Population Pharmacokinetics of Clobazam and its Active Metabolite in pediatric patients with epilepsy: Effect of weight, genotype and co-therapy

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What do we know?

- Lennox-Gastaut Syndrome (LGS)
  - Catastrophic childhood epilepsy with atonic seizures, developmental retardation, and behavioral disturbances
- Clobazam (CLB)
  - High Bioavailability (87%), Low oral clearance (2.5 L/hr)
  - Metabolized by CYP3A4 and 2C19 to the active metabolite- N-Desmethylclobazam (NCLB)
  - NCLB further metabolized by 2C19 to 4′ OH-NCLB (inactive metabolite)

Ochs H.R et al, Eur J Clin Pharmacol (1984) 26: 499-503
Kosaki K et al., Brain & Development (2004) 26: 530-534

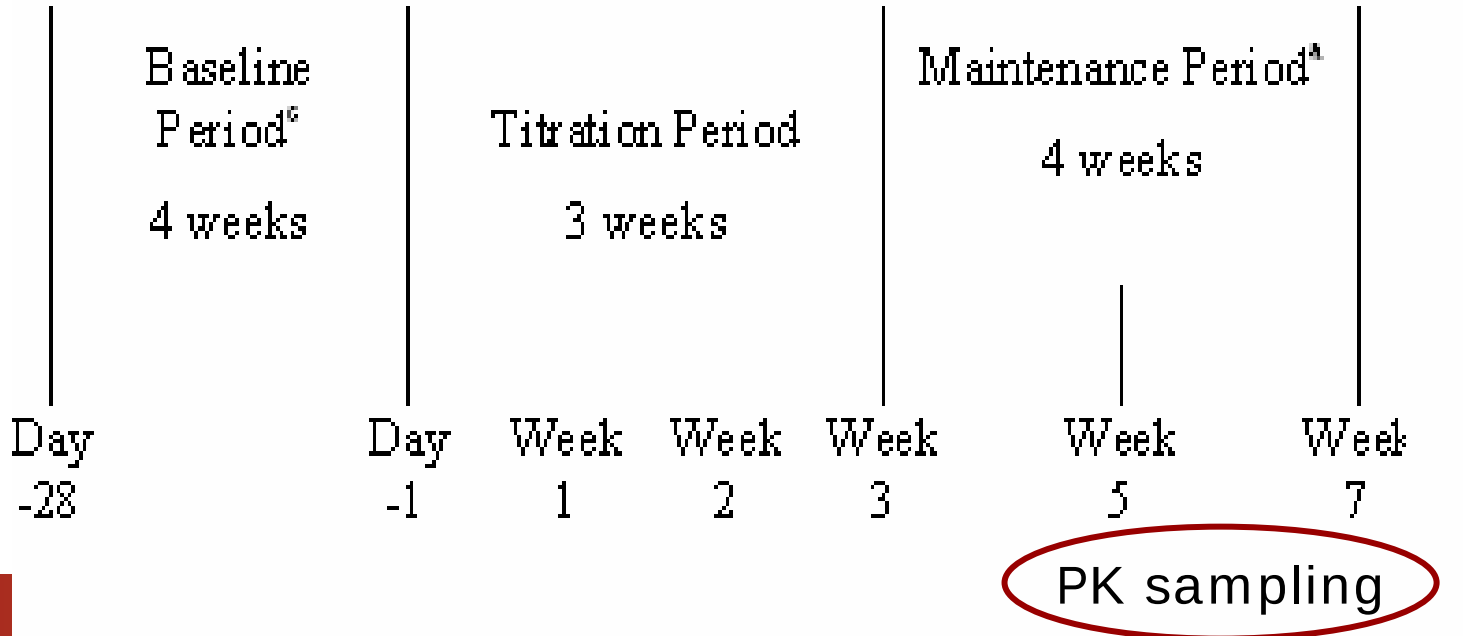
What do we want to know?

