Clinical Development & Analytics

Model-informed study design

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EFSPI
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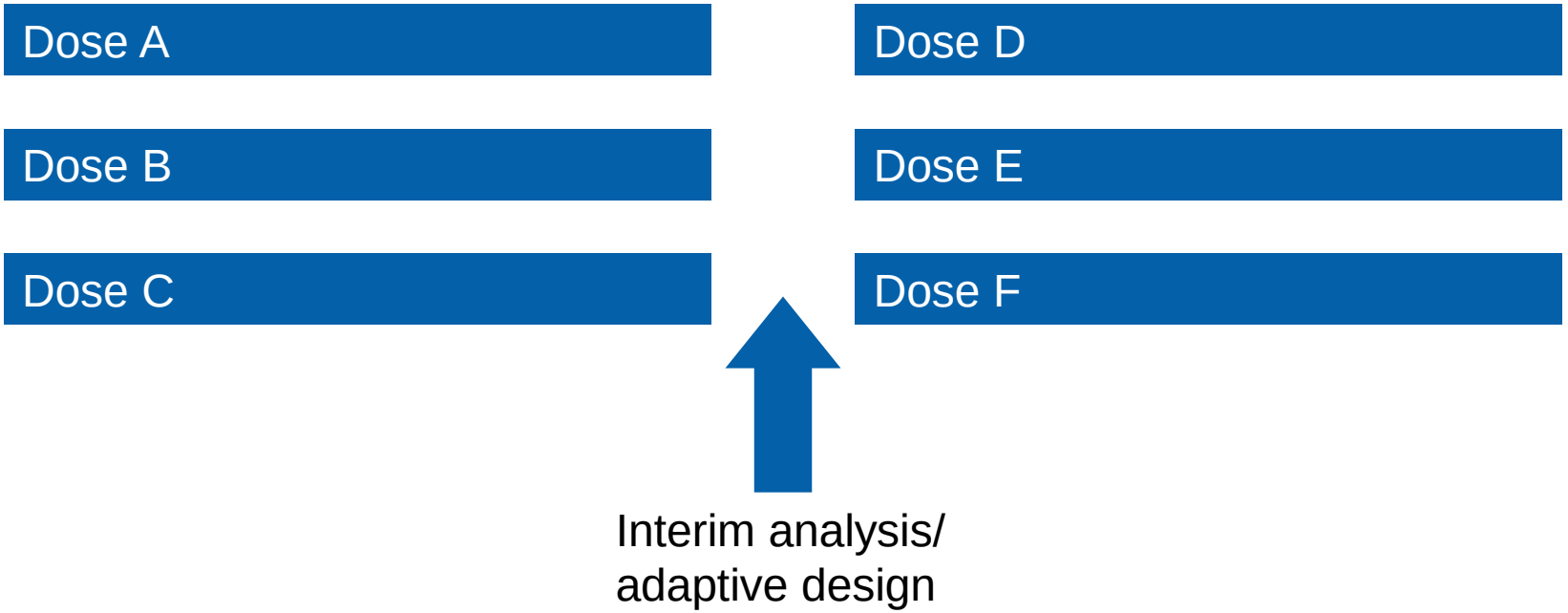
Outline

- More informative study designs are needed. Especially in the learning Phases (1+2) of drug development. Adaptive designs work well, but are often avoided due to time constraints and administrative overhead.
- We show ***three examples***, where substantially more information can be gained by non-standard dosing regimens and integrating all of the available data in model-based analyses.
- These allow us to explore alternative dose-regimens more efficiently. In the last example it enabled Novartis to study superior regimens in Phase 3 that had not been tested previously.

Standard designs: Similar parallel arms

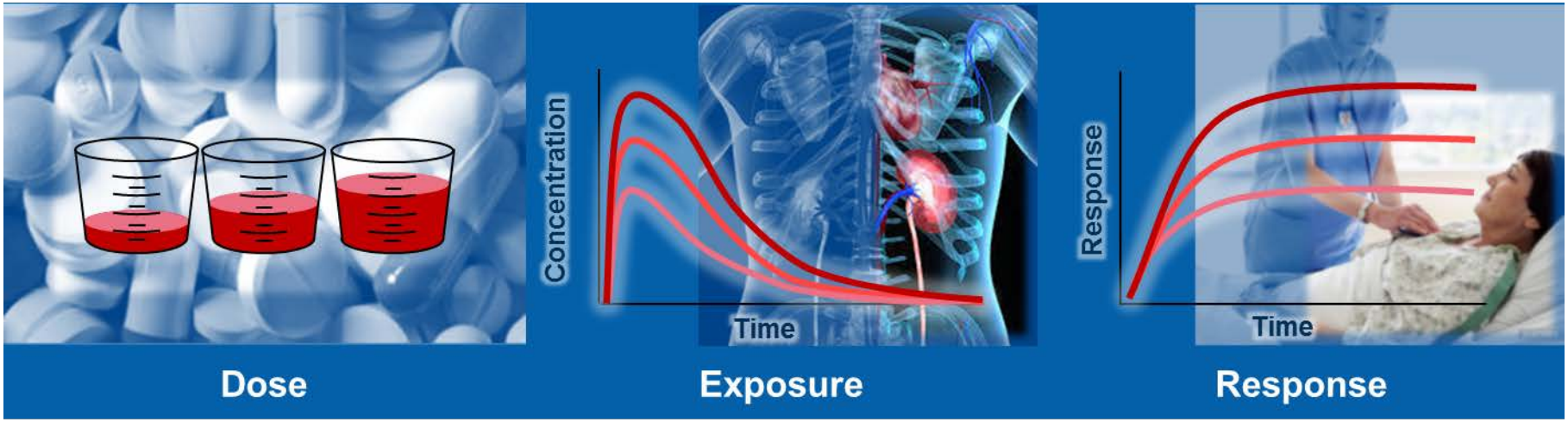


- Each subject => exactly one dosing-regimen
  - Except for Placebo switched to treatment (excluded in the analyses)
- Statisticians tasked with sample size/power calculation

Study design: More than sample size

- 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)**
  - **Which intervention (dosing regimen / creative designs)**
  - [Important to consider dependence on model uncertainty/misspecification]

