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Common concerns in visualization of pharmacometric data and models

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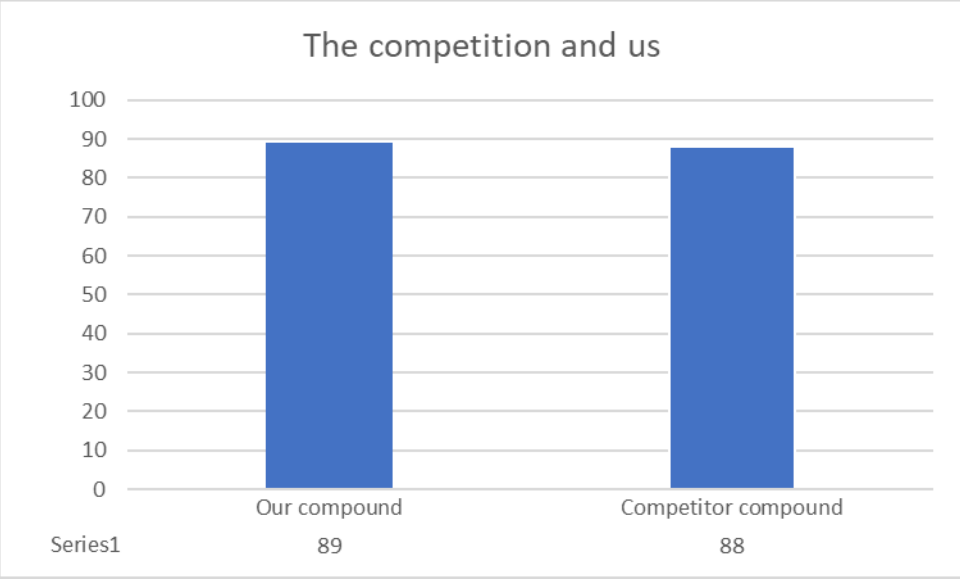
American Conference on Pharmacometrics (ACOP9)

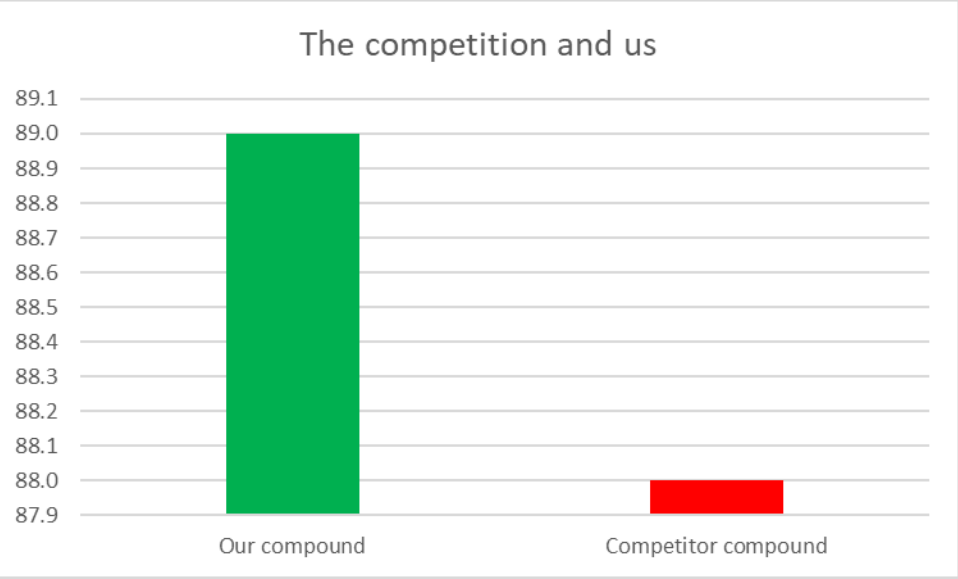
San Diego CA, October 2018

Bad intentions

Marketing Graph - A pictorial representation that uses 3 dimensions, 4 colors and 5 cartoons to show one fact that probably isn't true.

Source: The Devil's Drug Development Dictionaries. http://www.senns.demon.co.uk/wdict.html





Good intentions

The purpose of a visualization is to

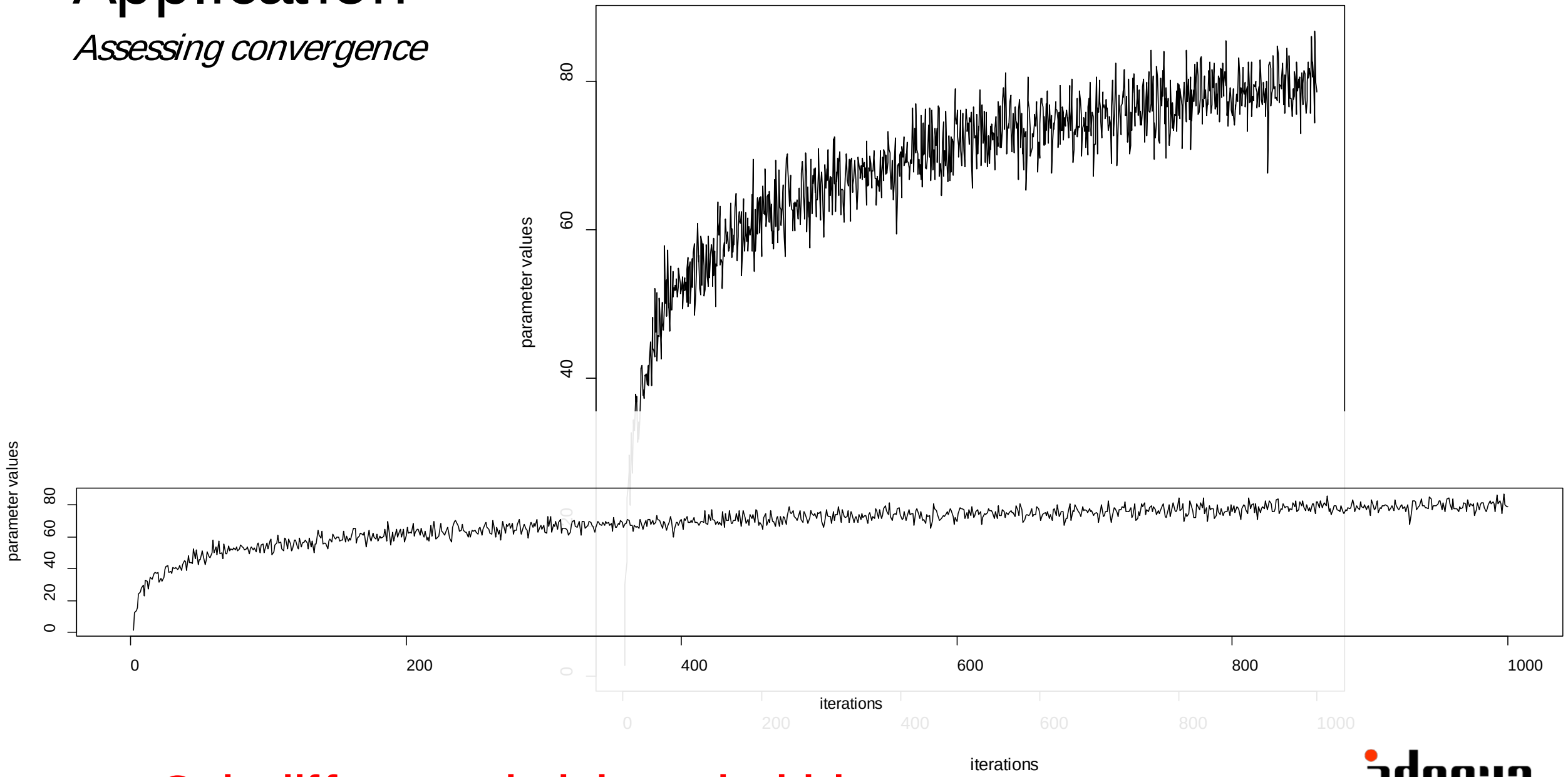
- show features of the data or the model
- in a scientific manner
- with interpretation not dependent on how it is displayed

