POPULATION PHARMACOKINETICS

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Population Pharmacokinetics

Definition

Advantages/Disadvantages

Objectives of Population Analyses

Impact in Drug Development

Definition

Population pharmacokinetics describe

- The typical relationships between physiology (both normal and disease altered) and pharmacokinetics/pharmacodynamics,
- The interindividual variability in these relationships, and
- Their residual intraindividual variability.

Sheiner-LB
Drug-Metab-Rev. 1984; 15(1-2): 153-71

Definition

E.g.: A simple Pk model

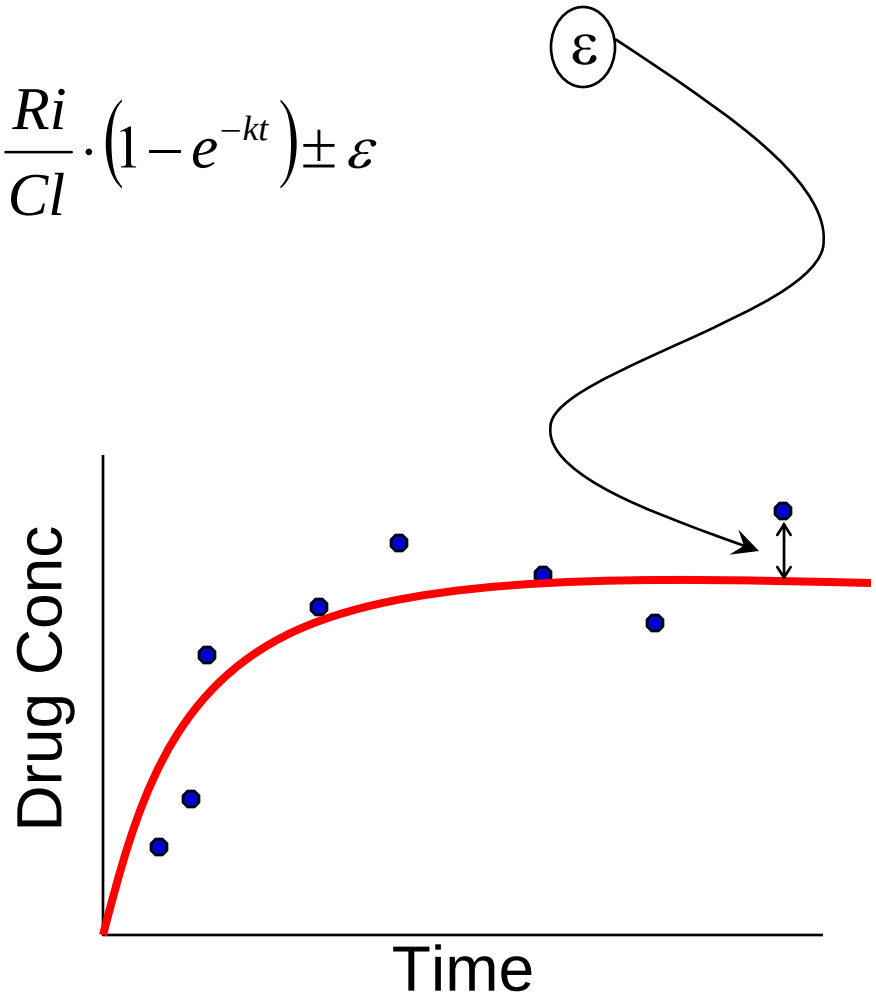
$$Cp = \frac{Ri}{Cl} \cdot \left(1 - e^{-kt}\right) \pm \varepsilon$$

Ri = infusion rate

Cl = drug clearance

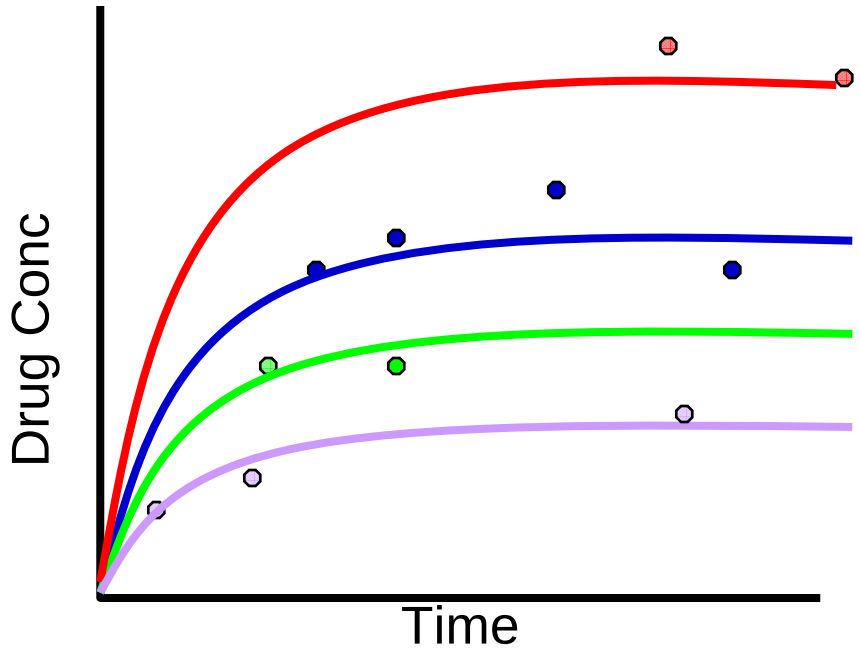
k =elimination rate constant

ε = measurement error, intra-individual error



$\varepsilon \approx N(0,\sigma)$

Definition



$$Cp = \frac{Ri}{Cl} \cdot \left(1 - e^{-kt}\right) \pm \varepsilon$$

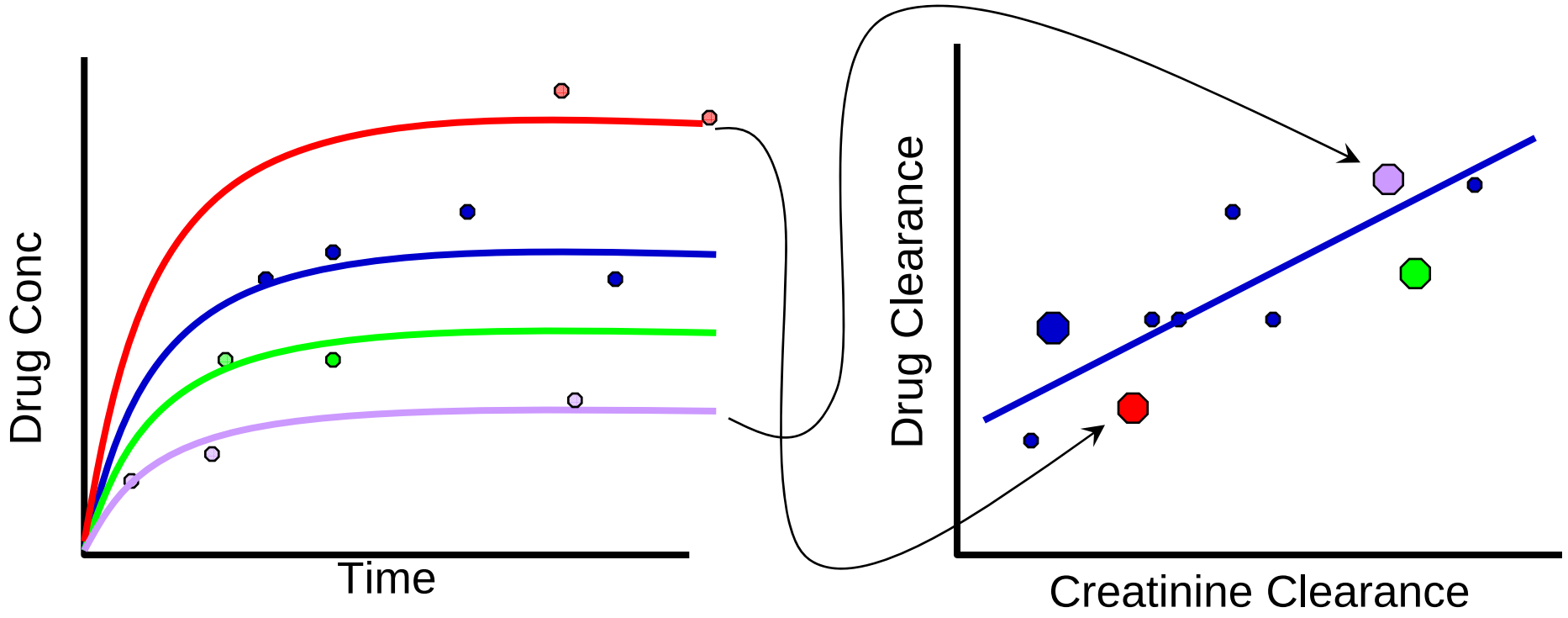
$$Cp = Cp_{ss} \cdot \left(1 - e^{-kt}\right) \pm \varepsilon$$