Model-informed = Dose – Exposure (Pharmacokinetics) – Response

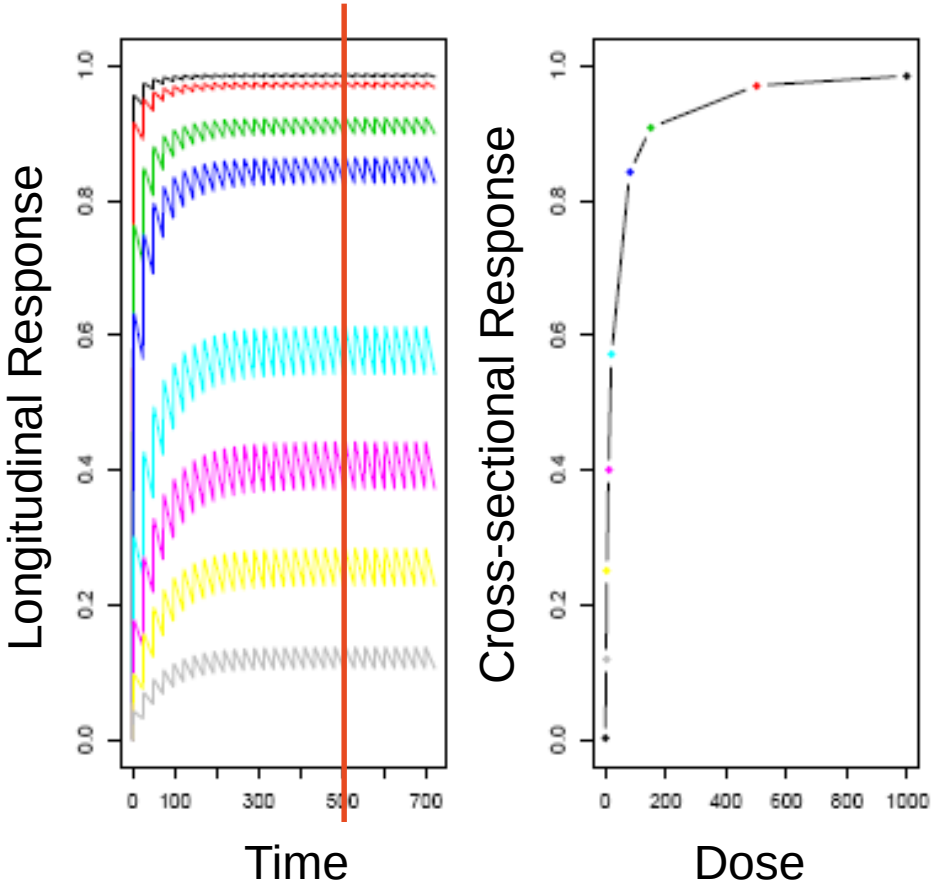


- Allows:
  - Non-steady state analysis
  - Analysis of different dosing regimens (QD, BID, ...)
  - Including information from induction doses
  - Inclusion of all time-points for longitudinal analysis
- Stephen Senn: “We should not ignore pharmacokinetics”

Senn S., Clin Pharmacol Ther. 2010

Longitudinal with continuous time

More power with model-based approach



Longitudinal model-based analyses can deal with:

- Non-steady state data
- Different dosing-regimens

- **Allows for informative, innovative designs**

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Example 1
“Espresso design”
Within-subject dose-escalation

Martin Fink, Mark Milton, Phil Lowe

Lowe P, et al., Clin Pharmacol Ther. 2017

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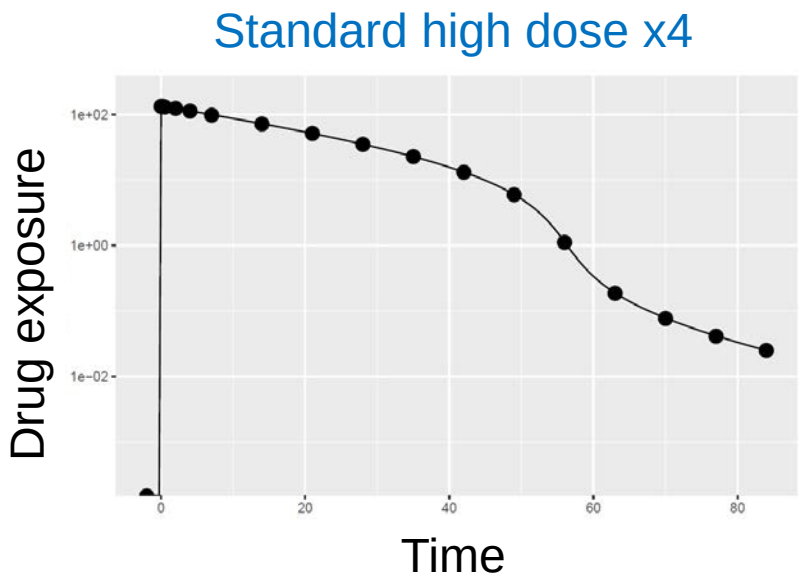
Example setting

- Monoclonal antibody, with target-mediated drug disposition (TMDD)
  - This means, here “longitudinal exposure” is a biomarker with information about target engagement
- Concept shown here for early non-human primate (NHP) studies, but is applicable for all learning studies
- Uncertainty regarding how in-vitro Kd (binding affinity) matches in-vivo Kd
- Goal was to construct study design that is robust against this uncertainty for first NHP study (with 4 animals only)

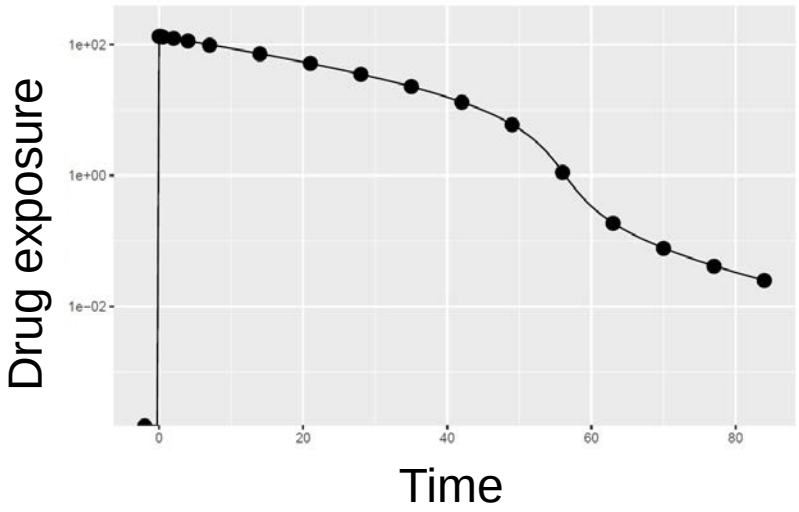
Kd... Binding affinity of drug to target