The visualization is

- accurate
- intuitive
- easy to interpret *correctly*

Application

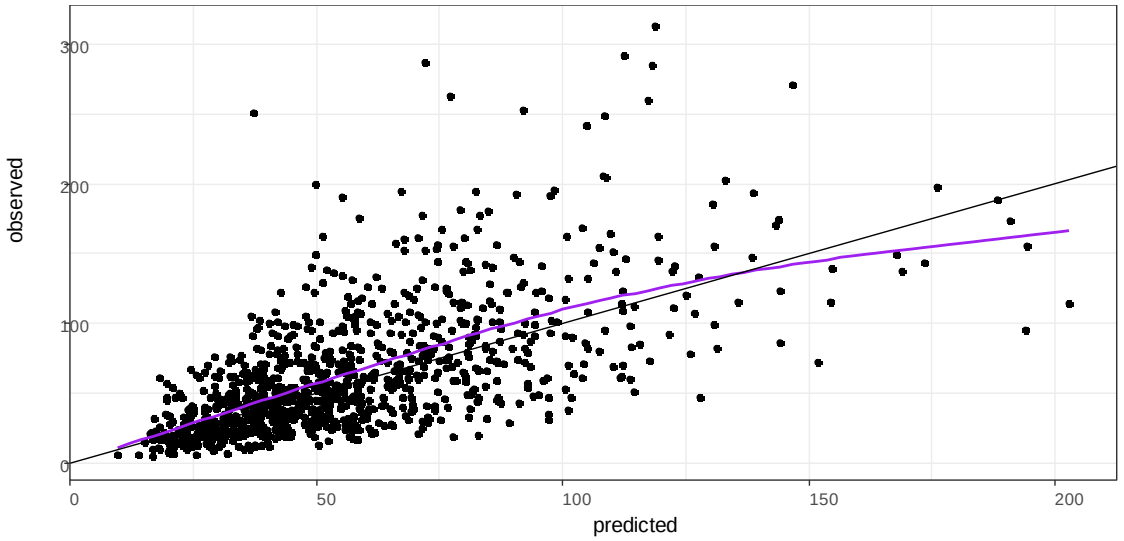
Assessing convergence

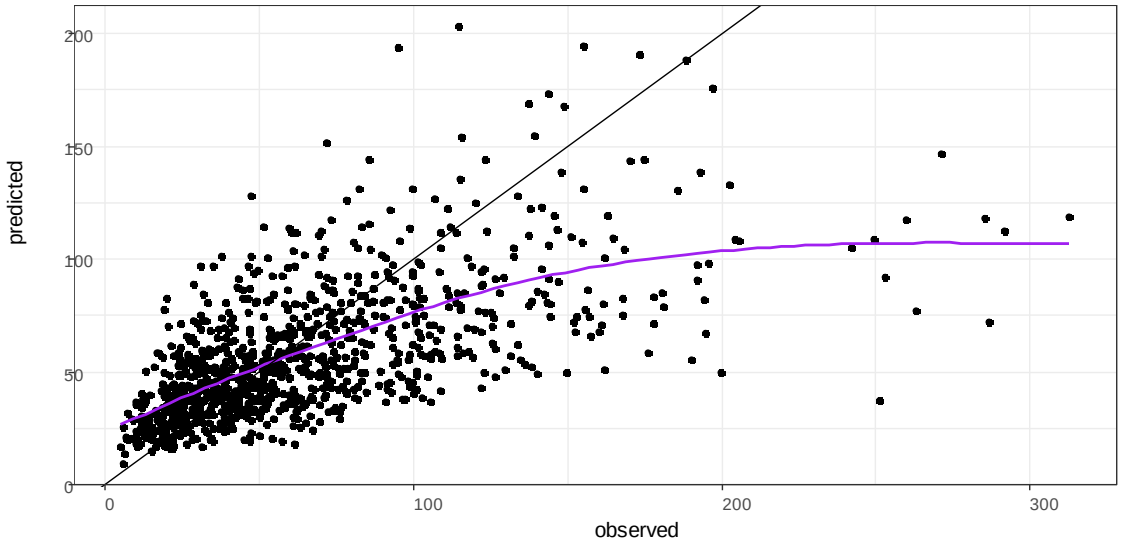


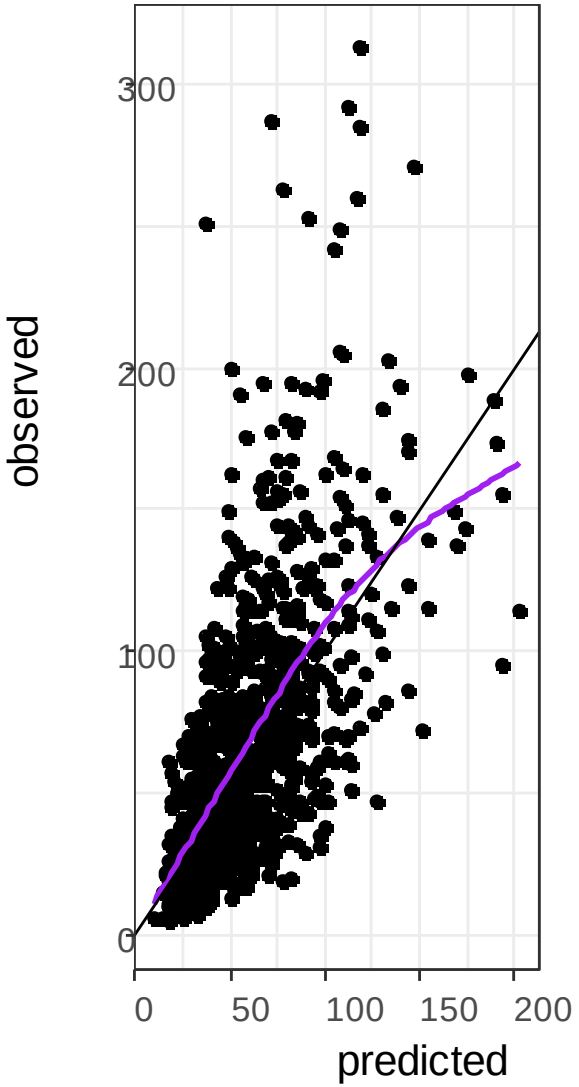
Only difference: height and width.

