AstraZeneca
IMED Biotech Unit

Dose response, design and analysis

Example from Quantitative Clinical Pharmacology @ AstraZeneca

European Statistical Meeting, Brussels November 2015
Dose Selection in Late Phase Clinical Development

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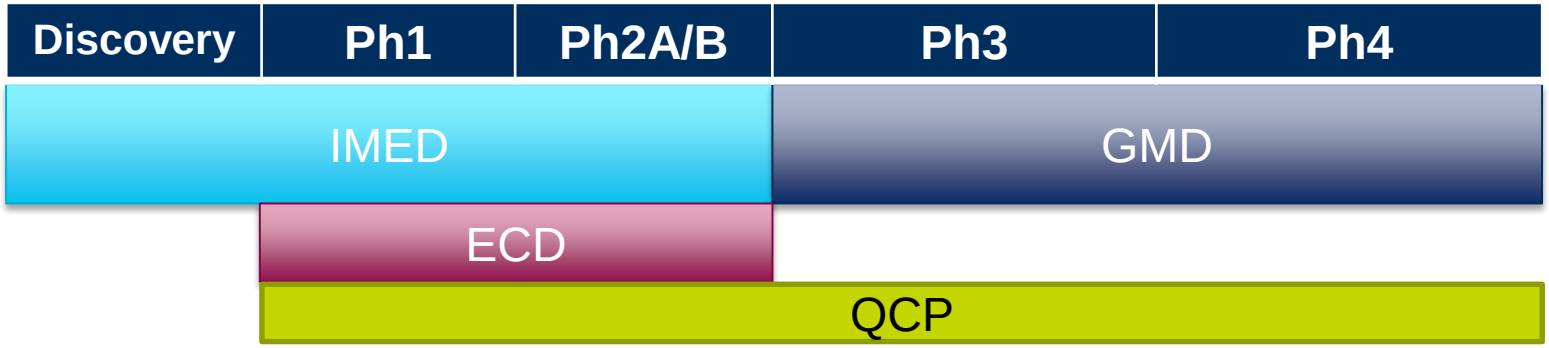
Pharmacometrics @ AstraZeneca



- GMD the late phase (Ph3-4)
- ECD (within IMED) responsibility for the early clinical phase (Ph1-Ph2)
  - Sections for Medical Units, Biometrics and **Quantitative Clinical Pharmacology**
- Quantitative Clinical Pharmacology (QCP)
  - Home of Pharmacology Scientists and **Pharmacometricians**
  - **Responsibilities in the early and late phase**
  - **Strategy for getting the dose right in Ph3**

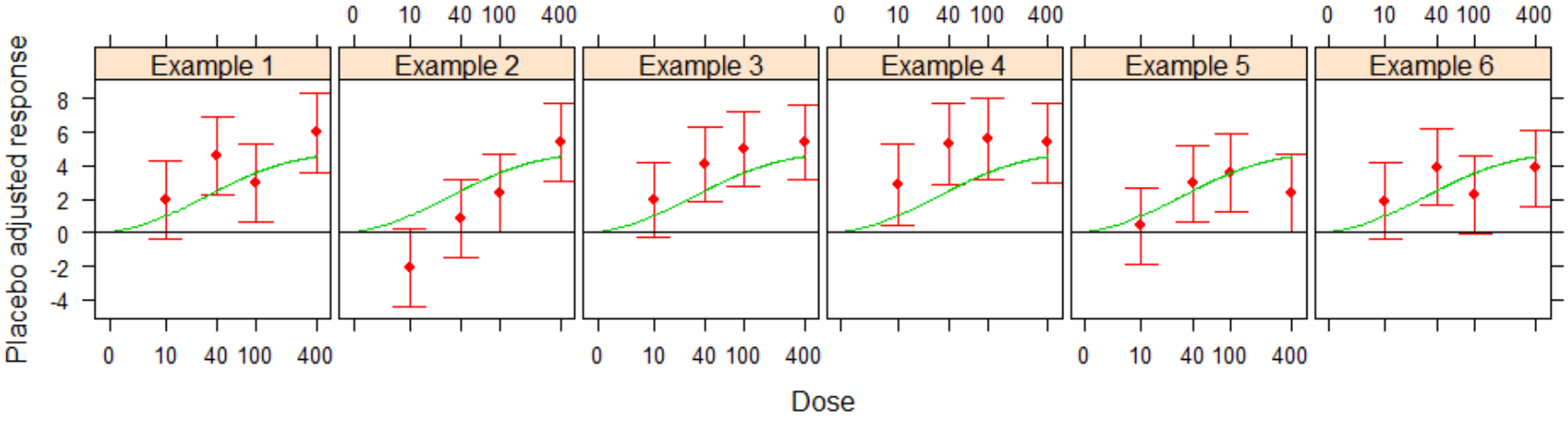
Dose response studies; how are they different?

