Supplementary Information

Clinical Pharmacokinetics

Immunoglobulin G receptors (FcγR), in addition to target-antigen and neonatal Fc receptor (FcRn), influence rituximab pharmacokinetics

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1 Structural model development

The development of structural models underwent the following steps:

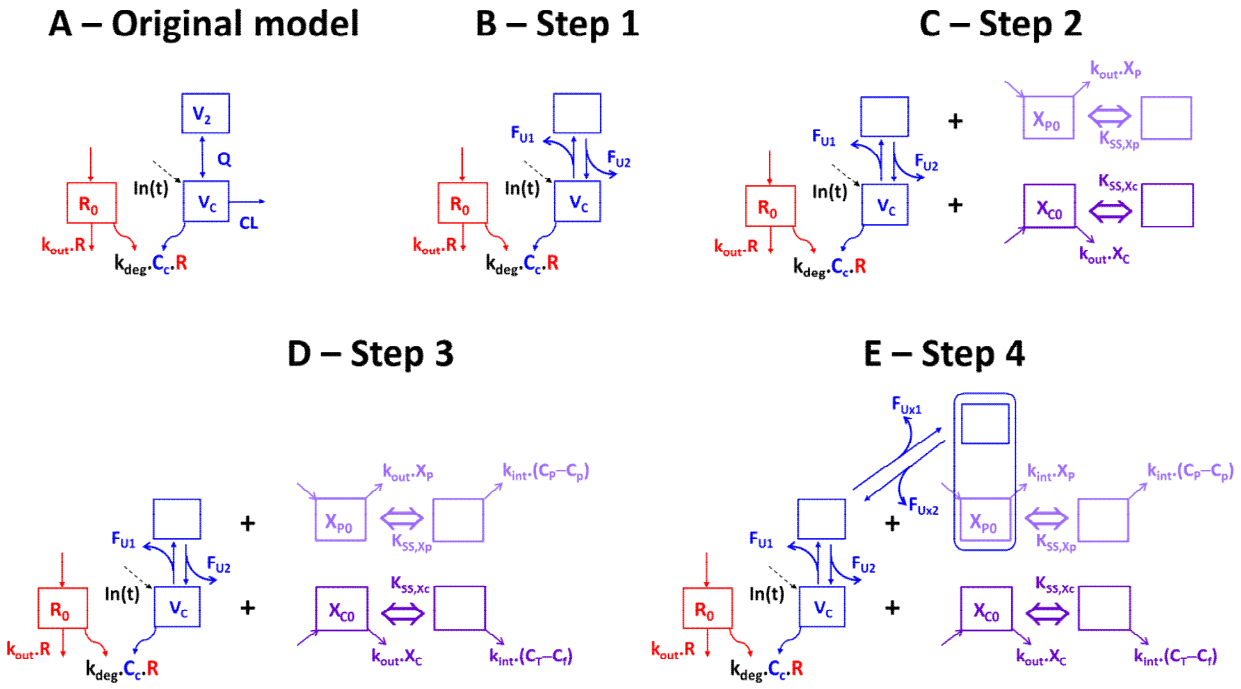

Figure S1.
Model building steps toward integrated model describing rituximab disposition mediated by target, neonatal Fc receptor (FcRn) and IgG Fc receptor (FcγR). **Legends.** V_C, V_P central volume of distribution; $K_{D,FN}$ dissociation constant of IgG and FcRn; R_0 baseline target amount; k_{out} first-order output rate constant; k_{deg} second-order target-mediated elimination rate constant; X_{C0} X_{P0} baseline level of FcγR unbound to rituximab in central and peripheral compartments, respectively; $K_{SS,Xc}$ $K_{SS,Xp}$ steady-state dissociation constants of rituximab-FcγR complexes in central and peripheral compartments, respectively; k_{out} first-order output of FcγR; $k_{up,Xp}$ first-order uptake rate constant in peripheral compartment; α proportionality factor between amount of FcRn in FcγR and FcγR levels in binding compartments; k_{int} first-order elimination rate constant of rituximab-FcγR complexes.

