Experiences in Optimal Design for Population PK/PD Models

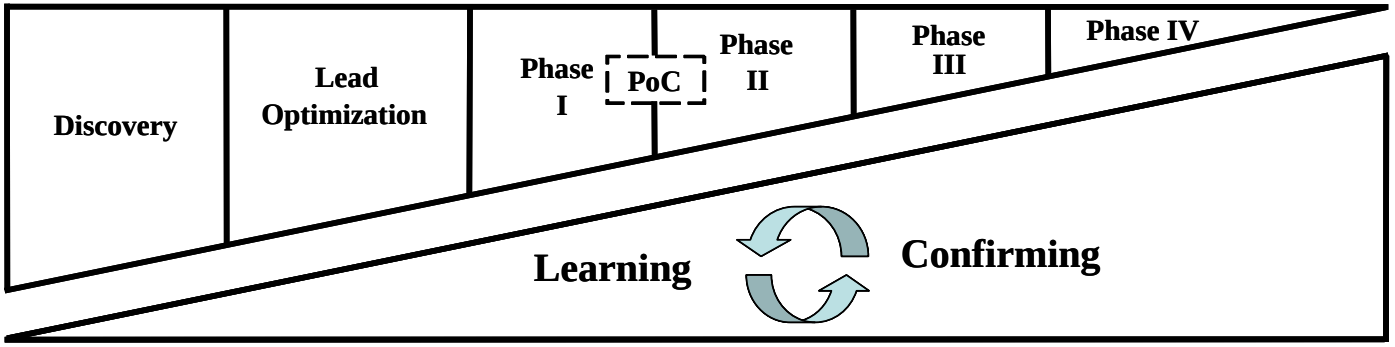
Tim Waterhouse

Pharmacometrics

Eli Lilly and Company

Population PK/PD models in drug development

- Used at all stages of drug development
  - Preclinical (evaluate biomarkers, predict human PK/PD, …)
  - Phase I (initial PK and PD models, predict response in target population, …)
  - Phase II (exposure-response relationships, assess impact of covariates, …)
  - Phase III (validate PK/PD model, assess need for dose adjustment in special populations, …)



Chien et al. 2005. Pharmacokinetics/Pharmacodynamics and the stages of drug development: role of modeling and simulation. AAPS Journal 7(3):544-559.

Population PK/PD model notation

- Typical model structure for PK or PD model:

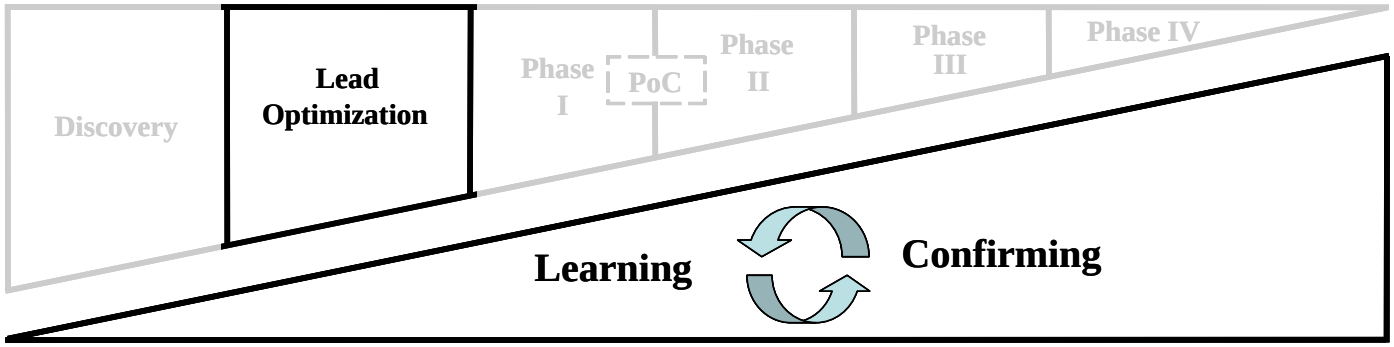
$$y_{ij} = f\left(\boldsymbol{\theta}_i, t_{ij}\right) + \varepsilon_{ij}$$

$$\boldsymbol{\theta}_i = \boldsymbol{\theta} e^{\boldsymbol{\eta}_i} \quad \text{or} \quad \boldsymbol{\theta}_i = \boldsymbol{\theta} + \boldsymbol{\eta}_i$$

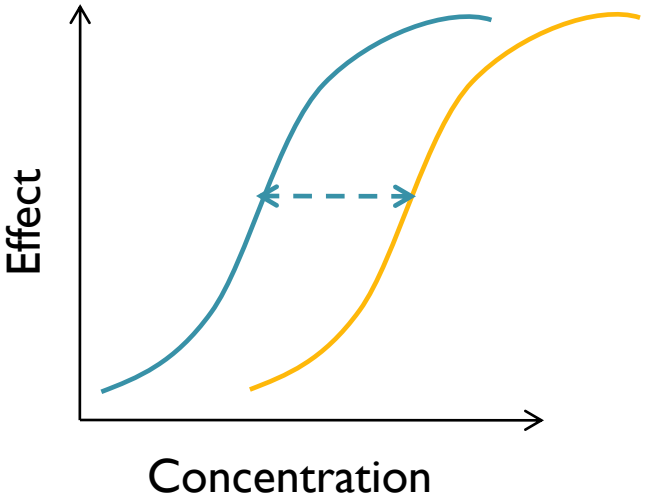
$$\boldsymbol{\eta}_i \sim N\left(0, \boldsymbol{\Omega}\right)$$

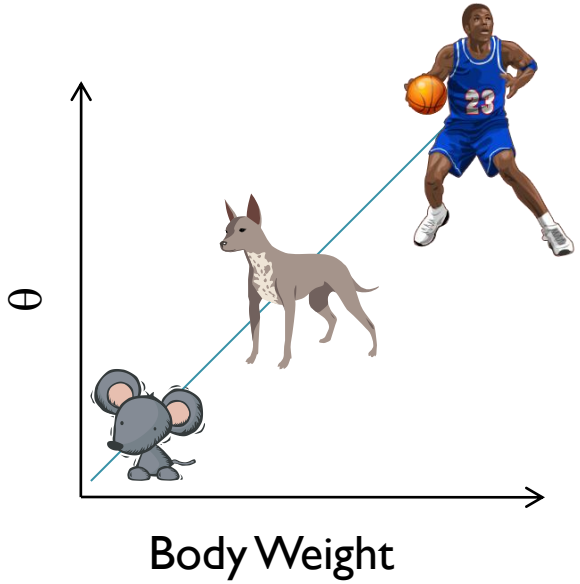
$$\varepsilon_{ij} \sim N\left(0, \sigma^2\right)$$

