Streamlining Clinical Development of C.E.R.A. (Continuous Erythropoietin Receptor Activator) in Pediatric Chronic Kidney Disease Patients by Integration of Clinical Trial and Real-World Data

32nd Population Approach Group Europe Meeting
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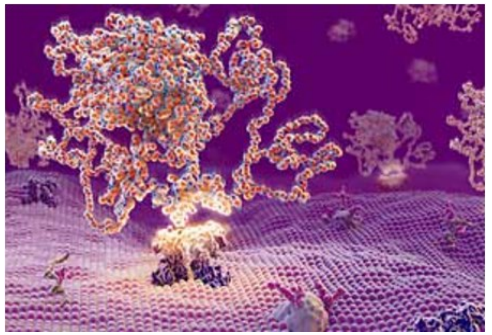
C.E.R.A. in anemia with chronic kidney disease

Continuous Erythropoetin Receptor Activator



C.E.R.A. (Mircera®, methoxy polyethylene glycol-epoetin beta)

- Erythropoiesis-stimulating agent (ESA) indicated in anemia associated with chronic kidney disease
- First approval for treatment of anemia of CKD in **2007** in US and EU in adults[1-3]
  - Correction (ESA-naïve) and maintenance of Hb levels when switching from a previous ESA to C.E.R.A.
  - On hemodialysis (IV), on peritoneal dialysis or not yet on dialysis (SC)
  - **Monthly dosing in maintenance**, dose adjustments based on Hb levels
- First approval in **pediatric** patients in US in **2018**, for treatment of pediatric patients 5 to 17 years of age on hemodialysis **(IV)** who are converting from another ESA after their hemoglobin level was stabilized with an ESA.[3,4]

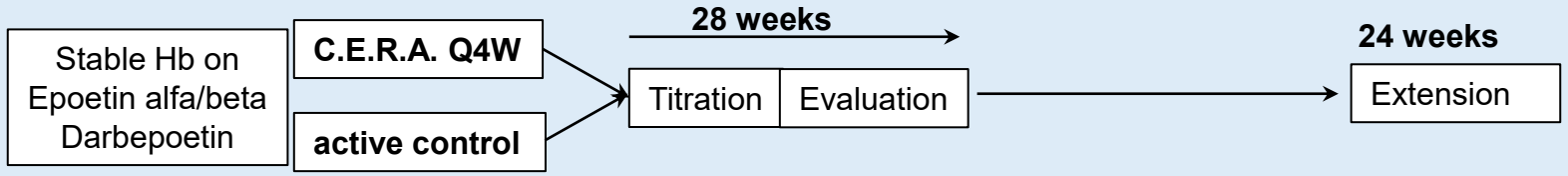
1) Mircera SmPC accessed online March 2024: https://www.ema.europa.eu/en/documents/product-information/mircera-epar-product-information_en.pdf
2) Mircera authorisation details: https://www.ema.europa.eu/en/medicines/human/EPAR/mircera#ema-inpage-item-authorisation-details
3) Mircera USPI accessed online March 2024: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125164s071s072s073lbl.pdf
4) Mircera FDA approval: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-mircera-anemia-associated-chronic-kidney-disease-pediatric-patients-dialysis#:~:text=On%20June%207%2C%202018%2C%20the,was%20stabilized%20with%20an%20ESA.

Optimization of the pediatric development plans to substitute phase III study

- Similar Exposure-Response relationship for C.E.R.A. in adult and pediatric populations following IV
- Simulations of clinical outcomes were confirmed by IV and SC RWD
- Optimized pediatric plans were approved by FDA and EMA

From

Initial NH19708, parallel group confirm conversion factor: 2-17yrs, SC and IV, n=150
haemodialysis (>30%), peritoneal dialysis (>30%), no dialysis (>30%), 2-11years: >30%

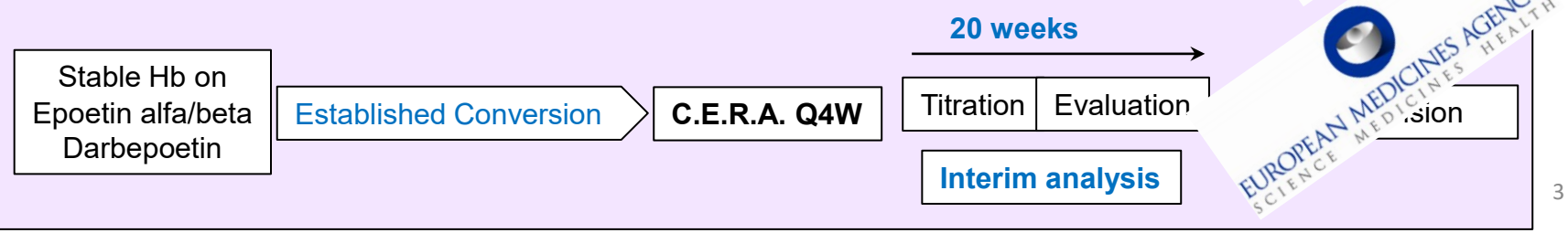


MIDD
MODEL-INFORMED DRUG DEVELOPMENT
QUANTITATIVE MEDICINE

↓ 3 years
↓ 45% budget
↑ Knowledge <2 years old

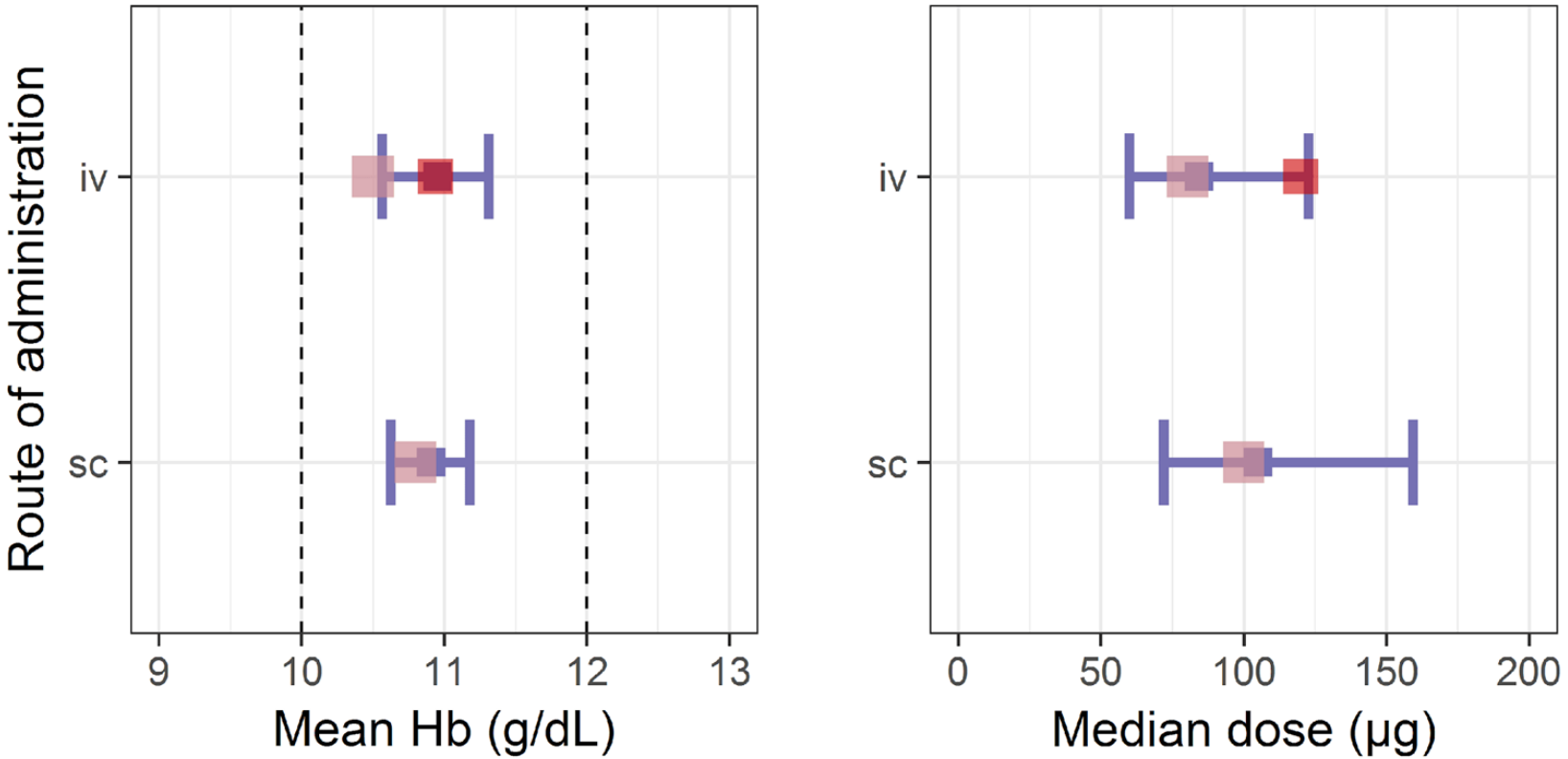
To

Revised NH19708, single arm to ascertain PK/PD modelling and simulation:
3months-17yrs, SC, n=40; peritoneal dialysis or hemodialysis (no more than 10
no dialysis (≥ 33%), 3months-11yrs: ≥33%, minimum of 3 under 5 years



More details in: Chanu et al.
Br J Clin Pharmacol. 2020;86:801–811

Model-based inferences confirmed by *initial* RWD



Assumption for SC simulations: 50% increase in bioavailability in pediatric patients compared to adults

Supported by darbepoetin data: F=37% in adults (USPI), F=54% in pediatric patients (PIP), resulting in 46% increase in bioavailability

|—| Simulated outcome and 95% prediction interval

■ Observed value in group 2 (N=36) of DOLPHIN, individual doses ranged from 16 to 675 µg

■ Observed value in IPDN registry (Schaefer et al. J Am Soc Nephrol 2018;29 (Suppl):TH-PO233):
IV, 32 hemodialysis patients, age [1.5;21.8]y
SC, 126 peritoneal dialysis patients, age [0.3;26.9]y

