

The human FcRn transgenic mice Tg32 as a model for early assessment and prediction of human pharmacokinetics of monoclonal antibodies

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OBJECTIVE
A key determinant of a monoclonal antibodies (mAbs) clearance (CL) is the binding affinity for the human neonatal Fc receptor (FcRn). Although preclinical pharmacokinetics (PK) studies are often performed in cynomolgus non-human primates (NHP), recently transgenic mice expressing the human FcRn have gained interest. We aim to assess the value of the human FcRn transgenic mice (Tg32 mice) during preclinical development for early candidate screening and to support early human PK prediction.

RESULTS
NHP PK studies are required by authorities and support phase 1 study design. The current PK studies between Tg32 mice and NHP were in accordance when predicting the human PK profile highlighting the potential of Tg32 mice for early screening offer a reliable pre-selection tool to limit the use of NHP

1 Study design

Tested mAbs	mAbs type
Trastuzumab (anti-HER2)	Humanized IgG1: reference
chAb	Chimera
mAb1, mAb2, mAb3, mAb4	Humanized

Preclinical species	Dosing	Duration	Sampling
Tg32 mice	Single intravenous	6 weeks	n = 3 per timepoint 1 – 2 samples / animal
Cynomolgus NHP	(iv) bolus administration of 40 mg/kg*	8 weeks	Individual subjects over time 4 animals/dose/ mAb

* mAb1 was also tested at 4 mg/kg iv bolus singles dose in cynomolgus NHP

2 PK analysis & prediction

A 2-compartmental model was applied. Linear, saturable elimination and empirical target mediated drug disposition (TMDD) model combining linear and saturable elimination from central compartment were assessed as needed.

Interindividual variability was fixed to small omega value of 0.1 (limited data points from the Tg32 and low subject numbers in NHP). Samples (Tg32) or subjects (NHP) with anti-drug antibodies (ADA) were excluded from analysis. Typical PK parameters in Tg32 and NHP for mAb were scaled by allometric scaling using single species fixed exponent (**table 1**) to predict a 70 kg human PK parameters and simulate human PK profile.

$$Y_{human\ predicted} = Y_{species} \times \left(\frac{BW_{human}}{BW_{species}} \right)^{Allometric\ exponent}$$

Y = PK parameter
 BW = Body Weight

Table 1: Allometric exponents used for scaling PK parameters from preclinical species to human

Parameter	Allometric exponent NHP	Allometric exponent Tg32	Source [1]
CL	0.81	0.90	Betts et al, 2018
Vc	1.04	0.97	Betts et al, 2018
Q1	0.57	0.67	Betts et al, 2018
Vp1	1.07	0.93	Betts et al, 2018
KM	1	1	Standard exponent
VMAX	0.75	0.75	Standard exponent

Data preparation, exploration and model pre- and post-processing was performed with Rstudio (3.6.3) and the R package IQRtools (1.8.0). NLME models were run using Monolix (2019R1).

3 Results

Preclinical PK models

- A 2-compartmental model with linear elimination best characterize the PK profile of tested mAbs except for chAb in NHP where saturable elimination was selected.
- The target of those mAbs is preserved across species. Interpretation of CL for chAb is limited by the use of one dose level only.
- PK parameters were estimated with relative standard error (RSE) < 35% .

Human predicted PK parameters from Tg32 and NHP (table 2)

Parameter (unit)	Trastuzumab	chAb	mAb1	mAb2	mAb3	mAb4
Human PK parameters scaled from Tg32 mice						
CL (mL/h/kg)	0.091	0.107	0.195	0.082	0.112	0.088
Human PK parameters scaled from cynomolgus NHP						
CL (mL/hr/kg)	0.107	.	0.256	0.043	0.066	0.046
KM (ug/mL)	.	5.7	.	.	.	.
VMAX (mg/h/kg)	.	41.2	.	.	.	.
Relative % change in predicted exposure						
AUCinf %	17	607	31	-42	-41	-47
C0 %	14	175	27	62	-4	-23

CL: clearance from the central compartment, KM: Michaelis-Menten constant, VMAX: Maximum apparent clearance rate, AUCinf = Area Under the Curve to infinity, C0 = Concentration at time 0.

% relative change = $(Tg32_{par}-NHP_{par})/NHP_{par} \times 100$

Studies validation from reference mAb trastuzumab

- CL predicted from preclinical species: within 30% of clinical CL** (**table 2**).
- The human predicted profile
 - from Tg32: in accordance with published clinical data
 - from NHP: shorter exposure vs the reported human data (**figure 1**) mostly due to lower volume of distribution ($Vd = Vc+Vp1$) estimated from NHP. Trastuzumab undergoes TMDD in NHP [2].