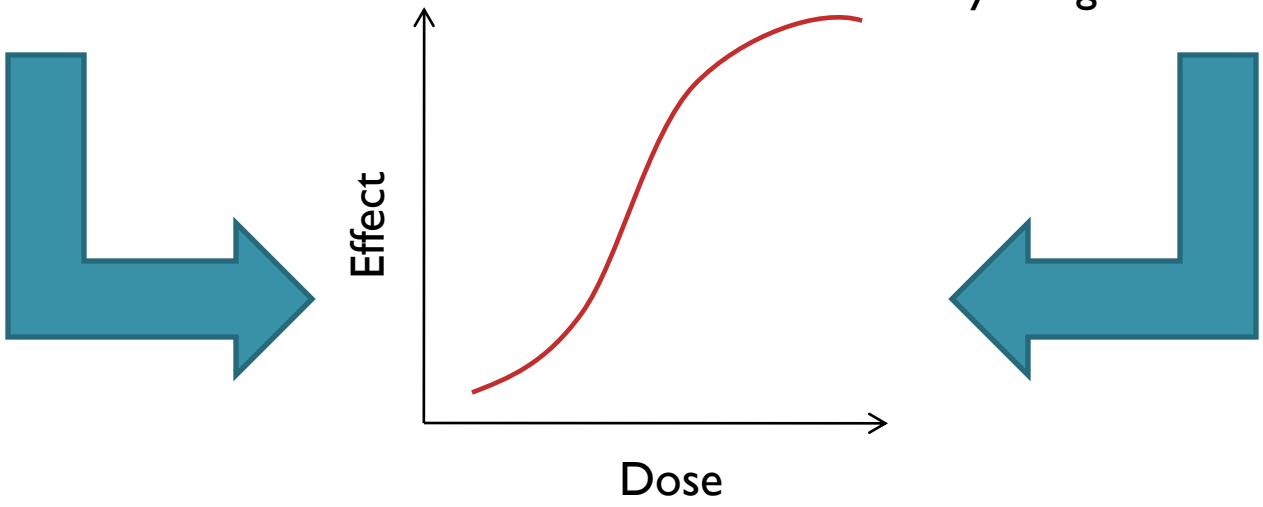
PRECLINICAL DESIGN



PK/PD in preclinical studies







Preclinical optimal design

- Testing Drug X for efficacy mice
- 14 animals per dose group, dosed for 4 months:
  - 2001-2014: 30.0 mg/kg. QW, sc
  - 3001-3014: 10.0 mg/kg. QW, sc
  - 4001-4014: 3.0 mg/kg. QW, sc
  - 5001-5014: 0.3 mg/kg. QW, sc
- PK samples by retro orbital bleed

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Feb	BW 14	15	16	17	18	19	20
Feb	21	22	23	24	25	26	27
March	28	1	2	3	4	5	6
March	BW 7	8	9	10	11	12	13
March	14	15	16	17	18	19	20
March	21	22	23	24	25	26	27
March	28	29	30	31	1	2	3
Apr	BW 4	5	6	7	8	9	10
Apr	11	12	13	14	15	16	17
Apr	18	19	20	21	22	23	24
Apr	25	26	27	28	29	30	1
May	BW 2	3	4	5	6	7	8
May	9	10	11	12	13	14	15
May	16	17	18	19	20	21	22
May	23	24	25	26	27	28	29
June	BW 30	31	1	2	3	4	5
June	6	7	8	9	10	11	12
June	13	14	15	16	17	18	19

retro orbital bleeding

Dosing

Urine

blood

BW

A. 2001-2014: 30.0 mg/kg. QW, sc

B. 3001-3014: 10.0 mg/kg. QW, sc

C. 4001-4014: 3.0 mg/kg. QW, sc

D. 5001-5014: 0.3 mg/kg. QW, sc

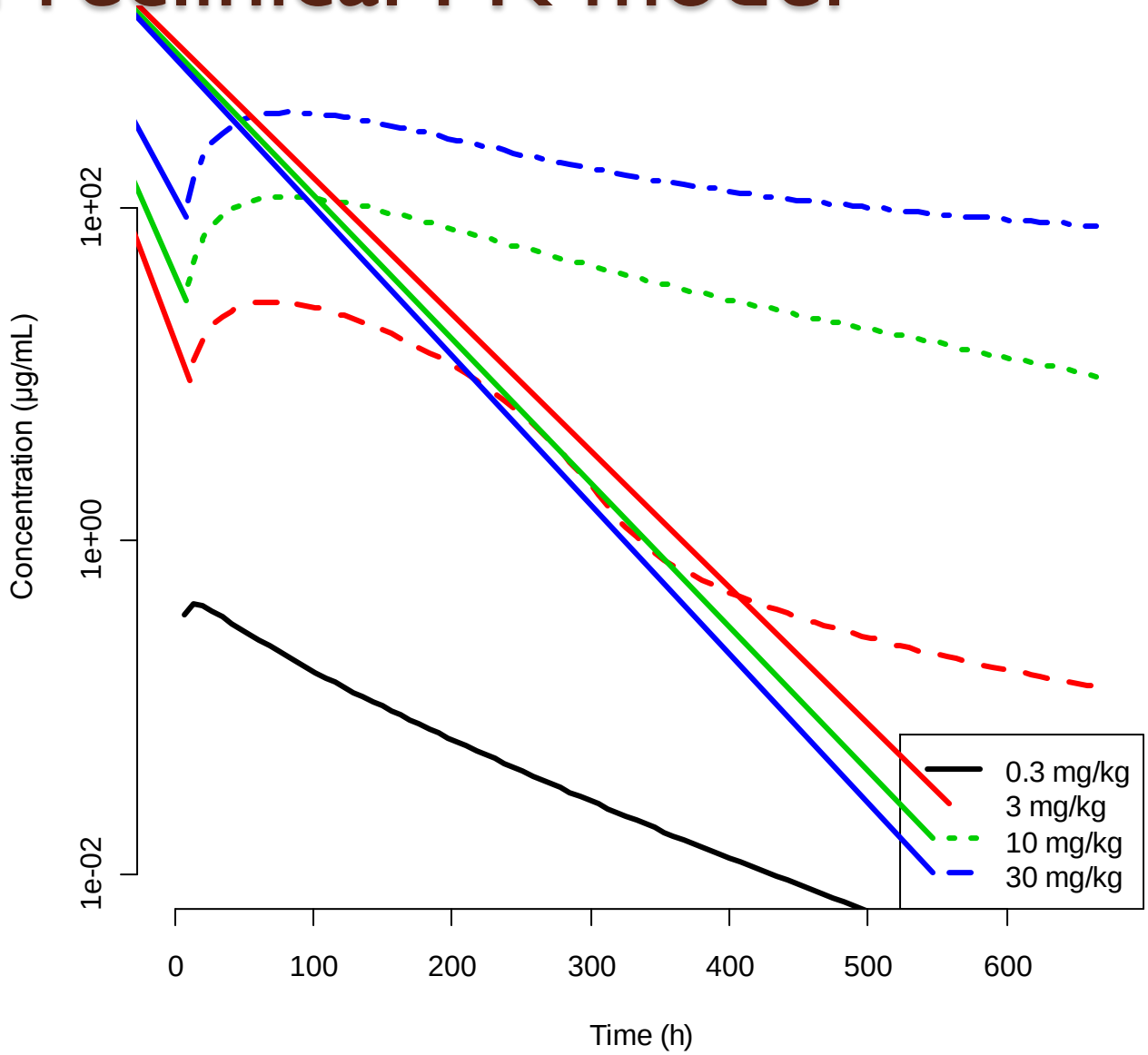
retro orbital bleeding	8-Mar	5-Apr	3-May	31-May	14-Jun
	2001-2	2003-4	2005-6	2007-8	terminal
	3001-2	3003-4	3005-6	3007-8	terminal
	4001-2	4003-4	4005-6	4007-8	terminal
	5001-2	5003-4	5005-6	5007-8	terminal

