Comparing Model Performance in Characterizing the PK/PD of the Anti-Myostatin Antibody Domagrozumab

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Supplementary Section

To calculate the target coverage using MM-BK (Equation 10)

$$Free = M_{tot} - Complex$$

$$Complex = \frac{D_C}{K_{SS} + D_C} \times M_{tot}$$

$$Free = M_{tot} - \frac{D_C}{K_{SS} + D_C} \times M_{tot}$$

$$Free = (1 - \frac{D_C}{K_{SS} + D_C}) \times M_{tot}$$

$$Free = \frac{K_{SS}}{K_{SS} + D_C} \times M_{tot}$$

$$Coverage = 100 - \%Free = 100 - \frac{Free}{M_0} \times 100$$

$$Coverage = \left(1 - \frac{M_{tot} K_{SS}}{(K_{SS} + D_C) \times M_0}\right) \times 100$$

In the Discussion section it is justified why the mathematical equivalency between IDR and QSS could be extrapolated to the MM-BK model. Therefore, for target coverage estimation using IDR K_{SS} and D_C were replaced by $IC50^{\gamma}$ and $D_C{}^{\gamma}$, respectively. Applying the MM-IDR2 model (Equation 11) and substituting $K_{SS} with\ IC_{50}^{\gamma}$ and $D_C\ with\ D_C^{\gamma}$, coverage follows as

$$Coverage = \left(1 - \frac{M_{tot} IC_{50}^{\gamma}}{\left(IC_{50}^{\gamma} + D_C^{\gamma}\right) \times M_0}\right) \times 100$$

Population Model

Inter-individual variability (IIV) was implemented as a log normal distribution $P_i = P_g e^{\eta_i}$, where P_i is the parameter for i[th] subject, P_g the population parameter value and η_i the IIV for the i[th] subject that is obtained from IIV distribution with mean 0 and variance ω^2. IIV was estimated for CL, V_P and M_0 in all models, for k_{int} in QSS and MM-like models, for v_{max} in MM-BK and MM-IDR models, and for I_{max}, S_{max}, IC_{50} and SC_{50} in MM-IDR models.

Residual unexplained variability (RUV) was implemented using an exponential error model which transforms to an additive error model in the log domain $\left(\log(Y_{obs,\ ij}) = log\left(Y_{pred,\ ij}\right) + \in_{ij}\right)$ for Domagrozumab and a proportional error model in the linear domain $\left(Y_{obs,\ ij} = Y_{pred,\ ij} * (1 + \in_{ij})\right)$ for myostatin, where $Y_{obs,\ ij}$ represents the observed value for the i[th] individual and j[th] measurement, $Y_{pred,\ ij}$ represents the predicted value for the i[th] individual and j[th] measurement obtained from the RUV with mean 0 and variance σ^2 (SIGMA).

Fits for each model were evaluated by examining objection function values (OFV), precision of parameter estimates, IIV and RUV estimates, and goodness of fit plots (Figure S3). These plots included observed (DV) vs. population predicted (PRED) concentrations, DV vs. and individual predicted (IPRED) concentrations, conditional weighted residuals (CWRES) vs. PRED, and CWRES vs. time after first dose. Performance of each final model was evaluated using PsN 3.5.4 where VPCs were conducted for 500 simulated datasets using parameter and variability estimates without parameter uncertainty.

