Extrapolation of a Brivaracetam Exposure-Response Model from Adults to Children

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We know about scaling PK from adults to children…

- A wealth of information and methods is available:
  - Allometric scaling
  - Accounting for maturation
  - PBPK models

But what about PD?

- How do you scale effects?
- If disease is the same in adults and children then perhaps the PKPD relationship does not change
- But what if the disease might be different (like in epilepsy)…?

Claim:
Brivaracetam (BRV) has the same effects in adults and children

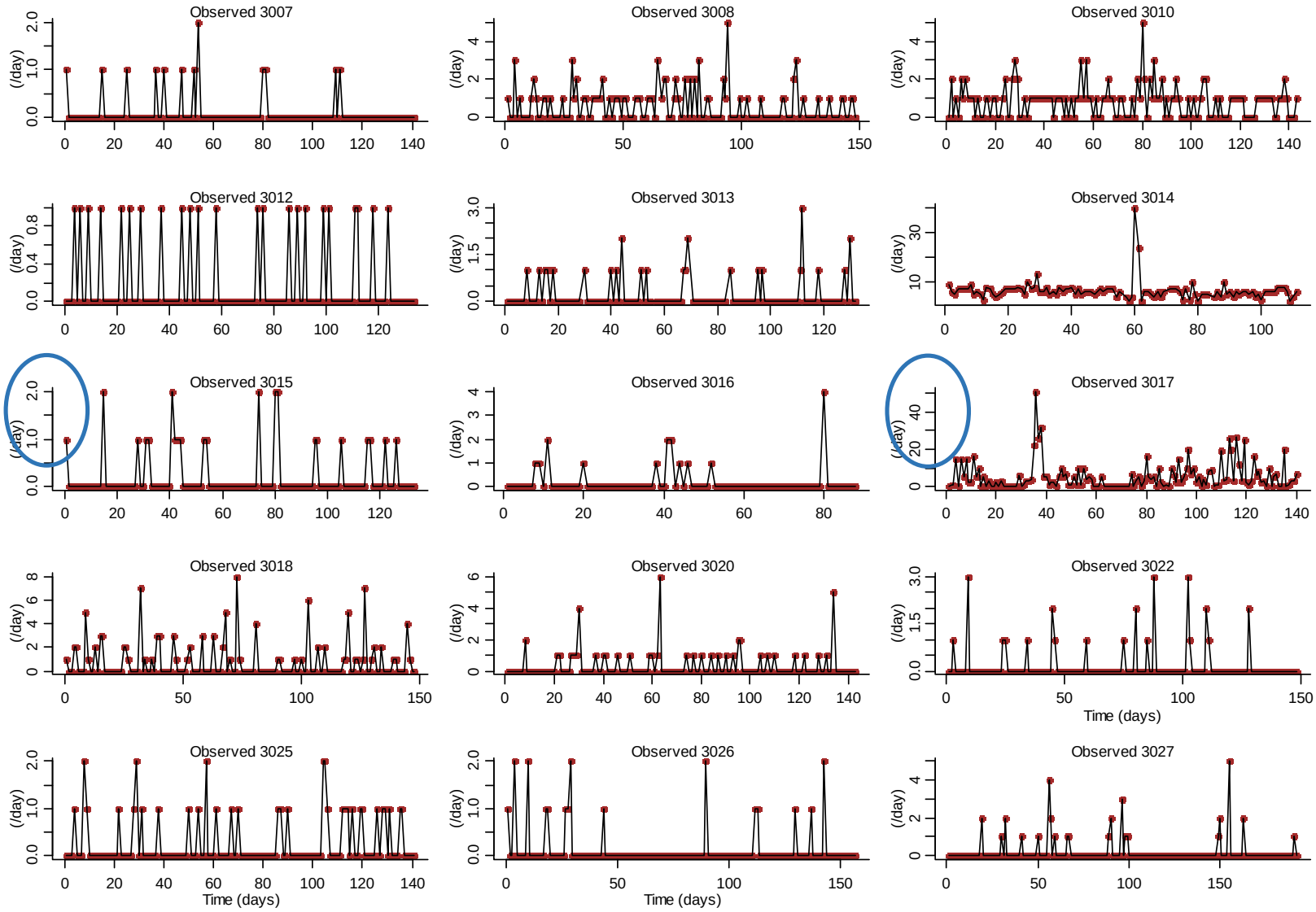
- How do you support this?

- A PK trial BRV in 96 children (29 below 2 years), but no PD
- A PKPD model for BRV in 1549 adults relating exposure to daily seizure counts*
- BRV (Briviact®) is a member of the SV2A ligand class that possesses a 15-30-fold higher affinity and a distinct pharmacological profile compared with Levetiracetam (LEV; Keppra®)
- PKPD data on LEV in 883 adults and 199 children

- Apply the BRV PKPD model to LEV data and see how children are different from adults

*Schoemaker R, Wade JR, Stockis A. Brivaracetam Population Pharmacokinetics and Exposure-Response Modeling in Adult Subjects With Partial-Onset Seizures. The Journal of Clinical Pharmacology (2016).

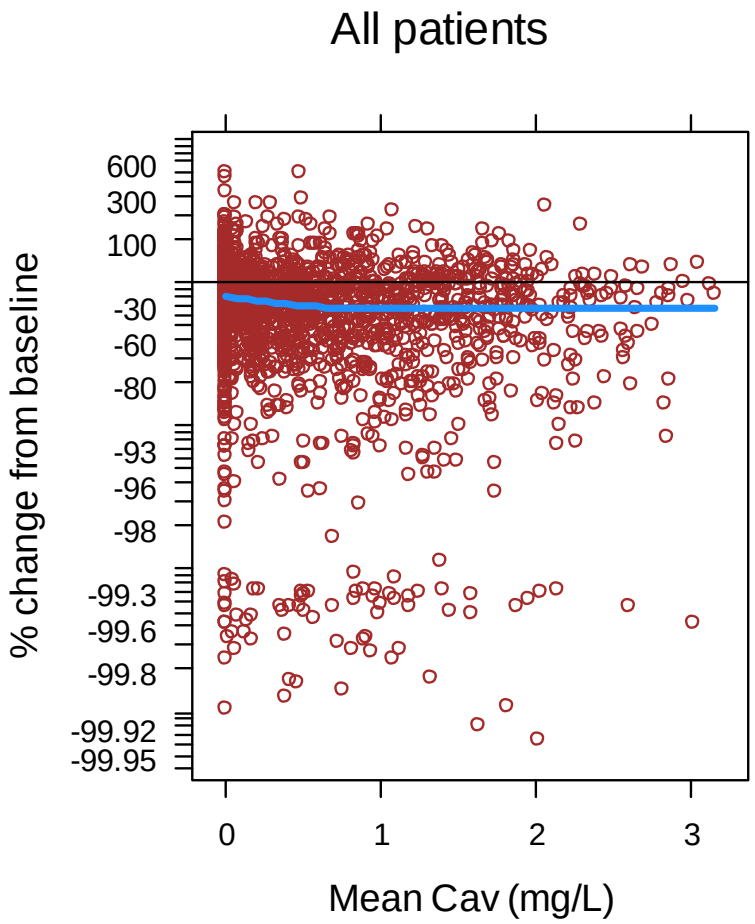
Daily seizure count patterns in epilepsy