Preclinical PK model

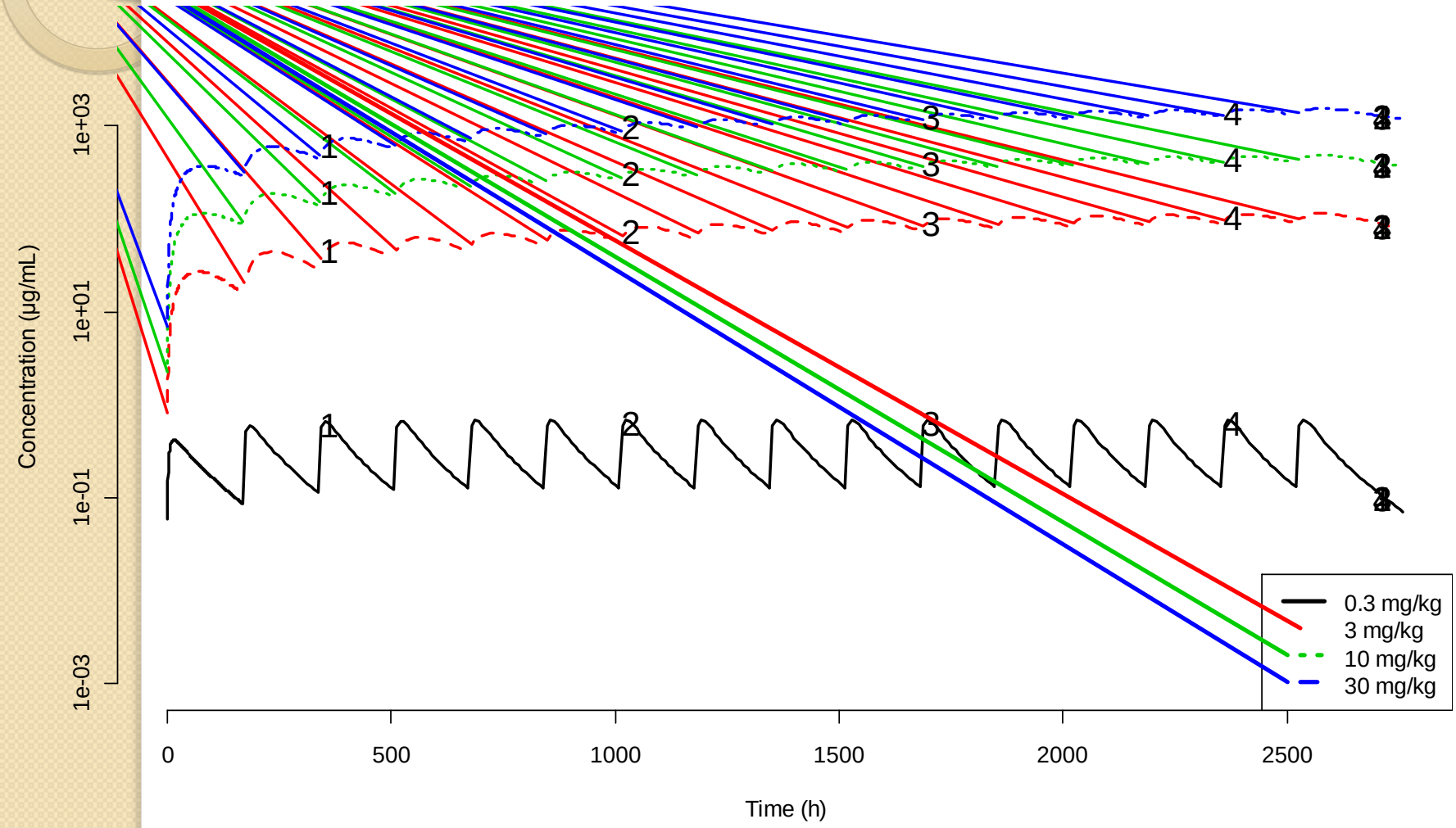
Parameter		Initial Estimate	Estimate	StdErr	%SEE
THETA #1	Ka_1/h	(0, 0.007)	0.00833	0.0000123	0.148
THETA #2	CL_mL/h/kg	(0, 0.19)	0.0973	0.000300	0.308
THETA #3	V_mL/kg	(0, 20)	18.9	0.0103	0.0545
THETA #4	VMAX_ug/h	(0,5.2)	5.24	0.00309	0.0590
THETA #5	KM_ug/mL	(0,0.6)	0.644	0.000597	0.0927
THETA #6	V2_mL	(0, 59)	115	0.474	0.412
THETA #7	Q_mL/h/kg	(0, 0.26)	0.260	0.000141	0.0542
OMEGA #1	ETA_CL	0.28	1.15	0.382	33.2
SIGMA #1	PROP	0.08	0.0569	0.0000616	0.108

```
$DES
   CP      = A(2)/S2
   DADT(1) = -Ka * A(1)
   DADT(2) = Ka * A(1) - (CL/V+K12)*A(2)-VMAX*CP/(KM+CP)+K21*A(3)
   DADT(3) = K12*A(2)-K21*A(3)
```