Supplementary Figures

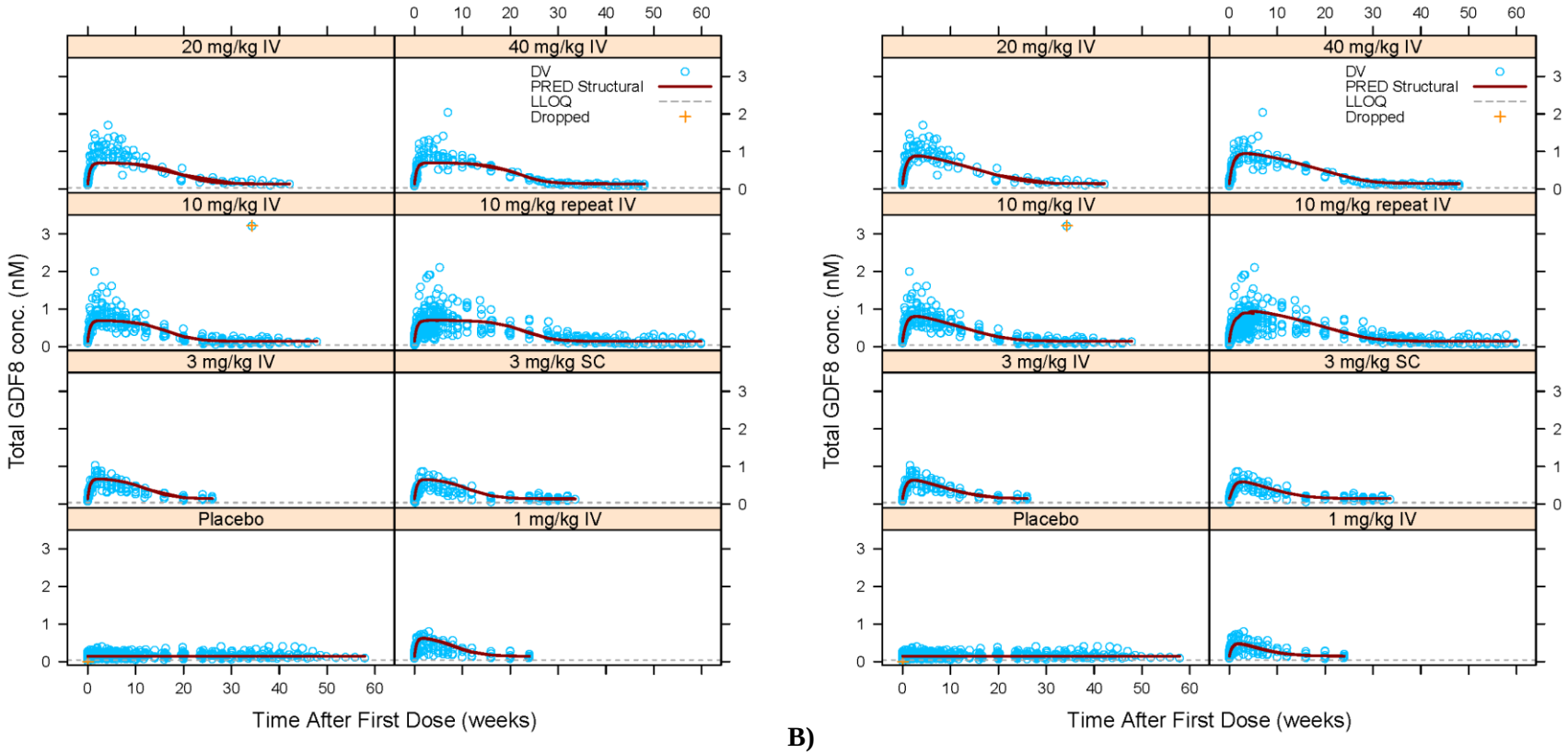