Standard high dose

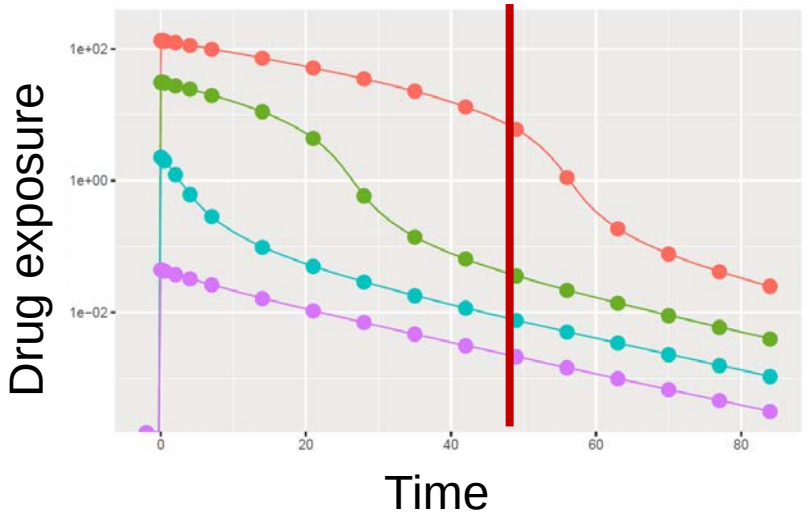


Standard high dose x4 or Dose spread 1 subject/level

Standard high dose x4



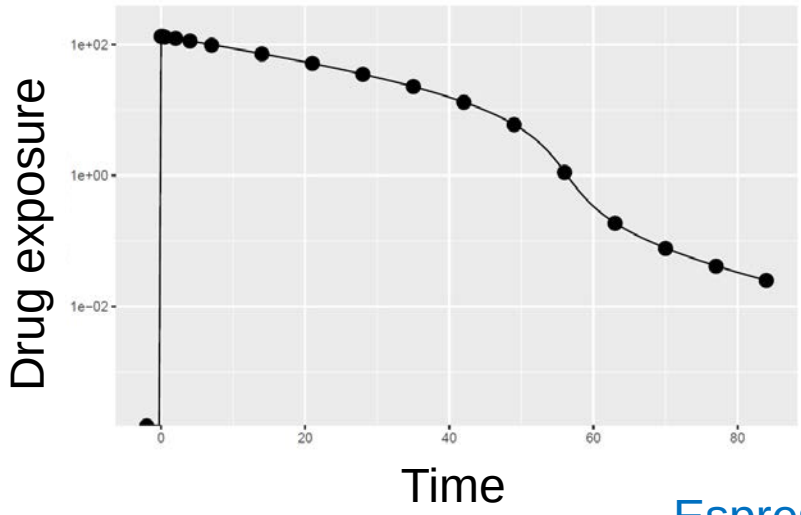
Dose spread 1/lvl



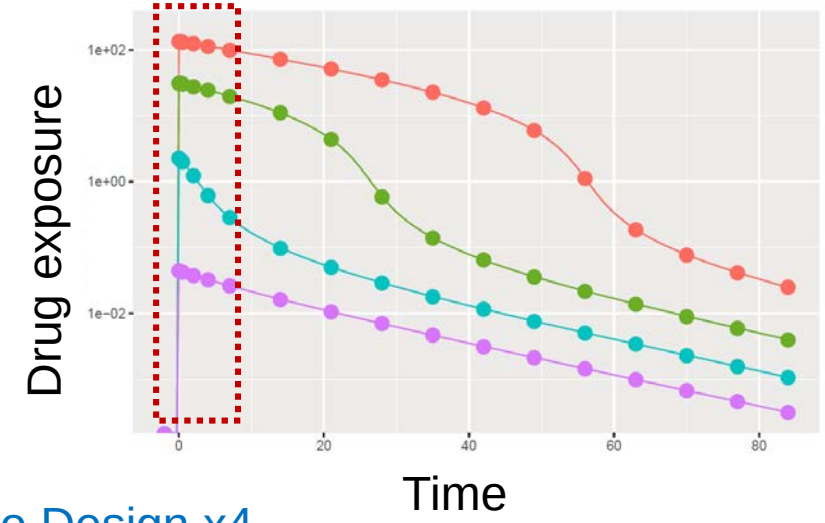
- Each curve has a different shape
- Each sampling time point adds different information
- A cross-sectional analysis would provide much less information

Espresso design: Within-individual dose escalation

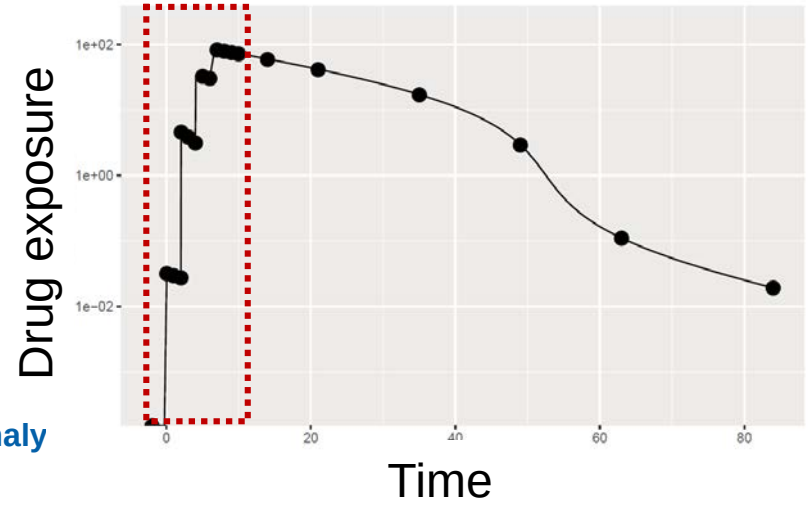
Standard high dose x4



Dose spread 1/lvl



Espresso Design x4



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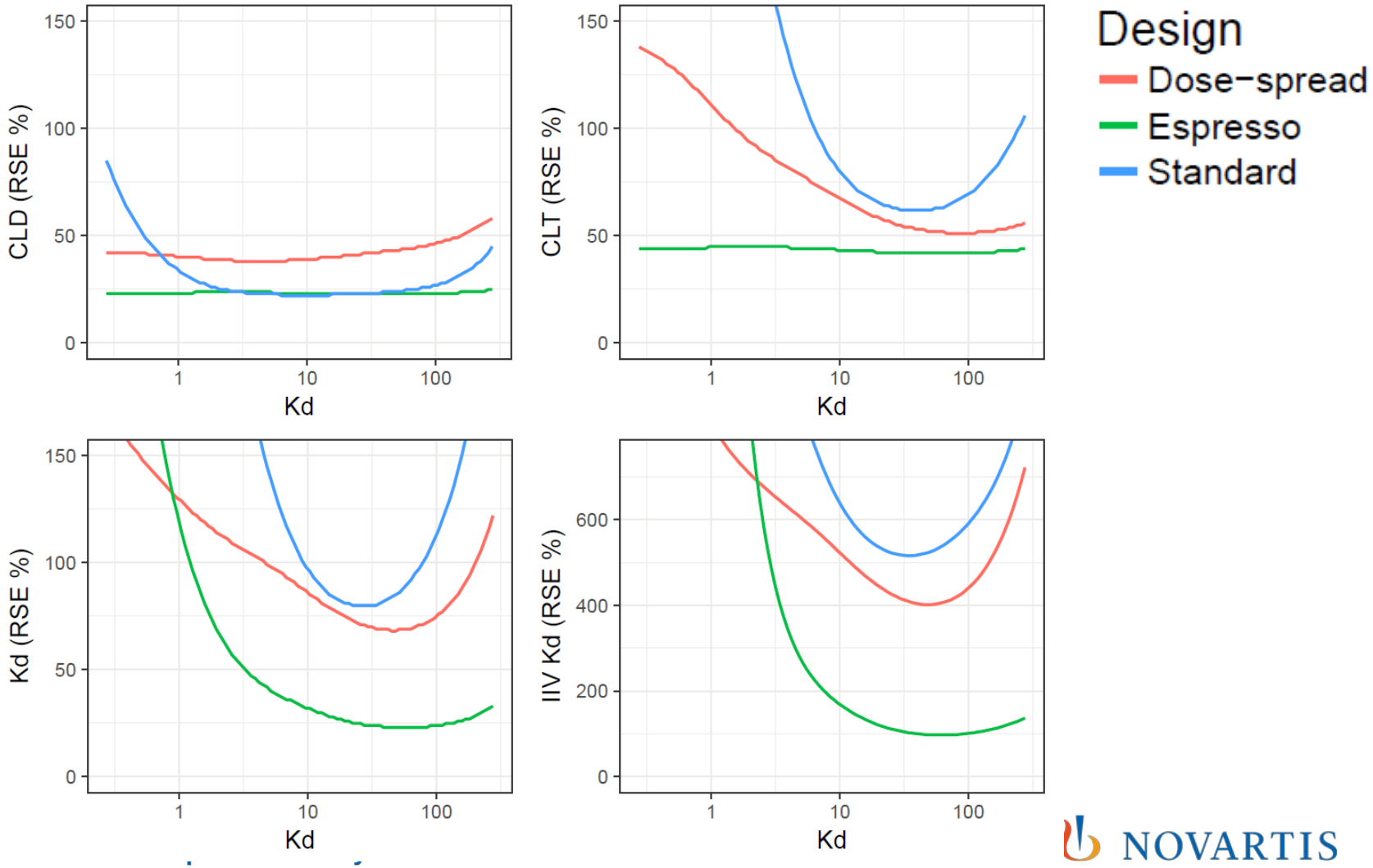
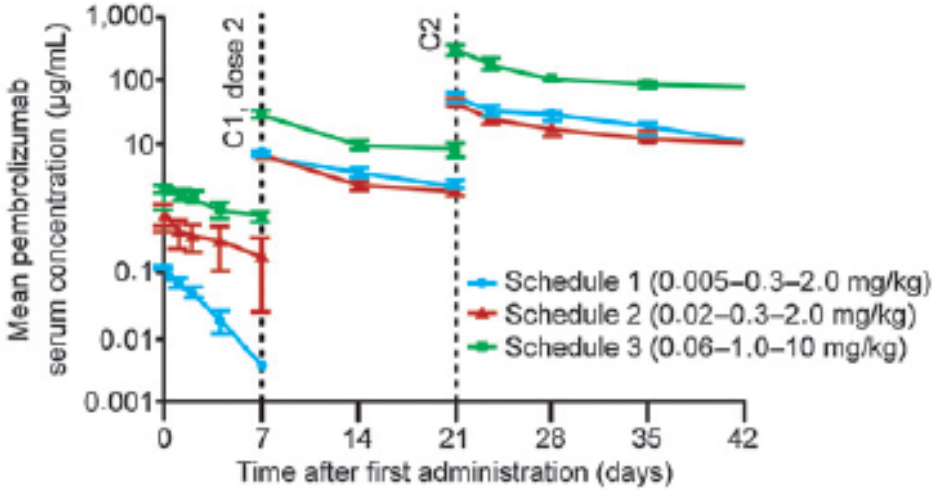
Espresso design (green) gives lowest relative standard errors



