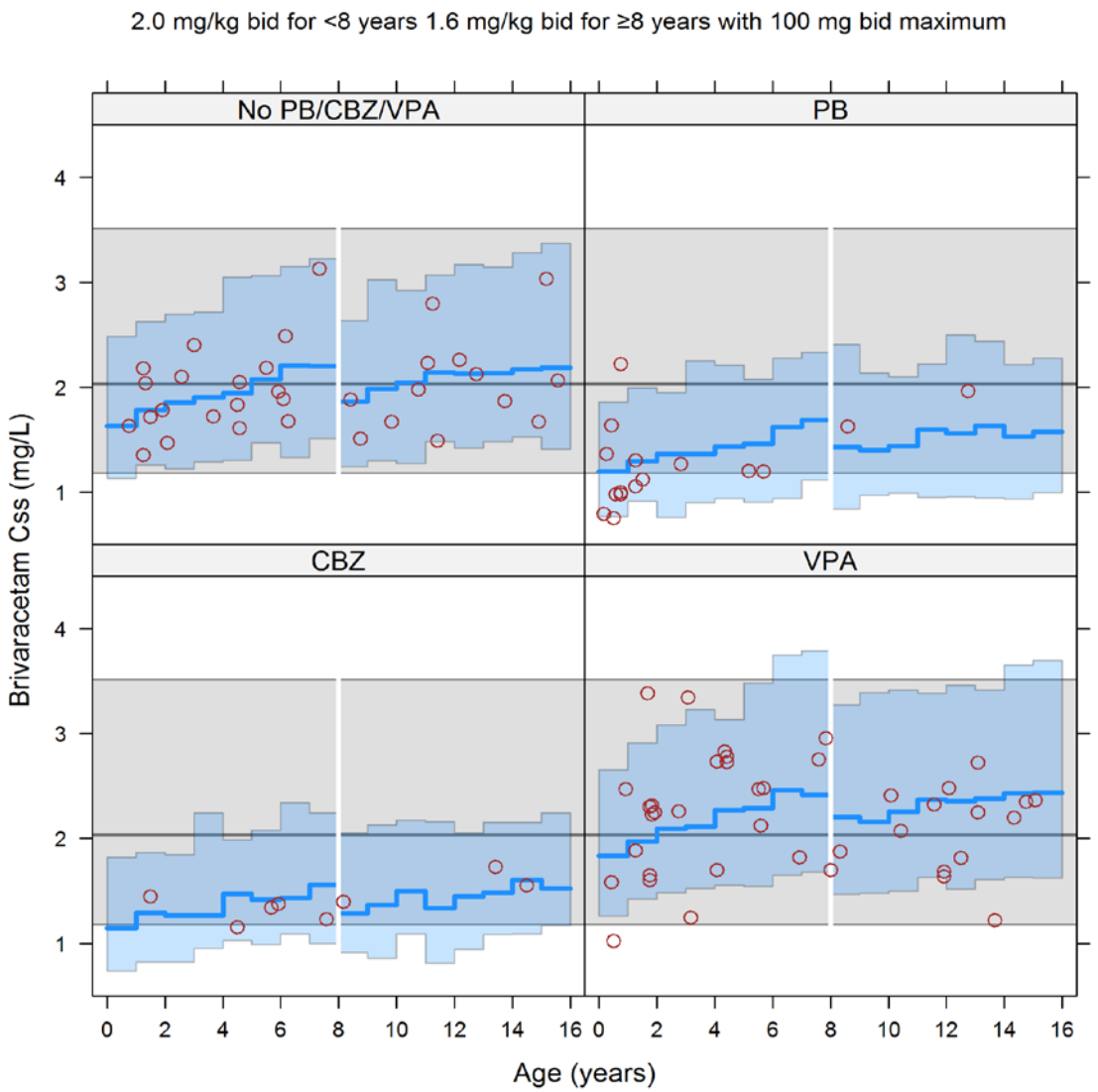
- 96 subjects contributed 600 plasma samples (200 at each dose level)
- Sex: 47 boys; 49 girls
- Race/ethnicity: 77 white; 4 black; 15 other; 18 Hispanic/Latino
- Age (years):

1 month to <2 years:	n=29
2years to <6 years:	n=26
6 years to <12 years:	n=24
12 years to <16 years:	n=17
Born pre-term (<3 years):	n=4

- Body weight: 3.9 to 75 kg
- eGFR: 49 to 218 mL/min/1.73m^2
- Concomitant medications:

Carbamazepine (CBZ)	n=9
Phenytoin (PHT)	n=1
Phenobarbital (PB)	n=16
Valproate (VPA)	n=49
CYP3A inhibitor	n=2
CYP2C19 inhibitor	n=7

4. Predicted Css,av vs age, by co-administered AED



PB mostly used in children <2 years

Associated with high clearance

7. Systematic literature review

- Limitations were minimized by selection criteria
  - Limitations included
    - Study design and conduct
    - Doses, population, length of treatment
    - Publication bias (more positive studies published)
  - Selected data presented for adjunctive POS therapy were robust and consistent

- Extrapolation of Efficacy in POS from adults only feasible in the age group 2 to 18 years
  - Suggests Efficacy in children and adults in POS is similar in clinical trials
  - Effect measures in children favor treatment over placebo

- Fewer studies in the younger age groups make literature reviews more difficult in these groups

Thanks!