$$Cl = \frac{Ri}{Cp_{ss}} \pm \varepsilon$$

Definition

Cl = metabolic clearance + renal clearance

$Cl = \Theta_1 + \Theta_2 \bullet CCr \pm \eta$

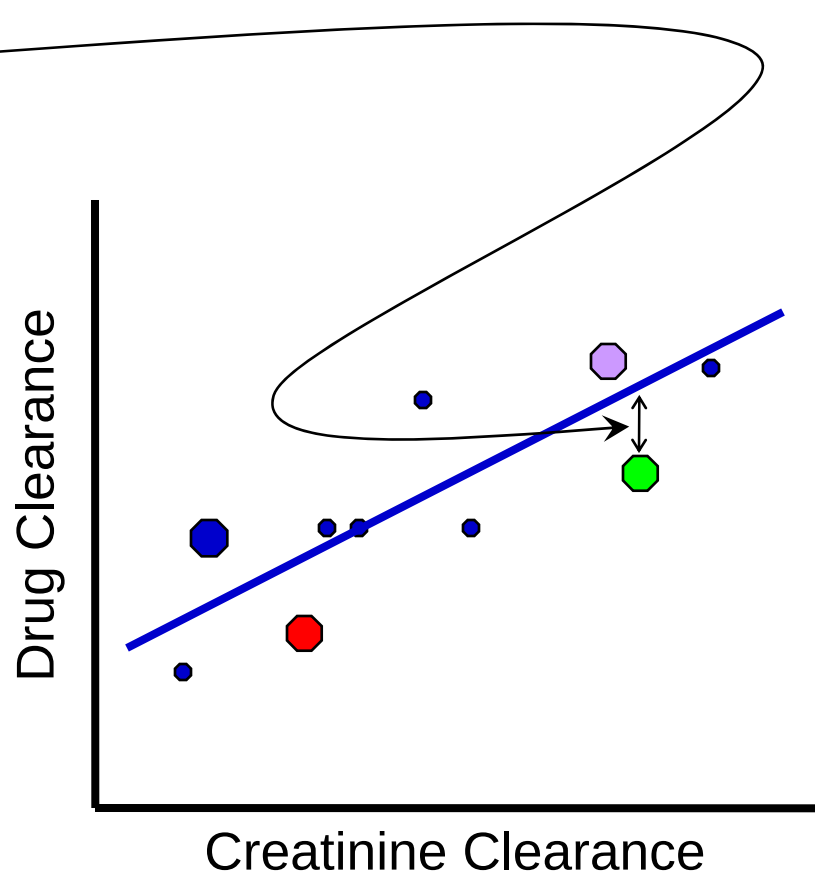


Definition

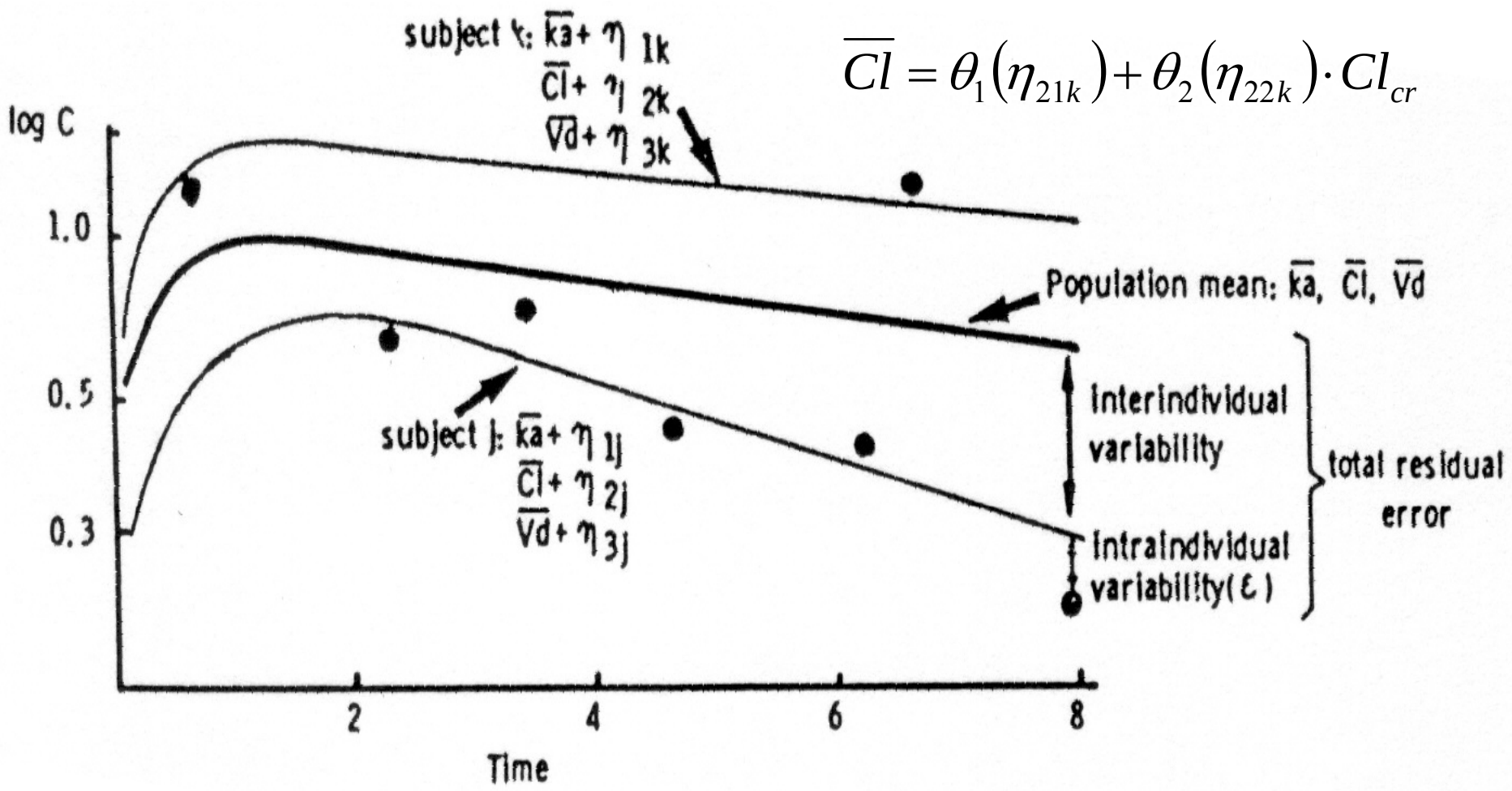
Cl = metabolic clearance + renal clearance

$Cl = \Theta_1 + \Theta_2 \bullet CCr \pm \eta$

$\eta \approx N(0,\omega)$



Graphical illustration of the statistical model used in NONMEM for the special case of a one compartment model with first order absorption. (Vozeh et al. Eur J Clin Pharmacol 1982;23:445-451)



Objectives

1. Provide Estimates of Population PK Parameters (CL, V) - Fixed Effects

2. Provide Estimates of Variability - Random Effects

   - *Intersubject Variability*
   - *Interoccasion Variability (Day to Day Variability)*
   - *Residual Variability (Intrasubject Variability, Measurement Error, Model Misspecification)*

Objectives

3. Identify Factors that are Important Determinants of Intersubject Variability

- *Demographic:* Age, Body Weight or Surface Area, gender, race
- *Genetic:* CYP2D6, CYP2C19
- *Environmental:* Smoking, Diet
- *Physiological/Pathophysiological:* Renal (Creatinine Clearance) or Hepatic impairment, Disease State
- *Concomitant Drugs*
- *Other Factors:* Meals, Circadian Variation, Formulations

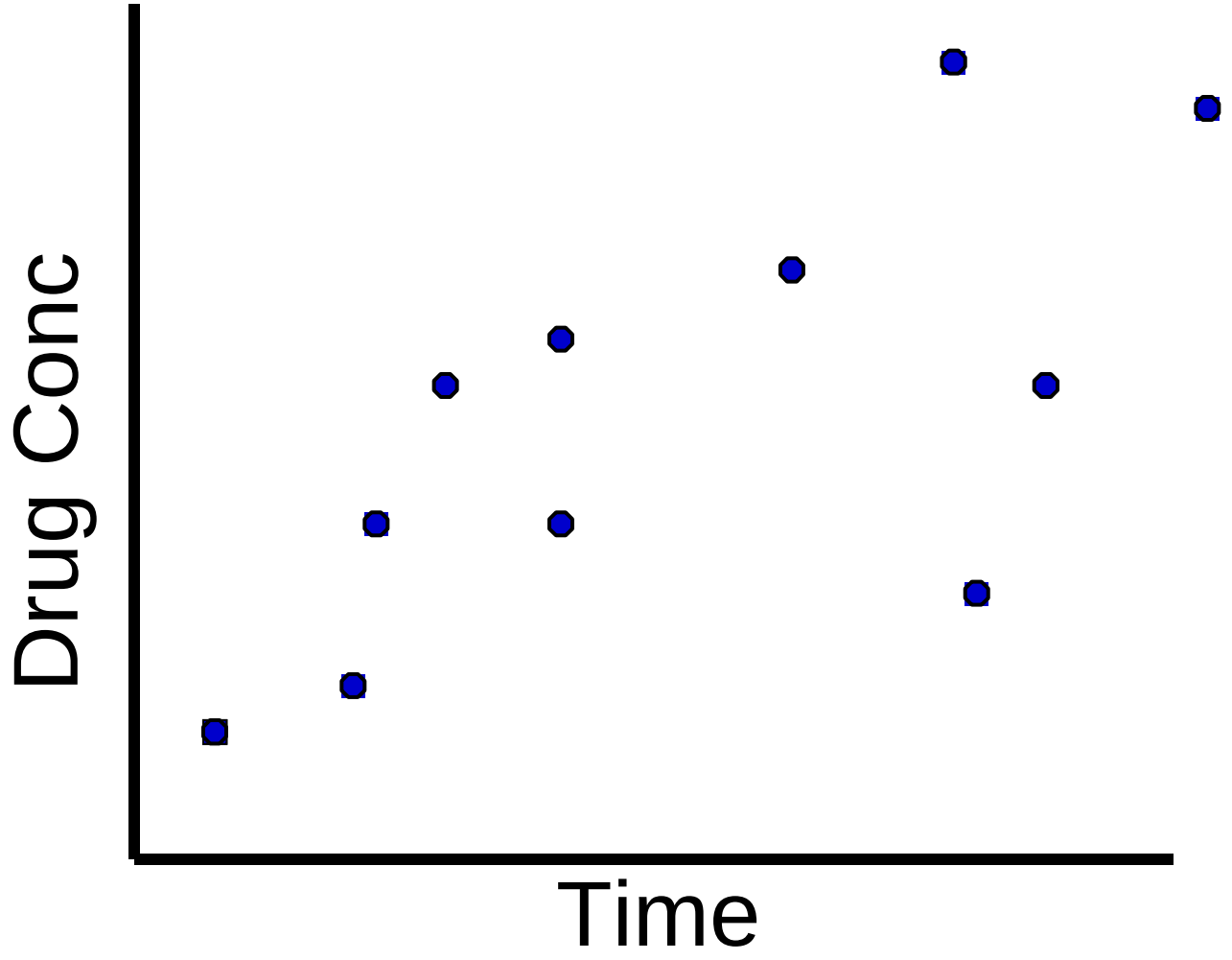
Advantages

- Sparse Sampling Strategy (2-3 concentrations/subject)
  - –Routine Sampling in Phase II/III Studies
  - –Special Populations (Pediatrics, Elderly)
- Large Number of Patients
  - –Fewer restrictions on inclusion/exclusion criteria
- Unbalanced Design
  - –Different number of samples/subject
- Target Patient Population
  - –Representative of the Population to be Treated

Disadvantages

- Quality Control of Data
  - Dose and Sample Times/Sample Handling/ Inexperienced Clinical Staff
- Timing of Analytical Results/Data Analyses
- Complex Methodology
  - Optimal Study Design (Simulations)
  - Data Analysis
- Resource Allocation
- Unclear Cost/Benefit Ratio

Models are critical in sparse sampling situations:



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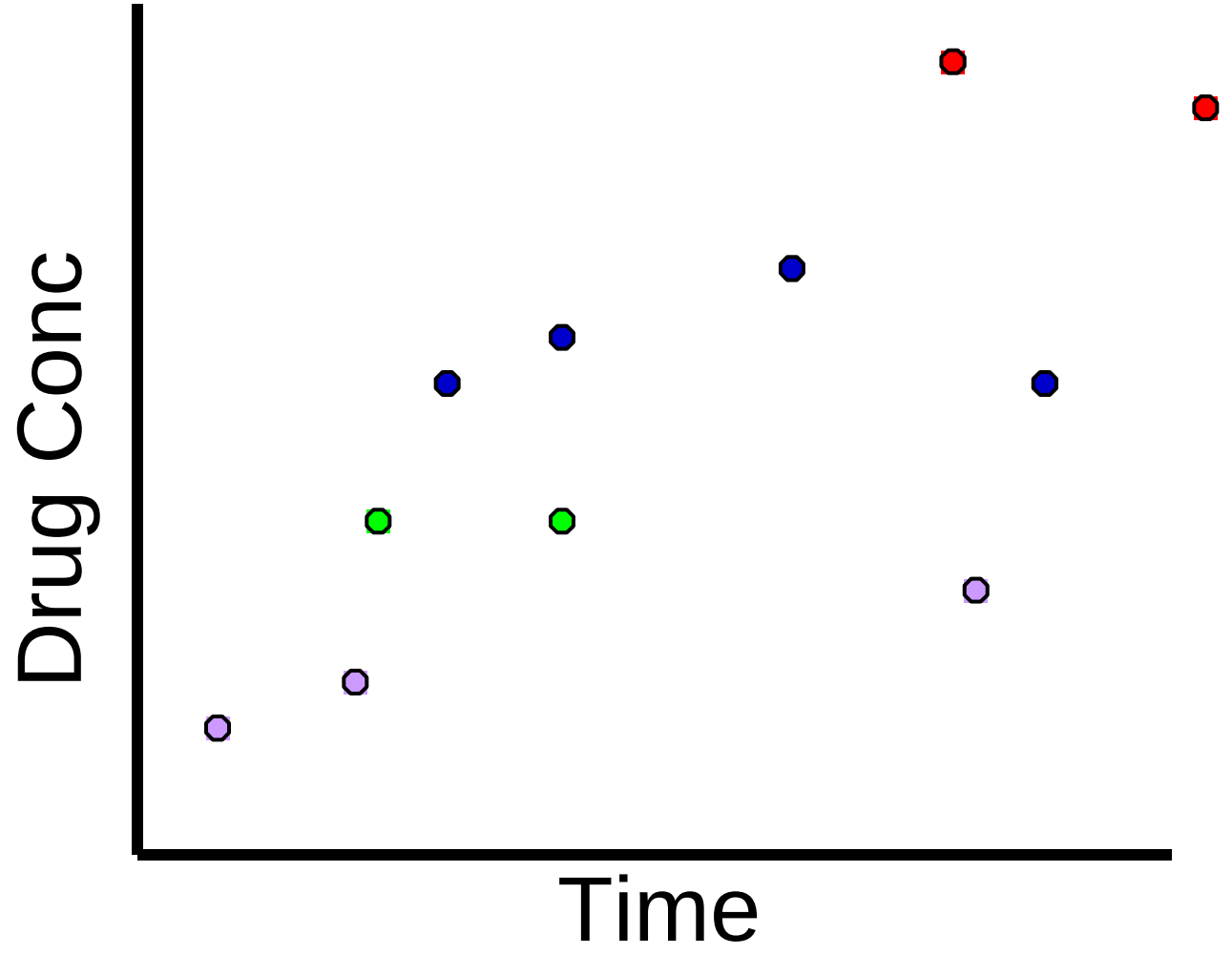

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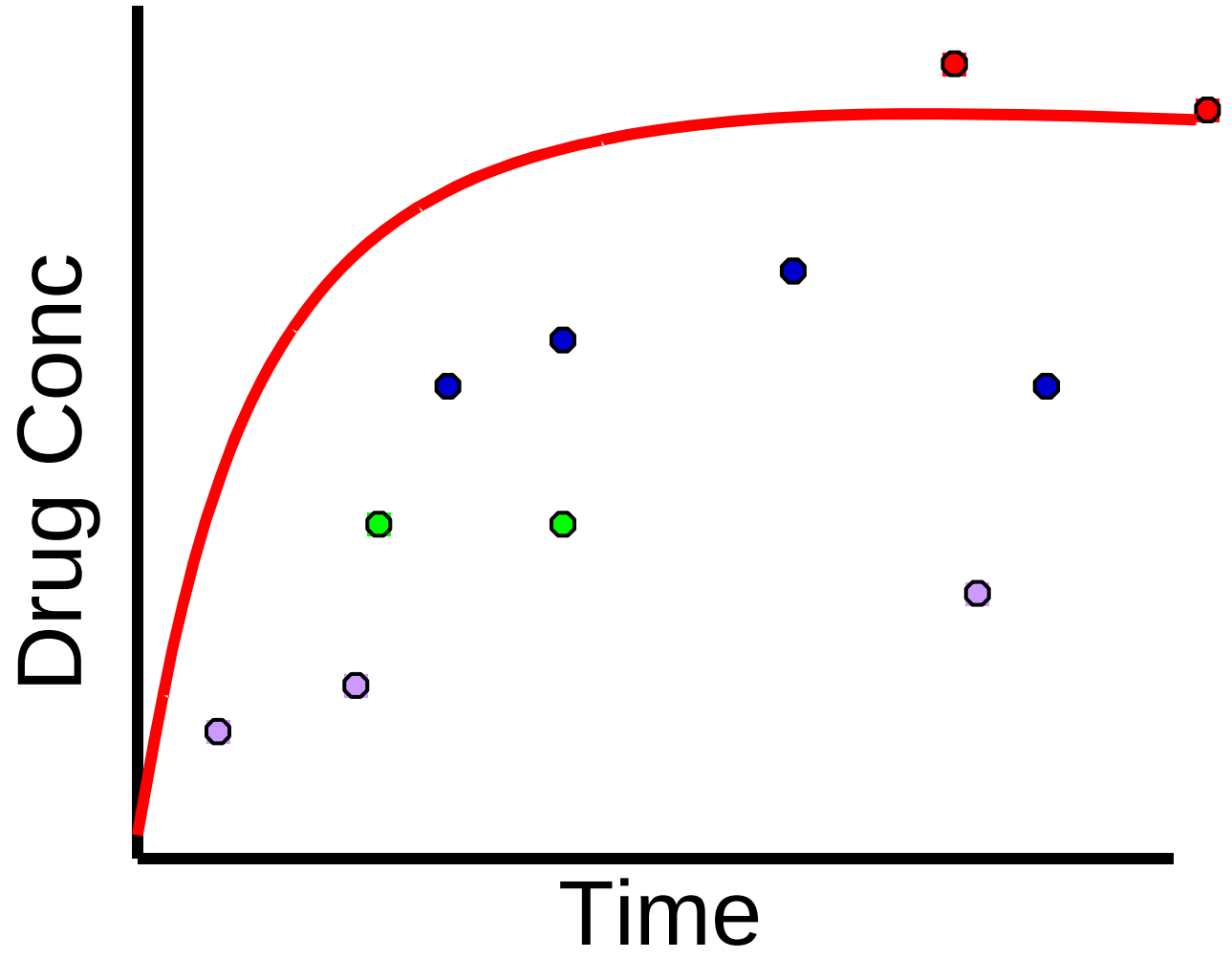

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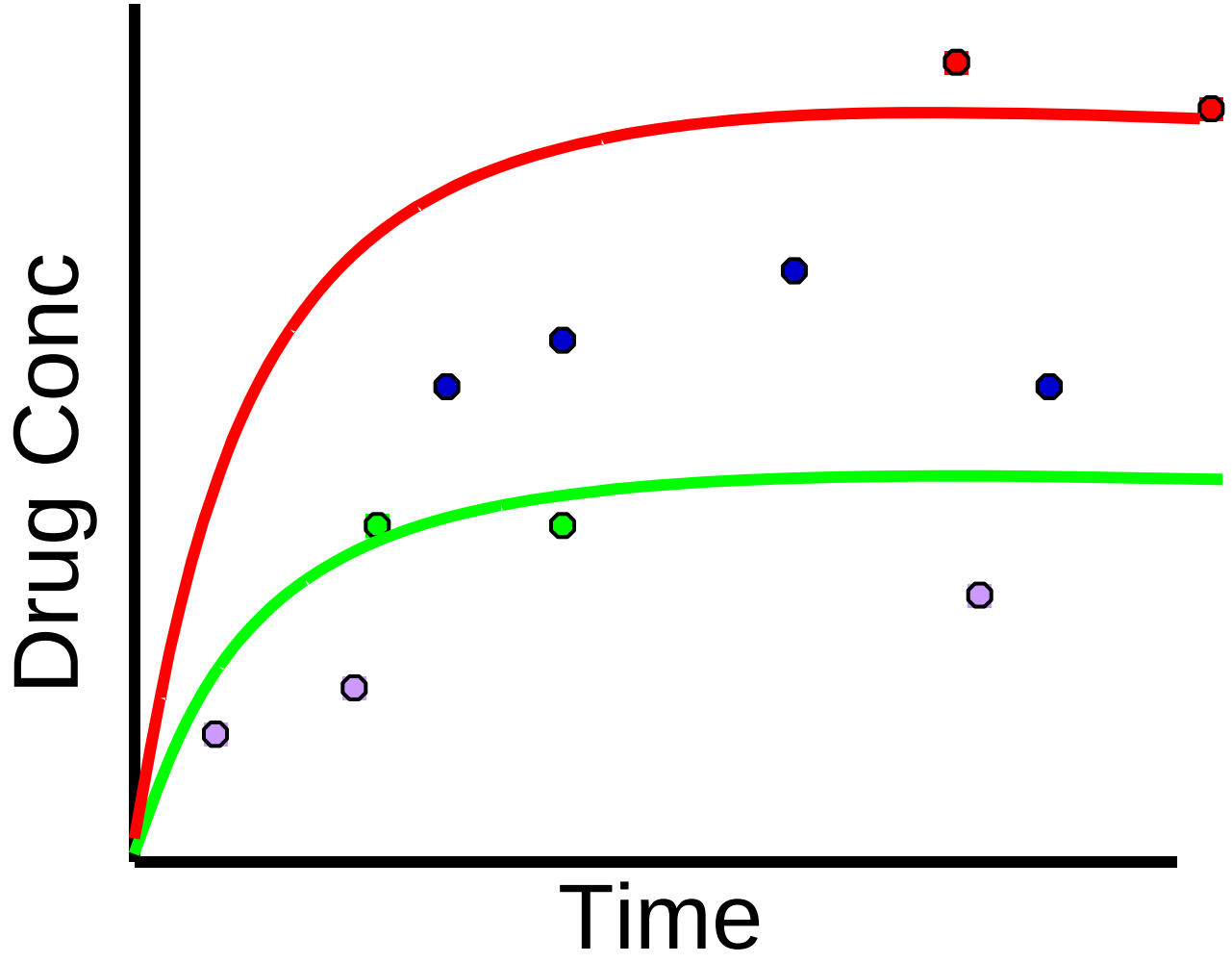

