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INTRODUCTION

- Specific biosimilarity guidelines for biotherapeutics are non-existent
- Bioequivalence (BE) guidelines (80-125 % similarity for AUC and Cmax) with non-compartmental analysis (NCA) applied
- Key difference small molecules and biotherapeutics: complex elimination
 - May compromise current approach
- Population pharmacokinetics (PPK) offers alternative
 - Allows assessment of complex PK
 - Better understanding biological system

AIM

- Investigate pharmacokinetic biosimilarity of the monoclonal antibody (Mab) using PPK analysis on **test** & **reference** product of trastuzumab and compare results to NCA

METHODS

PK data from biosimilarity trial (n=110) of trastuzumab in HV¹ which received IV doses of:

- 0.49, 1.48, 2.96, 5.96 mg/kg **test** product
- 6.44 mg/kg **reference** product
- NCA
 - Observed concentration-time data using software package R.
 - Exposure measures: Cmax and AUC (calculated by trapezoidal rule)
- PPK²
 - Combined PK model
 - All available data (incl. escalation part) **T** & **R** product
 - Separate PK models
 - Potential bias (analyzing **T** & **R** model simultaneously)
 - Structural similarity between all models
 - Covariates
 - Weight, height, age, BMI, BSA, LBW, shed antigen (ECD)
 - Formulation of compound (combined dataset)
- Dose correction
 - Actual dose (**T** = 5.96 mg/kg & **R** = 6.44 mg/kg)
 - NCA: linear normalization AUC_{ind}. (labelled dose 6 mg/kg)
 - PPK: simulations with actual & labelled dose profiles_{ind}.
- Biosimilarity
 - Geometric means of AUC (GMR_{AUC}) & Cmax (GMR_{Cmax})
 - 90%-confidence interval

RESULTS

PK of trastuzumab best described by 3-compartment model with linear- and Michaelis-Menten elimination (Fig. 1)

- Interindividual variability (Table 2)
 - Combined model: V1, KM, Ke
 - T** model: V1, Vmax, Ke
 - R** model: V1, Vmax, Ke
- Residual variability
 - Proportional error model
 - Additive error model
- Covariates (included)
 - Combined model: LBW vs V1 (0.61**) & BMI vs Ke (0.6**)
 - T** model: LBW vs V1 (0.56**) & BMI vs Ke (0.56**)
 - R** model: LBW vs V1 (0.64**) & BMI vs Ke (0.65**)
 - Trastuzumab product **not** identified
- Biosimilarity

AUCinf	% GM ratio T/R (90%-CI)
NCA	82.32 (78.17 – 86.69)
Dose correction	89.55 (85.03 – 94.30)
Separate models	82.54 (78.70 – 86.57)
Dose correction	91.74 (87.46 – 96.24)
Combined model	81.66 (77.93 – 85.56)

Table 1: AUCinf comparison between PPK and NCA.
AUCinf calculated from administration time until infinity, calculated as AUClast + Clast/Ke. CI, Confidence Interval

- Elimination pathway (Fig. 2)
 - Low conc. (<10µg/mL) : non-linear elimination
 - High conc.: saturation → linear elimination