Population pharmacokinetics of CLB and NCLB in target patient population

- Essentially pediatric patients

Study Design and Patient Characteristics

- **Phase 2, multi-center, randomized, double-blind, dose-ranging study**
  - **N: 60**
  - **Treatment length: 11 weeks**
- **6 weight groups (~ 10 per group) randomly assigned to low or high dose treatment group**
  - **Low-Dose target: 0.25mg/kg (≤ 10 mg)**
  - **High-Dose target: 1.0 mg/kg (≤ 40 mg)**

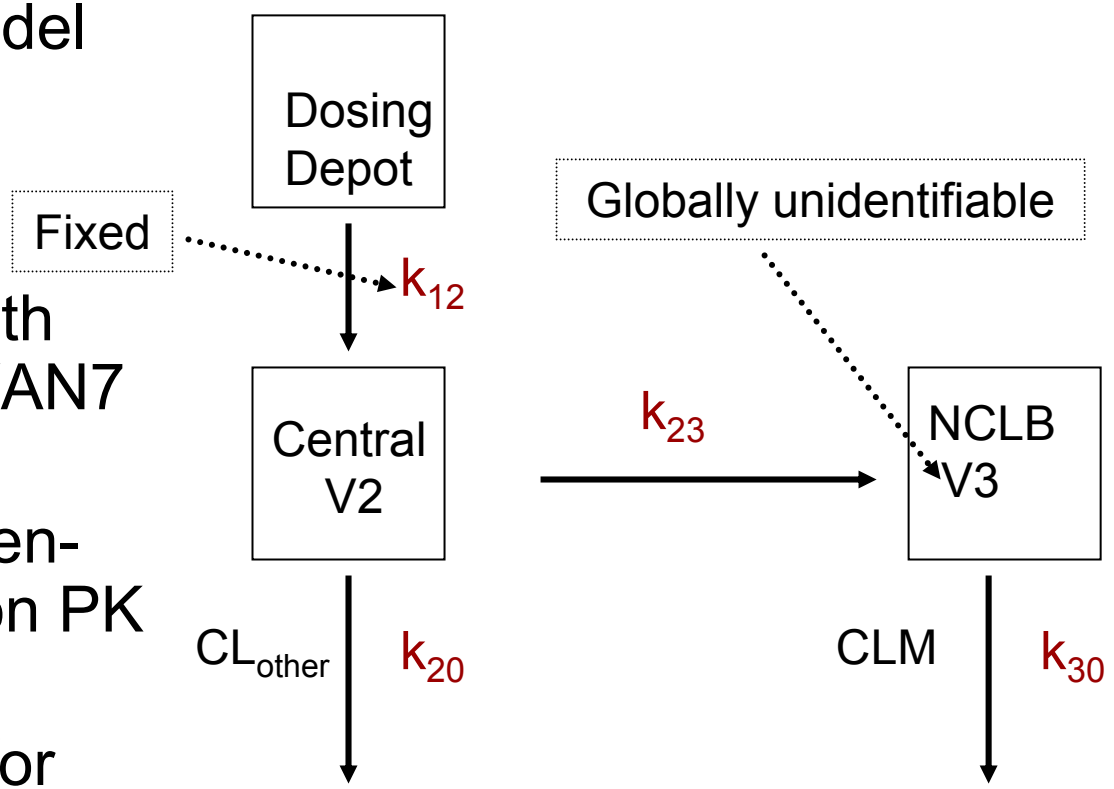


Patient Characteristics

	Mean (Range) / Percent
Age (years)	8 (1,23)
Gender	Females: 40% Males: 60%
Weight (kg)	26.6 (11.6,75.2)
CYP2C19 genotype status	Intermediate Metabolizers: 21%
Concomitant Drugs	VPA: 43% LTG: 19% FBM: 13%
Race	Non-White: 14% White: 85%