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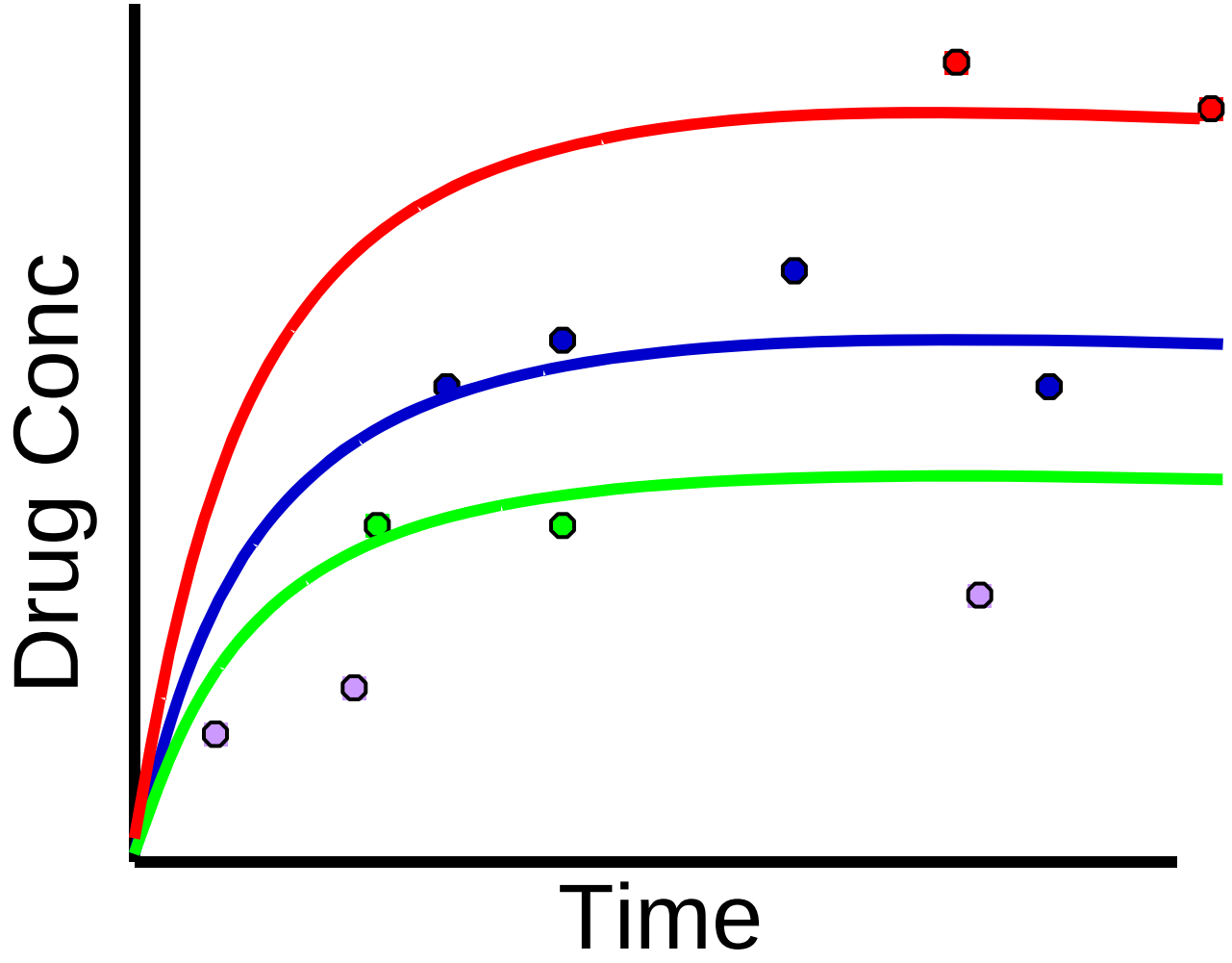

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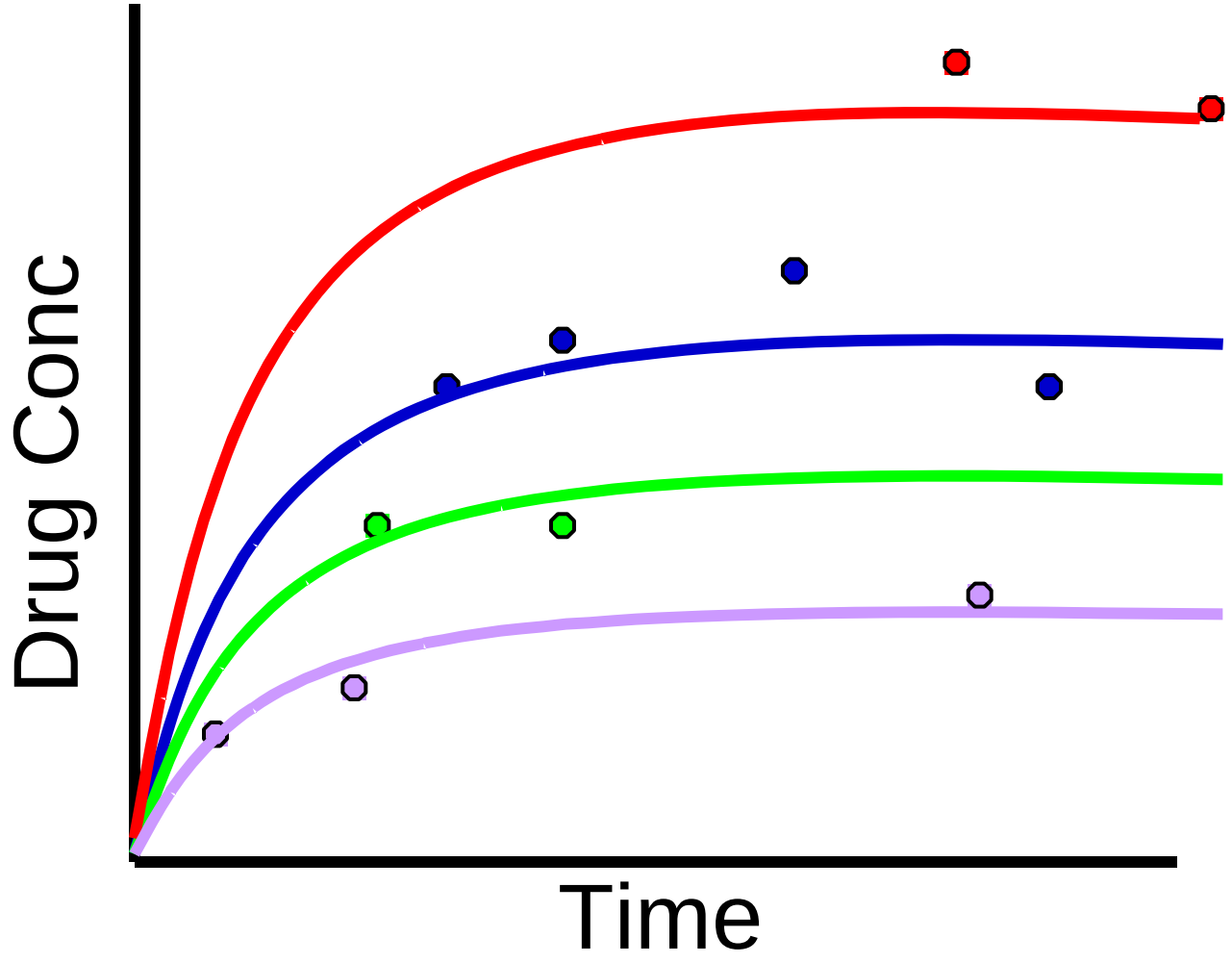
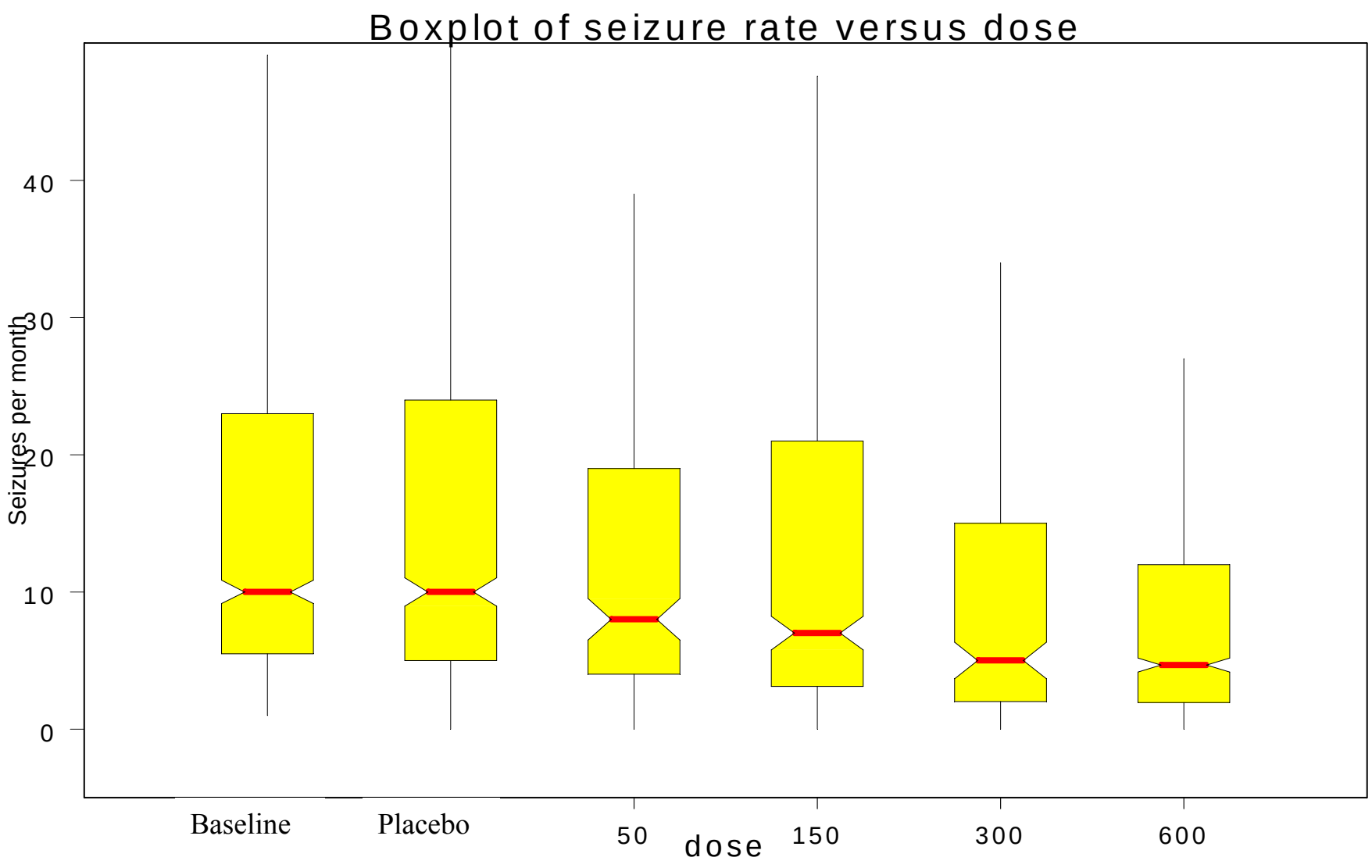


Study Objectives

- To evaluate the efficacy of drug treatment or placebo as add on treatment in patients with partial seizures.

