

Population pharmacokinetics of the anti–interferon-gamma monoclonal antibody emapalumab: an updated analysis

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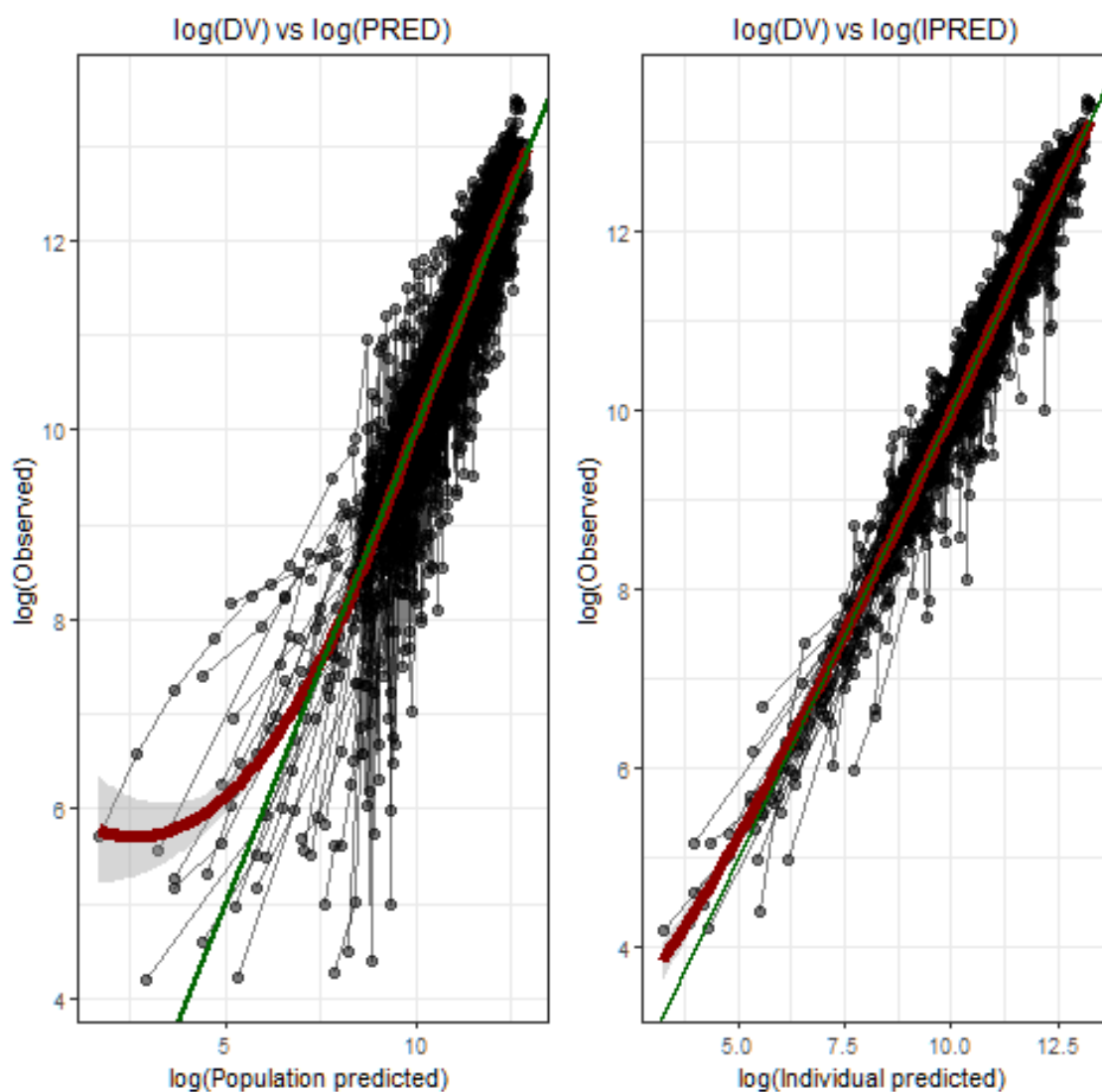
Supplementary Table 1. Sequence of model runs leading to development of the final model

