CLINICAL PHARMACOLOGY REVIEW

NDA Number	203565
Submission Date	01/29/2021
Submission Type	Efficacy Supplement (Supplement number: 016)
Generic name	Ferric Carboxymaltose
Brand name	Injectafer
Applicant	AMERICAN REGENT INC
Dosage form	Injection (500 mg/10 mL, 750 mg/15 mL)
Mechanism of action	Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that releases iron.
Proposed Indications	Injectafer is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients and in pediatric patients ages 1 to 17 years: • who have intolerance to oral iron or have had unsatisfactory response to oral iron, or (b) (4)
Proposed Dosing Regimen	For patients weighing 50 kg or more, the recommended dosage is 750 mg intravenously in two doses separated by at least 7 days for a total cumulative dose of 1,500 mg of iron per course. For patients weighing less than 50 kg, the recommended dosage is 15 mg/kg body weight intravenously in two doses separated by at least 7 days per course.
OCP Division	Division of Cardiometabolic and Endocrine Pharmacology (DCEP)
OND Division	Division of Non-Malignant Hematology (DNH)
Primary Reviewer	Anusha Ande, PhD; Jiajun Liu, PharmD, MSc
Secondary Reviewer	Sudharshan Hariharan, PhD; Eliford Kitabi, PhD

Contents

1 EXECUTIVE SUMMARY

1.1. Product overview

Injectafer (Ferric Carboxymaltose injection; FCM) is an iron replacement product for intravenous use. It is indicated for the treatment of iron deficiency anemia (IDA) in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron, or who have non-dialysis dependent chronic kidney disease (CKD).

Injectafer was first approved in 2013 for use in adults. For patients weighing ≥50 kg (110 lb) or more, Injectafer should be given in two divided doses of 750 mg each separated by at least 7 days (total cumulative dose not to exceed 1500 mg of iron per course), and for patients weighing <50 kg (110 lb), Injectafer should be given in two doses of 15 mg/kg separated by at least 7 days (total cumulative dose not to exceed 1500 mg of iron per course). The clinical pharmacology review of Injectafer for the original NDA submission supported efficacy, safety and the dosing of Injectafer. Later an alternative dose of 1000 mg single dose was approved for patients weighing 50 kg or more in a supplemental NDA submission.

In the current supplemental NDA submission, the applicant is seeking for a pediatric indication in patients aged 1 to 17 years who have intolerance to oral iron or have had unsatisfactory response to oral iron (b) (4) The applicant submitted two clinical study reports 1VIT17044 (Phase 3 active-controlled study to investigate the efficacy and safety of IV FCM in pediatric patients with IDA) and 1VIT18045 (extension study to 1VIT17044) to support the pediatric indication and to satisfy PMR 2064-2.

1.2. Recommendations

The Office of Clinical Pharmacology reviewed the results from the two study reports 1VIT17044, 1VIT18045, along with the results from the study 1VIT13036 (Single arm study to characterize the PK and PD profile of IV FCM in pediatric subjects 1 – 17 years old with IDA), population PK/PD modelling of IV FCM in pediatric subjects with IDA and conducted independent analysis to compare the PK and PD of pediatric subjects with that of adults. Our review and independent analyses suggest that there is similarity in pharmacodynamic response (Hgb) between pediatric patients and adults which further supports the action taken by the Division of Non-malignant Hematology to grant a pediatric indication for the treatment of IDA in patients who have intolerance or had unsatisfactory response to oral iron.

2 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

For details of clinical pharmacology information refer to reviews by Christy John, 05/30/2007 (NDA#22054), Bahru Habtemariam, 06/21/2012 (NDA#203565), and Eliford Kitabi, 04/23/2021 (NDA#203565, Efficacy supplement-14).

3 Population PK analysis

3.1. Review Summary

The Applicant's final population pharmacokinetic (PopPK) model and pharmacokinetic-pharmacodynamic (PK/PD) model are overall adequate in describing the total serum iron (TSI) PK data and linking PK data to hemoglobin (Hgb) PD outcome as a function of Ferric Carboxymaltose injection (FCM, INJECTAFER®) in pediatric patients with iron deficiency anemia (IDA) who have intolerance or had unsatisfactory response to oral iron therapy; however, several challenges presented within the Applicant's analyses, comparability of PK profiles between pediatric data and previously studied adult data. Herein, the reviewer will address the challenges presented along with FDA's independent analyses. Additionally, alternative approaches were undertaken to compare the PD response in pediatric patients and historic adult data to address the acceptability of this supplement submission.

3.2. Introduction

While oral iron is a frontline option for repleting iron (and subsequently improving Hgb levels) in IDA, intolerance to oral iron therapy or unsatisfactory responses in Hgb responses remain challenging aspects of clinical care. In this supplemental submission for intravenous FCM, the Applicant performed PopPK analyses in support of the pediatric indication and dosage via the following objectives:

- To characterize the PopPK profiles of TSI as a function of FCM dosages
- To link PK model to PD outcome (Hgb changes from baseline)
- To identify clinical covariates that impact PK/PD variability

3.3. Model development

Data

The PK and PK/PD analyses were based on pooled pediatric data from 2 studies, 1VIT13036 and 1VIT17044. **Table 1** describes the subjects providing the PK data by dosages and studies, as well as observation counts by studies and BLQ status. The final NONMEM data file for analysis contained 362 PK samples from 70 pediatric subjects. **Table 2** provides patient baseline characteristics and demographics by study and dose.

Study 1VIT13036: A multi-center, open-label, single-arm study to characterize the PK and PD profile following administration of a single IV dose of FCM in pediatric subjects with IDA. Subjects in Cohort 1 were treated with FCM 7.5 mg/kg with a maximum single dose of 750 mg and subjects in Cohort 2 were treated with FCM 15 mg/kg with a maximum single dose of 750 mg. Doses were administered as an undiluted IV push (100 mg/minute) of durations ranging from 1 to 10 minutes.

Total serum iron was sampled at regular intervals for 24 hrs prior to dosing and for up to 72 hrs post-dose (11 samples per subject). Hemoglobin was sampled pre-dose and at regular intervals up to Day 35 post-dose.

Study 1VIT17044: A multi-center, randomized, active-controlled study to investigate the efficacy and safety of IV FCM in pediatric subjects with IDA. Subjects in Group A received an IV dose of FCM 15 mg/kg with a maximum single dose of 750 mg on Days 0 and 7. Subjects assigned to Group B received oral ferrous sulfate and were not included in this analysis.

Total serum iron was sampled on both Day 0 and 7 (referred to as Day 1 and Day 8 in the current analysis), prior to dosing, immediately after dosing and at 1 hr post-dose (6 samples per subject). Hemoglobin was sampled pre-dose and at regular intervals up to Day 35 after the first dose.

Table 1. Summary of PK/PD dataset by Clinical Studies and FCM Doses

Category	Statistic	All Data[1,3]	Study 1VIT13036: 7.5 mg/kg[1]	Study 1VIT13036: 15 mg/kg[2]	Study 1VIT17044: 15 mg/kg[2,3]
Number of Subjects	N	70	14	19	37
Number of doses	n	108	14	19	75
PK Data					
Total number of quantifiable samples	n	396	91	132	173
Total number of BLQ samples	n	78	18	20	40
Predose quantifiable samples:					
Day 1	n	10	2	1	7
Day 8	n	25	-	-	25
Predose BLQ samples:					
Day 1	n	57	11	18	28
Day 8	n	12	-	-	12
PD Data					
Total number of quantifiable samples	n	362	70	95	197

[1] Subject (b) (6) excluded due to anomalously high total serum iron concentrations. Subject (b) (6) excluded due to missing covariate data.
[2] Up to a maximum single dose of 750 mg.
[3] Subjects (b) (6) and (b) (6) excluded due to anomalous total serum iron concentrations.

Source: Applicant's PK/PD Report, Table 4-1, page 31

Table 2. Pediatric Characteristics and Demographics by Studies and Doses

Covariate	Statistic or category	All Data[1,3]	Study 1VIT13036: 7.5 mg/kg[1]	Study 1VIT13036: 15 mg/kg[2]	Study 1VIT17044: 15 mg/kg[2,3,4]
Number of Subjects (%)	.	70	14 (20)	19 (27.1)	37 (52.9)
Actual Individual Dose (mg) [4]	Mean (SD)	531 (246)	262 (164)	512 (251)	642 (184)
	Median (Min-Max)	662 (90.0-750)	268 (90.0-480)	630 (195-750)	750 (140-750)
Age (yrs)	Mean (SD)	11.4 (5.4)	9.39 (6.19)	10.3 (5.77)	12.8 (4.6)
	Median (Min-Max)	14 (1-17.6)	9.8 (1.5-16.9)	12.4 (1.7-17.6)	15 (1-17)
Weight (kg)	Mean (SD)	43.4 (20.4)	34.9 (21.8)	39.2 (22.8)	48.8 (17.2)
	Median (Min-Max)	49.0 (9.30-78.8)	35.5 (12.1-64.0)	42.0 (13.1-74.0)	53.0 (9.30-78.8)
BMI (kg/m^2)	Mean (SD)	19.5 (3.93)	17.9 (3.09)	18.9 (3.94)	20.4 (4.05)
	Median (Min-Max)	19.2 (13.4-31.7)	18.5 (13.4-22.7)	18.5 (13.6-25.9)	19.5 (13.9-31.7)
BSA (m^2)	Mean (SD)	1.30 (0.461)	1.11 (0.528)	1.19 (0.503)	1.42 (0.378)
	Median (Min-Max)	1.50 (0.437-1.92)	1.16 (0.525-1.73)	1.38 (0.542-1.91)	1.56 (0.437-1.92)
Baseline Hemoglobin (g/dL)	Mean (SD)	9.22 (1.09)	9.16 (1.27)	9.54 (0.809)	9.07 (1.14)
	Median (Min-Max)	9.55 (6.00-11.1)	9.70 (6.70-10.8)	9.60 (7.70-10.8)	9.50 (6.00-11.1)
Baseline Transferrin Saturation (%)	Mean (SD)	5.44 (4.54)	6.67 (4.41)	3.44 (1.61)	6.00 (5.30)
	Median (Min-Max)	4.00 (1.80-29.0)	5.75 (1.80-17.5)	3.00 (1.90-7.00)	5.00 (2.00-29.0)
Baseline Ferritin (ng/mL)	Mean (SD)	10.5 (35.9)	9.69 (10.4)	21.0 (69.2)	5.74 (7.32)
	Median (Min-Max)	3.60 (0.750-298)	4.80 (1.70-36.4)	3.85 (0.750-298)	3.10 (1.50-28.9)
Gender N (%)	Female	48 (68.6)	8 (57.1)	9 (47.4)	31 (83.8)
	Male	22 (31.4)	6 (42.9)	10 (52.6)	6 (16.2)
Age Group N (%)	<12 years	24 (34.3)	7 (50)	9 (47.4)	8 (21.6)
	≥12 years	46 (65.7)	7 (50)	10 (52.6)	29 (78.4)
Baseline Hemoglobin Group N (%)	<10g/dL	52 (74.3)	10 (71.4)	11 (57.9)	31 (83.8)
	≥10g/dL	18 (25.7)	4 (28.6)	8 (42.1)	6 (16.2)
Baseline Transferrin Saturation Group N (%)	≤7 (%)	60 (85.7)	9 (64.3)	19 (100)	32 (86.5)
	>7 (%)	10 (14.3)	5 (35.7)	.	5 (13.5)
Country N (%)	Poland	6 (8.6)	.	.	6 (16.2)
	Russia	33 (47.1)	14 (100)	19 (100)	.
	Ukraine	19 (27.1)	.	.	19 (51.4)
	USA	12 (17.1)	.	.	12 (32.4)

BMI = Body Mass Index, BSA = Body Surface Area.
[1] Subject (b) (6) excluded due to anomalously high total serum iron concentrations. Subject (b) (6) excluded due to missing covariate data.
[2] Up to a maximum single dose of 750 mg.
[3] Subjects (b) (6) and (b) (6) excluded due to anomalously total serum iron concentrations.
[4] For Study 1VIT17044, two doses were administered, and the values for each individual dose are presented.

