Pharmacometrics, CD&A

Informative study designs

Where modelling and simulation based design features make a trial more informative than a comparable standard design

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Outline

- Study design is a topic of increasing interest.
- In the pharmacometrics field the focus lies on the methodologies to assess the information content and to improve the design based on adjusting sampling time points and/or dose levels.
- We show two examples, where the information content can be much more influenced by non-standard dosing regimen than by more exhaustive sampling in a standard design.

System identification in 1972
Design: Input => Observations

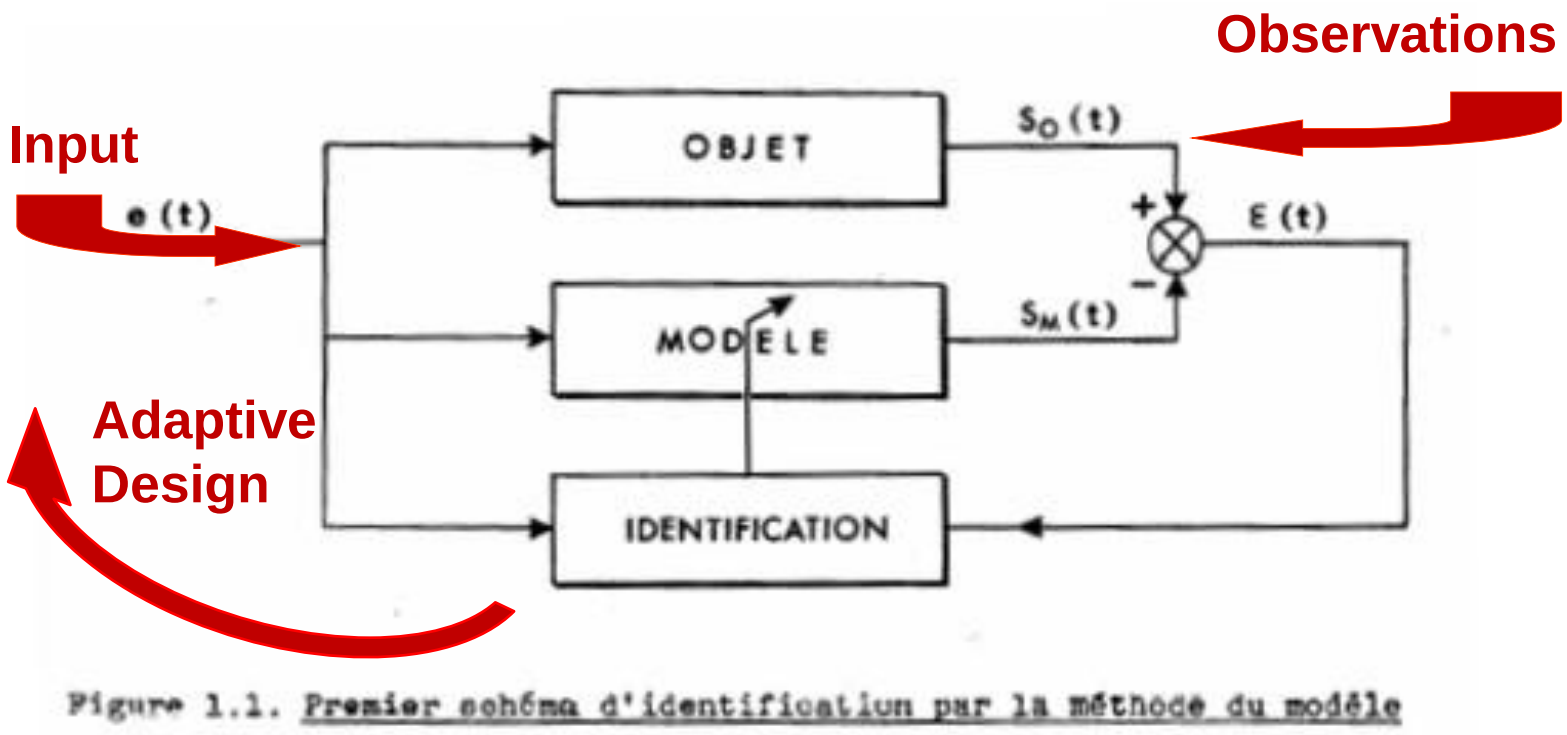


Figure 1.1. Premier schéma d'identification par la méthode du modèle

"Process identification by the modeling methodology"
J. Richalet, A.Rault, R.Pouliquen
Gordon & Breach, Paris, 1972

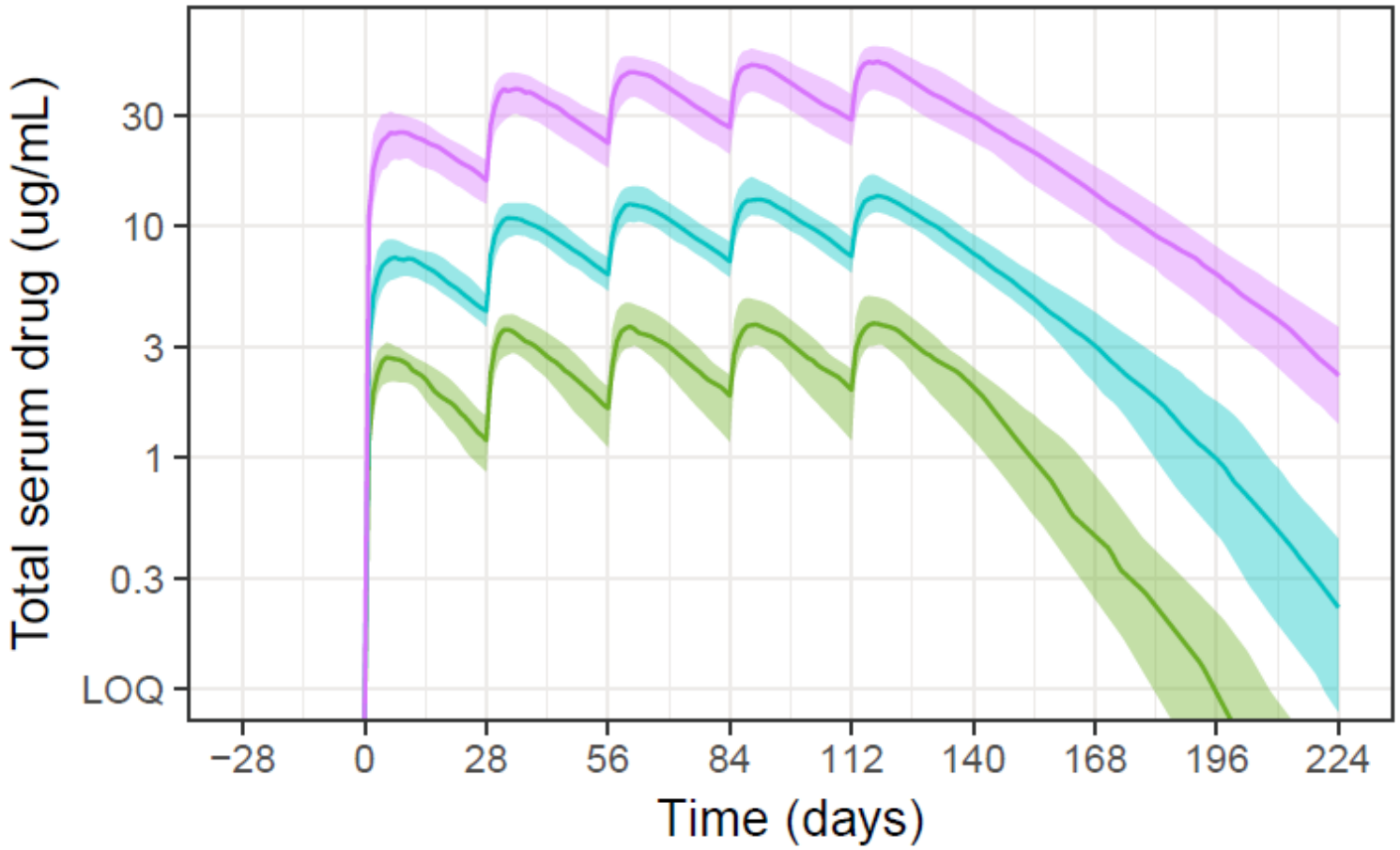
Pharma:
What is study design for us?