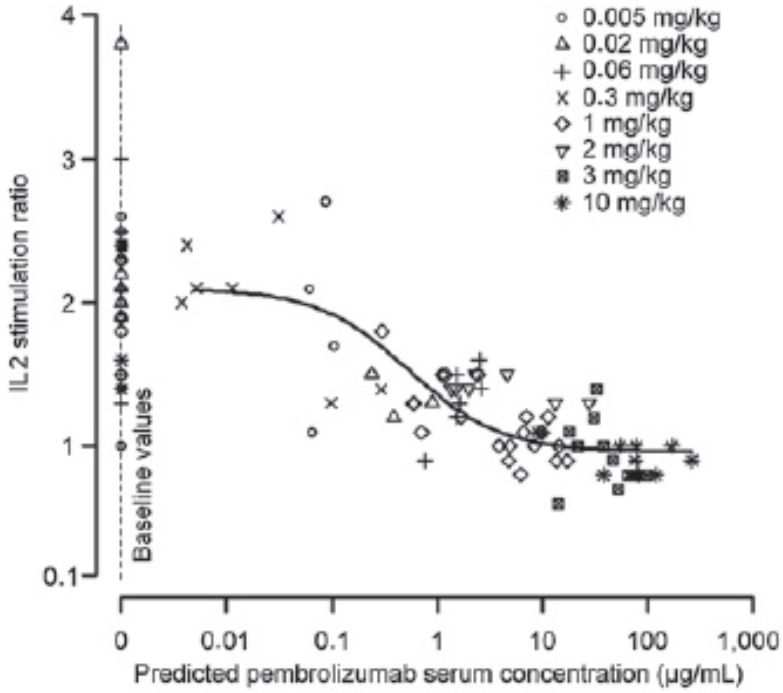
Applied in oncology Ph 1 trial(s)

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.*"

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Example 1 - Summary

- Within-subject dose escalation provides robust information on non-linear systems (exposure, biomarkers, efficacy,...)
- Especially, when normally low exposure levels would not be included (or only in the washout)
- Using a model-based approach this can be integrated efficiently and provides more power than cross-sectional analyses

Example 2
Ligelizumab Dose-Range-Finding study

Phil Lowe, Anne Kuemmel, Oliver Sander

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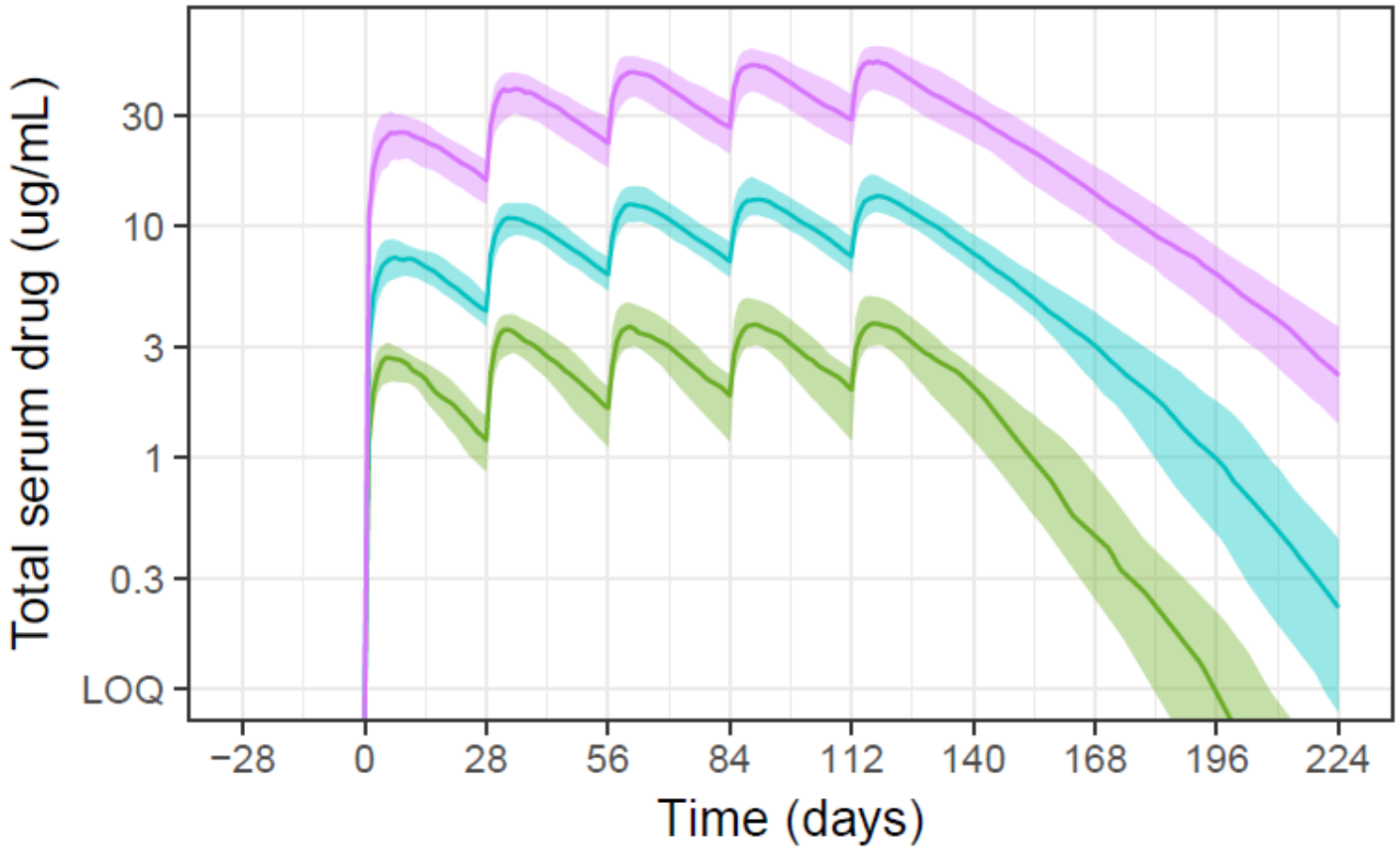
Example setting