Source: Applicant's PK/PD Report, Table 4-2, page 32

Base model for TSI PopPK

The base PopPK model to describe TSI was previously developed for 1VIT13036 pediatric subjects. This one-compartment model parameterizing BSA-scaled CL and V (combining additive and proportional error models) served as the base model for the combined dataset in this submission. Inter-individual variabilities (IIV) were estimated for all PK parameters in the base model.

Base model for PK/PD

An indirect-response PK/PD model was previously developed for 1VIT13036 to link PK and Hgb concentration as the PD in pediatric subjects with IDA. As shown in **Figure 1**, a linear model describing TSI (not shown) with first order-elimination provides its "effect" (dashed line) on the progenitor compartment (CPT1), where Hgb production takes place (carrying red blood cells). The maturation of progenitor cells is described by first-order mass transits in four delayed compartments.

In the PK/PD model, Rin is the Hgb production rate determined by k_{out} (first-order rate constant for Hgb turnover) and Hgb_0 (baseline Hgb). Delayed Hgb response is described by:

$$\frac{dA1}{dt} = Rin * effect - (k_{pt} * A1),$$

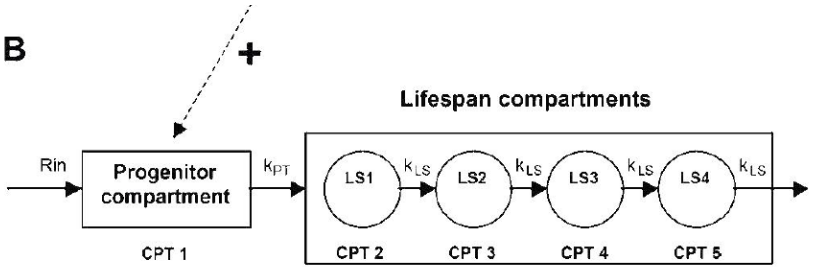
where A1 is the amount of Hgb in CPT1, *effect* is the TSI effect on Hgb production, and k_{pt} is the first-order rate constant of Hgb from CPT1 into the delayed compartments. Further, *effect* is described linearly by:

$$[1 + (SLPE * C_{TSI})]$$

$$C_{TSI} = Exogenous\ TSI + Endogenous/baseline\ TSI$$

where SLPE is the slope and C_{TSI} represents the TSI concentration, consisting of exogenous and endogenous (baseline) iron in the subjects.

Figure 1. Schematic of PK/PD Model



Rate constants, k_{PT} and k_{LS}, were assumed equal

Source: Applicant's PK/PD Report, Figure 3-1, Part B, page 21

Covariate analysis

For both PK and PK/PD models, **Table 3** lists covariates that were available for covariate model evaluation. Baseline values were obtained from first day of FCM dosage or, if not available, at screening. Covariate inclusion in the model and backwards deletion from full model were performed. Physiological relevance and prior modeling information (from Study 1VIT13036) were considered during covariate modeling.

Table 3. Evaluable Covariates for Pediatric Subjects

Continuous Covariates	**Categorical Covariates**
Age (years)	Gender
Body weight (kg)	Country
BMI (kg/m^2)	Age Category (<12 and >=12 years)
BSA (m^2)	Baseline ferritin (<=8 and >8 ng/mL)
Hgb at baseline (g/dL)	Baseline TSAT (<=7% and >7%)
Ferritin (ng/mL)	Hgb baseline (<10 and >=10 g/dL)
TSAT (%)	-
Reticulocyte count (%)	-

TSAT, transferrin saturation

Adapted from Applicant's PK/PD Report, section 3.7.5

3.4. Final Model

TSI PopPK Model

The final PopPK model included BSA (centered to 1.1 m^2) exponents on CL and V and actual dose (centered to 500 mg) exponent on CL. A separate proportional error model term was added for USA subjects for model fit improvement. The parameter estimates for the final covariate model are listed in **Table 4**. **Table 5** lists the backward deletion of covariates (dose and BSA) from the final model.

The goodness-of-fit plots for the final covariate model for all data are shown in **Figure 2** and **Figure 3**. The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in **Figure 4**. VPC plots stratified by nominal dose is shown in **Figure 5**. Random effects (ETA) vs covariates plots are shown in **Figure 6**.

Table 4. Parameter Estimates for TSI Final PopPK Model

Parameter	NONMEM Estimates			
[Units]	Point Estimate	%RSE	95% CI	
CL [L/hr]	0.105	1.65	0.0976 to 0.113	
V [L]	1.47	5.13	1.42 to 1.53	
BSA on CL[1]	1.30	8.00	1.10 to 1.50	
BSA on V[1]	1.36	3.35	1.27 to 1.45	
Actual dose (mg) on CL[1]	-0.271	22.8	-0.392 to -0.150	
Inter-individual variability[2]				**CV%**
ω^2_{CL}	0.0264	24.2	0.0139 to 0.0389	16.2
ω^2_{V}	0.0190	22.7	0.0105 to 0.0275	13.8
Residual variability				**SD*/CV%**
σ^2_{add}	1.22	26.1	0.597 to 1.84	1.10*
σ^2_{prop} Other Countries	0.00926	32.3	0.00340 to 0.0151	9.62
σ^2_{prop} USA	0.247	30.4	0.0996 to 0.394	49.7

[1] Scalars as power effects on CL and V

[2] Only diagonal elements of full covariance matrix presented.

Abbreviations: %RSE: percent relative standard error of the estimate = SE/parameter estimate * 100 (note calculated following exponentiation of the log-transformed parameter estimates), 95% CI= 95% confidence interval on the parameter, CL = clearance, V = volume of distribution, ω^2= variance of random effect, CV = coefficient of variation, CV of proportional error =$[\sigma^2 prop]^{0.5}$*100, σ^2prop = proportional component of the residual error model, σ^2add = additive component of the residual error model.

Source: Applicant's PK/PD Report, Table 4-4, page 41

Reviewer's comments: the reviewer reproduced and verified the results of the TSI PopPK model using SAEM algorithm and MU referencing in NONMEM. The PK parameters and IIVs were estimated with precision (under 24.2% RSE) while those were moderate for error model (26.1-32.3% RSE). Shrinkages for random effects of CL and V were modest at 18% and 14%, respectively (not shown in Applicant's referenced table).

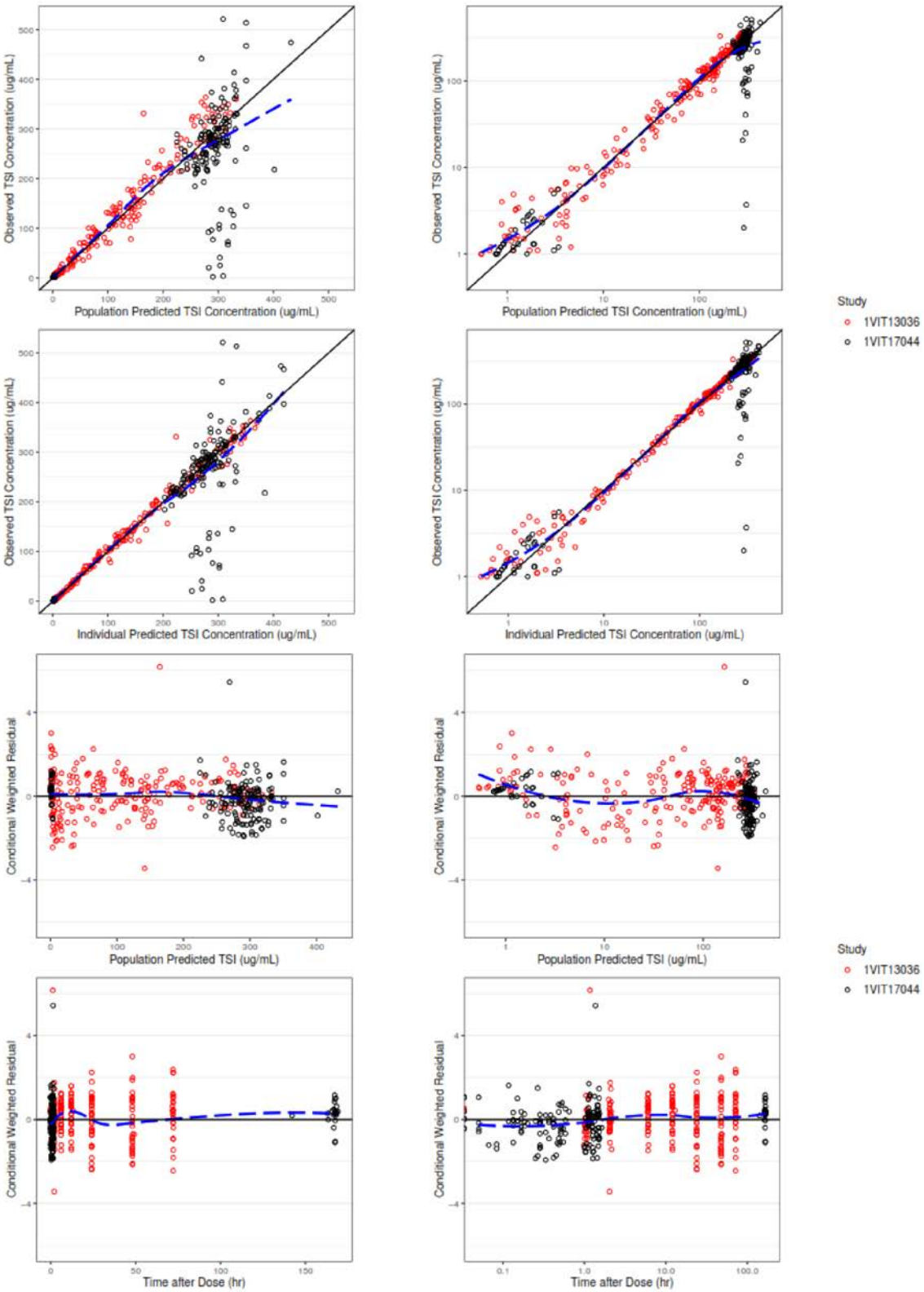
Table 5. Backwards Elimination of Covariates for TSI Final PopPK Model

Run	Covariate tested	OFV	ΔOFV	Comment
TSI3038	Full Model	2507.992	-	-
TSI3038back1	TSI3038 – Actual Dose on CL removed	2522.731	14.740	Significant covariate effect
TSI3038back2	TSI3038 – BSA scaling on CL removed	2570.099	62.108	Significant covariate effect
TSI3038back3	TSI3038 – BSA scaling on V removed	2662.497	154.506	Significant covariate effect

OBV: Objective Function Value, BSA: Body Surface Area, CL: Clearance, V: Volume of distribution.