Application: Observed vs. predicted

In search for an unbiased visual assessment



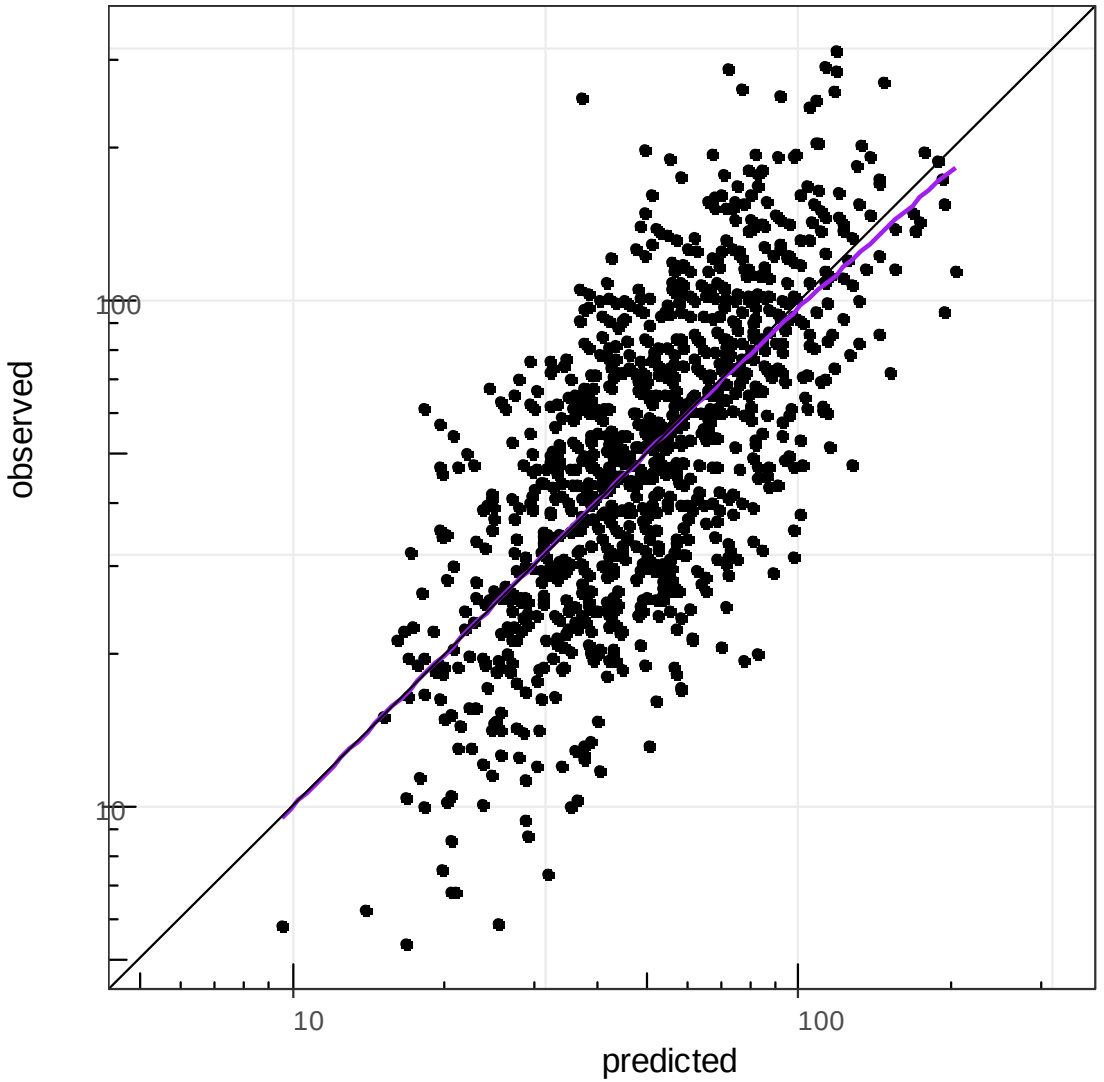




Application: Observed vs. predicted

Graphical settings

- **Same aspect ratio in x and y**
  - 1 observational unit (ng/mL, mmHg, …) = same length on x- and y-axis
  - Same axis range
  - ➢ Symmetry between x and y
- **Logarithmic scales**
  - Log-normal distribution assumptions
  - This is the scale for optimization
  - Extreme values distract less (visually)
- **Observed = f(predicted)**
  - log(obs.) ~ N(log(pred.), s) + e
  - ➢ Observed on the y-axis



Observed vs. predicted: R code

R code: no excuses.

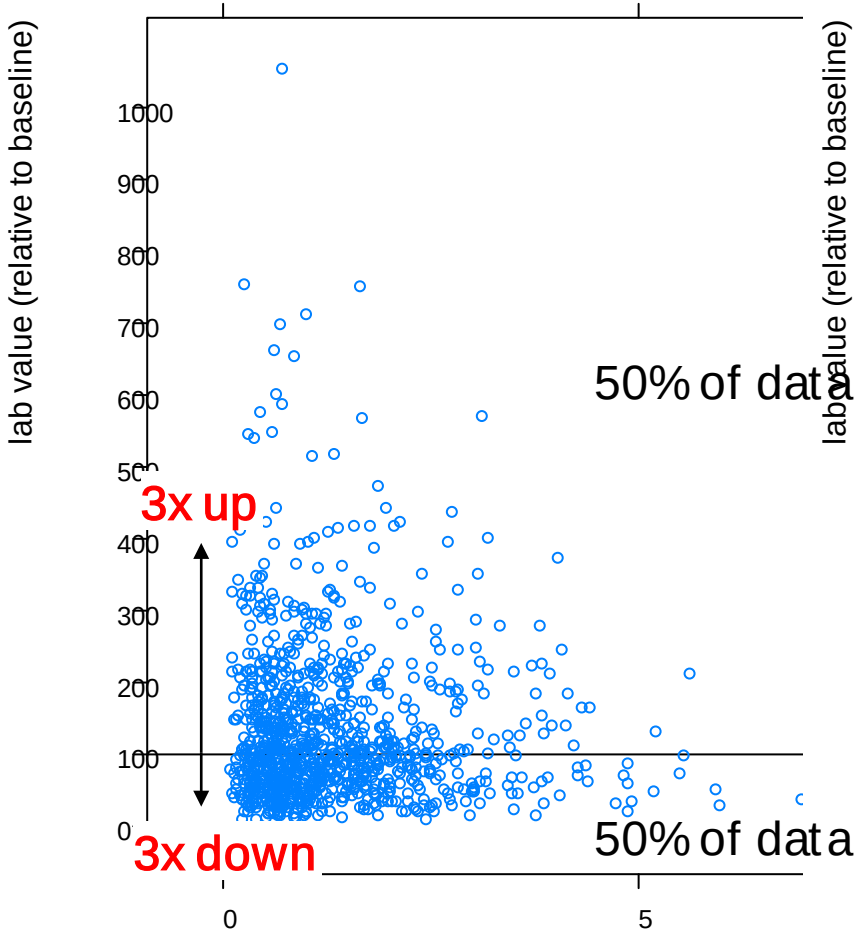
```
# Create a data set.
set.seed(348391)
df <- data.frame(predicted=exp(rnorm(1000, m=log(10), s=0.1)))
df$observed <- exp(rnorm(nrow(df), m=log(df$predicted), s=0.1))

library(ggplot2)
r <- range(c(df$observed, df$predicted))                    # range of obs. and pred.
ggplot(df, aes(x=predicted, y=observed)) +                  # observed = f(predicted) + e
        geom_point() +
        geom_smooth(col="pink") + theme_bw() +
        geom_abline(intercept=0, slope=1) +                 # diagonal y=x
        coord_fixed(ratio=1) +                              # aspect ratio 1
        scale_x_log10(limits=r) + scale_y_log10(limits=r)   # log. axes, same range
```

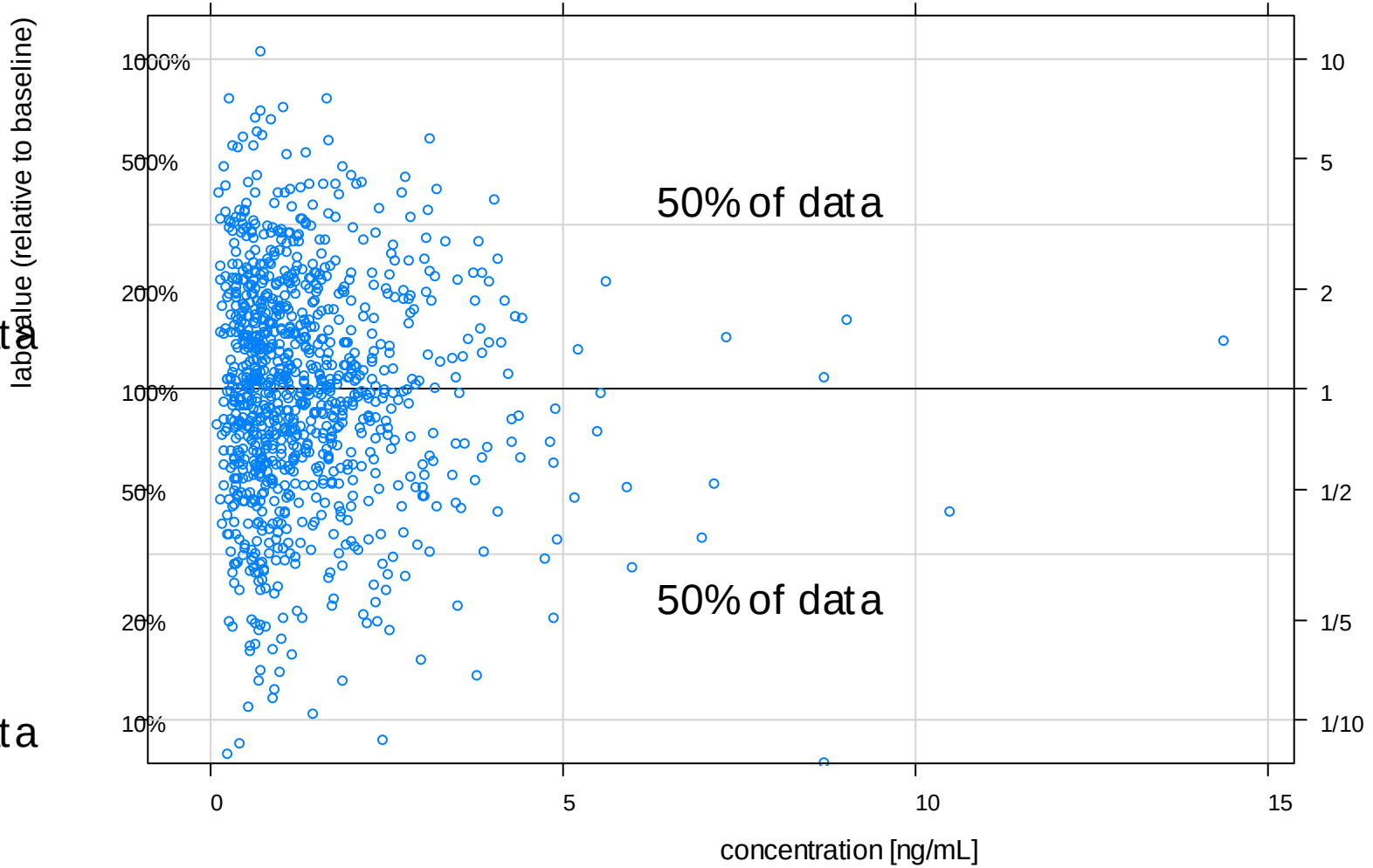
Relative (fold) change

- **If the data scatter symmetrically around "no change"**
  - Half the data are above, half the data below "no change"
  - Show that.
  - Use a logarithmic scale:
    - 2-fold up and down have the same distance to "no change".