	Combined model	Separate model T	Separate model R
Parameter ^a	Estimate (CI)		
Fixed effects			
V1 (L)	3.28 (3.185 - 3.367)	3.59 (3.418 - 3.752)	3.13 (3.028 - 3.232)
V2 (L)	1.89 (1.325 - 2.457)	6.82 (-5.572 - 19.21)	44 (28.18 - 59.77)
V3 (L)	1.96 (1.736 - 2.179)	2.15 (1.858 - 2.443)	2.09 (1.929 - 2.244)
Q1 (L·h ⁻¹)	2.91 (2.02 - 3.79) ·10 ⁻³	2.82 (1.081 - 4.566)	3.92 (3.58 - 4.25) ·10 ⁻³
Q2 (L·h ⁻¹)	4.34 (3.66 - 5.01) ·10 ⁻²	3.75 (2.787 - 4.706)	4.67 (4.12 - 5.21) ·10 ⁻²
V _{max} (µg·h ⁻¹)	178 (162.3 - 193.1)	172 (138.6 - 205.7)	127 (111 - 143.4)
K _M (µg·L ⁻¹)	937 (759.6 - 1115)	995 (674.6 - 1316)	1440 (1189 - 1699)
K _e (h ⁻¹)	2.20 (2.02 - 2.38) ·10 ⁻³	1.95 (1.33 - 2.57) ·10 ⁻³	1.76 (1.62 - 1.9) ·10 ⁻³
Random effects Estimate (CV%)			
Interindividual variability			
ω ² V1	0.0217 (14.8)	0.0270 (16.5)	0.0122 (11.1)
ω ² V _{max}	-	0.0163 (12.8)	0.0347 (18.8)
ω ² K _M	0.121 (35.9)	-	-
ω ² k _e	0.0292 (17.2)	0.0355 (19.0)	0.0286 (17.0)
Residual error			
