Modeling and Simulation in Drug Development

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Overview

- In the context of increasing the R&D productivity, Modeling and Simulation (M&S) techniques are quantitative integrative tools allowing to help better decision making for drug development
- Introduction: Context and overview of M&S benefit
- Three examples of M&S contributions in different drug development spaces
- Cautions
- Conclusions

R&D productivity issues can be tackled by new science and technology toolkit among which M&S

- Concerns re cost, inefficiency and challenges of drug development crystallized in FDA Innovation/stagnation paper nearly 10 years ago.
- Modeling and Simulation identified as one approach to improve knowledge management and decision making

> ***Opportunity:*** The concept of model-based drug development, in which pharmaco-statistical models of drug efficacy and safety are developed from preclinical and available clinical data, offers an important approach to improving drug development knowledge management and development decision making

Innovation/stagnation FDA paper 2004

- How is Human Pharmacology contributing to this opportunity 10 years later ?

M&S techniques are quantitative integrative tools to help better decision making for drug development

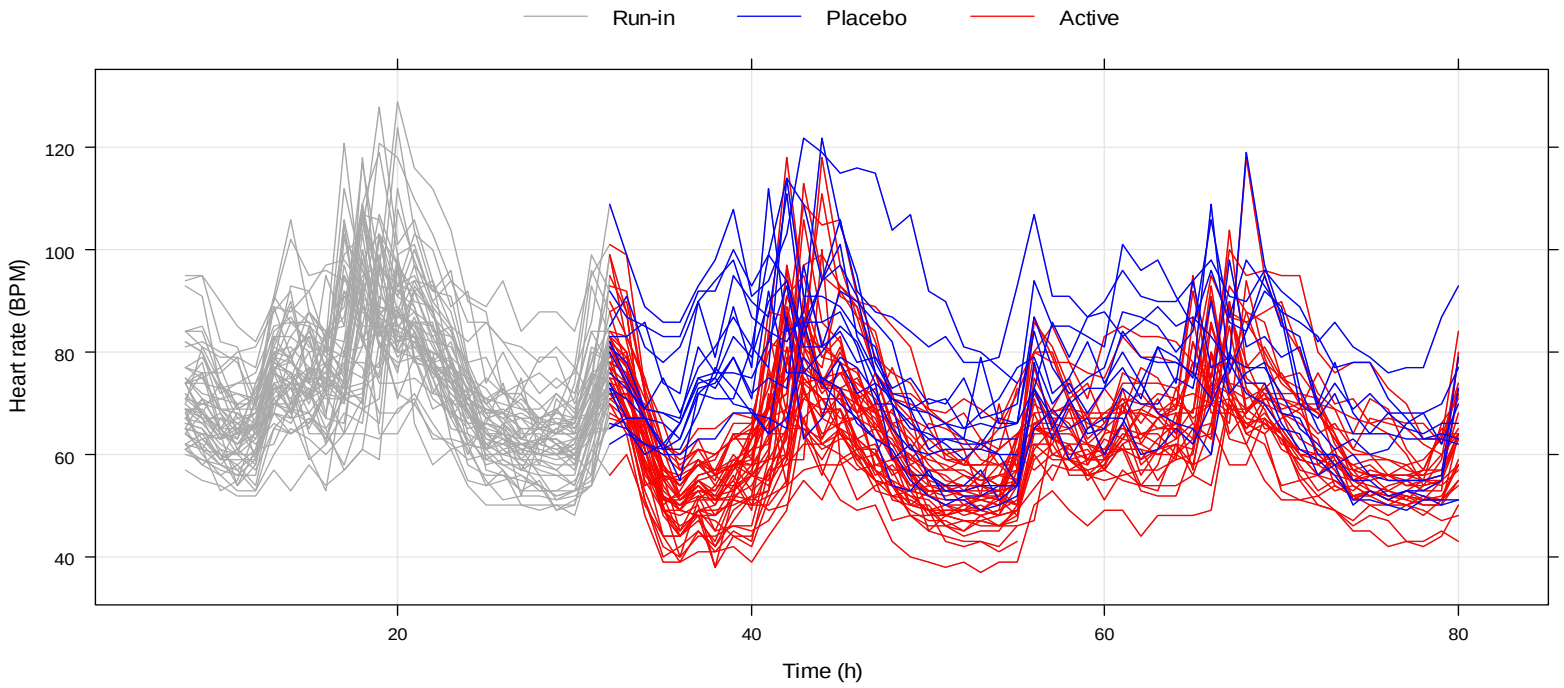
- There are several reasons why M&S is helpful
- Examples will illustrate few of them:
  - To predict and extrapolate
    - Predict scenarios which have not been studied
    - Provide answers to questions that were not pre-specified
  - To integrate information
    - Across time, dose-levels, studies, and even drugs
  - To optimize future studies

Example 1
PKPD Modeling of drug effect on heart rate from holter monitoring data

Specific M&S added value: Simulation scenarios to help select best study designs

For a non cardiovascular drug with a Heart Rate slowing effect, how do we mitigate?

Compound x has a clinically relevant effect on heart rate as measured by holter monitoring



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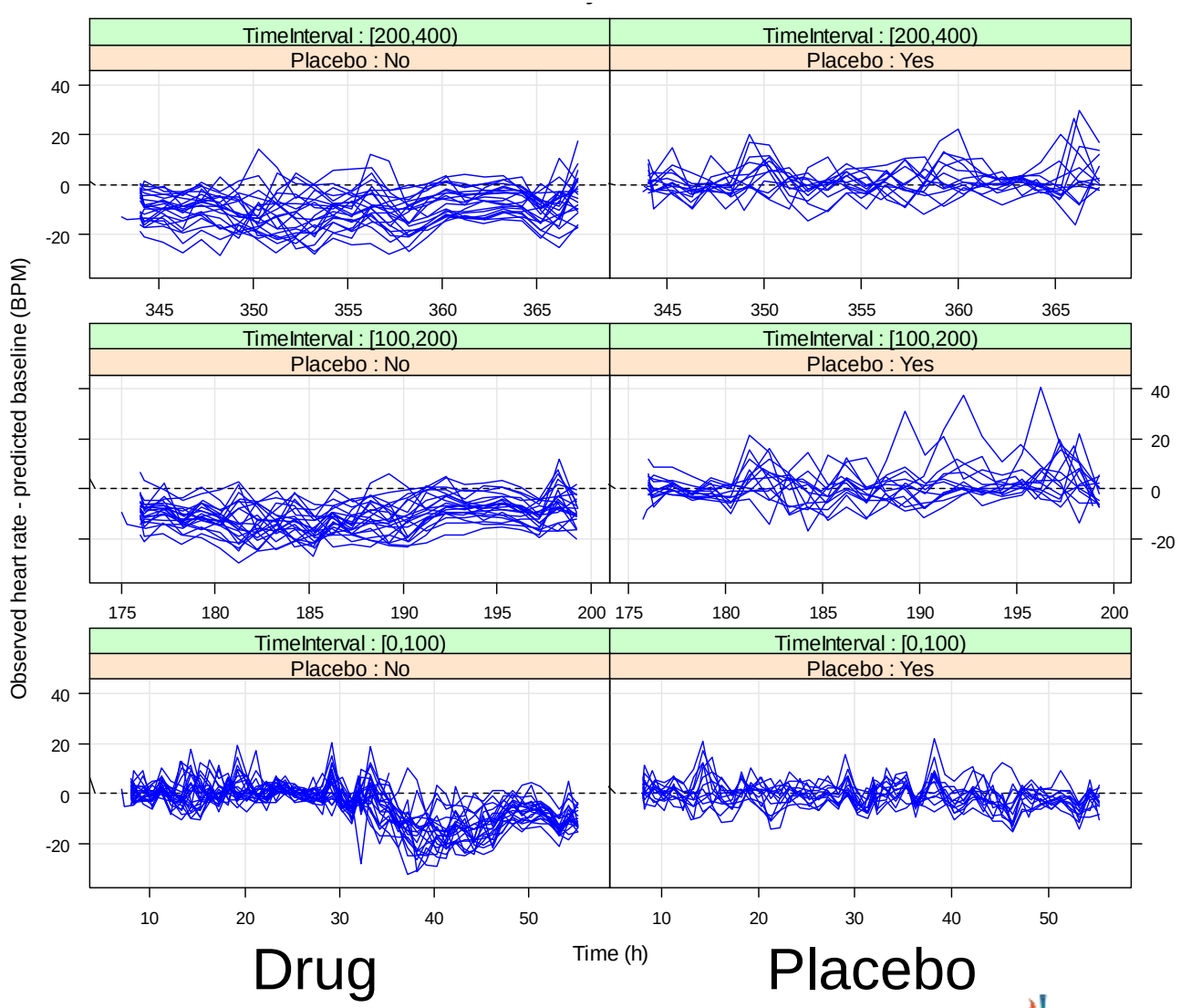
There is also a tendency for the drug effect to lessen with time despite continued o.d. dosing.