Source: Applicant's PK/PD Report, Table 4-3, page 40

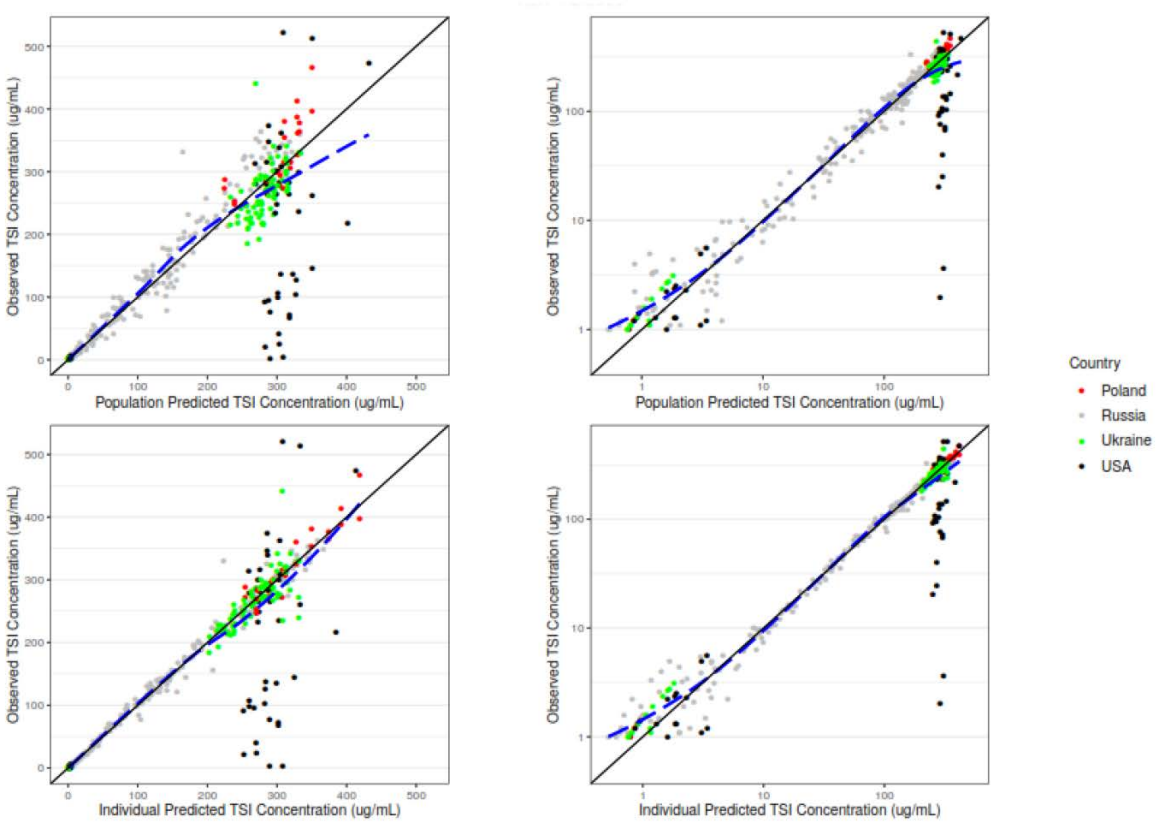
Figure 2. Goodness-of-fit Plots for TSI Final PopPK Model



The blue dashed lines represent the local regression (Loess) smoothing line.

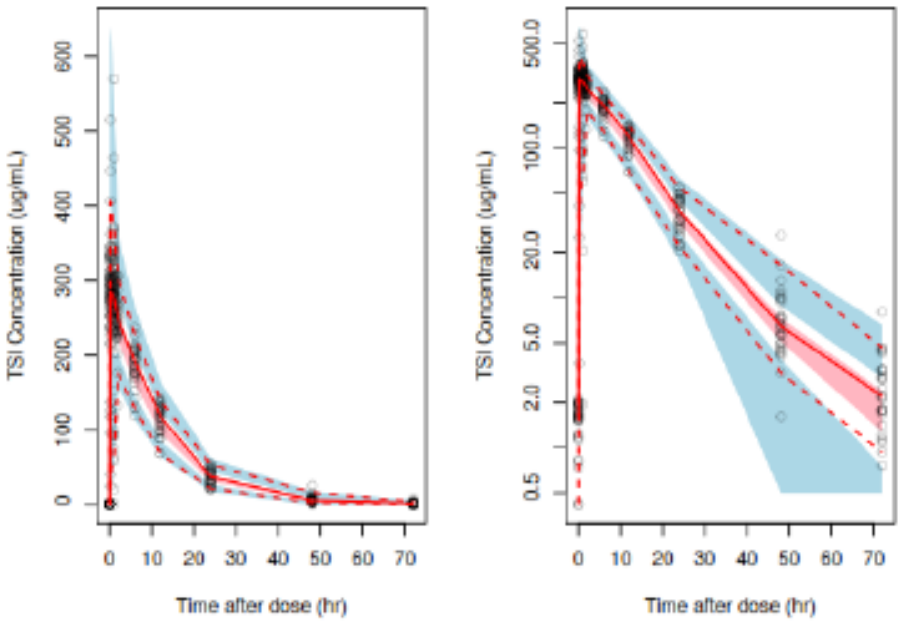
Source: Applicant's PK/PD Report, Figure 4-8, page 43

Figure 3. Goodness-of-fit Plots for TSI Final PopPK Model by Country



Source: Applicant's PK/PD Report, Figure 8-8, page 79

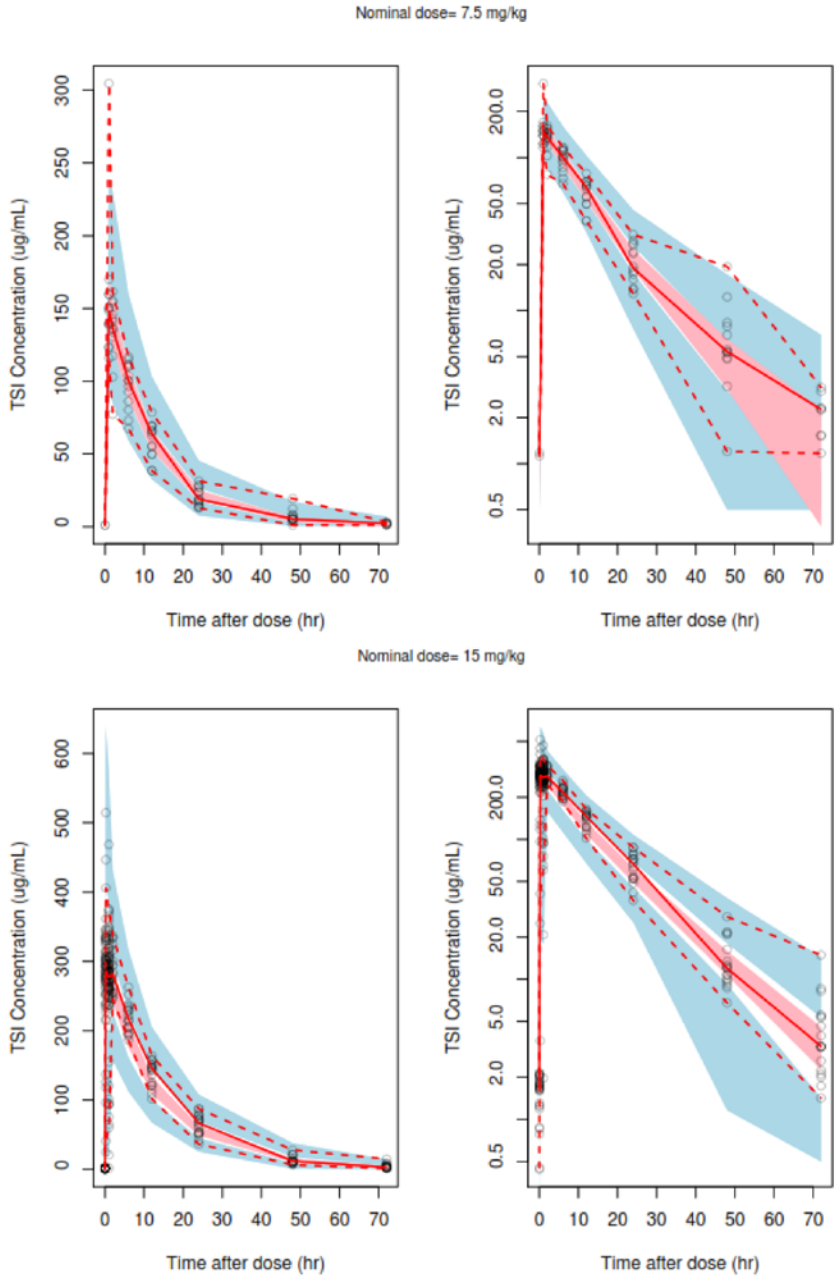
Figure 4. Visual Predictive Checks for TSI Final PopPK Model (Overall)



Solid Red Line: Median of Observed data; Dashed Red Lines: 5th and 95th percentile of observed data. Red Shaded Region: 90% Prediction Interval for Median of Predicted data. Blue Shaded Regions: 90% Prediction Intervals for the 5th and 95th percentiles of Predicted data.

Source: Applicant's PK/PD Report, Figure 4-9 Part 1, page 44

Figure 5. Visual Predictive Checks for TSI Final PopPK Model Stratified by Nominal Dose