- Based on a study protocol:
  - Given the purpose/objective of the study
  - A study population is selected
  - That undergoes a specified intervention/treatment
  - While various assessments are collected
  - Which are analyzed to answer the study objectives
- Focus from a quantitative perspective:
  - What to measure (endpoints)
  - When and how often to measure (sampling times)
  - How much to measure (sample size)
  - For non-linear systems:
    Which intervention (dosing regimen / creative designs)
  - Important to consider dependence on model uncertainty/misspecification

Example 1

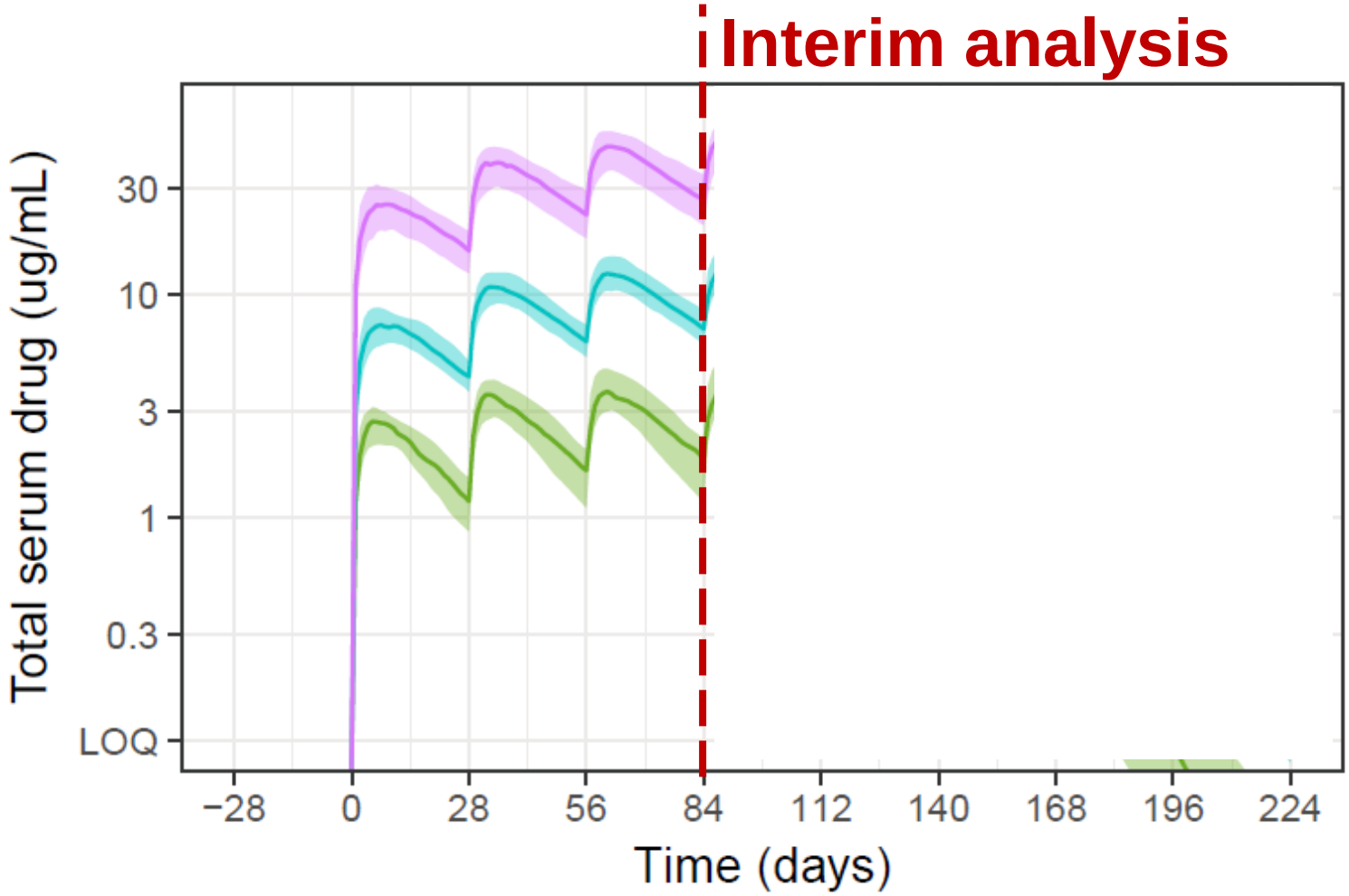
- Omalizumab is a monoclonal antibody that binds to IgE and reduces itch and hives in Chronic Spontaneous Urticaria (CSU)
  - Published omalizumab-IgE-itch-hives placebo and drug-effect model
- Ligelizumab has higher binding affinity but potential difference in CSU is unknown
  - In-vitro difference: 50-fold higher affinity to IgE
  - In healthy volunteers: 18-fold difference on skin prick test
- Goal to design Phase 2b study (NCT02477332)