- **Detecting dose response is much easier than estimating it**
  - A good and informative Ph2b study can be larger than the Ph3 studies (e.g. exacerbations in COPD)

- **Compared to the conventional Ph2b study (sized based on significance testing) <u>more informative studies are needed</u>**
  - More (detailed) data or better use of the existing data

Hypothetical data from conventional Ph2 study (90% power @ 100mg)

Green curve is the true dose response. Red points indicate result from ANOVA with 95% CI.



Dose response studies; how to improve

Beside choice of endpoint, length of study, study population, sample size...

Tools that can improve the ability to estimate dose response (DR)

- **Optimize doses & n/arm @ a fix total study size**
  - Good potential when having good knowledge on the expected DR
  - Base case: wide range and equally sized dose groups with boosted size for placebo & max dose

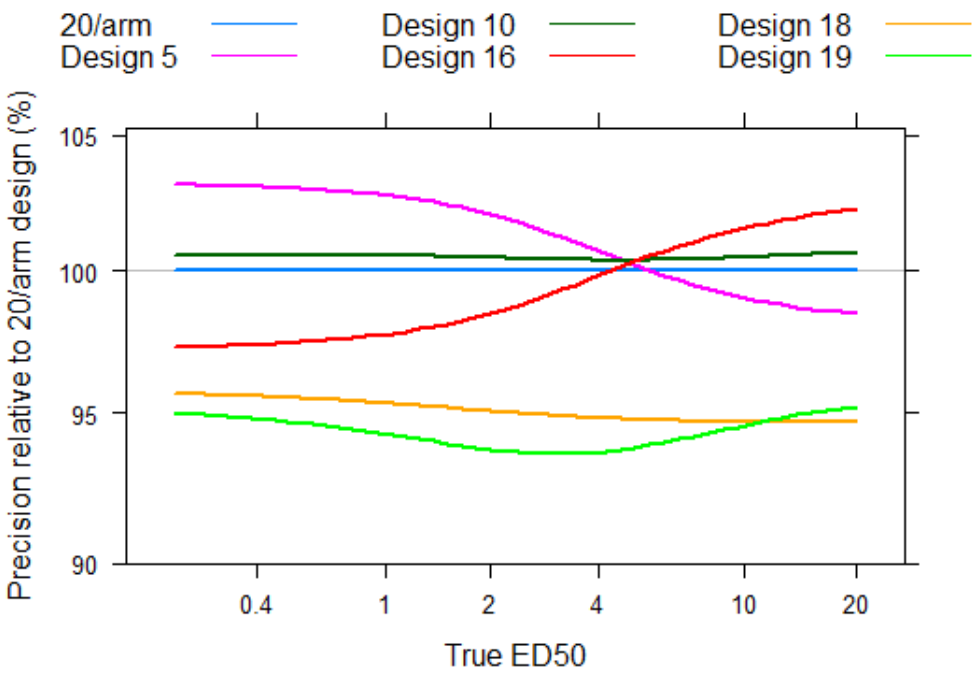
- **DR response analysis utilizing the *same data* as the pair wise ANOVA**
  - Cheap (!) & can easily be pre-planned with “template analysis plan”
  - Moderate to low potential improvement, however almost always better than pair wise

- **Longitudinal DR including *more data* than the pair wise ANOVA**
  - Requires good understanding of endpoint and tailored analysis plan explored with clinical trial simulations.
  - High to moderate potential depending on end-point properties e.g within versus between subject variability

Optimize doses & n/arm @ a fix total study size

- Expected dose response accuracy can be explored using optimal design theory.
  - Applicable for model based analysis only
- Should take into account current understanding on the true dose response including uncertainty
  - Chosen design should have good properties across a range of scenarios
- **Base-case often "optimal"**
  - Wide range of doses, equally sized
  - Boosted size for placebo & max dose may provide a good alternative
- Higher potential if pre-Ph2 knowledge on dose response is stronger

Example on design evaluation.