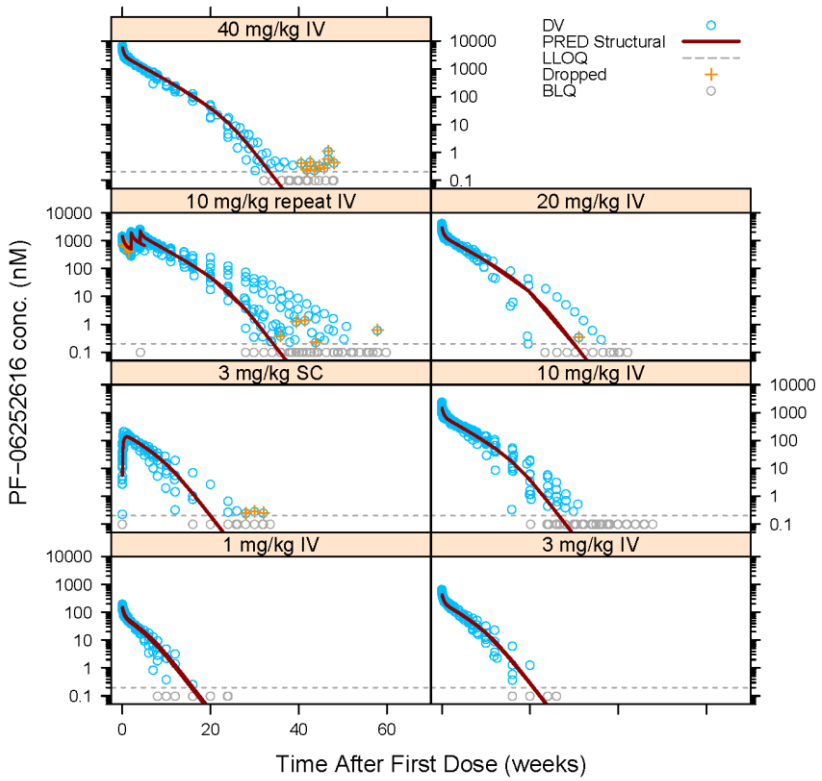
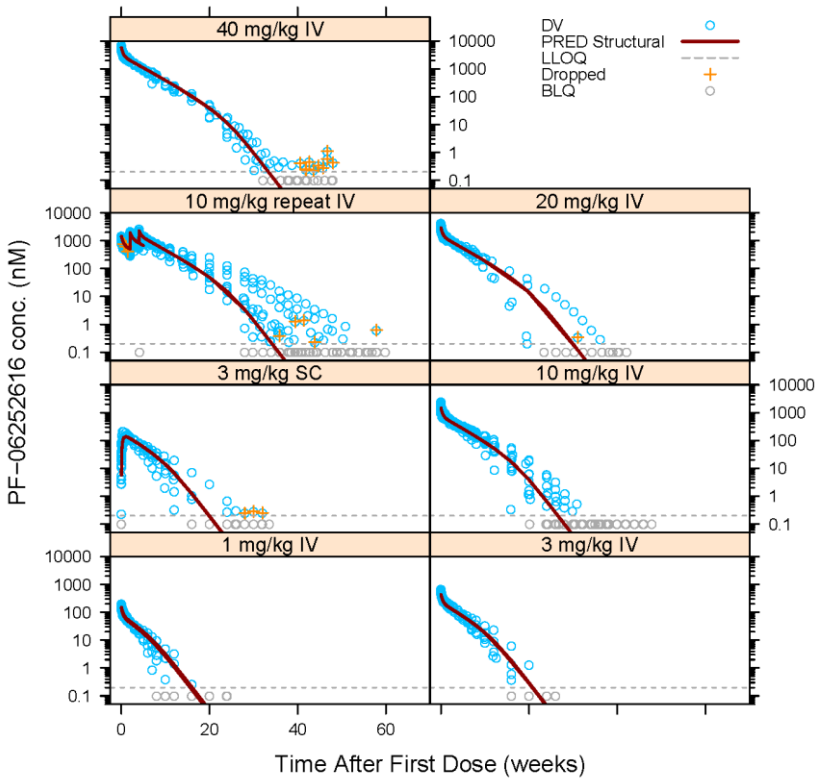