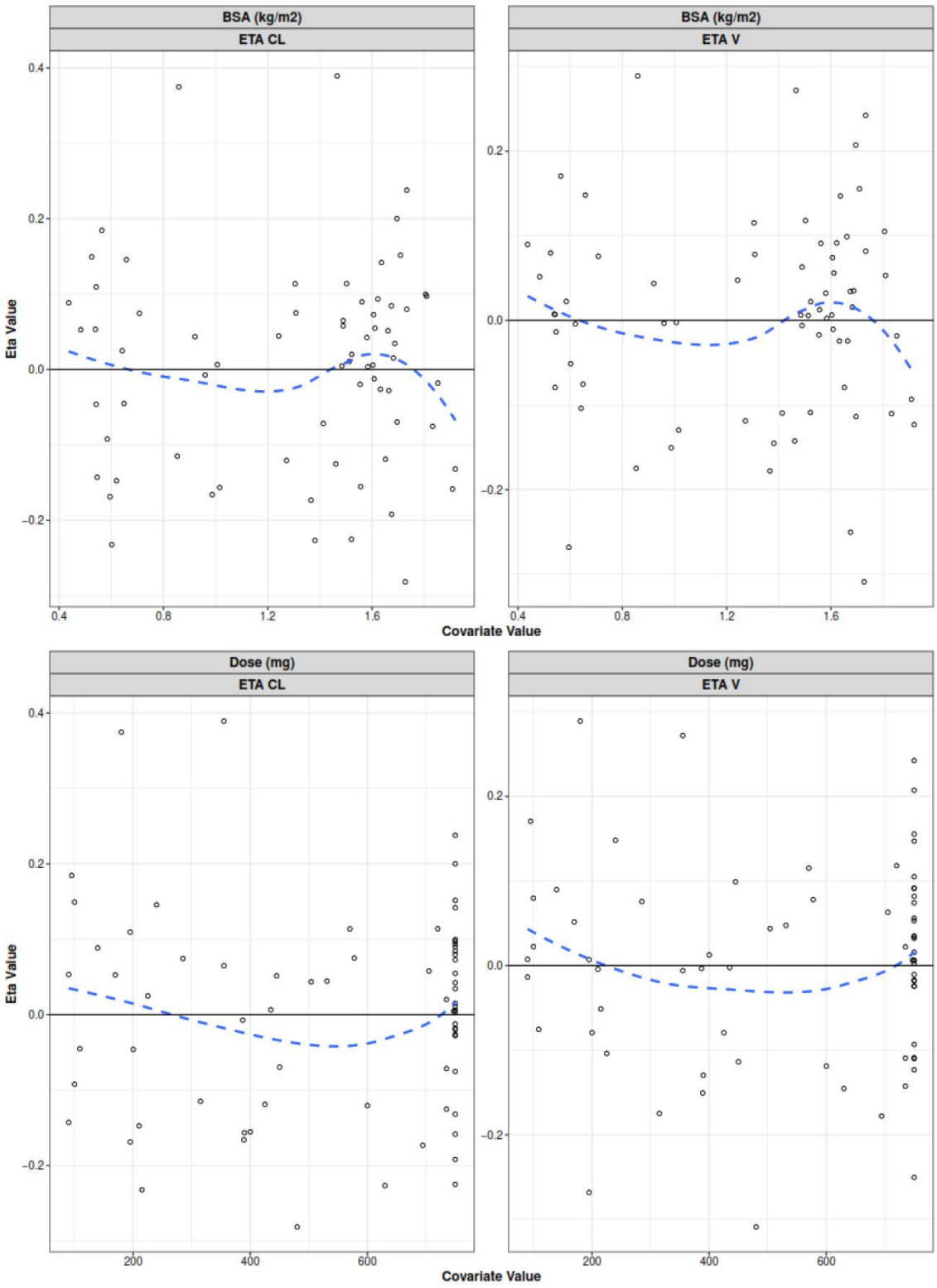


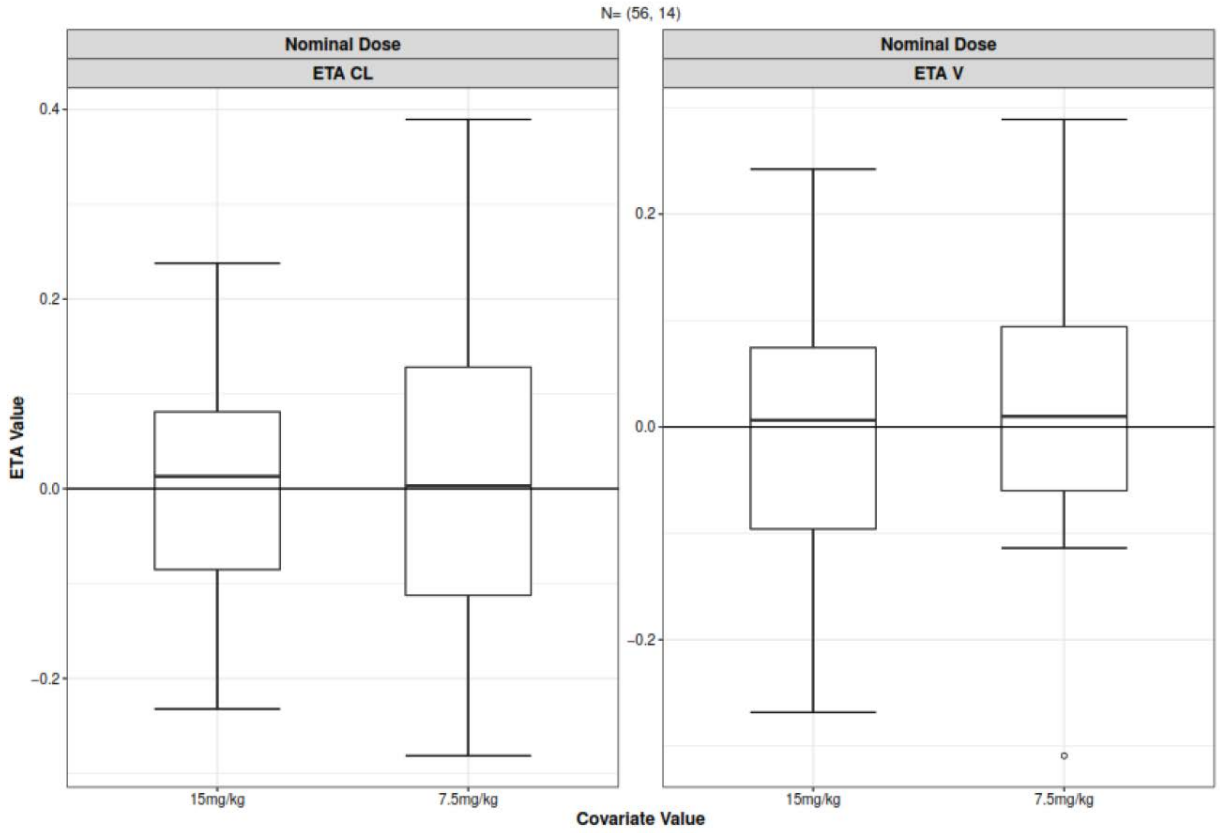
Solid Red Line: Median of Observed data; Dashed Red Lines: 5th and 95th percentile of observed data. Red Shaded Region: 90% Prediction Interval for Median of Predicted data. Blue Shaded Regions: 90% Prediction Intervals for the 5th and 95th percentiles of Predicted data.

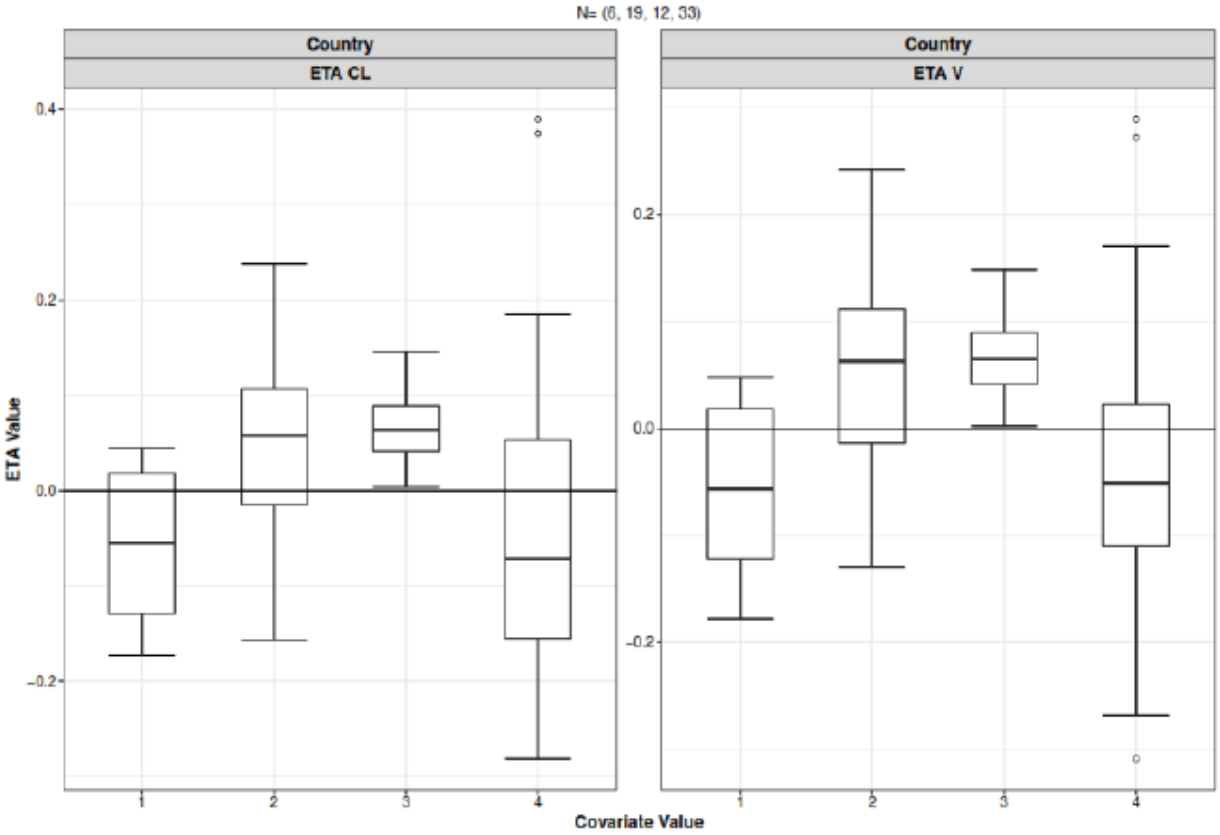
Source: Applicant's PK/PD Report, Figure 4-9 Part 2, page 45

Reviewer's comments: Figures 2 and 3 showed that the final PopPK model adequately described the data with no obvious bias, yet a cluster of observations were under-predicted from study 1VIT17044. Notably, there under-predictions represented observations from the USA subjects. The overall VPC and VPC plots stratified by nominal dose did not reveal model misspecification.

Figure 6. Select ETA vs. Covariates in TSI Final PopPK Model

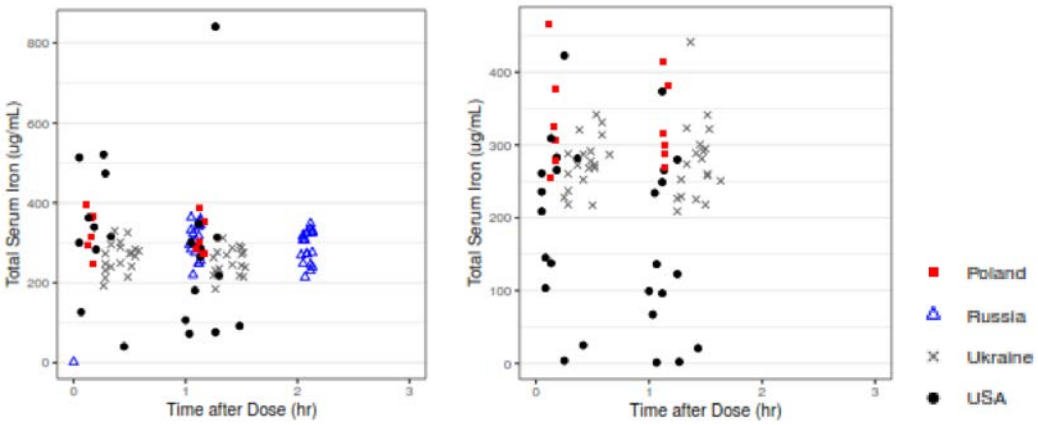






Source: Applicant's PK/PD Report, Figure 8-11, page 82-85

Figure 7. Observed TSI Concentration-Time Profiles by Country at 15 mg/kg



Source: Applicant's PK/PD Report, Figure 4-4, page 35-36

Reviewer's comments: Figure 6 demonstrated that ETAs were mostly randomly scattered along y=0 without obvious trends; however, consistent with the observed vs. predicted plots that USA subjects had highly variable observed TSI concentrations, the ETAs of CL and V for USA as a categorical variable

trended away from =0 with 95% CI not containing zero. The variability of observed TSI data among the USA subjects is also shown in Figure 7. Overall, the diagnostic plots demonstrated that the TSI PopPK model performed adequately in describing the TSI concentration data in pediatric subjects with IDA and in deriving PK parameters relating to FCM disposition.