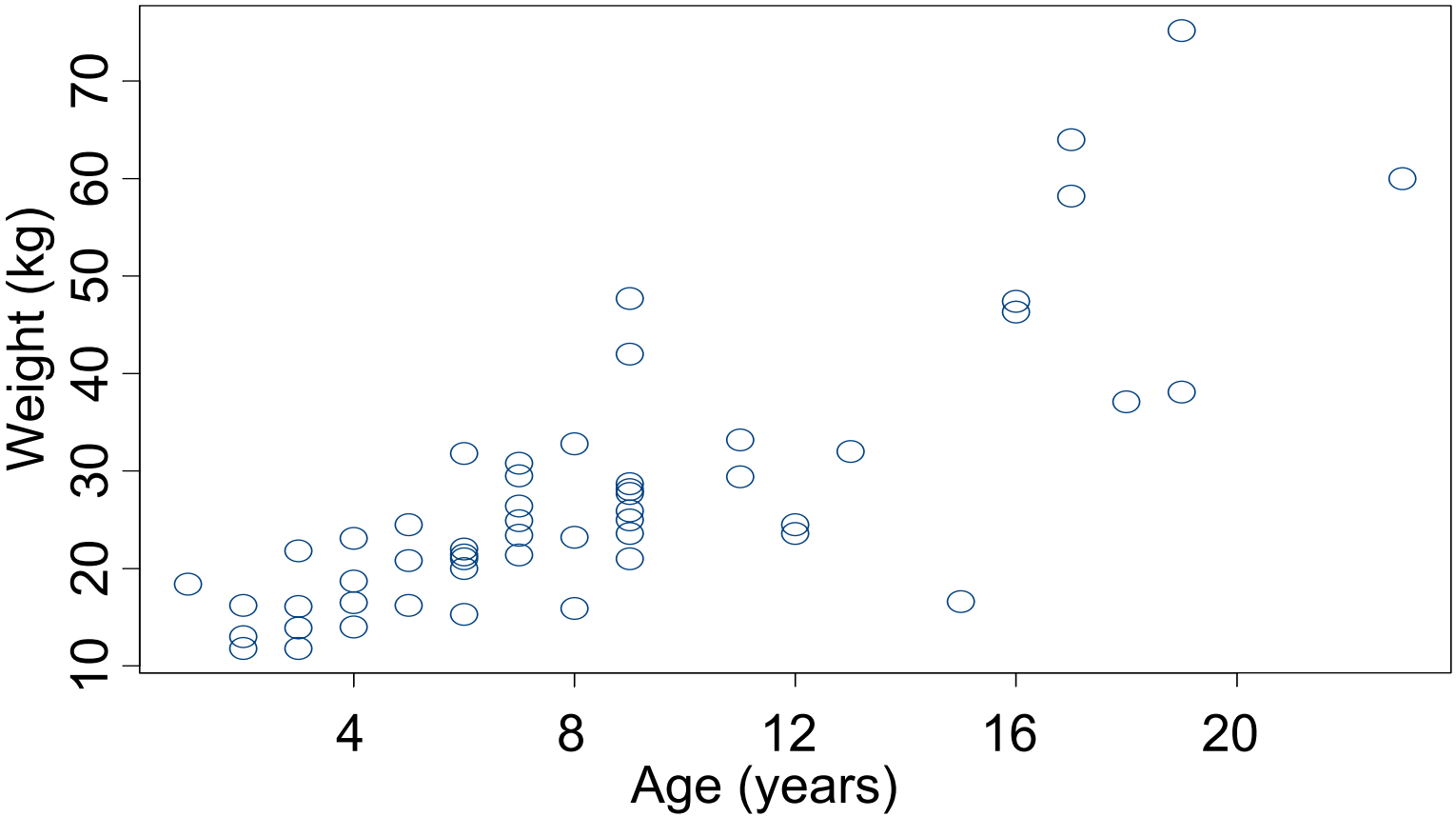
Structural Model

- 1-compartment model with first-order absorption and elimination
- Estimation done with FOCE-I using ADVAN7 in NONMEM-VI
- Exponential between-subject variability on PK parameters
- Proportional error for residual variability



Cosson V et al. in Pharmacometrics: The Science of Quantitative Pharmacology (2007)
Duffull SB et al. J Pharmacokinet Pharmacodyn. 2001 Feb;28(1):93-105

Size-Based Covariate Modeling



Holford NHG, Clin Pharmacokinet.(1996) 30(5):329-332
Anderson BJ et al., Eur J Pediatr (2006) 165:819-829

Size-Based Covariate Modeling

- Clearance standardized for body-weight of 70 kg with a power coefficient of 0.75

