



Hands on training Non Clinical PKPD data exploration

15 June 2022

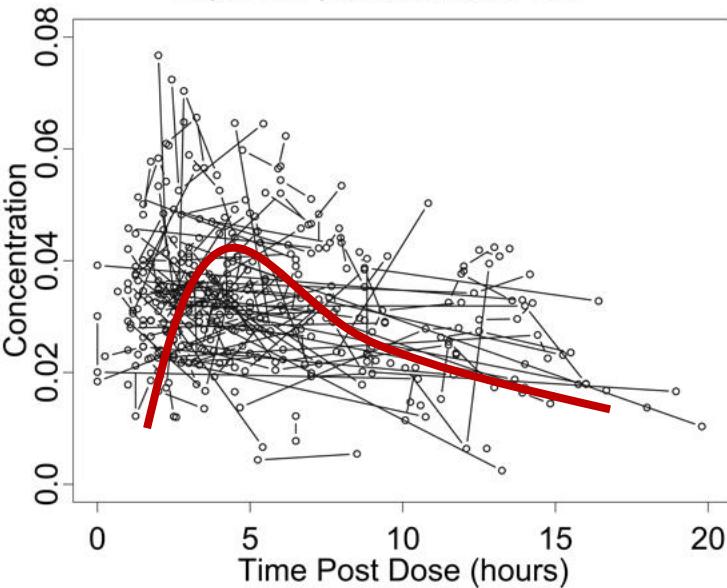
Concepts

Population modelling: Illustrative example

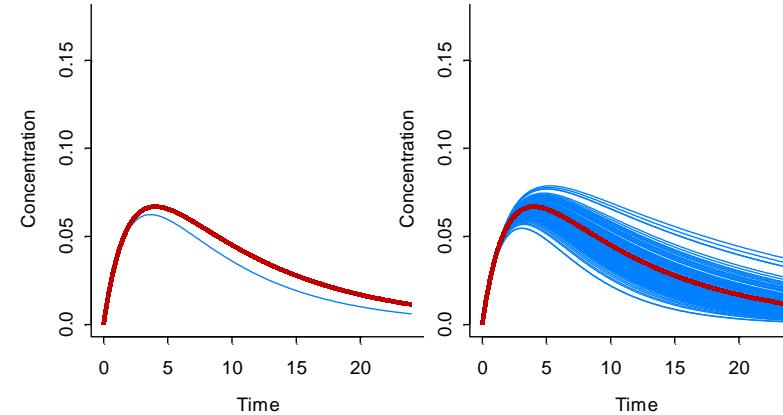
Quantification of inter individual variability and residual error

Fictive example :
Individual (line connections) PK
profiles after single
subcutaneous dose

Population pharmacokinetic data

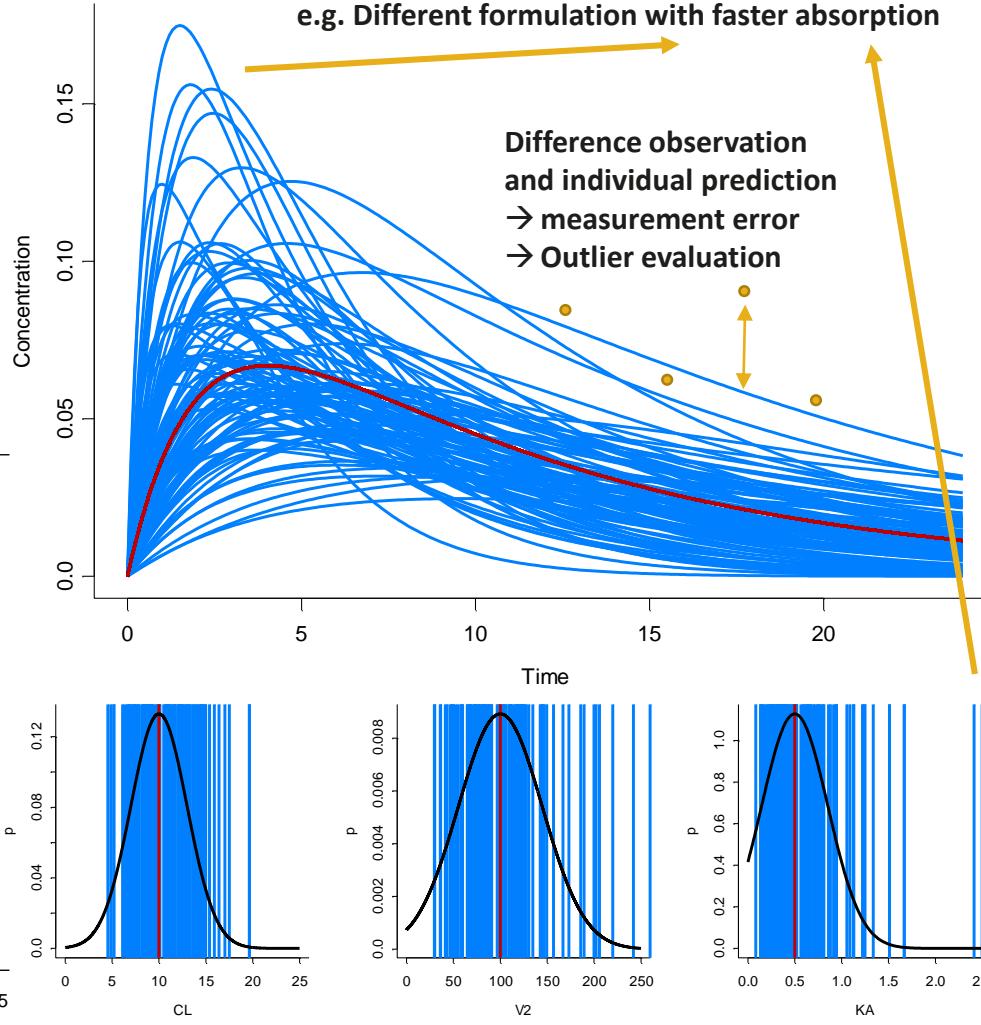


- Patients/Animals are different
- Assays are subjected to error



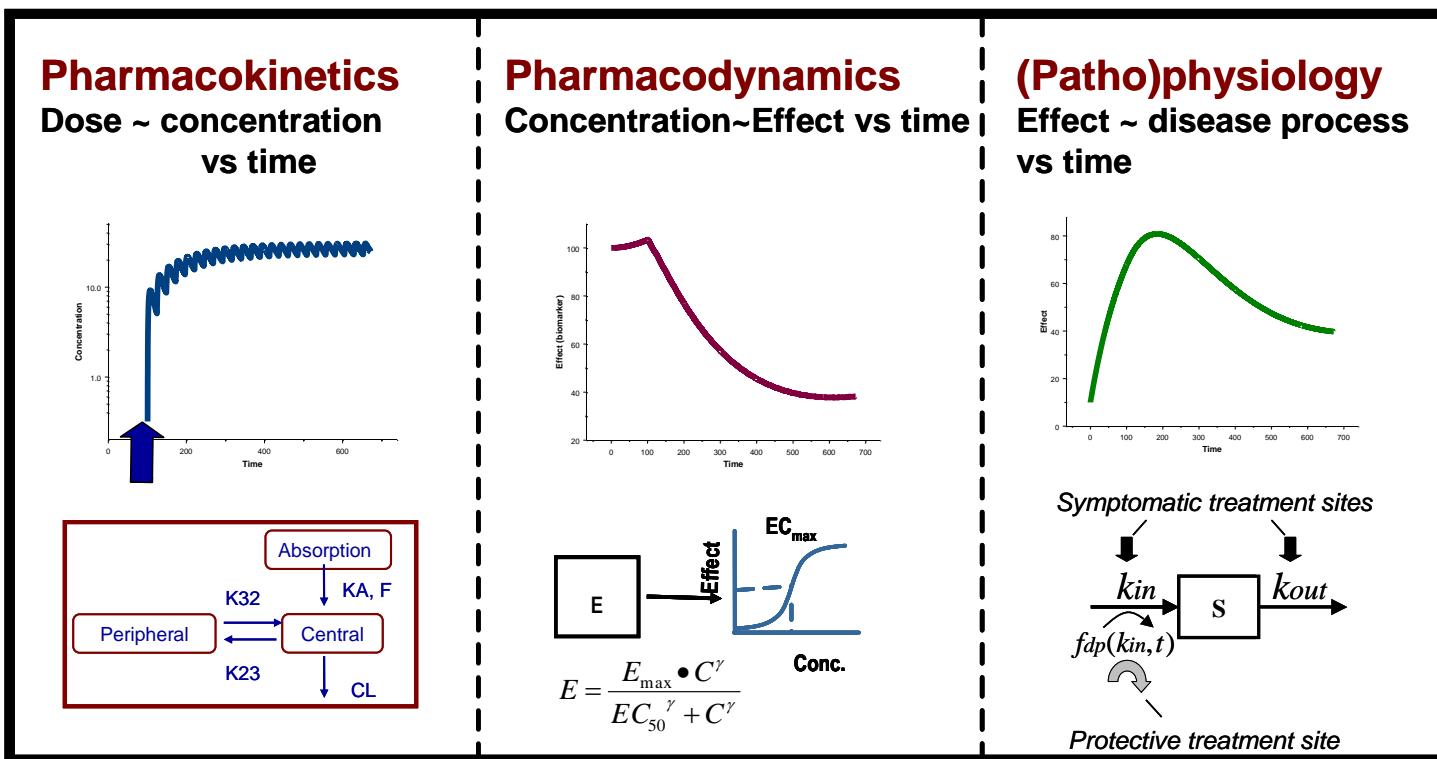
Exploration of covariate effects
e.g. Different formulation with faster absorption

Difference observation
and individual prediction
→ measurement error
→ Outlier evaluation



PK-PD-Effect integrated modeling

- Dose → Concentration → PD response → Clinical effect
 - Integrate pharmacokinetic, pharmacodynamic and physiological principles



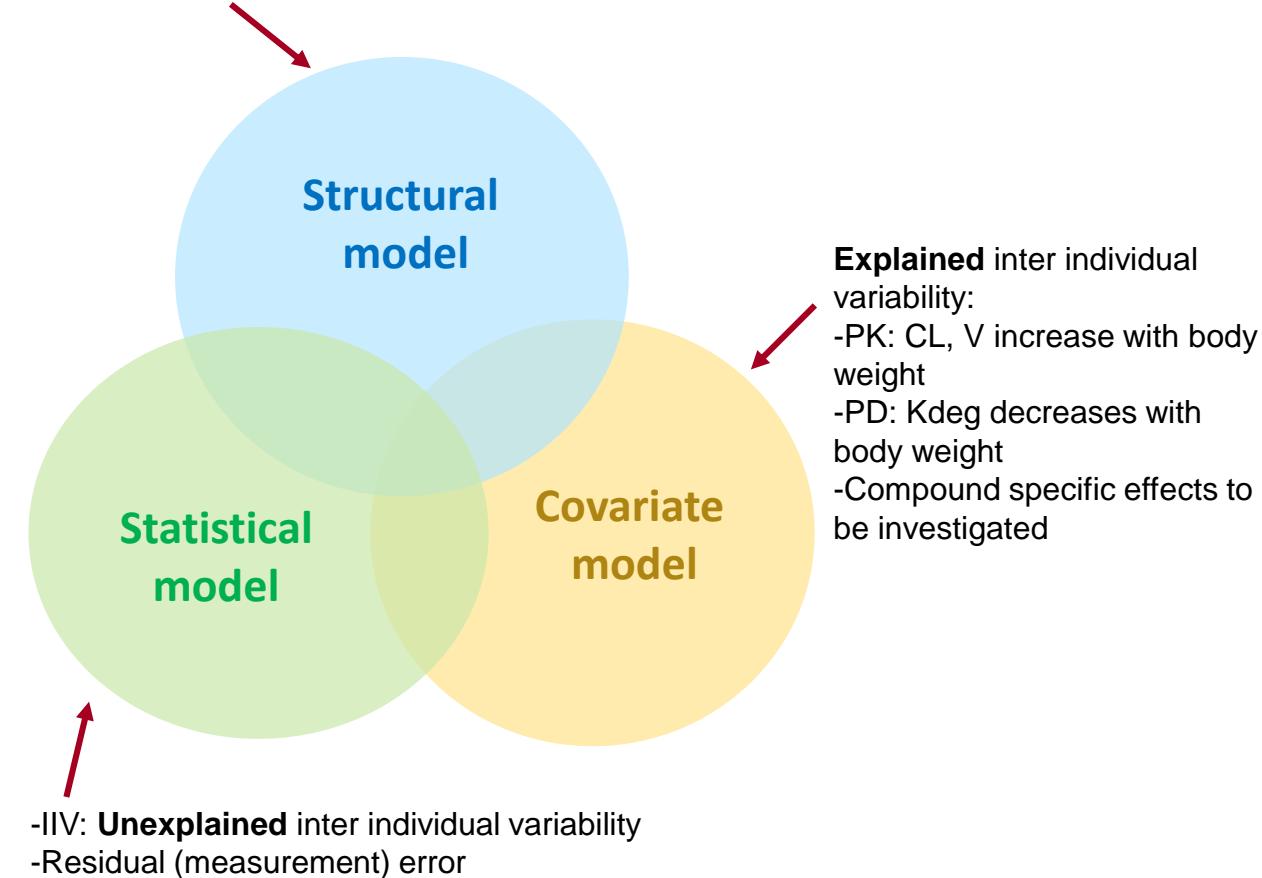
Data integration

- Across time points
- Across doses
- Across endpoints
- Across studies, populations and species
 - Evaluate and quantify differences in patient populations (e.g. disease severity), species ...
 - Analysis of sparse data is possible: Leverage information from rich (sub)studies
- Across drugs

Sheiner (1992) Learning and confirming in clinical drug development, CPT

Population modeling as a tool to integrate and summarize PK-PD-Response knowledge

- Population model as tool to answer questions
 - Try to capture the most important processes
 - Keep it as simple as possible
 - But not too simple
 - Helps summarize all available knowledge
 - Responses are described in a quantitative fashion
 - Information from different sources can be integrated
 - Allows data driven hypothesis testing
 - Model simulations
 - predictions can be used to explore untested situations to support decision making
- Three main components of a population model
 - PK: clearance (CL), volume of distribution (V) ...
 - PD: production (Kin), degradation (Kdeg), drug effect ...

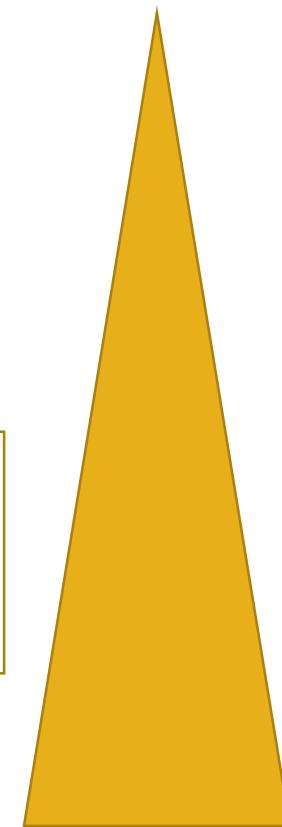


Selection of model type depends on question, data and knowledge of the system

Model types

- Non-compartmental models
 - Basic description of observations using linear regression
- Descriptive compartmental models
 - A series of interconnected compartments without any physiological interpretation
- Semi-mechanistic compartmental models
 - A series of interconnected compartments with some physiological interpretation
- Systems pharmacology - physiologically based PK models
 - PBPK: A series of interconnected compartments where each compartment represents a specific organ

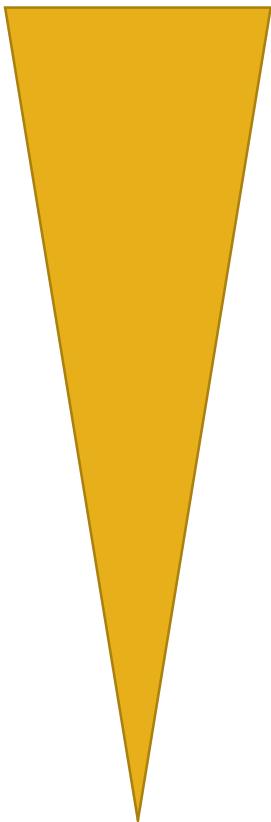
Purely descriptive - often limited value in predictions



Straightforward reporting and interpretation

Align model type choice to
-question
-available data
-system knowledge

→ Often feasible to develop/update along with drug development
→ Discuss assumptions and limitations
→ Predictions possible within boundaries



Drug independent & systems based; High value predictions and extrapolation possible

Time consuming (months to years)



Introduction to data exploration app

Practical information

- Link to shiny data exploration application
 - Account creation invitation via email address
- Live demonstration by Sven Hoefman: use of application
 - App developer (Richard Hooijmaijers) available online during course for help
- App remains accessible for certain period of time to allow participants to complete / re-visit exercises

Data exploration shiny app: essentials

- App designed for the present course: create explorative graphs for a dataset
 - All needed datasets are listed
- Getting started
 1. Select dataset: “sm_rat_pk_iv_sd.csv” (Optional: Click Table source data to get tabular overview)
 2. Select plotting panel (Default plotting)
 - Select following in Layer 1 → X value: “TIME”; Y value: “Cplasma”
 - Click create plots
 - Expand settings as desired → Create plots to re-generate plot
 - Re-set settings to starting point via “Clear fields”
 - Alternative: create plot via “show presets”
- Additional options
 - “Create plotly” instead of “create plots” → Interactive version of plot
 - Expert plotting: Allows more flexibility and plotting options → but less intuitive for users new to R programming
 - Save button to save plots
 - Complete refresh can be helpful: 