Chanu P et al., Br J Clin Pharmacol. 2020;86:801–811

Modeling and Simulation Objectif and Activities

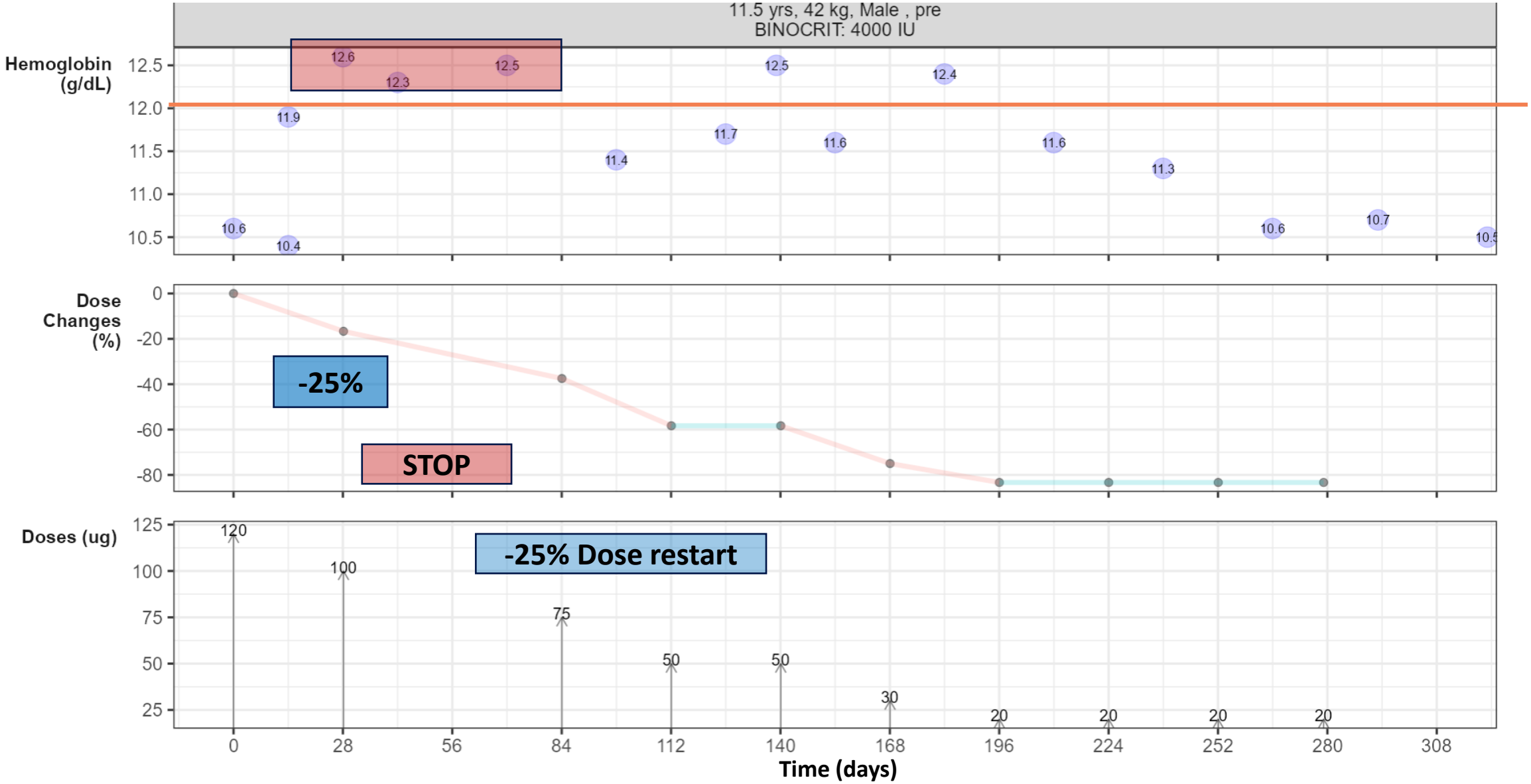
Objectives:

- Use of a M&S framework to integrate clinical trial data together with RWD to support C.E.R.A. filing in pediatric patients with CKD

Activities:

- Evaluate the previous PK/PD models and re-assess covariate relationships especially pediatric Frel of SC, Dialysis type on PK and or PK/PD, Age and Weight
- Update simulation PK/PD framework

MIRCERA Adjustment rules



Pediatric Maintenance Studies included in the M&S analysis

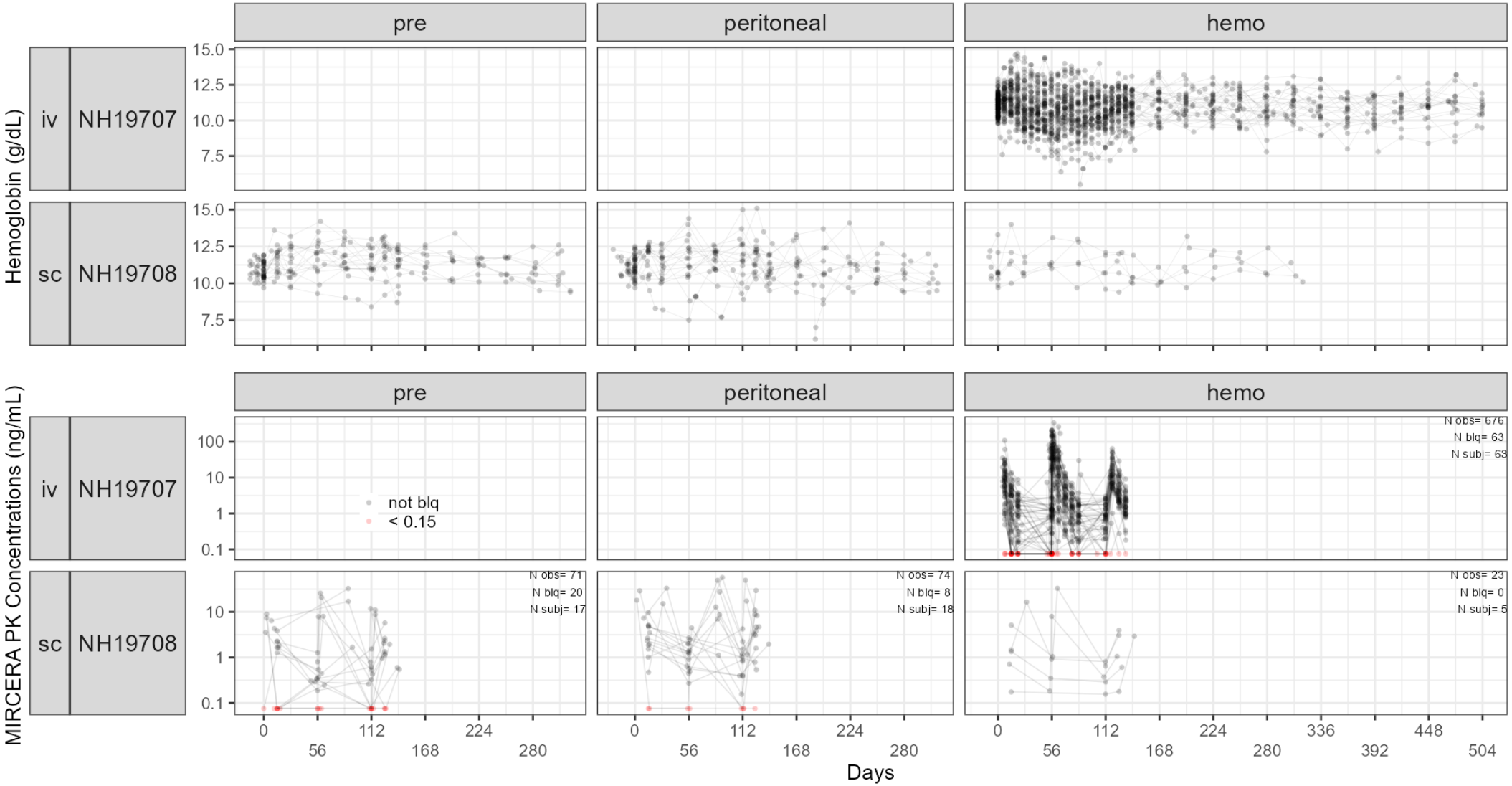
Clinical Trials data used for the M&S

RWD used for external validation

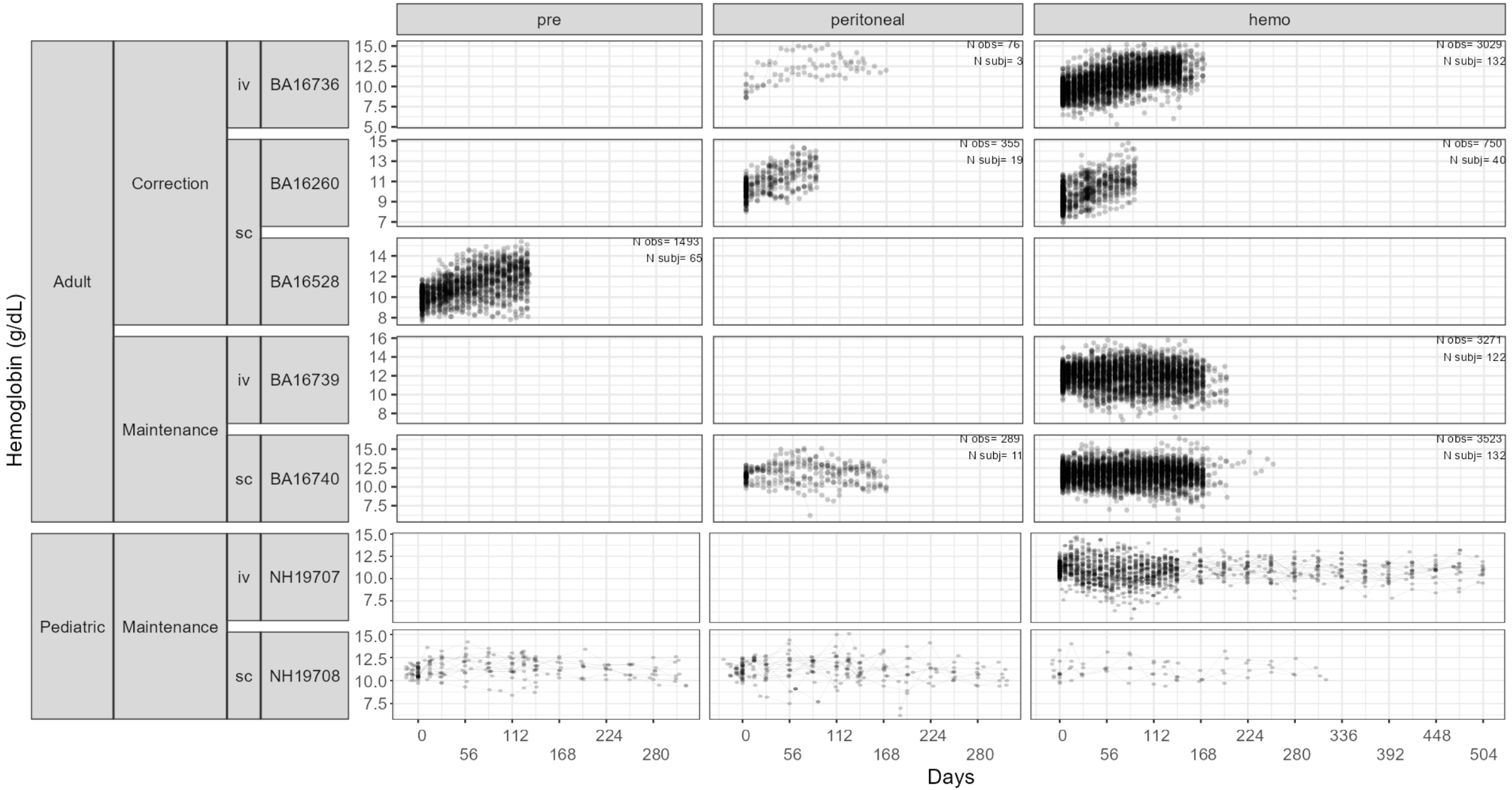
Route	Study	Age Groups	Pre dialysis	Peritoneal dialysis	Hemodialysis
iv	NH19707	2-6 y			1
		7-11 y			24
		12-18 y			38
sc	NH19708	3mo-2y	3	1	
		2-6 y	4	4	
		7-11 y	3	2	1
		12-18 y	7	11	4
iv	MH40258	3mo-2y			1
		2-6 y		3	18
		7-11 y		15	8
		12-18 y		31	14
sc	MH40258	3mo-2y			12
		2-6 y			8
		7-11 y			14
		12-18 y		3	40

https://www.ema.europa.eu/en/documents/variation-report/mircera-h-c-000739-ii-0092-epar-assessment-report-variation_en.pdf