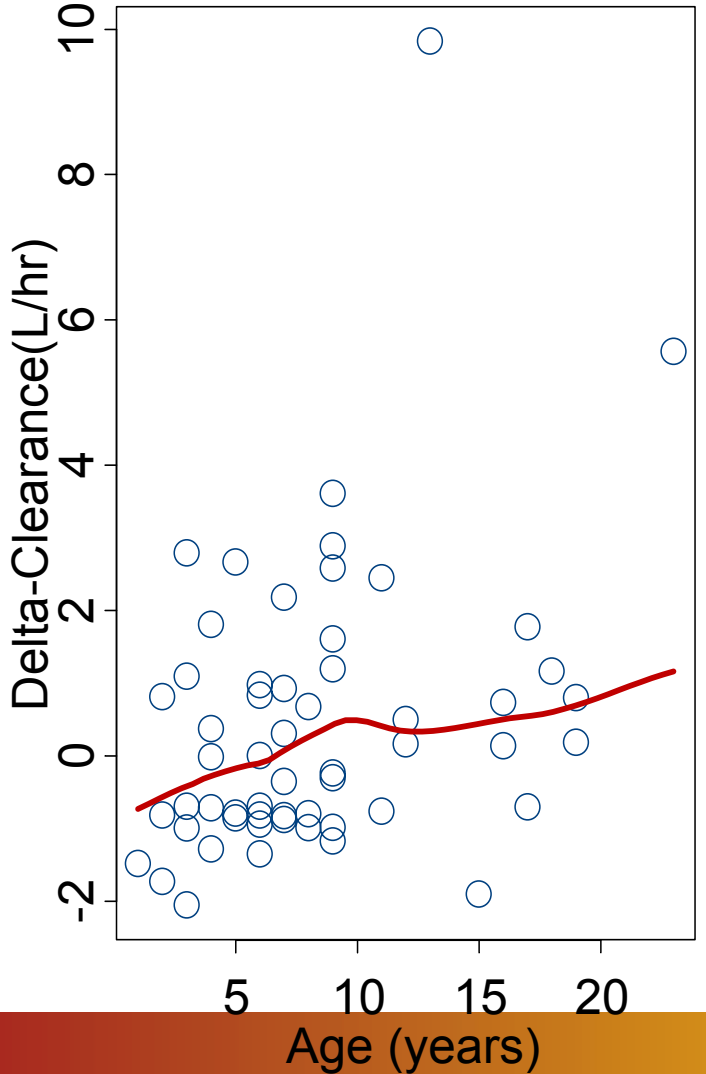
$$CL_i = CL_{pstd} * \left(\frac{W_i}{70}\right)^{0.75} * \exp(\eta_i)$$

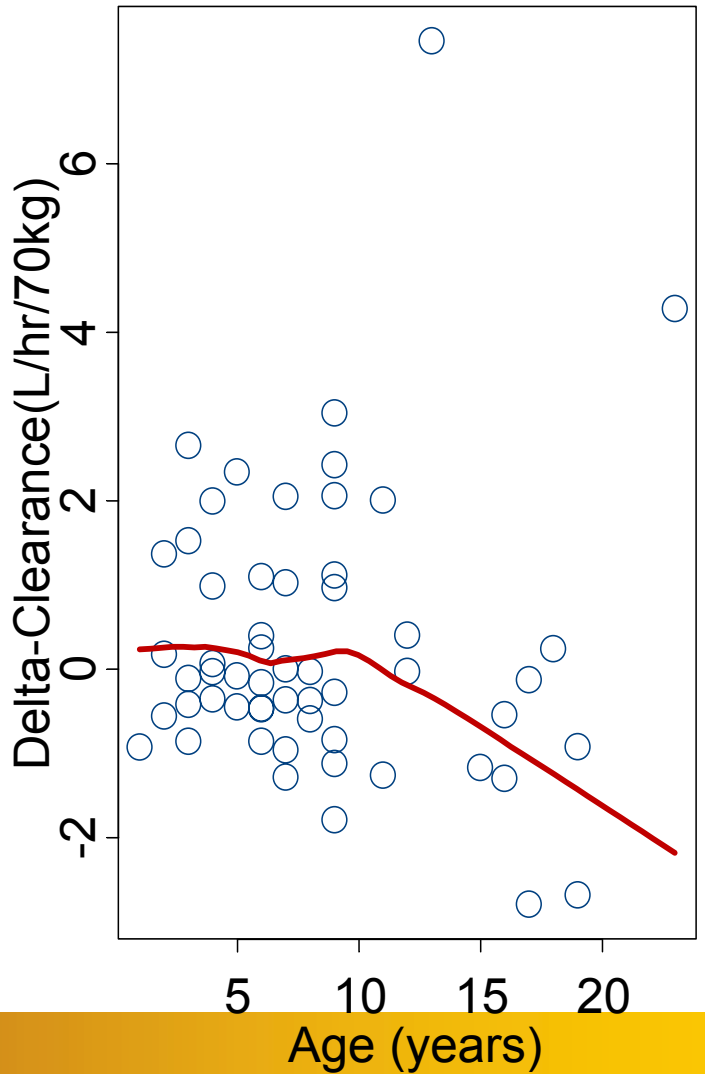
where:
i = CL in ith individual
CL_{pstd} = Population Standardized clearance
η_i = i^{th} subject's random deviation from CL_{pstd}

- All other covariates tested after '**size- standardization**' of clearance
- Categorical covariates (2C19 genotype status, gender, concomitant AED drugs) tested proportionally

Holford NHG, Clin Pharmacokinet.(1996) 30(5):329-332
Anderson BJ et al., Eur J Pediatr (2006) 165:819-829