Day 13 to day 14

Day 6 to day 7

Predose to 24h postdose



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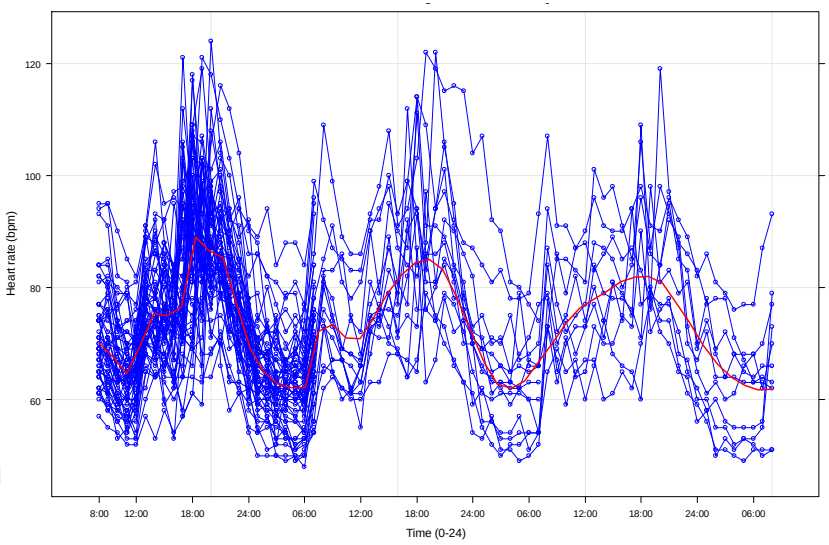
Normal Heart rate data display marked diurnal variation Can be modeled using sums of cosine functions

$$HR = HR_{ave} + Amp_1 \cdot \cos\left((t - \tau_1) \cdot \frac{2\pi}{per_1}\right) + Amp_2 \cdot \cos\left((t - \tau_2) \cdot \frac{2\pi}{per_2}\right) + \ldots$$

HR_{ave} = Average heart rate
Amp_1 = Amplitude of first cosine rhythm
τ_1 = Peak time of first cosine rhythm
per_1 = Period of the first cosine function (e.g. 24 hours)
Amp_2 = Amplitude of second cosine rhythm
τ_2 = Peak time of second cosine rhythm
per_2 = Period of the second cosine function (e.g. 12 hours)



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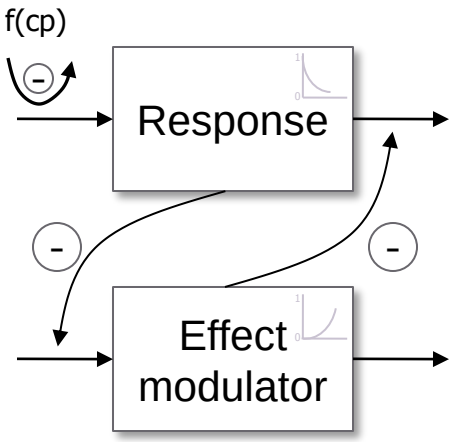
Effect on HR and tolerance are dose dependent
Tolerance component was requested for proper fit



$$\frac{dR}{dt} = k_{in} \cdot f(C_p) \quad - k_{out} \cdot R \cdot (1 - M)$$

$$\frac{dM}{dt} = ktol_{in} \cdot (1 - R) - ktol_{out} \cdot M$$

$$f(Cp) = 1 - \frac{E_{max} \cdot C_p}{(EC_{50} + C_p)}$$

$$\widehat{HR} = \widehat{HR}_{base} \cdot R$$

$\widehat{HR}$ Is the predicted HR under Trt

$\widehat{HR}_{base}$ Is the individually predicted baseline

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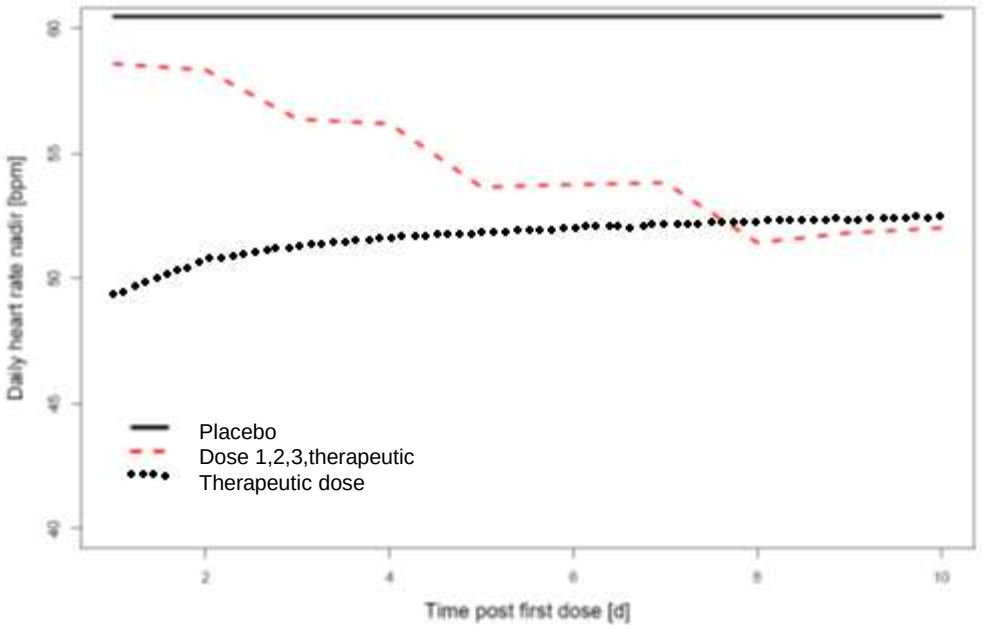
What if scenario exploration: Titration scenario: 4 steps over 7 days

Longitudinal evolution of average daily HR nadir for a range of daily doses



- This scenario compares esclating in 3 steps: 4 increasing doses over 7 day intervals

At each escalation step, HR decreases(2-5 bpm), but each single step is less than the initial drop for constant therapeutic dose (10-12 bpm)

By 7 days HR approaches the plateau that would have been reached if therapeutic dose had been given daily.