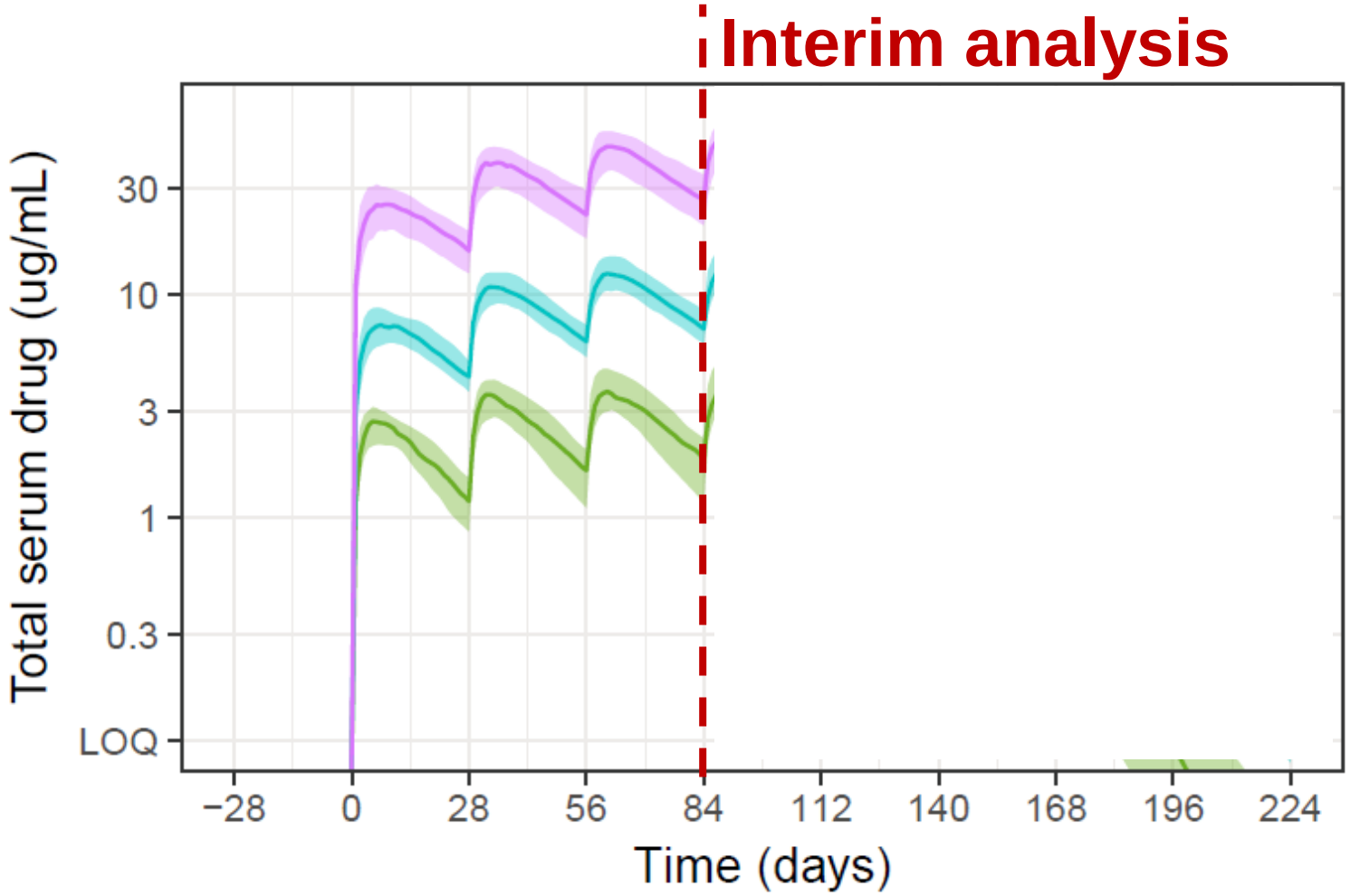
- Omalizumab is a monoclonal antibody that binds to IgE and reduces itch and hives in Chronic Spontaneous Urticaria (CSU)
  - Published omalizumab-IgE-itch-hives placebo and drug-effect model
- Ligelizumab has higher binding affinity but potential difference in CSU is unknown
  - In-vitro difference: 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



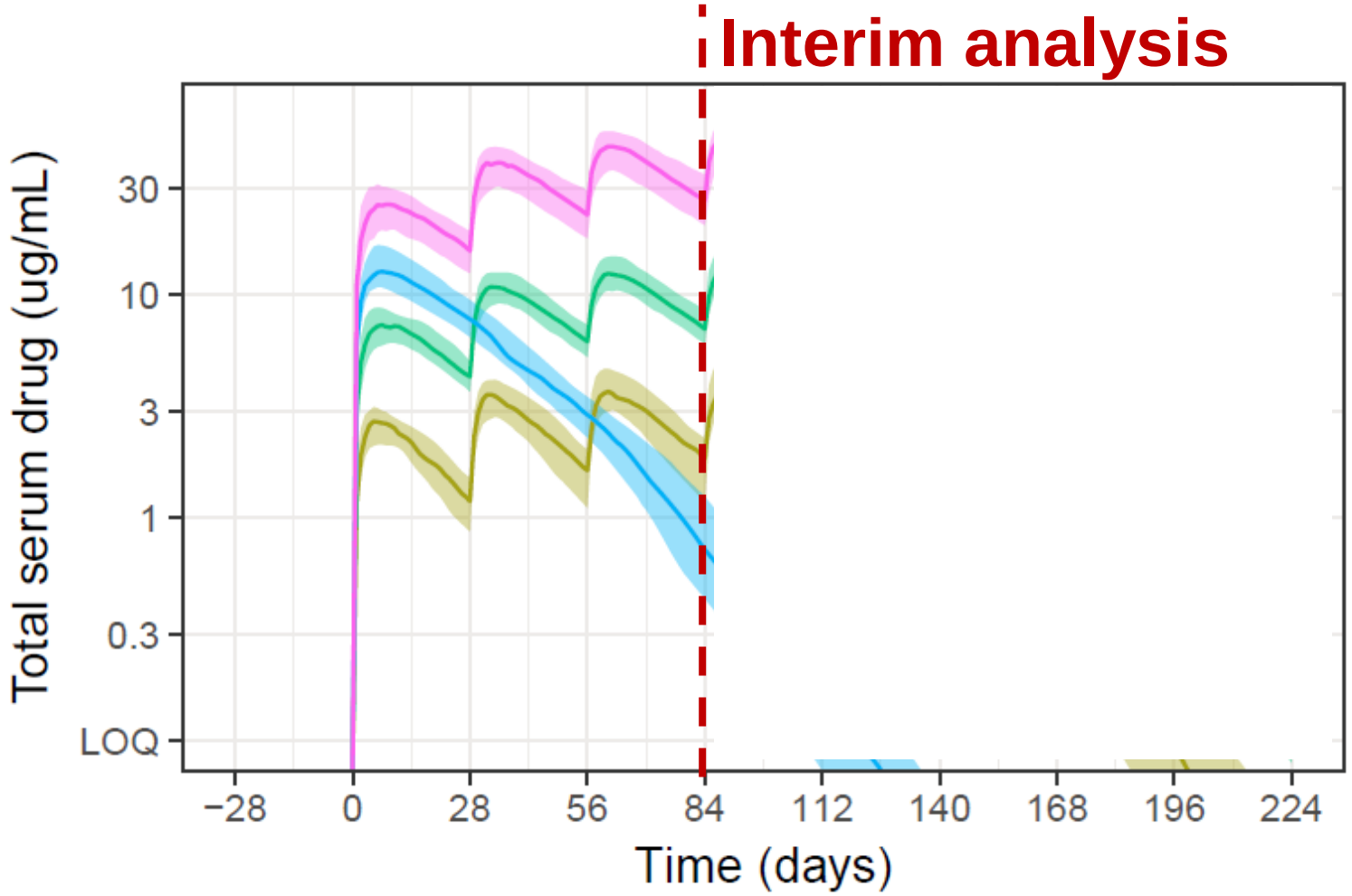
Three active dose levels plus placebo administered every 4 weeks for 20 weeks