Exploratory Graphs of CLB CL/F: Size Issues





Estimates of CLB

	NONMEM Estimate (95% CI)	Bootstrap Medians (95th percentile)
CL/F (L/hr/70kg)	5.99 (5.15, 6.83)	5.98 (5.23, 6.79)
V/F (L)	96.8 (22.7, 171)	108 (50.2, 219)
$BSV_{CL/F}$ (%)	47.1 (36.3, 54.8)	46.4 (34.2, 54.4)
Residual Error (%)	26.3 (17.2, 33.1)	26.5 (18.7, 34.4)

- After accounting for weight, random variability in CL/F ↓ from 56% to 47%

Estimates of NCLB

	NONMEM Estimate (95% CI)	Bootstrap Medians (95^{th} percentile)
CLM (L/hr/70kg)	1.07 (0.884, 1.26)	1.09 (0.922, 1.27)
Intermediate CYP2C19 metabolizers (% of CLM)	58.9 (30.3, 87.5)	56.7 (36.7, 97.9)
Felbamate cotherapy (% of CLM)	33.4 (19.4, 47.4)	32.4 (22.6, 57.4)
BSV_{CLM} (%)	57.3 (43.1, 68.5)	54.8 (42.0, 67.2)
Residual Error (%)	18.8 (13.6, 22.9)	18.6 (14.4, 22.9)

- **After accounting for covariates, random variability in CLM ↓ from 77% to 57.3%**
- Covariance between CL/F and CLM was not significant, very less and thus dropped

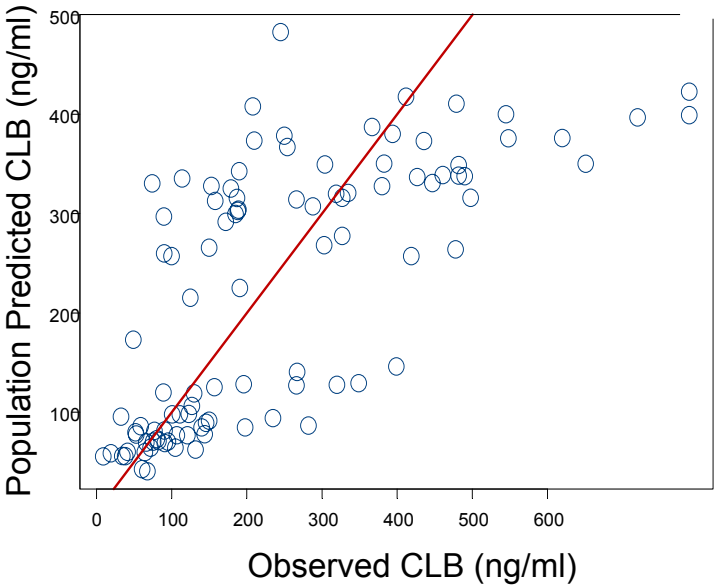
Results (continued)

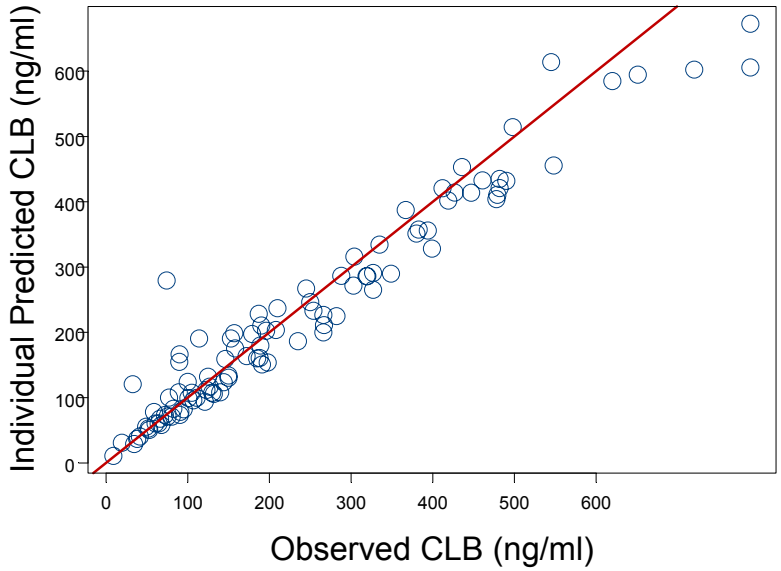
- After size standardization, no other covariate was statistically significant for CLB CL/F
- Between subject variability (BSV) on V/F of CLB could not be estimated
- Fraction metabolized to N-CLB 'posterior' un-identifiable
  - Fixed at 0.70