Several scenarios with various number of steps, and dose per step simulated to optimize trade off btw HR effect and logistical constraints

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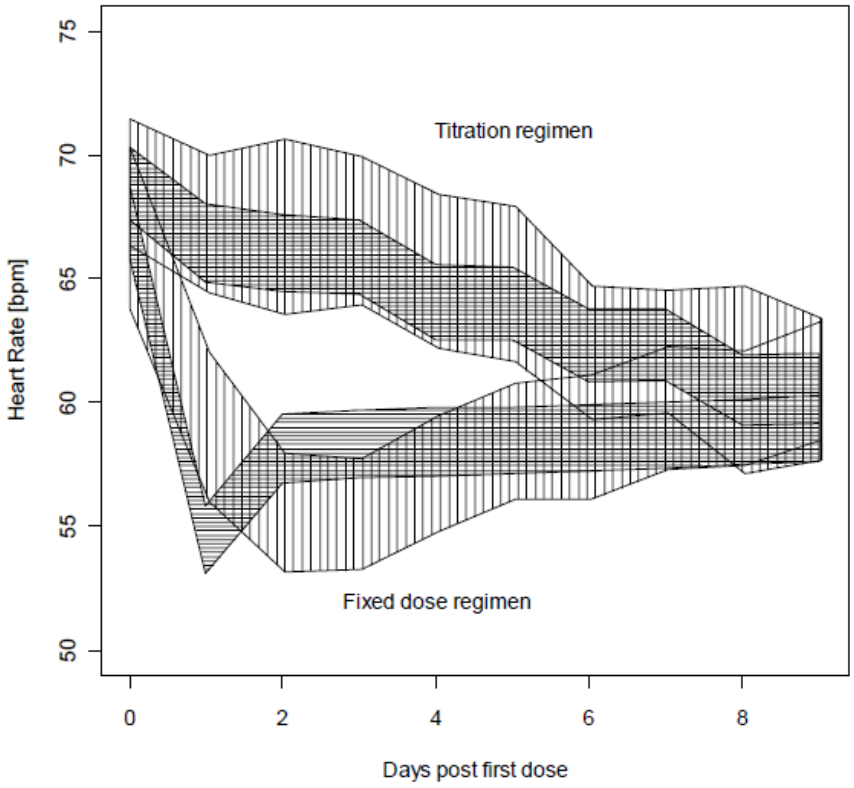
Validation of model by checking the predictions

Observed response intervals (vertical lines) vs. predicted intervals (horizontal lines)



- New study compared fixed dosing of x mg vs a titration regimen: dose 1 (3 days), dose 2 (3 days), dose 3 (2 days), dose x (2 days).
- In this instance, the model based prediction produced ***prior*** to study initiation broadly captures the time course and extent of response, particularly for the titration regimen
- As predicted, the titration regimen blunts the HR drop associated with the first dose and allows HR to decrease to the steady-state plateau in a smoother manner

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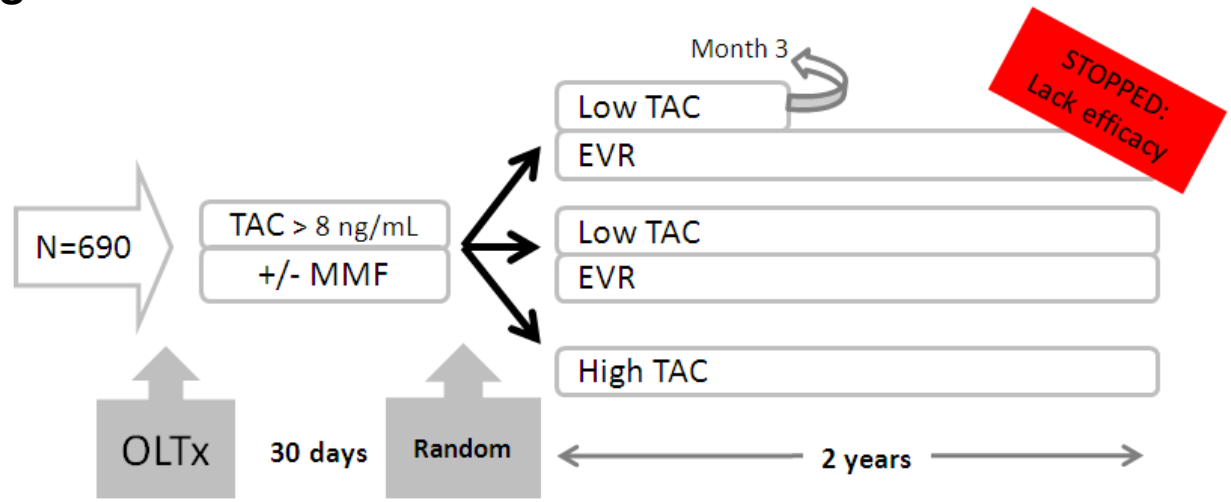
Example 2:
Exposure-response analysis of liver transplantation rejection rate

M&S specific value: more robust interpretations by comprehensive use of dosing and PK data

In Liver Transplantation, can we reduce the Tacrolimus (TAC) dose by combining it with Everolimus (EVR) ?

- **Study design:**



- **Objective for the combination**: better renal function and similar efficacy (rejection, ...) versus high TAC
- **Measures**: acute rejection time, graft loss, death / trough conc at TDM time points
- TAC and EVR doses adjusted to target concentrations

TAC=tacrolimus; Low TAC: 3-5 ng/mL; High TAC: 8-12 ng/mL till Month 3 then 6-10 ng/mL;
EVR=everolimus: 3-8 ng/mL