Pediatric PK and PD Data used in the Pop PK PD Model update



Pediatric PK and PD Data Pooled with Previous Dataset



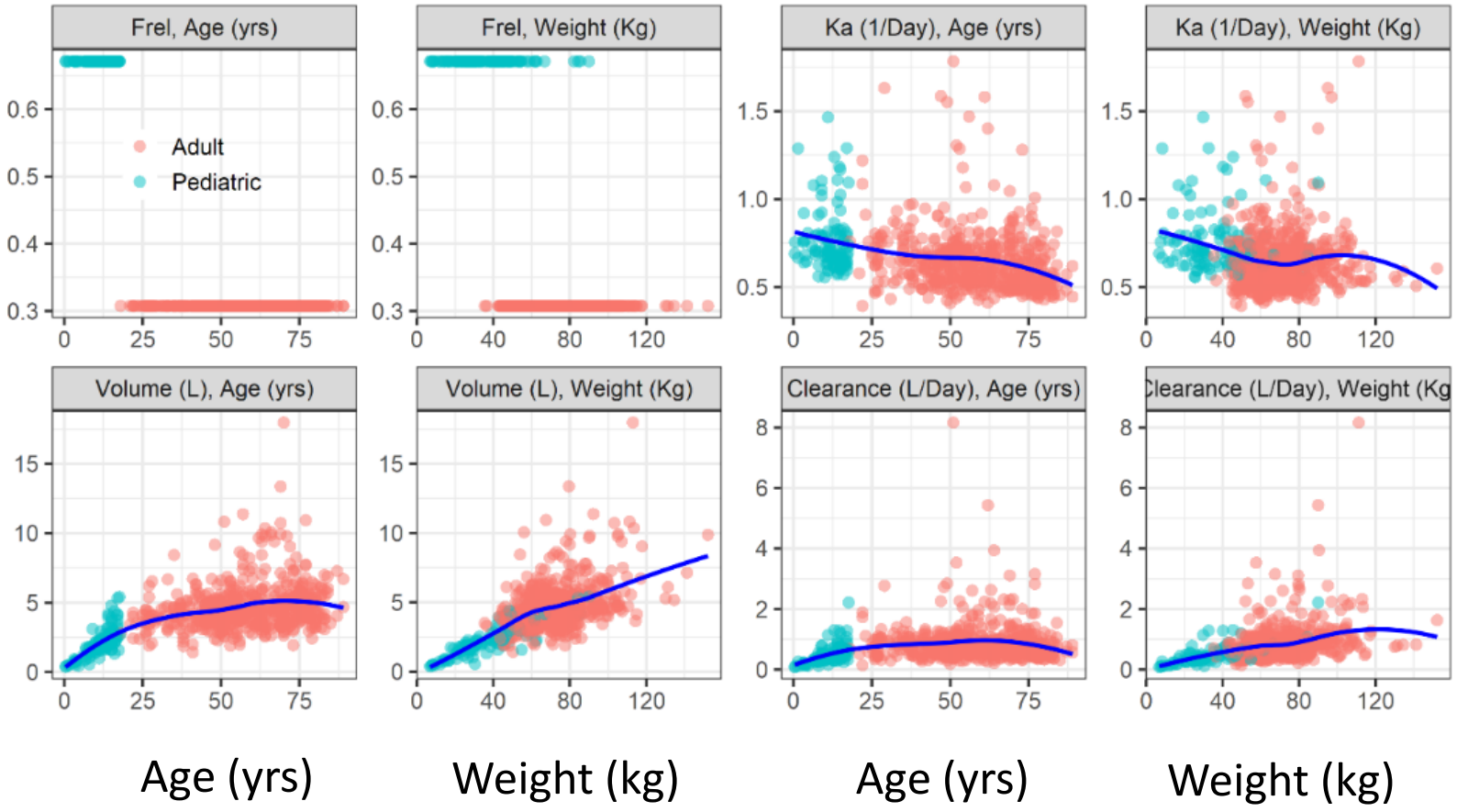
Updated Population PK model

One compartment (SC/IV, FREL)

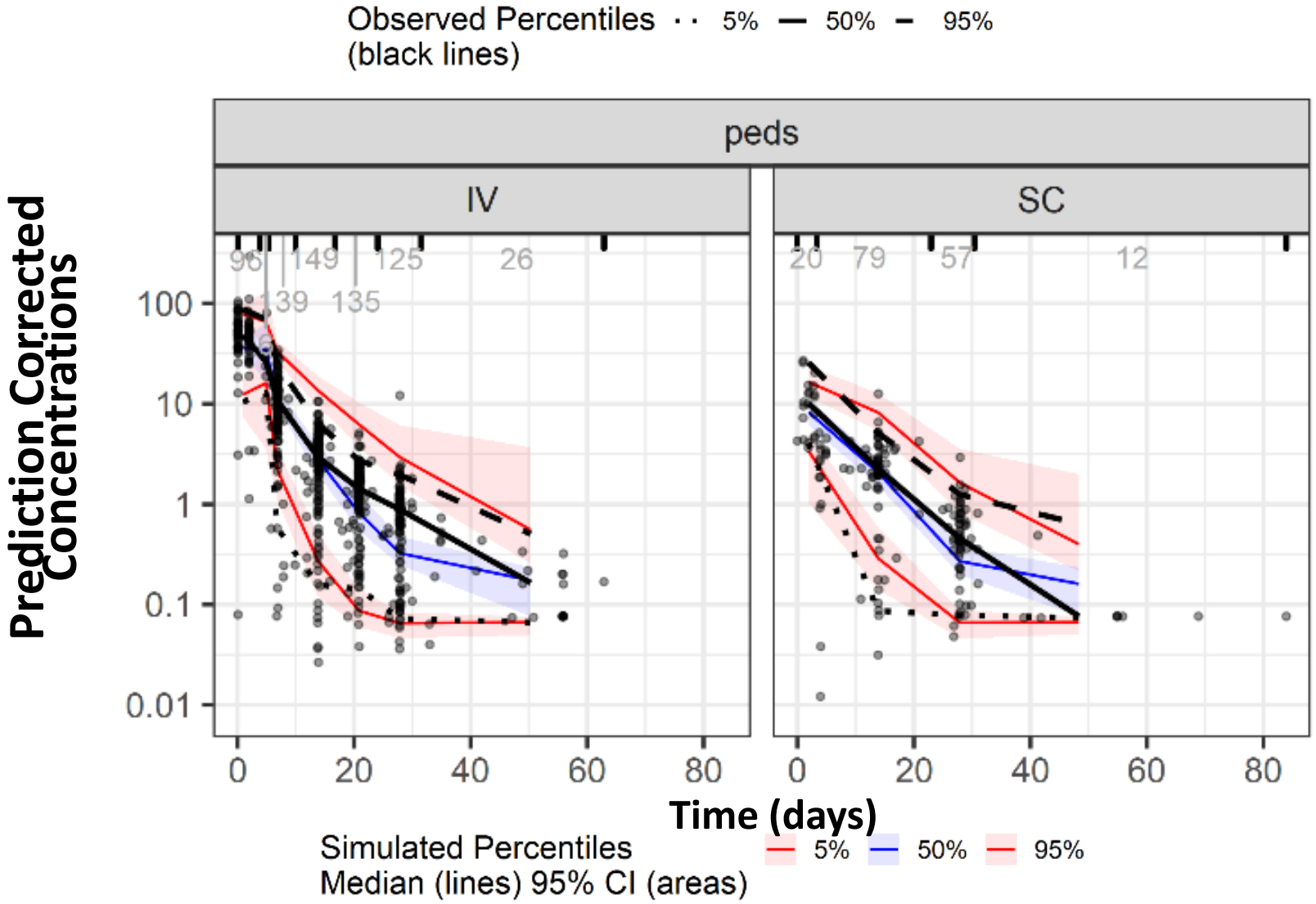
Body Weight on CL/V
Age on V

Pediatric effect on Frel

Adult Frel: 0.31
Pediatric Frel:0.67 X 2.1

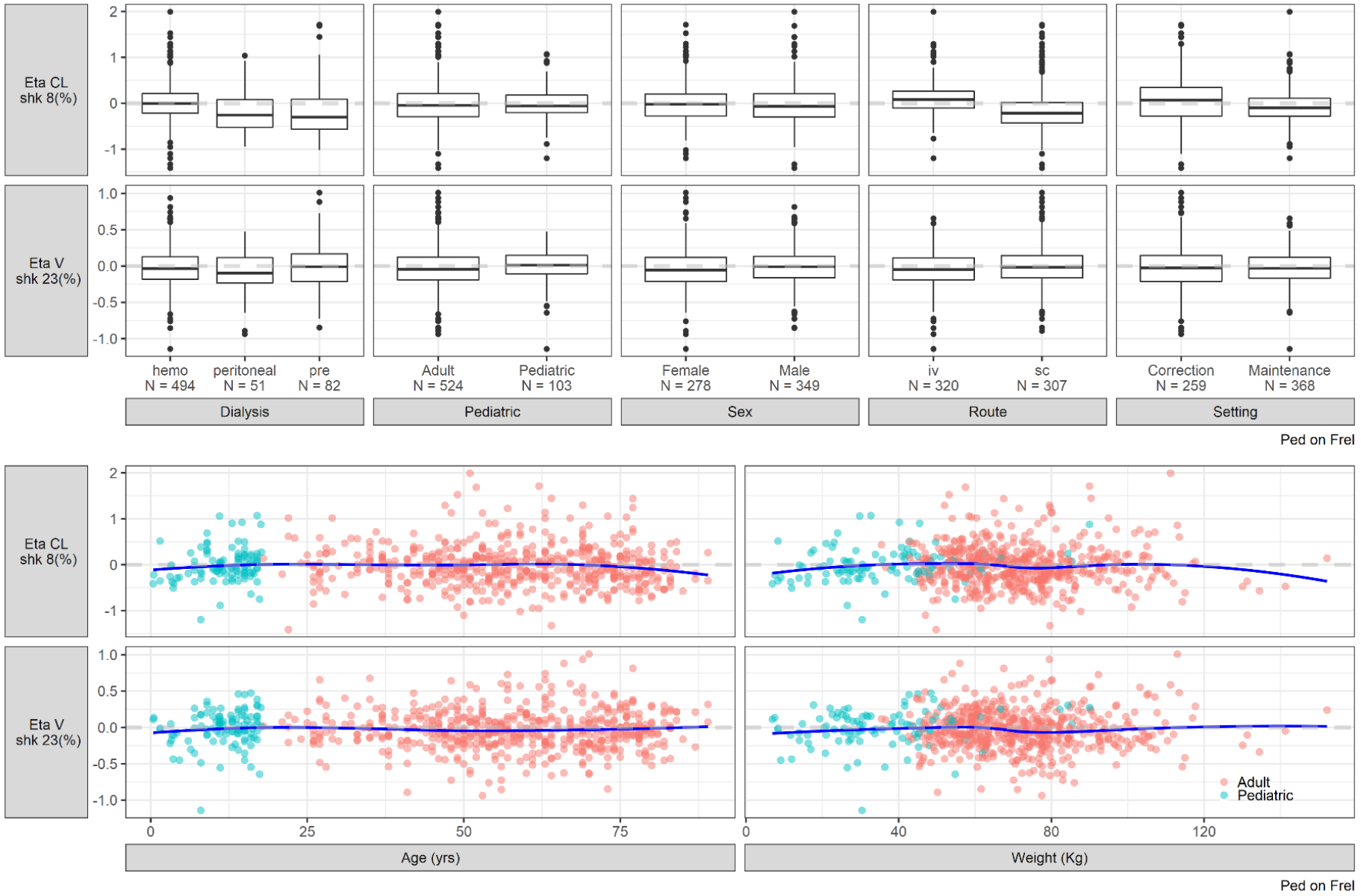


PK Model pcVPC



https://www.ema.europa.eu/en/documents/variation-report/mircera-h-c-000739-ii-0092-epar-assessment-report-variation_en.pdf

No trends of posthocs versus Age, Weight, Dialysis type, Sex and Treatment Setting



Similar exposure-response relationship in adult and pediatric patients

Pharmacodynamic model

Change in Hb over time

$$Hb'(t) = S(t) - S(t - LS) + S_{ESA}$$

Production of Hb

$$S(t) = \frac{Hb_0}{LS} \cdot \left(1 + \frac{S_{max} \cdot C(t)}{SC_{50} + C(t)}\right)$$