Dose-arms	x	y	z	v	w
Design 5	25	20	20	15	20
Design 10	25	15	20	15	25
Design 16	20	15	20	20	25
Design 18	15	25	20	25	15
Design 19	15	20	25	25	15

Dose response analysis utilizing the *same* data* as the pair wise ANOVA

- **Cheap (!) & can easily be pre-planned with a "template analysis plan"**
  - Multiple candidate dose response models can be used for robust output
  - Model average or model selection
- **Moderate to low potential improvement compared to pair wise ANOVA**
  - Potential is dependent on the true unknown dose response and differs across the dose range studied (e.g. 2-40% lower sd)
- **Sample size can therefore be motivated by the pair wise ANOVA**

However, the primary tool for decision making should be the dose response analysis since almost always better than the ANOVA

**) e.g. the observed change from baseline to end of study for each subject/patient*

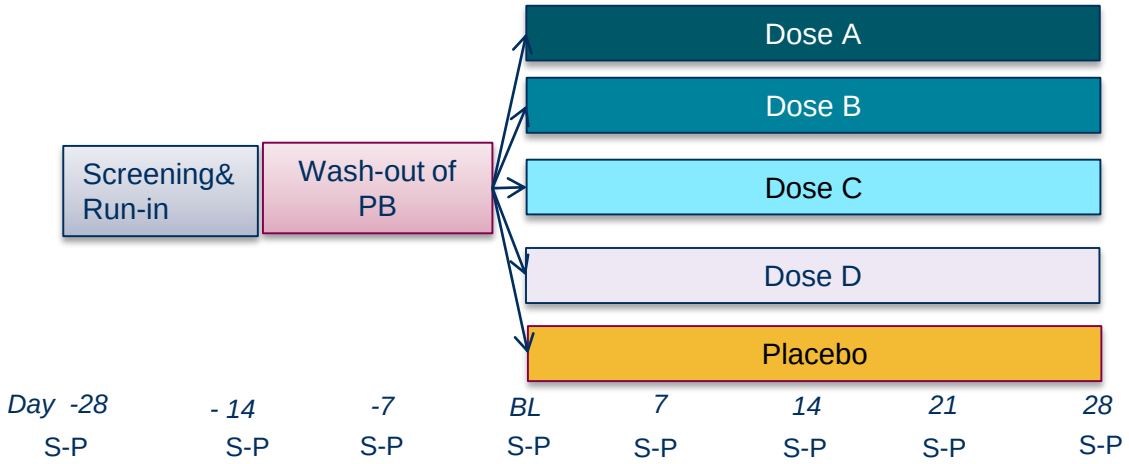
Longitudinal dose response including *more* data than the pair wise ANOVA

Can potentially be a game changer with reduced study size without reducing ability to estimate DR

- Can be substantially **more informative** since including **more information/data**
  - Include data from all study visits from BL to end of study as apposed to only change from baseline at end of study
- Prize-tag in man-hours & knowledge:
  - Requires understanding on time course of individual study data i.e. mechanistic knowledge and/or historical data
  - Careful planning of the analysis using clinical trial simulations
- **Case study, Longitudinal DR using data at 6 visits weeks -2 to week 4**

Ph2B study on hyperphosphatemia in Chronic Kidney disease (CKD) patients

- **Design concept for efficacy on serum phosphate levels**
  - Study including patients already on a conventional treatment
  - Treatment removed at screening followed by 2-3 weeks washout
  - Patients with increased levels randomized to experimental 4w-treatment



Can a model based dose response analysis provide better precision than the conventional analysis=ANOVA on change from BL to end of treatment?