Data Structure

Study	N	Doses Explored
1	308	0, 600 mg/day (bid & tid)
2	287	0, 150, 600 mg/day (tid)
3	447	0,50,150,300,600 mg/day (bid)
Total	1092	


Boxplot of seizure rate versus dose
Seizures per month
0
10
20
30
40
Baseline
Placebo
50
150
300
600
dose

Count Model

$$P(Y_i = x) = e^{-\lambda} \frac{\lambda^x}{x!}$$

λ represents the expected number of events per unit time

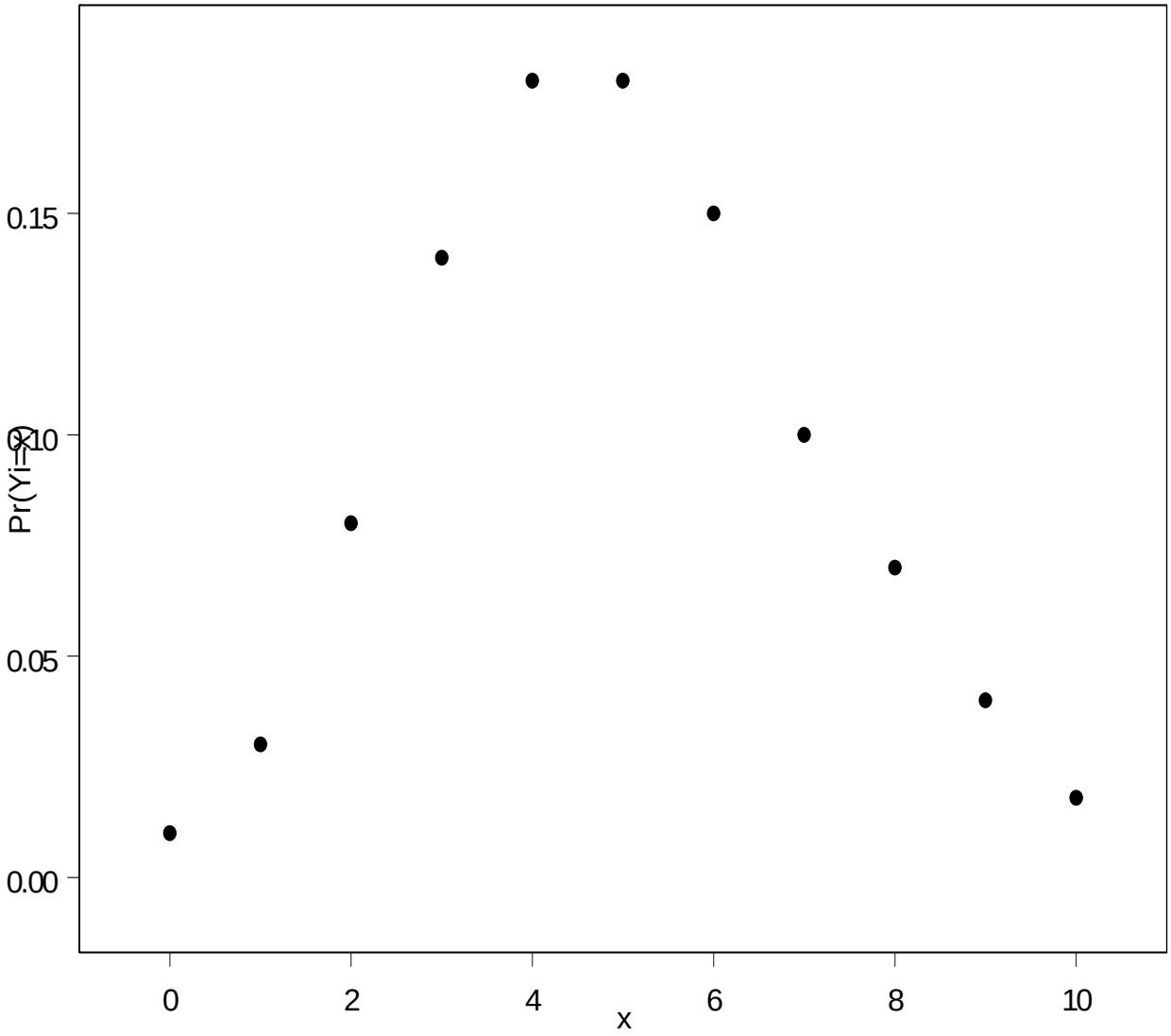
$$E(Yij)=\lambda_i t_{ij}$$

The natural estimator of λ is the overall observed rate for the group.

$$\lambda = \frac{Total\ counts}{Total\ time}$$

Suppose there are typically 5 occurrences per month in a group of patients:- λ=5

$$P(Y_i = x) = e^{-\lambda}\frac{\lambda^x}{x!}$$



X=	Pr(Y=x)
0	0.007
1	0.034
2	0.084
3	0.140
4	0.175
5	0.180
6	0.150
7	0.104
8	0.065
9	0.036
10	0.018

$$P(Y_i = x) = e^{-\lambda} \frac{\lambda^x}{x!}$$

The mean number of seizure episodes per month (λ) was modeled using NONMEM as a function of drug dose, placebo, baseline and subject specific random effects.

$$\lambda = Baseline + placebo + drug + \eta$$

Baseline = estimated number of seizures reported during baseline period

Placebo = function describing placebo response

Drug = function describing the drug effect

η = random effect

Initial Model

$$\lambda = BASE \cdot \left(1 - \frac{E_{\max} \cdot D}{ED_{50} + D} - PLAC\right) \cdot e^{\eta_1}$$

$$\lambda = 10.8 \cdot \left(1 - \frac{0.38 \cdot D}{48.7 + D} - 0.1\right) \cdot e^{\eta_1}$$

BASE= 10.8 (9.9,11.7)

ED_{50} = 48.7 (0,129.1)

E_{max} = 0.38 (0.15,0.61)

PLAC= -0.1(-0.22,0.02)

ω_1 = 1.1 (1.0,1.18)

Sub-population analysis

- Some patients are refractory to any particular drug at any dose.
- Interest is in dose-response in patients that respond
- Useful in adjusting dose in patients who would benefit from treatment
- Investigate the possibility of at least two sub-populations.

Mixture Model

A model that implicitly assumes that some fraction p of the population has one set of typical values of response, and that the remaining fraction 1-p has another set of typical values

Population A (p)

$$\lambda_1 = Baseline_1 + placebo_1 + drug_1 + \eta_1$$

Population B (1-p)

$$\lambda_2 = Baseline_2 + placebo_2 + drug_2 + \eta_2$$

Final Model

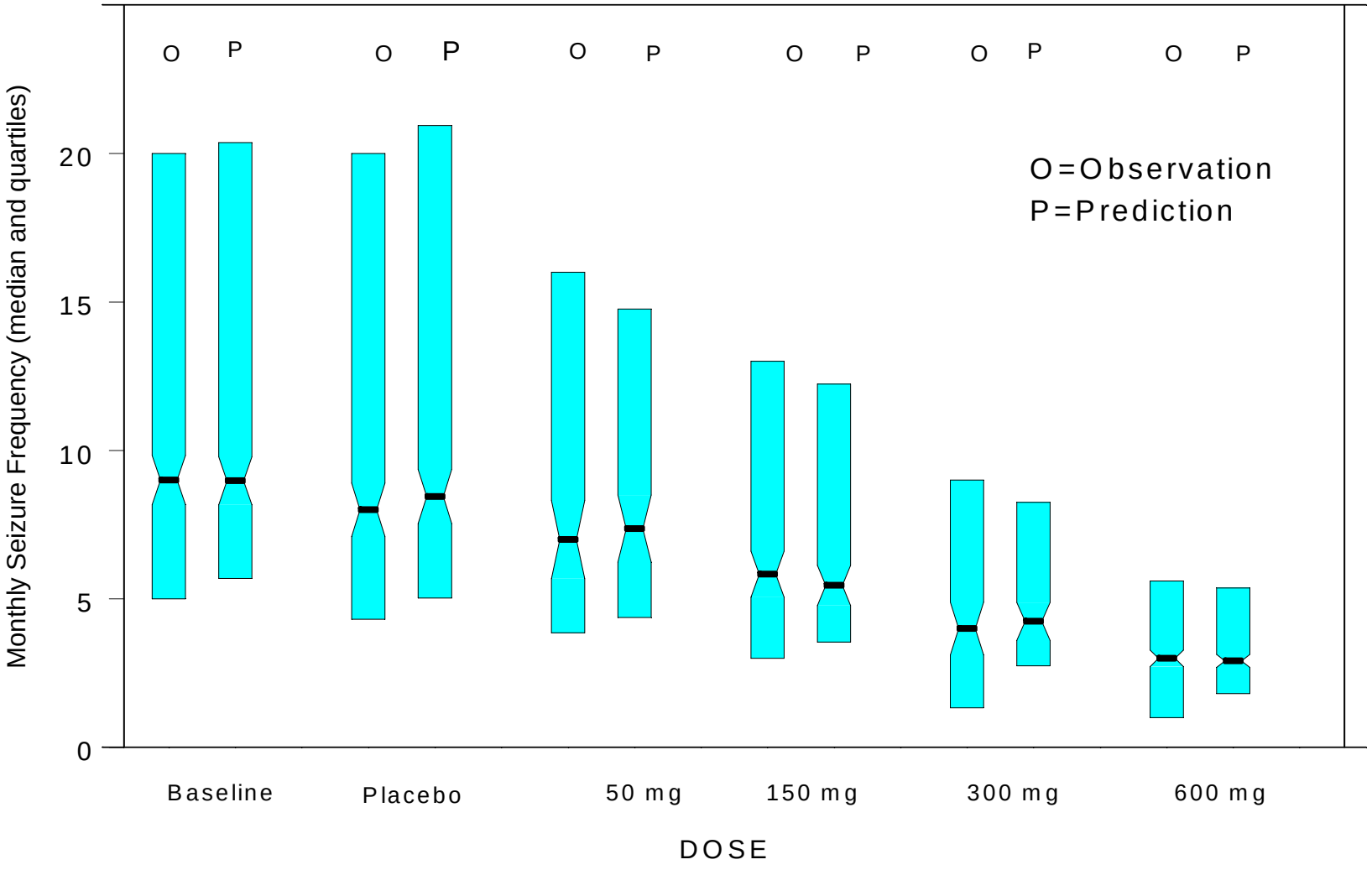
$$Population\ A = 75\%$$

$$\lambda = 11.1 \cdot \left(1 - \frac{1 \cdot Dose}{186 + Dose} \cdot D_1 - 0.11 \cdot D_0\right) \cdot e^{\eta_1}$$