Levy R.H. Drug Metabolism and Disposition; Vol 11, No. 4: 286-292

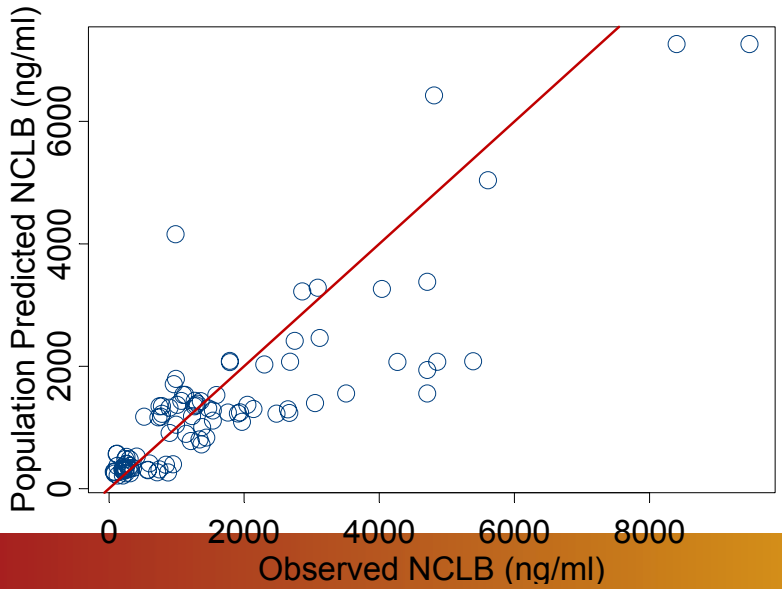
Diagnostic Graphs

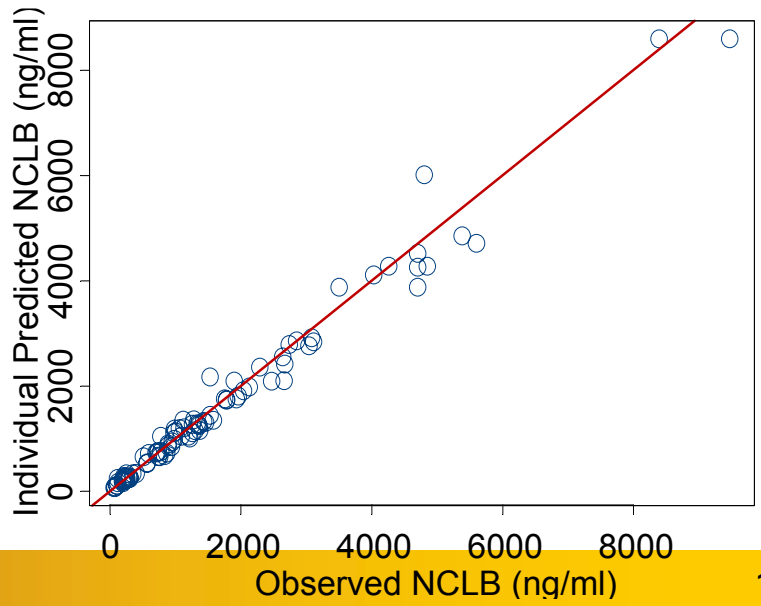
CLB





NCLB





How do we interpret the high clearance?

- Similar findings from literature:
  - Tedeschi et al. reported “CLB is more extensively metabolized in children”
  - Theis et al. reported increasing serum concentrations of CLB with age within pediatric patients
- CYP3A4 effect?
  - ‘Maturity’ of CYP3A4 with age?
  - However, very few patients above 16 years in this patient population
- Background Concomitant Drugs?
  - Each patient on at least three conmeds

Tedeschi G et al. Br. J. Clin. Pharmac. 1980; 11: 619-621
Theis GJ. et al. J Child Neurol. 1997 Apr;12(3):208-13

What do we know now?

- Population standardized clearance of CLB in LGS patients is twice as high as adult healthy volunteers/patients
  - No age effect is discernible after adjusting for weight in this patient population
  - May have implications for dosing of children : Confirm in future study
- Population standardized clearance of NCLB is similar to adults
  - Lower CLM relative to CL/F supports its elimination rate limited disposition
- Patients on felbamate co-therapy and intermediate metabolizers of CYP2C19 have markedly reduced clearance

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