Serum phosphate data in the Ph2b study

- **Serum phosphate measured weekly during washout and treatment period**
  - 7 data points/patient on serum phosphate will be available
  - Only 2 would be used in a traditional statistical analysis
- **Efficient use of all data requires a model based analysis**
  - Published data show a gradual increase during washout and a gradual decrease in serum phosphate after onset of treatment
  - A indirect response model (turn over model) can describe both phases and is a natural choice with a mechanistic interpretation
- **A indirect response model for serum phosphate**
  - A continuous elimination is used as a approximation for the piece-wise elimination during HD
  - Conventional and experimental treatment reduces the rate of a absorption (Kin)

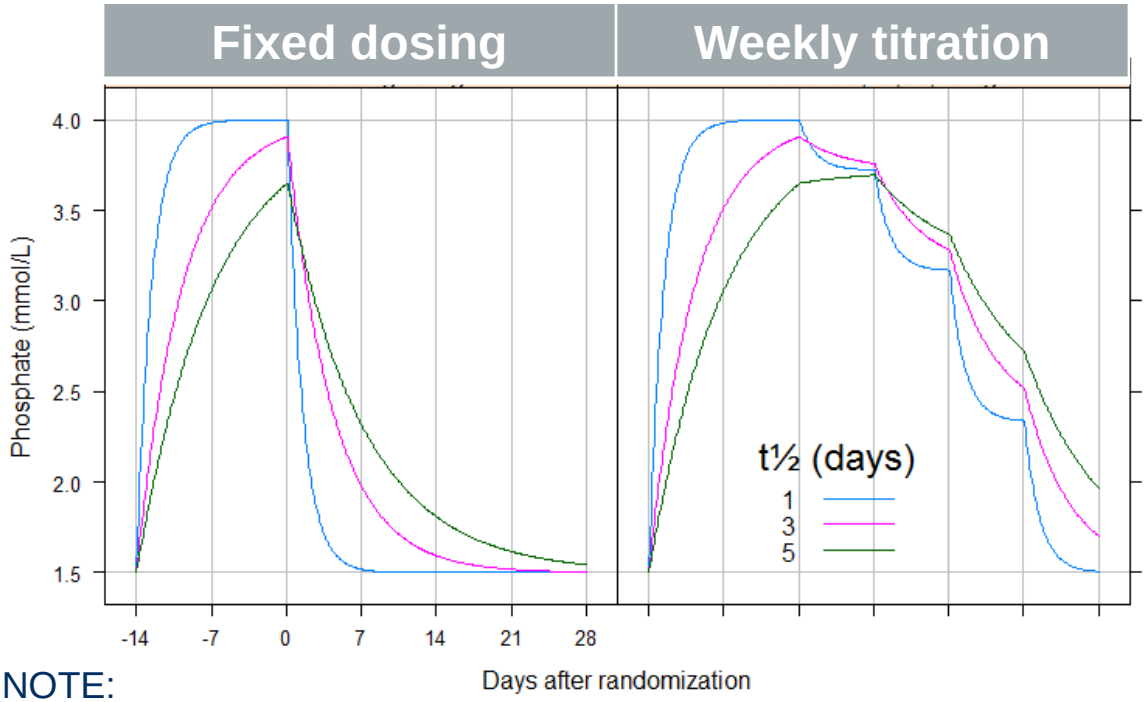
Kin=Kin0- Emax/(1-ed50/dose)

Time profile of the indirect response model

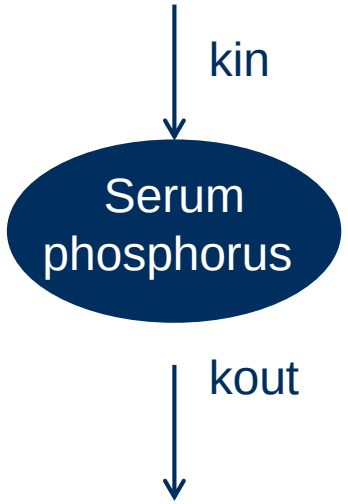
Sufficient flexibility for the current study setup

If t½ ≤1 day, a simple statistical model can be used

If t½ >1 day, a model based analysis is required to adequately describe the data and get unbiased estimated treatment effect



Kin=kin0- Emax/(1-ed50/dose)



