Supplemental Material

Mechanistic Modeling of a Human IgG4 Monoclonal Antibody (Tralokinumab) Fab Arm Exchange with Endogenous IgG4 in Healthy Volunteers

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DIFFFERENTIAL EQUATION SYSTEMS AND INITIAL CONDITIONS

Endogenous IgG4 and half molecules

$$\frac{dXX}{dt} = K_{syn} - \frac{CL}{V_c} \cdot XX + \frac{k_{on}}{V_c} \cdot X \cdot X - k_{off} \cdot XX - \frac{Q}{V_c} \cdot XX + \frac{Q}{V_p} \cdot XX_p \quad (1)$$

$$\frac{dXX_p}{dt} = \frac{Q}{V_c} \cdot XX - \frac{Q}{V_p} \cdot XX_p \quad (2)$$

$$\frac{dX}{dt} = -\frac{CL_{hf}}{V_c} \cdot X - 2 \cdot \frac{k_{on}}{V_c} \cdot X \cdot X + 2 \cdot k_{off} \cdot XX - 2 \cdot \frac{k_{on}}{V_c} \cdot A \cdot X + k_{off} \cdot AX - \frac{Q}{V_c} \cdot X + \frac{Q}{V_p} \cdot X_p \quad (3)$$

$$\frac{dX_p}{dt} = \frac{Q}{V_c} \cdot X - \frac{Q}{V_p} \cdot X_p \quad (4)$$

Tralokinumab and half maolecules

$$\frac{dAA}{dt} = -\frac{CL}{V_c} \cdot AA + \frac{k_{on}}{V_c} \cdot A \cdot A - k_{off} \cdot AA - \frac{Q}{V_c} \cdot AA + \frac{Q}{V_p} \cdot AA_p \quad (5)$$

$$\frac{dAA_p}{dt} = \frac{Q}{V_c} \cdot AA - \frac{Q}{V_p} \cdot AA_p \quad (6)$$

$$\frac{dA}{dt} = -\frac{CL_{hf}}{V_c} \cdot A - 2 \cdot \frac{k_{on}}{V_c} \cdot A \cdot A + 2 \cdot k_{off} \cdot AA - 2 \cdot \frac{k_{on}}{V_c} \cdot A \cdot X + k_{off} \cdot AX - \frac{Q}{V_c} \cdot A + \frac{Q}{V_p} \cdot A_p \quad (7)$$

$$\frac{dA_p}{dt} = \frac{Q}{V_c} \cdot A - \frac{Q}{V_p} \cdot A_p \quad (8)$$

Hybrid IgG4

$$\frac{dAX}{dt} = -\frac{CL}{V_c} \cdot AX + 2 \cdot \frac{k_{on}}{V_c} \cdot A \cdot X - k_{off} \cdot AX - \frac{Q}{V_c} \cdot AX + \frac{Q}{V_p} \cdot AX_p \quad (9)$$

$$\frac{dAX_p}{dt} = \frac{Q}{V_c} \cdot AX - \frac{Q}{V_p} \cdot AX_p \quad (10)$$