PK/PD Model

In the final PK/PD model, rate constant k_{LS} were estimated separately for subjects receiving single vs. two-dose regimen. TSAT as a categorical variable of >7% (and at or below 7%) and BSA (centered to 1.1 m^2) were modeled as power effects on k_{LS} (if receiving two doses). Parameter estimates of the final model are listed **Table 6**. **Table 7** lists the backward deletion of relevant covariates from the final PK/PD model. Diagnostic plots are shown in **Figure 8-11**.

Table 6. Parameter Estimates for Final PK/PD Model

Parameter	NONMEM Estimates			
[Units]	Point Estimate	%RSE	95% CI	
BASE [g/dL]	9.07	1.78	8.82-9.34	
SLOPE	0.124	3.04	0.110-0.141	
RBC_{PT} dose 1 [Days] [1]	17.6	0.408	16.8-18.5	
RBC_{PT} dose 2 [Days] [1]	33.5	0.208	32.6-34.4	
RBC_{LS} dose 1 [Days] [1]	70.5	0.408	67.1-74.0	
RBC_{LS} dose 2 [Days] [1]	134	0.208	130-138	
TSAT>7 ~ k_{LS} dose 2	0.436	0.0748	0.435-0.436	
BSA ~ k_{LS} dose 2	0.721	0.0487	0.720-0.722	
Inter-individual variability [2]				**CV%**
ω^2_{BASE}	0.0139	0.00849	0.0139-0.0139	11.8
$\omega^2_{KLS\ dose\ 1}$	0.0344	0.0146	0.0344-0.0344	18.5
$\omega^2_{KLS\ dose\ 2}$	0.0110	0.747	0.0108-0.0112	10.5
ω^2_{Slope}	0.240	0.316	0.239-0.241	49.0
Residual variability				**SD**
σ^2_{prop}	0.0472	8.45	0.0394-0.0550	4.72

[1] Both RBC_{PT} and RBC_{LS} are derived from the rate constants k_{PT} and k_{LS}, respectively, where $k_{PT} = k_{LS}$.
[2] Only diagonal elements of full covariance matrix presented.
Abbreviations: dose 1 = single dose, dose 2 = second dose administered 1 week after the first dose. %RSE= percent relative standard error of the estimate = SE/parameter estimate * 100 (note calculated following exponentiation of the log-transformed parameter estimates), 95% CI= 95% confidence interval on the parameter, BASE = estimated hemoglobin baseline, SLOPE = slope of the linear effect model, RBC_{PT} = progenitor transit time. RBC_{LS} = life-span red blood cell maturation time, ω^2= variance of random effect, CV = coefficient of variation, CV of proportional error = [σ^2prop]*100, σ^2prop = proportional component of the residual error model.

Source: Applicant's PK/PD Report, Table 4-6, page 49

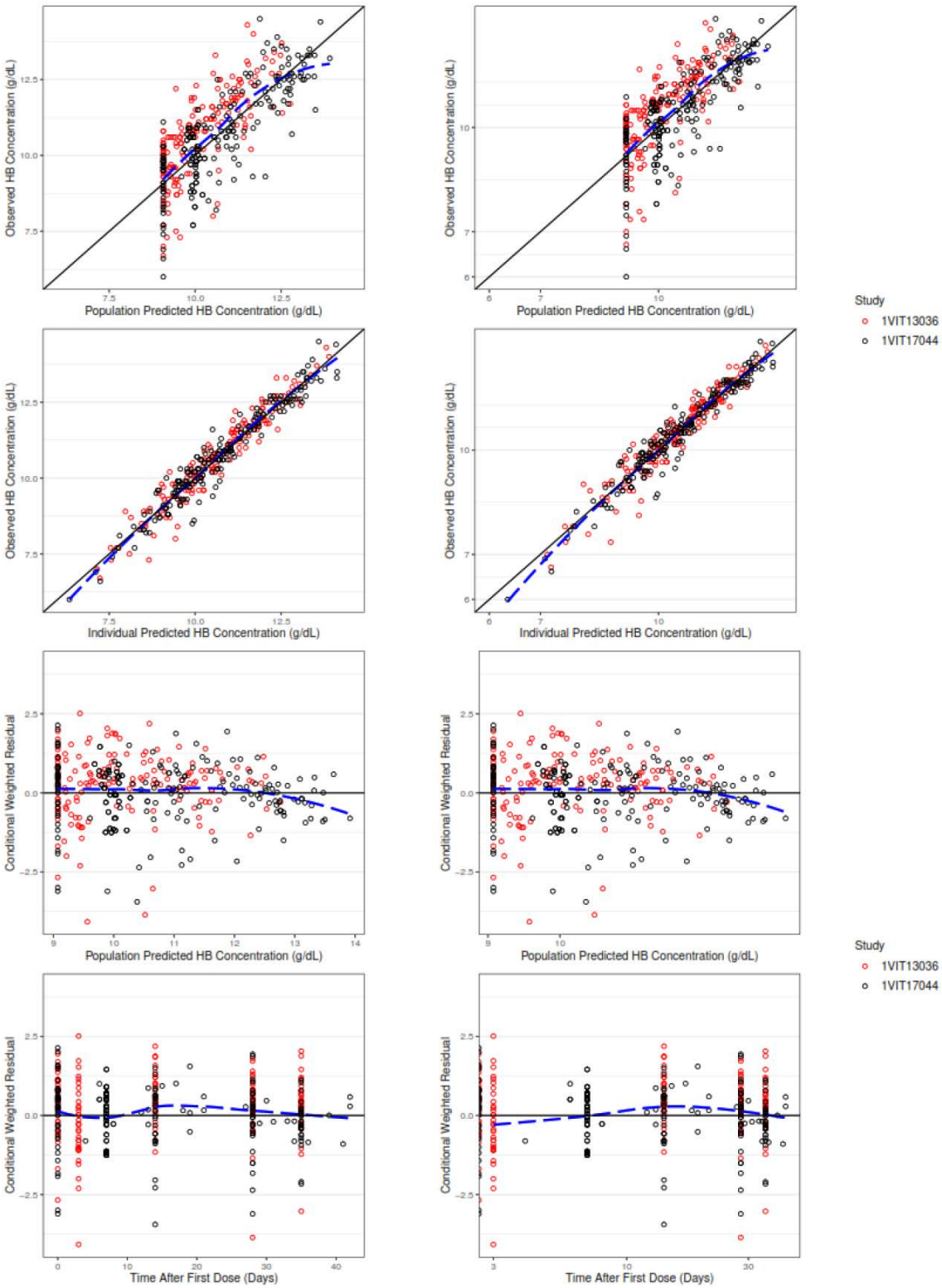
Table 7. Backwards Elimination of Covariates for Final PK/PD Model

Run	Covariate tested	OFV	ΔOFV	Comment
HB2200dc	Full Model	-1597.613	-	-
HB2200dcback1	HB2200dc – TSAT>7 on k_{LS} dose 2 removed	-1582.789	14.824	Significant covariate effect
HB2200dcback2	HB2200dc – BSA on k_{LS} dose 2 removed	-1584.229	13.385	Significant covariate effect

OBV: Objective Function Value, TSAT: Transferrin saturation, BSA: Body Surface Area, k_{LS}: first-order rate constant for transit between the life-span compartments.

Source: Applicant's PK/PD Report, Table 4-5, page 48

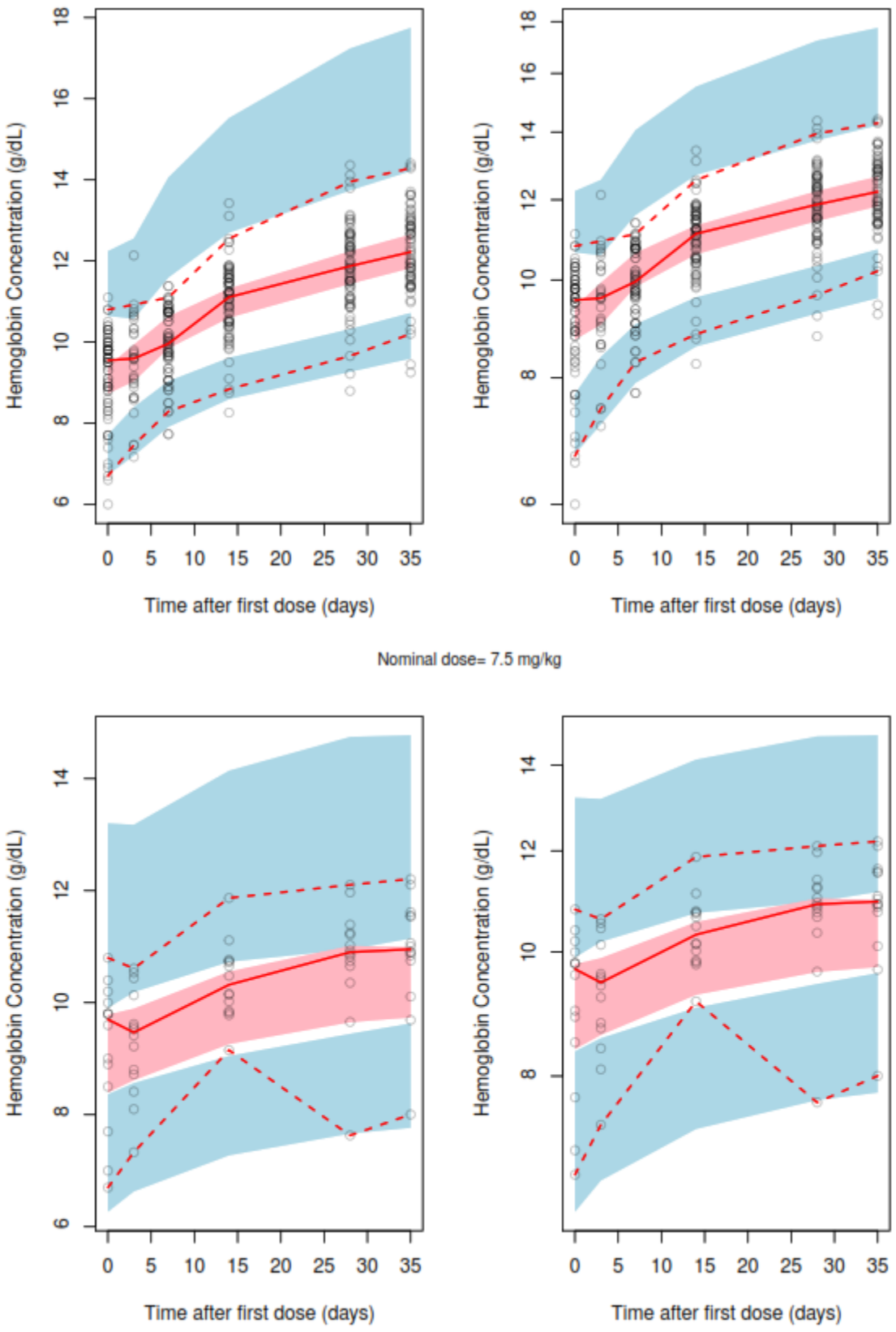
Figure 8. Goodness-of-fit Plots for Final PK/PD Model