A continuous elimination of serum phosphate used as proxy for HD

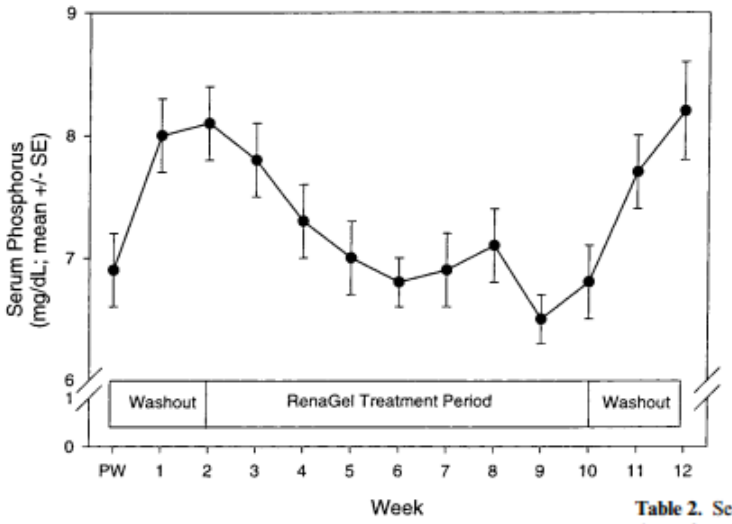
NOTE:
t½ is a parameter of the indirect response model (t½ = log(2)/kout) AND is estimated from the observed study data

The indirect response model evaluated on published data from a similar study

Adequate description of observed mean data

Effect of RenaGel®, a non-absorbed, calcium- and aluminium-free phosphate binder, on serum phosphorus, calcium, and intact parathyroid hormone in end-stage renal disease patients

Dennis I. Goldberg[1], Maureen A. Dillon[1], Eduardo A. Slatopolsky[2], Bruce Garrett[3], John R. Gray[4], Thomas Marbury[5], Marc Weinberg[6], Duane Wombolt[7] and Steven K. Burke[1]

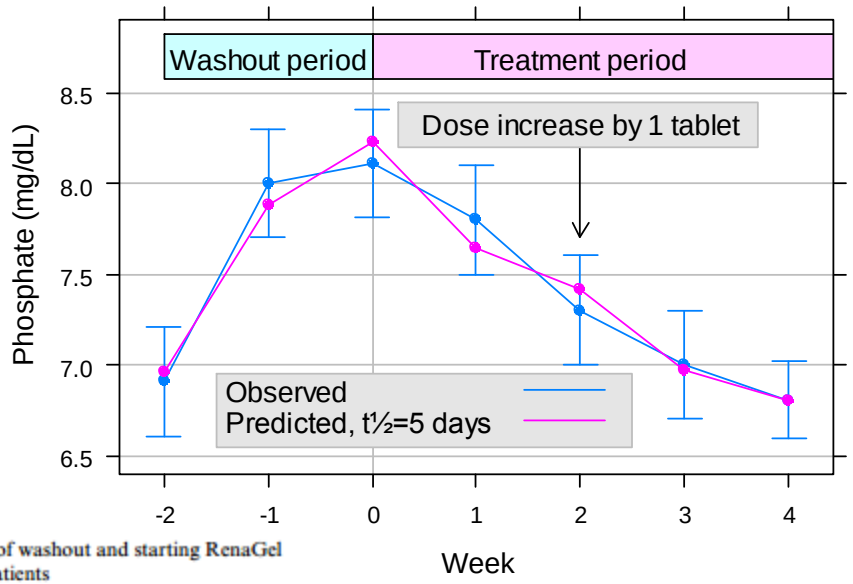


of one, two, or three capsules t.i.d. The majority of patients increased their RenaGel dose by one capsule t.i.d. at the study week 4 visit that resulted in a return of mean serum phosphorus levels to pre-washout levels. Additional dose titrations occurred in some patients at study weeks 6 and 8, resulting in a small continued

Table 2. Serum phosphorus at end of washout and starting RenaGel doses for end-stage renal disease patients

Number of capsules t.i.d.	Washout serum phosphorus mg/dl (mmol/l)	Patients (*n*)
1	⩾6.0 to <7.0 (⩾1.94 to <2.26)	12
2	⩾7.0 to <8.0 (⩾2.26 to <2.58)	8
3	⩾8.0 (⩾2.58)	26