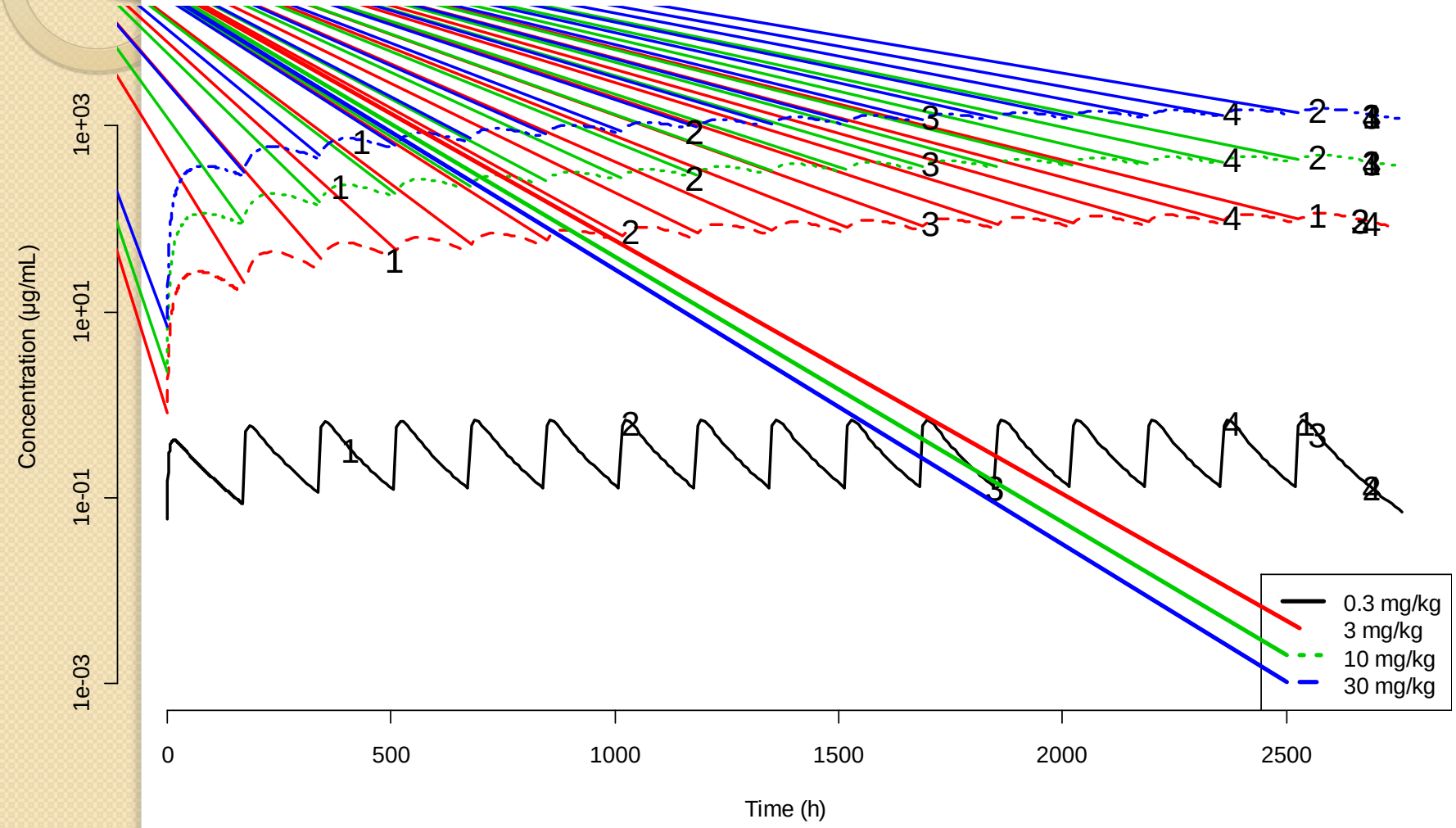
Preclinical PK model



Proposed PK sampling



Optimised PK sampling



WinPOPT output: optimised design

Parameters:	ka cl v vmax km v2 q
Fixed effect parameters:	0.00833 0.0973 18.9 5.24 0.644 115 0.26
Fixed fixed effects:	
Standard errors:	0.00054563 0.018244 2.0819 0.70897 0.13992 15.4268 0.023638
Standard errors(%):	6.5502 18.7498 11.0151 13.5299 21.726 13.4146 9.0917
Between subject variances:	0 1.15 0 0 0 0 0
BSV model:	1 1 1 1 1 1 1
Fixed random effects:	1 3 4 5 6 7
Standard errors:	0.26423
Standard errors(%):	22.9762
Residual standard deviations:	0.0569 0
Fixed residual effects:	2
Standard errors:	0.0056043
Standard errors(%):	9.8494
Prior Information Matrix:	No
Fisher Information Matrix:	FIM_model_1.csv
Determinant:	1.29408e+022
Criterion:	286.3417
Eigenvalues:	54239931.5461 10926.155 2966.9888 3148.8806 4.3962 0.2773 0.0041839 14.3234