Standard 3-arm design but at interim analysis missing information

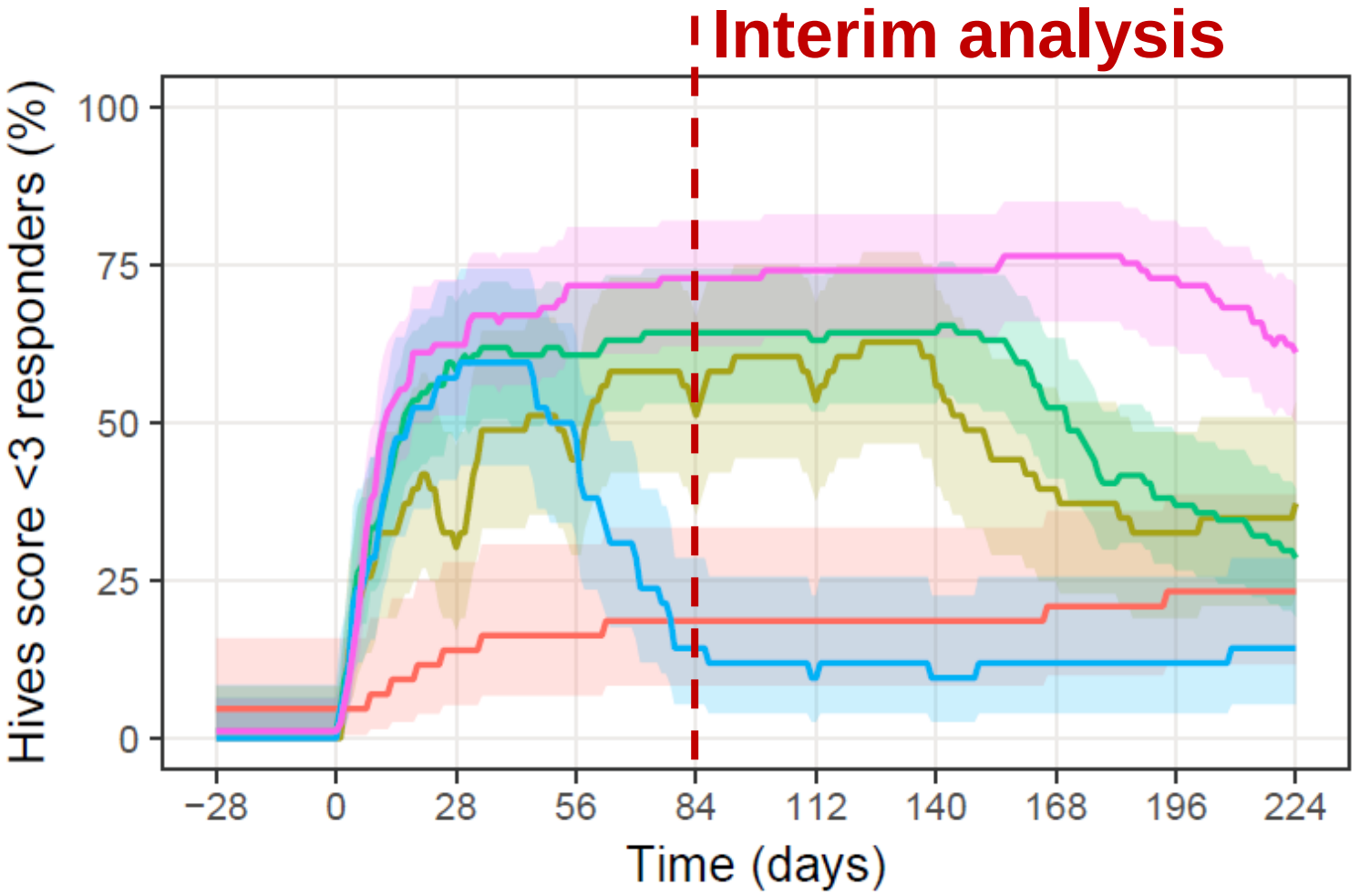


Three active dose levels plus placebo administered every 4 weeks for 20 weeks

Adding a single dose provides "washout information"



Single dose (SD) arm provides information on recovery timecourse



Example 2 - Summary

- Adding a single-dose arm includes blinded washout information (essential for subjective assessments)
  - Contrary to washout at end-of-study this is a blinded “washout” (double-dummy placebo)
- Regimen selection possible based on SD data
  - Standard parallel arms have all q4w regimen
- A model-based approach can be used to support dose-regimen selection, combining the information from the q4w regimen and the single dose – to use the totality of the collected data.

Example 3
Dose-regimen selection for Cosentyx® Phase 3

Oliver Sander, Achim Guettner

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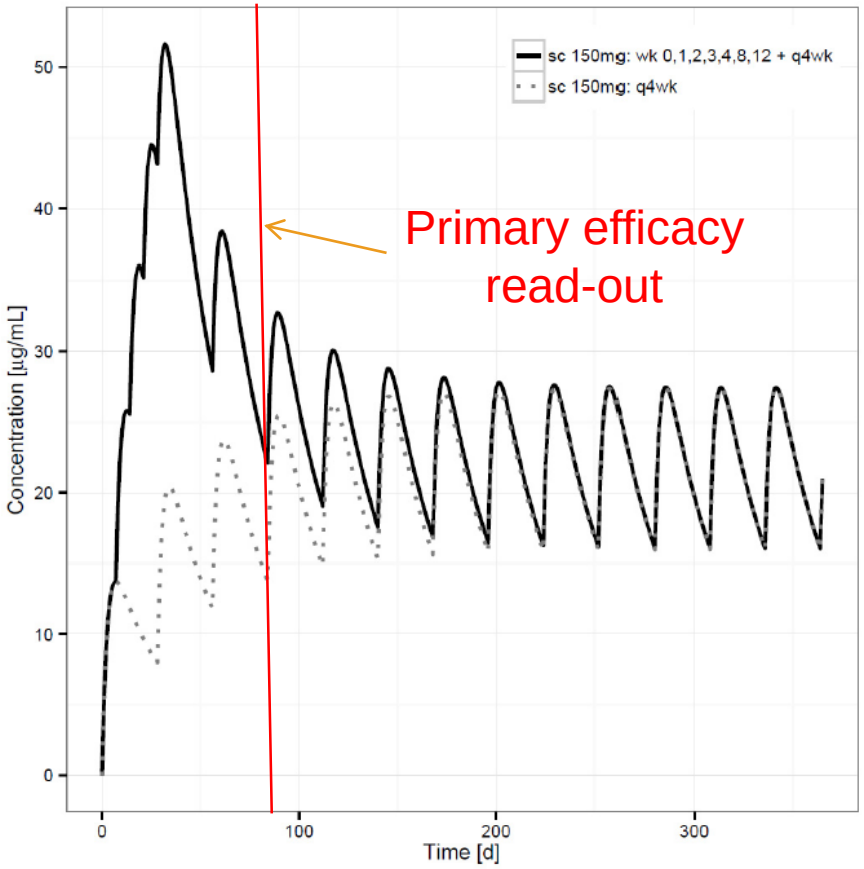
Example setting

- Cosentyx is a monoclonal antibody that has been developed for treating Psoriasis
- In Phase 2 different doses, regimens, and administration routes were tested
- Goal was to select Phase 3 regimen that would lead to quick relieve of the disease – and ensure superiority over the competition at the primary endpoint at 12 weeks (Day 84)

Selecting regimen needs optimization of doses and timing

Difficulties were:

- With q4wk dosing:
  - PK has not reached steady-state
  - PASI response lags behind even further
  - ***Need induction treatment to optimize 12 week response***
- How to select an induction regimen based on the collected Ph2 data?