Observed* (mean+-SE) & predicted serum phosphate



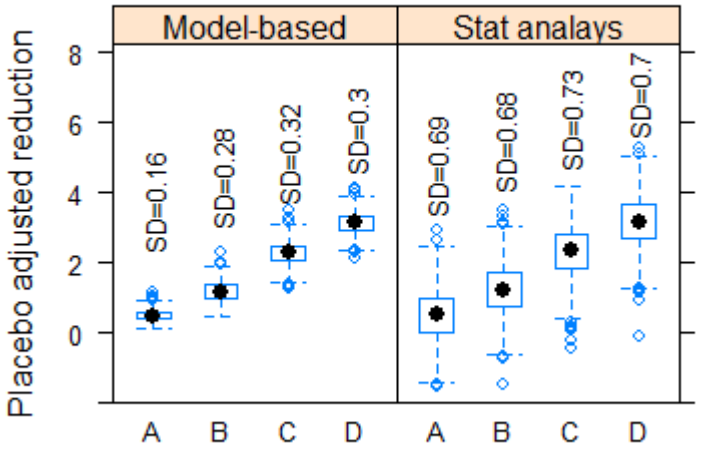
Design evaluation by clinical trial simulations

Iterate 1-3 to obtain distribution of predicted treatment effect

1. Simulate data according to design
2. Perform analysis on the simulated data
3. Record observed/predicted treatment effect
   - Traditional analysis on change from BL to end of study at week 4
   - Model based analysis on all available data