Standard 3-arm design



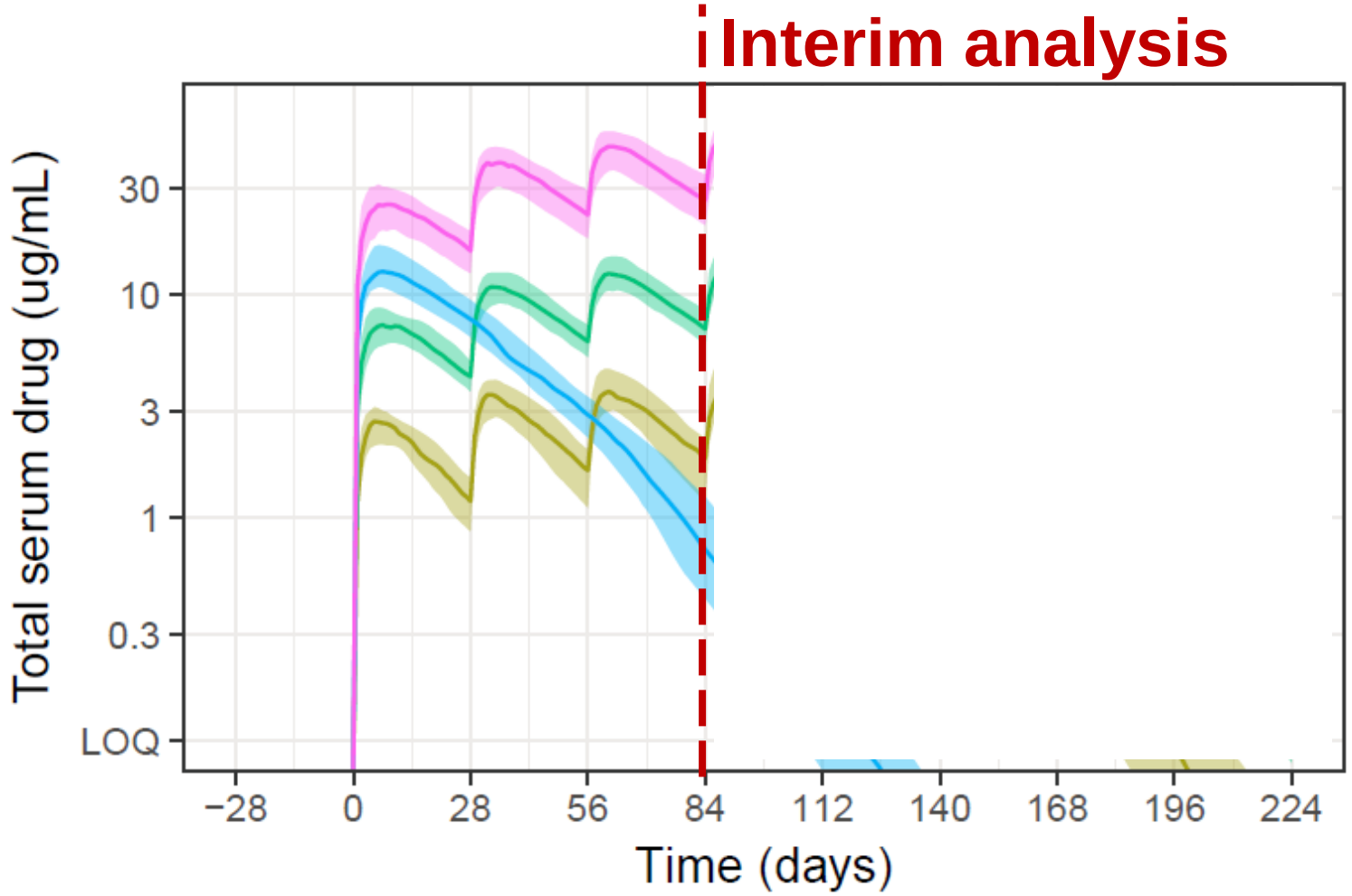
Three active dose levels plus placebo administered every 4 weeks for 20 weeks

Standard 3-arm design but at interim analysis missing information

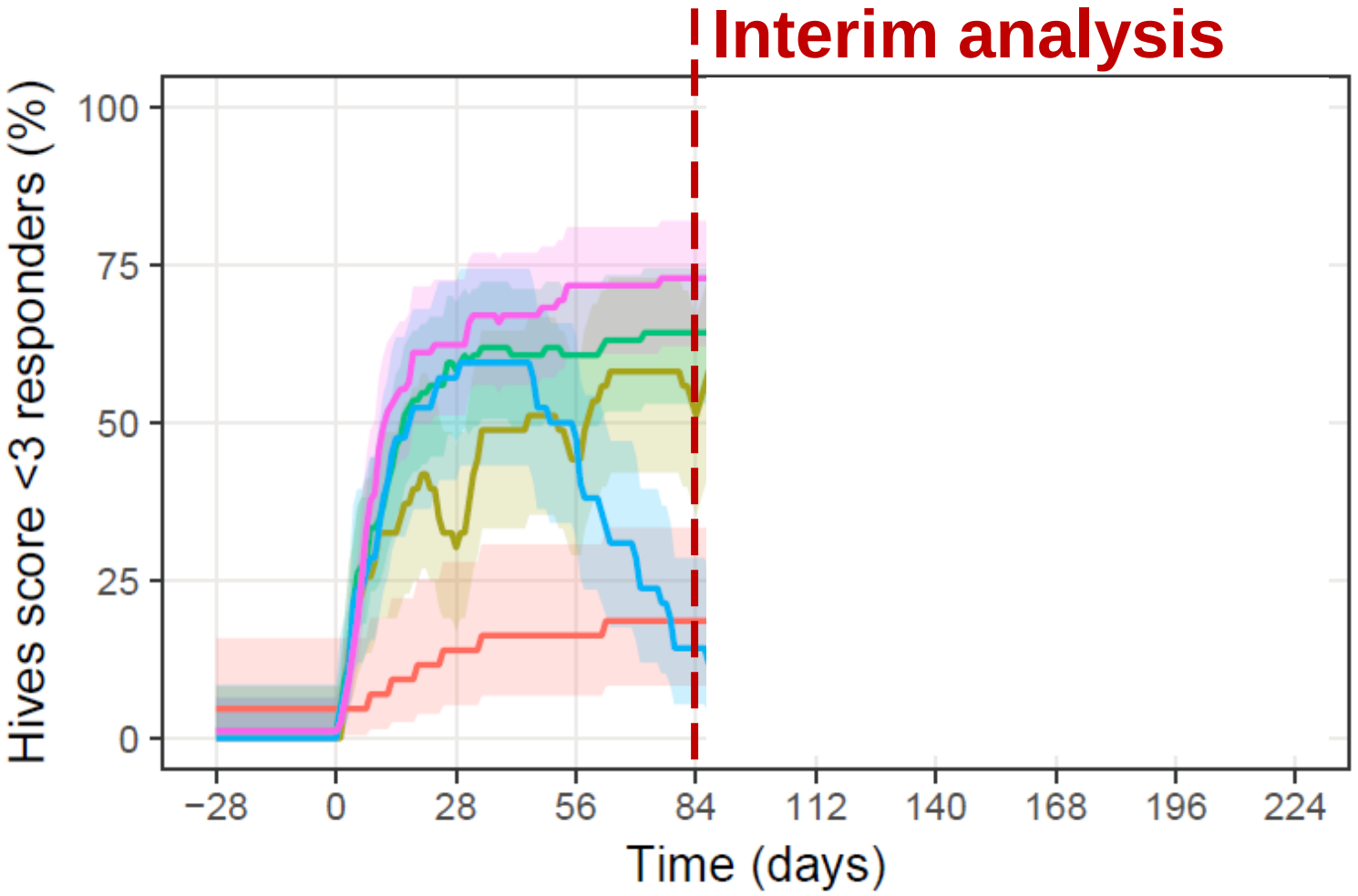


Three active dose levels plus placebo administered every 4 weeks for 20 weeks

Adding a single dose provides "washout information"