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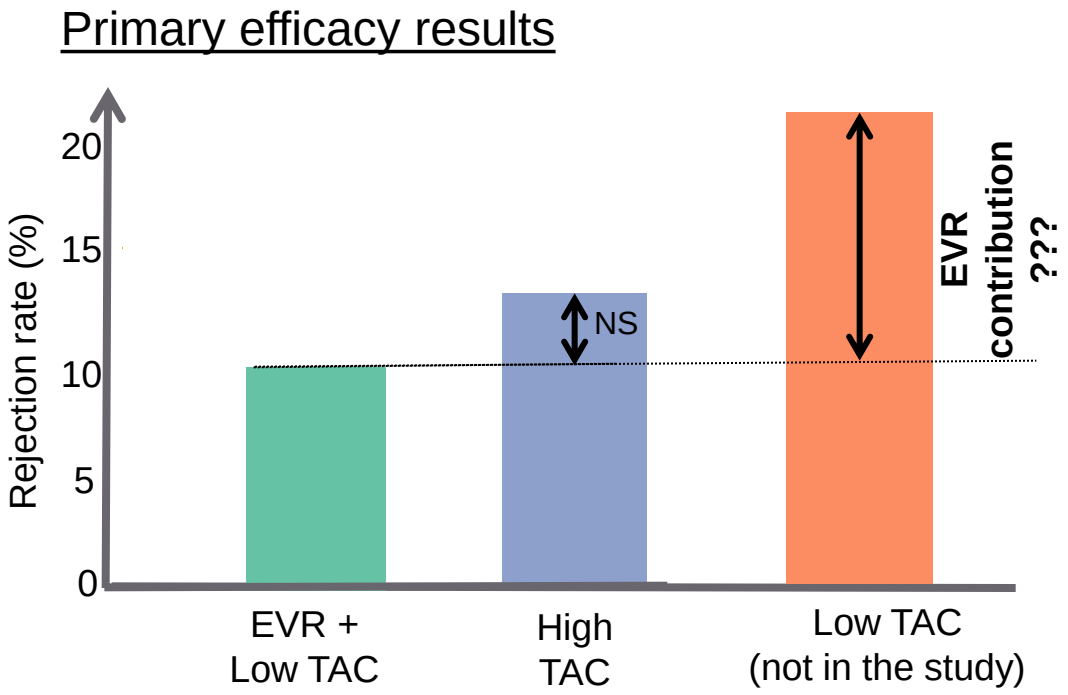
Major concern: if low TAC as effective as high TAC, no Everolimus contribution

- Good efficacy of EVR + low TAC
- Tacrolimus exposure-response not documented enough and no low TAC data in literature
- What would be the efficacy of low TAC alone?



NS: not significant

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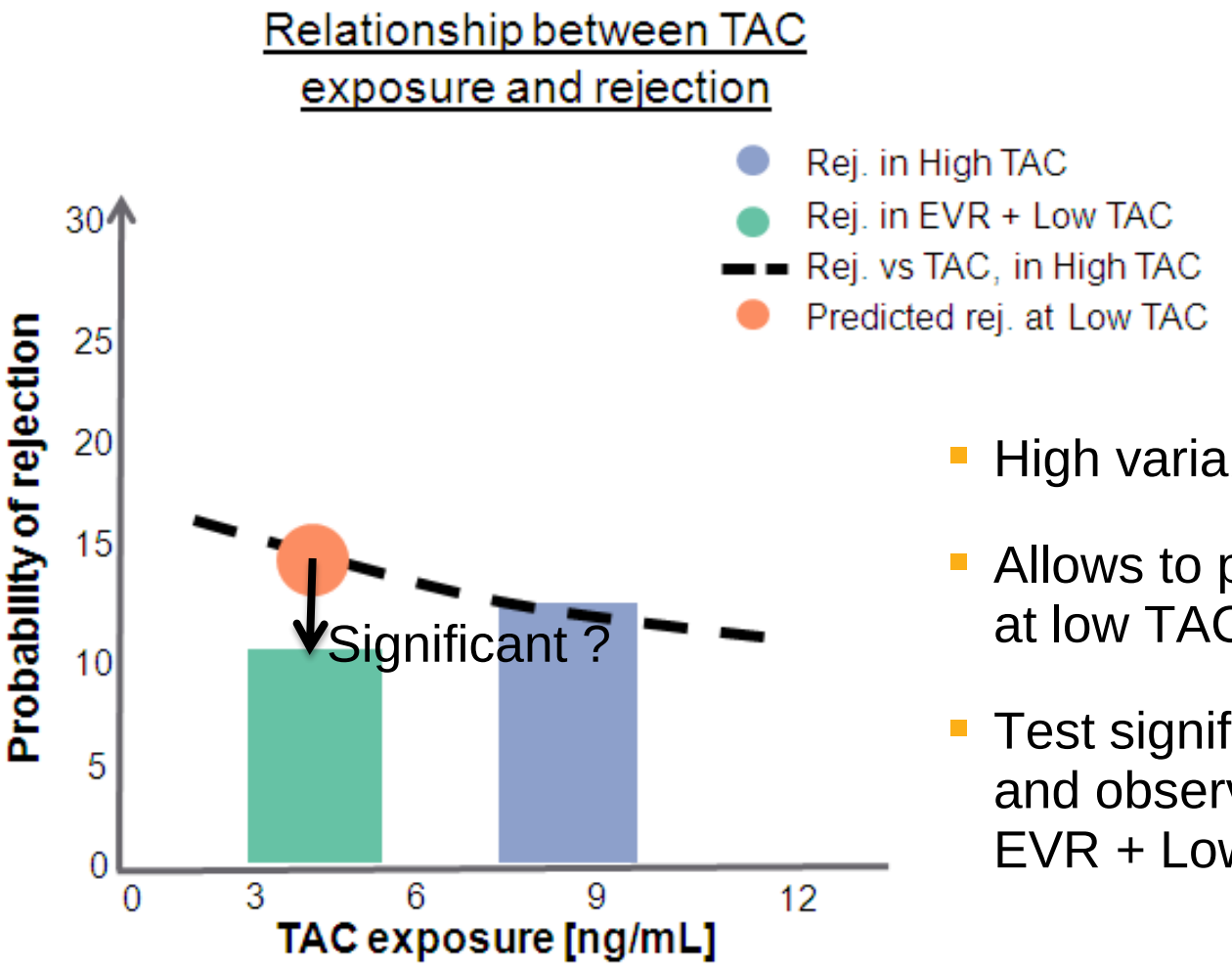
Approach: exposure-response analysis of Tacrolimus alone to predict its efficacy in low TAC arm



- High variability in TAC conc.
- Allows to predict rejection rate at low TAC exposure
- Test significance btw predicted and observed rejection rate in EVR + Low TAC arm

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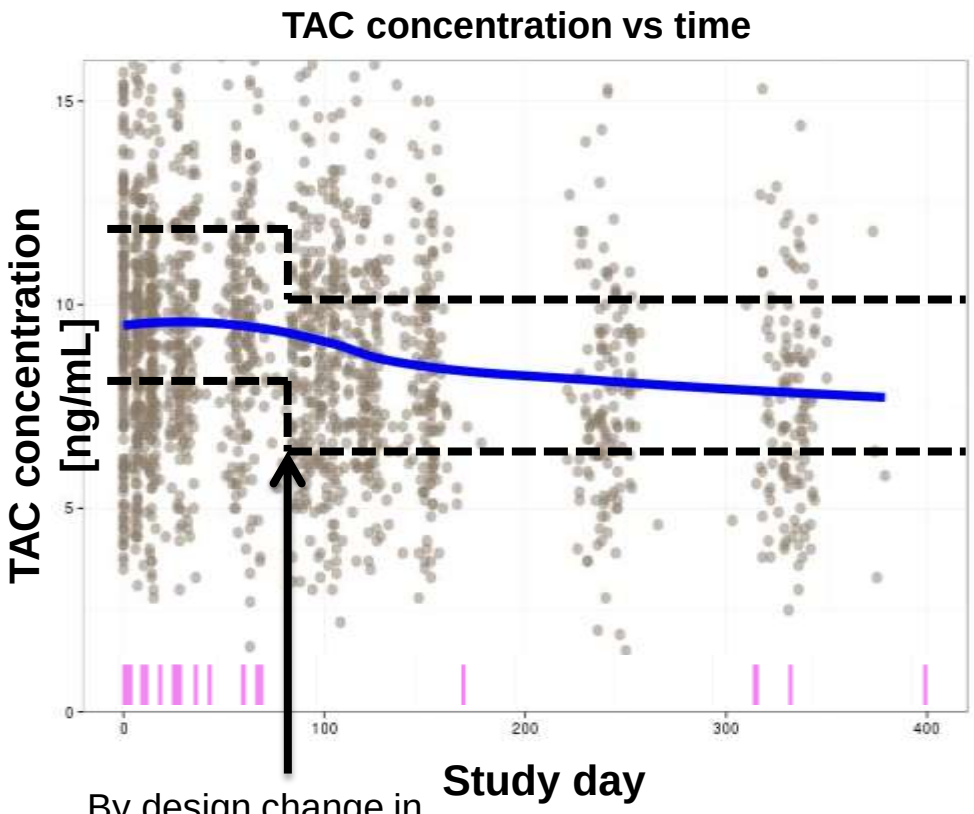
Several Complications: Time dependency for TAC dose and rejection rate + sparse PK sampling