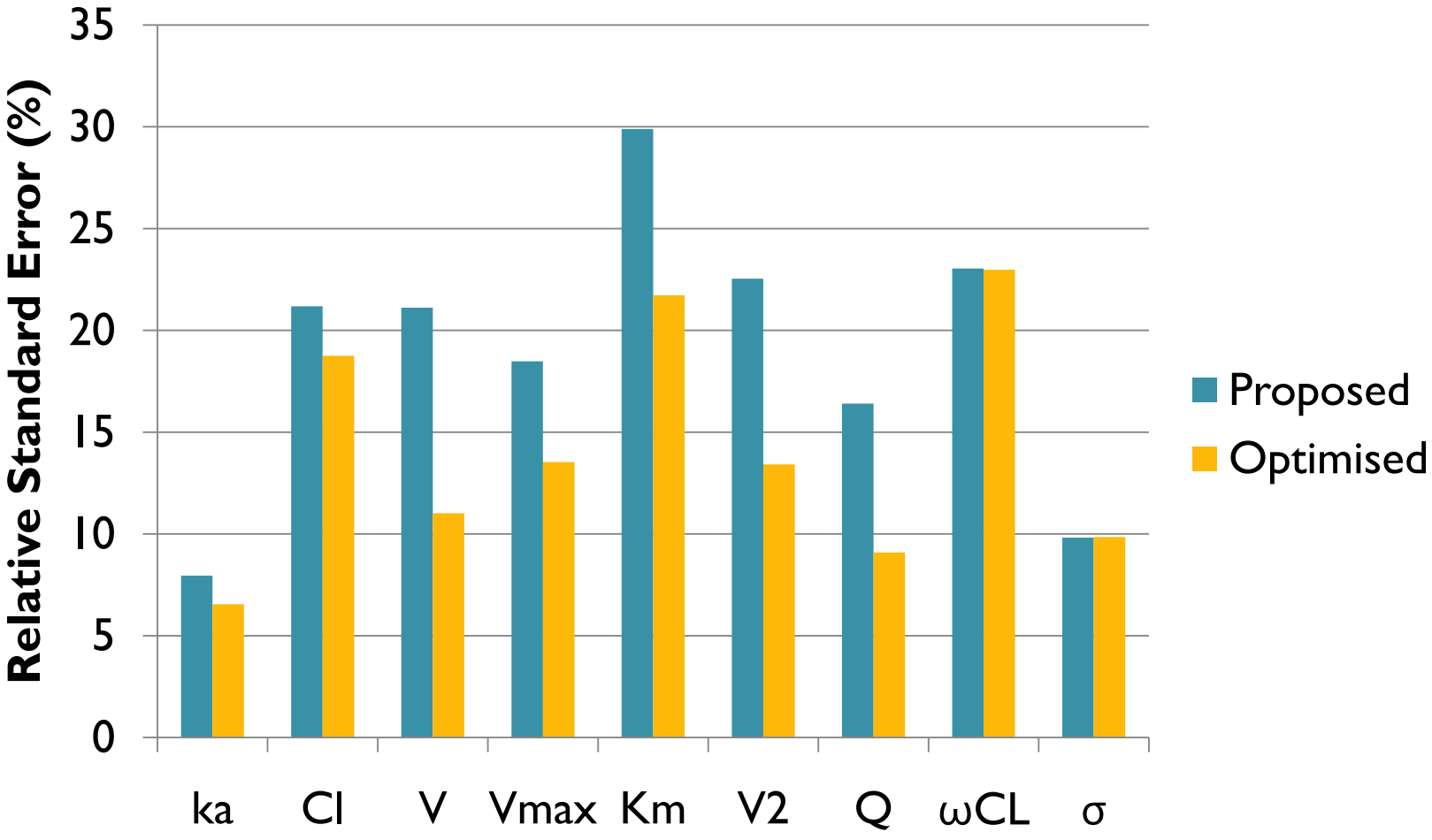
Time taken: 2 days 3 hrs 20 mins 18.2 secs

WinPOPT output: original design

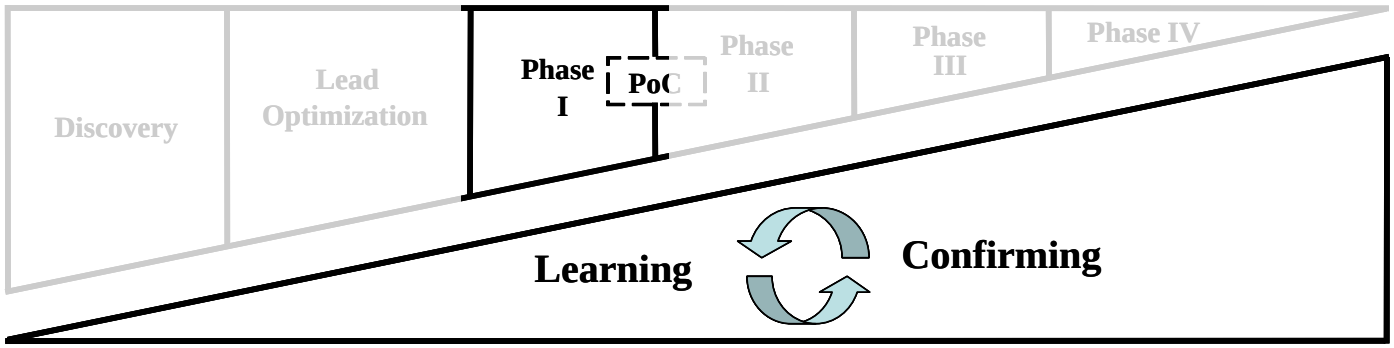
Parameters:	ka cl v vmax km v2 q
Fixed effect parameters:	0.00833 0.0973 18.9 5.24 0.644 115 0.26
Fixed fixed effects:	
Standard errors:	0.00066225 0.02061 3.99 0.96822 0.19248 25.9193 0.042638
Standard errors(%):	7.9502 21.1824 21.1111 18.4775 29.8875 22.5385 16.3994
Between subject variances:	0 1.15 0 0 0 0 0
BSV model:	1 1 1 1 1 1 1
Fixed random effects:	1 3 4 5 6 7
Standard errors:	0.2649
Standard errors(%):	23.0348
Residual standard deviations:	0.0569 0
Fixed residual effects:	2
Standard errors:	0.0055886
Standard errors(%):	9.8218
Prior Information Matrix:	No
Fisher Information Matrix:	FIM_model_1.csv
Determinant:	1.1675e+021
Criterion:	219.1828
Eigenvalues:	94786689.0306 10378.1204 2620.1368 3252.5771
	1.0997 0.18854 0.0014652 14.2506