Explanation of dataset column names

- ID: animal number
 - TIME: time (h)
 - DOSE_MGKG: dose (mg/kg)
 - CMPD: compound (SM, mAb)
 - SPEC: species (Monkey, Rat, Mouse)
 - BW: body weight (kg)
 - ROUTE: route of administration (1: IV; 2: PO)
 - NDOS: number of doses
 - ADA: Animal anti drug antibody status (0: No; 1: Yes)
 - C: Concentration ($\mu\text{g/mL}$), e.g. Cplasma, Cbrain
 - BQL: Below quantification limit (0: No; 1: Yes)
 - DV: Dependent variable
 - BSL: Baseline (for efficacy and Safety biomarker)
 - Percchange: Percent change from baseline (for efficacy and Safety biomarker)
- For the PKPD dataset, two differently structured datasets with same information is provided
 - Table “long” *versus* “wide”
 - Long: values of all variables in DV column; TYPE column specifies variable
 - TYPE: Cplasma, Cbrain, Efficacy_Biomarker, Safety_Biomarker
 - Wide: each variable as a separate column
 - Cplasma, Cbrain, Efficacy_Biomarker, Safety_Biomarker, Efficacy_Baseline, Safety_Baseline, Efficacy_Percchange, Safety_Percchange

Hands on introduction

Fictive non clinical drug development case – Compound properties

- Simplified compound properties + mechanisms of action
 - Selection between two lead compounds: small molecule and monoclonal antibody

Drug	SM	mAb
Format	Small molecule	Antibody
Administration	PO	SC
Target Selectivity	1A receptor 1B receptor	1A receptor
In vitro Potency ($\mu\text{g/mL}$)	1 $\mu\text{g/mL}$ for 1A receptor	1 $\mu\text{g/mL}$ for 1A receptor
Cross reactivity	Rodent & NHP	NHP, $\pm 10x$ worse affinity for rodent
MW (g/mol)	1000	150000

1A receptor mainly expressed in brain, associated increased satiety (desired)
1B receptor mainly expressed in liver, associated with liver toxicity,
relevance for potential clinical side effects unknown

Fictive study data availability

- Stepwise, simplified overview of drug development path
 - Dosage of 3, 10, 30 mg/kg; N=10 per arm; Set of time-points per study (sequential plasma sampling); Assay LLOQ 0.05 µg/mL

	Drug	Study Type	Dosing	Species	Exploration datasets
Step 1a	SM	PK	IV Single dose	Rat	Data: sm_rat_pk_iv_sd.csv NCA: sm_rat_nca_iv_sd.csv
Step 1b	SM	PK	IV Single dose	Rat, Monkey, Mouse	Data: sm_trans_pk_iv_sd.csv NCA : sm_trans_nca_iv_sd.csv
Step 2	SM	PK	IV/PO Single dose	Rat	Data: sm_rat_pk_ivpo_sd.csv NCA: sm_rat_nca_ivpo_sd.csv
Step 3	mAb	PK	IV Single dose	Rat, Monkey	Data: mab_trans_pk_iv_sd.csv NCA: mab_trans_nca_iv_sd.csv
Step 4	SM + mAb	PKPD	PO/SC Q2D	Rat, Monkey	Data: trans_pkpd_q2d_long.csv; trans_pkpd_q2d_wide.csv

- Step 1-4 can be performed using “default plotting”
 - For step 4: “expert plotting” option provides more flexibility

Purpose / goal(s) during each step

- Step 1
 - Toolbox practice: raw concentration profiles, NCA analysis results
 - Distinguish types of variability: inter- / intra-individual, inter-species
- Step 2
 - Compare effect of administration routes on PK
- Step 3
 - Inter-species PK variability for mAbs and its causes
- Step 4
 - Explore translational PKPD between compounds / doses / species
 - Plasma vs brain PK results
 - Safety and Efficacy biomarker results
 - Recommend safe/efficacious clinical dosing regimen per compound

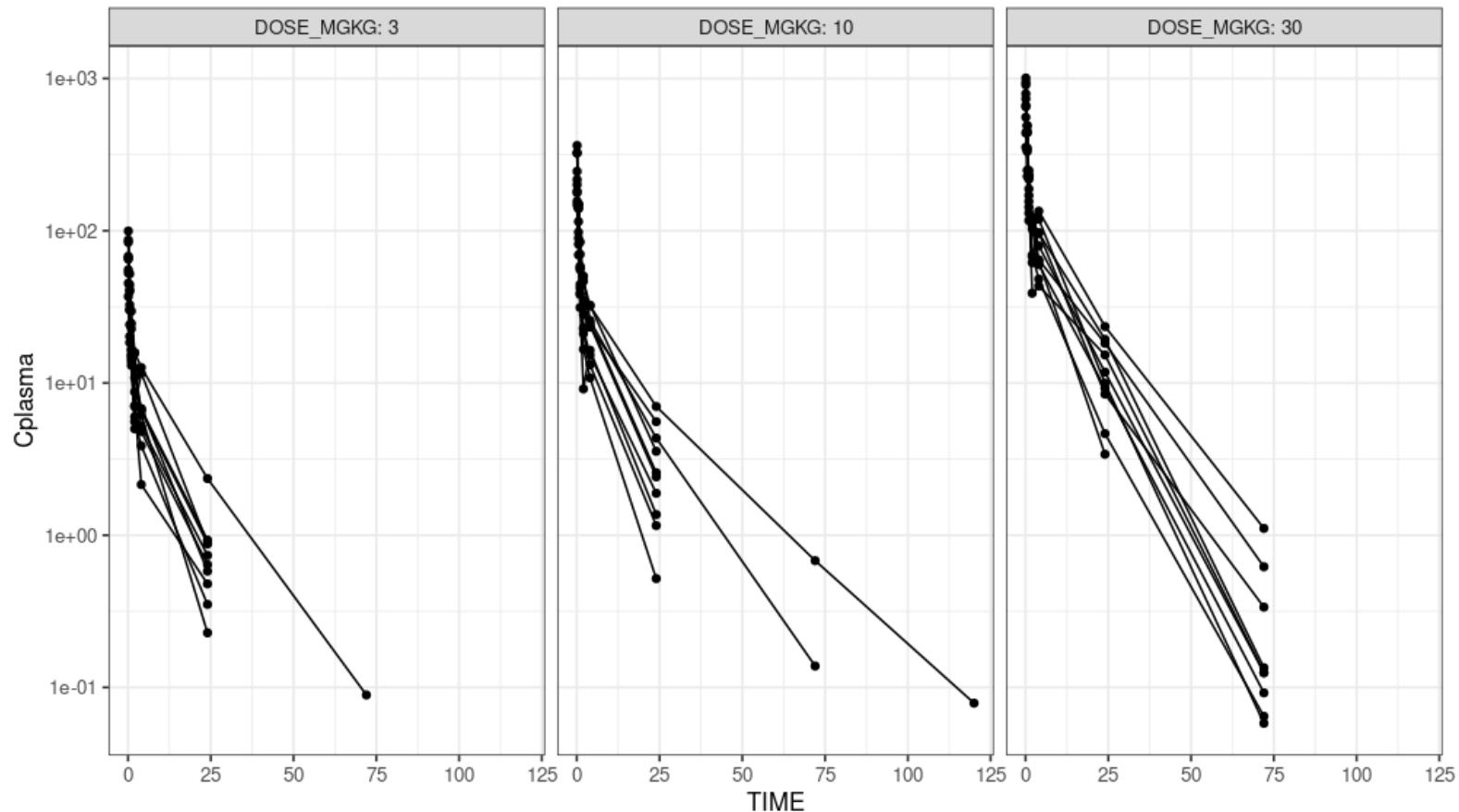
Step 1: Assess variability between and within animals

	Drug	Study Type	Dosing	Species	Exploration datasets
Step 1a	SM	PK	IV Single dose	Rat	Data: sm_rat_pk_iv_sd.csv NCA: sm_rat_nca_iv_sd.csv
Step 1b	SM	PK	IV Single dose	Rat, Monkey, Mouse	Data: sm_trans_pk_iv_sd.csv NCA : sm_trans_nca_iv_sd.csv

- Additional information
 - 1 week study; 3, 10, 30 mg/kg
- Step 1a
 - Explore PK profiles and NCA results
 - Discuss: variability – between (IIV) and within (measurement error) animals
 - Discuss: compare results between dose levels → E.g. Is the PK linear?
- Bonus - Step 1b
 - Explore NCA results: discuss species differences wrt allometric scaling

Step 1a

- Variability between animals and measurement error
- No signs of non-linearity



Data Selection Plotting

Layer 1 Layer 2

X value: TIME

Y value: Cplasma

Type: point

Colour by:

Factor colour

Stats:

Panel by: DOSE_MGKG

Subset: variable BQL

Subset: operator equal

Subset: value 0

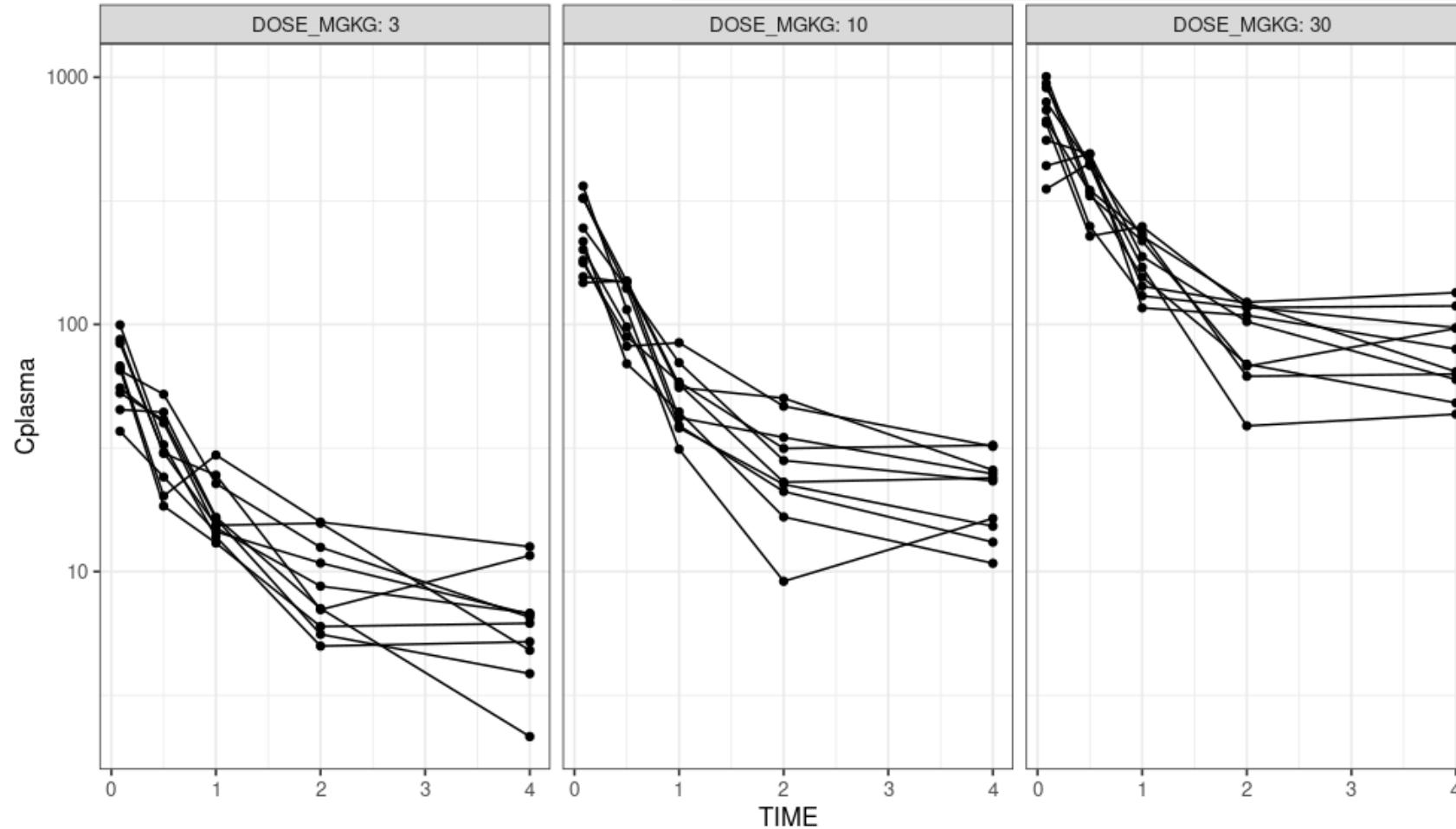
Set Y on log scale

Step 1a

- Zoom 4h: clear distribution phase

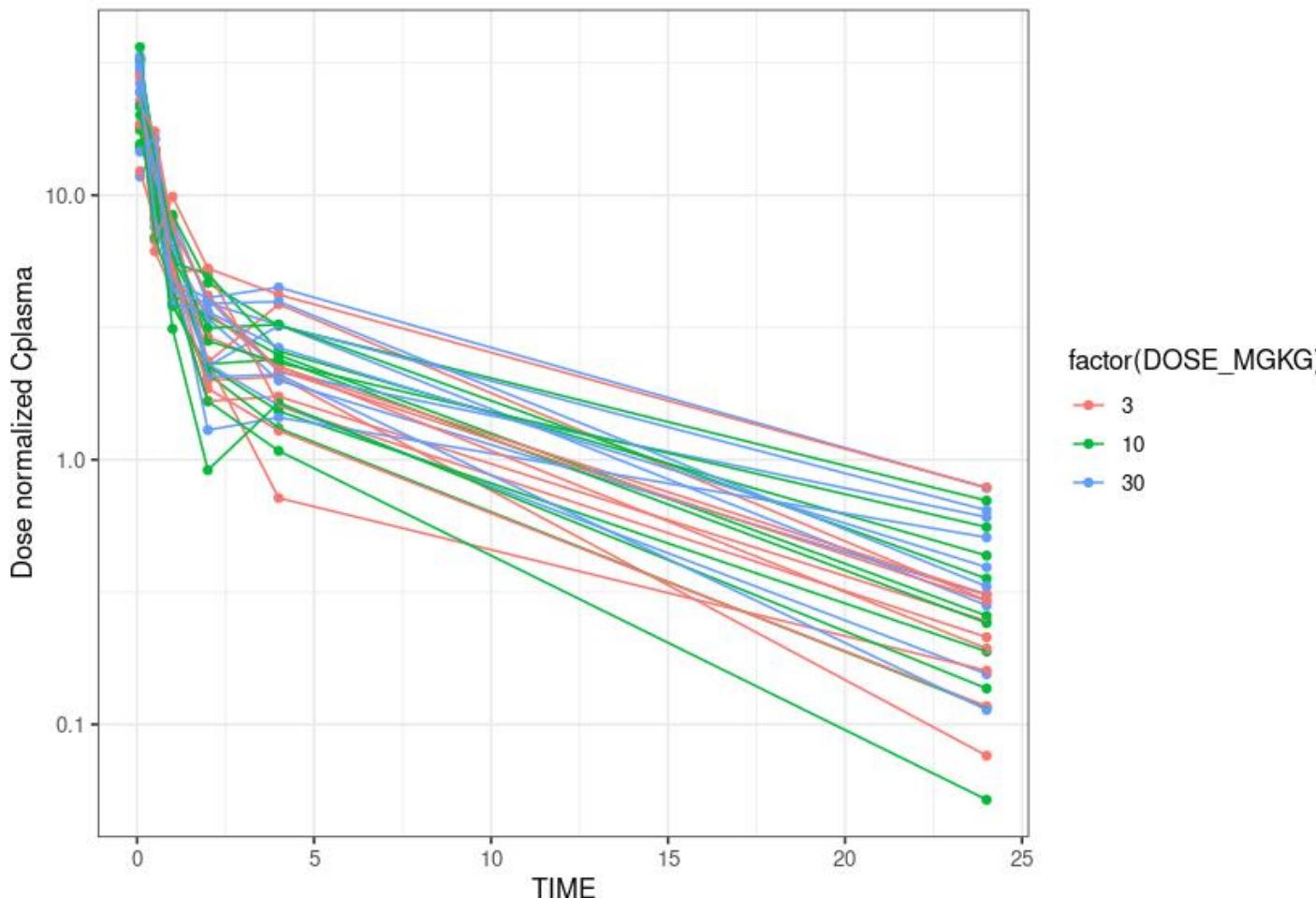
Subset: variable Subset: operator Subset: value