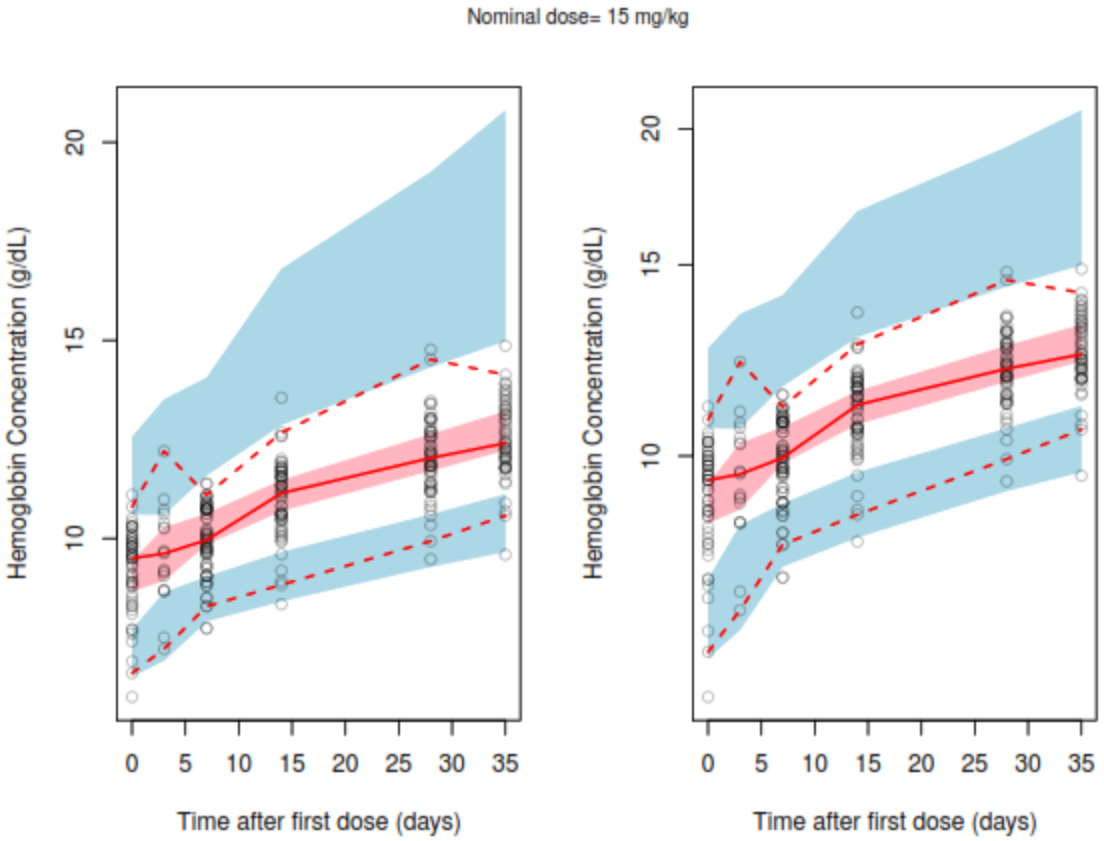


The blue dashed lines represent the local regression (Loess) smoothing line.

Source: Applicant's PK/PD Report, Figure 4-10, page 51

Figure 9. Visual Predictive Checks for Final PK/PD Model

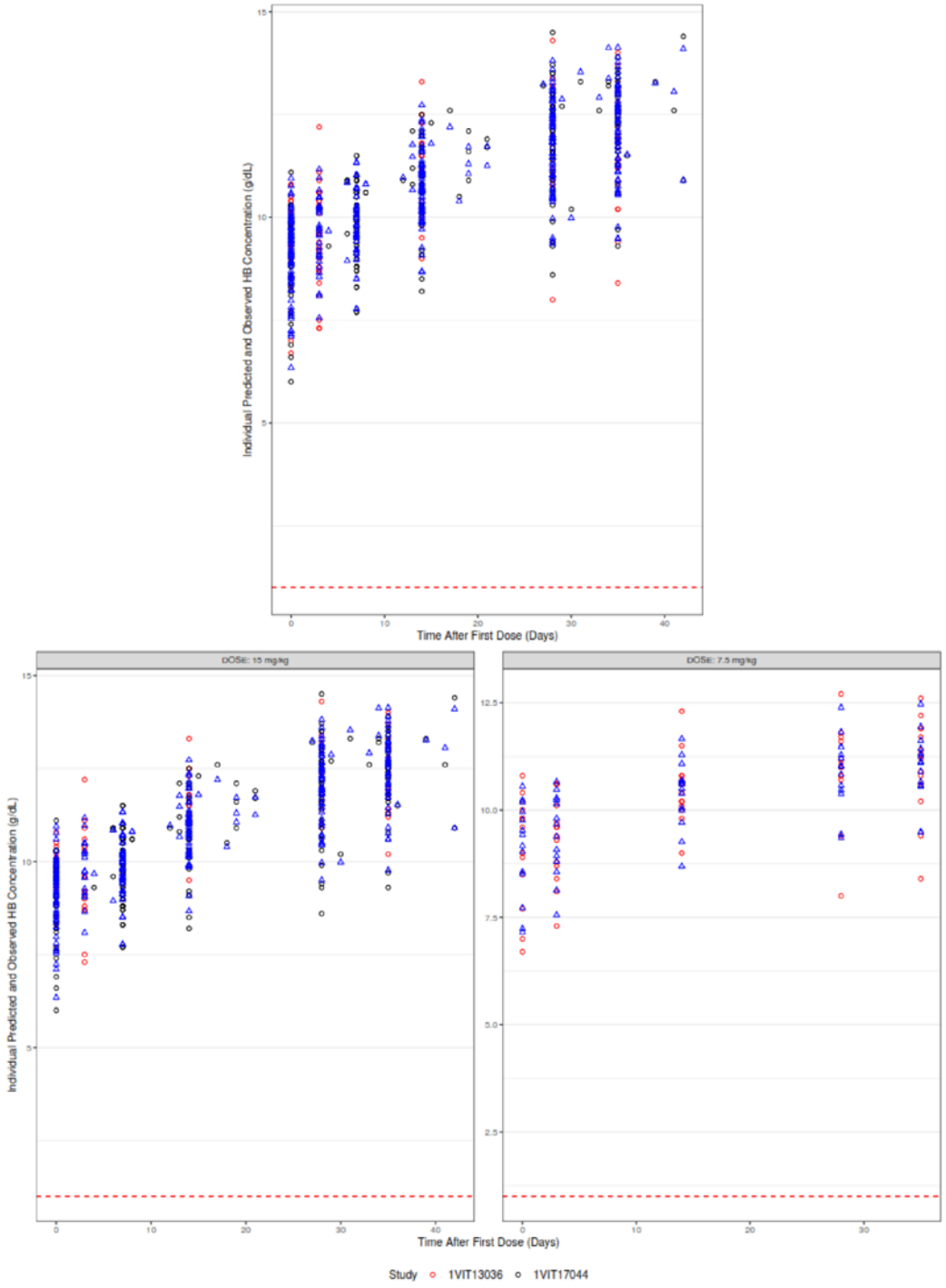




Solid Line: Median of Observed data; Dashed Lines: 5th and 95th percentile of observed data. Red Shaded Region: 90% Prediction Interval for Median of Predicted data; Blue Shaded Regions: 90% Prediction Intervals for the 5th and 95th percentiles of Predicted data

Source: Applicant's PK/PD Report, Figure 4-11, page 52-53

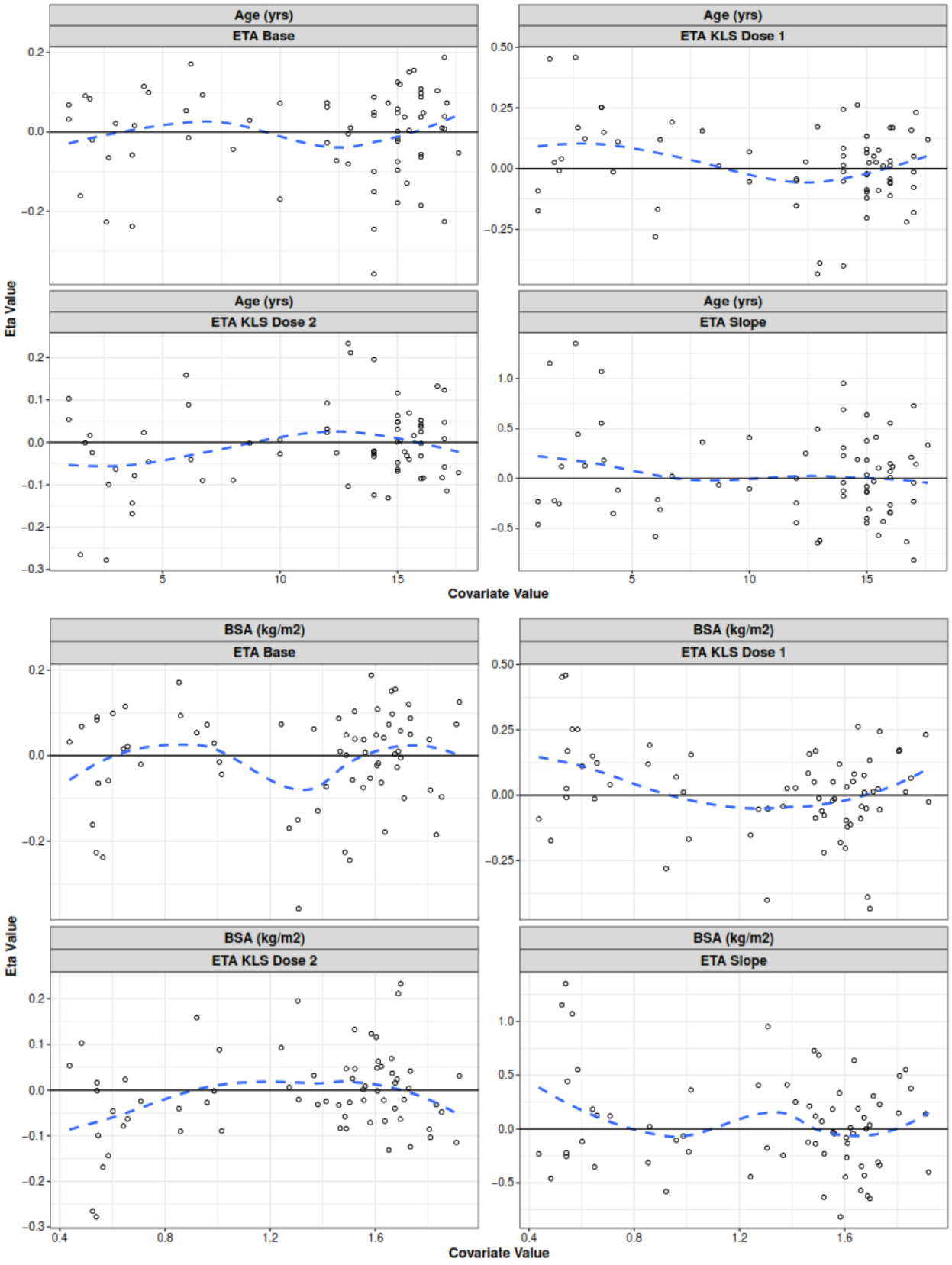
Figure 10. Individual Observed and Predicted Hgb Concentration vs. Time in Final PK/PD Model