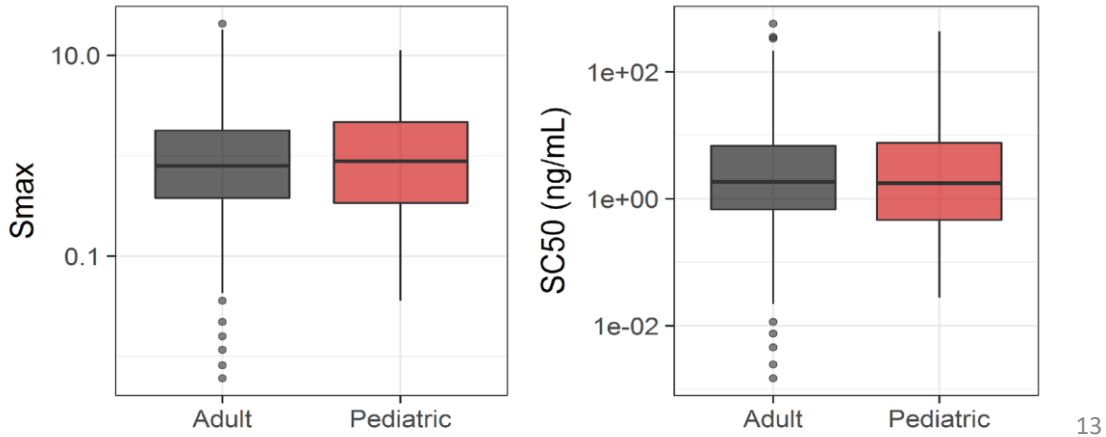
$$S_{ESA} = \frac{Hb_0 - Hb_{sw}}{LS} \; if \; 0 \leq t \leq LS \; otherwise \; S_{ESA} = 0$$

System parameters
-LS (d): apparent life span of red blood cells
-Hb_0 (g/dL): Hb level at baseline before ESA treatment

Drug related parameters
-S_{max}: maximum relative increase in Hb production rate
-SC_{50} C.E.R.A. concentration to achieve 50% of S_{max}

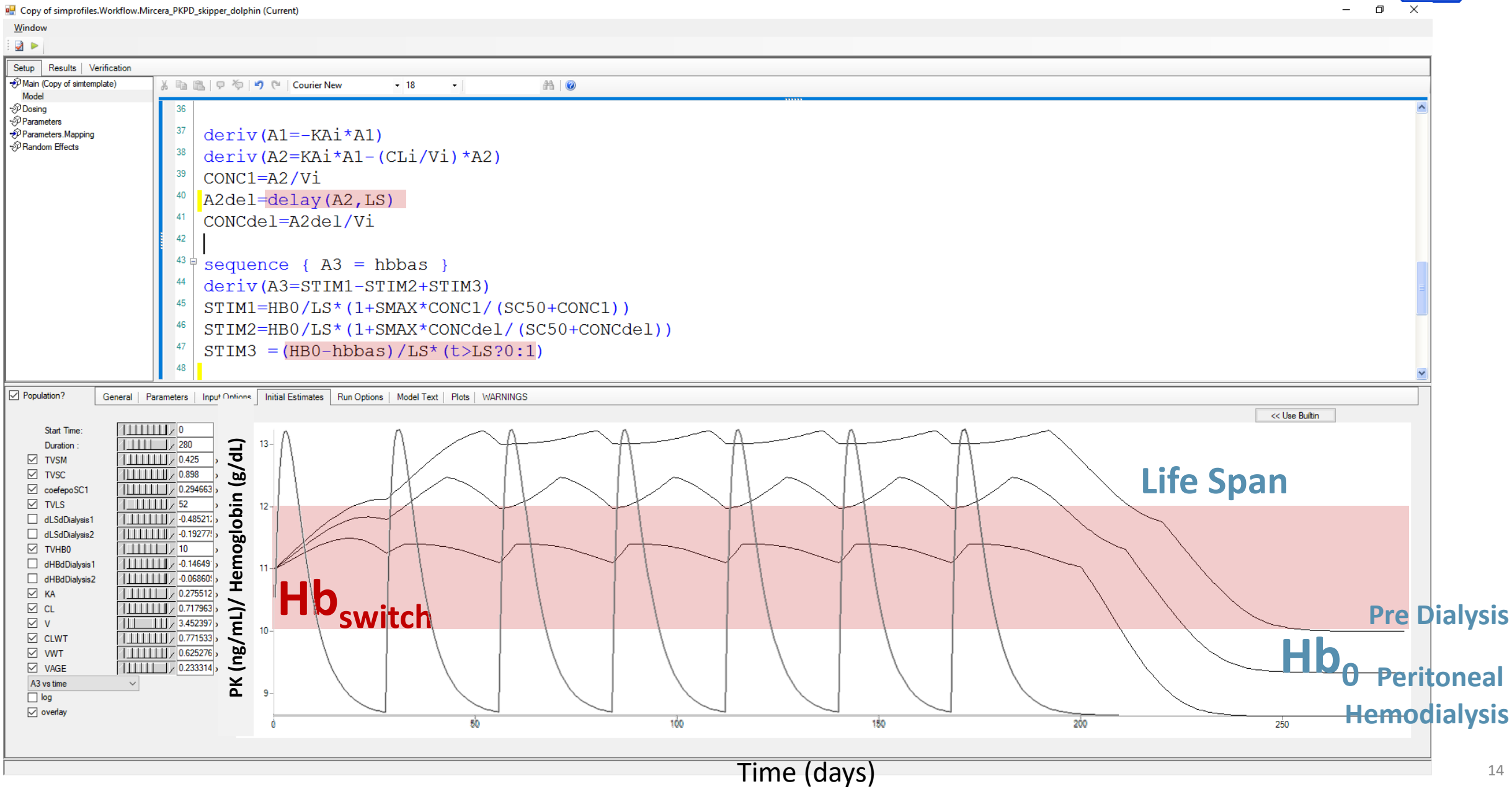
No difference in drug-related parameters between pediatric and adult patients

Similar exposure-response relationship

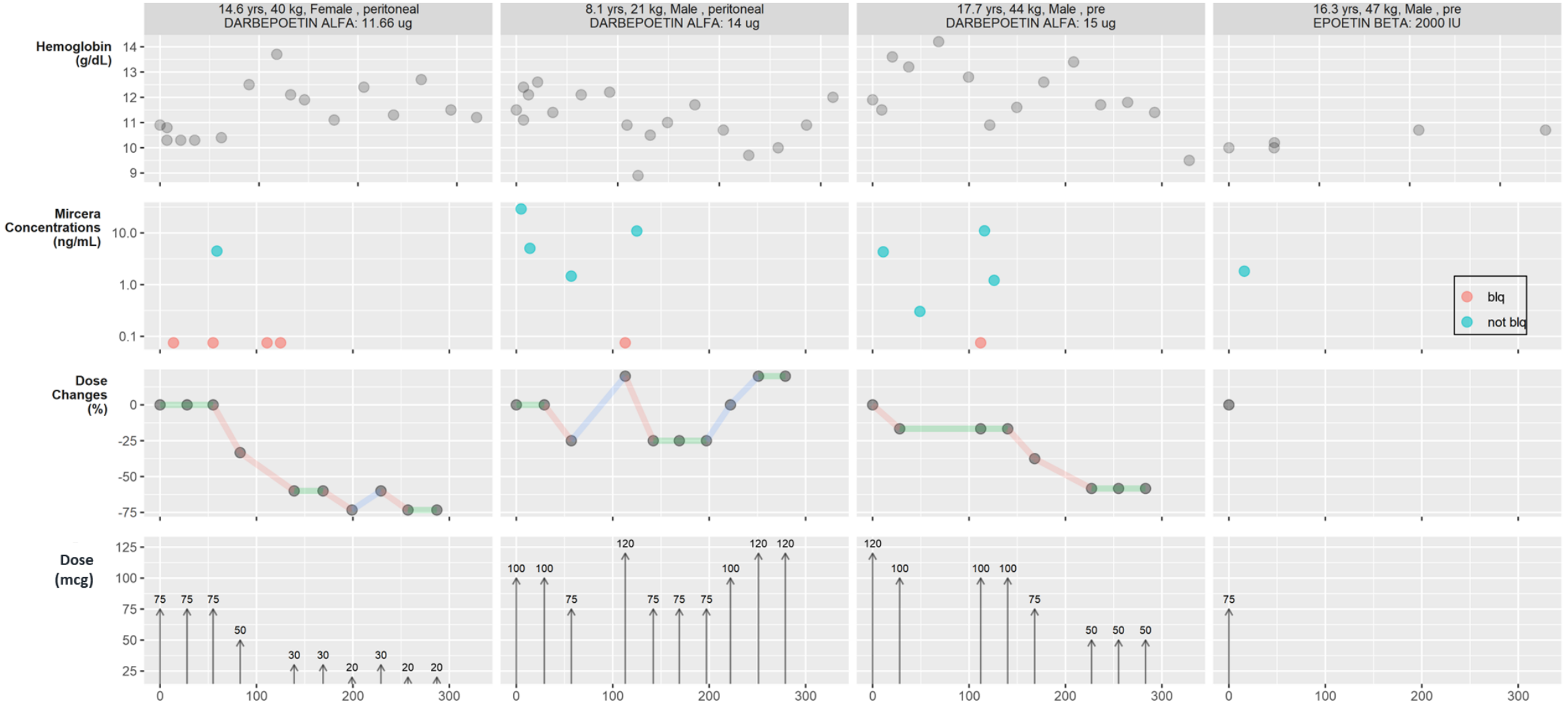


Chanu P et al., Br J Clin Pharmacol. 2020;86:801–811

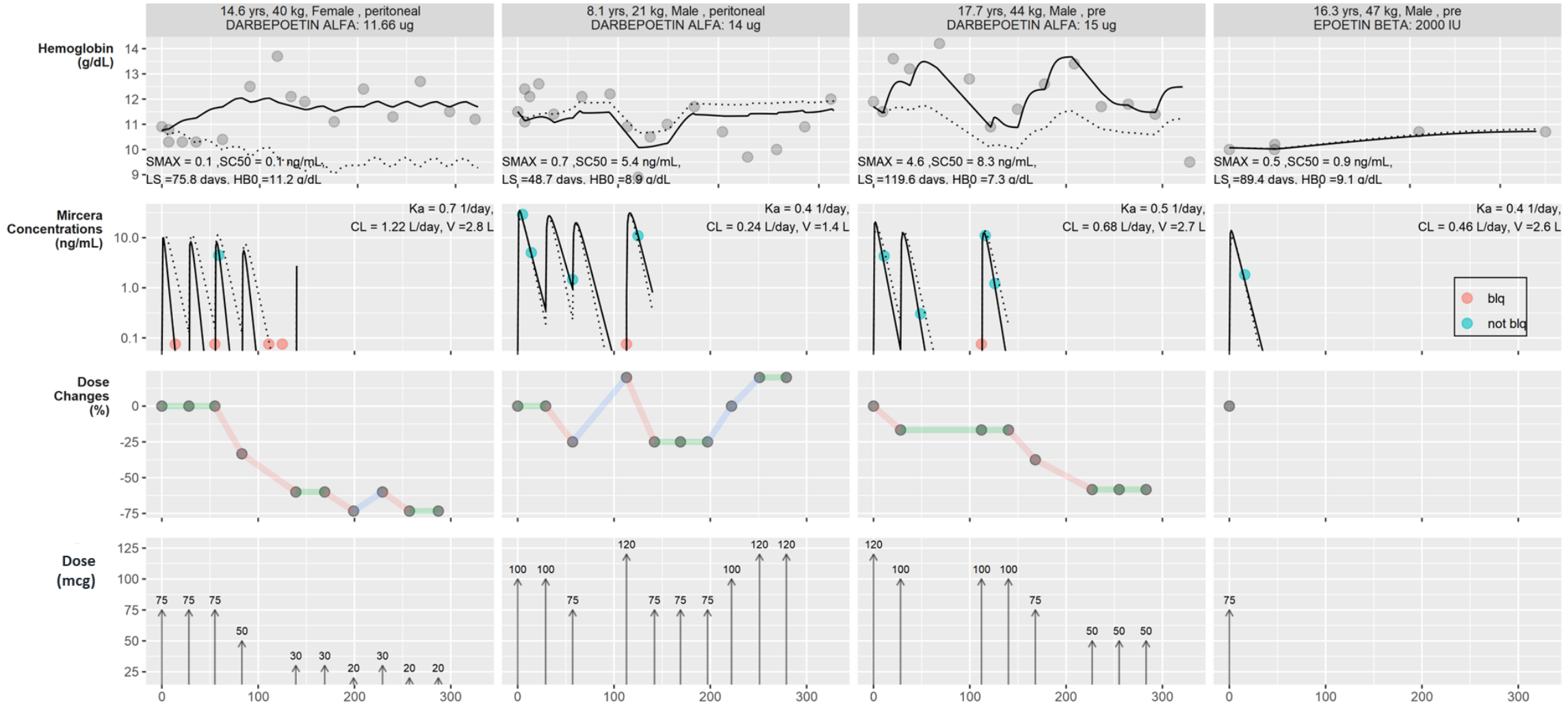
Population PK/PD model Simulation without Dose adjustments