- Even at constant TAC dose, rejections more frequent early
- By design and by TDM, TAC conc decrease with time
- PK samples not available at or close to rejection time, so how to use the conc information ?

← Rejections

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Models used: Time to event / Cox proportional hazard + Population PK

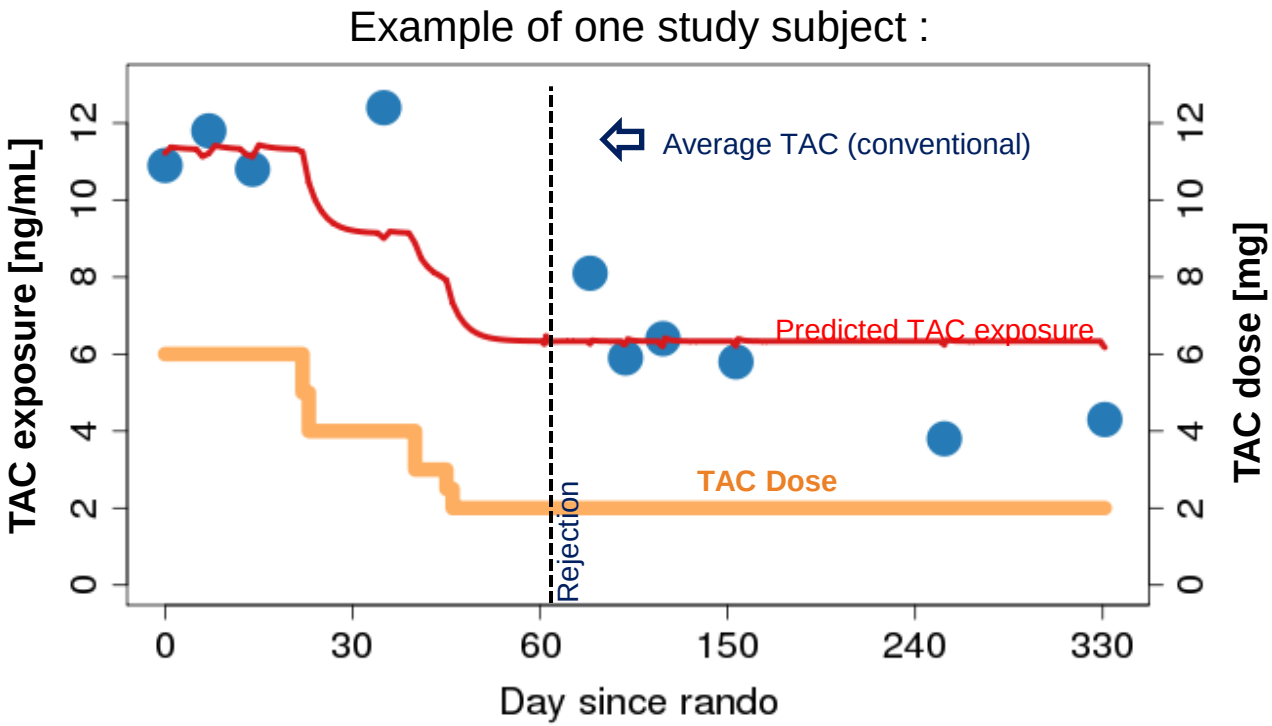
$$h(t, x_t) = h_0(t)e^{\beta . x_t}$$

- Hazard (instantaneous risk) of event = product of
  - Hazard of event in a typical untreated subject (not constant with time)
  - A function of the covariate (Tacrolimus conc, linear relation with log hazard)

- Population PK model from literature
  - Absorption parameter fixed to literature value
  - Apparent V and CL and their inter-individual variability estimated
  - Extensive dosing information and PK data used for parameter estimations
  - Individual conc predicted and used in hazard model

Illustration: predicted conc often different from average conc before the event

- Many TAC dose adjustments happened
- Conc at time close to event not available => Conventional approach would use pre-event average of observed conc => bias !



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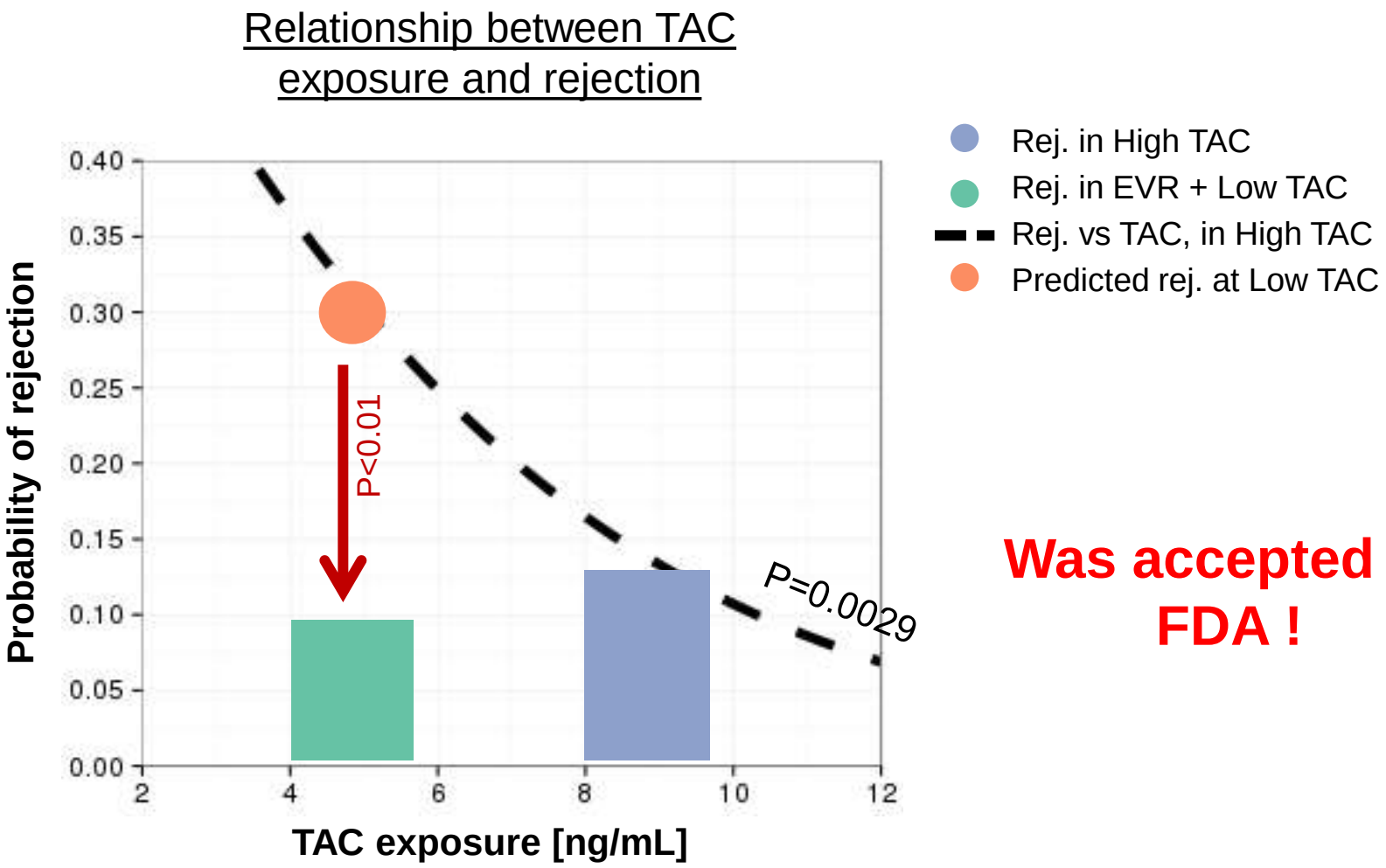
Final Results: significant exposure-rejection relationship + significant everolimus contribution