Single dose (SD) arm provides information on recovery timecourse



Advantages of the SD arm

- Possibility to test model adequacy
  - Check possible time-dependence (downregulation of target or efficacy tolerance)
- With high inter-individual variability longitudinal analysis of SD arm with wide concentration range advantageous
- Blinded washout
  - Contrary to washout at end-of-study this is a blinded “washout”
- Possible to unblind SD PKPD arm without interfering with multiple dose arms
- Model-based design but information directly from data
  - Regimen selection straight-forward based on SD read-out

Example 2

- Again, monoclonal antibody, with target-mediated drug disposition (TMDD)
- Concept shown here for early non-human primate (NHP) studies, but is applicable for all learning studies
- Scaling from small animal to NHP must consider uncertainties regarding amount and turnover of target and how the in-vitro Kd matches the in-vivo Kd
- Goal was to construct study design that is robust against Kd for first NHP study (with 4 animals)

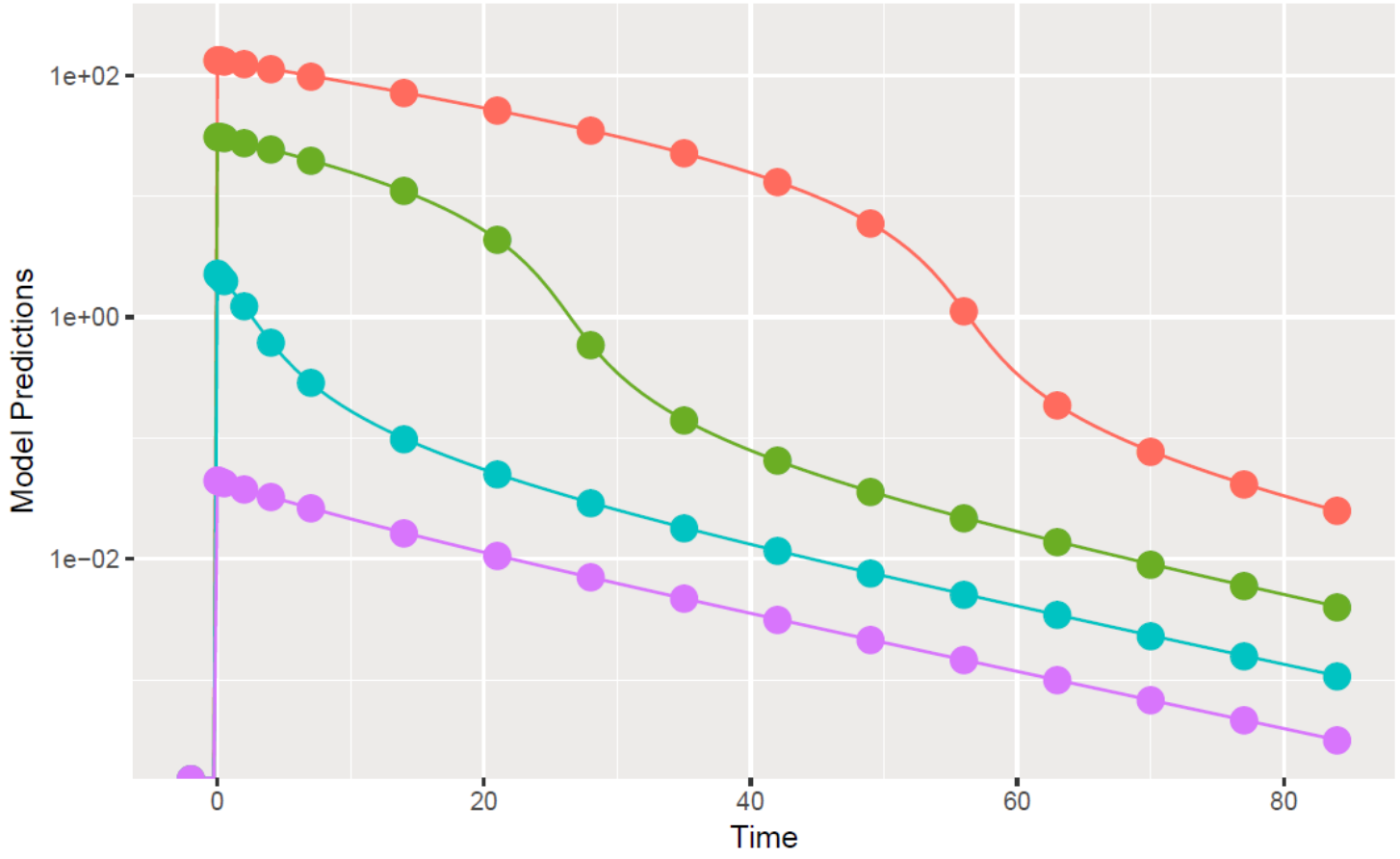
Comparing 3 designs for 1-cmt TMDD (sampling times based on gut-feeling)

- Standard: one high dose with n=4
- Spanning several doses: 4 doses with n=1
- Espresso: all having within-individual escalation (n=4)