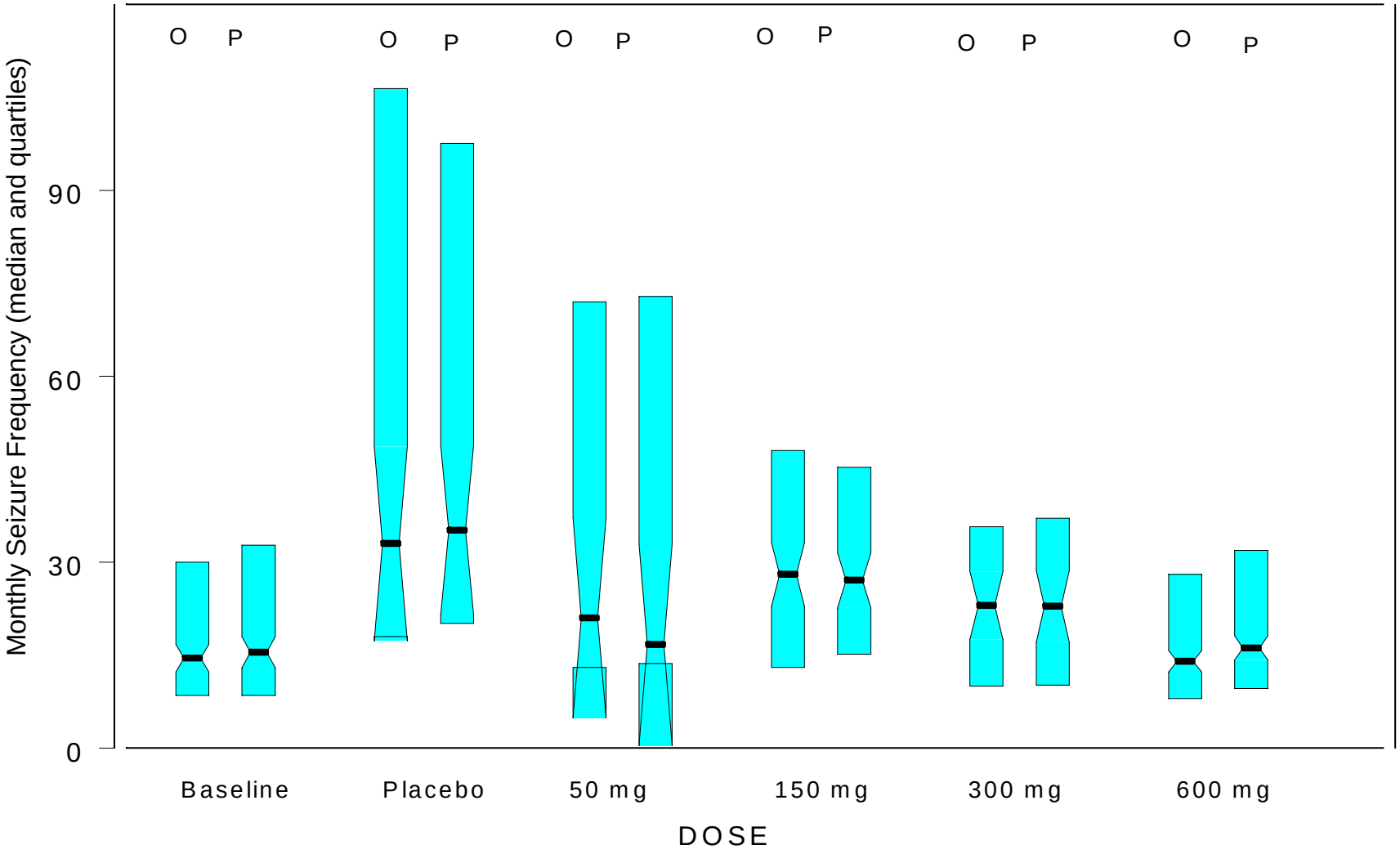
$$Population\ B = 25\%$$

$$\lambda = 15.1 \cdot \left(1 + 0.26 \cdot D_1 + 1.44 \cdot D_0\right) \cdot e^{\eta_2}$$

Patients demonstrating dose-response (75%)



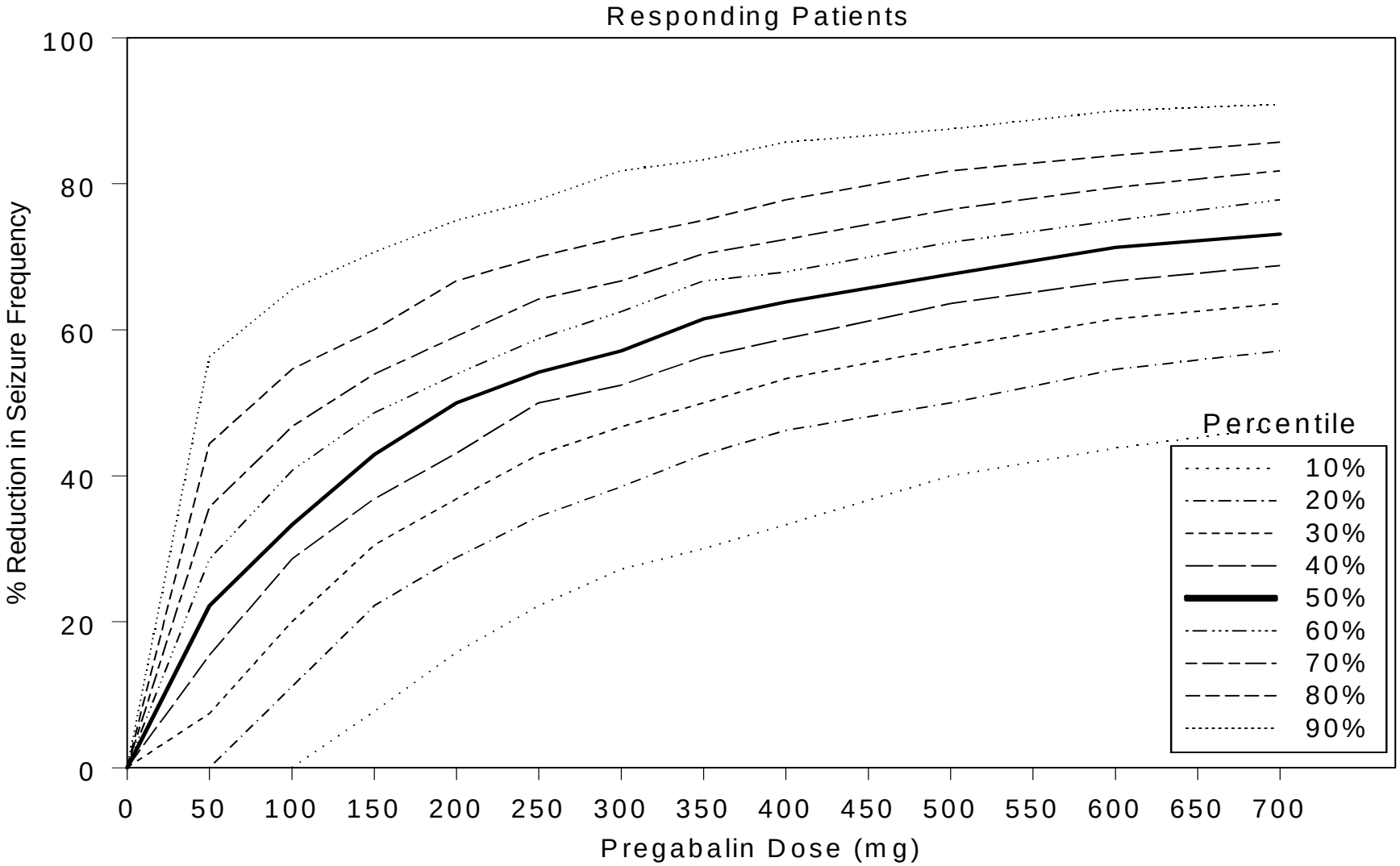
Patients not demonstrating dose-response (25%)



Expected percent reduction in seizure frequency

- Monte Carlo simulation using parameters and variance for Subgroup A
- 8852 individuals (51% female)
- % reduction from baseline seizure frequency calculated
- Percentiles calculated for % reduction in seizure frequency at each dose