2 Structural model

The best structural model was described using following equations:

$$\frac{dC_P}{dt} = -k_{up}.C_P + k_{up}.C_P(1 - F_{U1}) - k_{up,X_P}.C_P + k_{up,X_P}.C_{PX}(1 - F_{UX2}) - k_{int}.(C_{PT} - C_P)$$

$$\frac{dX_{CT}}{dt} = k_{in,X_C} - k_{out}.(X_{CT} - C_{CT} + C) - k_{int}.(C_T - C_C)$$

$$\frac{dC_{pX}}{dt} = -k_{up,X_P}.C_{PX} + k_{up,X_P}.C_P(1 - F_{UX1})$$

$$\frac{dR}{dt} = k_{in} - k_{out}.R - k_{deg}.C.R$$

$$C_{CU} = \frac{1}{2}\left[\left(Q_{FN} - C_C - K_{D,FN}\right) + \sqrt{\left(Q_{FN} - C_C - K_{D,FN}\right)^2 - 4.K_{D,FN}.Q_{FN}}\right]$$

$$C_{PU} = \frac{1}{2}\left[\left(Q_{FN} - C_P - K_{D,FN}\right) + \sqrt{\left(Q_{FN} - C_P - K_{D,FN}\right)^2 - 4.K_{D,FN}.Q_{FN}}\right]$$

$$F_{U1} = \frac{K_{D,FN}}{C_{CU} + K_{D,FN}}$$

$$F_{U2} = \frac{K_{D,FN}}{C_{PU} + K_{D,FN}}$$

$$C_C = \frac{1}{2}\left[\left(C_{CT} - X_{CT} - K_{SS,C}\right) + \sqrt{\left(C_{CT} - X_{CT} - K_{SS,C}\right)^2 - 4.K_{SS,C}.C_{CT}}\right]$$

$$C_P = \frac{1}{2}\left[\left(C_{PT} - X_{PT} - K_{SS,P}\right) + \sqrt{\left(C_{PT} - X_{PT} - K_{SS,P}\right)^2 - 4.K_{SS,P}.C_{PT}}\right]$$

$$C_{PXU} = \frac{1}{2}\left[\left(\alpha_P.X_{C0} - C_P - K_{D,FN}\right) + \sqrt{\left(\alpha_P.X_{C0} - C_P - K_{D,FN}\right)^2 - 4.K_{D,FN}.\alpha_P.X_{C0}}\right]$$

$$C_{XU} = \frac{1}{2}\left[\left(\alpha_P.X_{C0} - C_{PX} - K_{D,FN}\right) + \sqrt{\left(\alpha_P.X_{C0} - C_{PX} - K_{D,FN}\right)^2 - 4.K_{D,FN}.\alpha_P.X_{C0}}\right]$$

$$F_{UX1} = \frac{K_{D,FN}}{C_{PXU} + K_{D,FN}}$$

$$F_{UX2} = \frac{K_{D,FN}}{C_{XU} + K_{D,FN}}$$

Notations. V_1: central volume of distribution, C_C and C_P: rituximab concentrations unbound to Fab or Fc targets k_{up}: uptake rate constant, Q_{FN}: amount of FcRn protecting rituximab, F_{U1} and F_{U2}: fraction of rituximab unbound to FcRn from central and peripheral compartments, respectively, k_{out}, first-order elimination rate constant of target (R) and central FcγR (X_C), k_{int} first-order elimination rate constant of rituximab-FcγR complexes;R_0, X_{C0} and X_{P0}: baseline target, cell inside central and peripheral compartments, respectively, $K_{D,FN}$, $K_{SS,C}$ and $K_{SS,P}$: dissociation constants for FcRn and/or FcγR binding, α_P: proportionality factor between amount of FcRn in FcγR and FcγR levels in peripheral compartment.

3 Model diagnostics

Diagnostic plots showed no obvious bias or model misspecification (figure S2).