Was accepted by FDA !

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Example 3
Longitudinal model-based meta-analysis in Rheumatoid Arthritis (RA)

M&S specific value: inform go/no go decision through benchmarking compounds with existing drugs

RA literature database compiled for ACR20, design features, demographics and control treatment

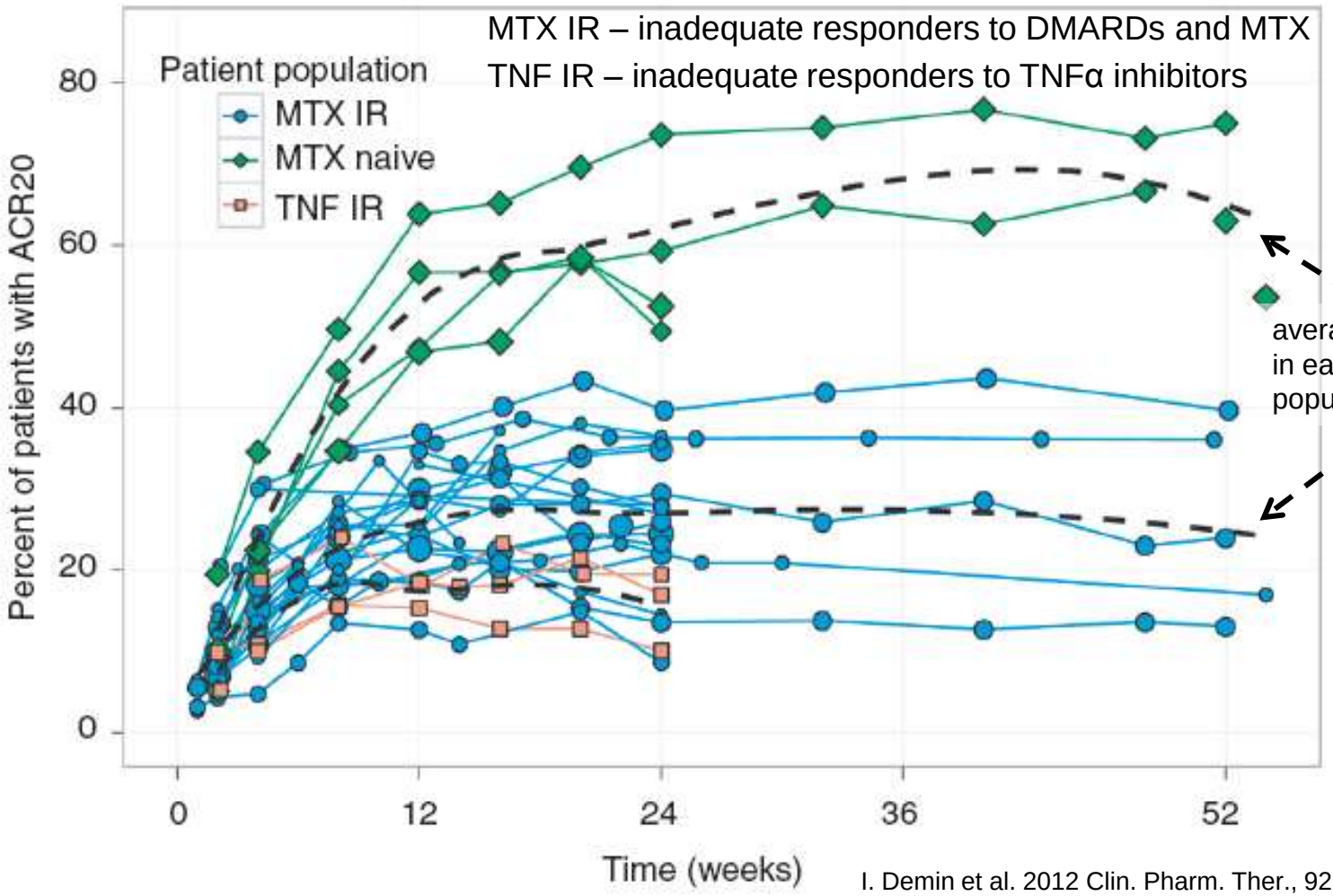
- ACR20 = proportion of patients reaching 20% improvement (American College of Rhumatology scale)
- Analysis included longitudinal ACR20 data from
  - 37 double-blind phase II-III studies (intent-to-treat (ITT) or modified ITT)
  - 9 biological drugs: adalimumab, anakinra, etanercept, rituximab, tocilizumab, abatacept, golimumab, certolizumab and infliximab
  - methotrexate (MTX) and true placebo
  - 75 treatment arms (only approved doses)
  - 13,474 patients