σ ² proportional	0.0222	0.0207	0.0198
σ ² additive	1520	3090	790

Table 2: Population PK parameters estimates from the full covariate model for trastuzumab.
a Explanation of parameters is given in figure 1.
CI, confidence interval; CV, coefficient of variation; ω2, between-subject variance; σ2, residual variance.

CONCLUSIONS

- PPK and NCA produce interchangeable results for Cmax and AUC
- However, PPK provides additional advantages
 - Insight in PK properties
 - Smaller cohorts and sparse sampling possible

DISCUSSION

- NCA continues firm position in biosimilarity research
- PPK is valuable extension
- Interchangeability of PPK in biosimilarity research is proven for therapeutic proteins³
 - Large monoclonal antibody trastuzumab
 - Non-linear PK
- Information and guidance on PPK for biosimilarity (e.g. antibodies) might be beneficial for both regulatory affairs as industry

References

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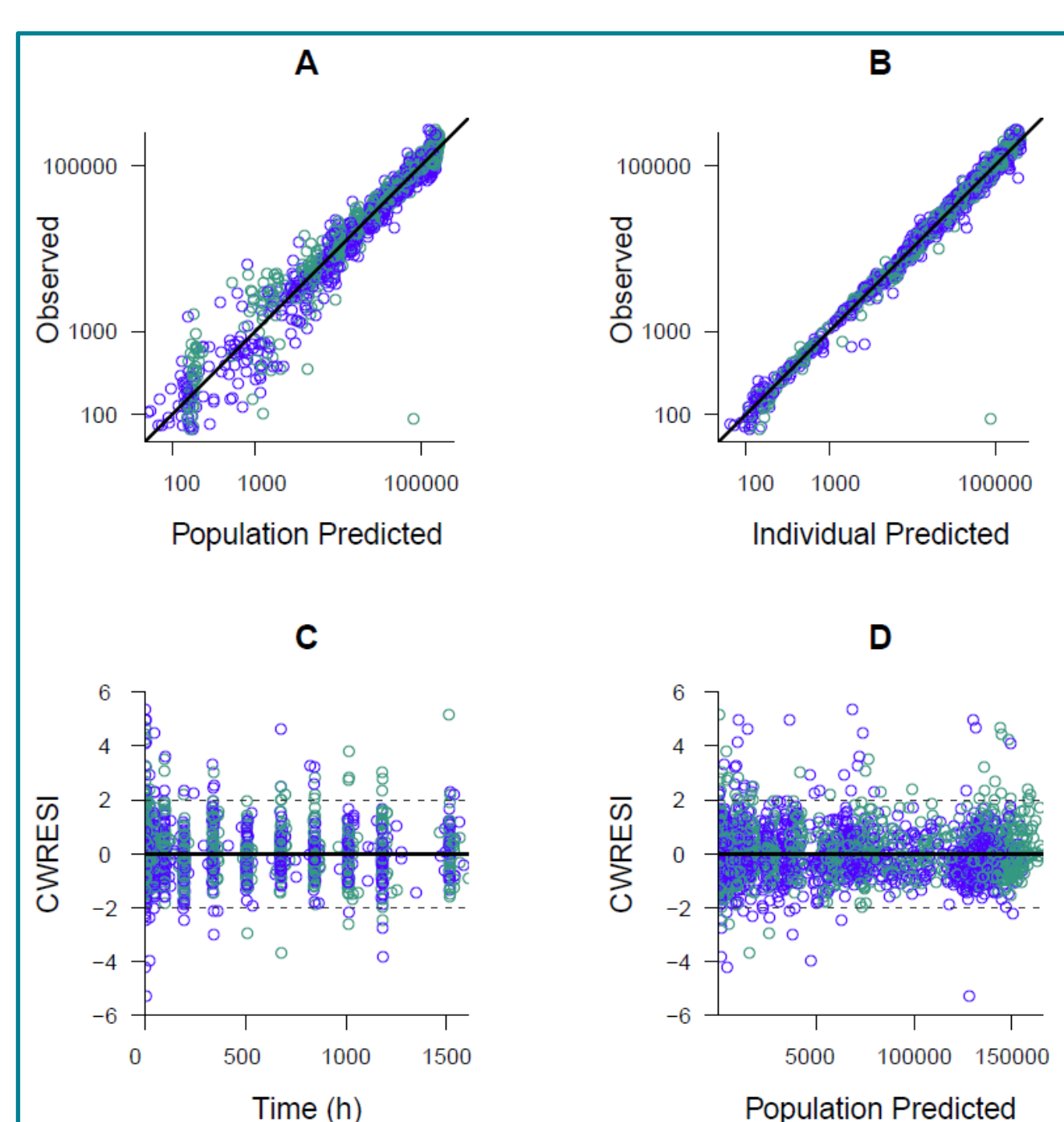