Individual data points



Comes to life with PK/PD model predictions



Updated Population PK/PD model

No weight on HB0

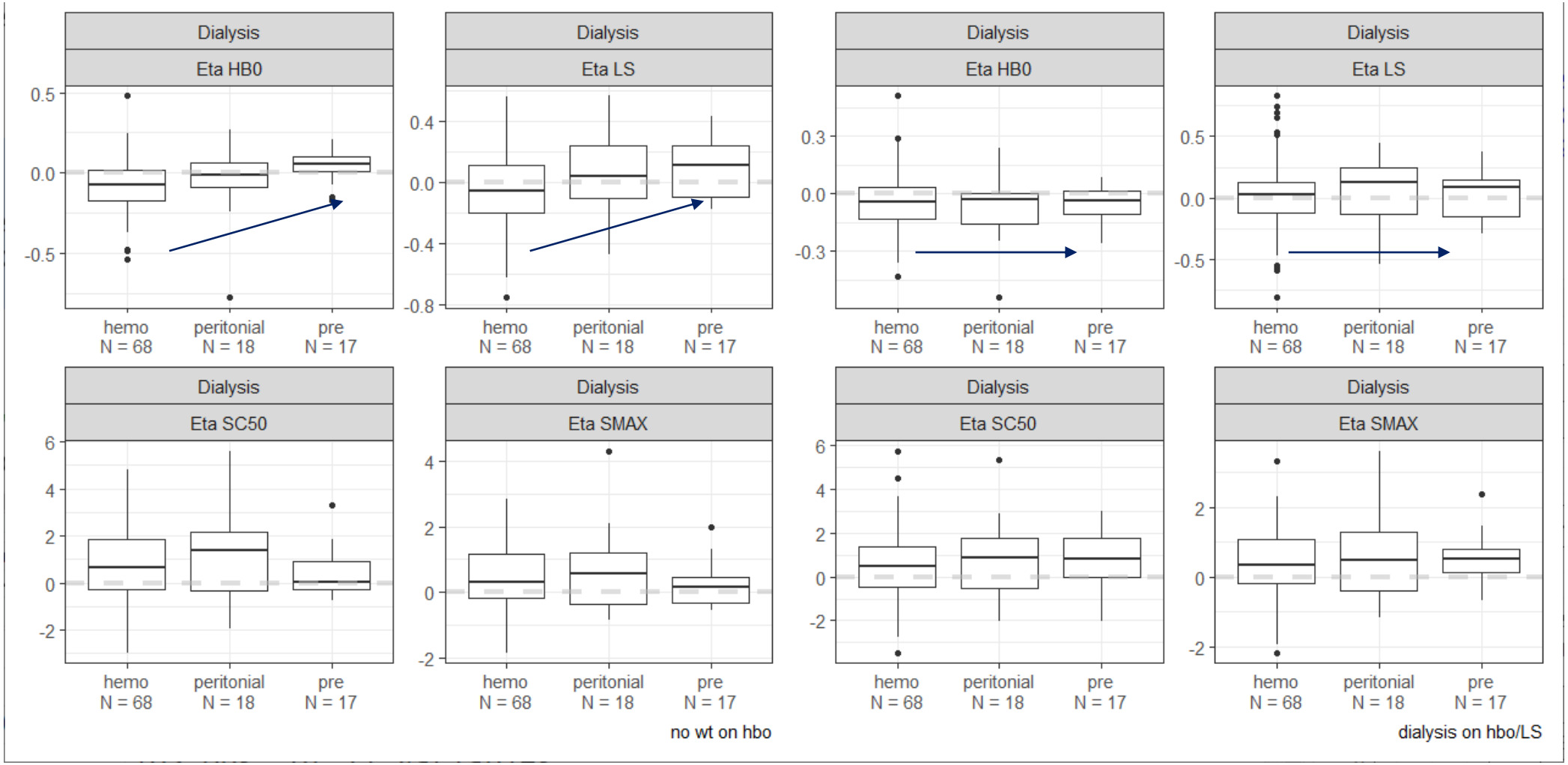
Previous erythropoietin dose on SC50

Dialysis on Hb0

Dialysis on LS

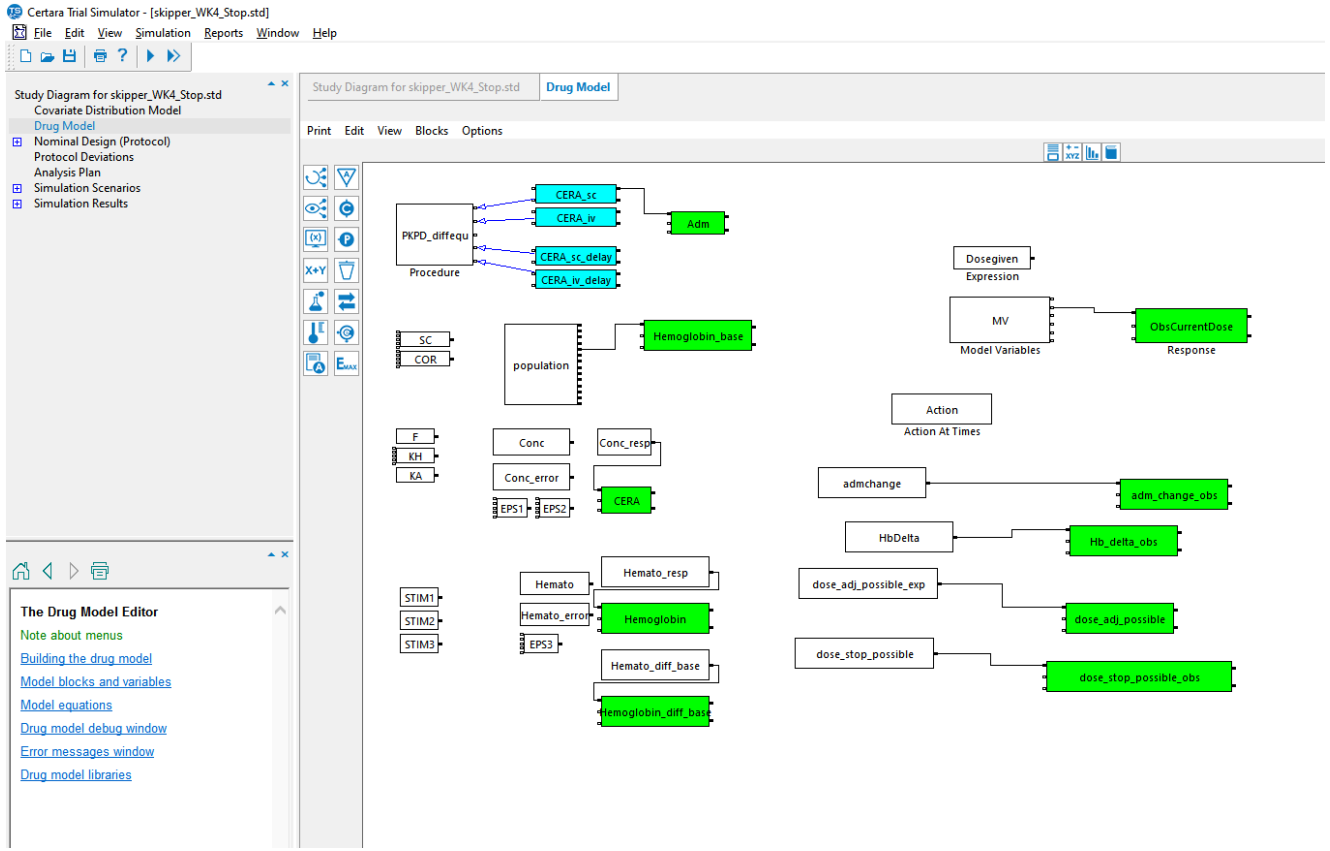
Base Model

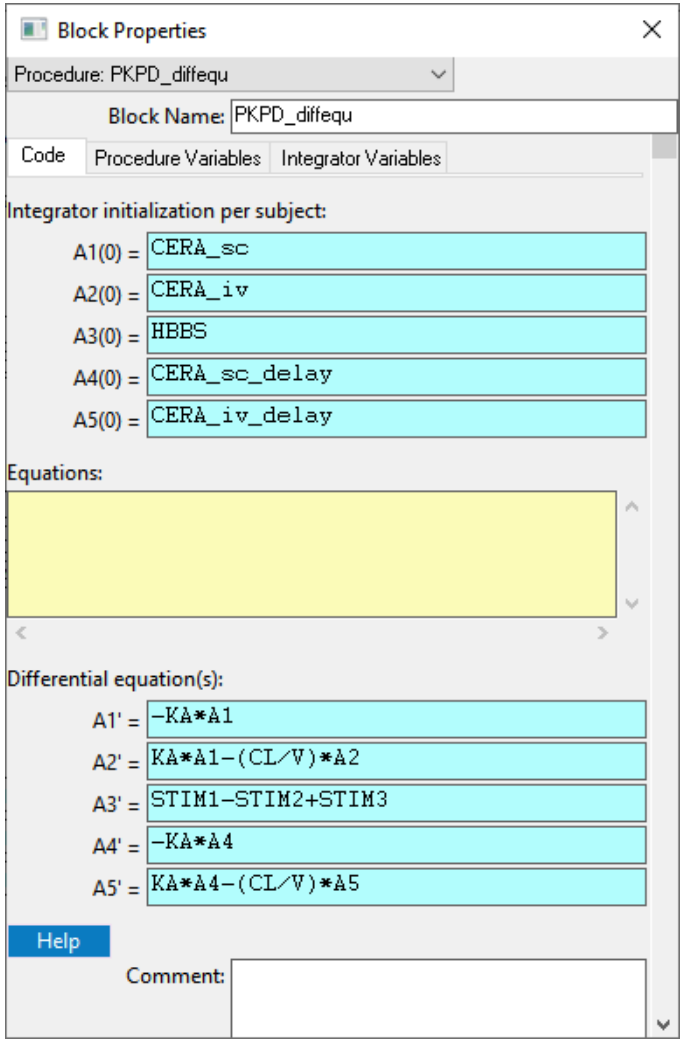
Dialysis on HB0 and LS



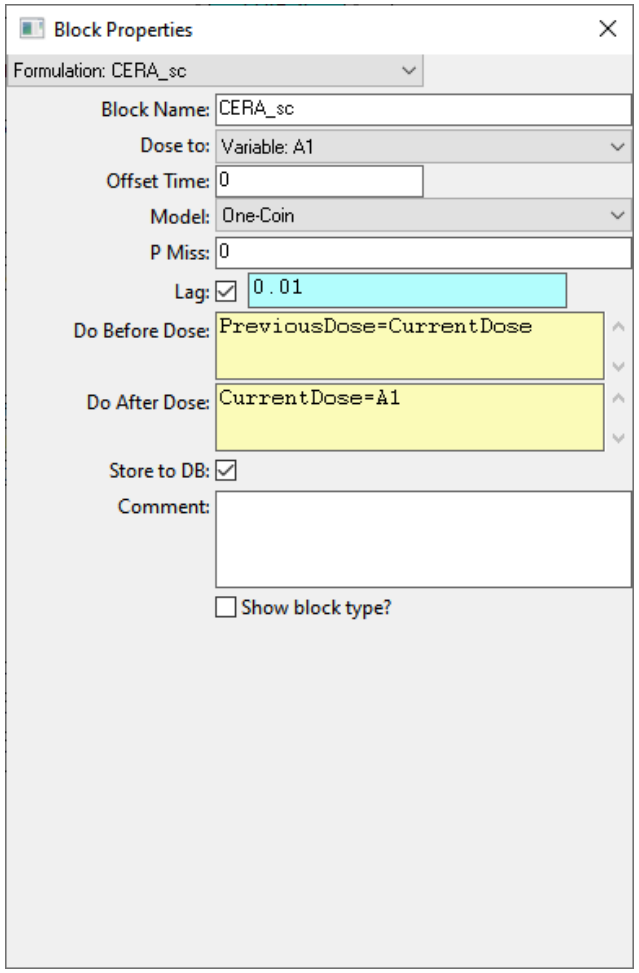
Hb0 (9.4 mg/dl) was **7%** and **14%** lower in peritoneal and hemodialysis patients.
LS (82 days) was **18%** and **38%** shorter in peritoneal and hemodialysis patients.