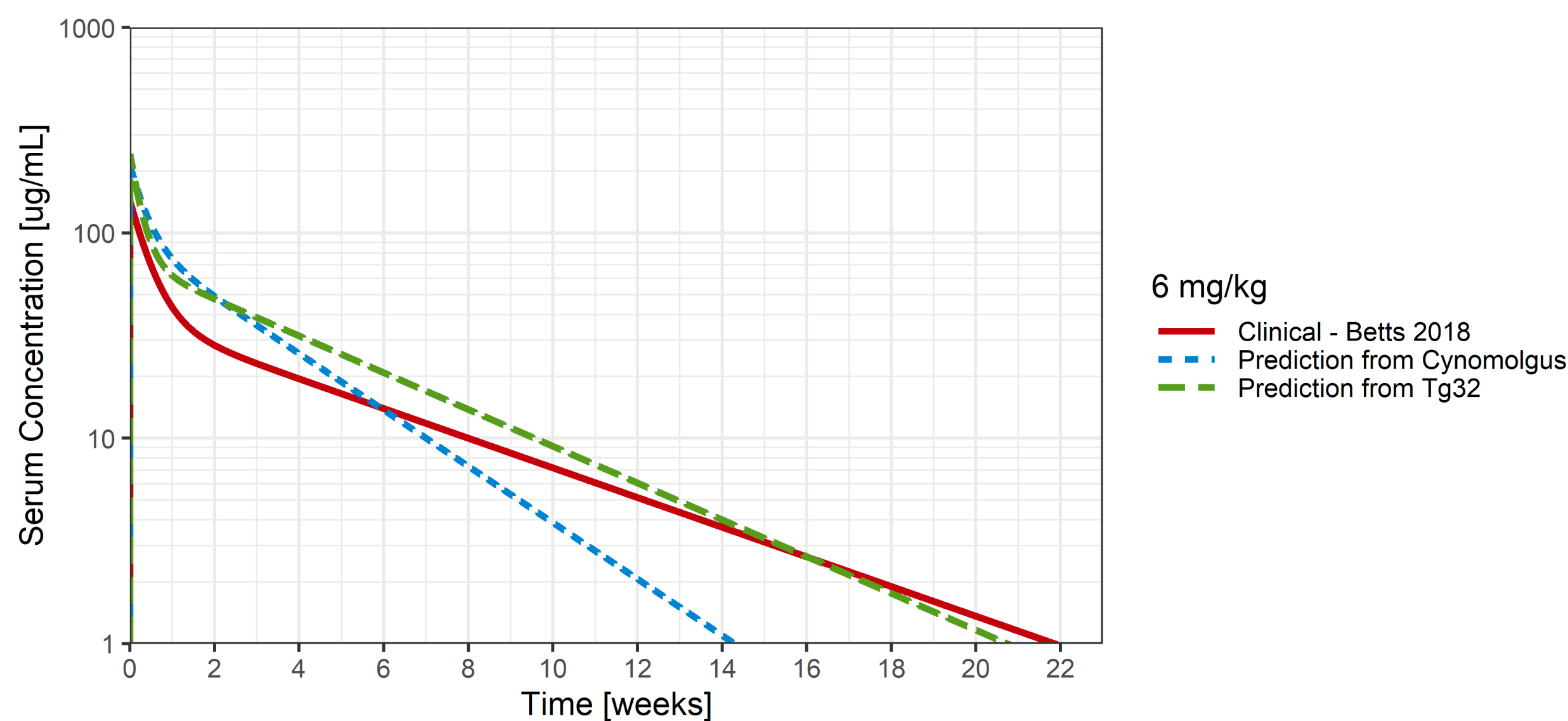


Figure 1: Trastuzumab human PK profile simulated for 6 mg/kg IV single dose based on single species allometric scaled PK parameters and published clinical PK parameters

Chimera and humanized mAbs

- The chimera has a distinct PK profile in NHP vs Tg32 leading to a different human PK prediction depending on the preclinical species.
- Humanized mAbs:
 - Human predicted CL, Vd, AUC and C0: within 2-fold difference between Tg32 mice and cynomolgus NHP (**table 2**).
 - mAb1: highest human predicted CL and Vd predicted from both Tg32 mice and cynomolgus NHP $\Rightarrow$ lowest and shortest human predicted exposure.
 - mAb2, mAb3, mAb4: prolonged human predicted exposure (**figure 2**).
 - The ranking based on the human predicted exposure was identical across the two preclinical species: mAb2 > mAb4 > mAb3 (**figure 2**). Clinical data should be generated to assess the predictive performance of the model used.