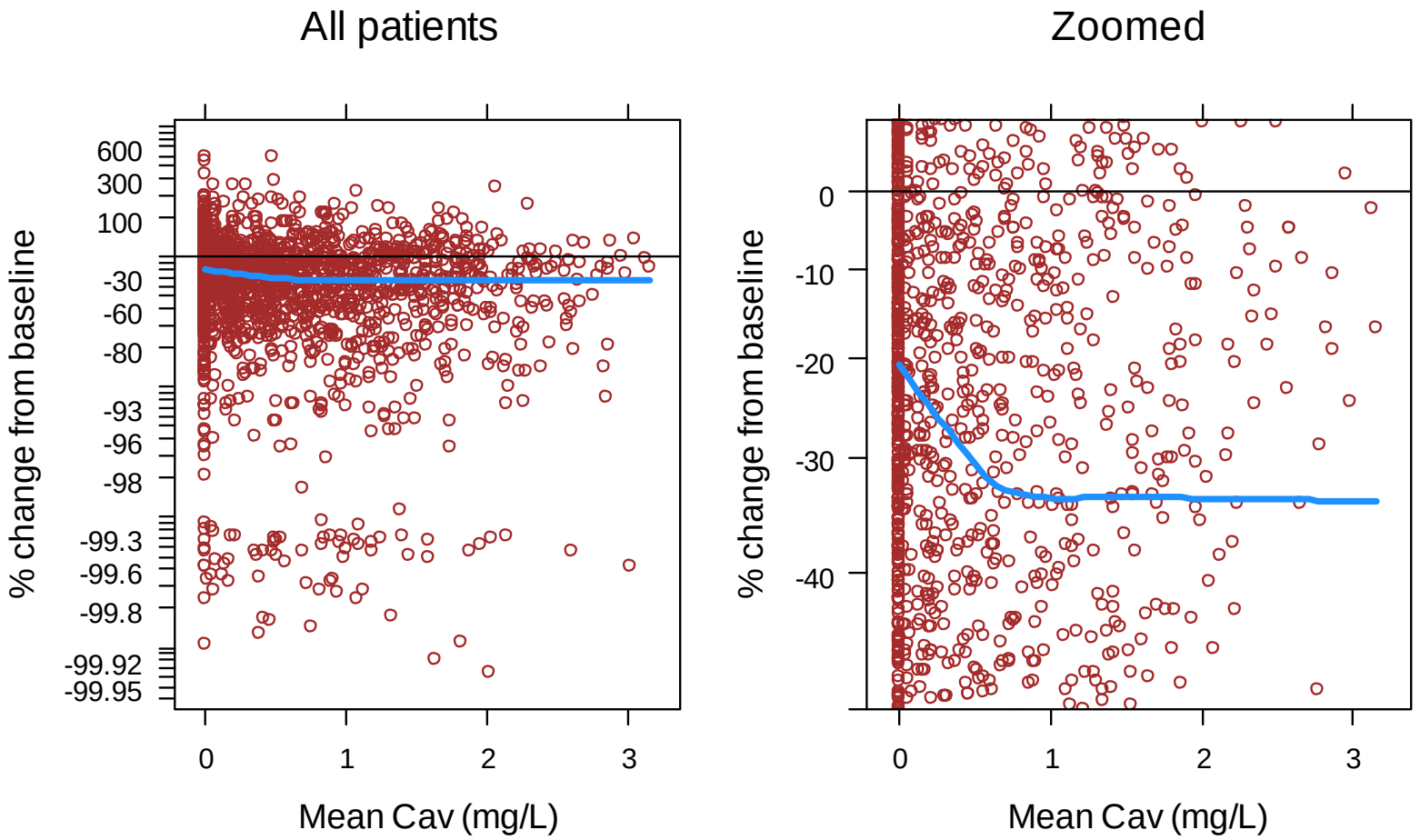
Model components

- Change due to placebo
- Effects driven by daily average concentrations (C_{av}) estimated using population PK model
- Drug effect using E_{max} model…

Look closely and you'll see an E_{max}-type response



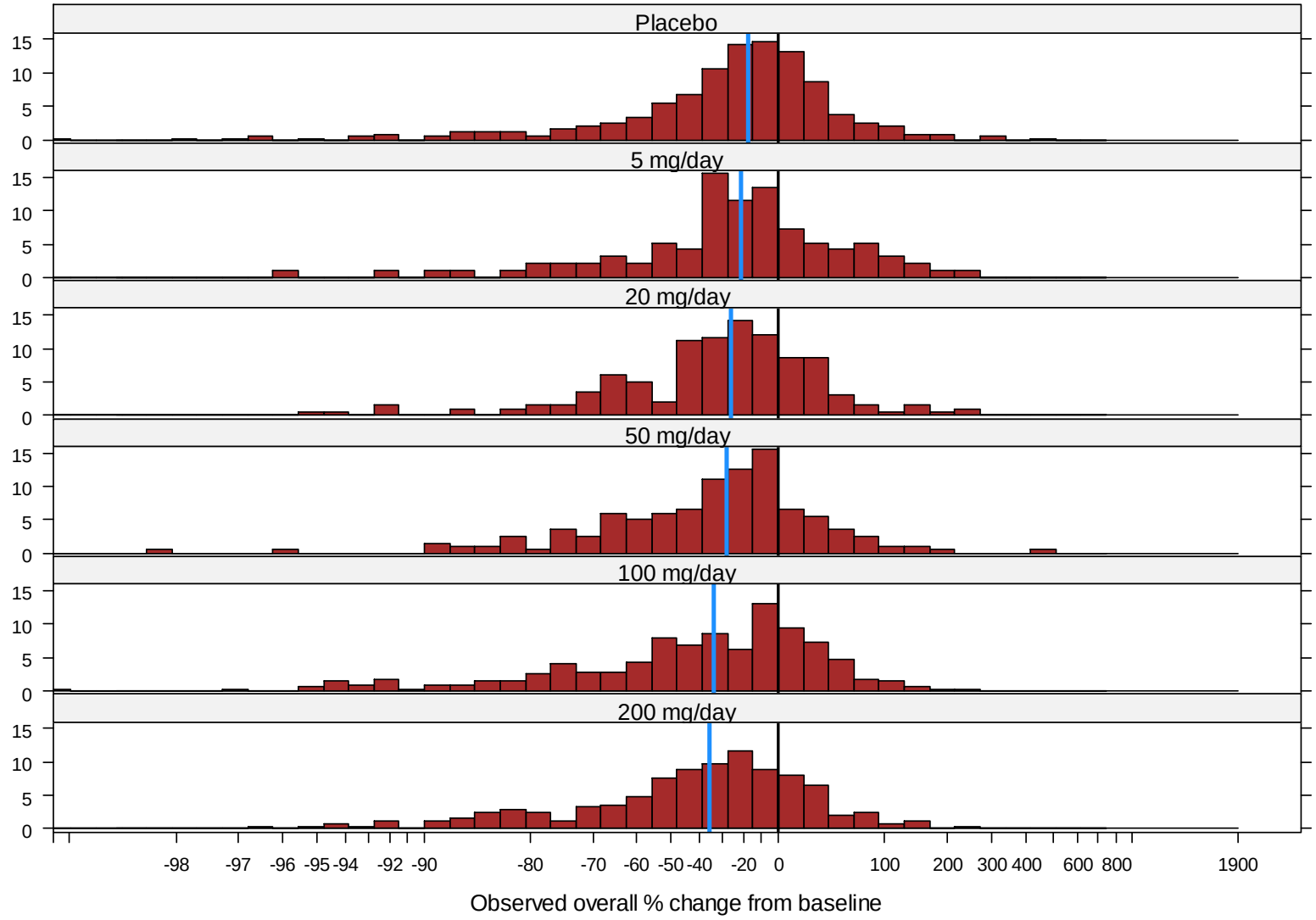
…when you zoom in



Model components

- Change due to placebo
- Effects driven by daily average concentrations (Cav) estimated using population PK model
- Drug effect using E_{max} model
- Mixture model assuming two populations…

Distribution of individual outcomes:



Model components

- Change due to placebo
- Effects driven by daily average concentrations (Cav) estimated using population PK model
- Drug effect using E_{max} model
- Mixture model assuming two populations:
  - One that acts like placebo
  - One that clearly decreases with increasing concentration

Daily count modelling

- Poisson
  - Discrete distribution: only non-negative integers
- Negative binomial (poisson extension)
  - Extra variability (e.g. more days with zero seizures)
  - Inter-individual variability on overdispersion

- Seizures are often observed in clusters: if a previous day showed seizures, maybe the next day has a higher chance of seizures

- Markov-like influence of the previous day where seizure rate is an E_{max} function of the observed number of seizures on the previous day*

*Ahn JE, Plan EL, Karlsson MO and Miller R. Modeling Longitudinal Daily Seizure Frequency Data From Pregabalin Add-On Treatment. J Clin Pharmacol 2012 52: 880-892.