Relative (fold) change

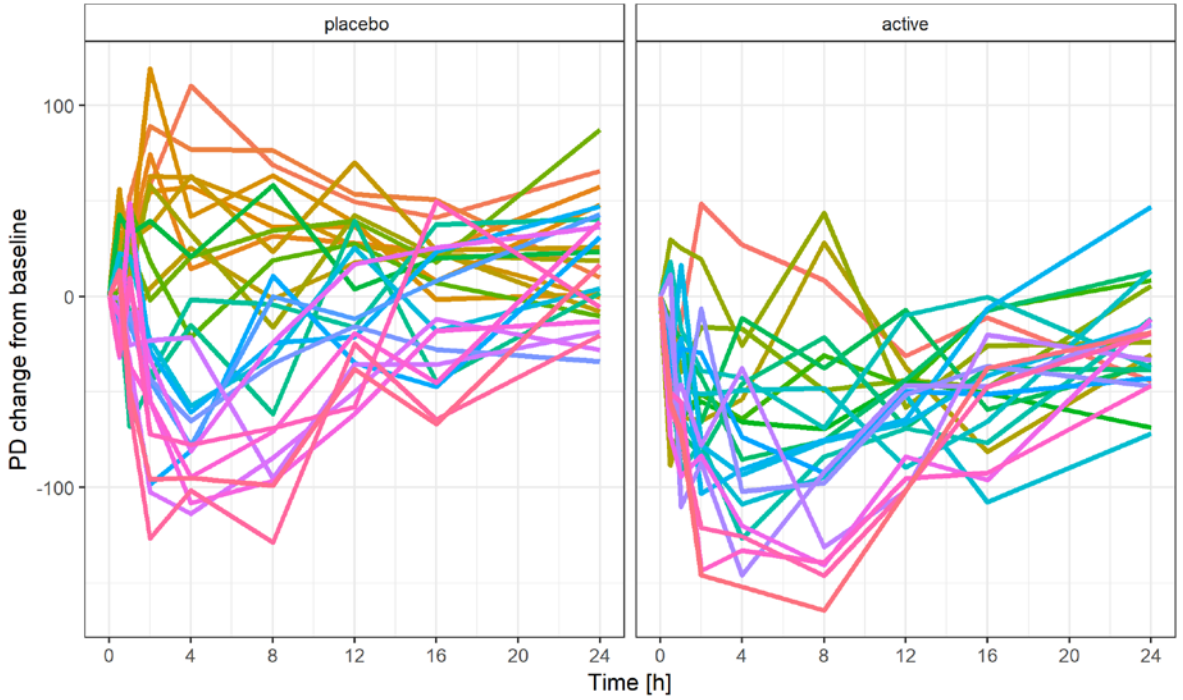
Linear vs. logarithmic axis (when there is no change)

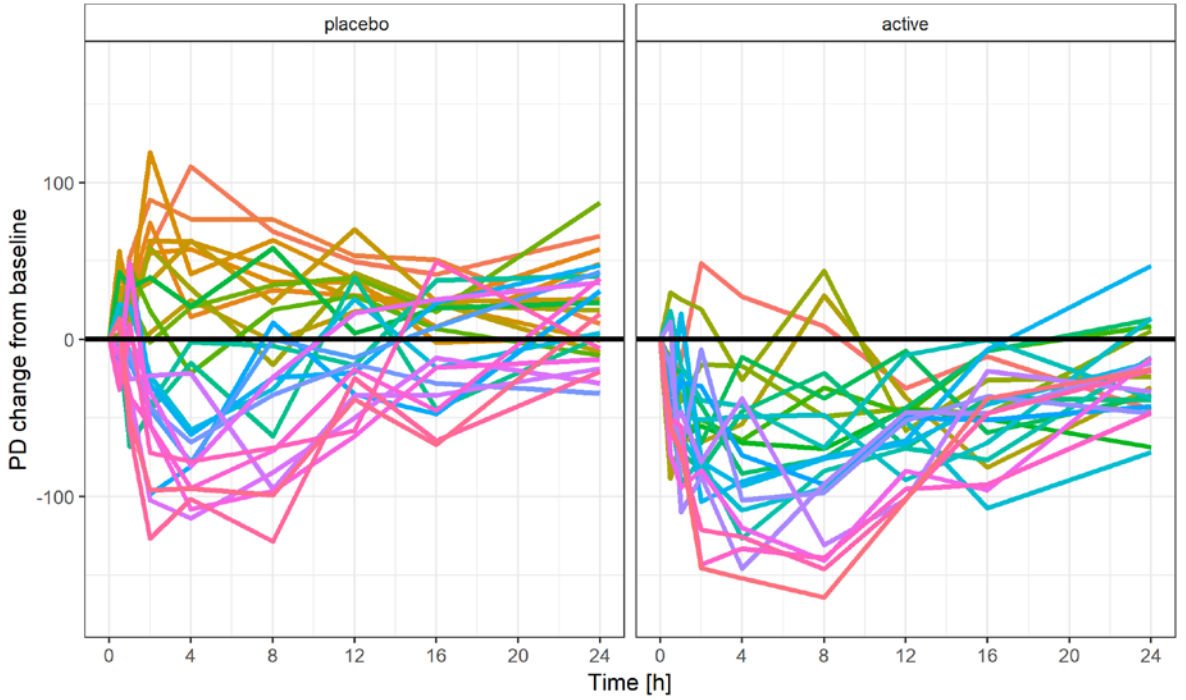




Change from baseline

Adding visual support





- Symmetric axis range
- Line of no change indicated

A modeler talks to an MD

- Modeler: So what is it you want to find out with your study?
- *MD: Whether the drug works or not.*
- Modeler: What does “works” mean?
- *MD: If the drug is better than placebo.*
- Modeler: What does “better” mean?
- *MD: Lower the blood pressure by more than 10 mmHg.*
- Modeler: On average, for 90% of the patients, or what else?
- *MD: For 80% of the patients.*
- Modeler: At steady state over 24 h, at trough, or what else?

etc. with improving precision over time, occasionally in circles.