TIME less equal 4



Step 1a

- 24h subset: Dose normalized Cplasma



Default Expert

Data Selection Plotting

Subset: variable Subset: operator Subset: value
BQL equal 0

Subset: variable Subset: operator Subset: value
TIME less equal 24

Subset: variable Subset: operator Subset: value
DOSE_MGKG equal

Normalize variable Normalize by
Cplasma DOSE_MGKG

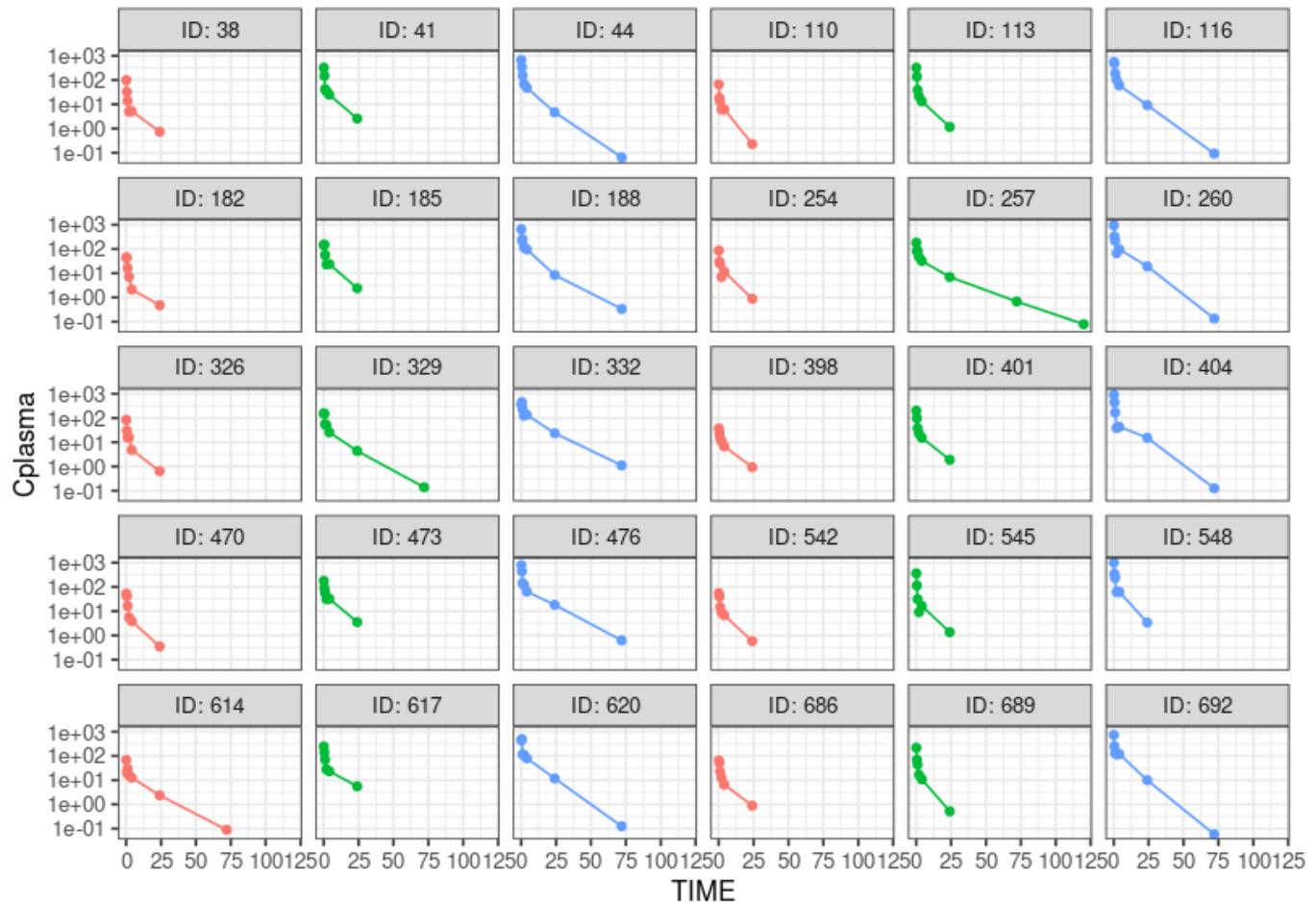
Layer 1 Layer 2

X value: TIME
Y value: Cplasma
Type: point
Colour by: DOSE_MGKG
 Factor colour
Stats:

Y value:
Type: line
Grouping (separate lines): ID
Colour by: DOSE_MGKG
 Factor colour
Title: title
X label:
Y label: Dose normalized Cplasma
 Set X on log scale
 Set Y on log scale

Step 1a

Individual plots



factor(DOSE_MGKG)

- 3
- 10
- 30

Layer 1

X value:

TIME

Layer 2

Y value:

Plasma

Y value:

Type:

point

Type:

line

Colour by:

DOSE_MGKG

Grouping (separate lines):

ID

Factor colour

Colour by:

DOSE_MGKG

Stats:

Factor colour

Stats:

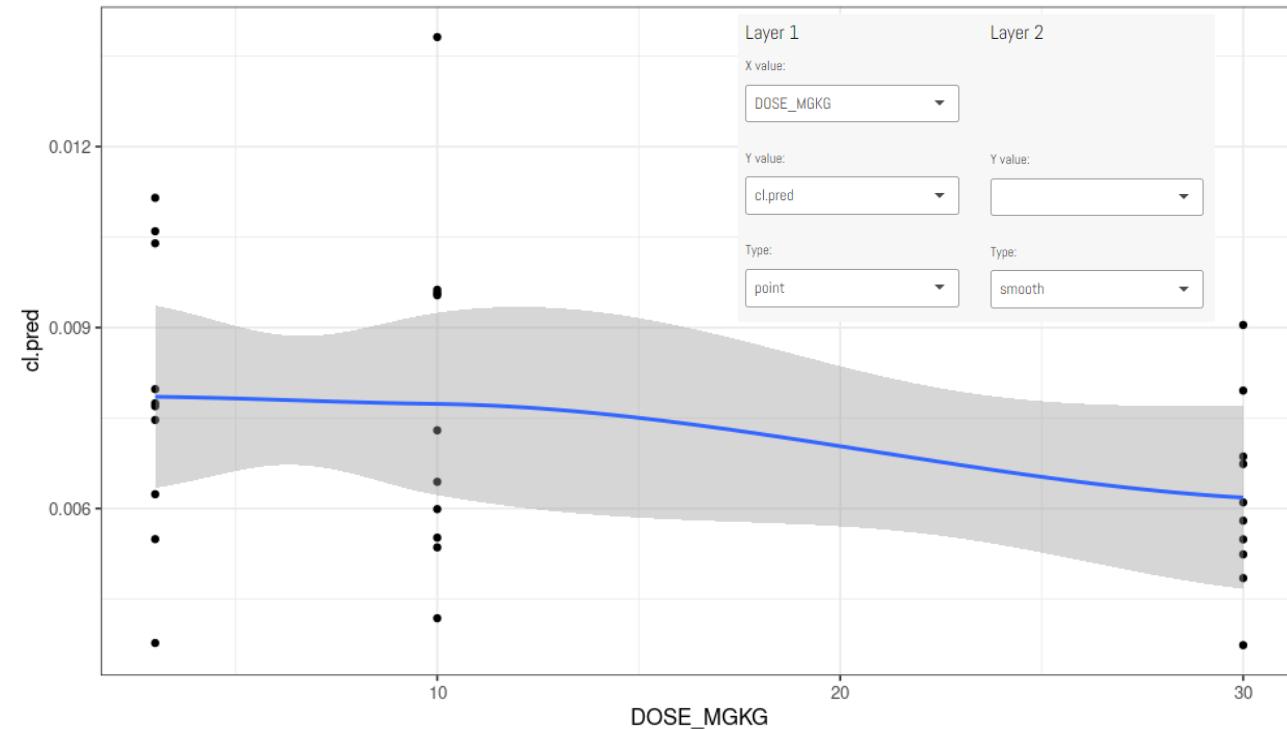
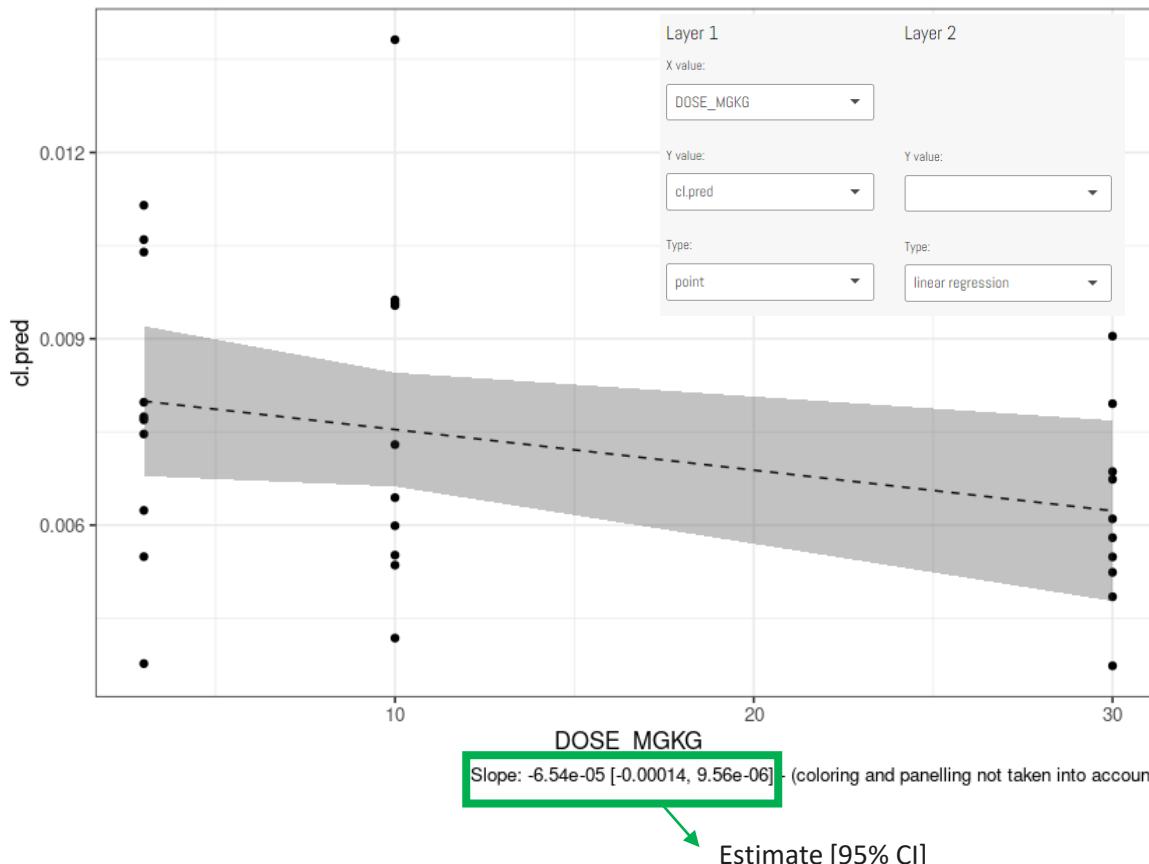
Panel by:

ID

Set Y on log scale

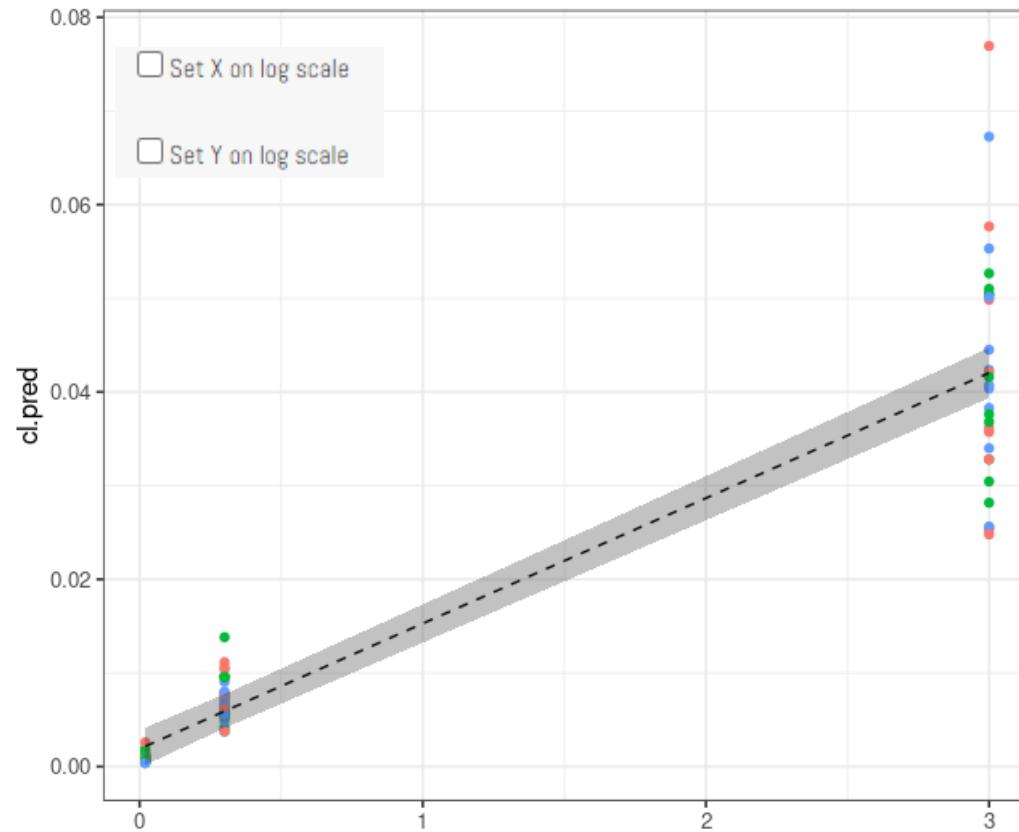
Step 1a

- No signs of non-linearity: e.g. 95% Confidence interval of slope of linear regression contains 0