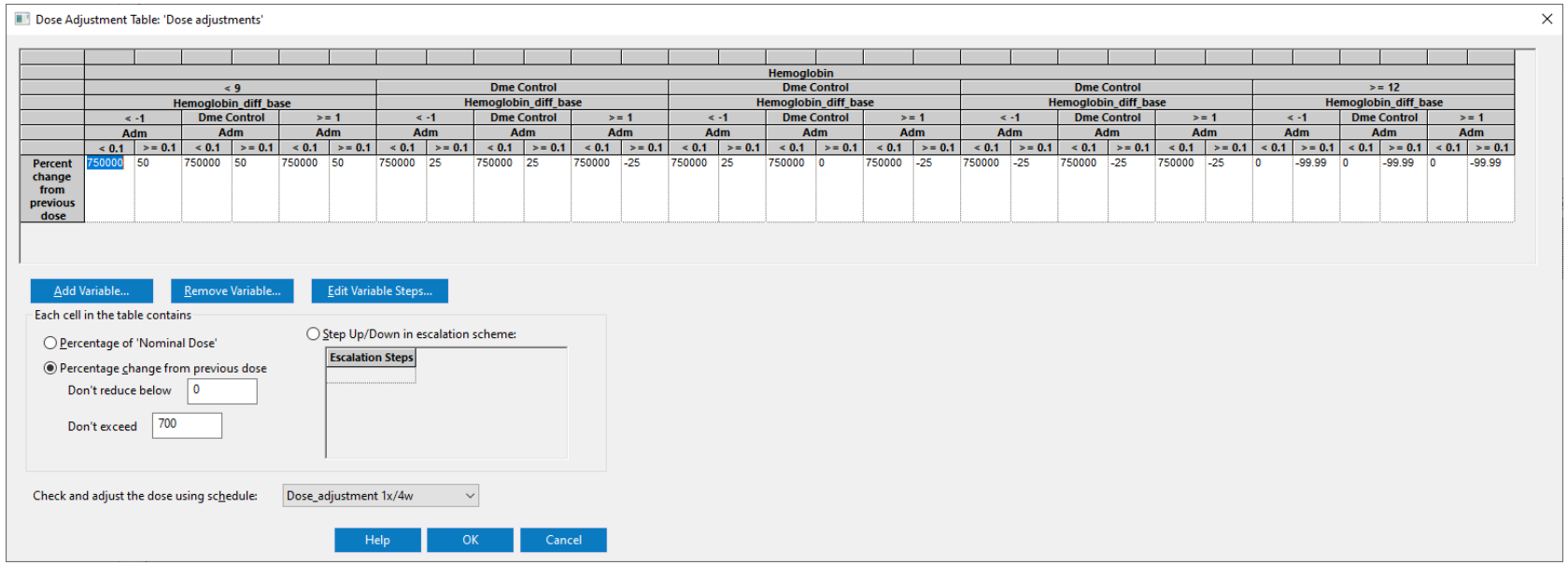
Trial Simulator Based Adaptive dosing Framework



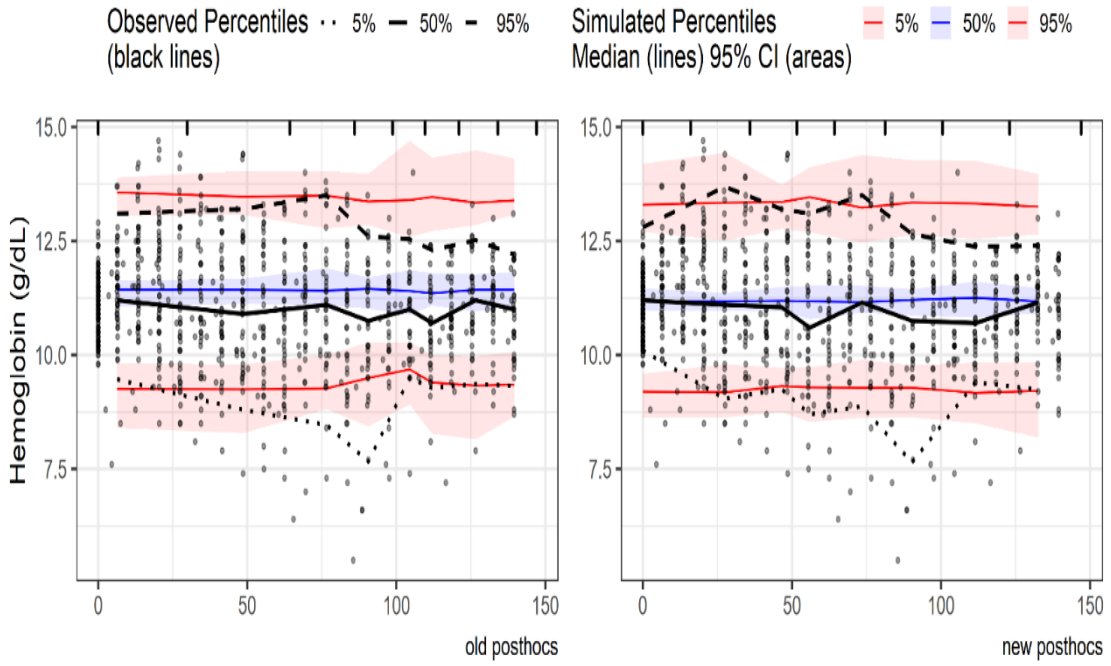


Trial Simulator Based Adaptive dosing Framework

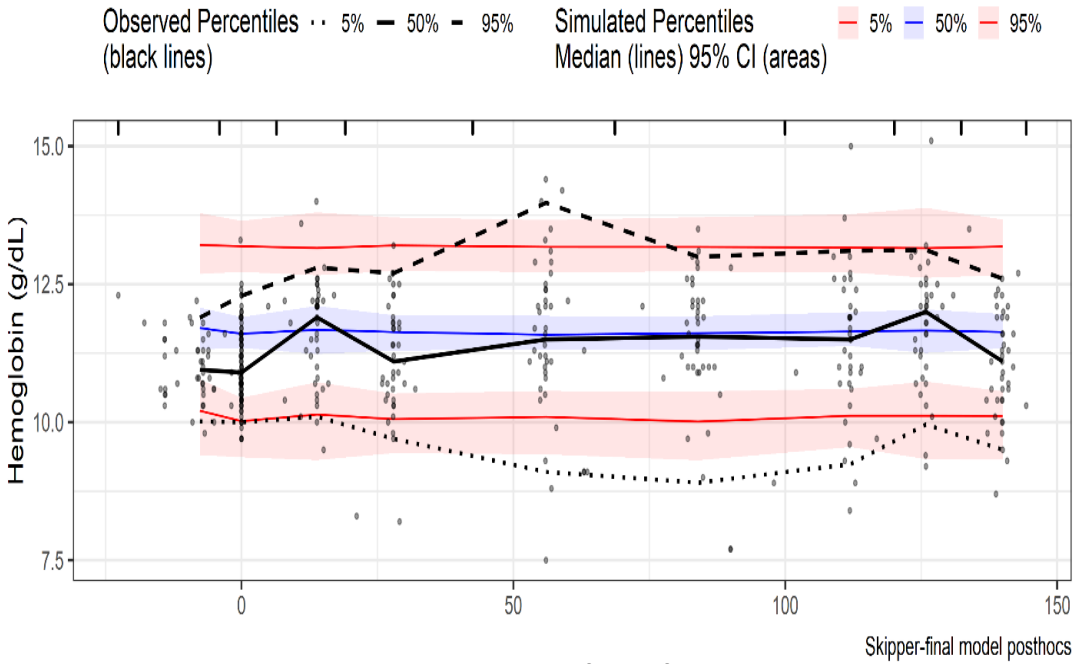




Trial Simulator Based Adaptive dosing VPC



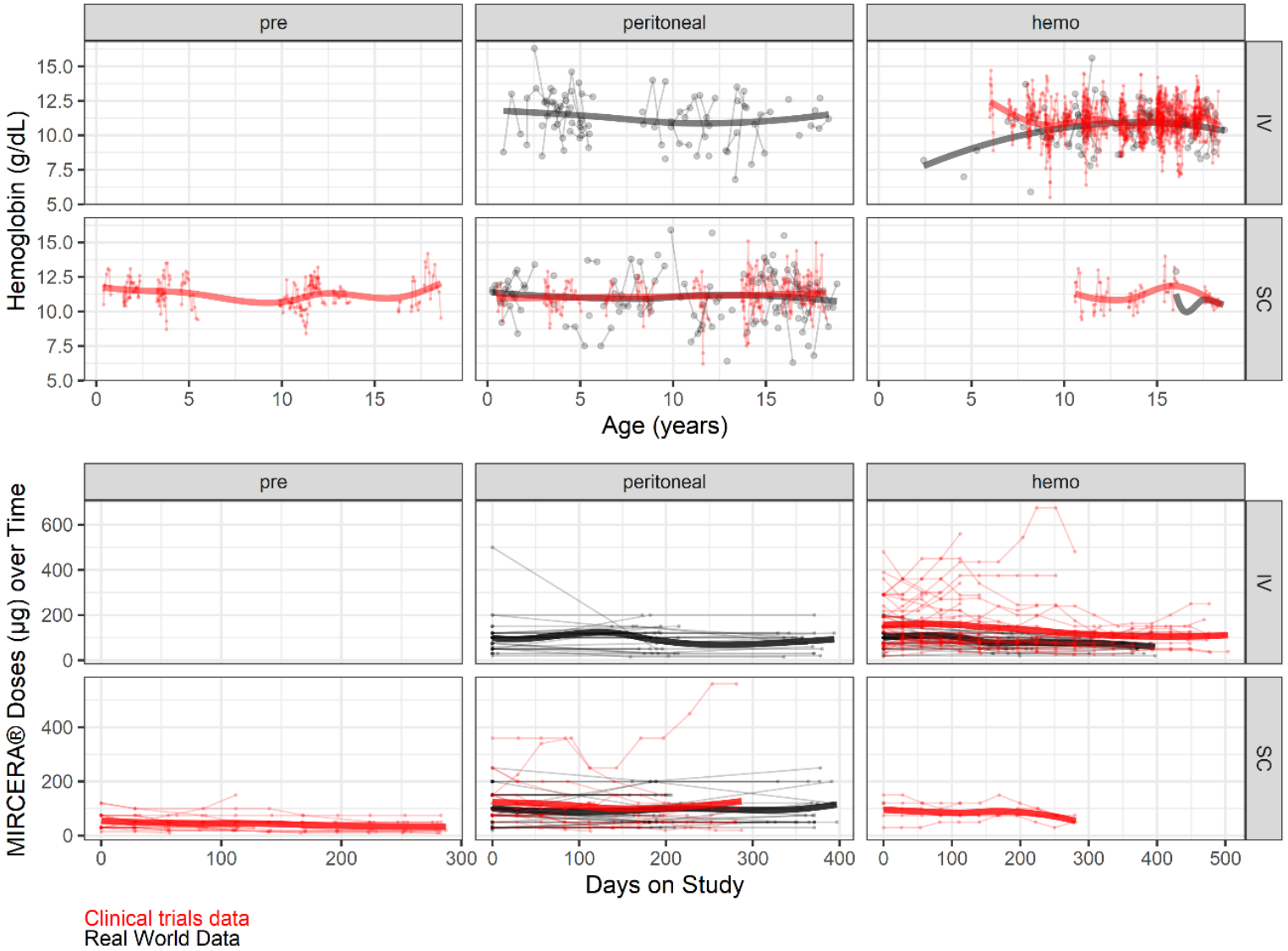
Time (days)