Time taken: 1 mins 46.7 secs

Predicted relative standard errors



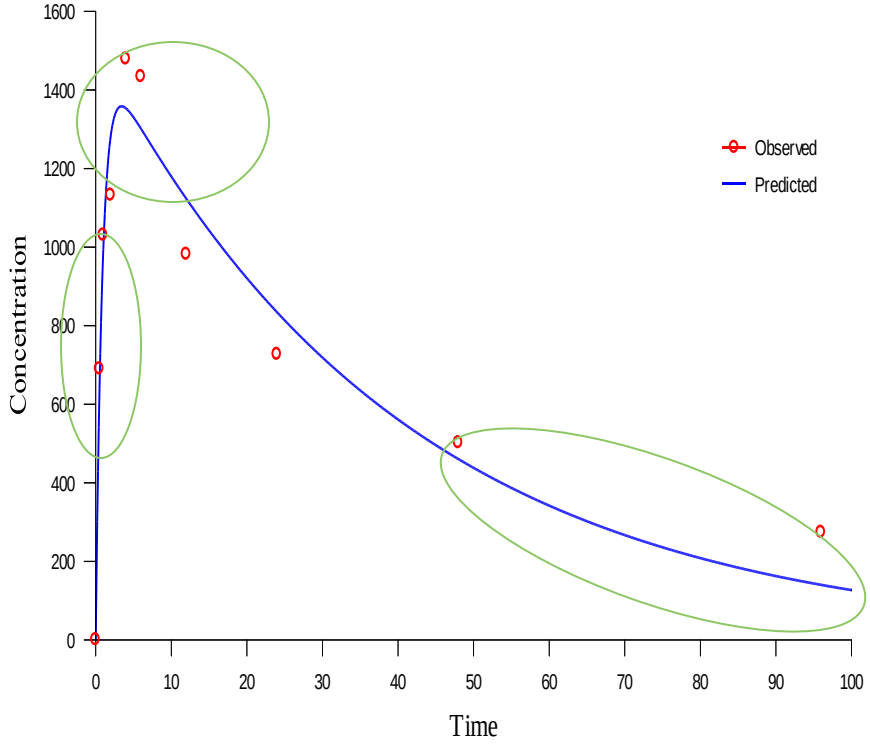
PHASE I DESIGN

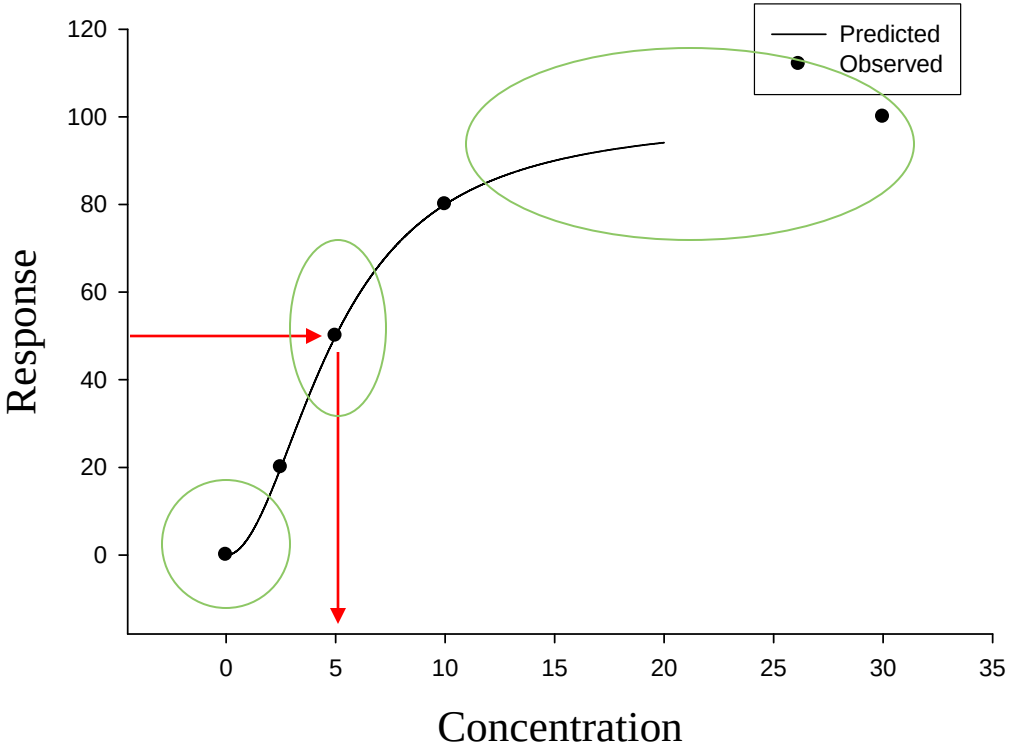


Phase I PK study design: conventional analysis

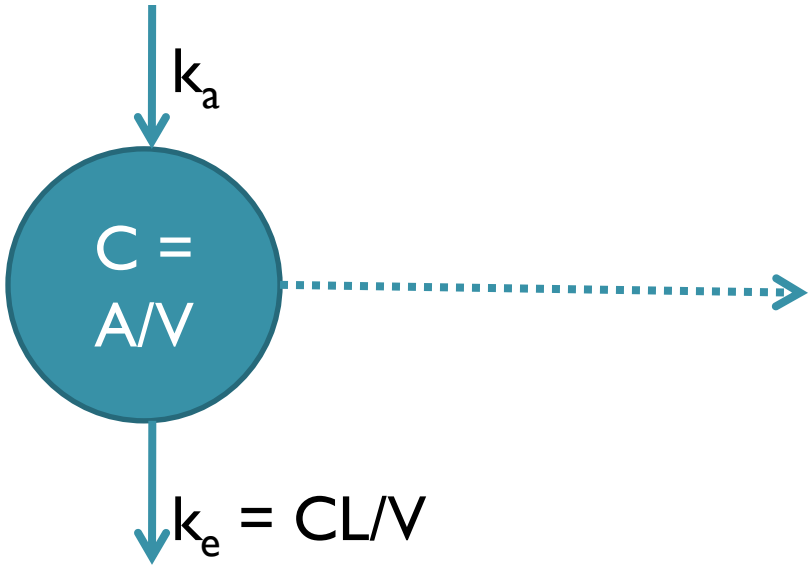
- General rules of thumb:
  - 12-18 samples total at pre-specified increasing intervals
  - Absorption phase: >2 samples from time 0 to peak
  - C_{max}: Bracket around t_{max}
  - Distribution phase: more frequent sampling
  - Half-life: 3-6 points in log-linear portion of terminal elimination phase
  - Sample up to 5 half-lives
- Multiple dose:
  - First and last dose + trough levels at steady-state.