Percent Reduction in Seizure Frequency



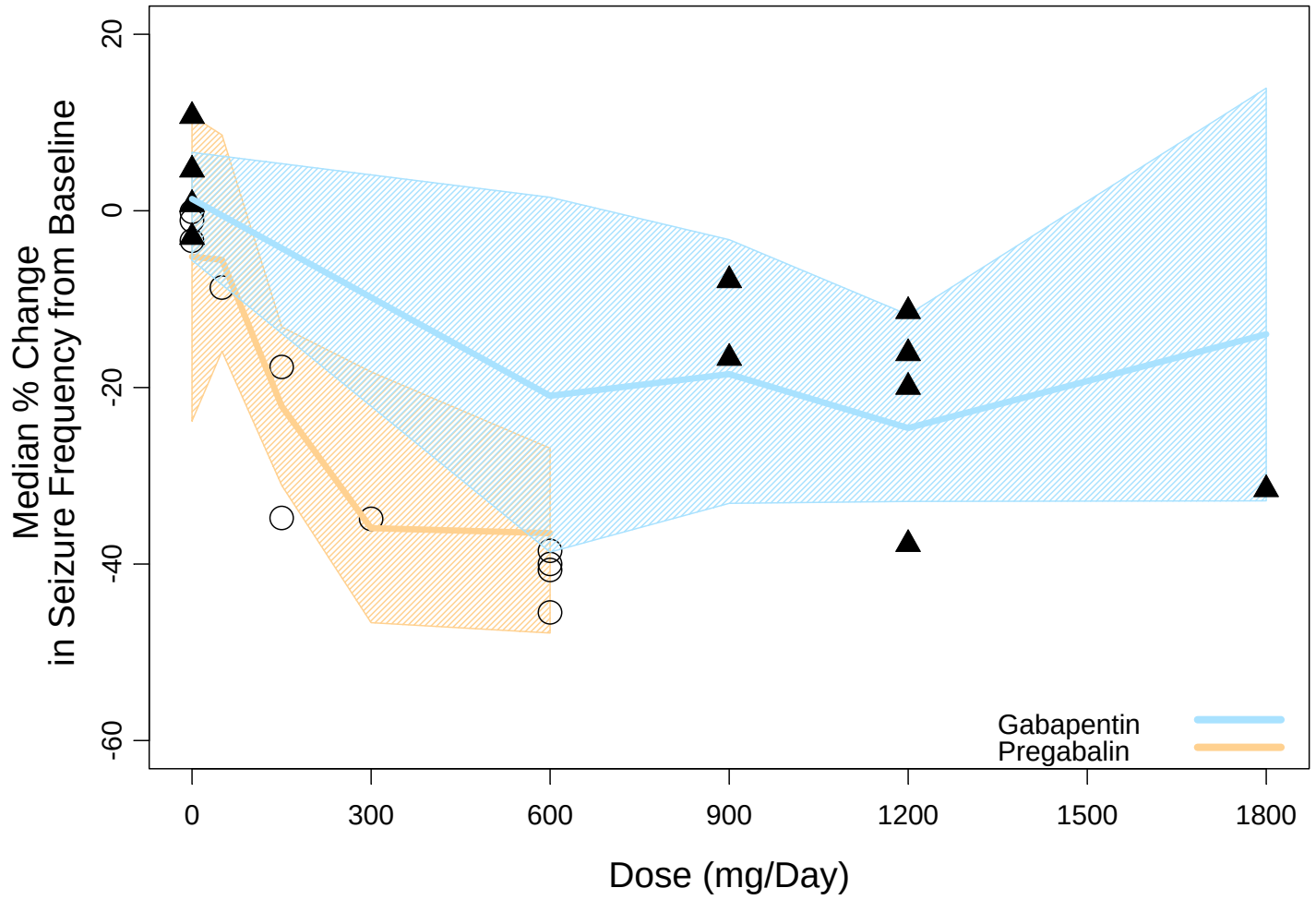
Results

Estimated population parameters for the exposure-response relationship of seizure frequency to pregabalin or gabapentin dose.		
Parameter	Parameter Estimates (95% CI)	
	Gabapentin	Pregabalin
$Base_A$ (seizures/month)	14.0 (12.4,15.6)	11.1 (10.2,12.0)
$Base_B$ (seizures/month)	16.8 (8.8,24.8)	15.1 (12.3,17.9)
$Emax_A$ (maximal fractional change)	-0.25 (-0.31,-0.18)	-1.0
$Emax_B$ (maximal fractional change)	2.34 (0.20,4.48)	0.26(-0.15,0.66)
$Placebo_A$ (maximal fractional change)	-0.15 (-0.29,-0.009)	-0.11 (-0.18,-0.03)
$Placebo_B$ (maximal fractional change)	4.34 (-0.80,9.47)	1.44 (0.66,2.22)
ED_{50} (mg)	463.0 (161.3,764.7)	186.0 (91.4,280.6)
$Proportion_A$	0.95 (0.93,0.98)	0.75(0.61,0.88)

Conclusions

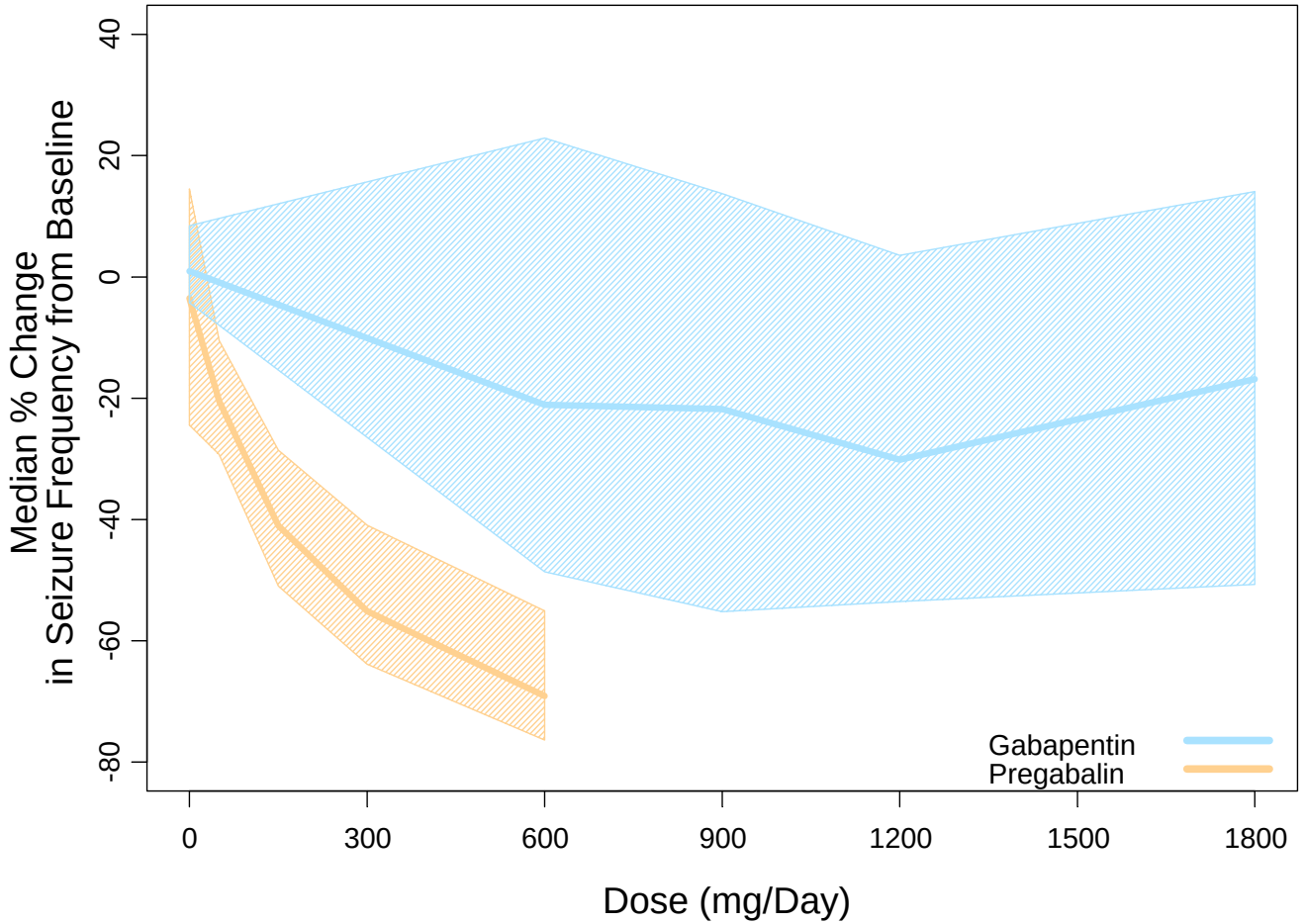
- A comparison of the dose-response relationship for gabapentin and pregabalin reveals that pregabalin was 2.5 times more potent, as measured by the dose that reduced seizure frequency by 50% (ED50).
- Pregabalin was more effective than gabapentin based on the magnitude of the reduction in seizure frequency (Emax)
- Three hundred clinical trials for each drug were simulated conditioned on the original study designs. Each simulated trial was analyzed to estimate % median change in seizure frequency. The observed and model-predicted treatment effects of median reduction in seizure frequency for gabapentin and pregabalin are illustrated for all subjects and for responders. Data points represent median percentage change from baseline in seizure frequency for each treatment group (including placebo). The shaded area corresponds to predicted 10th and 90th percentiles for median change from baseline in seizure frequency.

Relationship Between %Change in Seizure Frequency (Relative to Baseline) and Daily Dosage of Gabapentin and Pregabalin



Relationship Between %Change in Seizure Frequency (Relative to Baseline) and Daily Dosage of Gabapentin and Pregabalin in Responders to Treatment

Dose-response model in epilepsy using pooled analysis of 4 gabapentin studies + 3 pregabalin studies



Clinical Trial Simulation

- Used to assess how different design and drug factors may affect trial performance.
- May be viewed as an extension of statistical design evaluation.

Planning Phase 2 POC for Alzheimer's Disease Drug

Because the mechanism of action of CI-1017 was untested clinically, the principle objective of the clinical study was to ascertain whether CI-1017 improved cognitive performance at least as fast and as well as tacrine.

This would be considered proof of concept (POC).

Typical Effectiveness Trials (AD)

- Parallel group design
- Two to four treatment groups + placebo
- Powered to detect 3 point improvement in ADAS-Cog
- Minimum 12 weeks of treatment

  - Require about 80 subjects per dose group to have 90% power (2 sided 50% sig. Level)

Simulation Model

$$ADAS-Cog = BASELINE + DISEASE\ PROGRESSION + PLACEBO + DRUG + \varepsilon$$

Where:

$BASELINE = \theta_{base}$

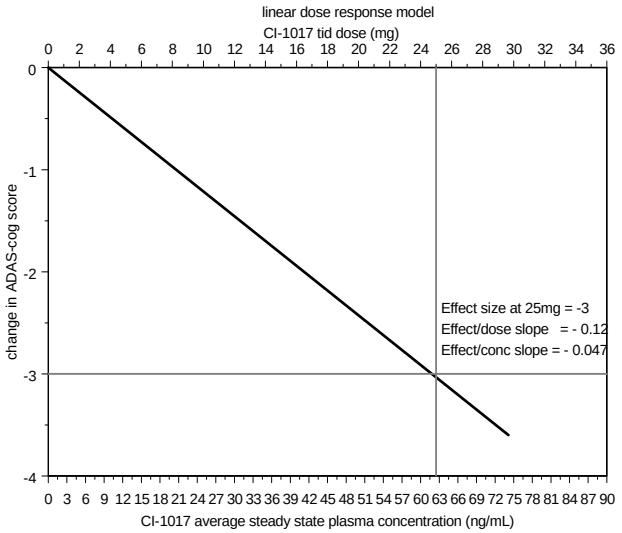
$DISEASE\ PROGRESSION = \theta_{rate} \cdot time$

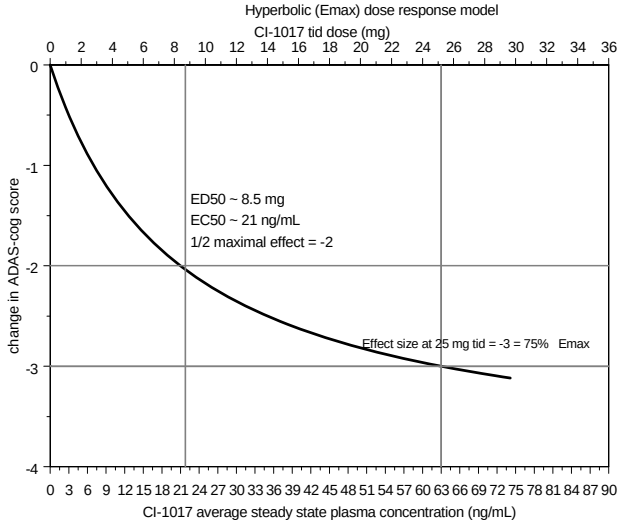
$PLACEBO = \theta_{Scale} \cdot \left(e^{\theta_{off} \cdot t} - e^{\theta_{on} \cdot t} \right)$