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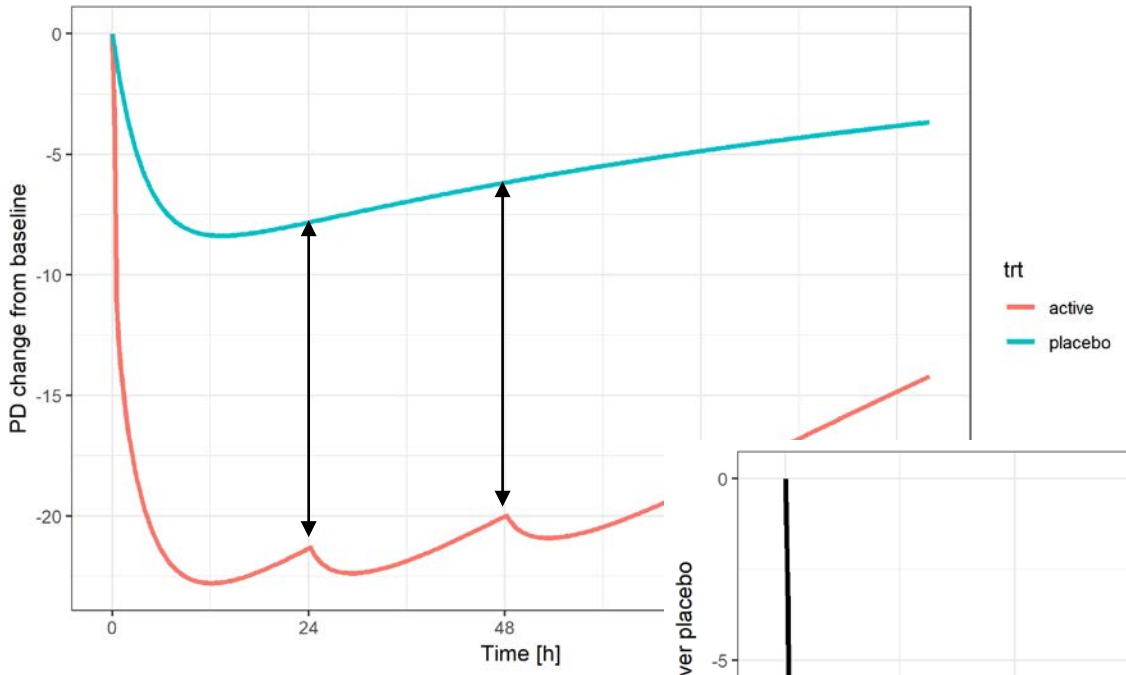
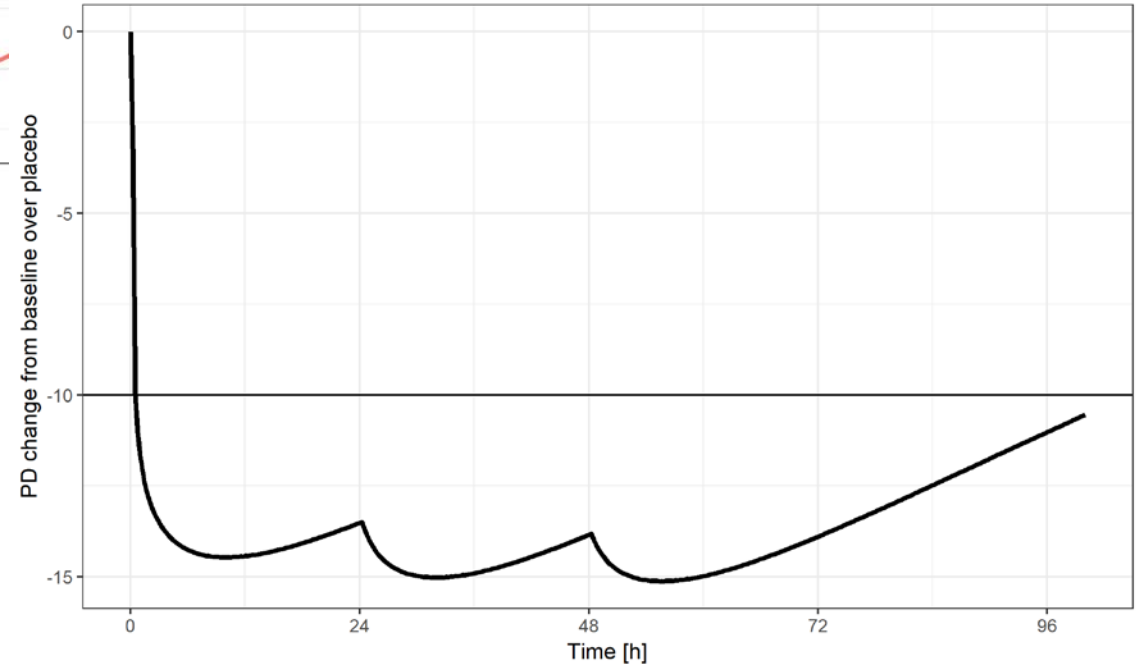
Show the quantity of interest

Here: the placebo-corrected change from baseline

The quantity of interest is *not* shown here:

the difference between active and placebo

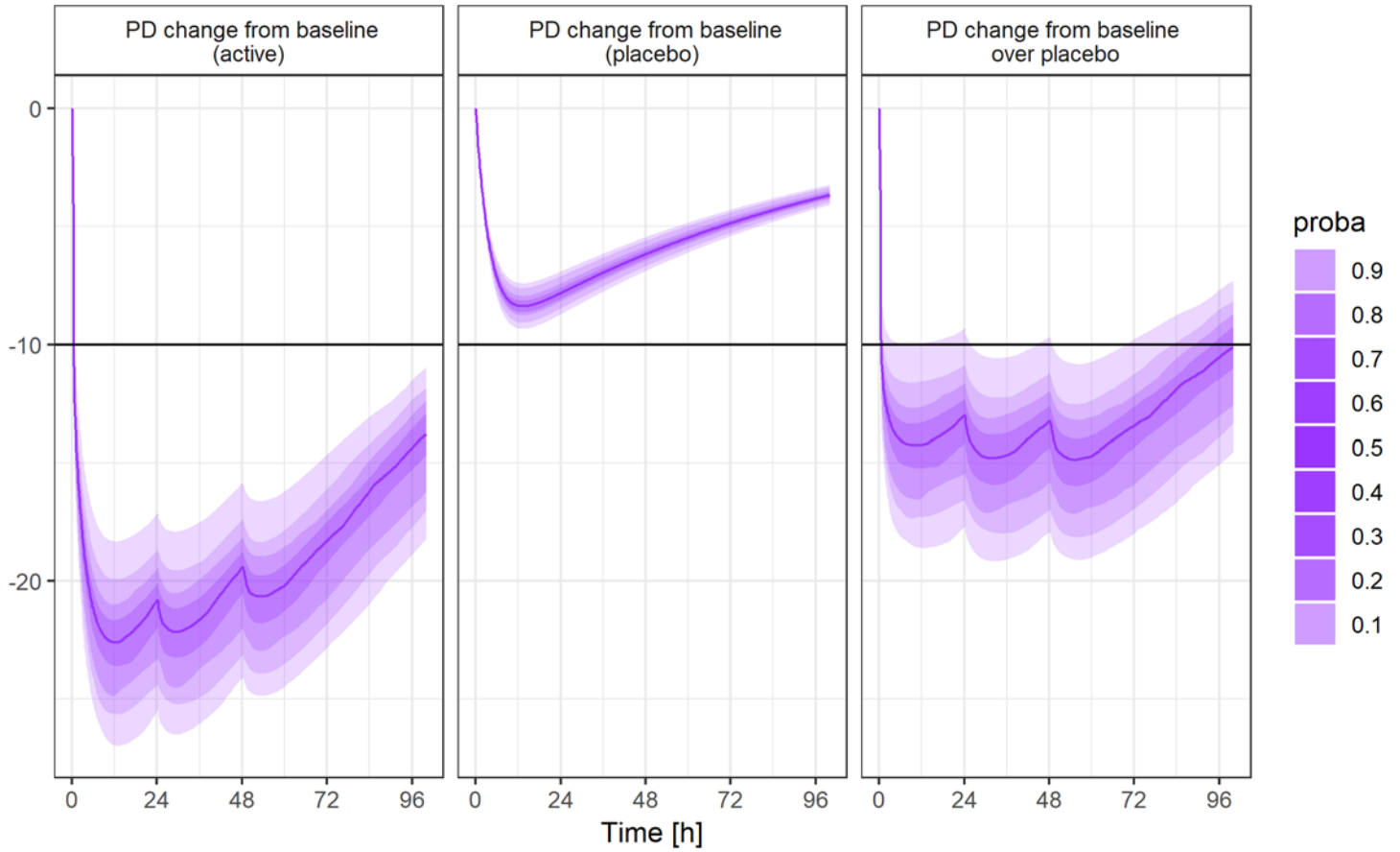




Show the quantity of interest

Here: the placebo-corrected change from baseline

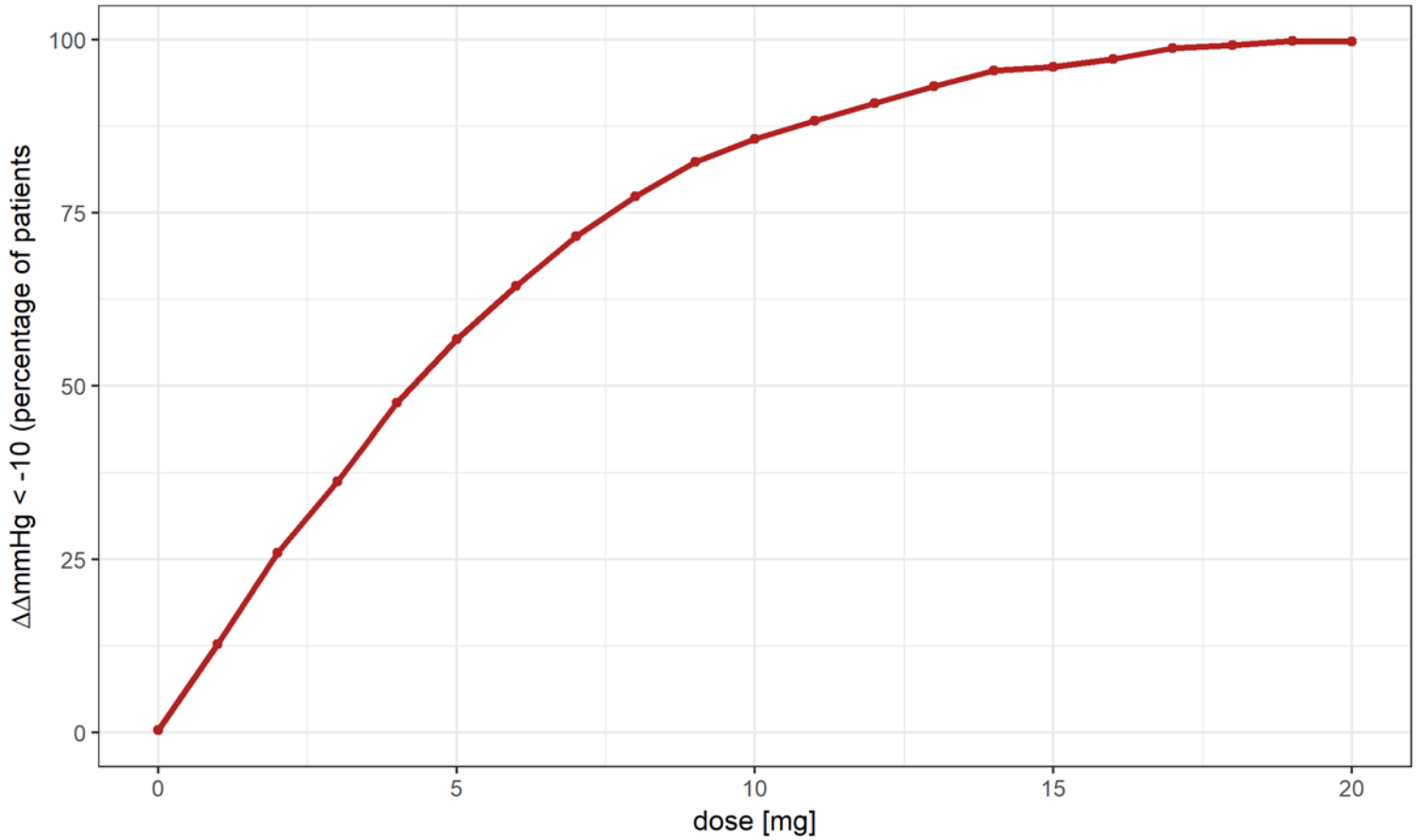
- **Distribution of response**
  - Bands indicate quantiles (10-90%)
  - Clinical threshold indicated (y=-10)



Show the quantity of interest

Here: the placebo-corrected change from baseline

- **Percentage of patients predicted to reach clinical response**
  - for a set of doses



Covariate selection: differences btw. patients

Fixed-effects quantification

- **Statistically significant differences**
  - Age, sex, body weight, race, baseline, disease status, etc.
  - Driven by parameter estimate and precision (variability and n)

- **Clinical relevance**
  - For a clinical audience

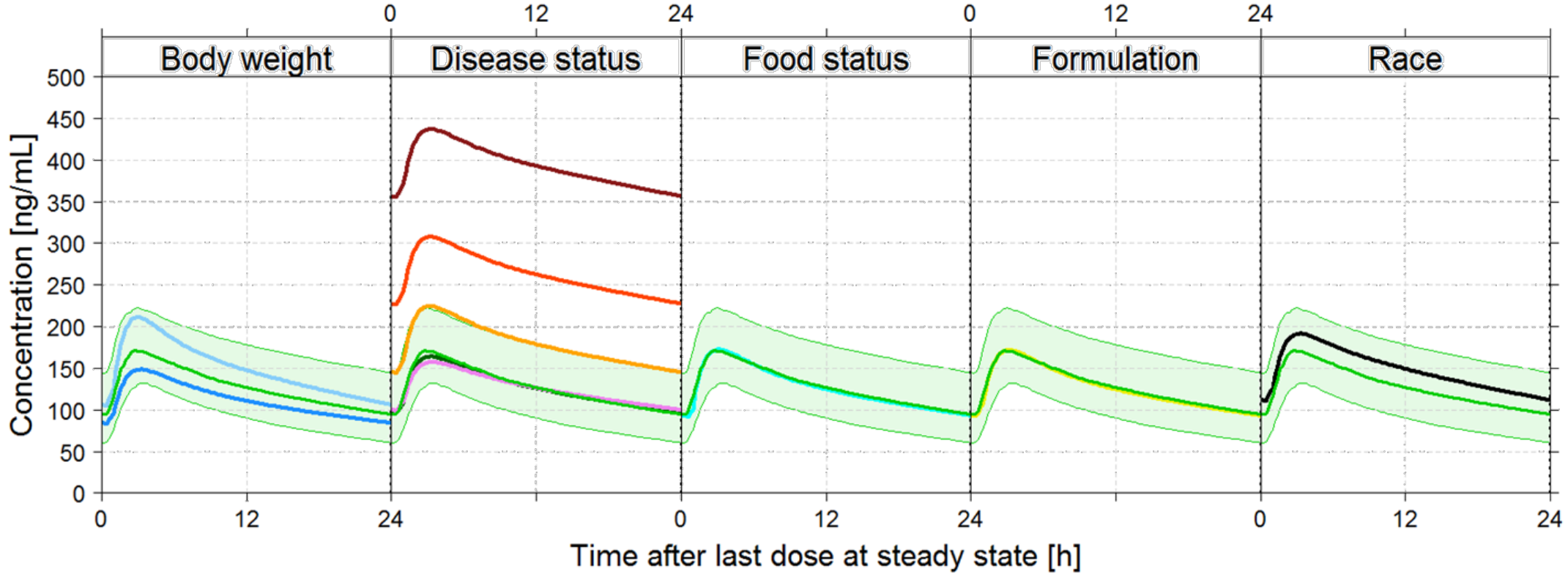
Covariate selection: Modeler's answer

Of no relevance to the MD, probably not even understood. ***Kills any interest quickly.***

Parameter	Description	Estimate (r.s.e.%)	IIV, %CV (r.s.e.%)	Shrinkage
T_{lag} (h)	Absorption lag time (ref)	0.40 (6)	43 (8)	6%
T_{lag} (h)	T_{lag} with capsule C	0.59 (5)		
T_{lag} (h)	T_{lag} with the intake of food	0.64 (13)		
Tk_0 (h)	Duration of the zero-order absorption process	0.58 (5)	56 (8)	1%
Fr	Fraction absorbed via zero order	0.15 (8)	62 (10)	3%
k_a (1/h)	Absorption rate constant	0.93 (7)	61 (6)	2%
V_c/F (L)	Apparent central volume of distribution (ref))	165 (2)	22 (6)	8%
V_c/F (L)	V_c for a subject with psoriasis	239 (12)		
V_c/F (L)	V_c for a subject with MS	200 (4)		
Body weight on V_c	Covariate effect of body weight on V_c	0.85 (4)		
V_p/F (L)	Apparent peripheral volume of distribution (ref)	107 (4)	29 (9)	5%
V_p/F (L)	V_p for a subject of race Black	67 (11)		
Body weight on V_p	Covariate effect of body weight on V_p	0.69 (21)		
Q/F (L/h)	Apparent inter-compartmental flow	21 (11)	10 (244)	6%
CL/F (L/h)	Apparent clearance (ref)	6.64 (1)	26 (3)	5%
CL/F (L/h)	CL for a subject of race Black	5.65 (4)		
CL/F (L/h)	CL for a subject with mild HI	4.66 (9)		
CL/F (L/h)	CL for a subject with moderate HI	3.18 (8)		
CL/F (L/h)	CL for a subject with severe HI	2.13 (9)		
Body weight on CL	Covariate effect of body weight on CL	0.42 (10)		
Residual error terms				
a	Additive error	0.006 (28)		
b	Proportional error	0.21 (1)		