ΔOFV values

- Poisson
- Change to negative binomial:
  ΔOFV = -37,428.9
- Change to IIV on overdispersion:
  ΔOFV = -21,273.7
- Change to seizures on previous day (Markov-like):
  ΔOFV = -6,754.8

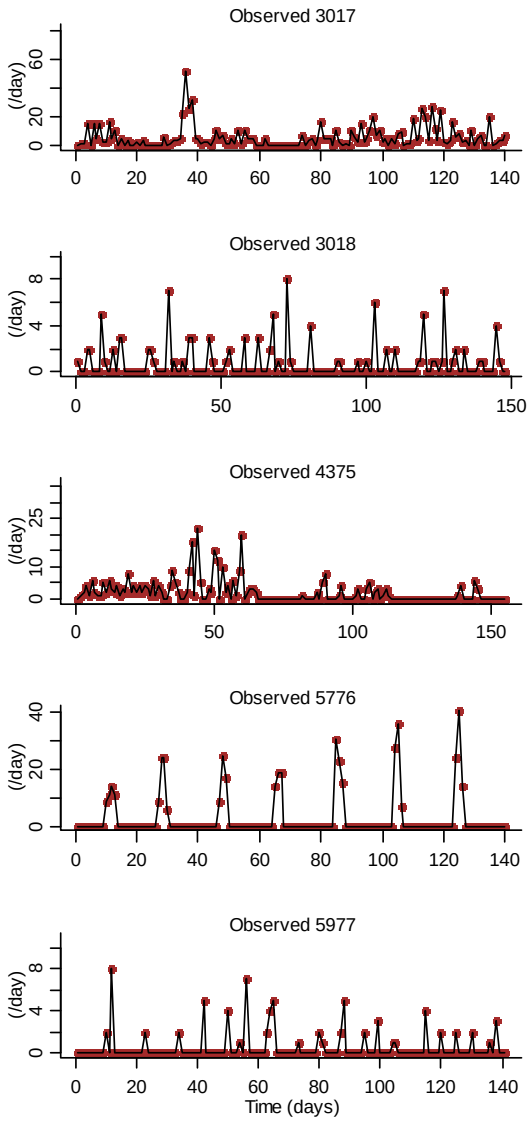
- If you like big changes in OFV values, count modelling is your ticket!

Simulations

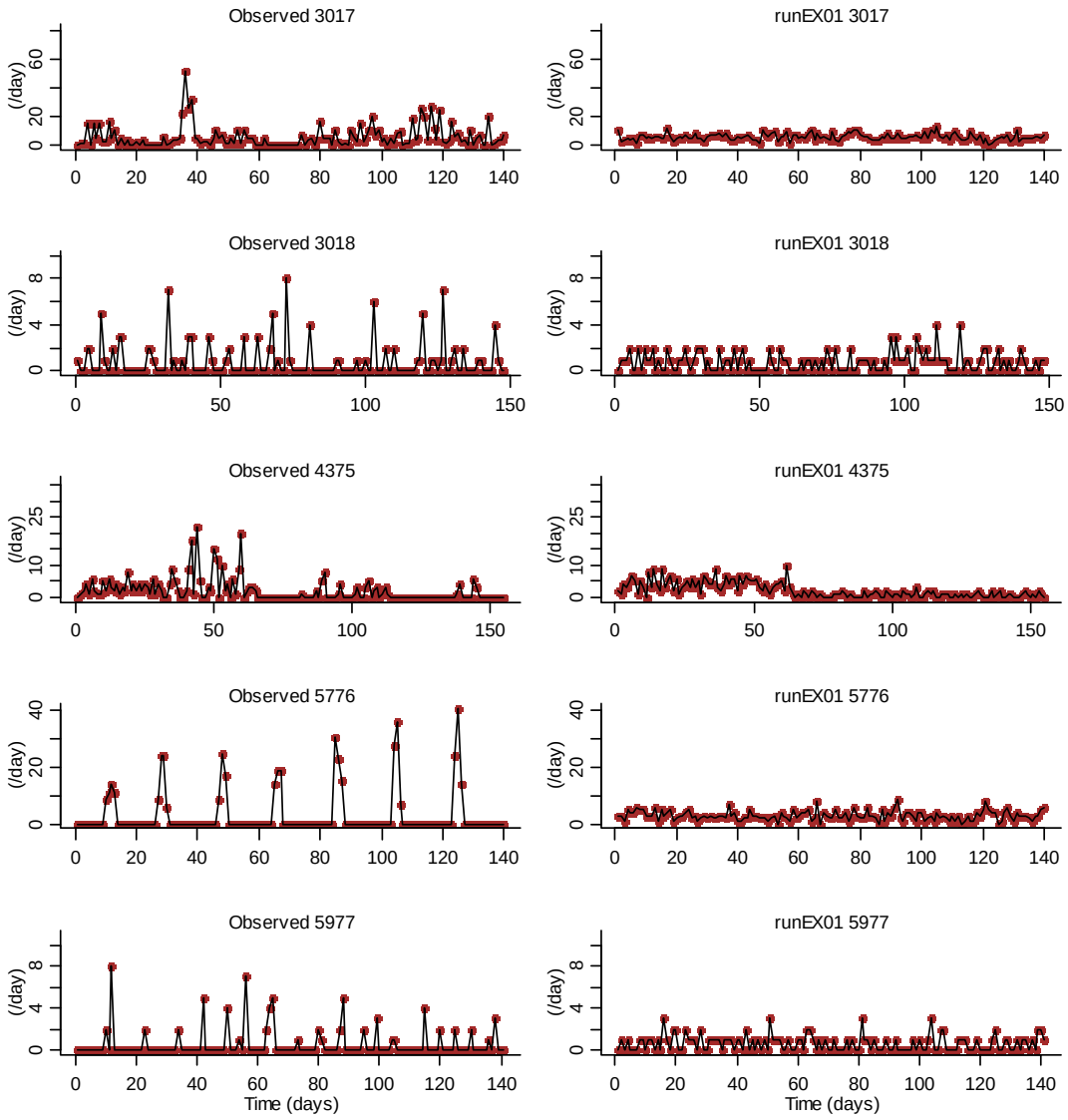
- Traditional goodness of fit plots are not possible or useful with count modelling:
  - Simulation is the only way to go

- NONMEM allows count simulation
- NONMEM can remember the simulation outcome on the previous record (= previous day)
- This allows simulating profiles with Markov properties