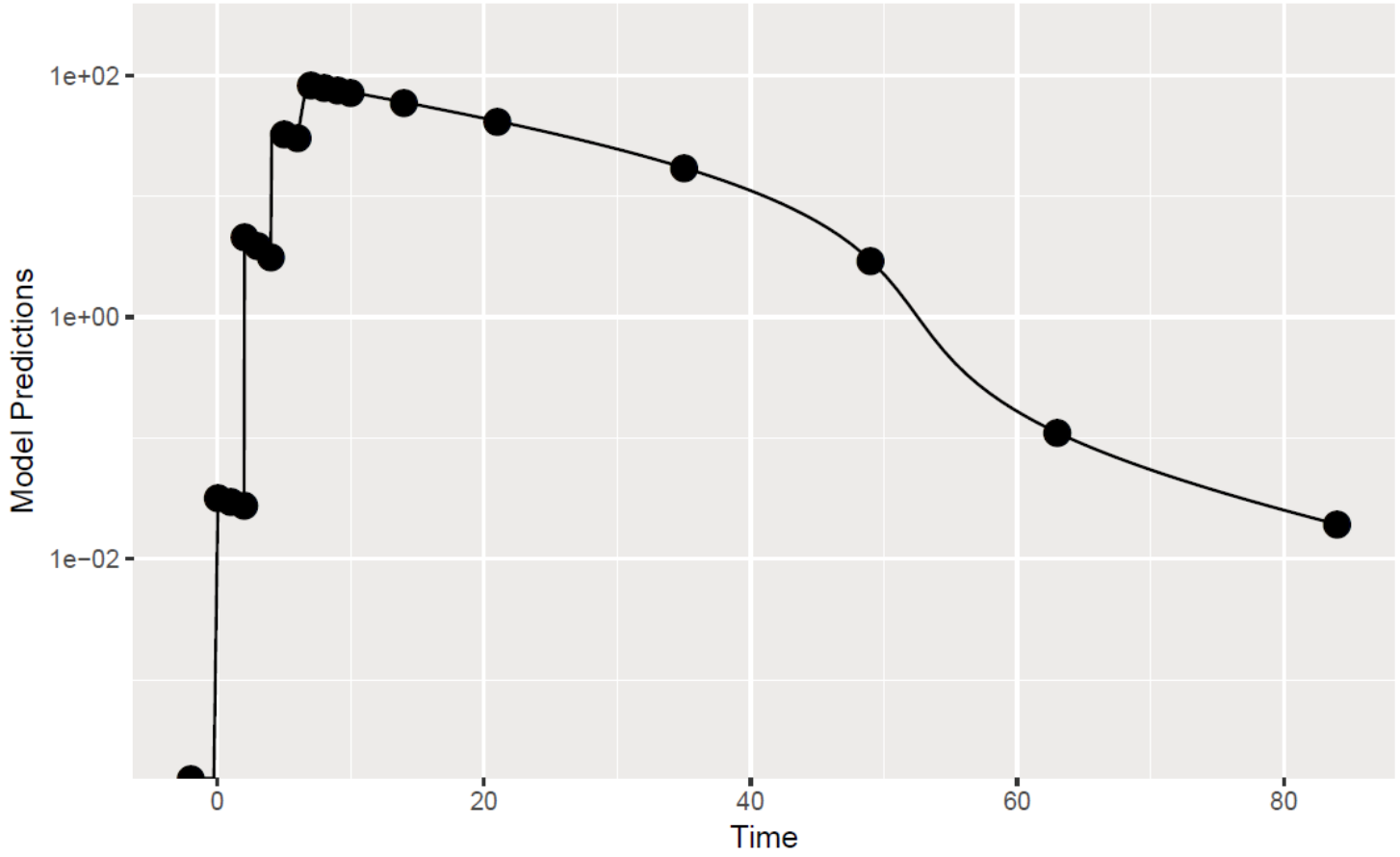
- Assessment: Free drug concentrations in plasma

- 1-cmt TMDD model with 5 parameters
  - V, CL-Drug, CL-Target, ProductionRate-Target, Kd
  - Immediate binding approximation

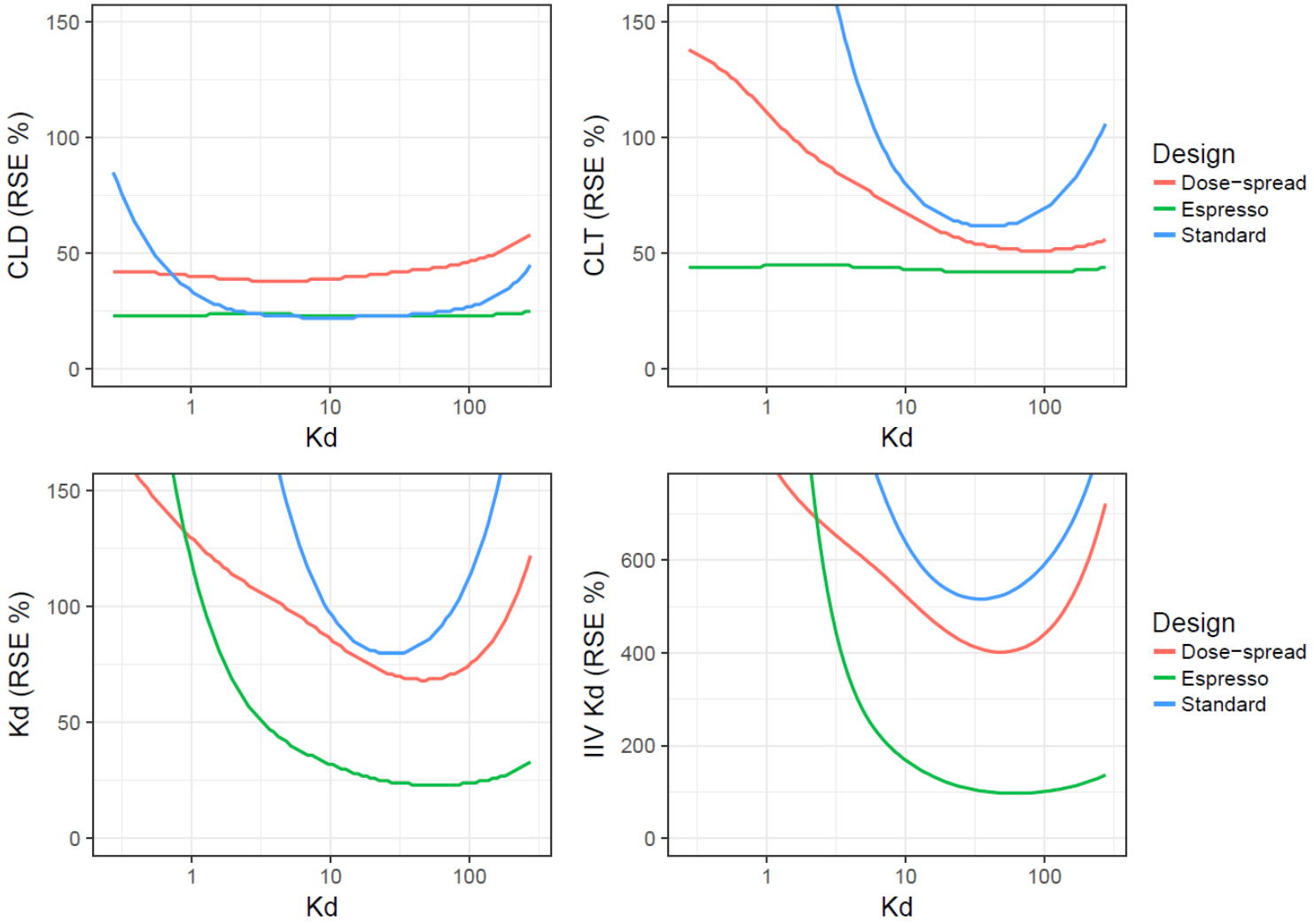
Standard high dose (4x red) or Dose spread: one level per individual