Time (days)

https://www.ema.europa.eu/en/documents/variation-report/mircera-h-c-000739-ii-0092-epar-assessment-report-variation_en.pdf

RWD Matches the Clinical Trial Data



https://www.ema.europa.eu/en/documents/variation-report/mircera-h-c-000739-ii-0092-epar-assessment-report-variation_en.pdf

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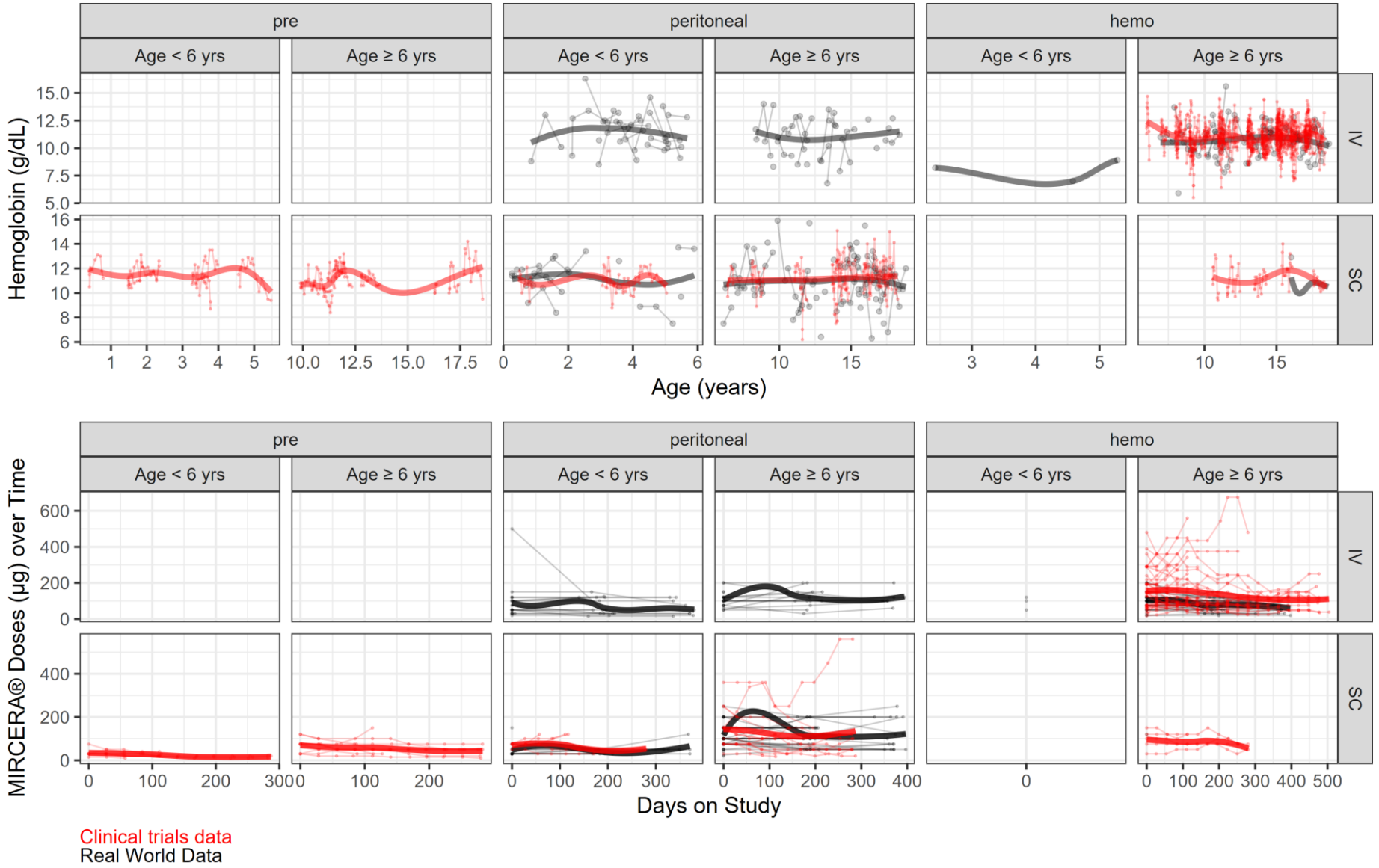
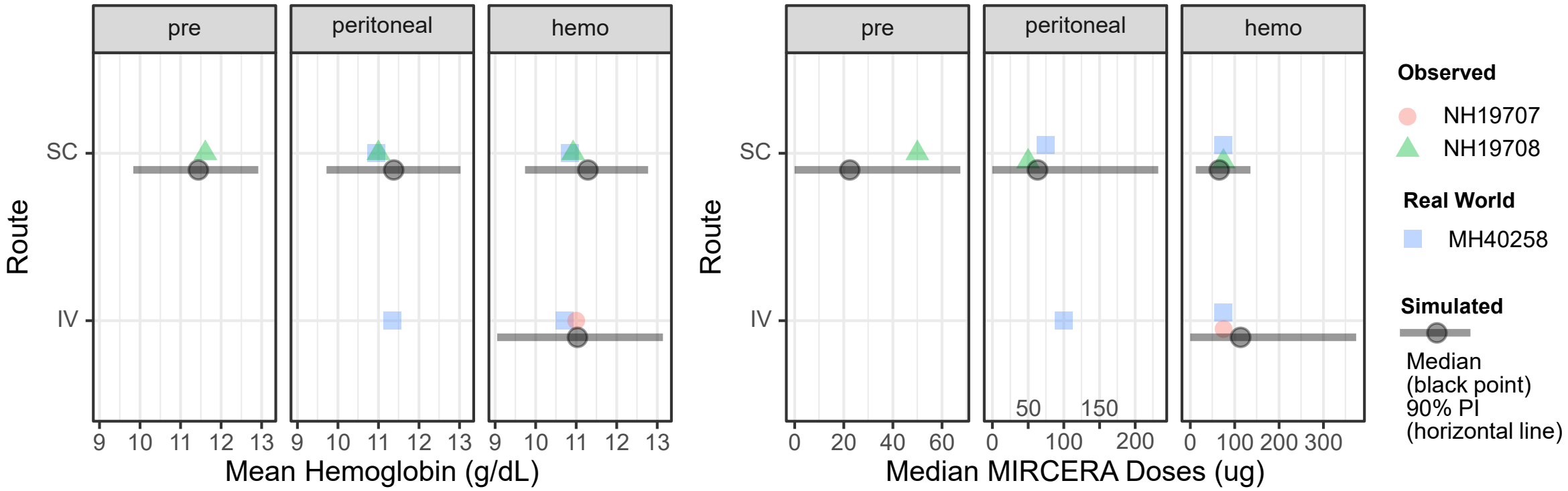


https://www.ema.europa.eu/en/documents/variation-report/mircera-h-c-000739-ii-0092-epar-assessment-report-variation_en.pdf

The modeling and Simulation Framework was successful with external PPC on RWD



https://www.ema.europa.eu/en/documents/variation-report/mircera-h-c-000739-ii-0092-epar-assessment-report-variation_en.pdf

PK/PD Modeling and Simulation Contributions

- Lower Hb0 and shorter LS associated with more advanced disease are consistent with the current understanding of the pathophysiology of anemia due to CKD
- There is no effect of age and or weight on system-related parameters (LS and Hb0) or on drug related parameters (SC50 and Smax)
- The good alignment between clinical trial data and RWD **confirmed** the clinical experience of C.E.R.A. in the Real-World setting and contributed to **the clinical evidence** of the proposed dosing regimen for C.E.R.A. IV and SC in pediatric patients (RWE)
- The model-based approach, integrating clinical trial data and the RWD, contributed to accelerating the EMA approval of C.E.R.A. in the pediatric population

↓ 3 years
↓ 45% budget
↑ Knowledge <2 years old

- **EMA** approved Mircera **IV** and **SC** for **pediatric patients** from **3 months to less than 18 years** of age who are converting from another ESA after stable haemoglobin levels with the previous ESA in **June 2023**.
- **FDA** expanded Mircera approval administered **SC** for the treatment of anemia associated with chronic kidney disease (CKD) in **pediatric patients 3 months to 17 years of age** on dialysis and not on dialysis who are converting from another erythropoiesis-stimulating agent (ESA) after their hemoglobin level was stabilized with an ESA, on **April 30th 2024**.

https://www.ema.europa.eu/en/medicines/human/EPAR/mircera#ema-inpage-item-authorisation-details
https://professionals.optumrx.com/publications/library/clinicalupdate_micera_2024-0503.html

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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  - IPDN: Franz Schaefer, Bradley Warady, Claus Schmitt
- Certara Team: Vincent Duval
- Serge Guzy
- Genentech Clinical Pharmacology management: Amita Joshi, Jin Jin

Extra Slides

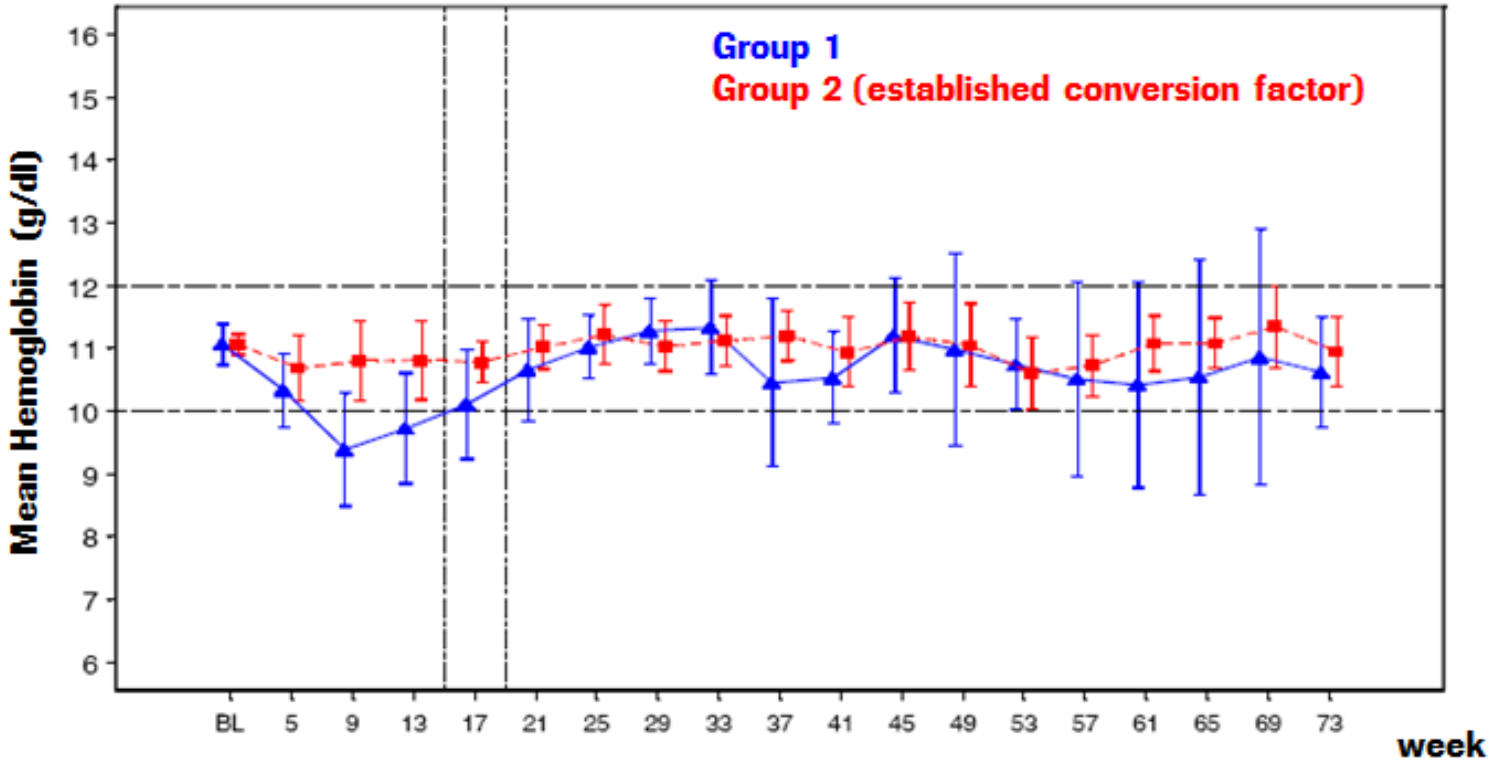
Model-based evaluation

- Scope: Optimize Pediatric Investigation Plan (PIP, EMA) and Pediatric Study Plan (PSP, FDA) by re-designing the confirmatory trial
- Available data for pooled analyses