Observed example profiles

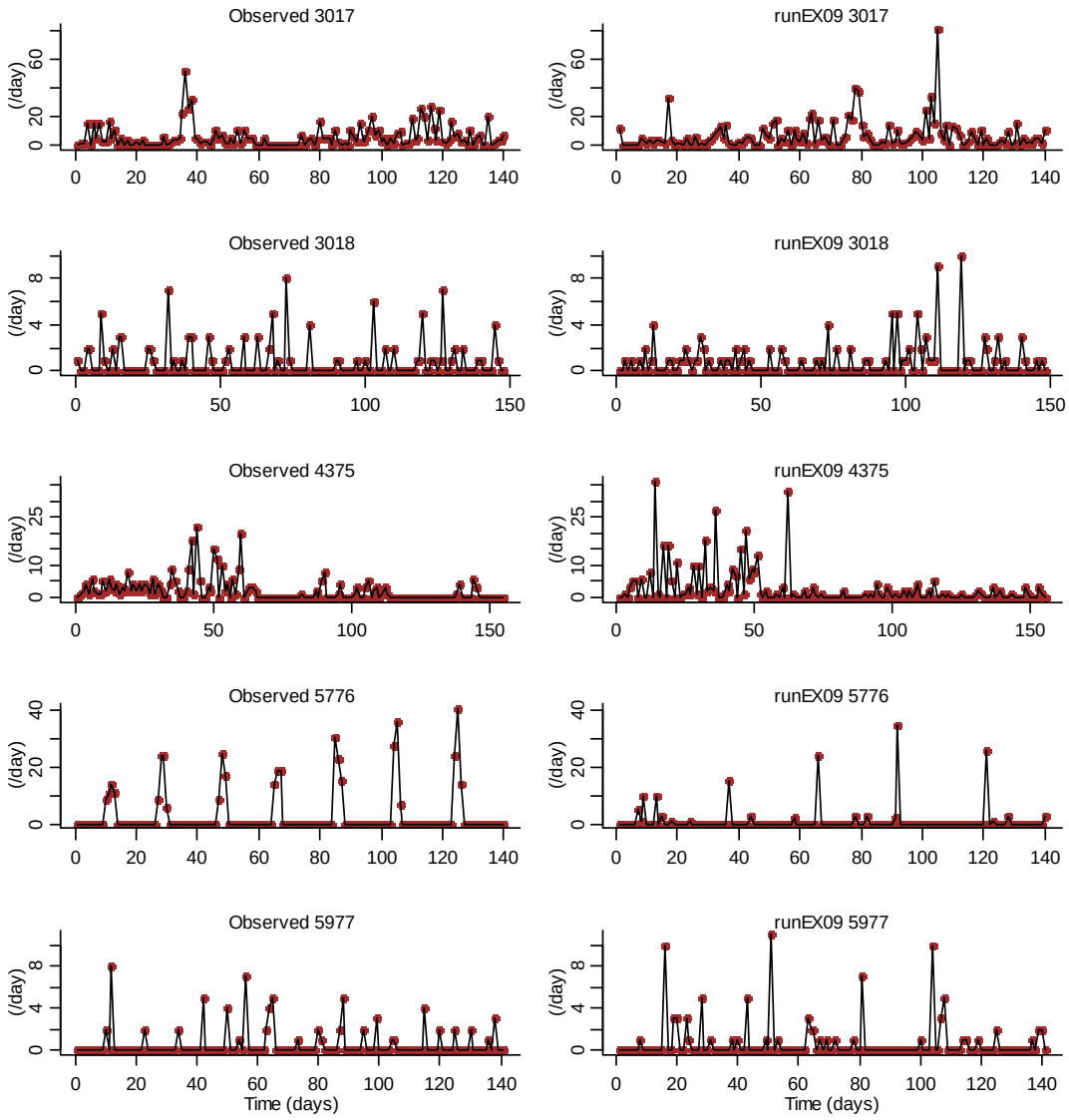


Simulated profiles for the simple Poisson model



Switch to the final count model…

…and the highly variable profiles are nicely captured

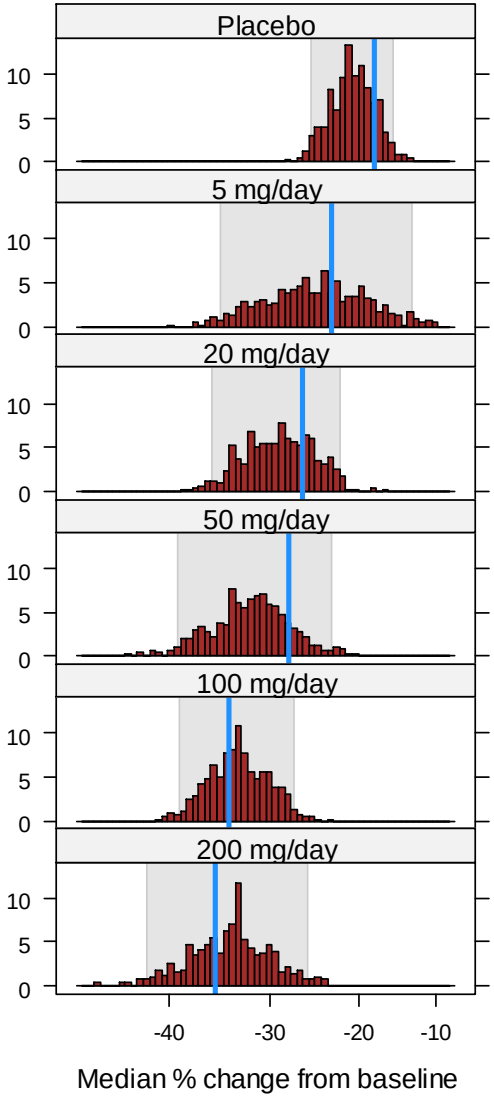


When you can simulate, you can do VPCs

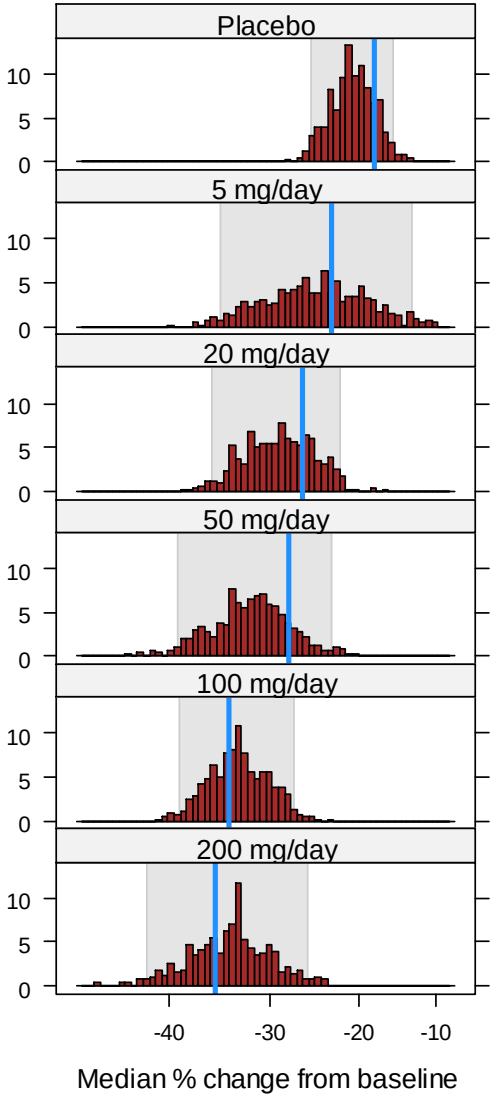
Trial outcomes by applied dose:

- Median percentage change from baseline
- Fraction responders (>50% decrease from baseline)

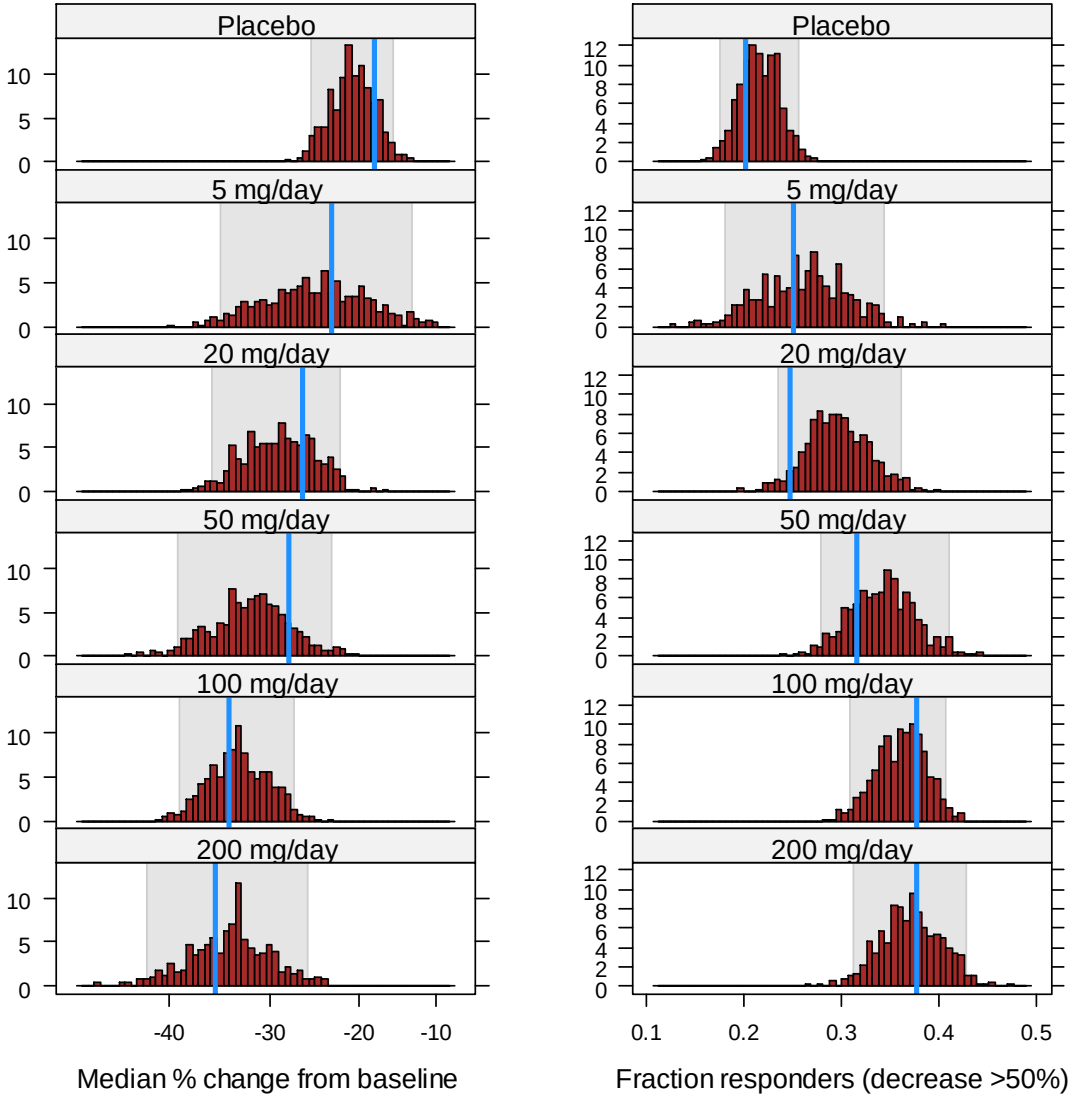
VPCs nicely cover the observed outcomes…