Espresso design: Within-individual dose escalation, here every 2 days

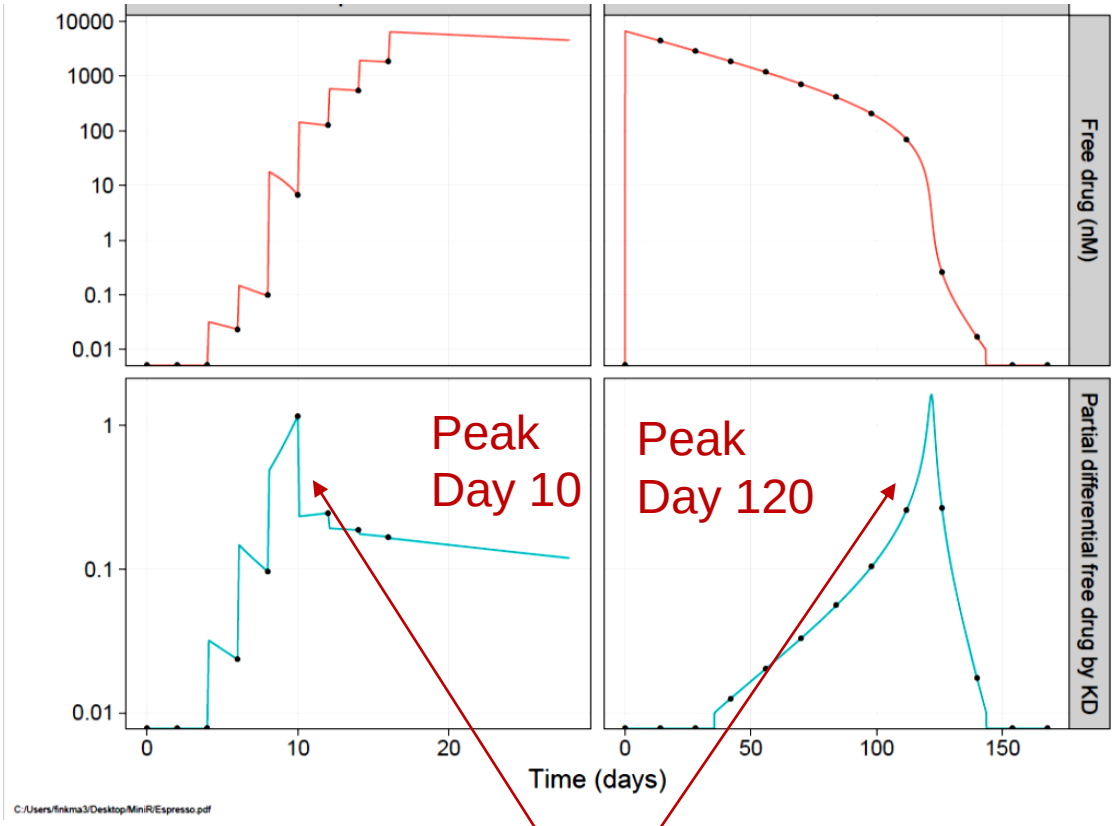


The Espresso design gives much lower relative standard errors



The “Espresso” design element collects information in short time

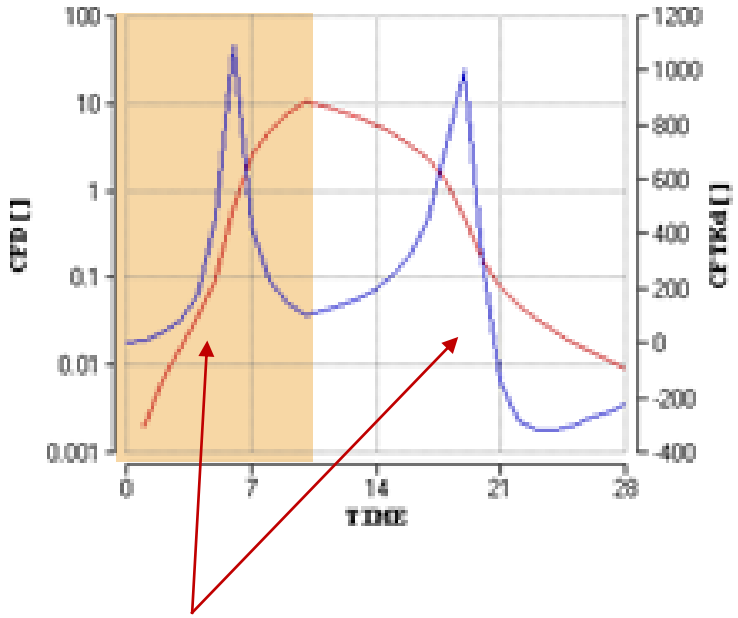
- Fast within-subject up-titration
- Exponentially increasing dose-levels
- Covers several magnitudes of concentrations
- Contains main information on KD (available only model-based)



Information content on KD – early in “Espresso” design

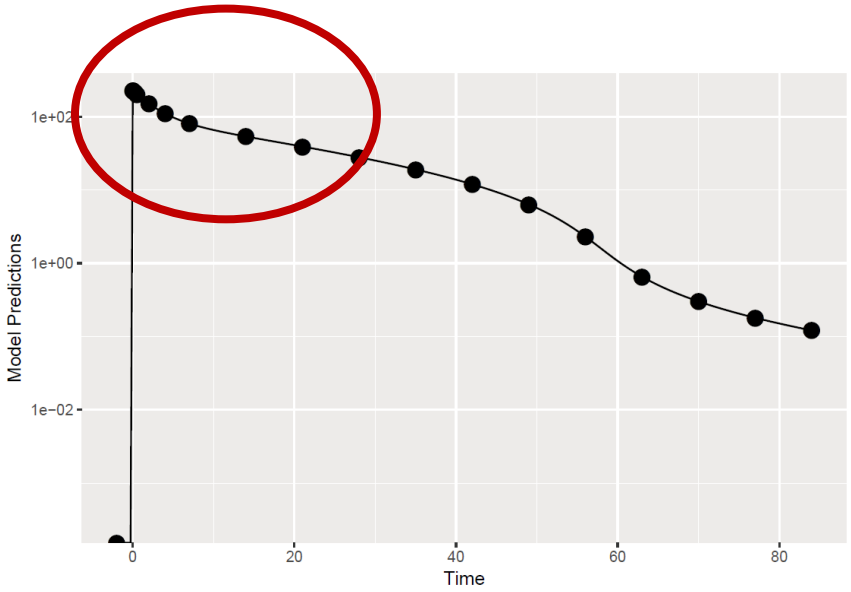
And provides the ability to assess time-dependence in parameters