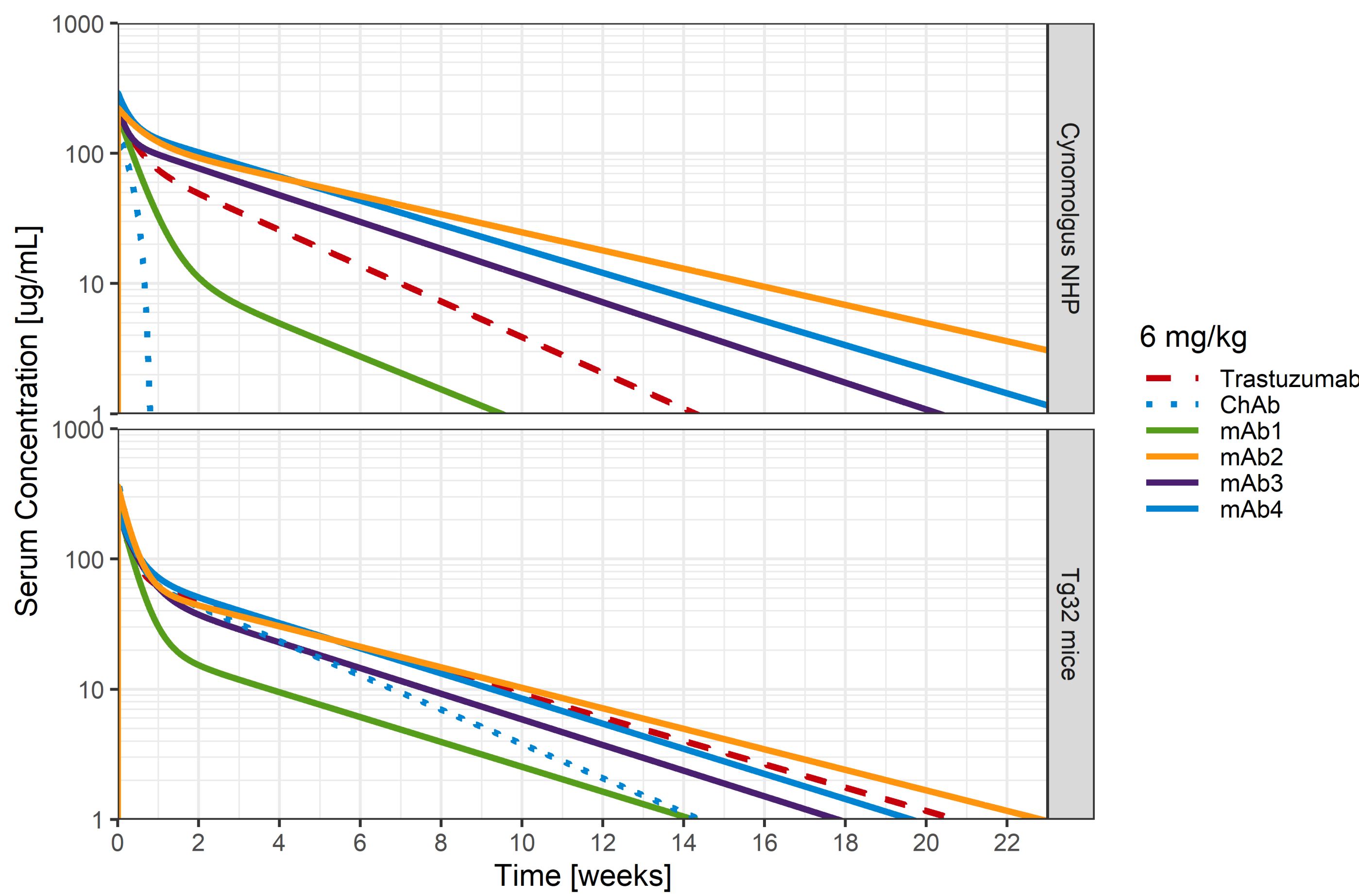


Figure 2: Human PK profile simulated for 6 mg/kg IV single dose based on single species allometric scaled PK parameters for tested mAbs

SUMMARY

- $\Rightarrow$ Human PK prediction from Tg32 and NHP were within 2-fold difference and led to the same ranking of tested humanized mAbs.
- $\Rightarrow$ Tg32 mice allow early prediction of the PK in humans, for linear clearance evaluation, before NHP studies are initiated.
- $\Rightarrow$ Using Tg32 mice would allow to select a limited set of candidates for NHP PK studies, reducing the use of NHP and enhance the early selection of potential clinical candidates.

[1] Betts et al. MABS 2018, 10:751.. [2] European Medicines Agency. Herceptin: EPAR Scientific Discussion.