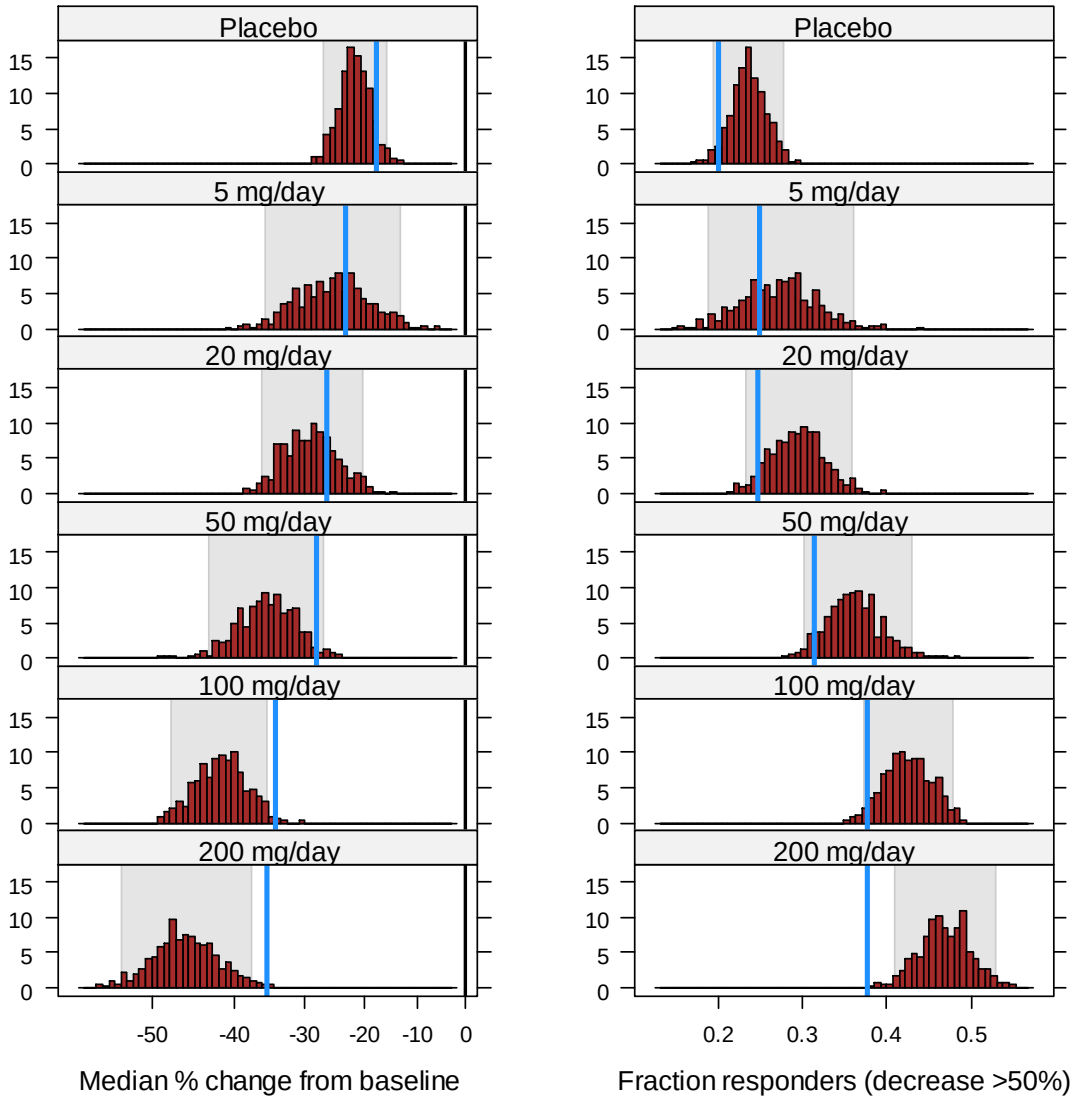
…for percentage change from baseline…



…and fraction responders with >50% decrease



Without a mixture component the effect is over-estimated

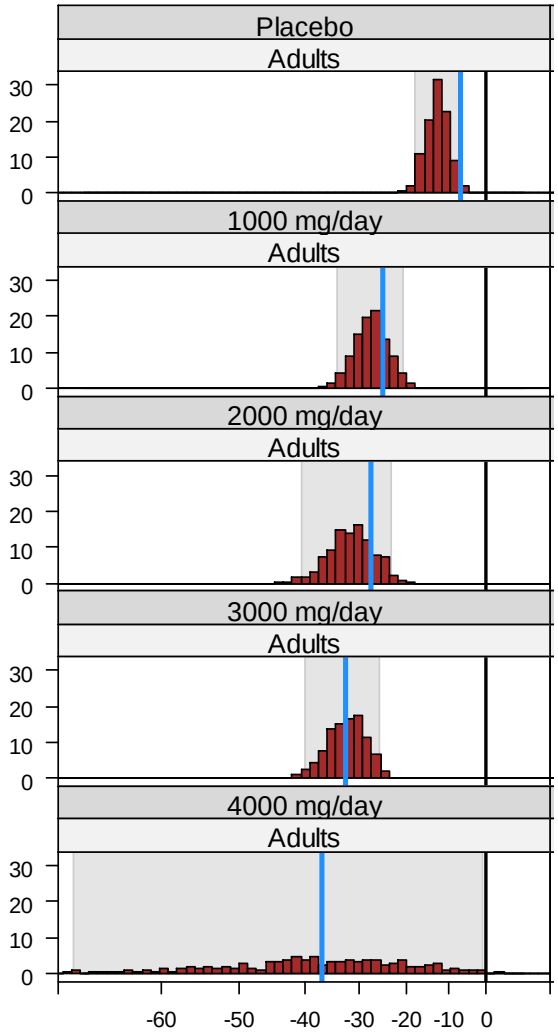


Modelling effects of LEV in adults and children

- Apply the BRV model to LEV data with both adults and children
- How do the PKPD model parameters change from adults to children?

Jumping straight to the results…

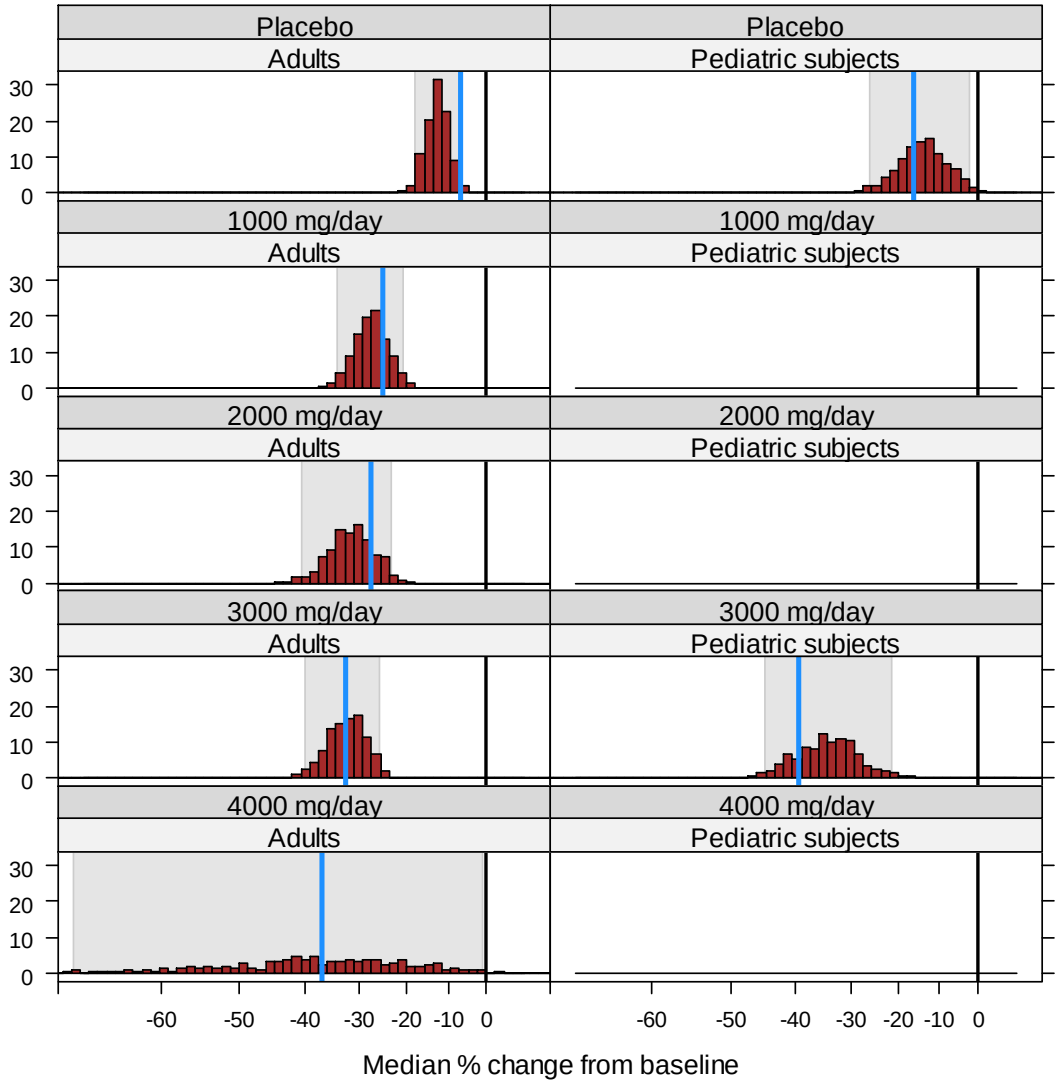
Aggregated LEV adult data are well described…