PK and PD study design: conventional analysis





Phase I PD study design



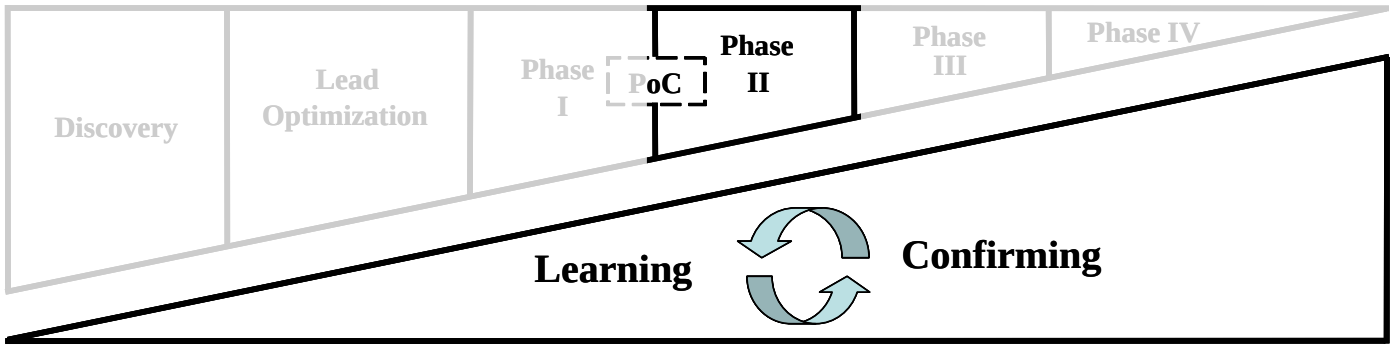
$$E = \frac{E_{\max} C^{\gamma}}{EC_{50}^{\gamma} + C^{\gamma}}$$

Phase I PD study design

- PK will be estimated via conventional analysis, so focus on estimation of PD parameters
- Some flexibility in sample size and doses

# Subjects	# Subjects per group	Doses (mg)	# Groups per dose	CV(EC50) (%)	CV(γ) (%)
8	2	0.1, 0.5, 1, 10	1	38.4	25.3
24	3	1, 5, 50, 200	2	22.5	8.3
24	6	0.1, 0.5, 1, 10	1	22.1	14.6
⋮	⋮	⋮	⋮	⋮	⋮

PHASE II DESIGN



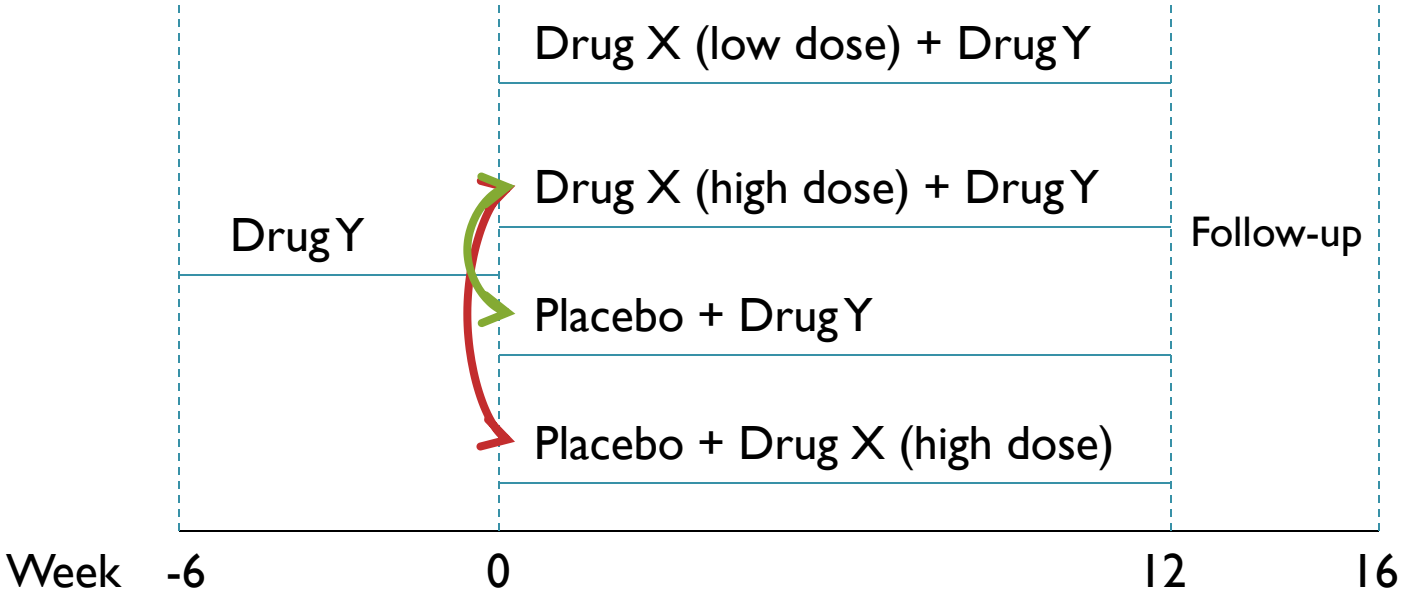
Phase II optimal design

- Phase II study with more subjects, but fewer PK samples per subject
- Optimal PK sampling already determined for Drug X, based on population PK model built from rich Phase I data
- Drug X developed as a monotherapy in Phase I
- From Phase II onwards, Drug X will be developed as a combination therapy with Drug Y
- Sampling scheme also efficient for Drug Y
  - Drug Y already on the market, PK is well understood
- Potential for PK Interaction between Drugs X and Y

Drug-drug interactions (DDI)

- Drug Y is known to be metabolised primarily by a particular enzyme
- Drug X is known to be a mild inhibitor of this enzyme
- High doses of Drug X may increase Drug Y concentrations by up to 30% by slowing its elimination
- Potential safety issues for Drug Y
- May affect interpretation of study results

Phase II optimal design



Simulations to assess ability to detect Drug X effect on PK of Drug Y

- Simulate PK data for 200 replicate studies
  - 2 arms: Drug Y with/without Drug X
    - Assume Drug Y clearance reduced by 0, 20, 33 or 50% in presence of Drug X (corresponding to 0, 25, 50, 100% increase in AUC)
  - 40 patients/arm
  - 7 PK samples/patient
- Fit population PK model to simulated data
  - Estimate AUC for each patient
- For each of the 200 replicates, test for significant DDI
  - Construct 90% confidence interval for difference in log-transformed AUC
  - Does back-transformed confidence interval lie entirely within 0.8 – 1.25?