placebo-plus-MTX response is different across three patient populations

MTX naive – patients naive to traditional DMARDs

MTX IR – inadequate responders to DMARDs and MTX

TNF IR – inadequate responders to TNFα inhibitors



I. Demin et al. 2012 Clin. Pharm. Ther., 92 ,(3), 352-359

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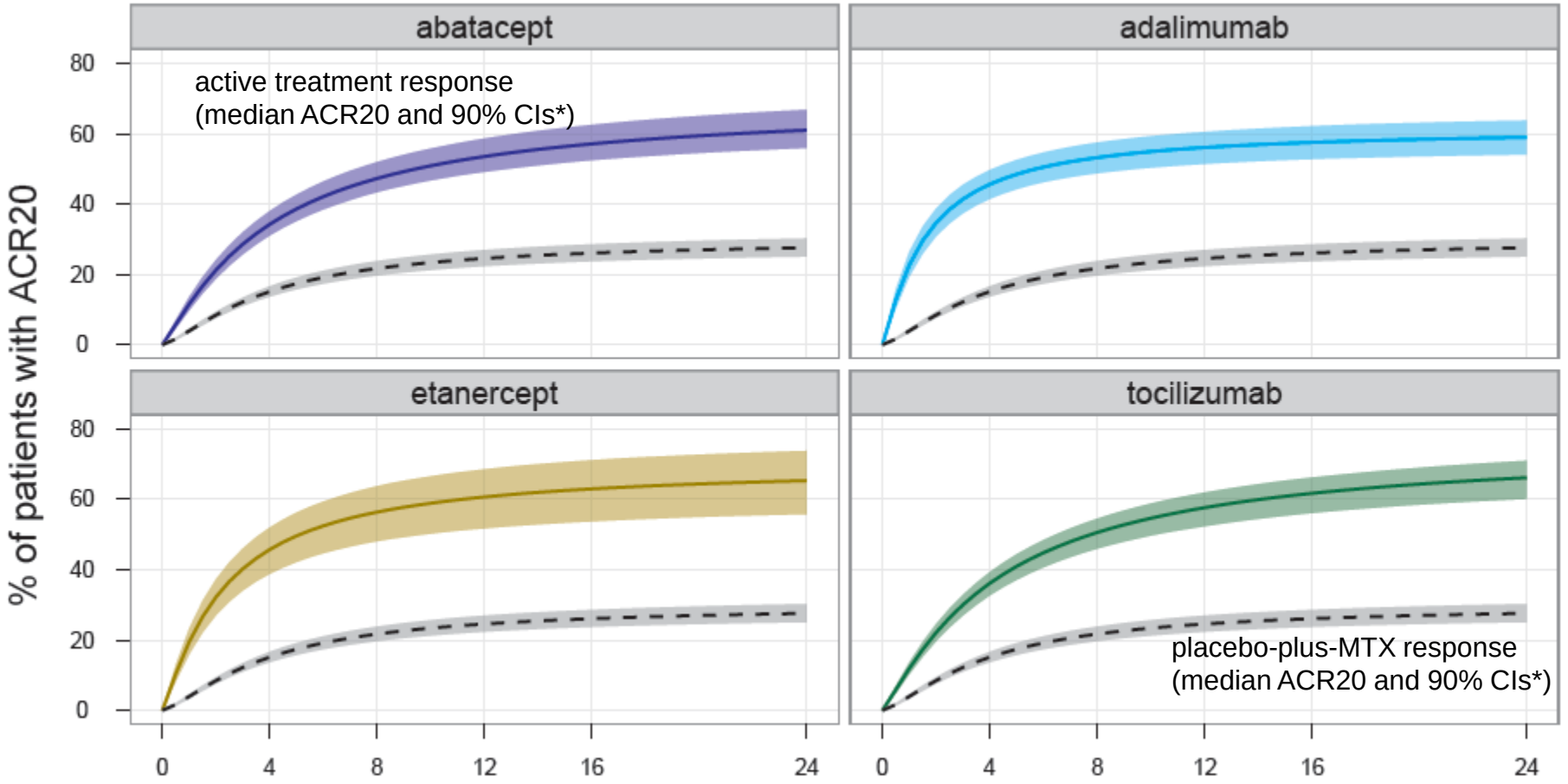
Model-based time course of ACR20 responder rates for adjusted indirect comparison of competitor compounds



Time to achieve 50% of maximum ACR20 response ranges between 1-4.5 weeks

**CIs - confidence intervals*

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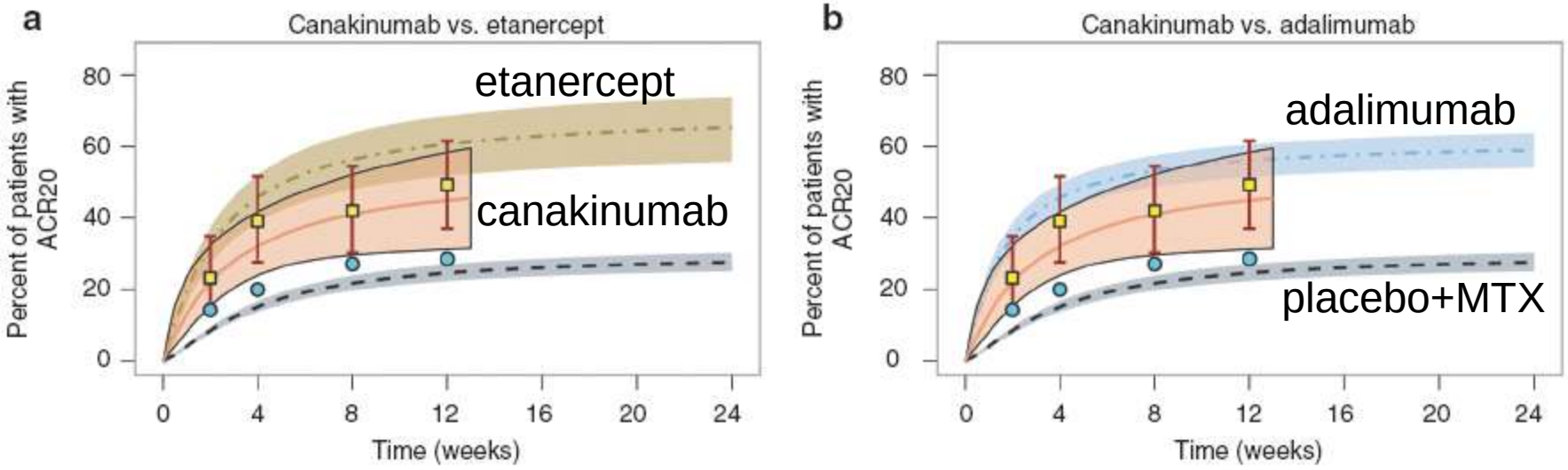
Integrated model-based assessment allows internal decision making within competitive landscape

- Retrospective analysis of phase IIb study results for canakinumab
  - Two arms of the study (150 mg Q4W and placebo+MTX) were compared to the competitor data
  - Low probability of canakinumab beating competitors on maximum efficacy or in onset of effect supports no-go decision



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Cautions re Modeling and Simulation use

- What modelling cannot do
  - Provide one “true” answer
  - Explain everything
  - Find an effect where there isn’t one
  - Give you the answer you want
  - Make good studies unnecessary
  - Make your decisions for you
- What you need to be cautious about:
  - Check the assumptions made during model building
  - Garbage in = garbage out

Conclusions

- Modelling and simulation is a quantitative integrative tool allowing to guide drug development decision making
- M&S allows to integrate information across all stages of drug development
- Regulatory agencies increasingly use the methodology in their approval process