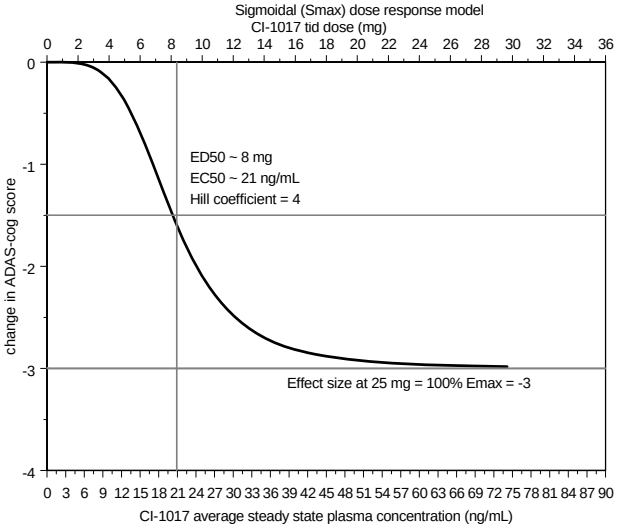
$DRUG = 4$ theoretical dose – response curves

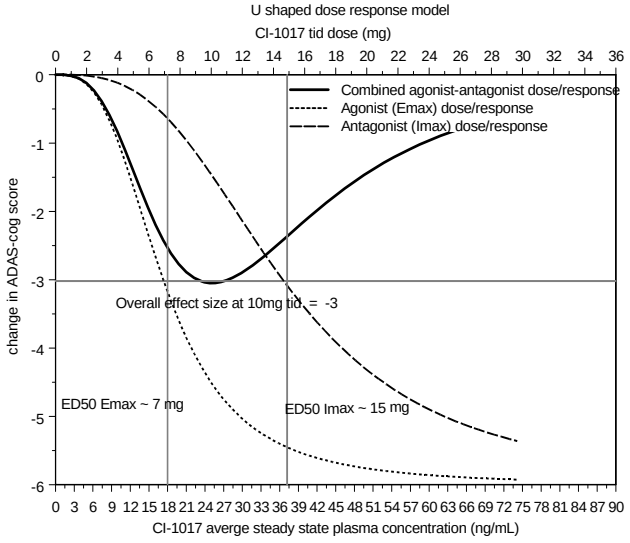
Random IIV = 30%

Drug effect models considered in simulations study. Parameters characterizing the model are displayed in the individual panels (Lockwood et al.)









TRIAL DESIGN

Design number	Design description	Number of sequences	Subjects per sequence	Number of treatments periods	Period length (weeks)	Measurements per period
1	6X6 Latin Square	6	10	6	2	1
2	6X3 Incomplete block	6	10	3	4	2
3	Parallel group	6	10	1	12	6
4	6X4 Incomplete block	6	10	4	3	1
5	6X3 Incomplete block with 2 parallel groups	8	8	Seq 1-6: 3 Seq 7-8: 1	Seq 1-6: 4 Seq 7-8:12	2 6
6	4X4 Latin Square	4	15	4	3	1
7	4X4 Latin Square with 2 parallel groups	6	10	Seq 1-4: 4 Seq 5-6: 1	3 12	1 6
8	4X4 Latin Square	4	15	4	4	2

DATA EVALUATION

- DOES THE DRUG WORK?
  - AOV to test null hypothesis of no drug effect
  - Rejection of null hypothesis judged correct
  - Dose trend test
- IS THE SHAPE MONOTONIC OR U-SHAPED?
  - Similar to the above two steps
  - Non-positive trial pattern classified as flat
  - Inference between monotonic and u-shaped based on highest dose having best mean outcome.

SIMULATION

- 100 Trial simulations
- Pharsight trial simulator (TS2)
- Data from each trial analyzed
- Conclusions scored

DRUG EFFECT

Percent of 100 trials (power) that detected a drug effect for design number 6, 7 and 8.

Design number	8	7	6
Dose response shape			
Linear	84	41	51
Emax	88	58	67
Smax	96	75	85
U-shape	57	40	49
AVERAGE	*81*	*54*	*63*

Design number 6: 4X4 Latin Square, 3 weeks per treatment.
Design number 7: 4X4 Latin Square with 2 parallel groups,
Design number 8, 4X4 Latin Square, 4 weeks per treatment

SHAPE

Percent of 100 trials (power) that correctly identified dose-response shape for design number 6, 7 and 8

Design number	8	7	6
Dose response shape			
Linear	96	69	72
Emax	84	62	74
Smax	96	83	89
U-shape	45	34	39
AVERAGE	80	62	69

Simulation Conclusions
Design

- 4x4 LS with 4-week periods using bi-weekly measurements
  - Was best among alternatives considered for detecting activity and identifying DR shape
  - Met minimum design criteria (80% average power)

Results

- 4x4 LS design was accepted, conducted, and analyzed more-or-less as recommended

- Unfortunately, drug didn’t work
  - But we were able to find this out more quickly and with less resources than with conventional design

Gabapentin – Neuropathic Pain NDA

- Two adequate and well controlled clinical trials submitted.
- Indication – post-herpetic neuralgia
- Trials used different dose levels
  - 1800 mg/day and 2400 mg/day
  - 3600 mg/day
- The clinical trial data was not replicated for each of the dose levels sought in the drug application

FDAMA 1997

FDA review staff decided to explore whether PK/PD analyses could provide the confirmatory evidence of efficacy.

"—based on relevant science, that data from one adequate and well controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness."

Gabapentin Study Designs for PHN

Overview of PHN Controlled Studies: Double-Blind Randomized/Target Dose and ITT Population

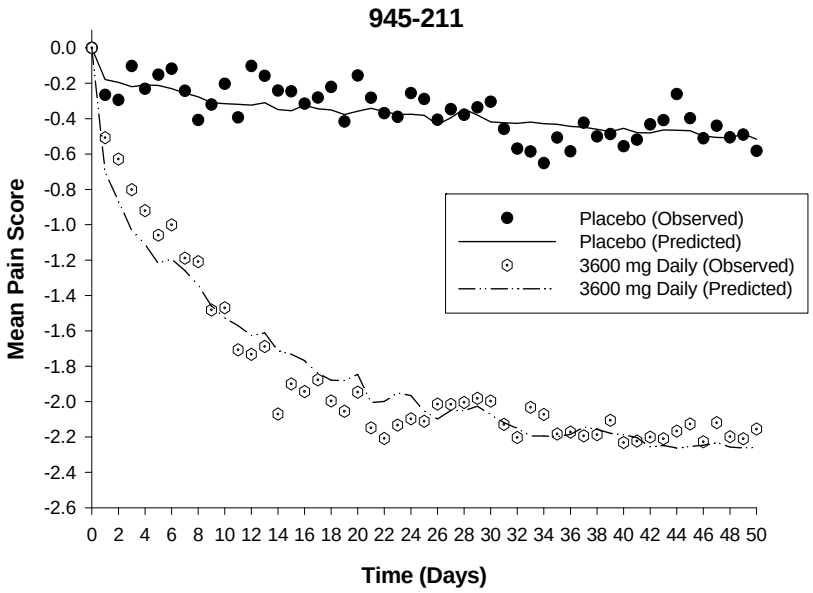
Duration of Double-Blind Phase			Number of Patients							
				Final Gabapentin Dose, mg/day						
Titration	Fixed Dose	Overall Duration	Placebo	600	1200	1800	2400	3600	Any Gabapentin	All Patients
4 Weeks	4 Weeks	8 Weeks	116	--	--	--	--	113	113	229
3 Weeks	4 Weeks	7 Weeks	111	--	--	115	108	--	223	334
4 Weeks	4 Weeks	8 Weeks	152	--	--	--	153	--	153	305
			379	0	0	115	261	113	489	868

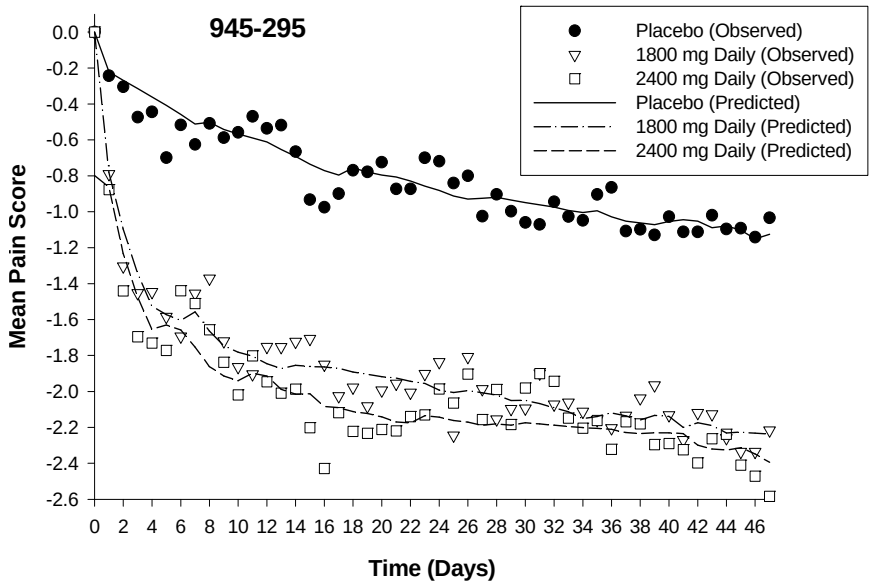
included in study design

All randomized patients who received at least one dose of study medication.

- Used all daily pain scores (27,678 observations)
- Exposure-response analysis included titration data for within-subject dose response

Gabapentin Response in PHN





Time Dependent Placebo Response, Emax Drug Response and Saturable Absorption,

Results

- Summary statistics showed pain relief for both studies at different doses concur.
- M & S showed pain scores for both studies can be predicted with confidence from the comparative pivotal study (cross confirming).

Conclusion

- The use of PK/PD modeling and simulation confirmed efficacy across the three studied doses, obviating the need for additional clinical trials.
- Gabapentin was subsequently approved by FDA for post-herpetic neuralgia
- The package insert states “pharmacokinetic/pharmacodynamic modeling provided confirmatory evidence of efficacy across all doses”