Run number	Description	Number of estimated parameters	OFV compared with reference run	Δ OFV	Comment
002	Previous PK model in patients with HLH – 2-compartment elimination CL & CLNL, allometry with fixed exponents IIV:CL, V1, V2 Residual: additive on log-scale	11	-2837.970	NA	
004	Remove CLNL for patients with MAS	11	-2852.446	-14.476	No need CLNL for patients with MAS
006	Estimate CLNL 7 days after HSCT	12	-2981.519	-129.073	Better than 004
007	Estimate CLNL 14 days after HSCT	12	-3008.971	-27.452	Better than 006
008	Estimate CLNL 21 days after HSCT	12	-3044.138	-35.167	Better than 007
009	Estimate CLNL 28 days after HSCT	12	-3067.783	-23.645	Better than 008
010	Estimate CLNL 35 days after HSCT	12	-3047.505	+20.268	Worse than 009
011	Fix CLNL_HSCT to -1	11	-3067.207	+0.576	Selected base model
012	Run011 + CL, V1, Q, V2=F(AGE power)	4	-3131.488	-64.281	p<0.001 similar for CL & Q very low for V2
013	Run012 with same age effect for CL/Q, and no age effect on V2	2	-3131.168	+0.320	Not significant; keep this model
014	Run013 with age effect on CLL rather than CL	0	-3118.679	+12.489	Worse than run013
015	Run013 + CL, V1, Q, V2=F(TBIL power)	4	-3289.168	-158.000	p<0.001 similar for CL, V1 & V2, but different for Q
016	Run013 + CLL, V1, Q, V2=F(TBIL power)	4	-3314.850	-183.682	Better than run015
017	Run013 + CLNL, V1, Q, V2=F(TBIL power)	4	-3241.068	-109.900	Worse than run016
018	Run016 – Q=F(TBIL power)	1	-3298.721	+16.129	p<0.001 need Q=F(TBIL), but badly

					estimated in run016 (RSE 72%); not kept
019	Run018 with same TBIL effect on CLL, V1 & V2	2	-3286.368	+12.353	p<0.01 Final model

CL, clearance; CLNL, non-linear clearance dependent of total interferon- γ ; F, function; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplant; IIV, interindividual variation; NA, not applicable; OFV, objective function value; PK, pharmacokinetic; Q, inter-compartmental clearance; RSE, residual standard error; TBIL, total bilirubin; V1, volume of the central compartment; V2, volume of the peripheral compartment.

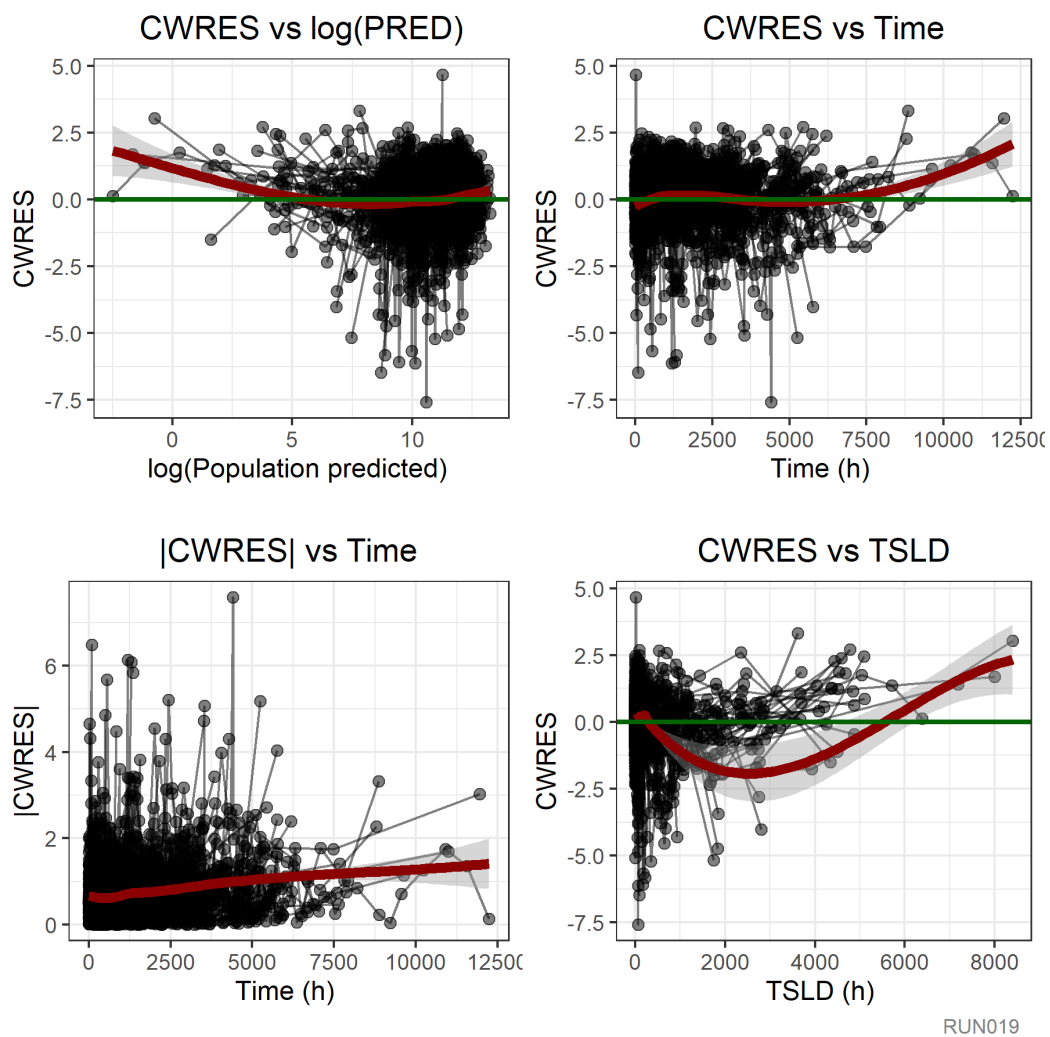
Supplementary Figure 1. Goodness-of-fit plots for final PK model in all patients



Black dots are observations. The red line is a smooth through the data. The green line is the line of identity. Grey shaded area represents the 95% prediction interval of the smooth.