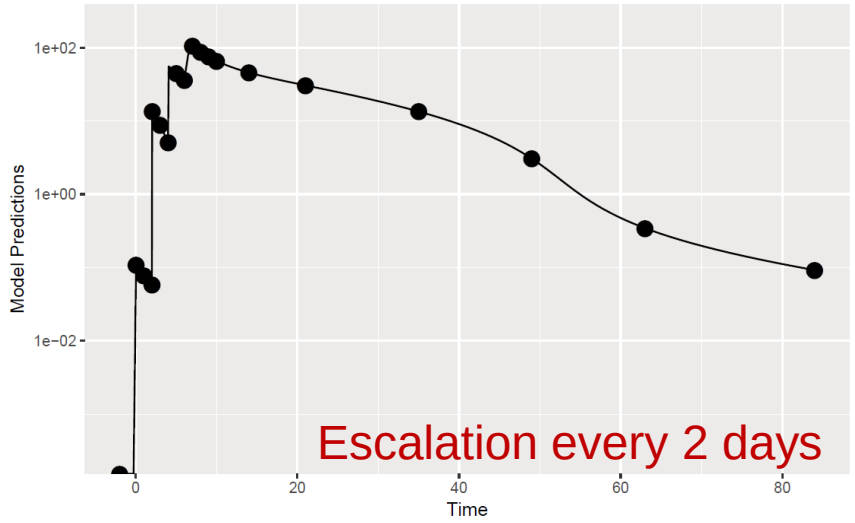
- Early readout from initial “Espresso” design part
- Then get estimates from washout part
- Comparison possible due to good precision in both assessments

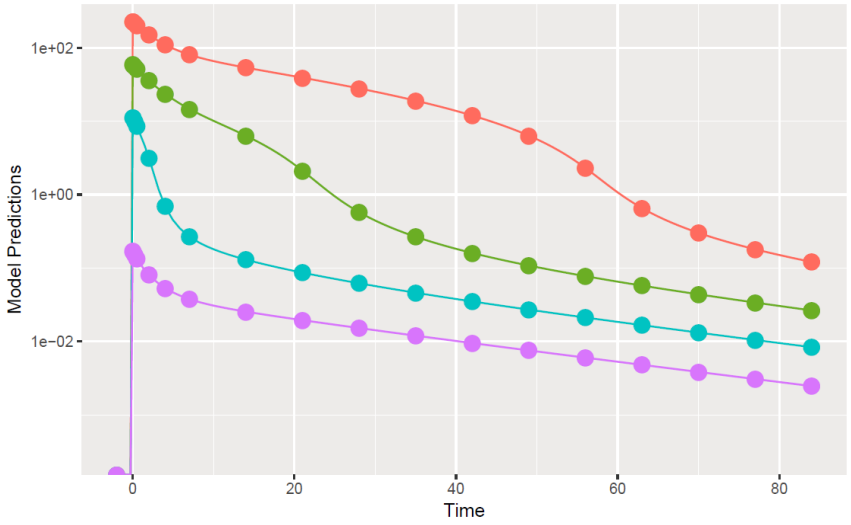


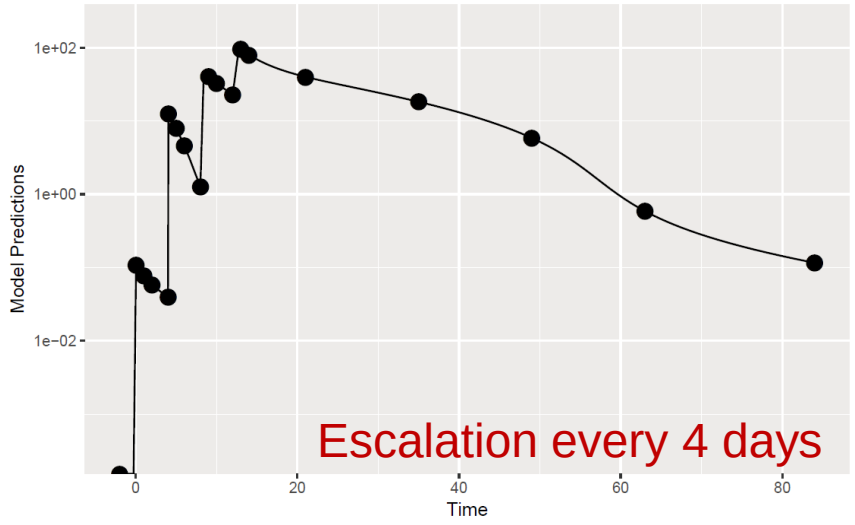
If there is time-dependence we would notice