Figure S1: Predictions of total myostatin serum concentration for QSS model (A) and MM-IDR3 model (B) following single and repeat dose administrations of Domagrozumab. Symbols, assay LLOQ and data analysis is same as Figure 3.



A)



B)

Figure S2: Predictions of free Domagrozumab serum concentration for MM-IDR2 model (A) and MM-IDR3 model (B) following single and repeat dose administrations of Domagrozumab. Symbols, assay LLOQ and data analysis is same as Figure 2

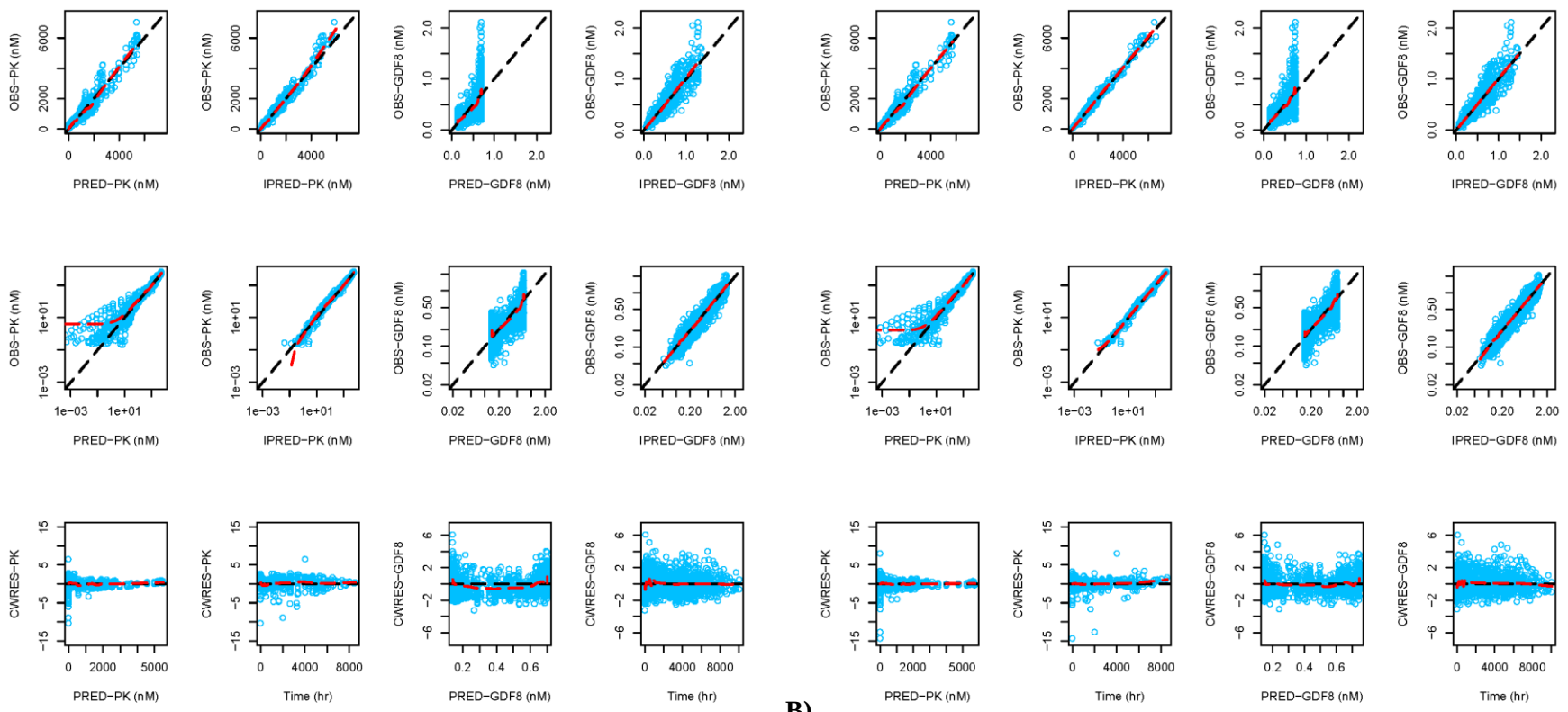
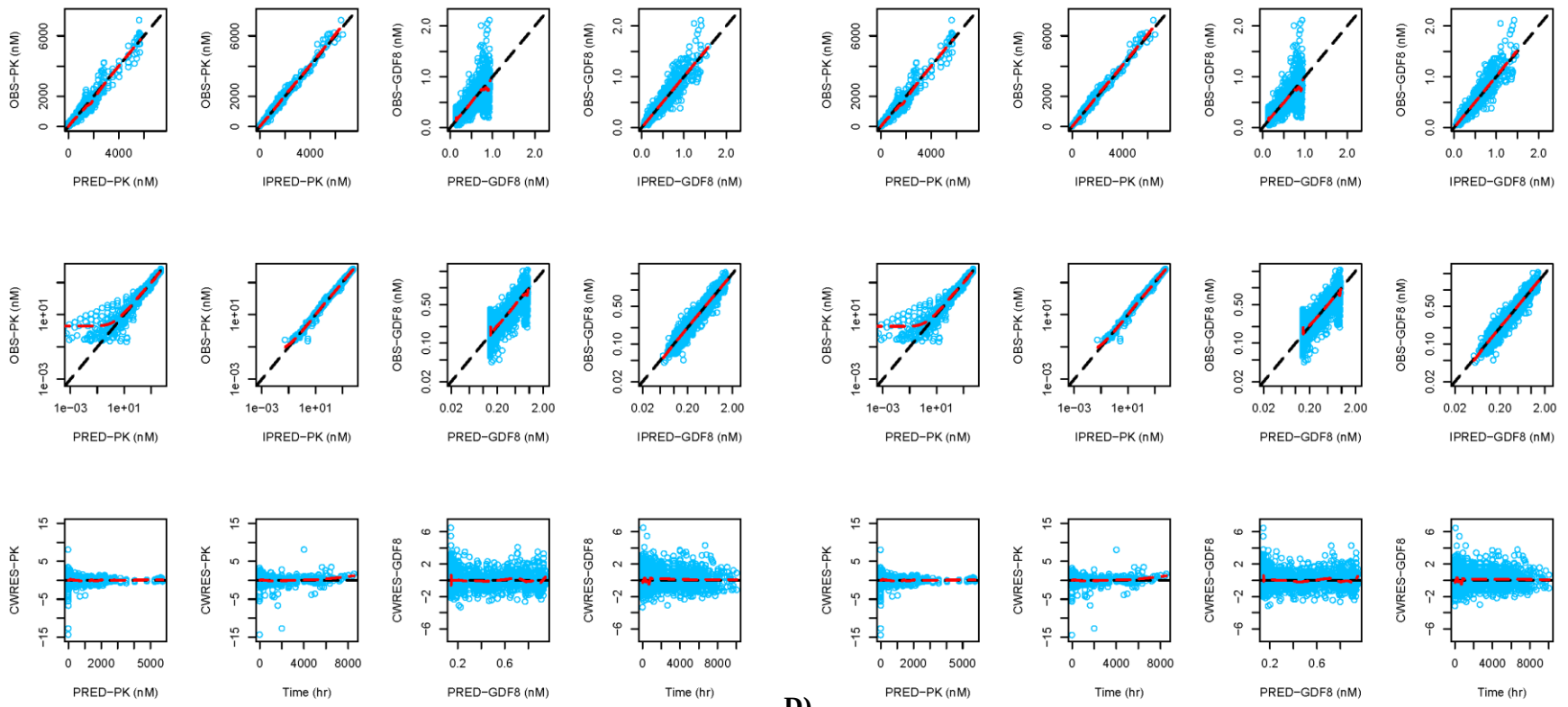