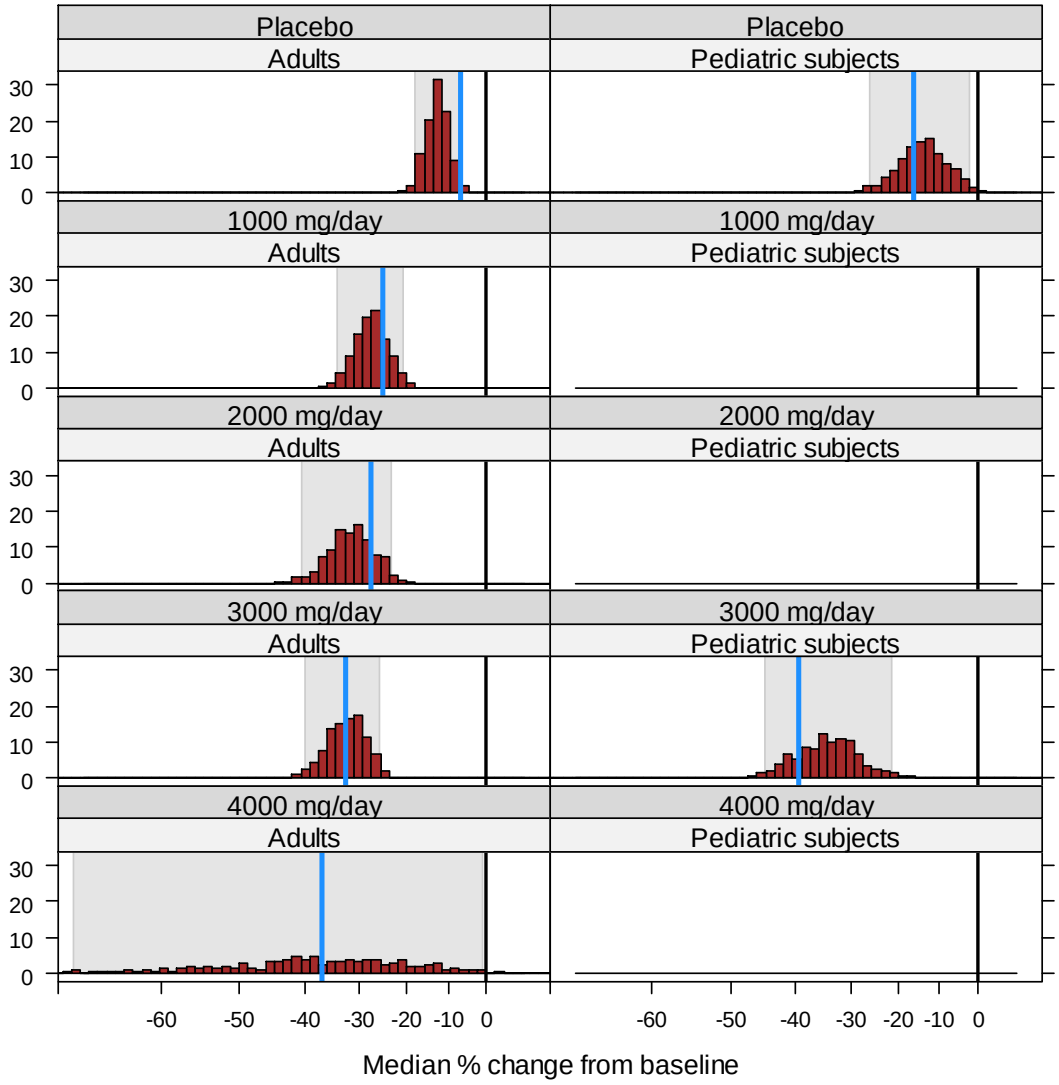
…paediatric covariates are non-significant…

Model	*ΔOFV*
Paediatric covariate on mixture fraction	-0.55 vs. runP231 (p=0.4566)
Paediatric covariate on placebo effect	0.00 vs. runP231 (p=1.0000)
Paediatric covariate on E_{max}	-0.08 vs. runP231 (p=0.7721)
Paediatric covariate on EC_{50}	-0.12 vs. runP231 (p=0.7323)

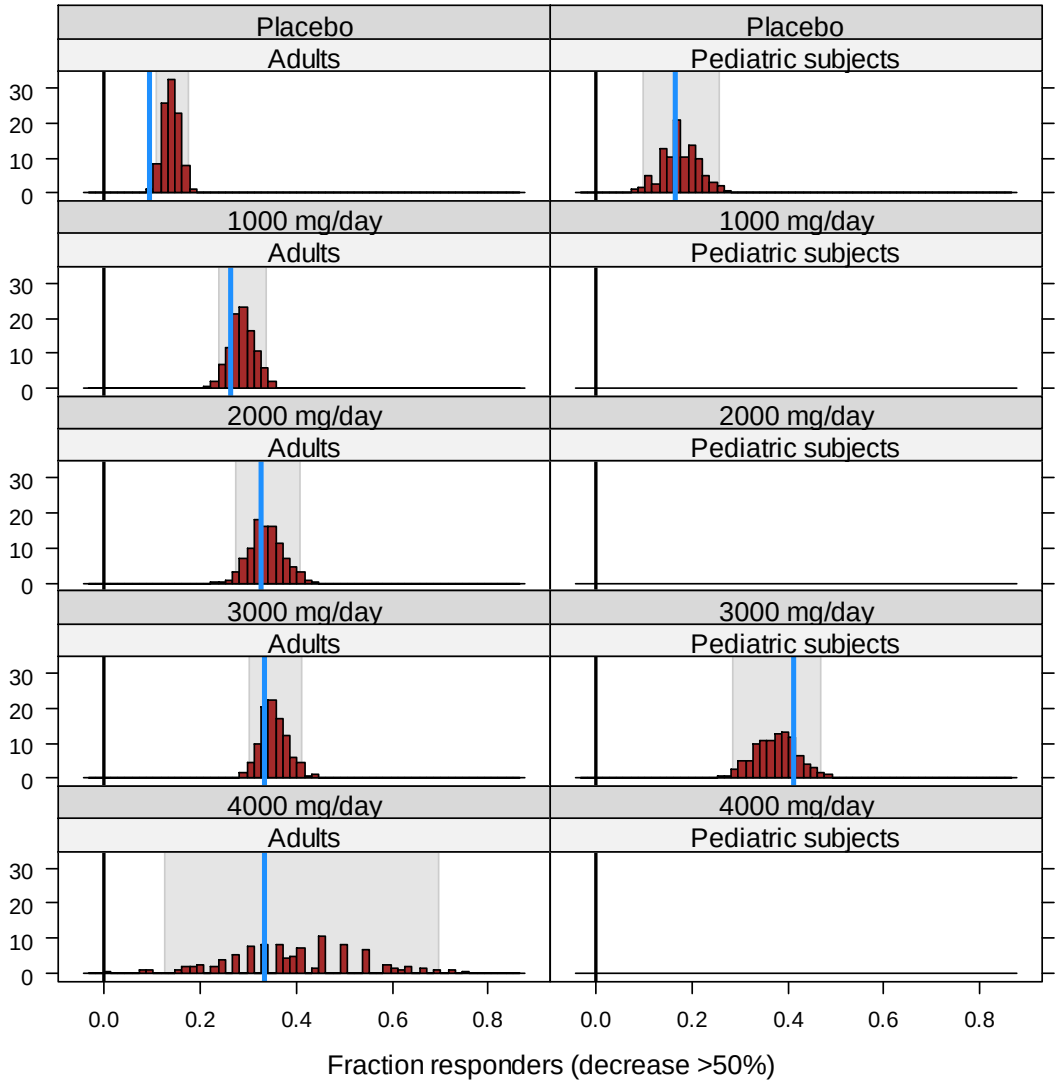
…meaning adult parameters describe children as well…