Covariate selection: Clinical answer

This is what it means

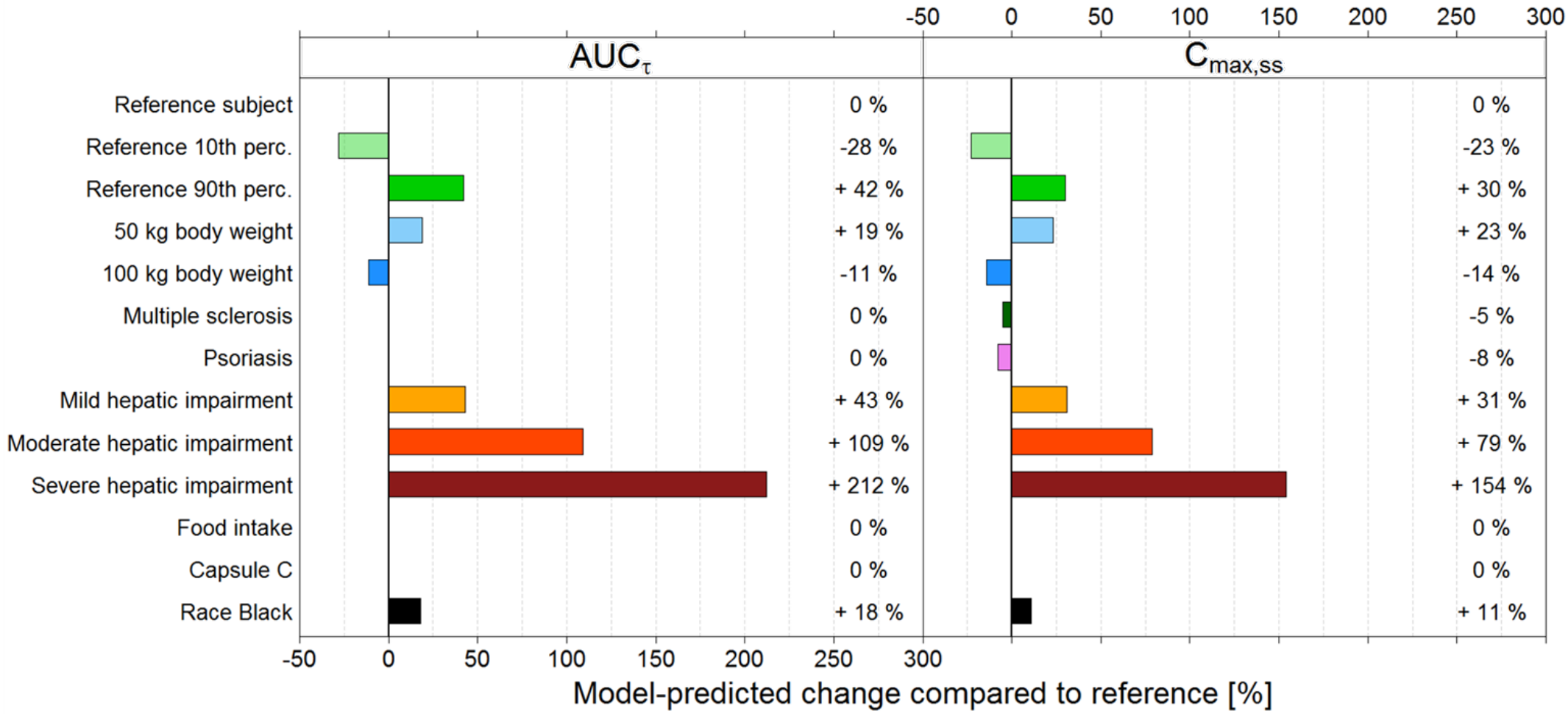


50 kg body weight
100 kg body weight
Mild hepatic impairment
Moderate hepatic impairment
Severe hepatic impairment
Psoriasis
Multiple sclerosis
Food intake
Capsule C
Race black

Lott et al.: Impact of Demographics, Organ Impairment, Disease, Formulation, and Food on the PK of Ponesimod. CPK 2017.

Covariate selection: Clinical answer

This is what it means

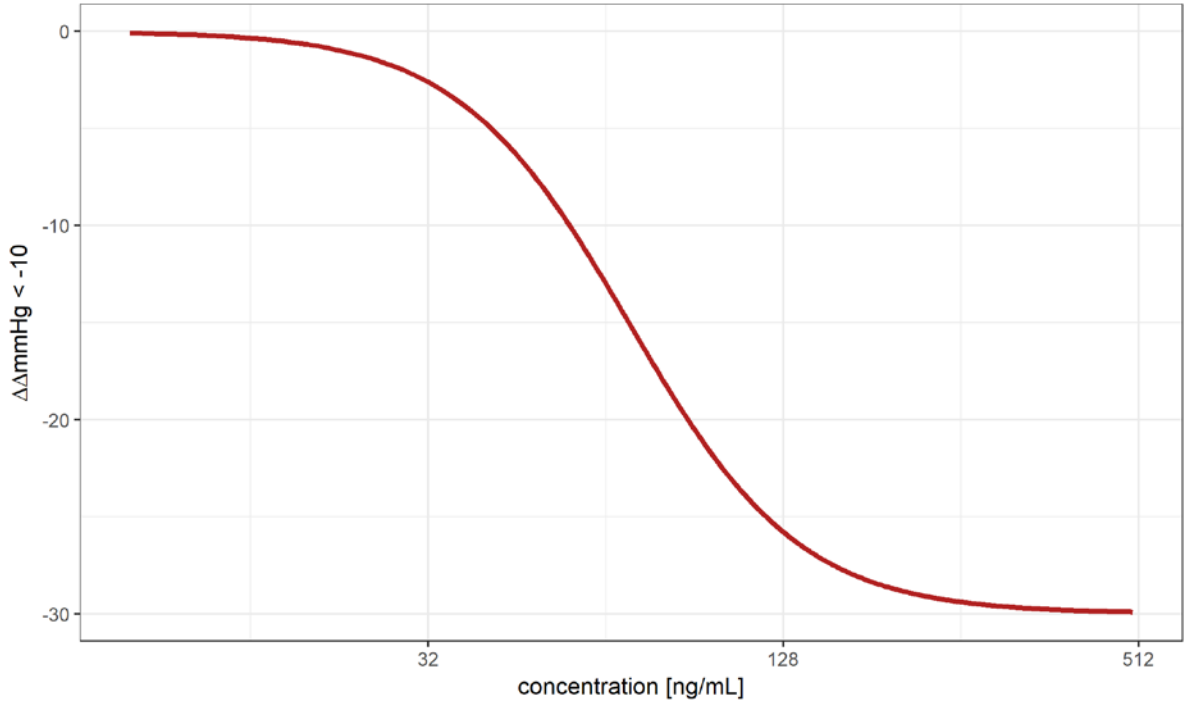


Lott et al.: Impact of Demographics, Organ Impairment, Disease, Formulation, and Food on the PK of Ponesimod. CPK 2017.

Covariate effect: Clinical answer

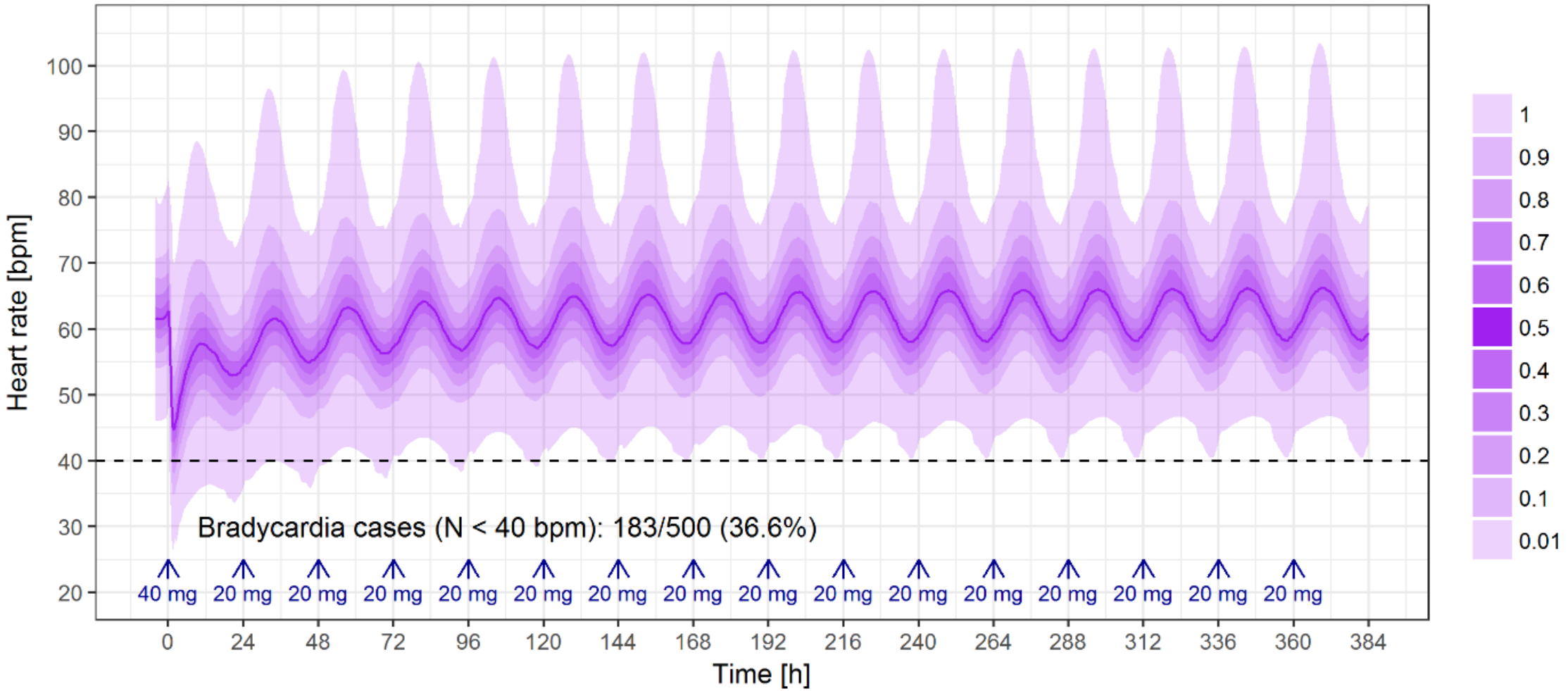
Translation of double (half) the exposure into clinical effect