Total IgG4

$$DV = \ AA + XX + AX + \frac{1}{2}A + \frac{1}{2}X \tag{11}$$

Total tralokinumab

$$DV = \ AA + \frac{1}{2}A + \theta \cdot AX \tag{12}$$

Initial condition from total IgG4 assay,

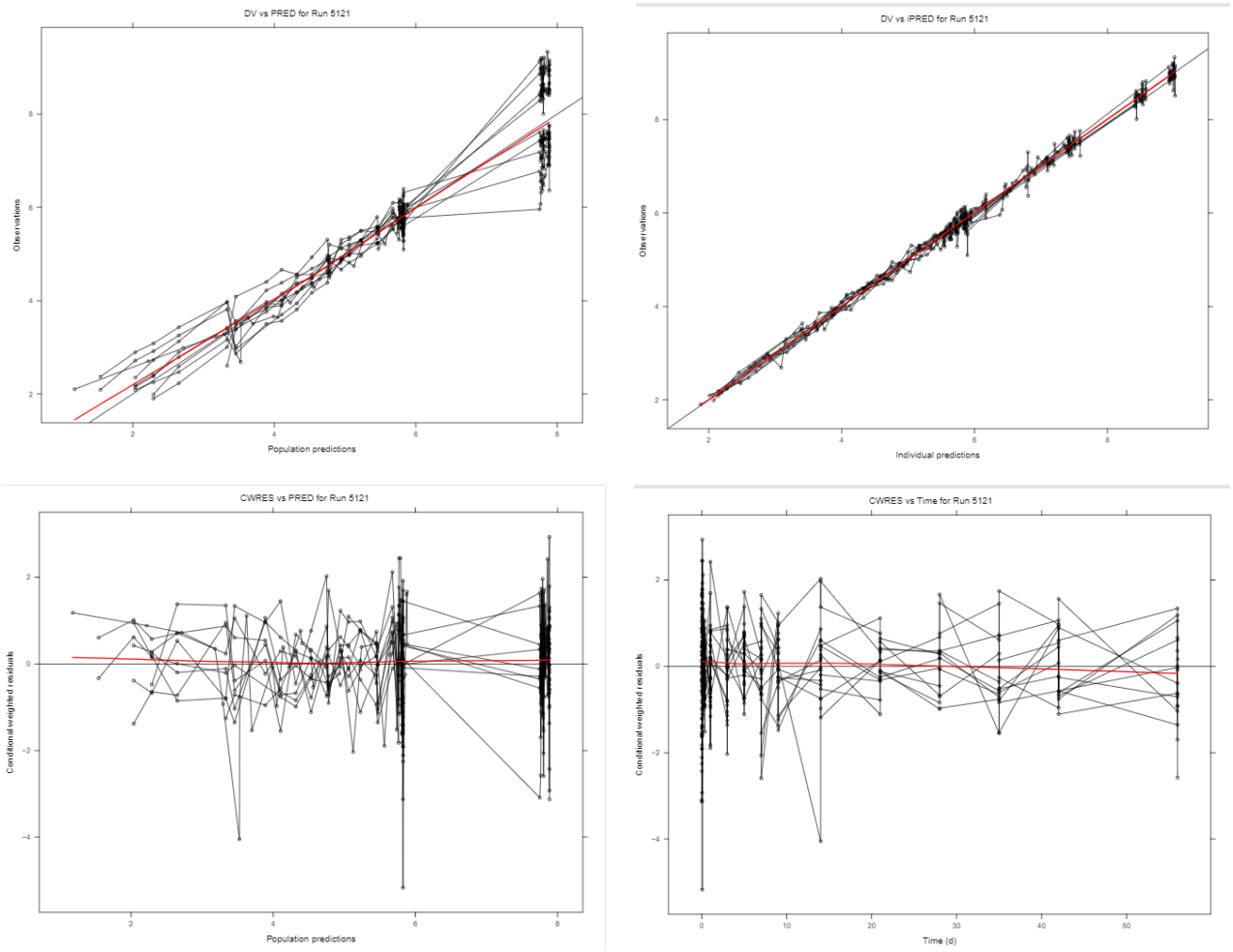
$$G_0 = IgG4_{baseline} \cdot V_c = \ XX_0 + \frac{1}{2}X_0 \tag{13}$$

$$X_0 = \ \frac{-(k_{hf}+k_{off})+\sqrt{(k_{hf}+k_{off})^2+16 \cdot k_{on} \cdot k_{off} \ \cdot \ G_0}}{4 \cdot k_{on}} \tag{14}$$

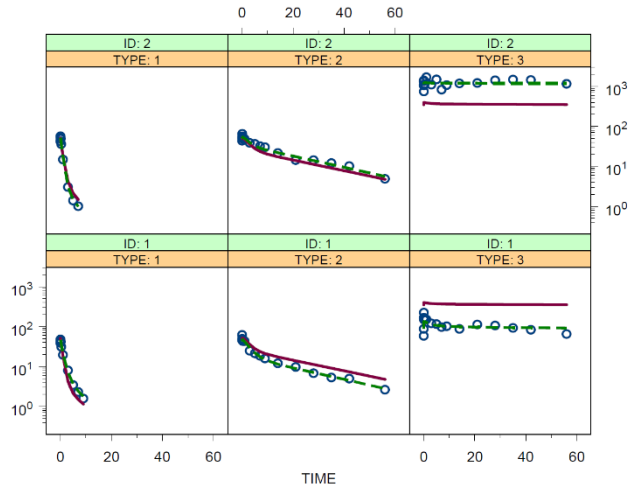
$$K_{syn} = k_{ab} \ \cdot \ XX_0 \ + \ \frac{1}{2}k_{hf} \ \cdot \ X_0 \tag{15}$$