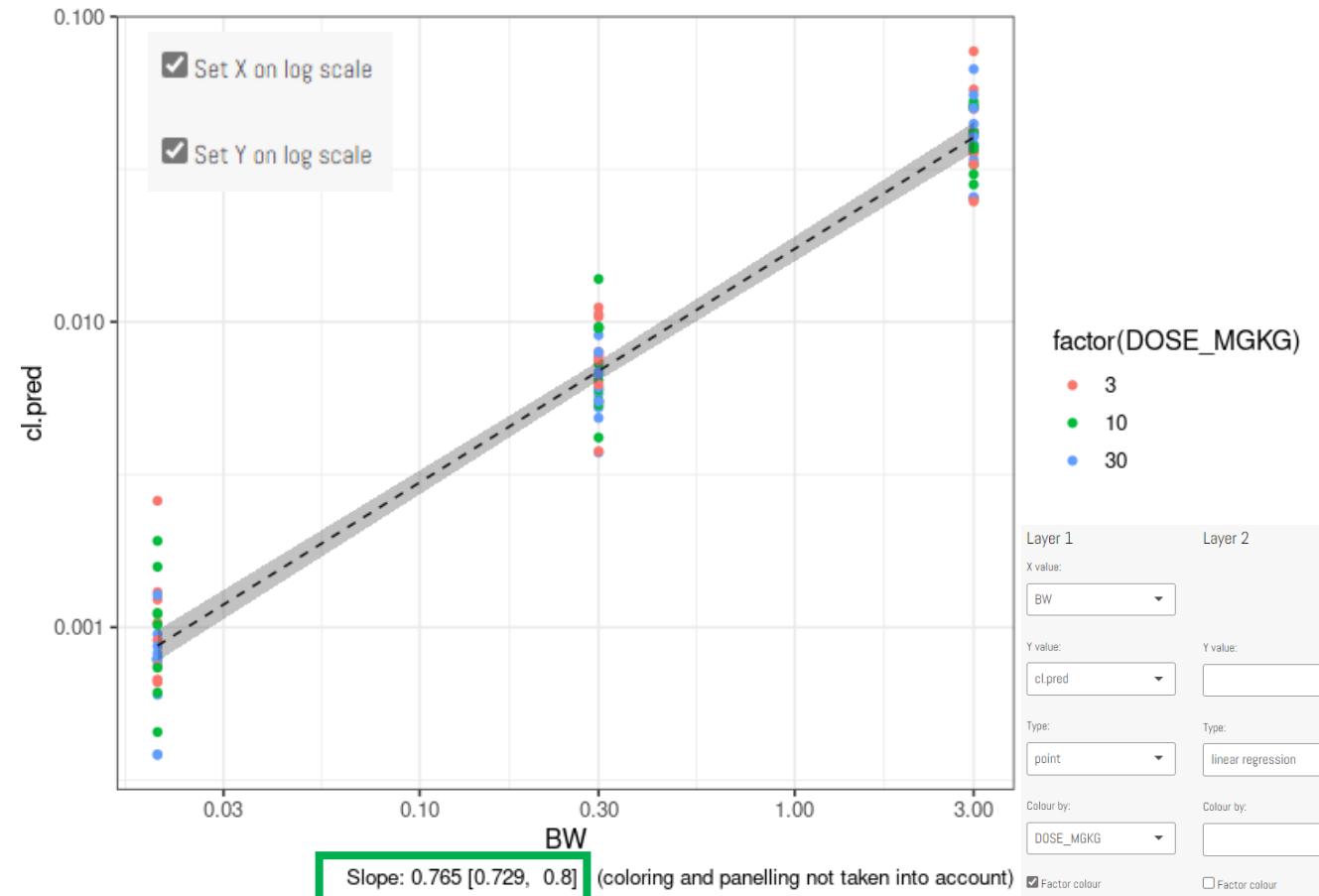


Step 1b

- CL: lin-lin plot

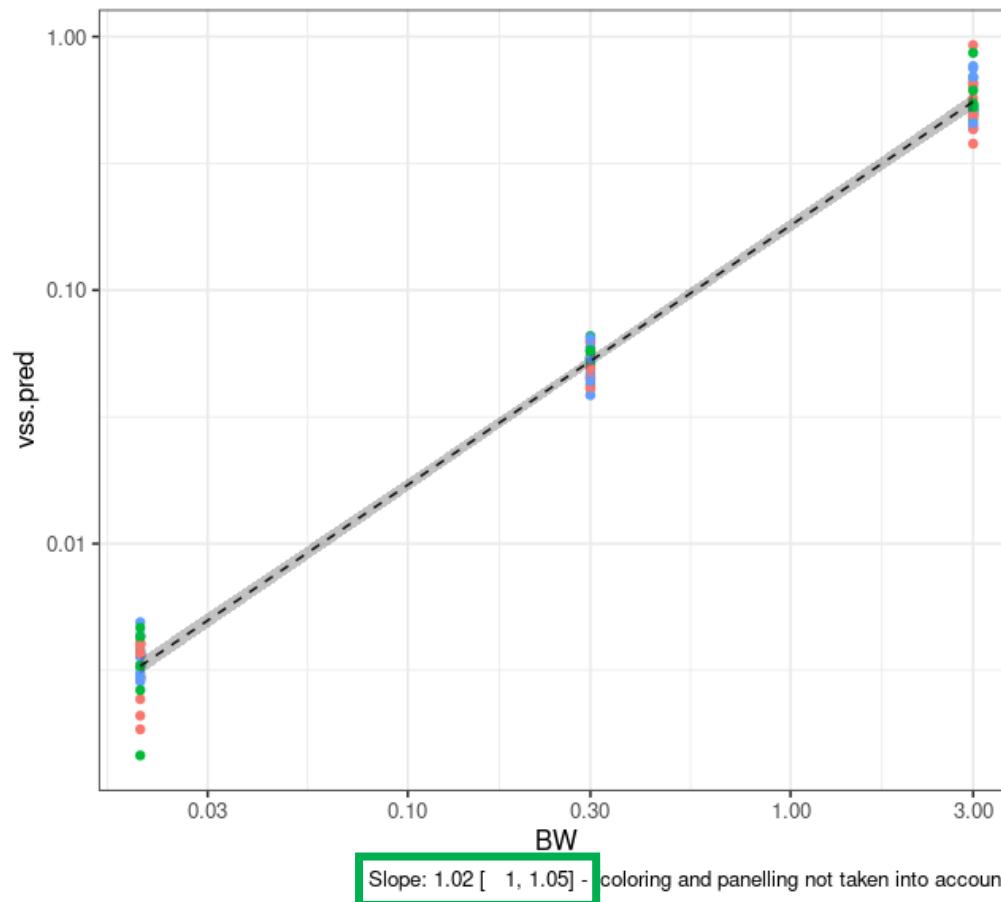


- CL: log-log plot → Slope is exponent of power relationship →
Scaling: $CL_{\text{human}} = CL_{\text{monkey}} * (BW_{\text{human}}/BW_{\text{monkey}})^{0.75}$

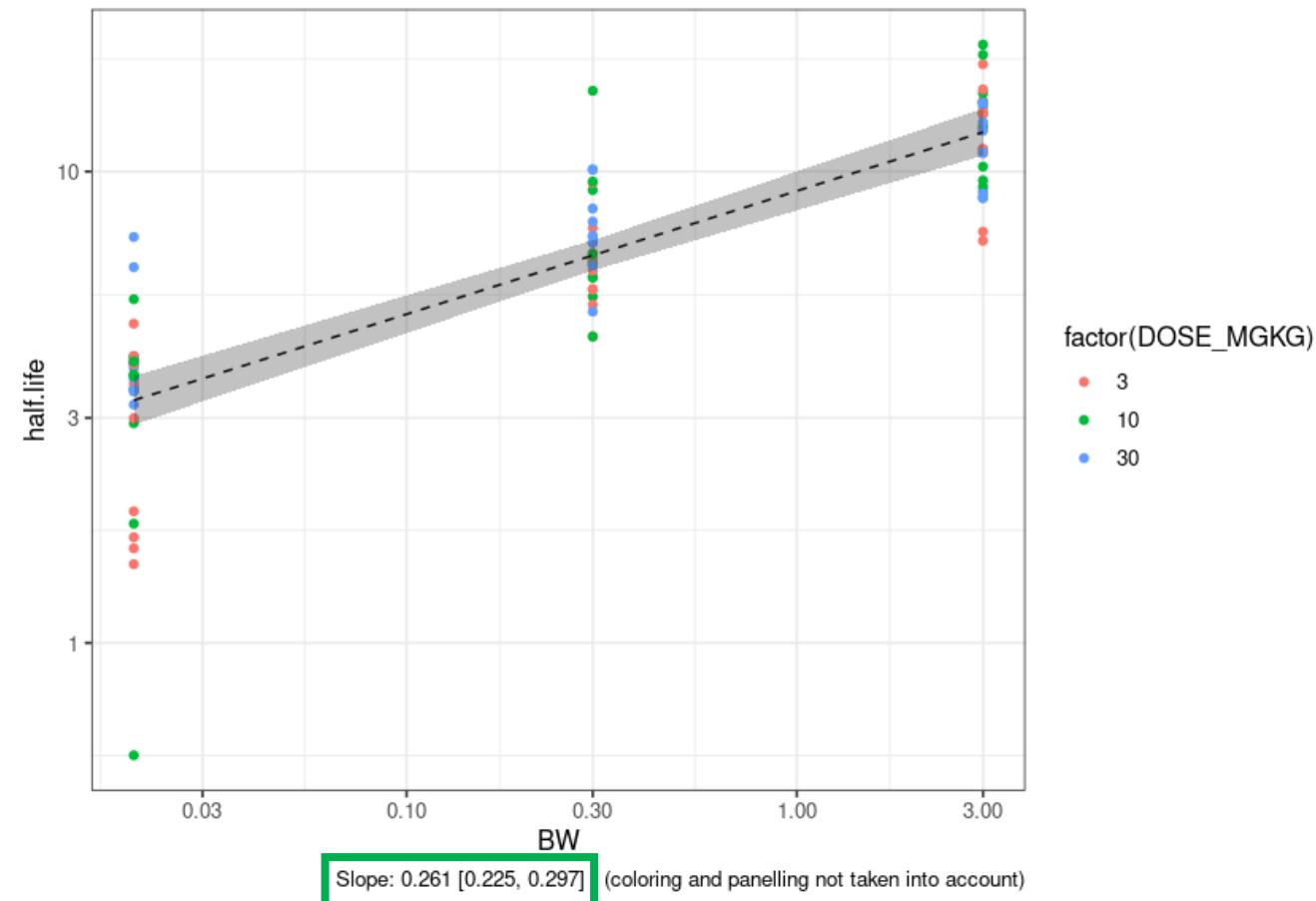


Step 1b

- Vss: Slope = 1.02 = Allometric scaling coefficient →
Scaling: $V_{\text{human}} = V_{\text{monkey}} * (\text{BW}_{\text{human}}/\text{BW}_{\text{monkey}})^{1.02}$



- $t_{1/2}$: Slope = 0.261 = Allometric scaling coefficient
 - Coefficients $V - CL \approx 1 - 0.75 = 0.25$



Step 2: Compare effect of administration routes on PK

Drug	Study Type	Dosing	Species	Exploration datasets
Step 2	SM	PK	IV/PO Single dose	Rat Data: sm_rat_pk_ivpo_sd.csv NCA: sm_rat_nca_ivpo_sd.csv

- Additional information
 - 1 week study; 3, 10, 30 mg/kg
- Step 2
 - Explore and discuss: Compare PK profiles / NCA results between administration routes
- Bonus – Step 2
 - Discuss: impact of sampling schedule on NCA results

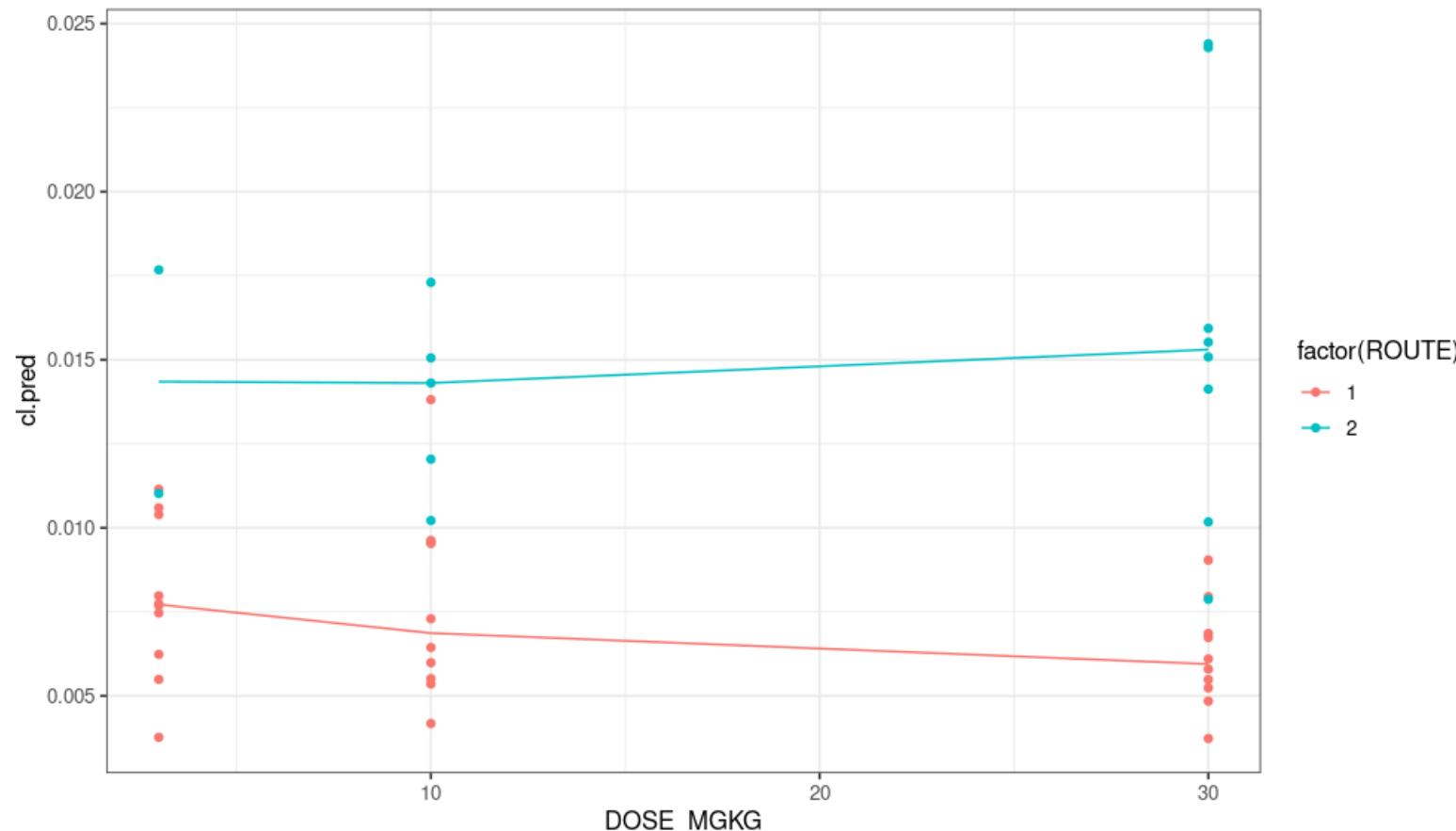
Step 2: Compare effect of administration routes on PK

Drug	Study Type	Dosing	Species	Exploration datasets
Step 2	SM	PK	IV/PO Single dose	Rat Data: sm_rat_pk_ivpo_sd.csv NCA: sm_rat_nca_ivpo_sd.csv

- Additional information
 - 1 week study; 3, 10, 30 mg/kg
- Step 2
 - Explore and discuss: Compare PK profiles / NCA results between administration routes
- Bonus – Step 2
 - Discuss: impact of sampling schedule on NCA results → **Hint: Focus on Cmax**

Step 2

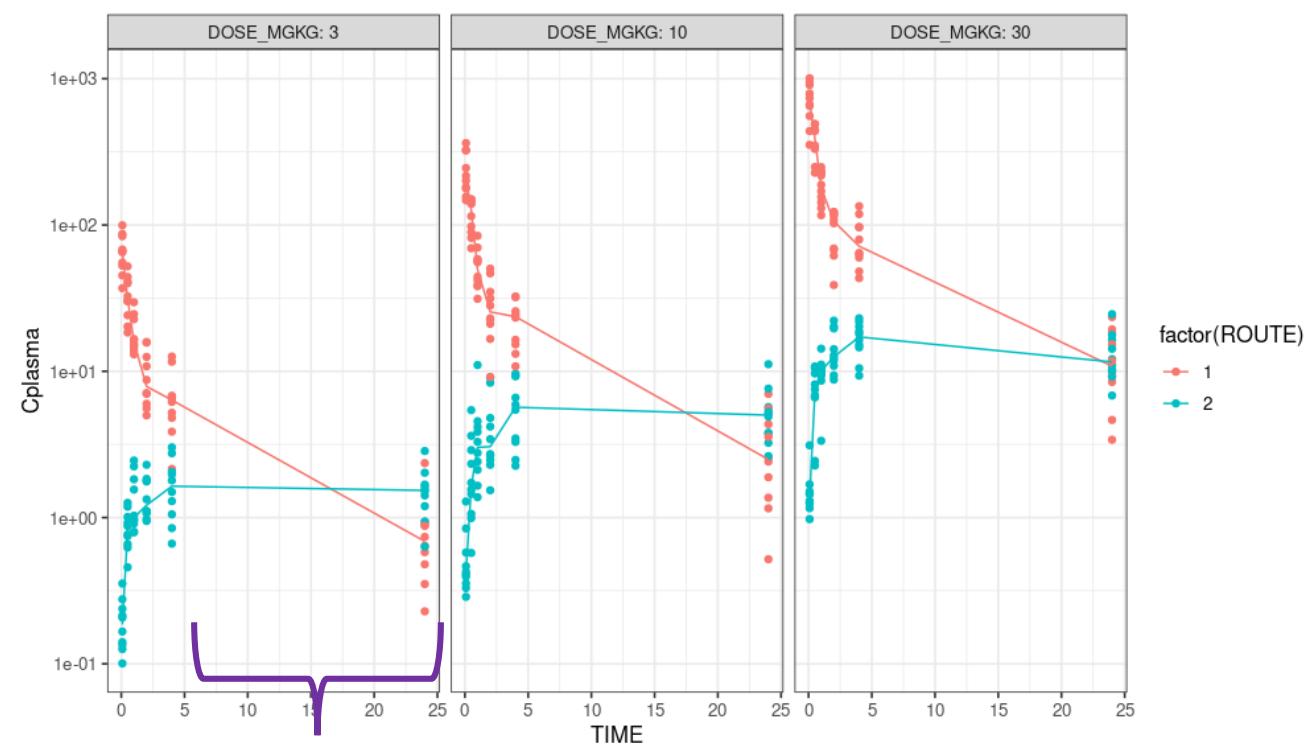
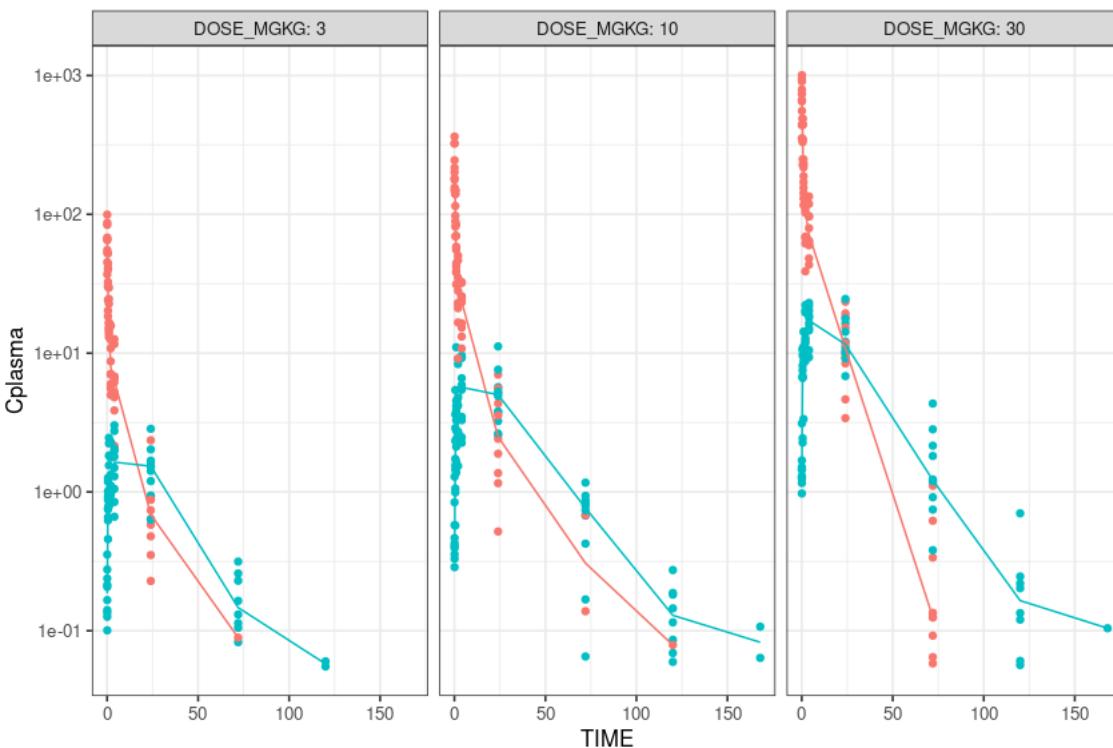
- Clearance larger for oral dosing, indicating a bioavailability lower than 1