- **Where are we on the concentration-effect range**
  - Flat part (limited clinical relevance) or
  - Steep part (possibly clinically relevant)



Covariate effect: clinical impact

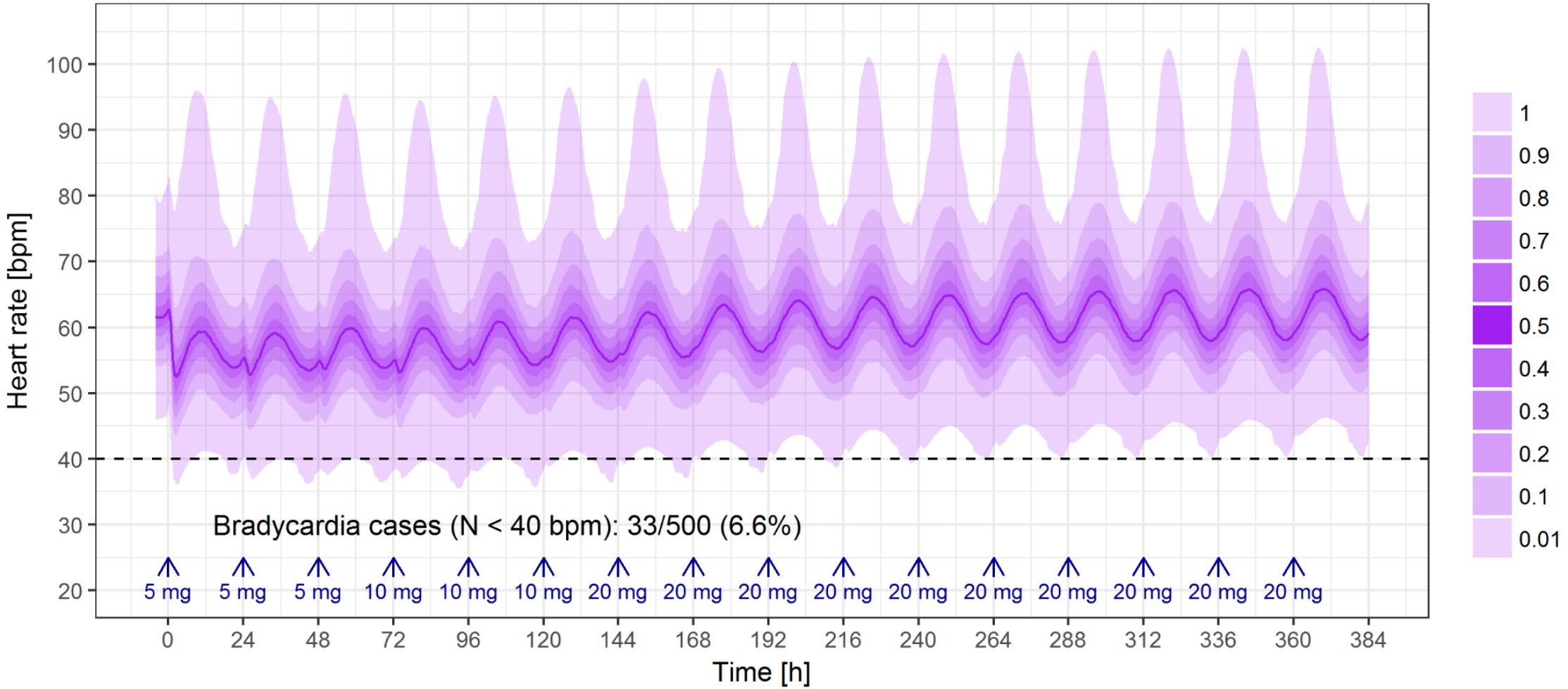
Tolerance with up-titration



Lott et al.: Heart rate tolerance modeling of ponesimod. CPT 2018.

Covariate effect: clinical impact

Tolerance with up-titration

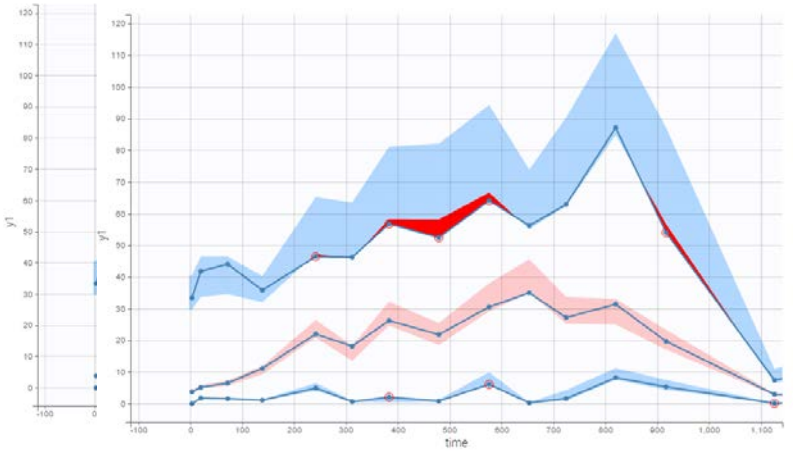


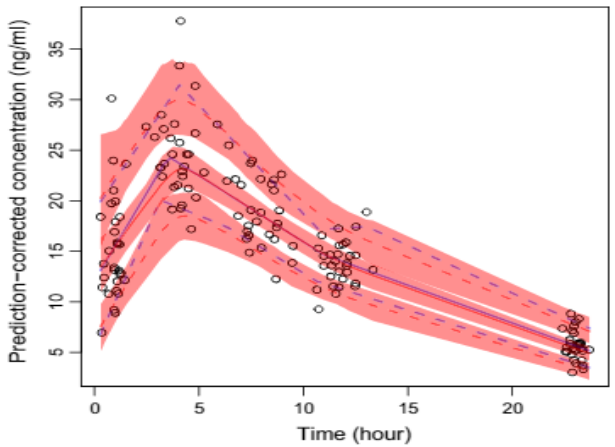
Lott et al.: Heart rate tolerance modeling of ponesimod. CPT 2018.

VPC: visual judgment

Possible distortions

- **Options**
  - Bins: same width, same no. of obs., other
  - Quantiles to show: 80%, 90%, etc.
  - Intervals: blocks, interconnected lines
  - Model shortcomings: red areas, white
  - Subsets: Stratification, pcVPC
- **Visual impression and judgment depends on the type of graphic chosen**
  - Bins: Lavielle JPKPD 2011
  - Jamsen et al., CPT:PSP 2018: quantile regression





Summary (1)

Visualization topics in pharmacometrics and statistics

- **Visualization**
  - intuitive, easy to grasp, accurate (by the audience!)
- **Data**
  - Appropriate scale (logarithmic or linear)
  - Comparison must be facilitated
- **Models and simulations**
  - What is the question again?
  - Show the quantity of interest
- **Clarity on what is shown (axis labels, intervals with SD or CI, …)**
- **Get the message across to the decision maker**

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Summary (2)

Potential collaborative work between statistics and pharmacometrics (SIG SxP)

- **Goodness of fit: observed vs predicted**
  - Is a smoother appropriate that minimizes in the y-direction only?
    - Alternative: errors-in-variables regression (errors in x and y)
  - A statistic to summarize an obs-vs-pred plot (beyond R^2)?
- **VPC**
  - Log-likelihood (OFV, AIC), Shrinkage are established
  - How about a statistic to summarize a VPC? (qq-plot idea?)
  - Can a fit be "too good to be true" (100% of data stats inside 80% VPC band)?

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Thank you for your attention.