For 2-cmt model need to adjust, due to distribution phase

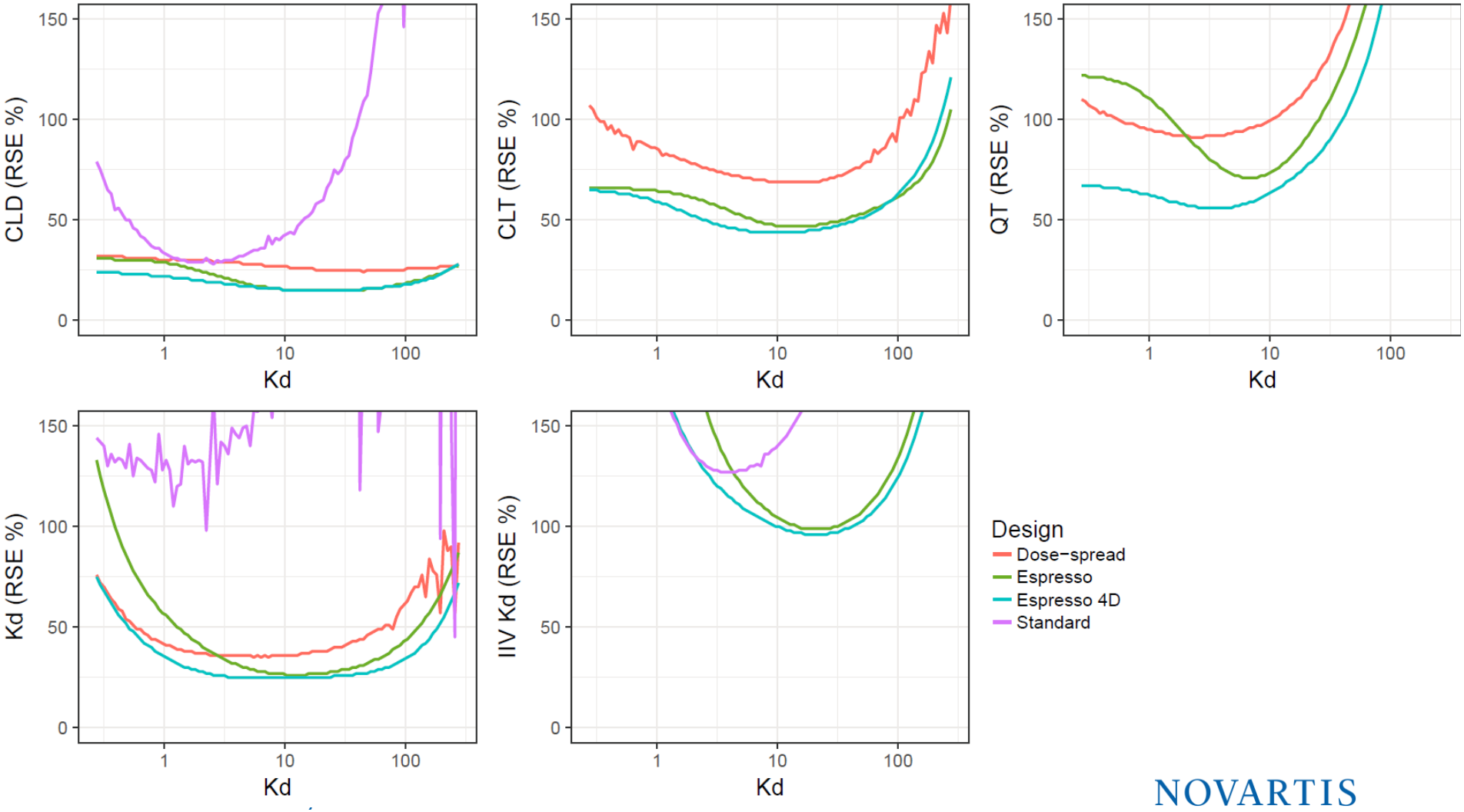








4-day interval for up-titration slightly better than only 2 days



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Up-titration interval depends on pharmacology and biology

- Dynamics of the system
  - With rapid responses (e.g., food- or aero-allergen challenges) in atopic individuals, the entire procedure can take place within a few hours
  - Delayed responses need longer to reach steady-state, so longer intervals between up-titration are better
  - For a long-term response requiring many weeks to equilibrate Espresso may offer no advantage compared with a standard parallel arm design
- Other considerations preferring shorter intervals
  - ADAs (anti-drug antibodies) that develop after 10-12 days in NHPs
  - Time-dependent adjustments of the system (down-regulation of receptors or other tolerance phenomena)

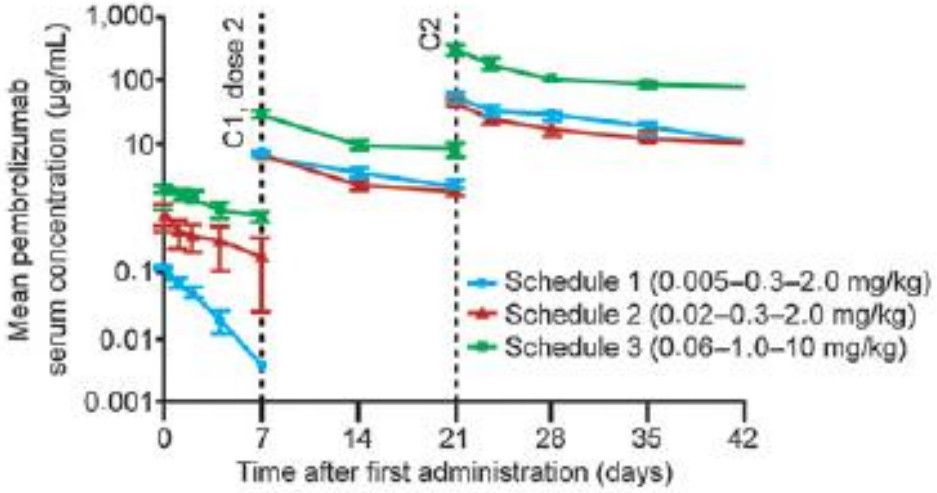
Robustness of overall design by redundancy and mixing elements

- To account for model uncertainty/misspecification it is essential not to fully optimize the system, but rather to add some redundancies
- This was exemplified in our first example but for the Espresso design could also mean to mix the within-individual dose escalation with standard parallel group designs
  - Parallel arms also help to be able to interpret the data without a model (or without knowing the correct model)

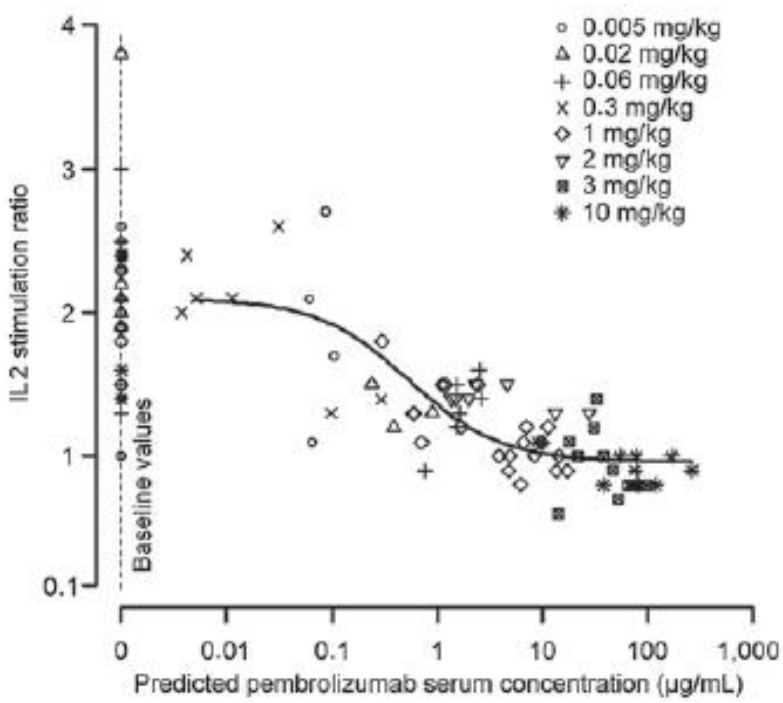
Applied in oncology Ph 1 trial(s)

By Patnaik et al. (Merck) Clin Cancer Res 21(19), 2015

3 arms – each 3 dose-levels



Concentration-response



"*To provide a robust assessment of dose linearity and target engagement potency, Part A-2 was designed to include doses substantially lower than those expected to demonstrate pharmacodynamics activity.*"

Summary

- Optimizing sampling time points plays only a minor part when considering study designs – information content depends on the input functions
- Robustness w.r.t. model uncertainty/misspecification needs redundancy rather than fully optimized designs

- How can we come up with more creative dosing regimen schemes to elicit the most information?
- How can we sell that to the clinical teams if one can only interpret the data with a (possibly biased) model?

Thank you!

- Thanks also to:
  - Phil Lowe
  - Mark Milton
  - Anne Kuemmel
  - Oliver Sander
  - Jean-Louis Steimer
- As well as:
  - Andy Hooker et al. (PopED)
  - France Mentre et al. (PFIM)