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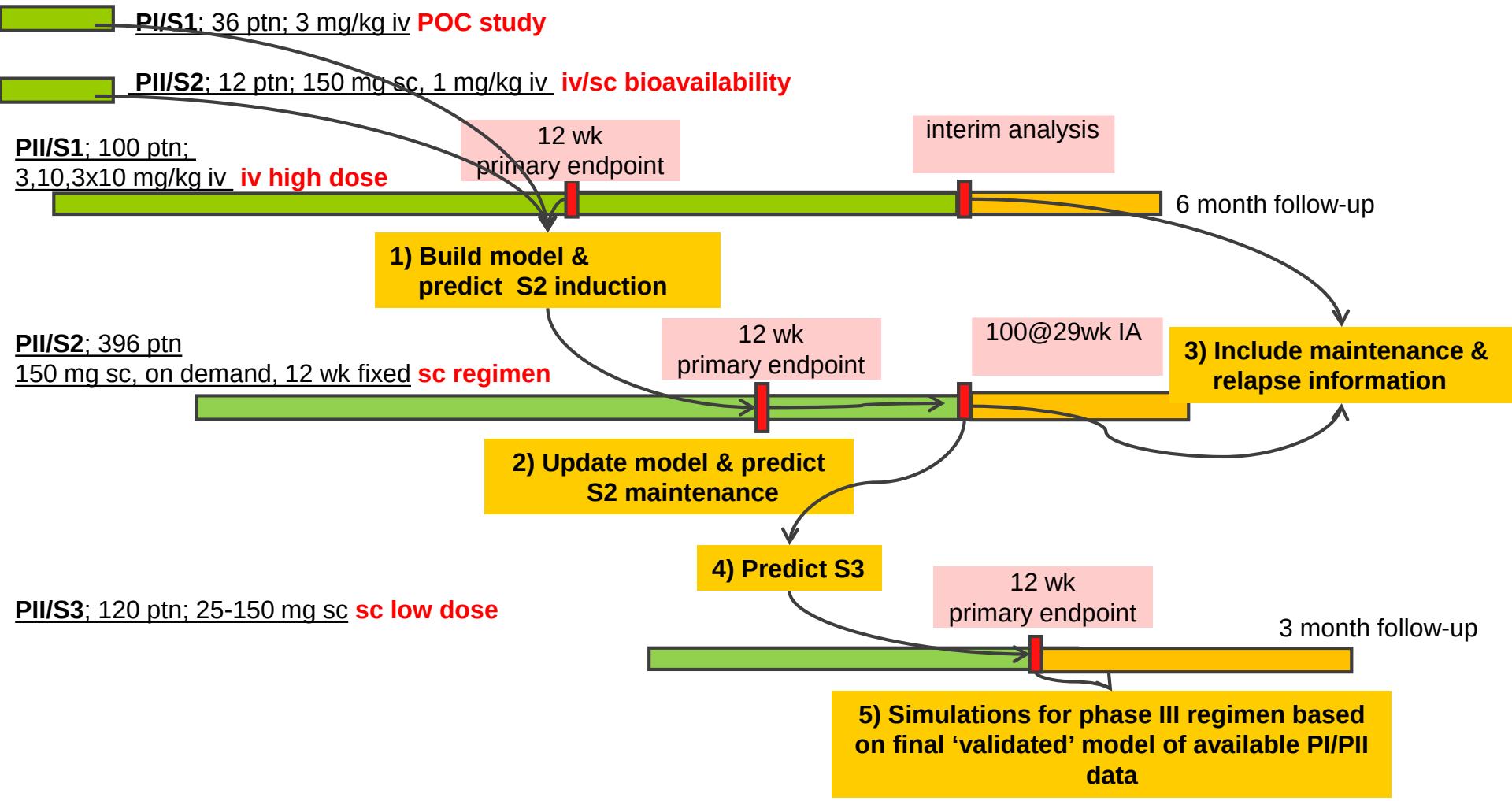
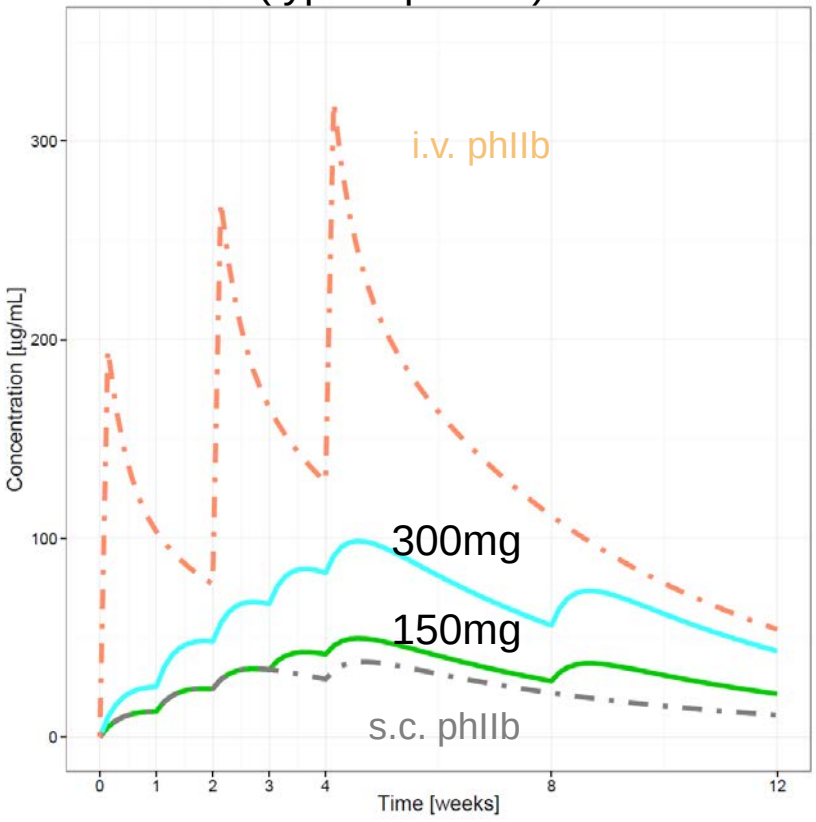
Sequential model building gives confidence in predictions