Study	Phase	Route	Treatment Setting	Population	Number of patients Used in analysis/Total
BA16260	II	SC	Correction	Adult on dialysis	59/61
BA16528	II	SC	Correction	Adult not on dialysis	65/65
AMICUS	III	IV	Correction	Adult on dialysis	135/165
MAXIMA	III	IV	Maintenance	Adult on dialysis	122/223
PROTOS	III	SC	Maintenance	Adult on dialysis	143/190
DOLPHIN	**II**	**IV**	**Maintenance**	**Pediatric on dialysis**	**N=63/64**

  - Pharmacokinetic (PK) analysis
  - Pharmacodynamic (PD) analysis
  - Model-based simulations and comparison to RWD

Conversion factor from a previous ESA to C.E.R.A. established on DOLPHIN data



Blue: Group 1 (n=16): conversion: 4 x previous weekly epoetin dose (IU)/250 or 4 x previous weekly darbepoetin alfa dose (µg)/1.1
Red: Group 2 (n=48): conversion: 4 x previous weekly epoetin dose (IU)/125 or 4 x previous weekly darbepoetin alfa dose (µg)/0.55

Fischbach et al. Clin J Am Soc Nephrol 2018;13:81–90

MIRCERA Conversion→ Starting Dose and Adjustment rules

Previous Weekly Epoetin Alfa or Epoetin Beta Dose [IU/Week]	Previous Weekly Darbepoetin Alfa Dose [µg/Week]	Every 4-week Mircera Dose [µg]
<1300	<6	30
1300–<2000	6–<9	50
2000–<2700	9–<12	75
2700–<3500	12–<15	100
3500–<4200	15–<19	120
4200–<5500	19–<24	150
5500–<7000	24–<31	200
7000–<9500	31–<42	250
≥9500	≥42	360

Hemoglobin Assessment	Compared with the Previous Mircera Dose
Hb decreases by more than 1.0 g/dL compared with baseline Hb.	Increase dose by approximately **25%** (or closest higher PFS strength).
Hb is less than 10 g/dL and greater than or equal to 9 g/dL (Hb < 10.0 and ≥ 9.0 g/dL).	Increase dose by approximately **25%** (or closest higher PFS strength).
Hb is less than 9 g/dL (Hb < 9.0 g/dL).	Increase dose by approximately **50%** (or closest to **50%** increase PFS strength).
Hb increases by more than 1.0 g/dL compared with the baseline Hb.	Decrease dose by approximately **25%** (or closest lower PFS strength).
Hb is increasing and is approaching 12 g/dL or Hb is greater than or equal to 12 g/dL (Hb ≥ 12 g/dL).	Decrease dose by approximately **25%** (or closest lower PFS strength).
If Hb exceeds 12 g/dL and continues to increase following a dose reduction.	Stop doses until Hb is less than 12.0 g/dL. Resume dose at approximately 25% below previous dose (or closest lower PFS strength) at next scheduled dosing day.

Roche data on file, NH19708 Clinical Study Report

Real World Data from IPDN registry

- Real World Data from pediatric patients were obtained from two global registries maintained by the International Pediatric Dialysis Network (IPDN, www.pedpd.org)
- RWD on C.E.R.A. from IPDN (Schaefer et al. J Am Soc Nephrol 2018;29 (Suppl):TH-PO233)

	IPPN (n = 126)	IPHN (n = 32)
Median age, years (range)	12.9 (0.3–26.9)	14.8 (1.5–21.8)
Mean Hb, g/dL (SD)	10.8 (1.7)	10.5 (1.8)
Mean ferritin, µg/L (SD)	264 (289)	499 (339)
Median time on dialysis, years (interquartile range)	1.6 (0.7–3.2)	1.2 (0.4–2.3)
Median monthly C.E.R.A. dose, µg (IQR)	100.0 (60.0–150.0)	80.4 (53.6–107.1)

- Roche was collecting RWD from IPDN in a non-interventional study, MH40258 (**RWD**)

kohlhas, et al. Pediatr Nephrol 39, 807–818 (2024)

Additional safety data from RWD

- Additional safety information from RWD from IPDN registry (Schaefer et al.) was comparable to what has been reported previously (Locatelli et al.), no new safety signals observed
  - 132 hospitalizations reported in IPPN registry receiving SC C.E.R.A., most common reasons were hypertension (19 patients) and peritonitis (19 patients)
  - 41 hospitalizations reported in the IPHN registry receiving IV C.E.R.A., most common reasons were hypertension (7 patients) and pyelonephritis (5 patients)

- Additional safety information from literature: two independent studies did not report any different safety profile in children as seen in DOLPHIN and in adults (Cano et al., Wedekin et al.)

Schaefer et al. J Am Soc Nephrol 2018;29 (Suppl):TH-PO233
Locatelli F, et al. Clin Nephrol 2010;73:94–103.
Cano F, et al. Pediatr Nephrol. 2011;26:1303-1310
Wedekin M, et al. Pediatr Transplant. 2011;15:329-333

Dialysis, Weight, Age and Sex in the included pediatric studies

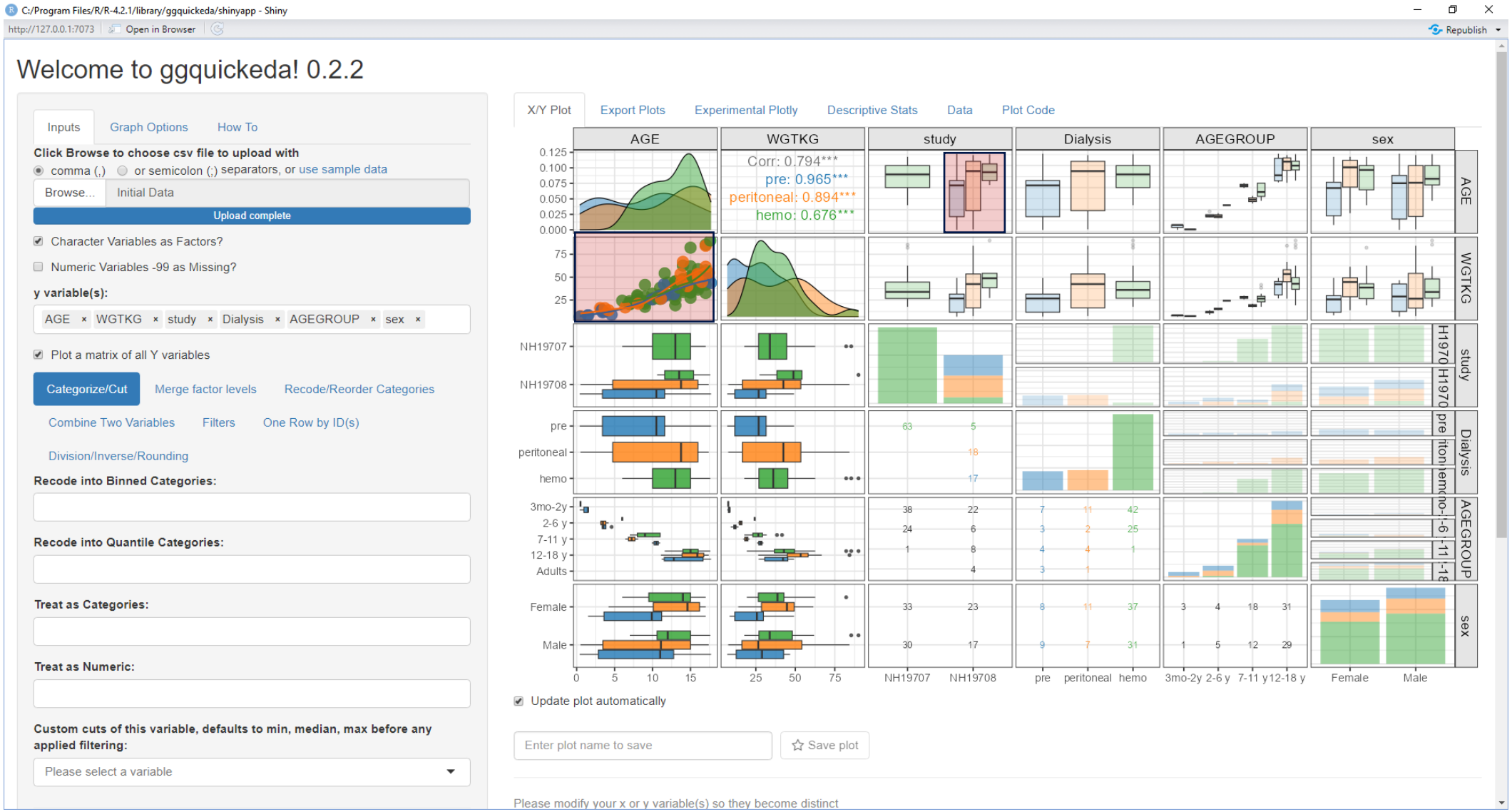


Table 12. Parameter estimates of the final PK/PD model

Parameter	Unit	Estimate	SE	RSE (%)	Variability (%)	Shrinkage (%)
Fixed Effects						
S_{max}		0.425 fixed				
SC_{50}	ng/mL	0.898 fixed				
LS	day	82.33	2.586	3		
Hb_0	g/dL	9.44	0.205	2		
Random Effects (variance)						
S_{max}		1.637	0.130	8	128	20
SC_{50}		4.389	0.343	8	209	24
LS		0.146	0.020	14	38	23
Hb_0		0.041	0.004	10	20	20
Covariate effects					**covariate form**	
ESA dose on SC_{50}		0.295	0.072	24	x(ESA Dose/6000)^ESAdoseeff	
Hemo Dialyis Effect on HB0		0.86	0.018	2	x Effect when Dialysis = peritoneal	
Peritoneal Dialyis Effect on HB0		0.93	0.030	3	x Effect when Dialysis = hemodialysis	
Hemo Dialyis Effect on LS		0.62	0.024	4	x Effect when Dialysis = peritoneal	
Peritoneal Dialyis Effect on LS		0.82	0.061	7	x Effect when Dialysis = hemodialysis	
Residual variability (standard deviation)						
Additive	g/dL	0.76	0.007	1		

SE: standard error; RSE%: relative standard error. nParm = 18, nObs = 2128, nSub = 103, -2LL = 5593.817 (QRPEM)
EpsShrinkage = 0.01843, Condition number = 298.0486
Source: Phoenix model peds_estim_hb0_LS_dialysishb0_LS

Population PK/PD model Enables Dynamic Predictions