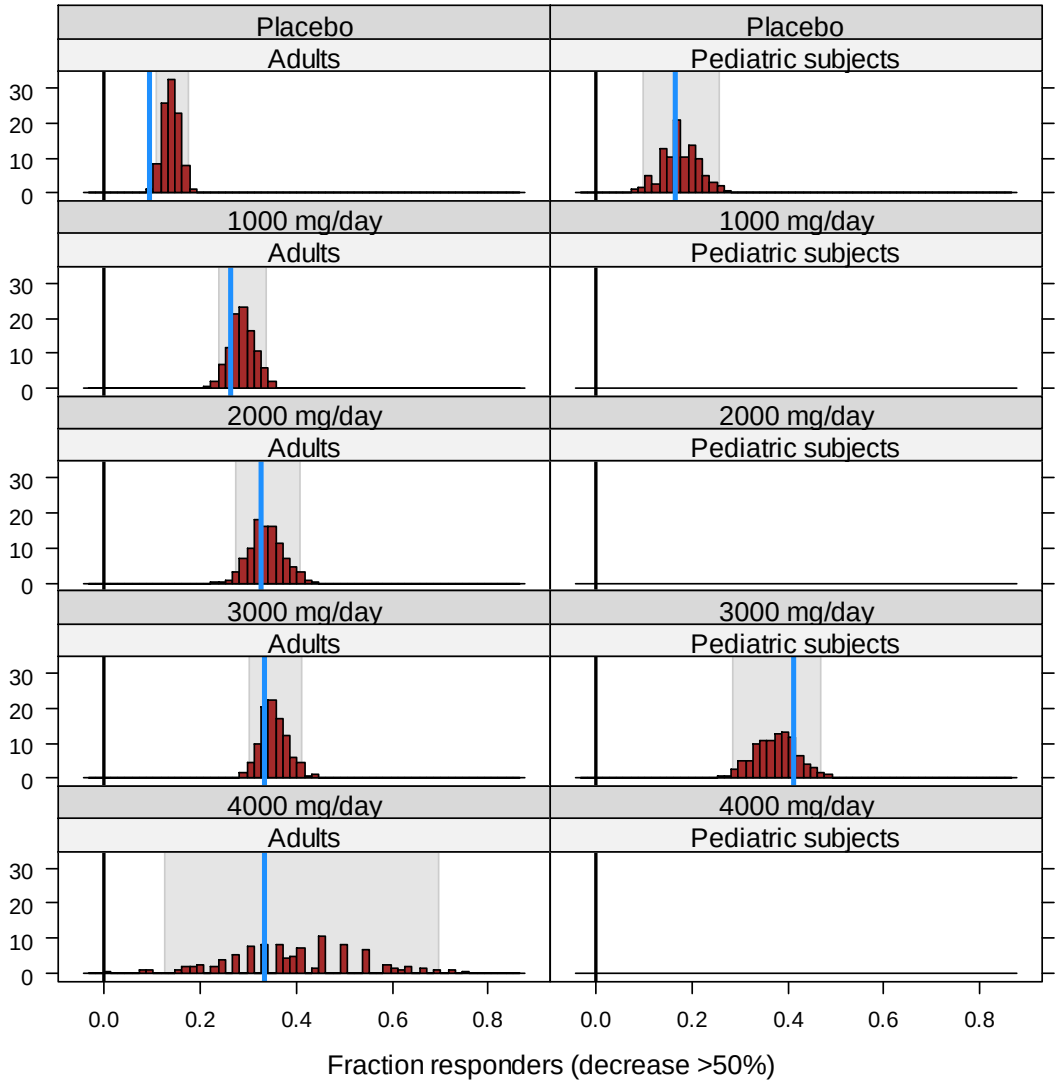
…both for median percentage change from baseline…



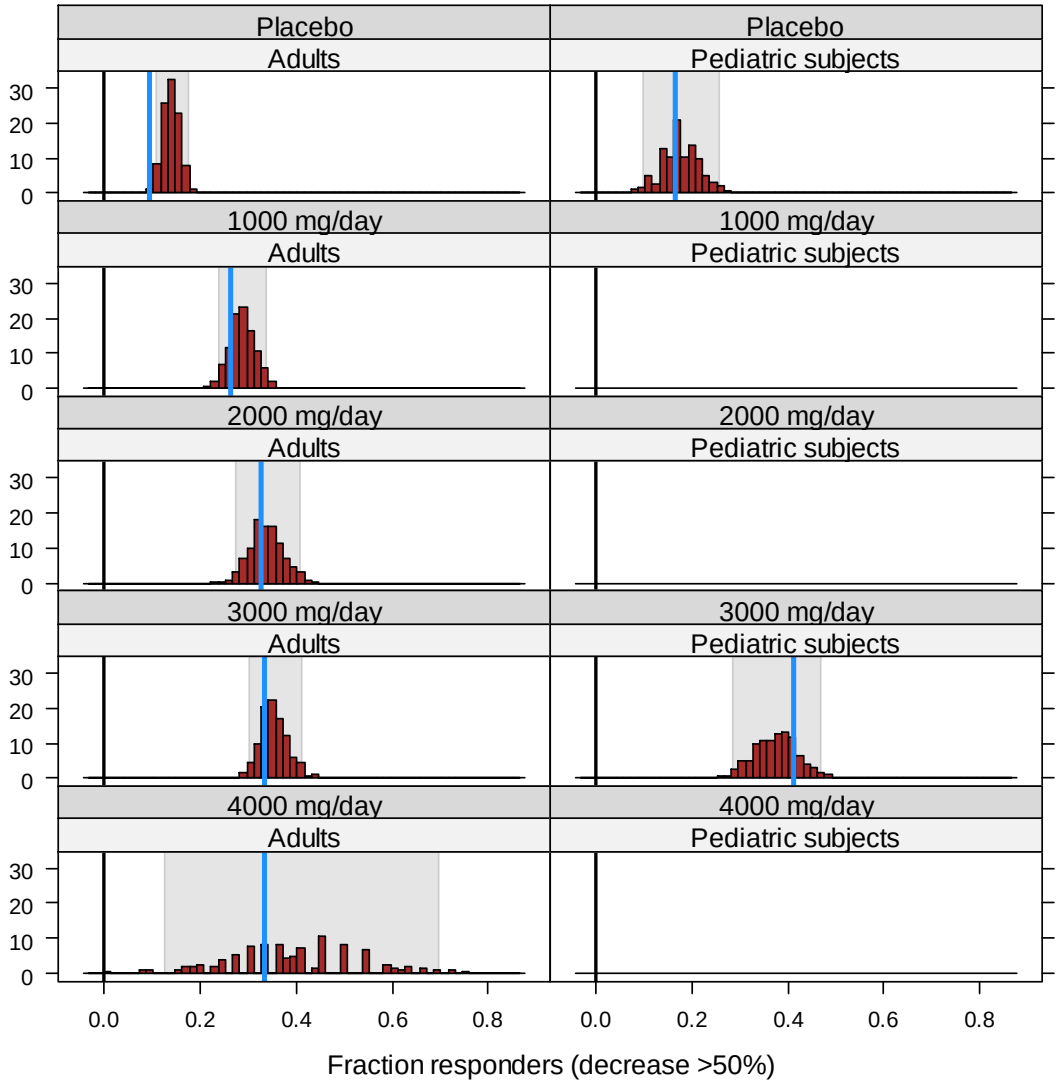
...and for the fraction responders



So the model works…

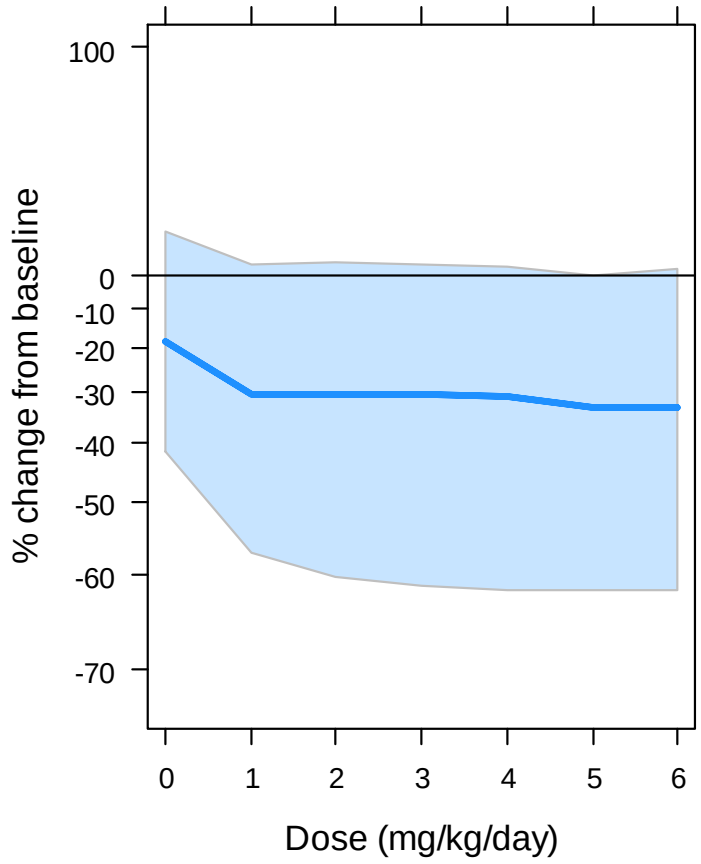


…and we can use the adult parameters for children!