Layer 1	Layer 2
X value:	Y value:
DOSE_MGKG	
Type:	Type:
point	line
Colour by:	Grouping (separate lines):
ROUTE	
<input checked="" type="checkbox"/> Factor colour	Colour by:
Stats:	ROUTE
<input checked="" type="checkbox"/> Factor colour	Stats:
median	median

Step 2

- Absorption controlled kinetics: absorption slower than elimination
 - Left: complete profile; Right: zoom in on first day; Line: median



Careful with interpreting C_{max} from NCA results: poor sampling design

Step 3: inter-species PK variability for mAbs and its causes

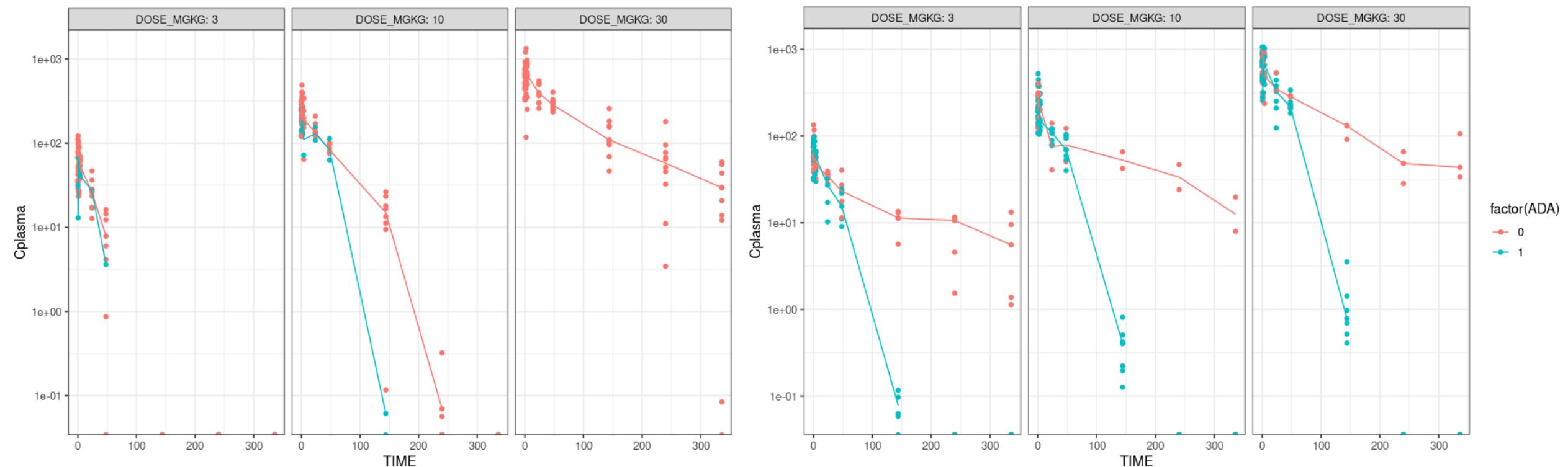
	Drug	Study Type	Dosing	Species	Exploration datasets
Step 3	mAb	PK	IV Single dose	Rat, Monkey	Data: mab_trans_pk_iv_sd.csv NCA: mab_trans_nca_iv_sd.csv

- Additional information
 - 2 week study; 3, 10, 30 mg/kg
- Step 3: Explore based on PK profiles / NCA results:
 - Discuss: Compare results between doses in **monkey**
 - Discuss: Compare results in terms of species differences between **monkey and rat**
- Bonus – Step 3
 - Generate hypotheses regarding differences between **individual animals**
 - Are there predictors of this variability in the dataset?

Step 3

Left: "Monkey" subset; Right: "Rat" subset; Lines: median

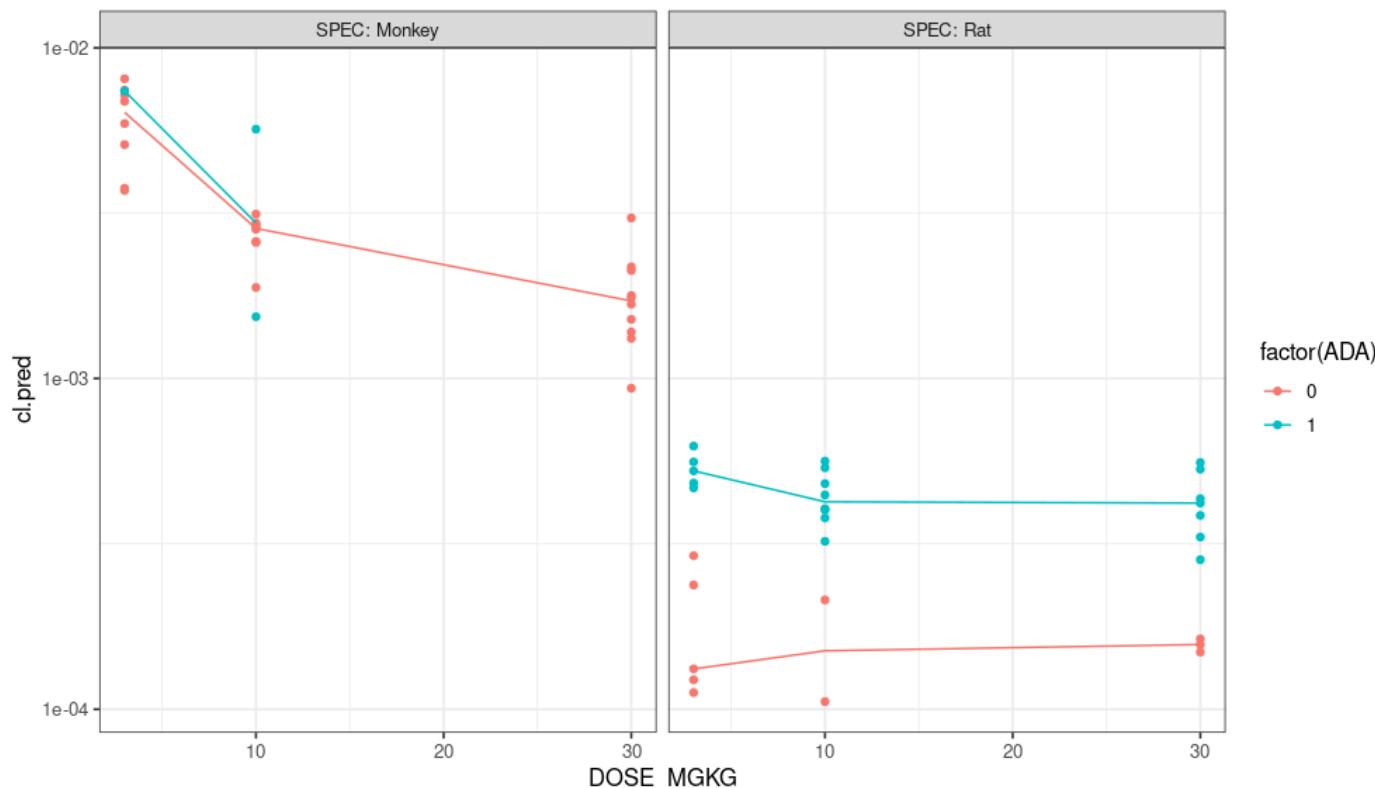
- For this mAb: probability of ADA appears higher for rat vs monkeys
 - ADA appear to be clearing: Drug eliminated faster after a couple of days → Time dependent kinetics
- For the ADA negative monkeys: elimination increases at lower concentration → TMDD: concentration dependent kinetics
 - No TMDD apparent for ADA negative rats → Species differences in target expression/turnover?



Step 3

Left: "Monkey" subset; Right: "Rat" subset; Lines: median

- NCA can be useful, but comes with limitations → interpret with caution
 - Picking up / interpreting concentration and time dependencies is difficult
 - Assumes a single CL per animal, derived from dose/AUC



Step 4: Translational PKPD

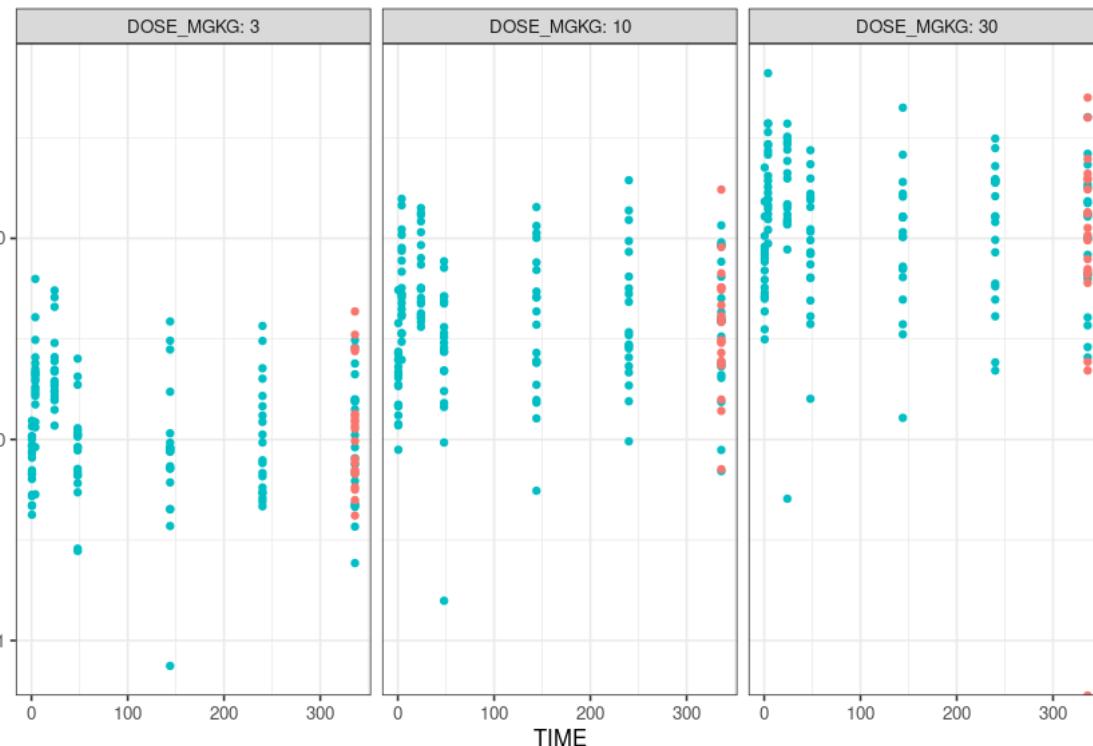
Drug	Study Type	Dosing	Species	Exploration datasets
Step 4	SM + MAB	PKPD	PO/SC Q2D	Rat, Monkey Data: trans_pkpd_q2d_long.csv; trans_pkpd_q2d_wide.csv

- Additional information
 - 2w study; 3/10/30 mg/kg q2d dosing: Plasma PK + terminal brain PK sampling; PD: two biomarkers: efficacy and safety
 - 2 datasets contain same information but structured differently, depending on plot of interest dataset can be selected
 - Long: values of all variables in DV column; TYPE column specifies variable
 - Wide: each variable as a separate column
- Step 4
 - Explore Plasma vs brain PK results between compounds / doses / species
 - Explore Safety and Efficacy biomarker results between compounds / doses / species
- Bonus – Step 4
 - Explore expert plotting option → In general tab: multiple panelling, subsetting and transformation options available
 - Underlying R code can be explored via: [» Code](#)
 - Discuss: impact of time point selection
 - Discuss: anticipated recommended safe/efficacious clinical dosing regimen per compound

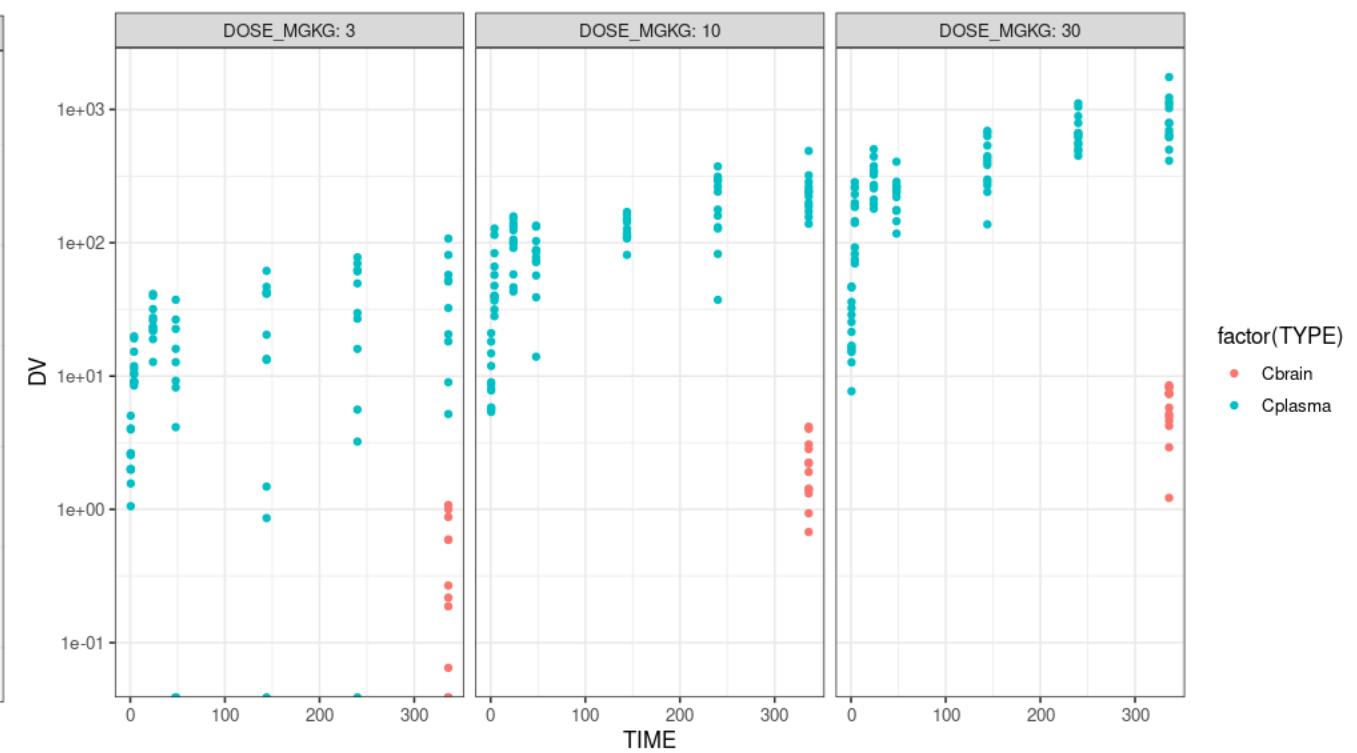
Step 4: Plasma versus brain PK

- For SM, Cbrain and Cplasma similar levels → For mAb relatively low Cbrain vs Cplasma: indicating distribution mAb issue

SM



mAb



Step 4: Plasma versus brain PK

- Settings previous slide - long dataset:

Panel by: DOSE_MGKG

Subset: variable Subset: operator Subset: value
CMPD equal mAb

Subset: variable Subset: operator Subset: value
TYPE in Cbrain,Cplasma

Subset: variable Subset: operator Subset: value
ADA equal 0

Normalize variable Normalize by

Title: mAb

X label:

Y label:

Set X on log scale

Set Y on log scale

Default Expert

Data Selection Plotting

Layer 1 Layer 2

X value: TIME

Y value: DV

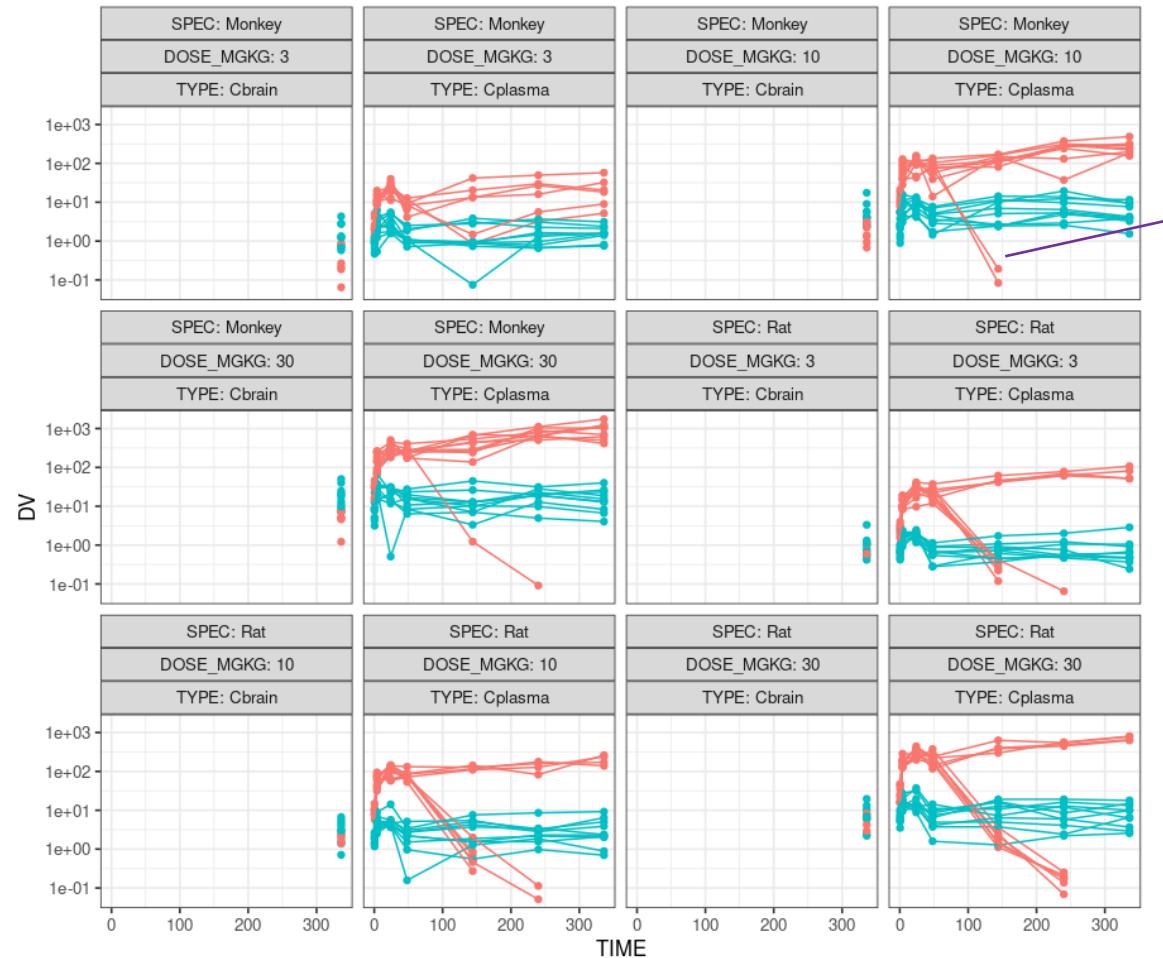
Type: point

Colour by: TYPE

Factor colour

Step 4: Plasma versus brain PK

- Alternative via expert option



Careful: ADA positive animals bias results
 → Can be subsetted out: "& ADA==0"

Long dataset:

Subset

```
TYPE %in% c("Cbrain", "Cplasma") & BQL == 0
```

Data Selection Base layer Second layer Third layer

General

X value:

Grouping:

X value:

Grouping:

Y value:

Colour:

Y value:

Colour:

Type:

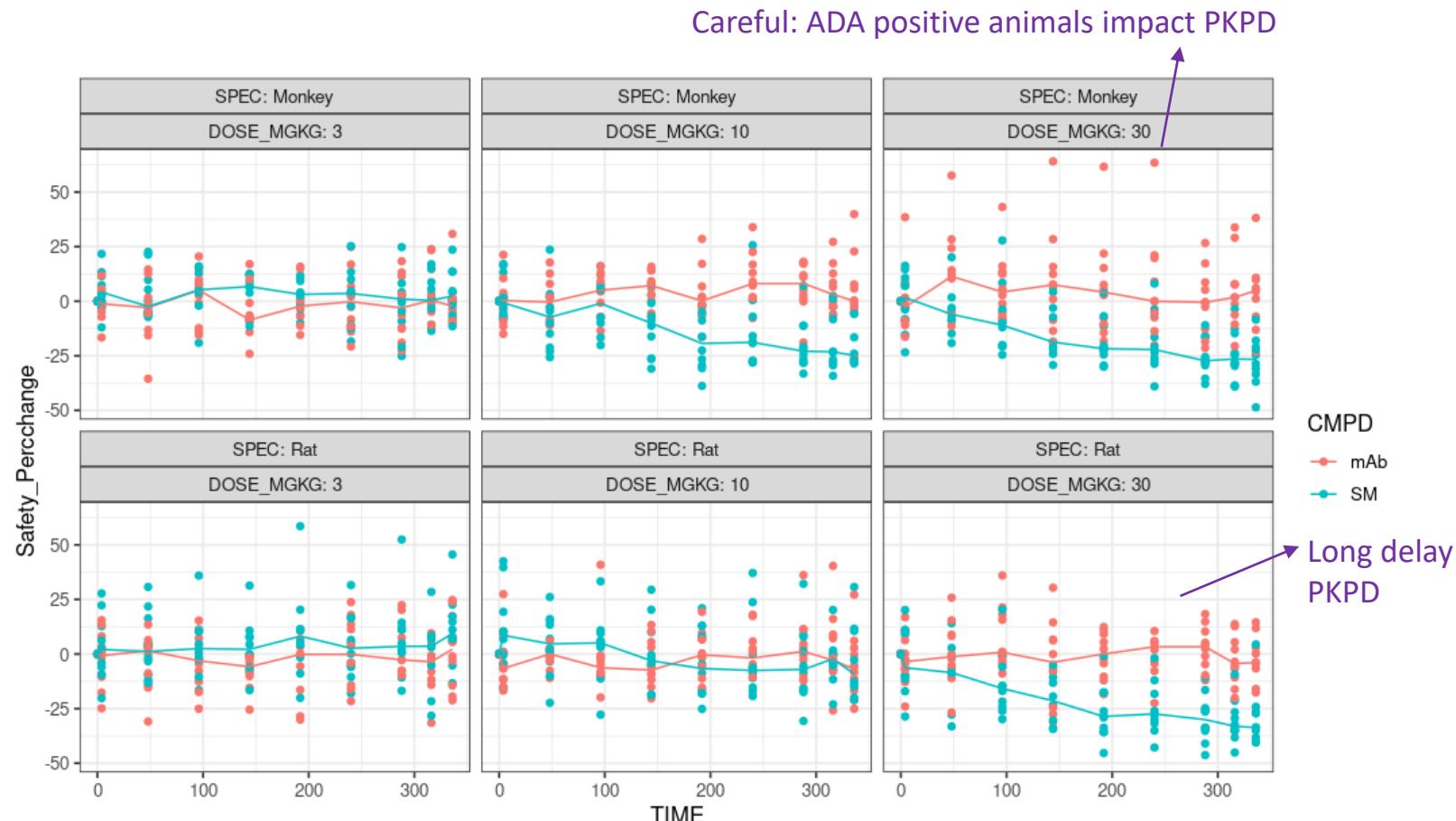
Shape by:

Type:

Shape by:

Step 4: Safety biomarker

- Safety: dose response for SM, but signal unclear for mAb



Long dataset – Expert settings:

panel by (1):

SPEC

panel by (2):

DOSE_MGKG

X value:

Grouping:

TIME

Y value:

Colour:

Safety_Perchange

CMPD

Type:

Shape by:

point

Data Selection

Base layer Second layer Third layer General

X value:

Grouping:

Y value:

Colour:

CMPD

Type:

Shape by:

line

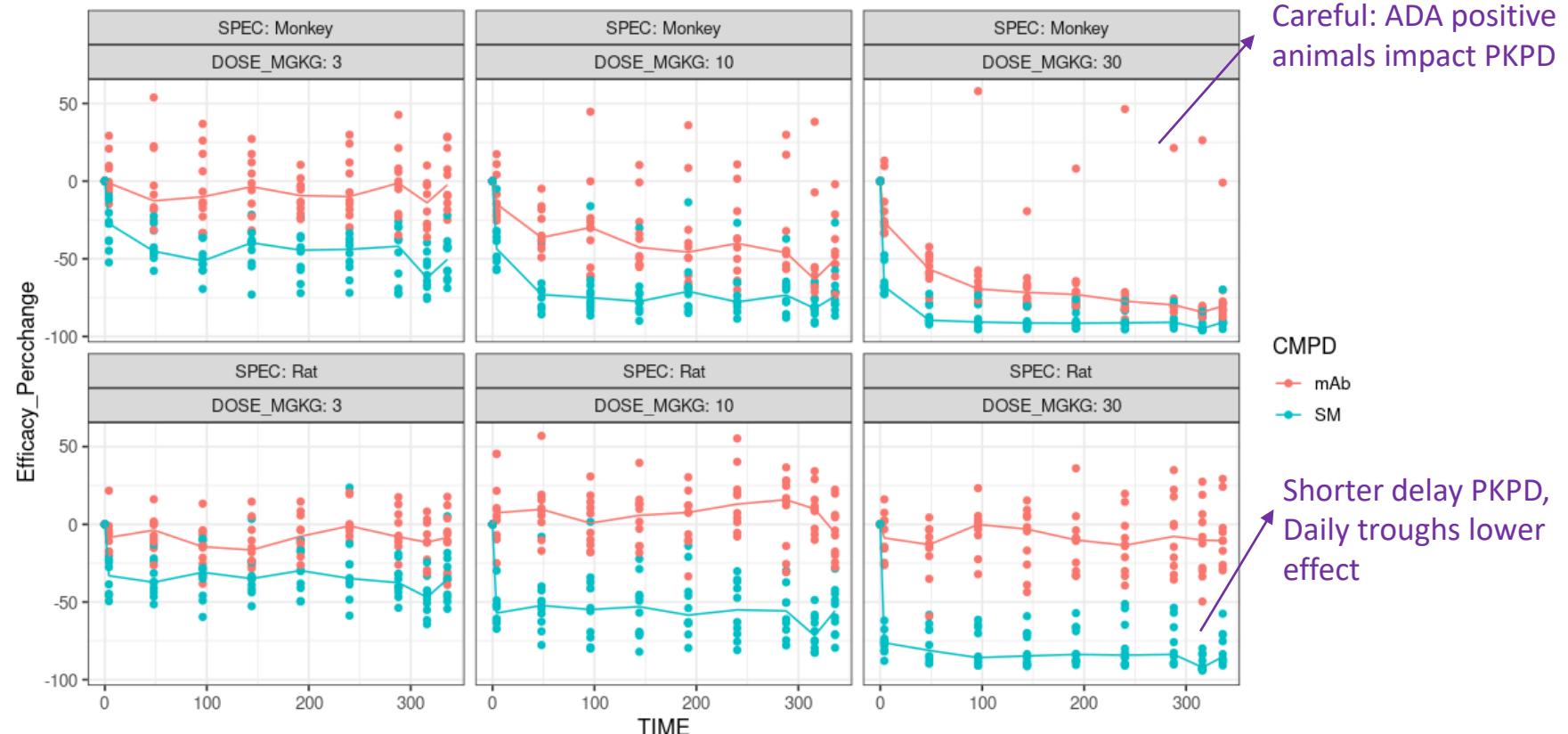
Stats:

Size by:

median

Step 4: Efficacy biomarker

- Efficacy: clear dose response → effect for both compounds in monkeys, despite inherent variability
 - Effect unclear for mAb in rats → Recall: also no TMDD
→ Different target expression/turnover/engagement → less effective in rat



Long dataset – Expert settings:

panel by (1):
SPEC

panel by (2):
DOSE_MGKG

Data Selection Base layer Second layer Third layer General

X value: TIME Grouping:

Y value: Efficacy_Percchange Colour: CMPD

Type: point Shape by:

Data Selection Base layer Second layer Third layer General

X value: Grouping:

Y value: Colour: CMPD

Type: line Shape by:

Stats: median Size by:

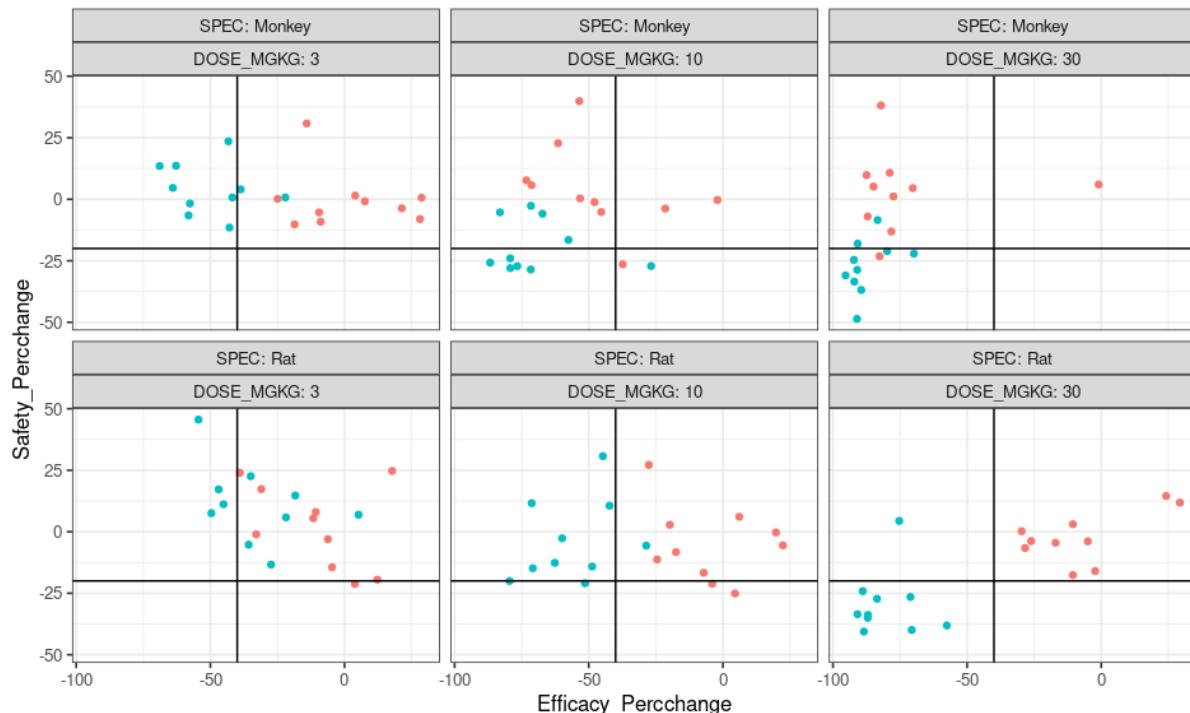
Step 4: Efficacy vs Safety

- Based on arbitrary desired response lines
 - >3 mg/kg undesired for SM (safety signal)
 - <10-30 mg/kg undesired for mAb (poor efficacy)
 - Note: signal can differ within a dosing interval (plots for 2 timepoints), depending on delay between exposure and response

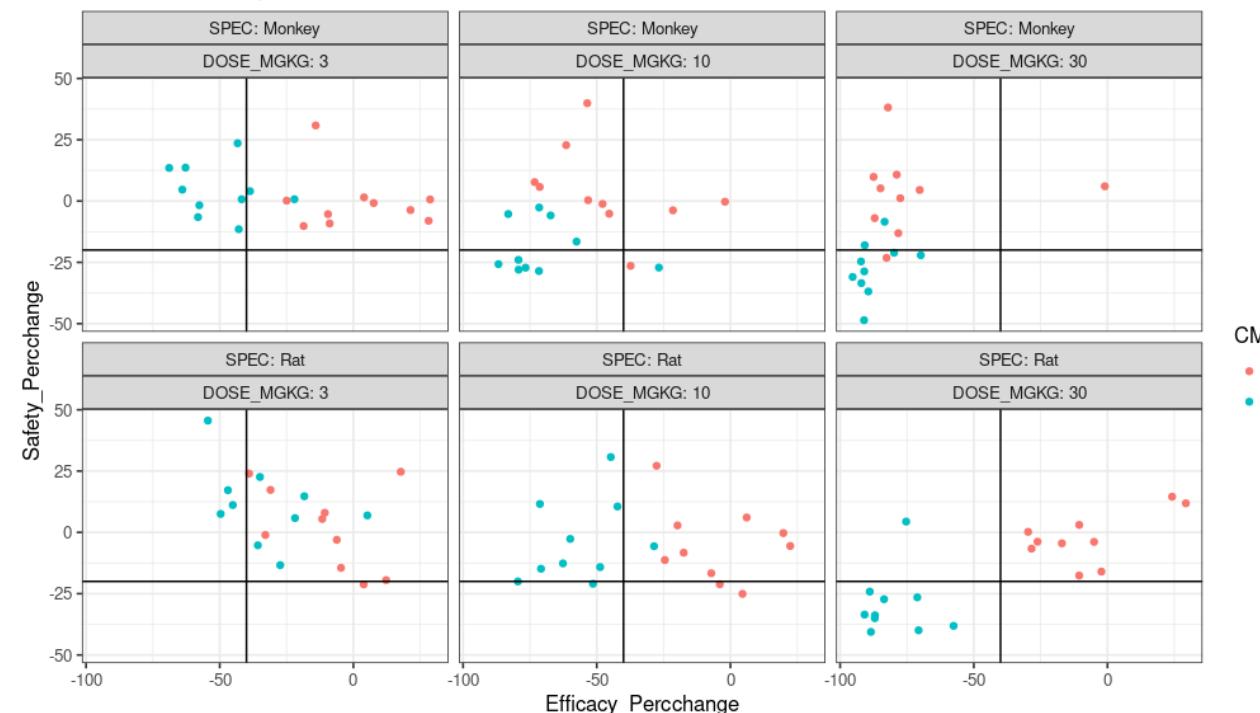
Long dataset – Expert settings:

Subset	Subset
TIME==316	TIME==336

subset at 13.17 days



subset at 14 days



CMPD
● mAb
● SM

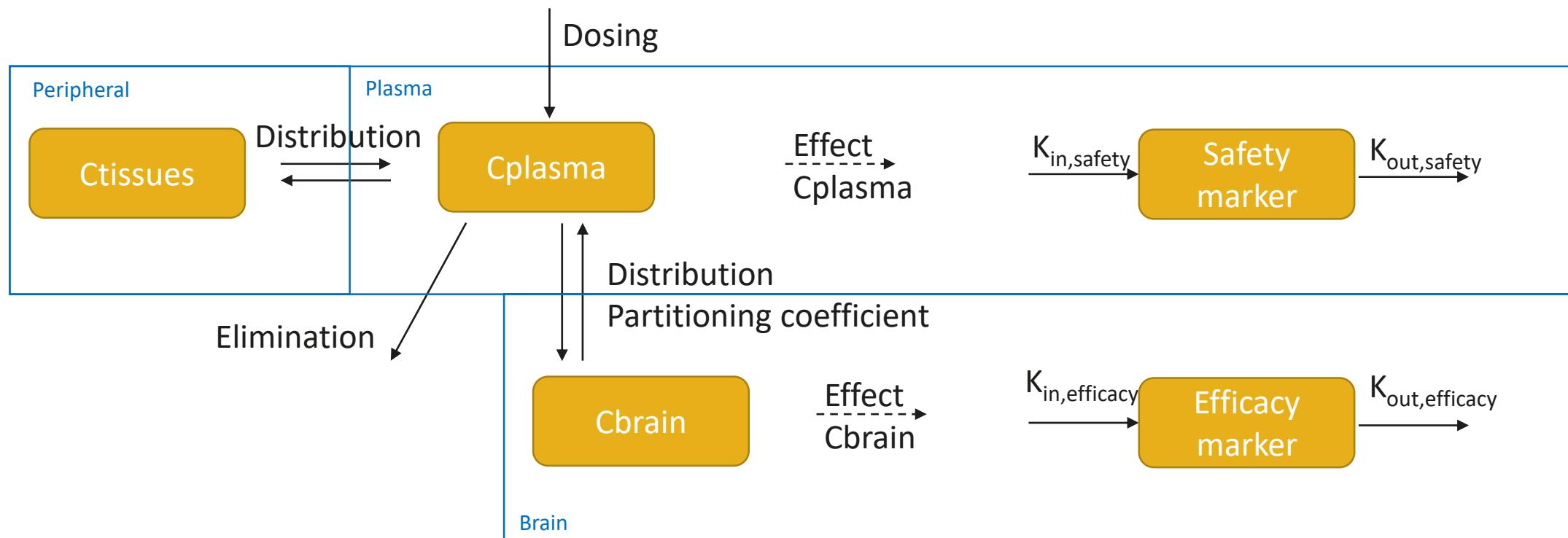
Underlying PKPD dynamics

General model scheme

■ PK model component

■ PKPD relationship

■ PD model component



Model scheme: specifics

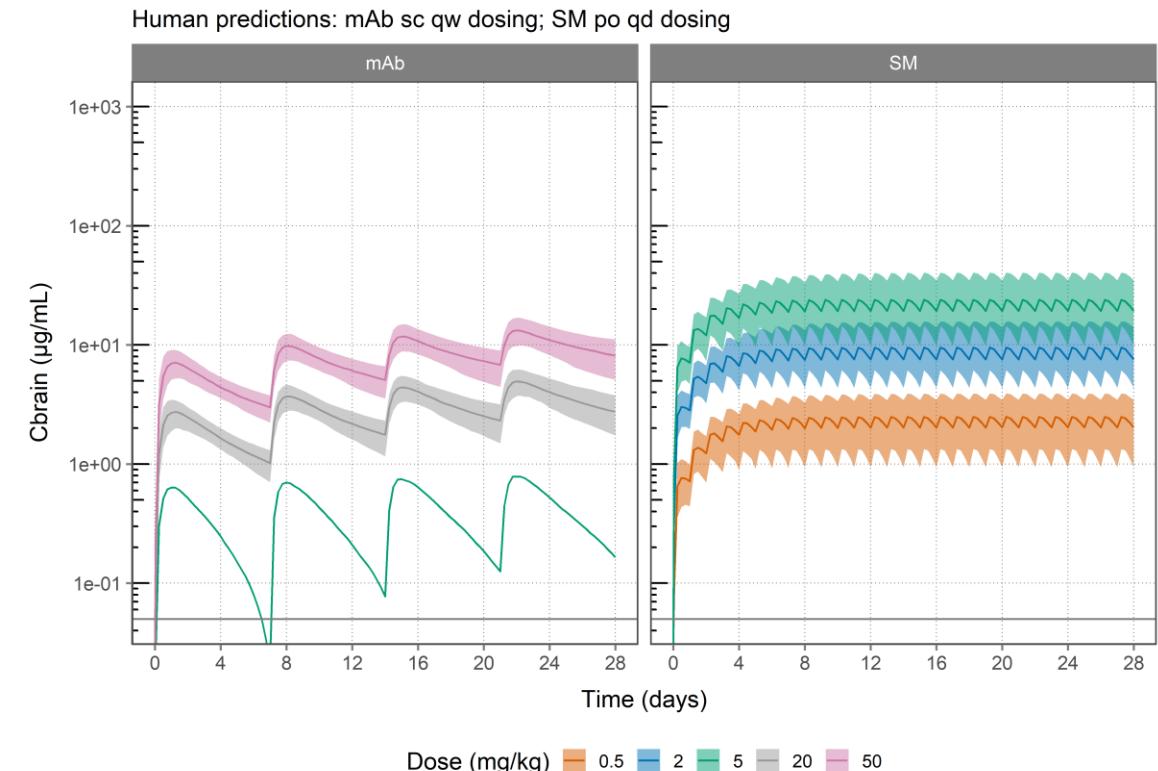
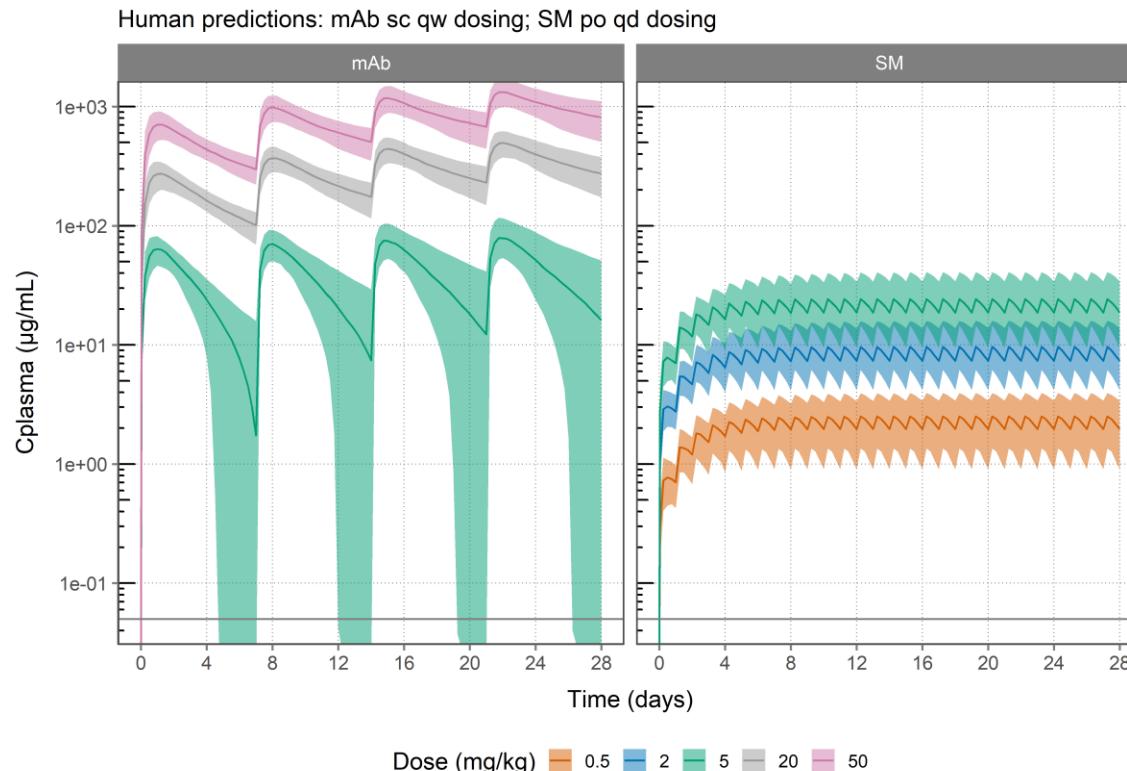
- Implemented drug differences
 - Specific set of PK parameters per compound (and additional non linear clearance for mAb)
 - Safety signal specific for the small molecule (reflecting binding to “1B” receptor)
 - Brain/Plasma partitioning coefficient is 100x lower for mAb vs small molecule
 - Steady state brain concentrations lower vs plasma for mAb, efficacy effect implemented as function of brain concentration
 - Brain conc to effect relationship is implemented as identical between compounds (note: same EC50 in µg/mL, not molar scale)
- Implemented species differences
 - Volumes increase proportionally with body weight
 - Clearances/flows increase less than proportionally with body weight with allometric coefficient of 0.75 (Note: mAb literature 0.8-0.9)
 - Biomarker elimination rate constants decrease with body weight, with allometric coefficient of -0.25
 - For mAb
 - 0/10/50% ADA chance for human/monkey/rodents, respectively (additional strong clearance after 3 days)
 - Combined saturable and linear clearance for human/monkey (reflecting mAb target mediated disposition)
 - Apparent linearity in rodents (reflecting poor rodent cross reactivity)
- Implemented assay error and inter individual variability in PK and PD parameters to reflect real life situation

PKPD model – assumptions for human projections

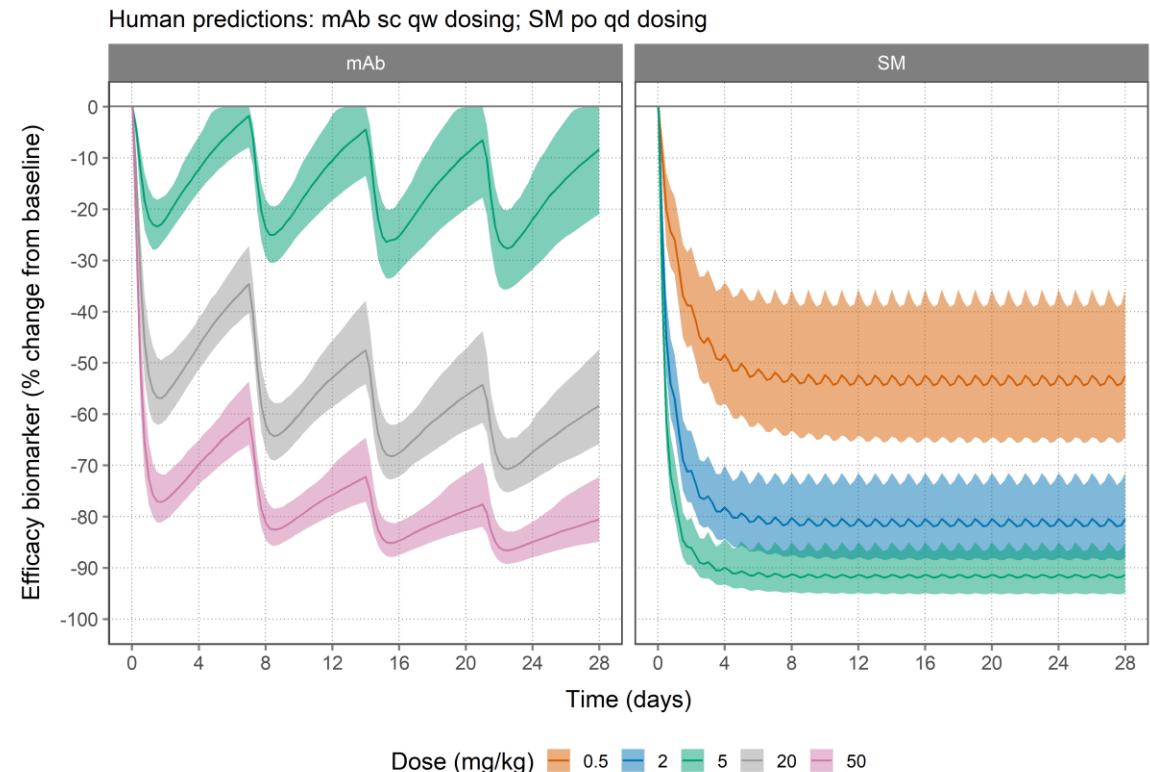
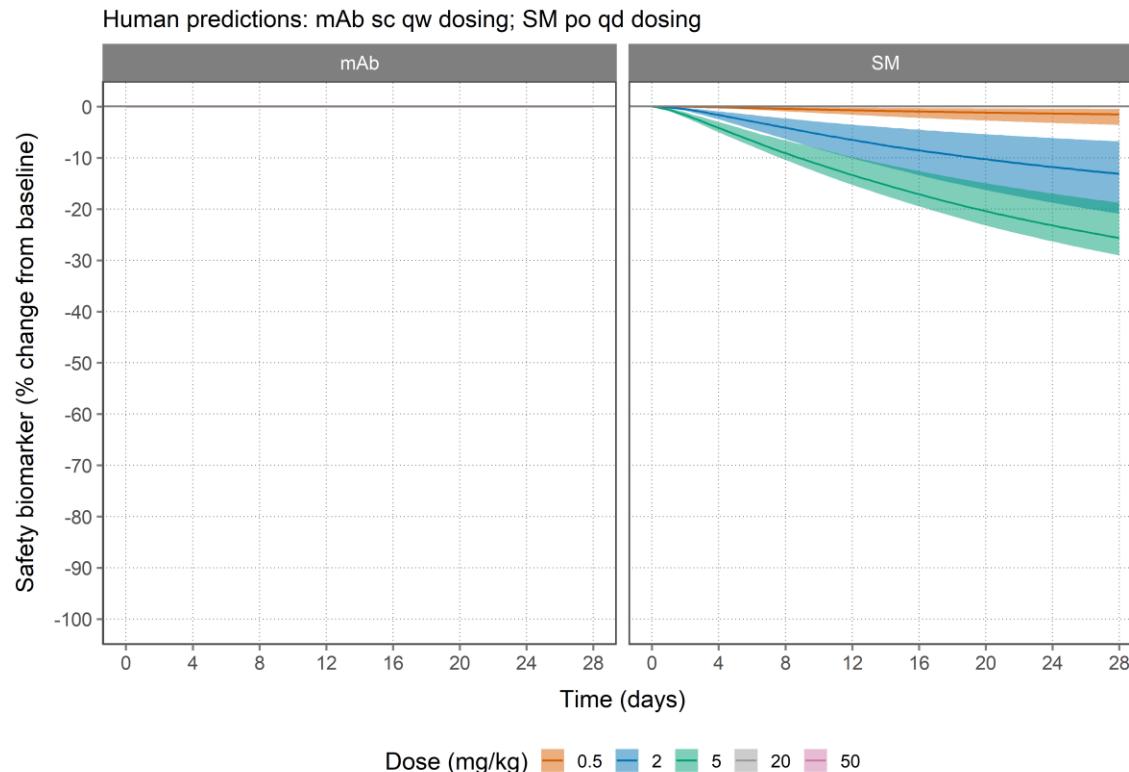
- Assumptions, in absence of any (literature/inhouse) information
 - Volumes/Clearances/flows/PD elimination rate constants increase with body weight (previous slide)
 - Absorption parameters in monkeys ≈ humans
 - mAb PK non linearity
 - KM in monkeys ≈ humans
 - Vmax scales with body weight similar to clearance
 - Concentration – Safety and Efficacy effect relationships in monkeys ≈ humans

Human predictions – Anticipated proof of concept

PKPD model – human projections



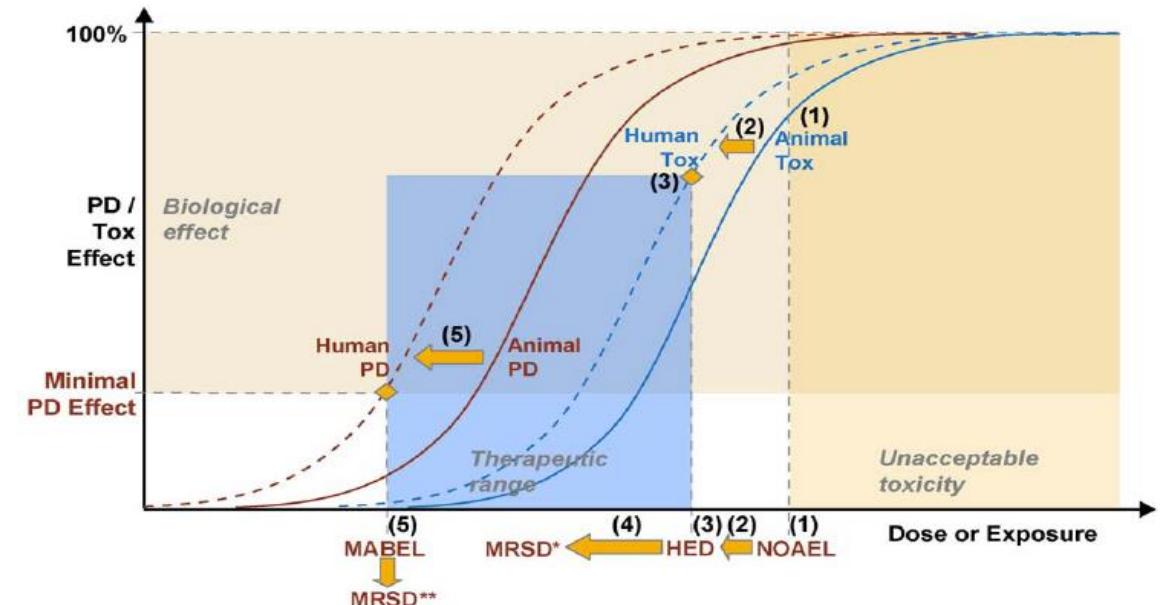
PKPD model – human projections



Human predictions – Human starting dose support

Approach for First in human (FIH) dose

- Some definitions for FIH dose selection
 - Safety (preclinical)
 - NOAEL = No observed adverse event level
 - HNSTD = Highest non-severely toxic dose (manageable toxicity)
 - Efficacy (preclinical)
 - MABEL = minimal anticipated biological effect level
 - Dose projections
 - HED = human equivalent dose (Safety)
 - PAD = pharmacologically active dose (Efficacy)
 - MRSD = maximum recommended starting dose
 - Antagonists versus agonists
 - EC₅₀ for antagonists in MABEL assessments (system suppression)
 - Cavg may be used
 - For agonists, EC₁₀ or EC₂₀ is more applicable (system activation)
 - Cmax is more applicable as safety hazards are a reality