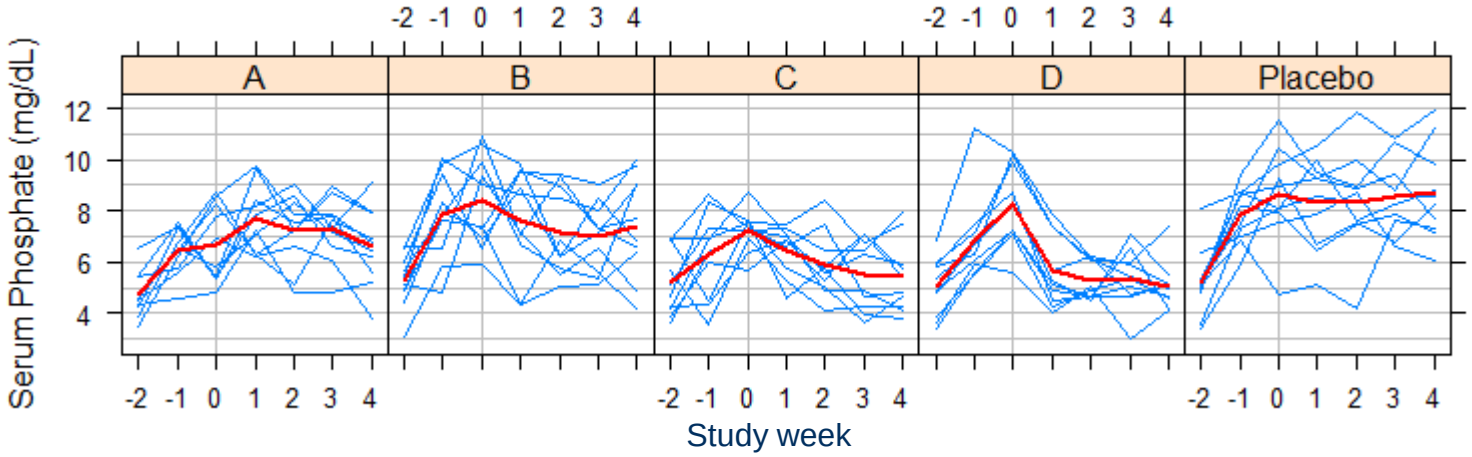
Clinical trial simulation summary

10 000 simulated studies



Evaluation suggested a reduction of sample size by a factor 4

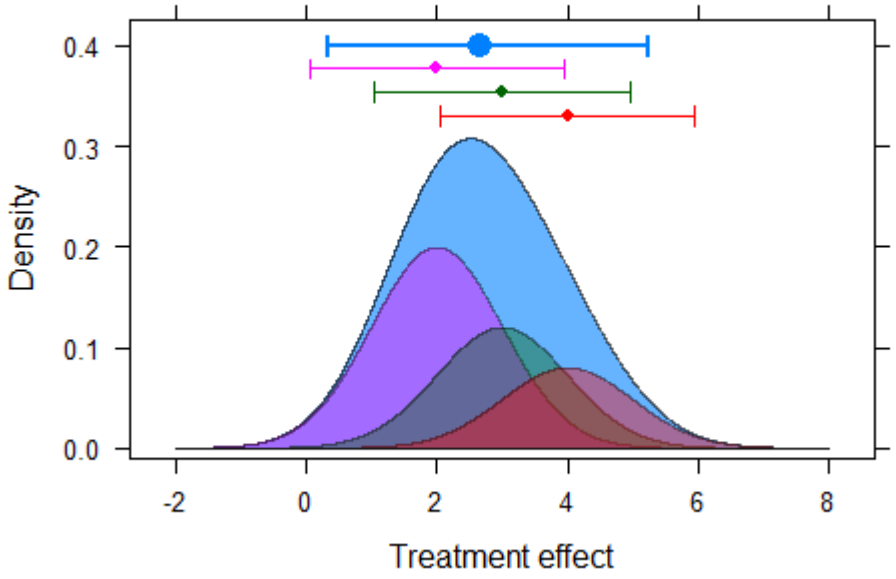
Clinical trial simulation, individual data(blue) and mean(red)



Analysis of observed study data

- A detailed analysis plan was agreed on before study readout
- Model averaging using 4 pre-defined dose response functions
  - Partly to unsure a bullet proof analysis and robust results
  - Predictions with uncertainty computed for each model (a distribution)
  - Model weights set using the Bayesian Information Criteria (BIC); $\boldsymbol{w \propto Exp(-0.5 \cdot BIC)}$
  - Joint predictions derived by using weighted averages of individual model predictions

Model average predictions with CI from a set of 3 models, hypothetical data



Model	Estimate	CI (95%)	Weight
No 1, Pink	2	[0,4]	50%
No 2, Green	3	[1,5]	30%
No 3, Red	4	[2,6]	20%
Model average, Blue	2.7	[0.29,5.28]	NA

Individual model predictions with uncertainty

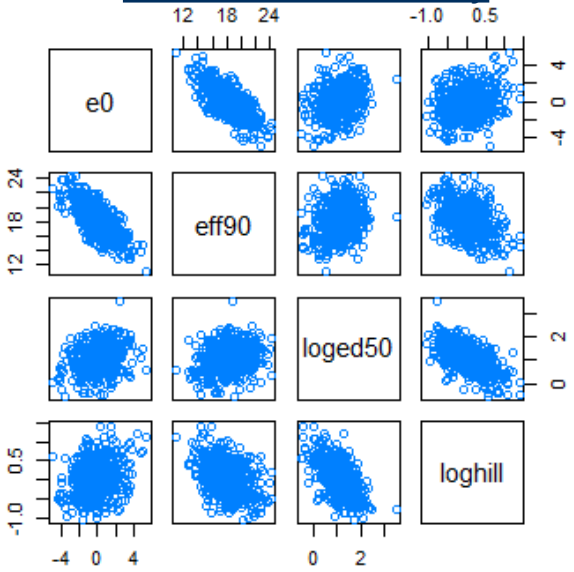
Principles used on the observed study data

- Model parameter uncertainty estimated by the estimated covariance matrix Σ
  - Parameter vector $\theta \sim Multivariate\ Normal\ \hat{\theta}, \Sigma$
  - Alternatively bootstrap of data & re-estimating => distribution for θ

- Prediction uncertainty computed from the parameter uncertainty
  - Large set (10 000) of parameter vectors simulated from the multivariate normal
  - Model predictions computed for each parameter vector; $f(\theta, dose)$ => distribution of predictions