Figure S3 (1): Diagnostic plots for the final QSS model (A), MM-BK model (B)

Top row: Observations of serum concentrations of Domagrozumab and myostatin vs. population and individual predictions. **Middle row:** Same plots as in top row but shown in log-log scale. **Bottom row:** CWRES vs. TAFD and population predictions for serum concentrations of Domagrozumab and myostatin. Dashed black line is line of unity and dashed red line is Friedman's super smoother. 21 Domagrozumab concentrations and 1 myostatin concentration were dropped from this analysis.



C) D)

Figure S3 (2): MM-IDR2 model (C) and MM-IDR3 model (D).

Top row: Observations of serum concentrations of Domagrozumab and myostatin vs. population and individual predictions. **Middle row:** Same plots as in top row but shown in log-log scale. **Bottom row:** CWRES vs. TAFD and population predictions for serum concentrations of Domagrozumab and myostatin. Dashed black line is line of unity and dashed red line is Friedman's super smoother. 21 Domagrozumab concentrations and 1 myostatin concentration were dropped from this analysis.

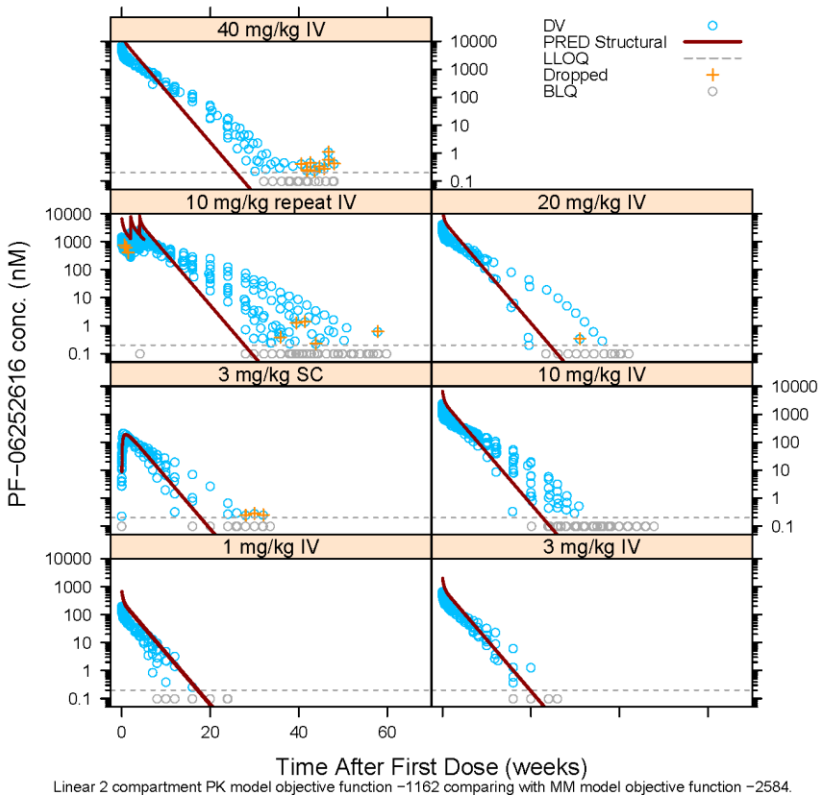


Figure S4: Predictions of free Domagrozumab serum concentration for Linear 2 compartment PK model following single and repeat dose administrations of Domagrozumab. Blue circles are observations, solid red curve is population prediction, and dashed gray line is LLOQ of PK assay (0.2 nM). Orange crosses represent samples dropped from analysis. For plotting purposes Domagrozumab serum concentrations below LLOQ were imputed as 0.1 nM (gray circles).