Acknowledgements

- M Looby
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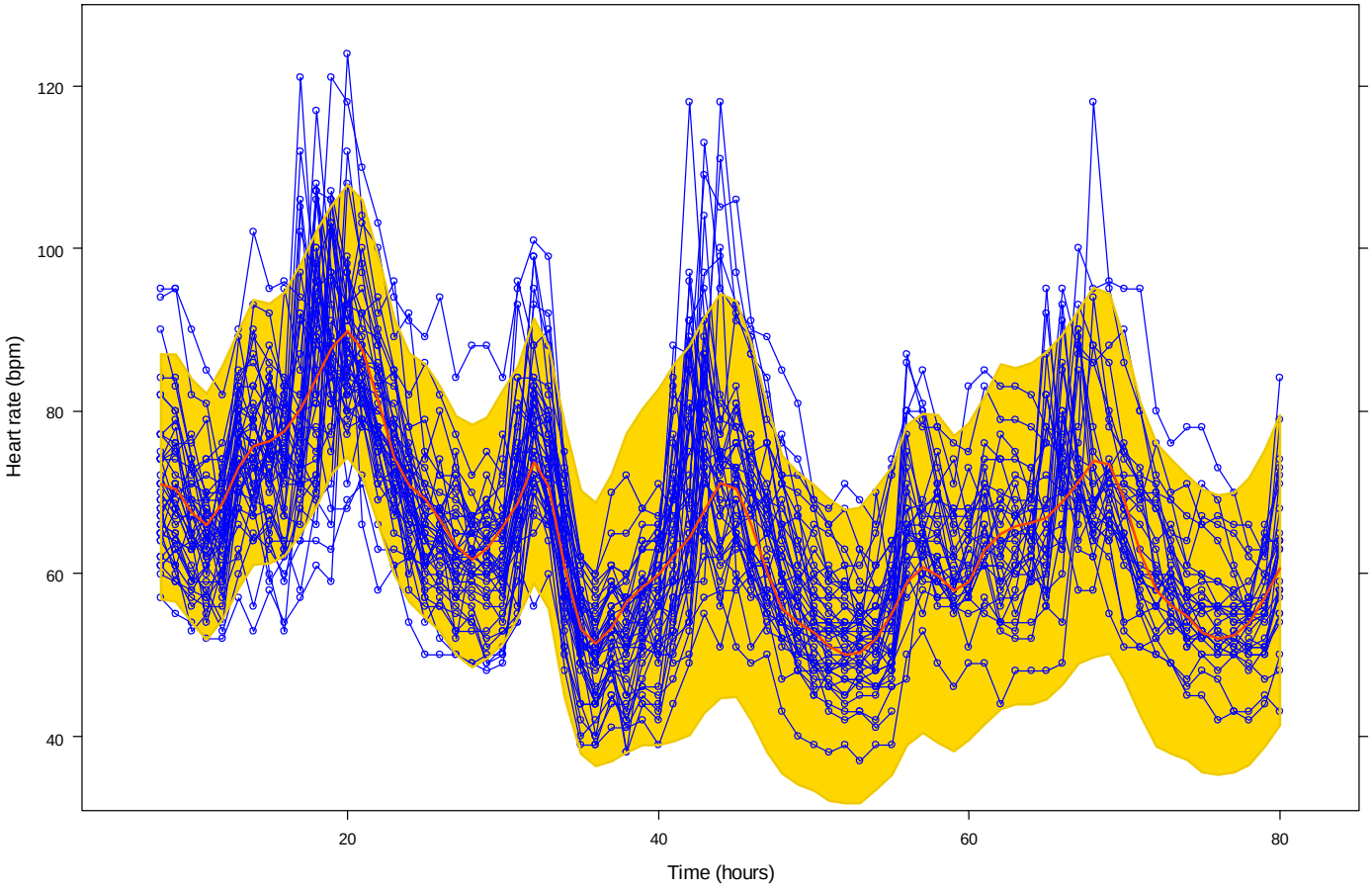
- O Luttringer
- JL Steimer
- G Junge
- I Demin
- B Hamren

Back up slides

The model could describe the data well for all periods as well as for doses around therapeutic range



Blue = observed data, yellow = 90% prediction interval

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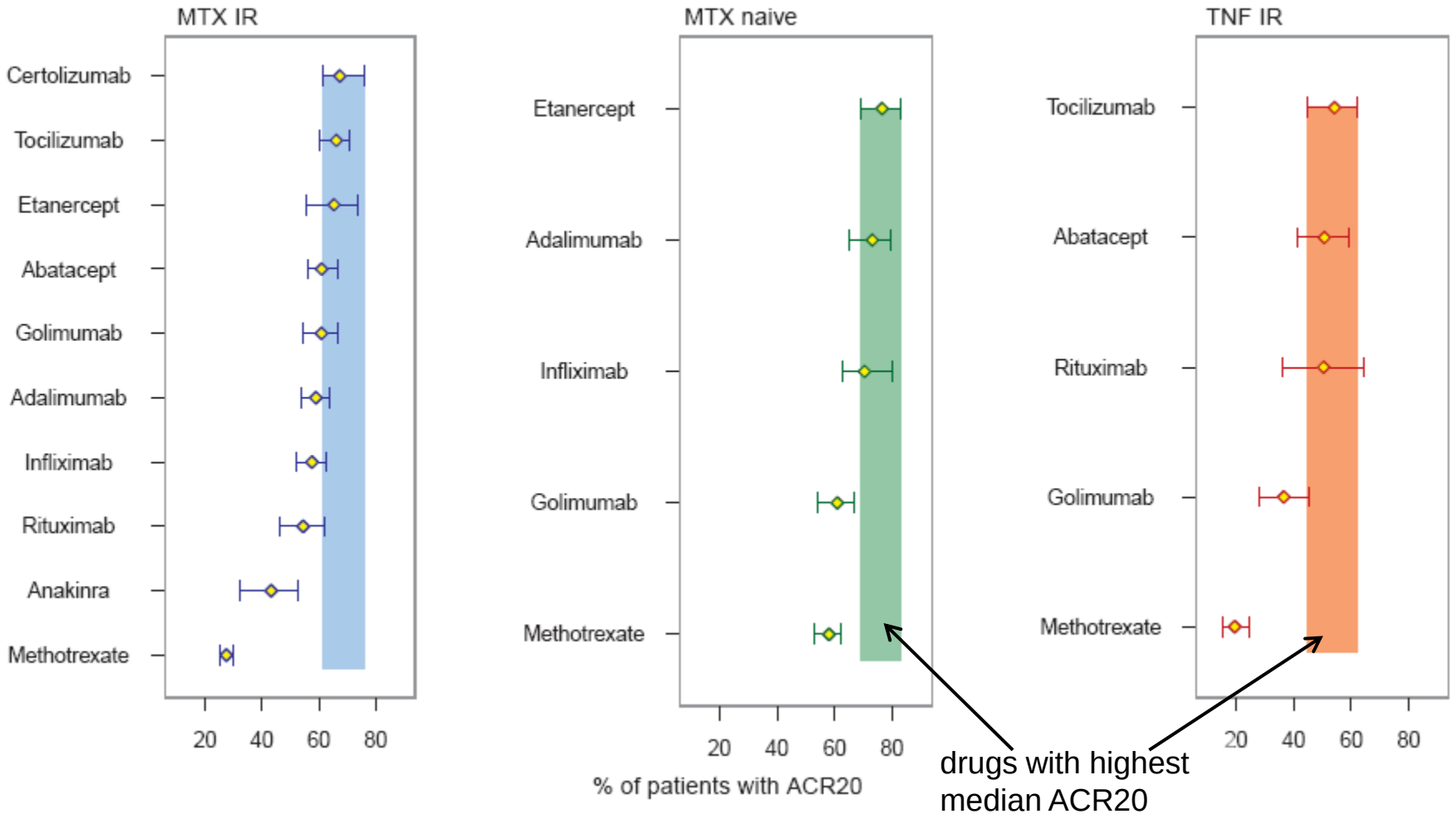
Such an integrated framework can be used to inform decisions about drug potential

Week 24 model-based predictions of median ACR20 responder rates for approved drugs across 3 patient populations characterizes the competitive landscape in RA

not all drugs were studied across all patient populations



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