Figure 3: Goodness of fit plots combined model.
Observed vs population predicted concentration (A), observed vs individual predicted concentration (B), conditional weighted residuals with interaction (CWRESI) vs time (C), and conditional weighted residuals vs population predictions (D).

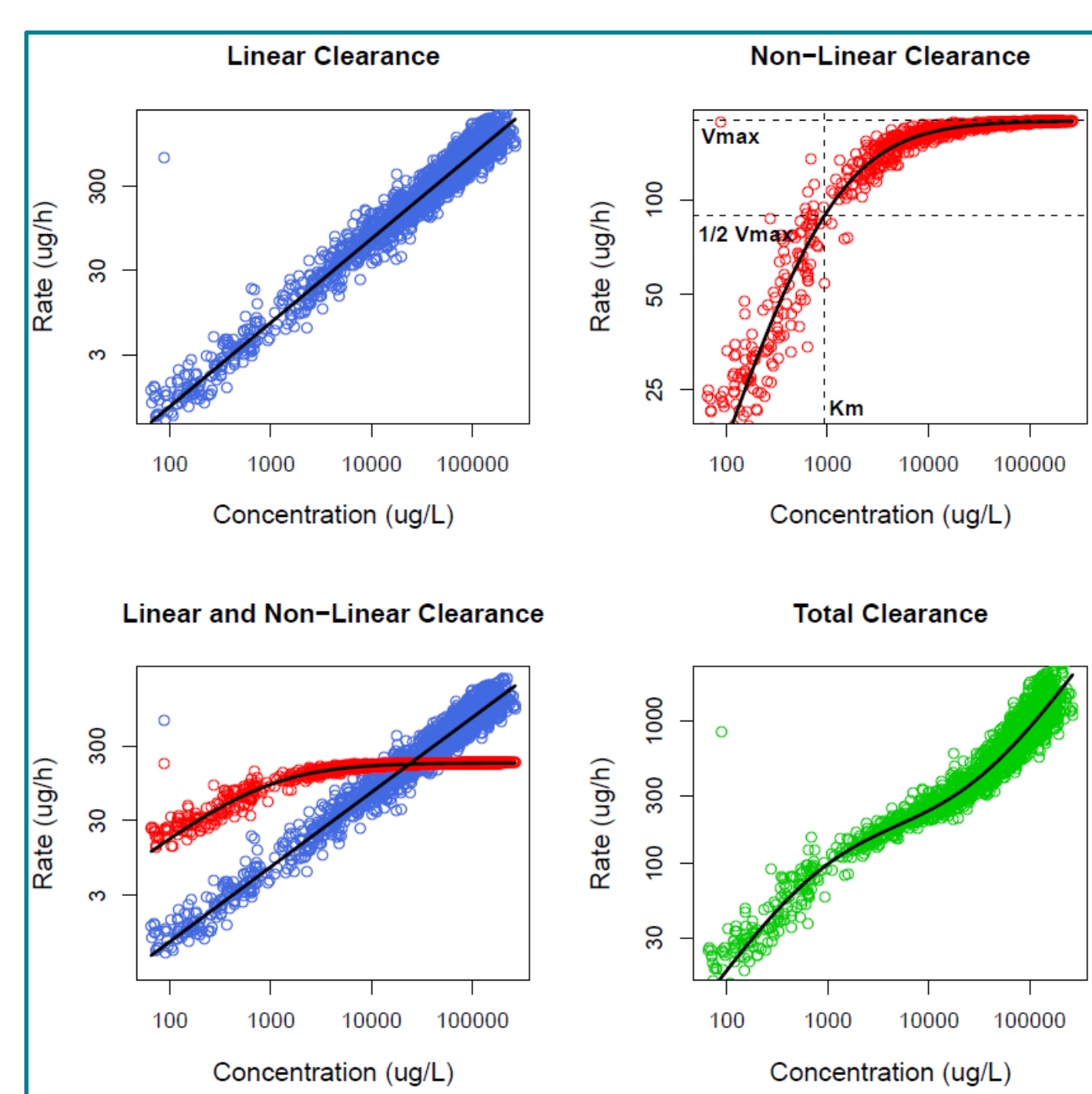


Figure 2: Linear and non-linear clearance of combined model.

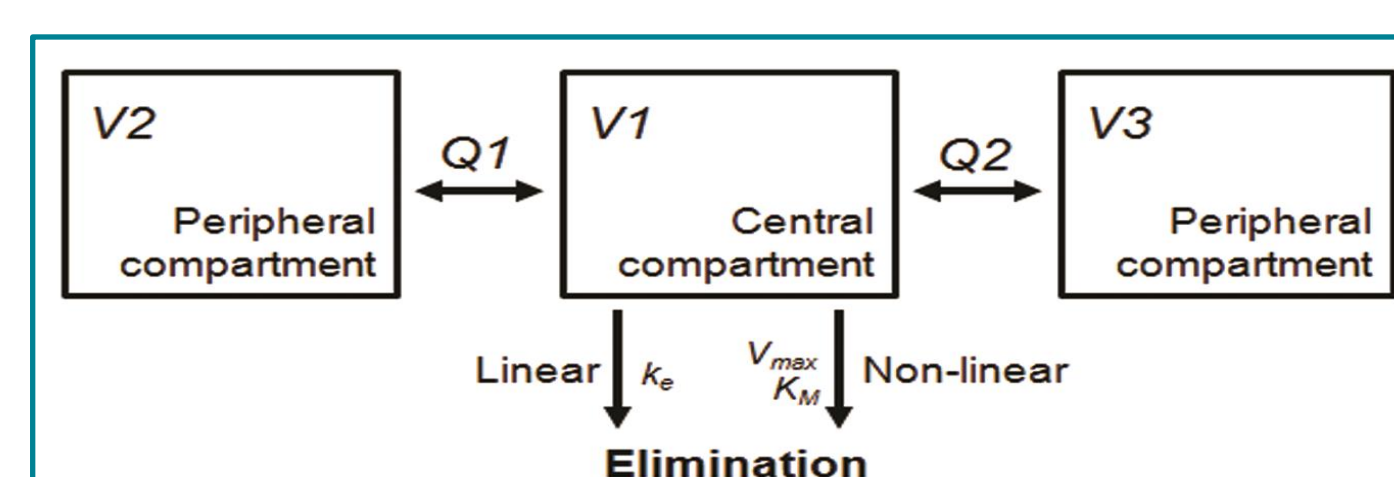


Figure 1: Schematic representation of structural PK model with parallel linear and non-linear elimination pathway.