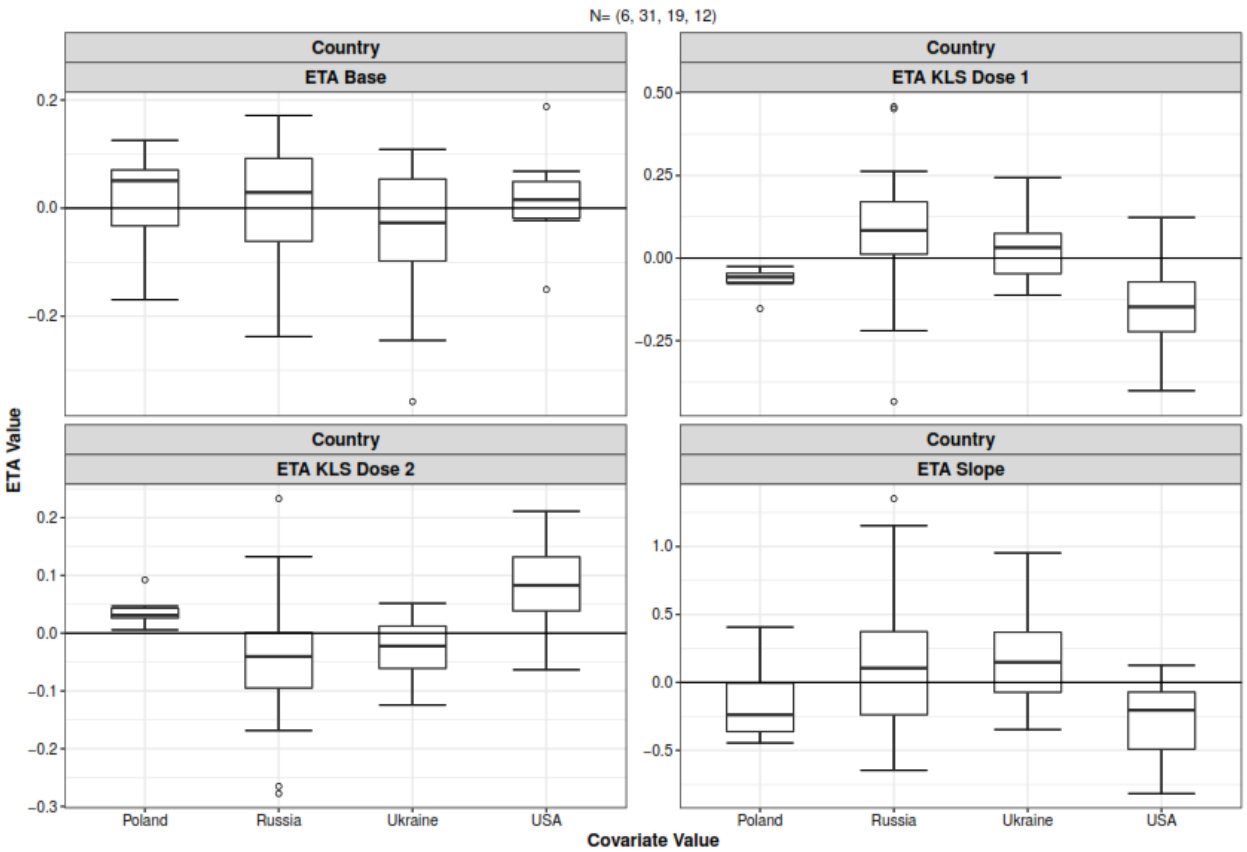


Red circles: Observed concentrations for Study 1VIT13036; Black circles: Observed concentrations for Study 1VIT17044. Blue triangles: Population predicted concentrations.

Source: Applicant's PK/PD Report, Figure 8-20, page 103

Figure 11. Select ETA vs Covariates in Final PK/PD Model





Source: Applicant's PK/PD Report, Figure 8-23, page 107-114

Reviewer's comments: the reviewer was able to conduct the model run with unmodified and modified model files (modified NITER=300 for importance sampling). While the model run results were not exactly reproducible by either approach, the model estimates of parameters, IIVs and residual error models were numerically similar. The final OFVs were almost identical between Applicant's and reviewer's independent results (OFV -1597.613 vs. -1597.322, respectively). The final model demonstrated precision with low RSEs (<8.45% RSE). IIVs were below 50%. No model bias or misspecifications were identified via the diagnostic plots (VPC plots, ETA vs covariate plots, and CWRES vs prediction/time plots) as shown.

Overall, the final PK/PD model is adequate in describing the Hgb data with the following considerations:

- *Baseline TSAT of 7% (<=7% or >7%) as a categorical covariate demonstrated a difference in trend for observed Hgb [Figure 4-13 in the PK/PD report (not shown here)]. As such, this term was included to improve model fitting (also verified by reviewer's independent analysis); however, the physiological and clinical relevance is unclear as this is not a routine benchmark in clinical practice and no relevant literature demonstrated the*

significance of this threshold clinically. Notably, when stratifying by study country, USA subjects exhibited relatively higher TSAT than those from the other countries (median, 6.5% vs. 4.0% for other countries; maximum TSAT, 29% in the USA vs. 6%, 7%, or 17.5% for other countries). Per Information Request dated 14JUL2021 from the FDA, the relevant response from the Applicant was "…choice of TSAT category (≤7% vs >7%) was based on the fact that median TSAT for USA subjects was 6.5%, rather than any clinical relevance." Future investigation may be warranted to study the impact of TSAT on Hgb response, controlling for potential confounders.

- *The reviewer noticed that the predicted Hgb concentrations had a range that was wider than observed data. See Section 1.5 for reviewer's independent analysis.*

3.5. Reviewer's Independent Analysis

3.5.1. Introduction

The reviewer conducted independent analyses to verify the PK/PD model and to support relevant pediatric information in the Injectafer labeling.

3.5.2. Objectives

The objectives of the additional analyses are:

- To compare observed vs. model-predicted baseline Hgb in the final PK/PD model
- To compare pediatric FCM exposure to historic adult exposure
- To utilize alternative approach to compare pediatric data to historic adult data using various PD endpoints

3.5.3. Methods

All data was extracted and manipulated in R 3.6.3 and relevant packages. All plots were generated using *ggplot2* package for R (Wickham H (2016). ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York. ISBN 978-3-319-24277-4, https://ggplot2.tidyverse.org.). Exposure metrics were derived using NONMEM 7.4.3. Databases utilized for reviewer's independent analyses are listed in **Table 8.**

Baseline Hgb in PK/PD model

The observed vs. predicted baseline Hgb with boxplots/dotplots were generated and descriptive statistics were summarized.

FCM $AUC_{0\text{-}72h}$ in pediatric data and historic adult data

NCA-derived PK parameters were extracted for adult subjects from reviewer-identified adult phase 1 and 2 clinical trials (VIT-IRON-2011-003, VIT-IV-CL-02, VIT-IV-CL-03, and Z213-01). Two additional studies were also identified but were excluded due to: 1) no PK data from study and 2) different iron product was used. Extracted subject-level exposure data were joint with another database to match individual doses received.

For pediatric exposure data (N=70), the reviewer reproduced final TSI PK model using revised database generated by NONMEM (version 7.4.3) FINEDATA utility. A finer time grid with 0.25-hour increment from hour zero to last available PK time point for each subject was generated. Individual exposure $AUC_{0\text{-}72h}$, consistent with available exposure metric from available adult data, was derived using trapezoidal rule. Only subjects receiving 15 mg/kg were retained. Visual examination and statistical procedures were performed for exposure comparison.

FCM PD endpoints in pediatric data and historic adult data

In order to compare PD endpoints (ferritin, TSAT, and Hgb response) between pediatrics and adults, efficacy/safety data from a phase 3 study (1VIT09031) were extracted for adults with unsatisfactory response to oral iron and were randomized to receive IV FCM (Cohort 1, Group A) or continued oral iron therap. For the purposes of this independent analysis, only cohort 1-group A subjects were retained.

For pediatric data, Hgb was extracted from the PK/PD database while ferritin and TSAT% were extracted from a separate database (only available for study 1VIT17044). All continuous days were binned to nominal days of 0, 7, 14, 21, 28, 35 and 42 for pediatric and adult databases.

Table 8. Databases for Reviewer's Independent Analyses

Description	Name	Link to EDR
Adult TSI exposure data (VIT-IRON-2011-003, VIT-IV-CL-02, VIT-IV-CL-03, Z213-01)	adpp.xpt*	\\CDSESUB1\evsprod\nda203565\0531\m5\datasets\na\tabulations\send\
Adult TSAT and ferritin data (1VIT09031)	adlbfe.xpt	…\sNDA_203565-S-16_Injectafer\PPK_Analysis\data_adults\09031_study
Output table from NONMEM run for pediatric TSI PK with finer time grid	mytabJLIU	…\sNDA_203565-S-16_Injectafer\PPK_Analysis\NONMEM\runs\7_TSI_metrics\
Pediatric population PK/PD dataset for Hgb data (1VIT13036, 1VIT17044)	hgb.xpt	…\sNDA_203565-S-16_Injectafer\PPK_Analysis\NONMEM\dataset
Pediatric TSAT and ferritin data (1VIT17044)	adlb.xpt	…\sNDA_203565-S-16_Injectafer\PPK_Analysis\data_peds\1vit17044\analysis\datasets

**Subject-level dosages of FCM were extracted from \\CDSESUB1\evsprod\nda203565\0531\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\na\integrated-pk-pd-report.pdf*

3.5.4 Results

Baseline Hgb in PK/PD model

Observed and predicted Hgb at baseline were available for 70 pediatric subjects. The lower and upper bounds of predicted baseline Hgb are numerically different from those observed in pediatric subjects (Table 9, Figure 12). The following points should be considered with the model-predicted baseline Hgb values:

- While it is conventional to incorporate assay noise in the measurement data (i.e., observed Hgb), the clinical relevance should also be taken into account without much compromise in model performance. As per inclusion criteria (Applicant's Clinical Study Report Synopsis for 1VIT17044 version 1.0, Section 2 Synopsis and Applicant's Data Analysis Plan for 1VIT13036 dated 05APRIL2017) of pediatric subjects, Hgb should be

<11 g/dL at screening for enrollment. When comparing the range, the predicted Hgb values has a much higher upper bound that would warrant clinical intervention.