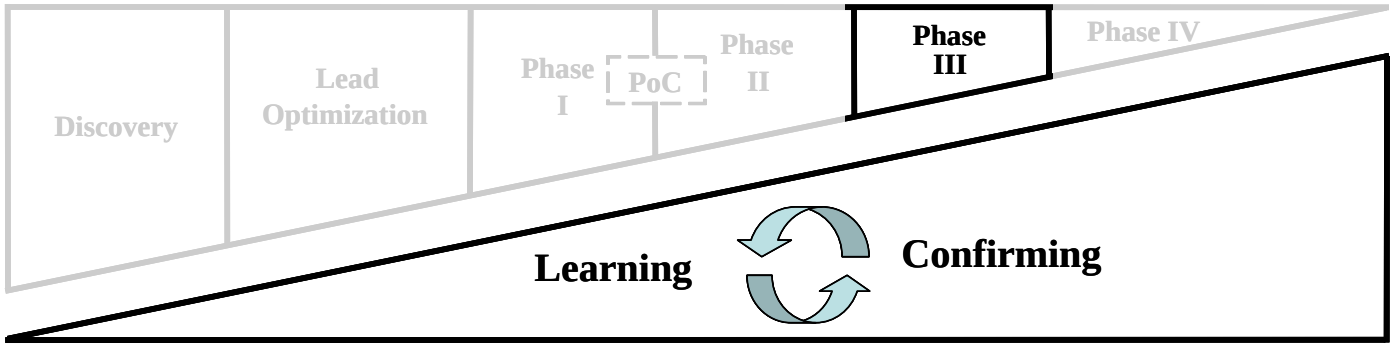
True effect of Drug X on Drug Y AUC	Pr(Correct Conclusion)
0%	91%
25%	85%
50%	100%
100%	100%

Simulations to assess ability to detect Drug Y effect on PK of Drug X

- Simulate PK data for 200 replicate studies
  - 2 arms: Drug X with/without Drug Y
    - Assume Drug X clearance reduced by 0, 20, 33 or 50% in presence of Drug Y(corresponding to 0, 25, 50, 100% increase in AUC)
  - 40 patients in Drug X alone arm, 60 patients in combo arm
  - 7 PK samples/patient
- Fit population PK model to simulated data
  - Estimate AUC for each patient
- For each of the 200 replicates, test for significant DDI
  - Construct 90% confidence interval for difference in log-transformed AUC
  - Does back-transformed confidence interval lie entirely within 0.8 – 1.25?

True effect of Drug Y on Drug X AUC	Pr(Correct Conclusion)
0%	64%
25%	82%
50%	100%
100%	100%

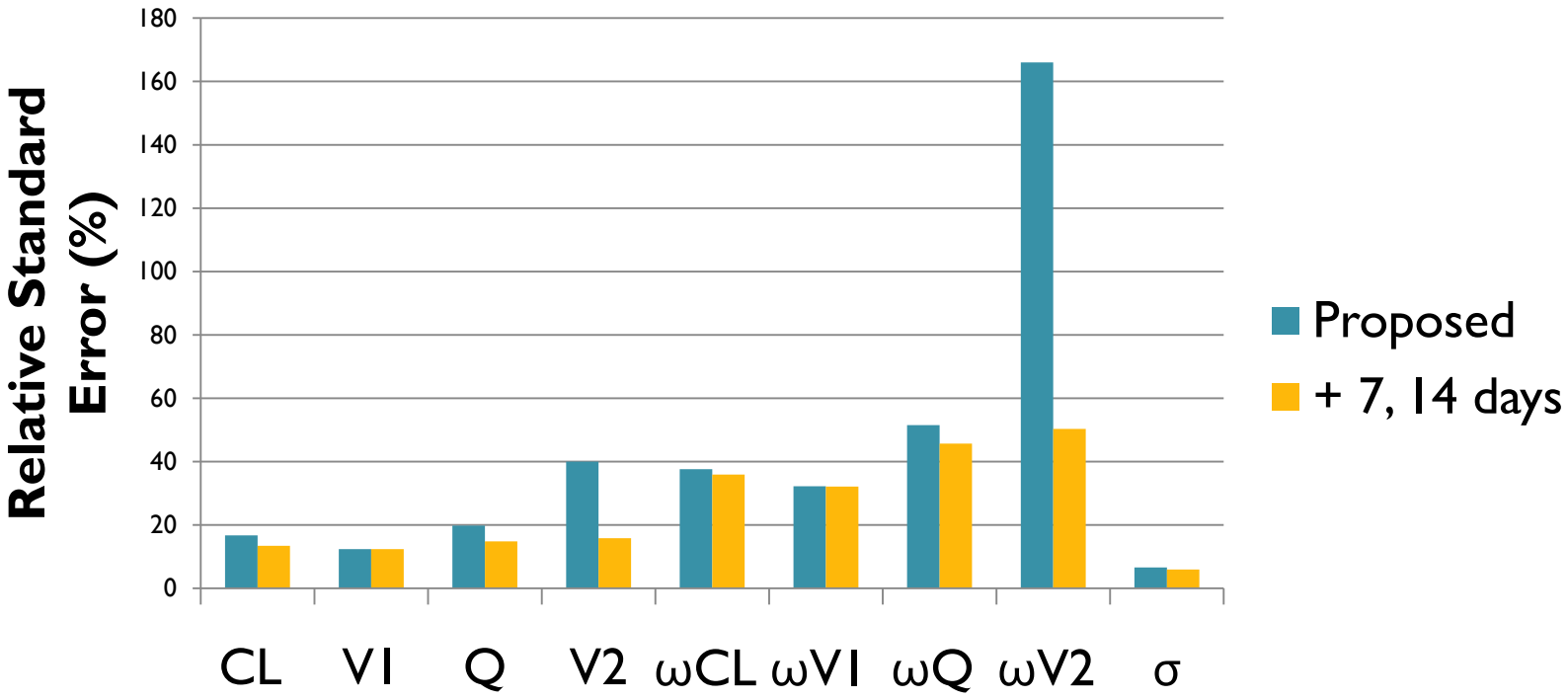
PHASE III DESIGN



Phase III optimal design

- Drug X will be tested in combination with Drugs Y and Z, in 1,000 patients
- Drug X may affect PK of Drug Y and/or Drug Z, so PK samples will be collected from 20 patients
- End of Phase II meeting with FDA:
  - Q: "Does FDA agree that the PK data collected in Study ABCD will be adequate for assessing the effect of Drug X on the PK of Drugs Y and Z?"
  - A: "No. Additional samples at 7 and 14 days will be required for Drug Z."

Phase III design: PFIM output



Response to FDA:

"The addition of sample times at 7 and 14 days slightly improve the precision of the parameter estimates, but not significantly. Lilly believes that these samples may be excluded from the design while still allowing robust characterization of the PK of Drug Z."

Summary

- Optimal design for population PK/PD models used throughout all stages drug development
- Current software tools serve very well for the most part
- However…

Optimal design wish list

- Design optimisation for both…
  - Parameter estimation &
  - Power to detect DDI/treatment effect (Retout *et al*)
- Flexibility in model structure
  - E.g. form of additive/proportional residual error model
- Plot of model with dose/sampling times overlaid
  - Sanity test
  - PFIM does this. Others?
- Batch processing
  - Automatically evaluate/optimise designs for multiple sample sizes, numbers of elementary designs, dose levels, and combinations thereof
- Parallel computing
  - PopED