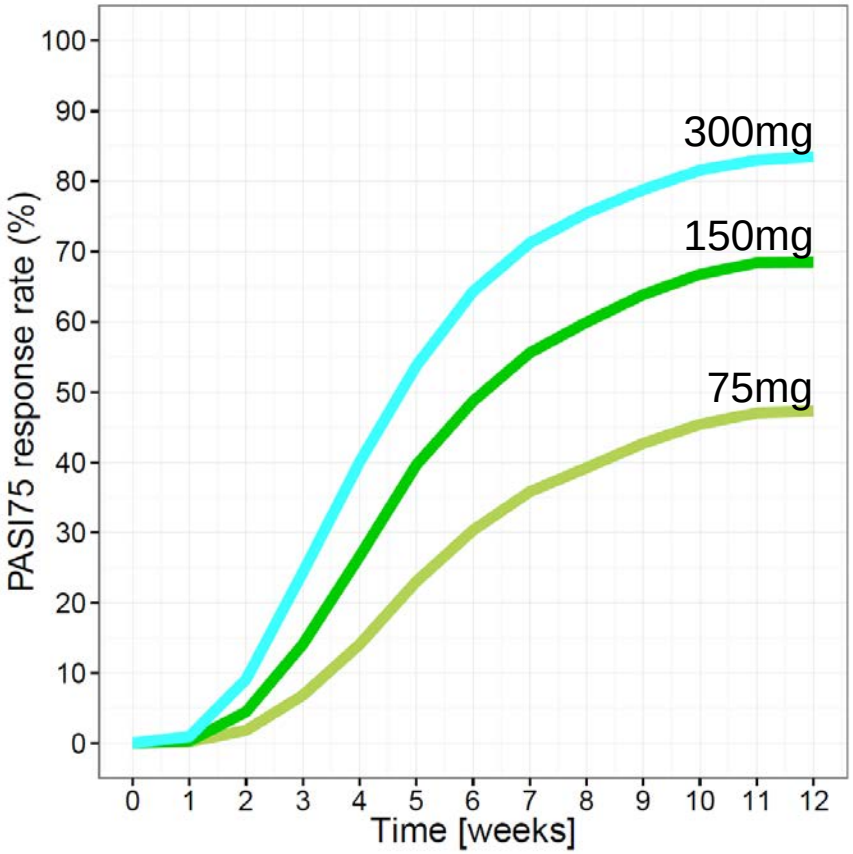


Response predictions used for PIII regimen finding
150mg or 300mg s.c. at weeks 0,1,2,3,4,8 + q4wk

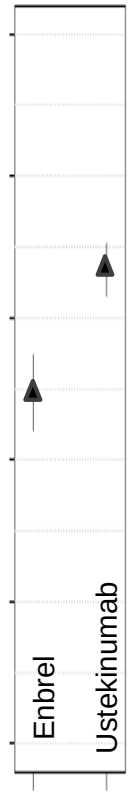
PK simulation
(typical patient)



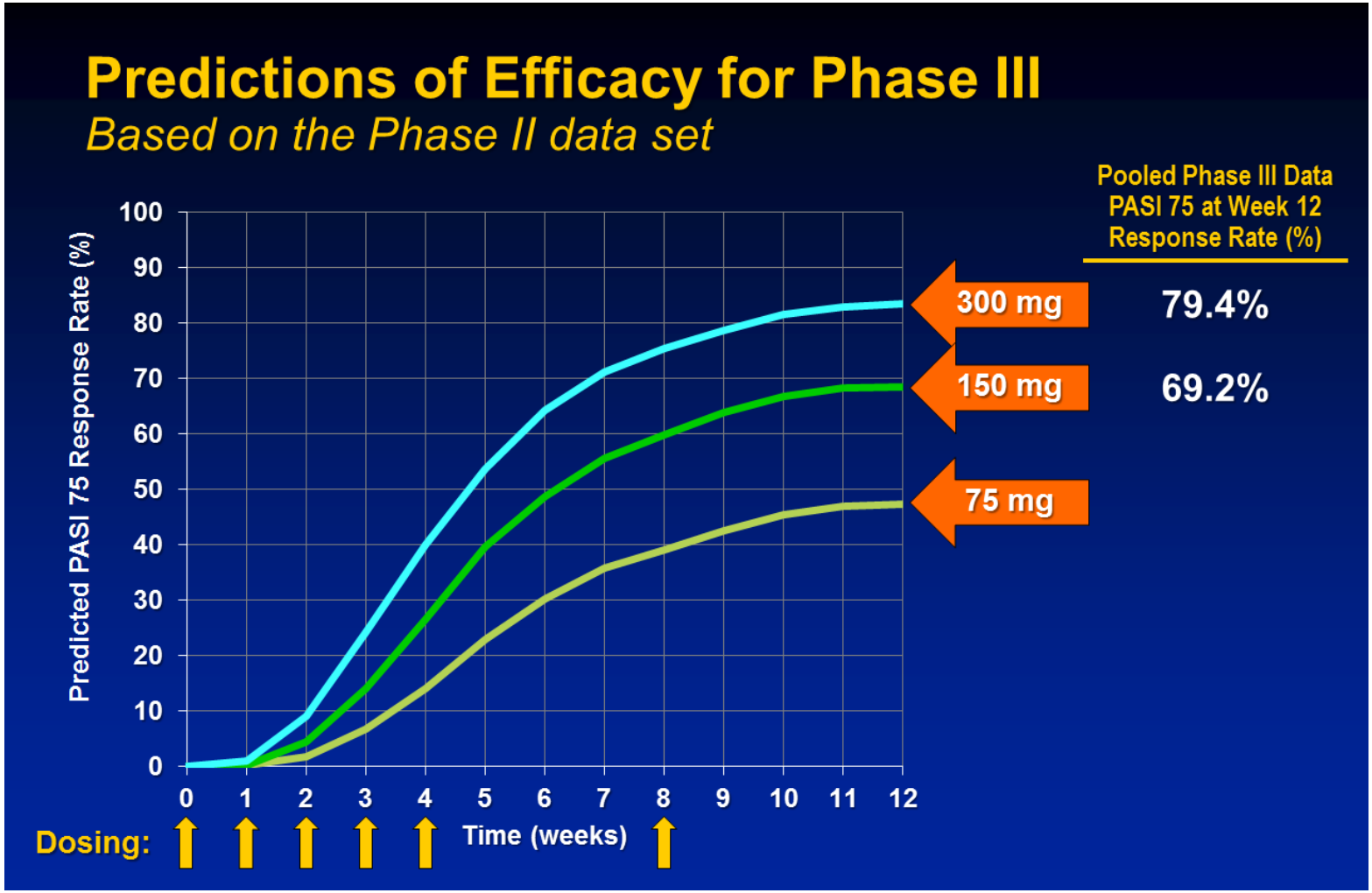
PASI simulation
(population response rate)



Competitors
at wk12



Predictions confirmed in Ph3



Example 3 - Summary

- How do you find the best route and dosing regimen for
  - a delayed
  - non-steady-state response
  - with a variety of doses
  - regimens
  - and 2 administration routes to choose from?
- Traditional approach could only select one of the regimens tested in PII
- A PK-PD model is the most efficient way to integrate all this complexity

Summary

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Summary

- More informative model-based study designs that exploit the full time-course are needed.
- We showed three examples, where substantially more information can be gained by integrating all of the available data in model-based analyses.
- These allow us to explore alternative dose-regimens more efficiently. In the last example it enabled Novartis to study superior regimens in Phase 3 that had not been tested previously.
- The combination of model-based PKPD methods and innovative designs have the potential to make drug development more efficient.

Thank you!

- Thanks to my Novartis colleagues:
  - Phil Lowe
  - Mark Milton
  - Anne Kuemmel
  - Oliver Sander
  - Jean-Louis Steimer
  - Achim Guettner
  - Mick Looby
- Thanks also to:
  - Andy Hooker et al. (PopED)
  - France Mentre et al. (PFIM)