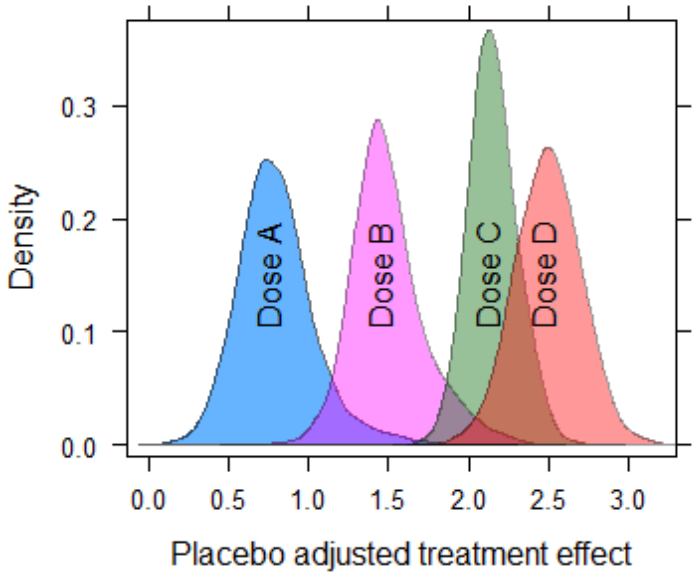
Parameter and prediction uncertainty for a set of 4 doses, hypothetical data

Parameter uncertainty



$f(\theta, dose)$

Prediction uncertainty represented as distributions

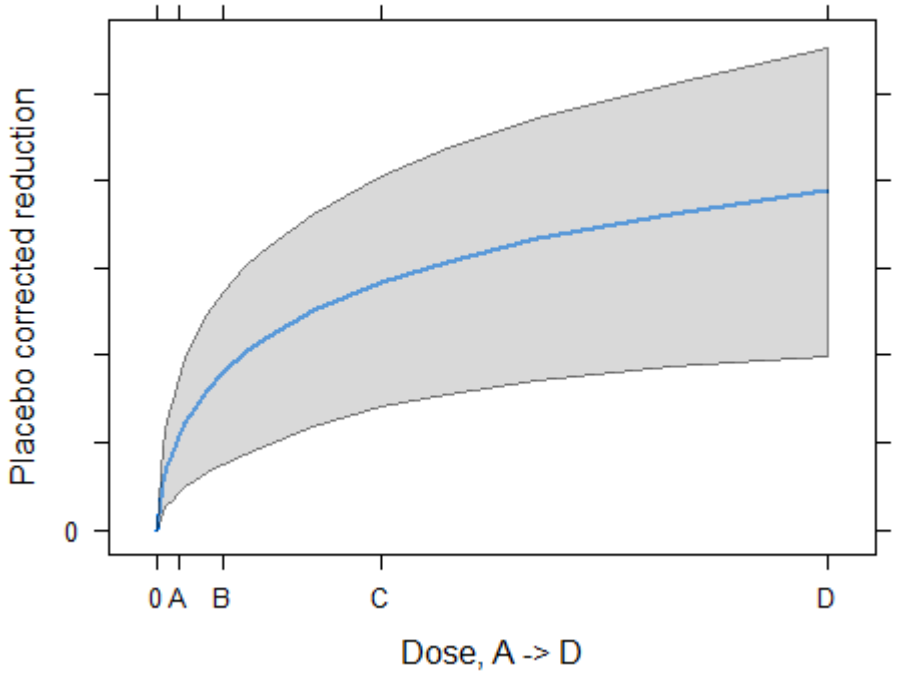


Presented results for decision making

- Analysis was carried out according to the analysis plan
- The observed precision matched well the precision in clinical trail simulations

Dose response for both efficacy safety was presented
The modeling provided clear data for internal decision making

Placebo adjusted serum phosphate reduction at end of study
Model average predictions with CI



Summary

- Dose selection remains a critical step in the drug development but improvements from the significance testing paradigm have been made
- Optimal design and dose response (DR) analysis are useful tools in Ph2B
  - Can improve the ability to estimate dose response (DR)
  - These have been and are used in multiple AstraZeneca projects
- Highest potential for longitudinal DR by using more data
  - Concept explored in AstraZeneca projects when applicable
- DR can be used for efficacy as well as for safety to describe the benefit risk and to provide informative input to Ph3 dose selection
  - Expectation @ AstraZeneca: *Ph3 dose selection should be supported by dose and or exposure response analysis*
  - Important part of the regulatory justification of the labeled dose