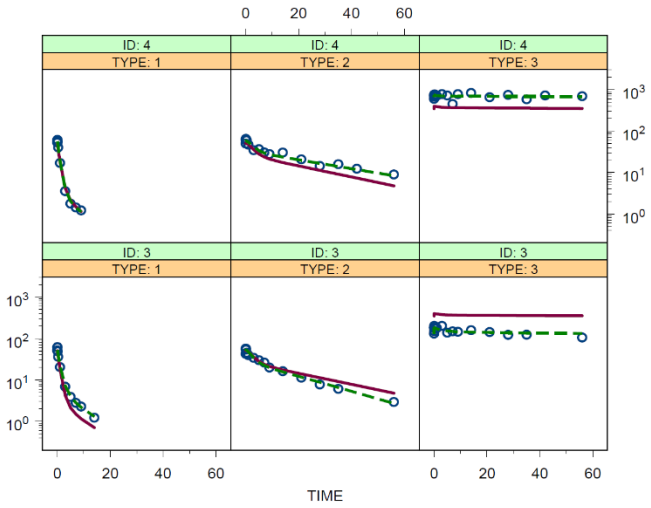
$$XX_{0,p} = \frac{V_p}{V_c} \cdot \ XX_0 \tag{16}$$

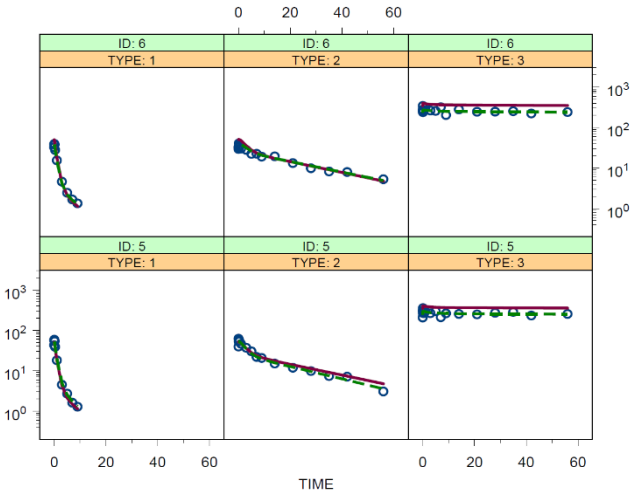
Supplemental Figure S1 Basic goodness-of-fit plots for mechanistic IgG_4 Fab-arm exchange model.

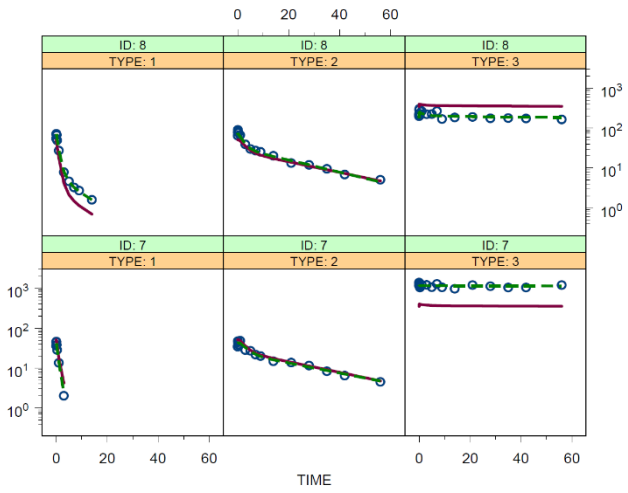


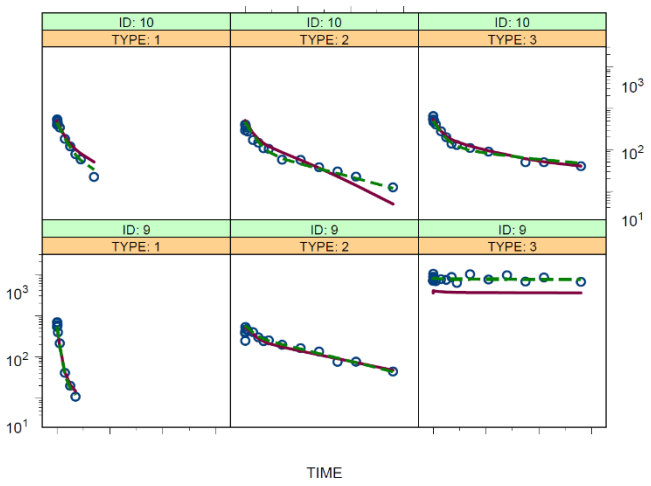
Supplemental Figure S2 Observed and model-predicted tralokinumab and IgG_4 serum concentration.











Supplemental Figure S3 Model-predicted typical half- and hybrid IgG_4 profiles.