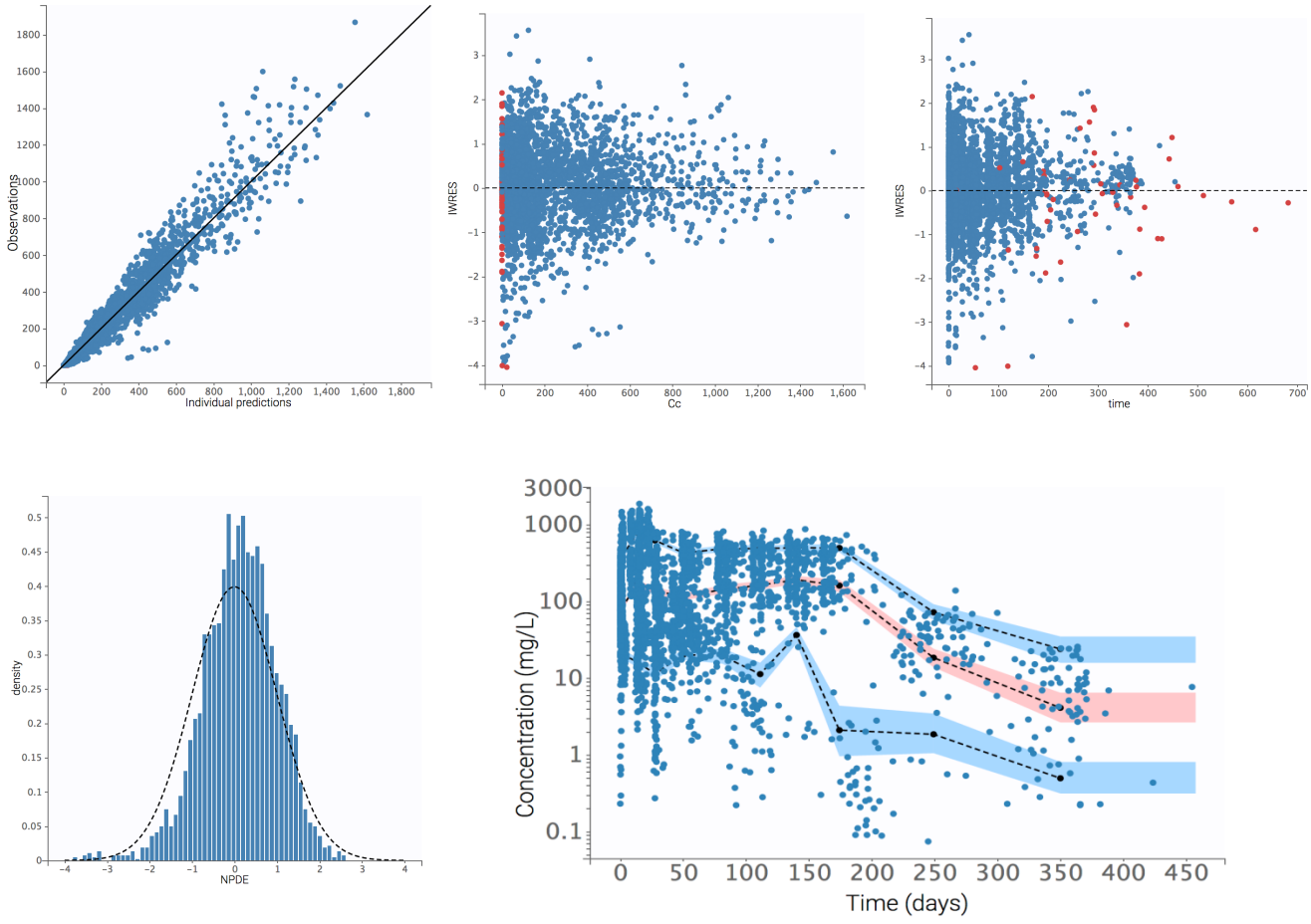

Figure S2. Goodness-of-fit plots of the population final model. **Top, left**: observed vs. model fitted rituximab concentrations; solid line represents the identity line. **Top-middle:** individual-weighted residuals (IWRES) vs. time. Red dots represent censored data. **Top-right:** IWRES vs. fitted concentrations. **Bottom, left:** Normalized prediction distribution error (NPDE) density. Dotted line represents theoretical center-reduced Gaussian distribution. **Bottom, right:** visual predictive check (VPC) plot. From bottom to top: 10%, 50% and 90% percentile prediction intervals and their respective median concentration lines.