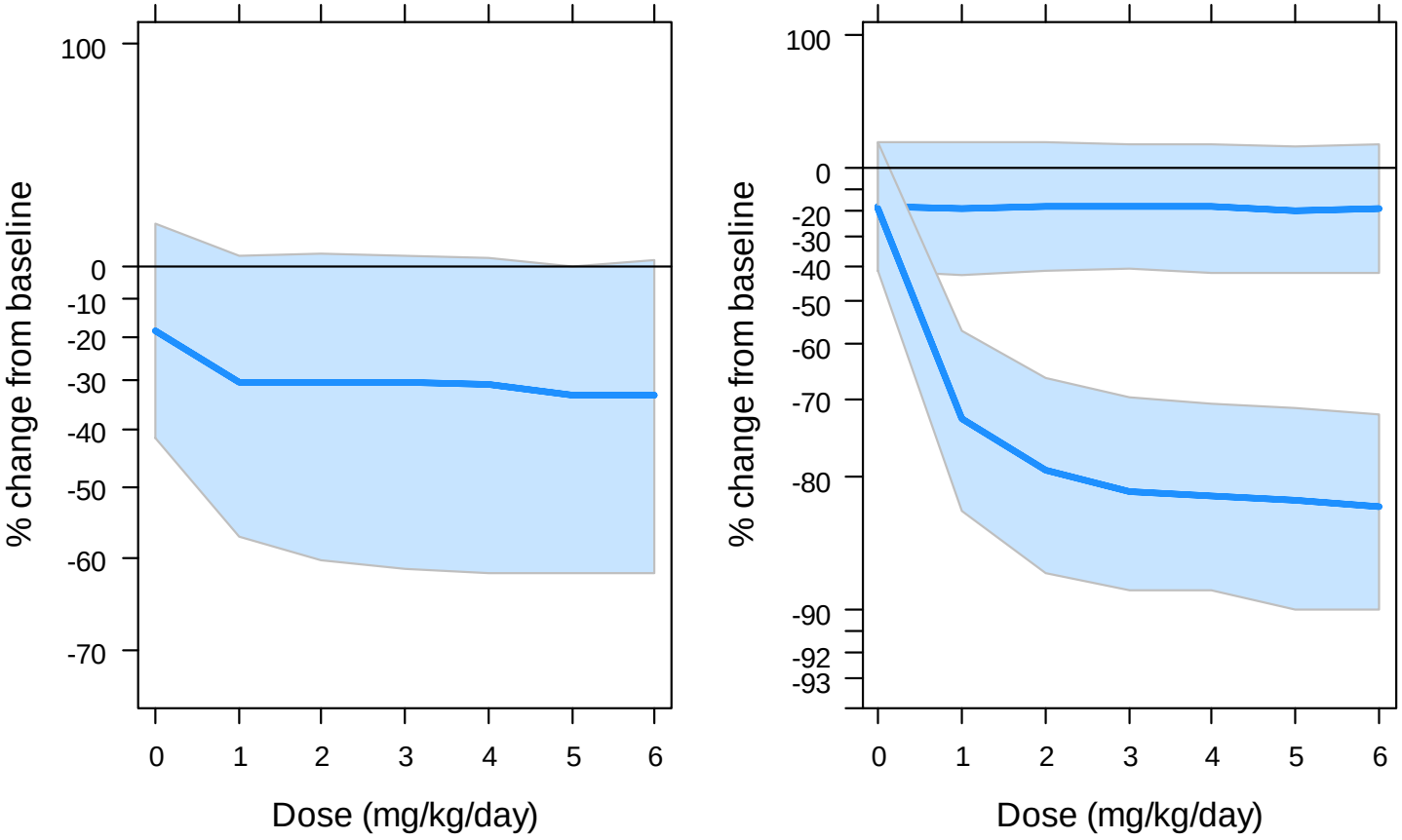


This supports prediction of BRV effects in children

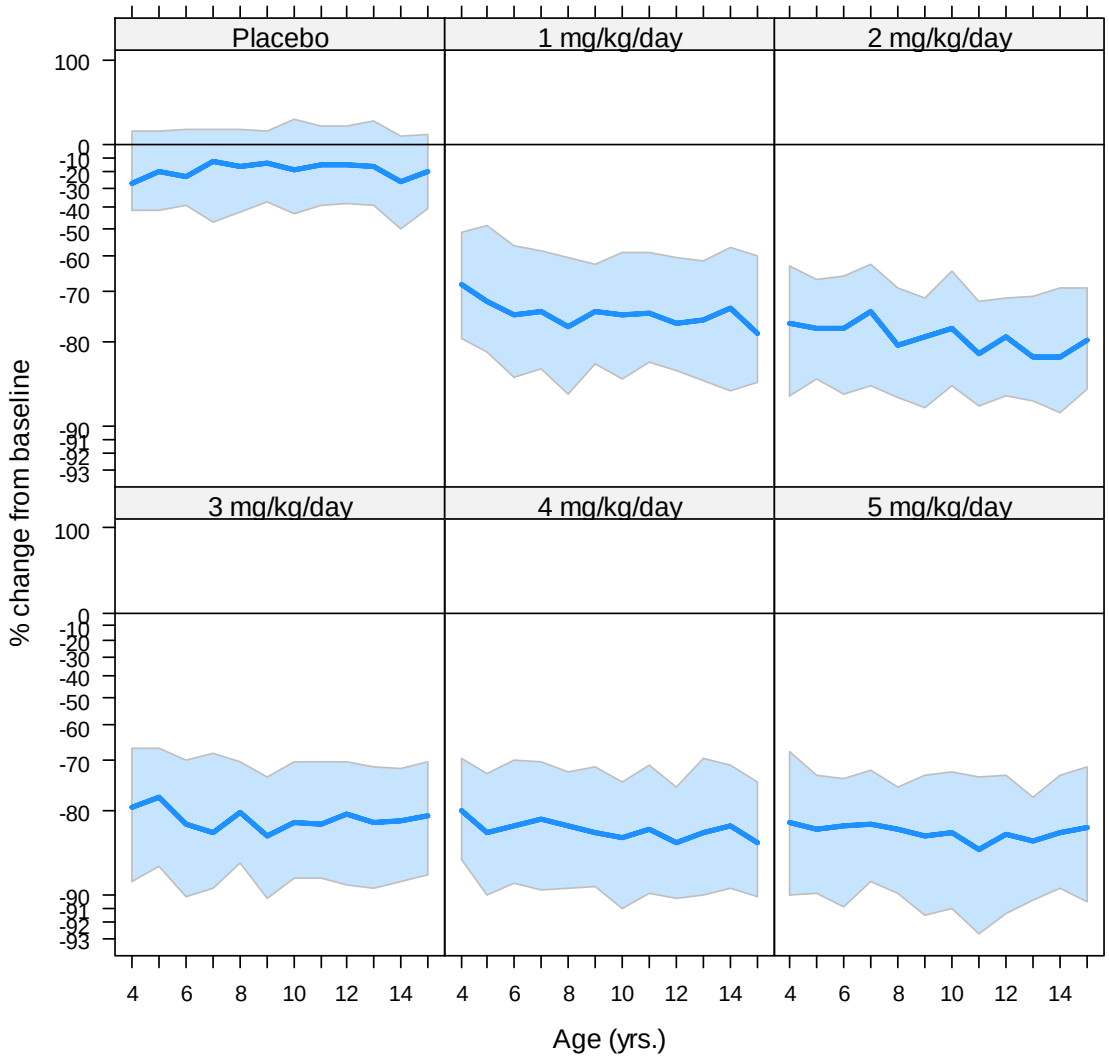
For the entire population…



…and split by mixture-model responder population



Effects as a function of age for the mixture-model responder population



In conclusion: scaling PD from adults to children

- If the disease is the same in adults and children:
  - Scale PK and investigate safety
- If the disease is potentially different:
  - Estimate the change in PKPD relationship using a comparable compound
- We now have a clearer picture of what BRV doses to administer