DV, observations; IPRED, individual predictions; PK, pharmacokinetic; PRED, population predictions.

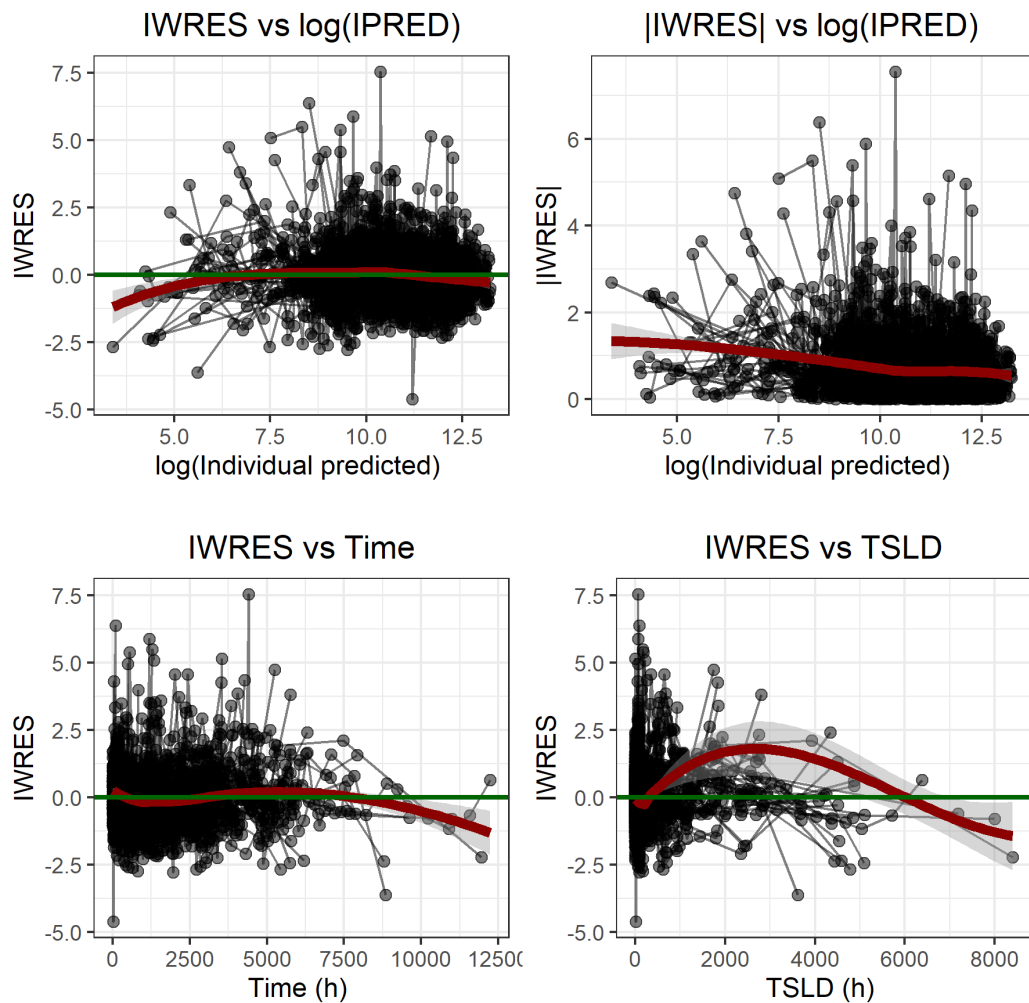
Supplementary Figure 2. Residual plots (CWRES) for the final PK model



Black dots are observations. The red line is smooth through the data. The green line is the reference line (no trend). Grey shaded area represents the 95% prediction interval of the smooth.

CWRES, conditional weighted residuals; PRED, individual prediction; PK, pharmacokinetic; TSLD, time since last dose.

Supplementary Figure 3. Residual plots (IWRES) for the final PK model



RUN019

Black dots are observations. The red line is smooth through the data. The green line is the reference line (no trend). Grey shaded area represents the 95% prediction interval of the smooth.

IPRED, individual predictions; IWRES, individual weighted residuals; PK, pharmacokinetic; TSLD, time since last dose.