Current Opinion in Biotechnology

(e.g. Cytokine Release Syndrome - TGN1412: From Discovery to Disaster, Attarwala (2010) J Young Pharm. 2(3): 332–336)

Starting dose discussion – example for our discussed mAb

- mAb Additional information
 - Human projected dose regimen: weekly sc
 - 4 weekly sc repeated tox in cyno: NOAEL established at 100 mg/kg (no issues at highest dose tested)
 - In vitro potency assay similar between cyno and human, no species differences of note
 - Team considers reaching average first-week plasma concentrations around EC50 as good low effect starting dose, for this antagonist
- Every case is different, and potentially requires different approach
 - Agonist: consider e.g. 20% receptor occupancy or anticipated activity for relevant marker(s) (e.g. Cytokine release assay)
 - Consider what exposure metric is most relevant, Cmax versus Coverage
 - Consider protein binding species differences for small molecules / peptides
 - Account for other anticipated species differences where applicable
 - FIH in patients (oncology): avoid too low starting dose (sub-pharmacological)

Examples FDA oncology analyses: case by case

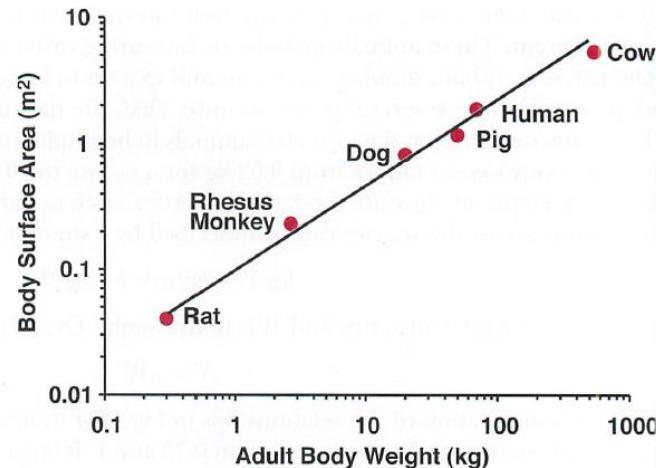
- **CD3 bispecific constructs**
 - Approaches based on receptor occupancy, highest non-severely toxic dose, or no-observed adverse effect level are **not acceptable** for selecting the FIH dose as they resulted in doses close to or above the MTDs, HHDs, or the RHD.
 - A FIH dose corresponding to **10%-30% pharmacologic activity (PA)** was an acceptable approach.
- **Antibody-drug conjugates**
 - a FIH dose that is **1/6th the highest non-severely toxic dose** (HNSTD) in cynomolgus monkeys or 1/10th the STD10 in rodents scaled according to body surface area (BSA) generally resulted in the acceptable balance of safety and efficient dose-escalation in a Phase 1 trial.
- **Immune activating antibodies**
 - For approximately half the antibodies (44%) examined, the **FIH doses were at least a hundred-fold lower than the doses safely administered to patients**, indicating optimization of FIH dose selection and/or optimization of dose-finding trial design is needed to minimize patient exposure to sub-therapeutic doses.
 - However, selection of the FIH dose for antibodies based on animal toxicology studies using **1/6th the HNSTD or 1/10th the NOAEL resulted in human doses that were unsafe** for several antibodies examined.
 - We employed two methods for computing the FIH dose; FIH doses based on **20%-80% PA, and those based on 20%-80% RO**. The FIH doses computed based on 20%-80% PA had acceptable toxicities for all antibodies examined, which included checkpoint inhibitors and stimulators. For the purpose of this research, “acceptable toxicities” refers to no drugrelated death, no CRS/IRR greater than Grade 3 (per the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE)), and overall manageable toxicities. The range of potential FIH doses was large for a specific product when EC50s had a large range. FIH doses based on 20%-80% RO also had acceptable toxicities for all antibodies examined.

Note: appears high, but keep in mind:
Cmax method used

Starting dose discussion – example for our discussed mAb

- Model independent methods
 - NOAEL-based HED: BSA-based with safety margin of 10
 - $100 \text{ mg/kg} * 0.32 / 10 = 3.2 \text{ mg/kg}$
 - “Starting dose is recommended to be lower than 3.2 mg/kg”
 - Note: no modeling needed, but careful – assumes that both linear and target mediated saturable clearance scale with BSA
 - Factor 0.32 for monkeys: see Table 1: FDA 2005 - Estimating the Maximum Safe Starting Dose in Healthy Volunteers
 - BSA-based: $\text{HED} = \text{animal NOAEL} * (\text{BW}_{\text{animal}}/\text{BW}_{\text{human}})^{(1-0.67)} = \text{monkey NOAEL} * 0.32$

FIGURE 22-3. Allometric relationship between body surface area of mammals and typical adult body weight for each species. The exponent is close to two thirds (0.67). The body surface area for the typical adult was obtained from the allometric relationship for a range of body weights within each respective species. (From: Calder, WA III. Size, Function, and Life History. Harvard University Press, Cambridge; 1984.)



Rowland and Tozer Clinical Pharmacokinetics and Pharmacodynamics Concepts and Applications - 4th ed.

Species	To Convert Animal Dose in mg/kg to Dose in mg/m ² , Multiply by k _m	To Convert Animal Dose in mg/kg to HED ^a in mg/kg, Either:	
	Divide Animal Dose By	Multiply Animal Dose By	
Human	37	---	---
Child (20 kg) ^b	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys ^c	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

^a Assumes 60 kg human. For species not listed or for weights outside the standard ranges, HED can be calculated from the following formula:

$$\text{HED} = \text{animal dose in mg/kg} \times (\text{animal weight in kg}/\text{human weight in kg})^{0.67}$$

^b This k_m value is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

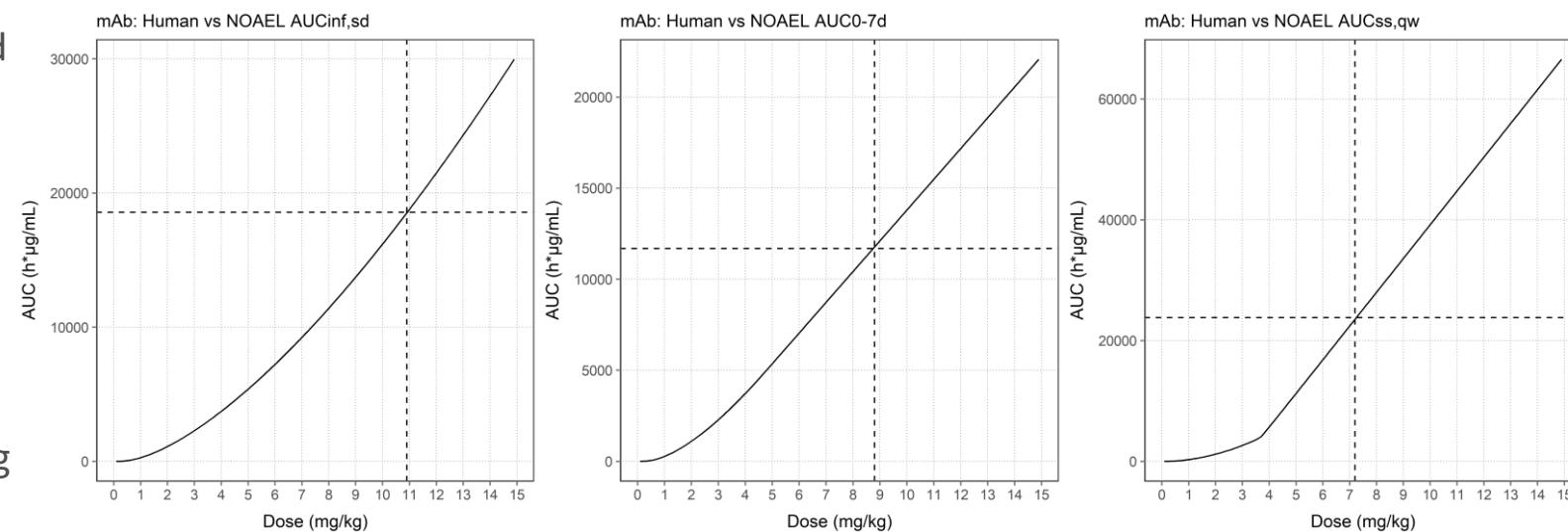
^c For example, cynomolgus, rhesus, and stump-tail.

Starting dose discussion – example for our discussed mAb

- Model independent methods
 - Cmax-based MABEL: with 2.8 L plasma volume assumed for 70 kg volunteer
 - After iv (or sc with high k_a & F), Cmax can be approximated by Dose / plasma volume
 - $EC50 = 1 \mu\text{g/mL} \rightarrow \text{Corresponding dose} = 1 \text{ mg/L} * 2.8 \text{ L} / 70 \text{ kg} = 0.04 \text{ mg/kg}$
 - Note for any other pharmacological activity (PA), assuming a sigmoidicity of 1 in hill equation
 - E.g. PA 80% $\rightarrow \text{Corresponding dose} = (V/BW) * (PA * EC50 / (1-PA)) = (2.8/70) * (0.8 * EC50 / (1-0.8)) = 0.16 \text{ mg/kg}$
 - “A starting dose of 0.04 mg/kg is anticipated to correspond with $\leq 50\%$ activity”
 - No modeling needed, but with large peak to trough ratios anticipated PA at Cmax might lead to unnecessary low starting dose
 - Alternative, especially relevant for agonists (and for FIM in patients)
 - Similar calculations can be performed to predict receptor occupancy (RO), via binding affinity (KD), instead of EC50
 - Consider PA from multiple assays : T-cell activation, Cytotoxicity/lysis, Cell depletion, Cytokine release (IL2 , IFNg , TNFa)
 - Example: FDA-analysis paper - An FDA oncology analysis of immune activating products and first-in-human dose selection

Starting dose discussion – example for our discussed mAb

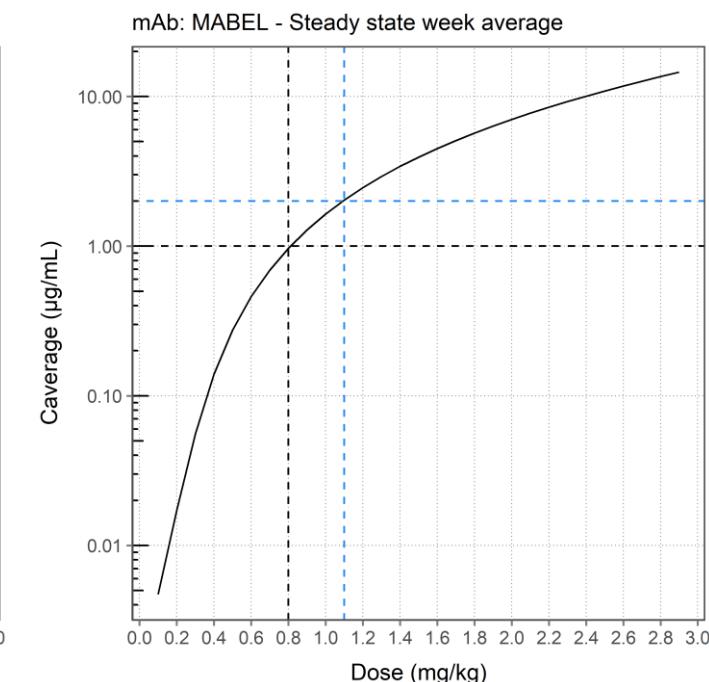
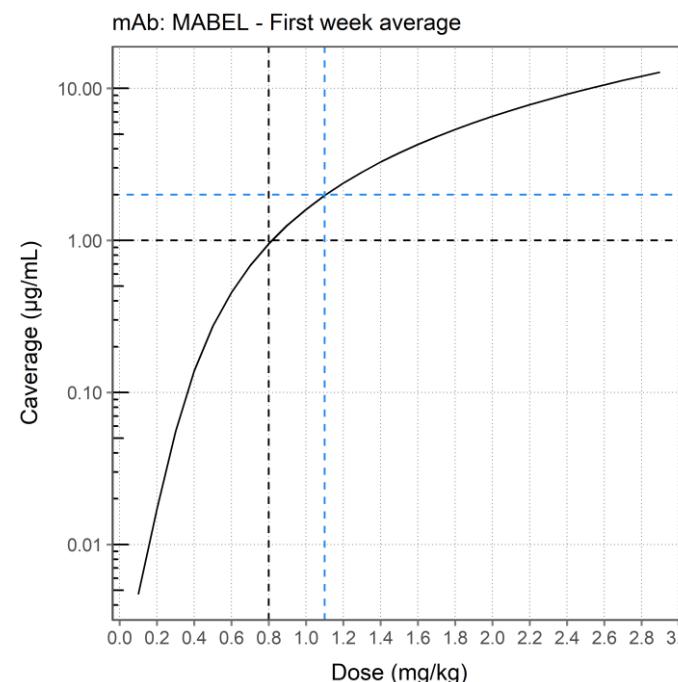
- Model dependent methods
 - NOAEL-based HED: PK model derived exposure based with safety margin of 10
 - Instead of BSA based scaling, scaling factors estimated in PK modeling (if multi-preclinical species data available)
 - For our mAb, based on linear CL/flow scaling factor ≈ 0.75 (established, rat to monkey)
 - Non linearity: scaling very likely unknown → Sensitivity analysis advised
 - E.g. Vmax scales allometrically (0.75; our current assumption) or is body weight independent
 - Typical simulations performed
 - Cyno 100 mg/kg: AUC's calculated and divided by 10 (safety margin)
 - Target AUC in human
 $AUC_{inf, sd} = 18562 \text{ h}^*\mu\text{g/mL}$
 $AUC_{0,7d} = 11686 \text{ h}^*\mu\text{g/mL}$
 $AUC_{ss,qw} = 23800 \text{ h}^*\mu\text{g/mL}$
 - Corresponding human doses:
sd based: 10.9 mg/kg
first week based: 8.8 mg/kg
steady state based: 7.2 mg/kg



To achieve 10 fold lower exposure, less than 10 fold lower dose needed, even though lower clearance in human vs monkeys, since much higher clearance at lower concentrations due to non linearity

Starting dose discussion – example for our discussed mAb

- Model dependent methods
 - Coverage-based MABEL
 - PK model vs in vitro EC50 and/or in vivo EC50 established by preclinical PKPD modeling
 - For our mAb: in vivo EC50 \approx 2 $\mu\text{g/mL}$ (2x higher than in vitro; Cbrain vs Cplasma KP ignored for simplicity – could be accounted for in real case); Note: Sigmoidicity can also be estimated in vivo for more reliable EC20 – EC80 calculation when needed
 - MABEL dose (in vitro EC50)
 - 0.8 mg/kg
 - MABEL dose (in vivo EC50)
 - 1.1 mg/kg
 - Note: not a lot of accumulation expected for this compound at these lower doses (due to non linearity) → First week or steady state week average concentrations similar



Starting dose discussion – example for our discussed mAb

- Summary
 - NOAEL BSA assumed; model independent: 3.2 mg/kg
 - NOAEL PK model based: 7 - 11 mg/kg, depending on AUC choice (given a set of PK assumptions)
 - Cmax – in vitro EC50 based MABEL; model independent: 0.04 mg/kg
 - Coverage – in vitro/in vivo EC50 based MABEL; PK/PKPD model dependent: 0.8-1.1 mg/kg
- Possible recommendation (pending other factors)
 - 1 mg/kg starting dose
- Note: similar calculations can be performed to assess the pharmacologically active dose

Addressed concepts

Overview of addressed concepts

- Key concepts where PKPD modeling and simulation can support translational non clinical drug development
 - Data exploration to guide understanding PKPD behavior of different compounds
 - Acknowledge inherent inter/intra animal variability; search for predictors of variability
 - Absorption, distribution and (non-linear) elimination; impact of ADA on PKPD of mAbs
 - Inter-species allometric scaling
 - PKPD: assess delay between response and plasma concentration
 - Summarize and quantify non clinical knowledge within modeling framework to predict clinical PKPD
 - Support FIM dose selection using model (in-) dependent methods