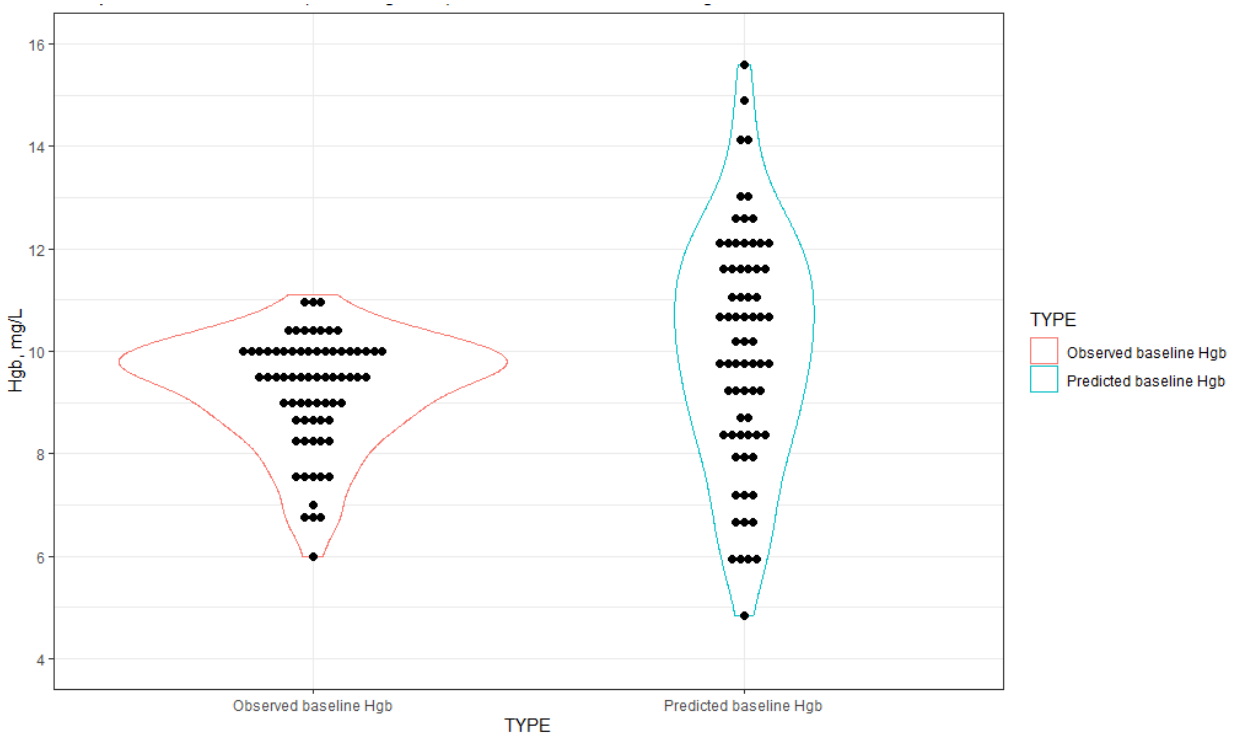
- Similarly, the lower bound of predicted Hgb may trigger packed red cell transfusion over intravenous iron therapy in a clinical setting.
- While the model performance was adequate in describing the data, alternative approaches (i.e., sensitivity analysis) could have been undertaken by the Applicant to restrict the parameter space to be concordant to protocol-defined Hgb thresholds, as well as clinically meaningful Hgb bounds.
- Due to the differences observed in pediatric and adult drug exposure (TSI exposure) detailed in next section, no further analyses were pursued to assess alternative models with restricted baseline Hgb parameter.

Table 9. Descriptive Summary of Predicted and Observed Baseline Hgb in Pediatric Patients

Data Type	Min	1st quartile	Median	3rd quartile	Max
Observed Hgb	6.0	8.7	9.6	10.0	11.1
Predicted Hgb	4.8	8.4	10.1	11.6	15.6

Unit, g/dL

Figure 12. Comparison of Predicted and Observed Baseline Hgb in Pediatric Subjects



FCM $AUC_{0\text{-}72h}$ in pediatric data and historic adult data

The reviewer compared exposure using two approaches:

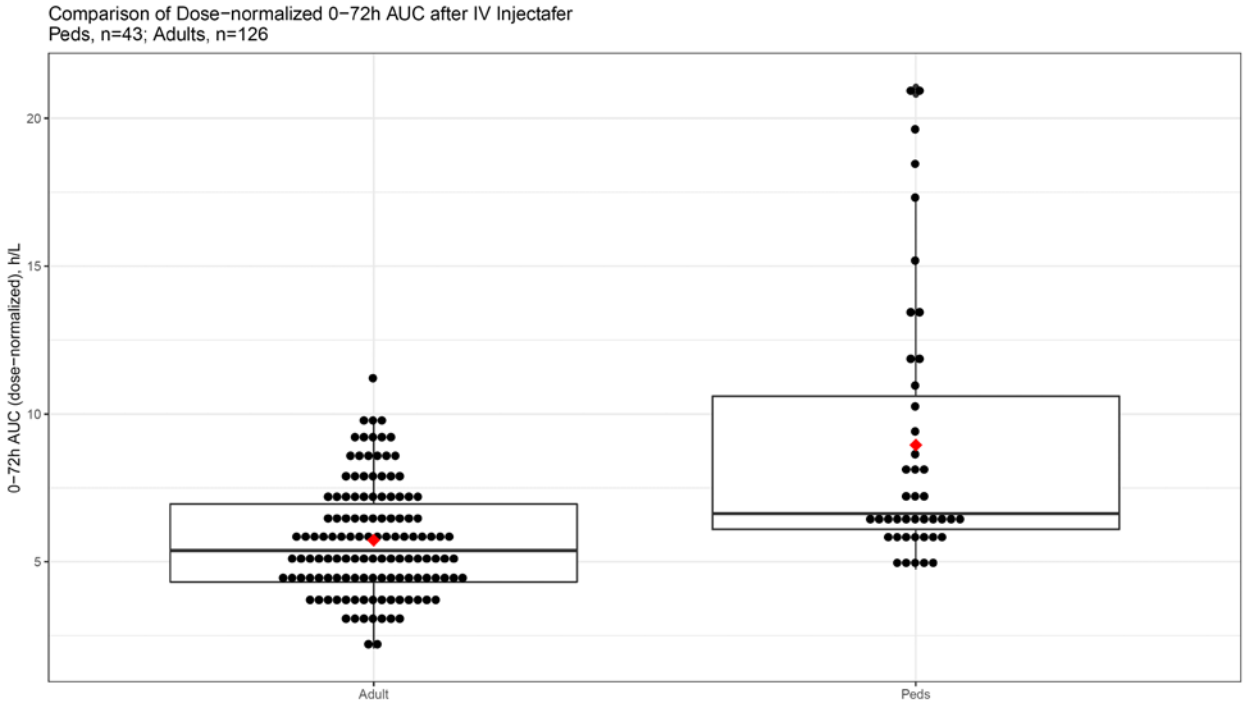
1) Compare dose-normalized $AUC_{0\text{-}72h}$ between pediatric and adult subjects
2) Compare cumulative $AUC_{0\text{-}72h}$ between pediatric and adult subjects receiving 1000 mg only

Note that among 56 pediatric subjects receiving 15 mg/kg. For the purpose of this analysis, only 43 pediatric subjects had TSI exposure data due to limited PK samples for model-prediction in desired time window of 0-72 hours.

Approach #1

A total of 126 adults from 5 studies were included for analysis. Single doses ranged from 100 to 1000 mg. The median (IQR, h/L) dose-normalized $AUC_{0\text{-}72h}$ were 5.4 (4.3-7.0) and 6.6 (6.1, 10.6) for adults and pediatric subjects, respectively. The observed difference was statistically significant (p=0.00005; 95% CI of mean difference, -1.77 to -4.67; assuming heteroscedasticity).

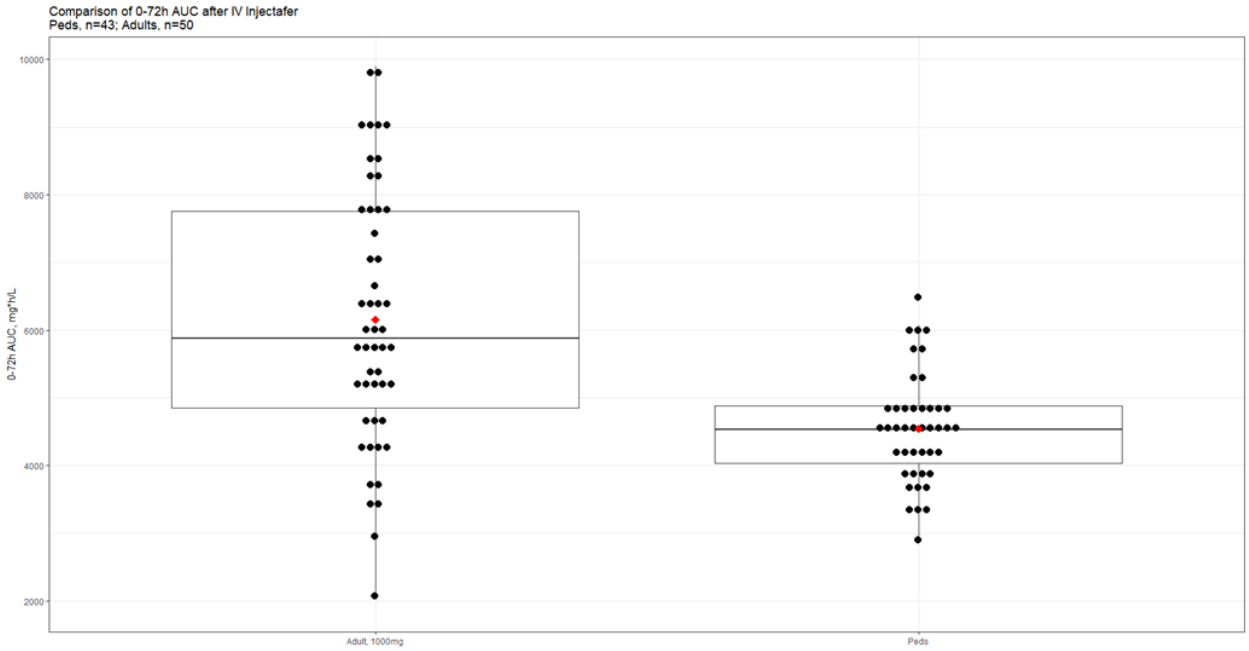
Figure 13. Comparison of Pediatric and Adult Dose-normalized TSI Exposures



Approach #2

A total of 50 adults who received 1000 mg from 4 studies were included for analysis. The median (IQR, mg·h/L) $AUC_{0\text{-}72h}$ were 5875.3 (4849.1-7758.0) and 4529.7 (4037.2-4880.8) for adults and pediatric subjects, respectively. The observed difference was statistically significant ($p<0.00005$; 95% CI of mean difference, 1021.084, 2195.785; assuming heteroscedasticity). When a subgroup of Asian adults (n=18) was removed due to numerically elevated $AUC_{0\text{-}72h}$ as a sensitivity analysis, pediatric TSI exposure remains significantly lower compared to those of Caucasian adults (n=32) (data and figure not shown).

Figure 14. Comparison of Pediatric and Adult TSI Exposures (No Dose-normalization)

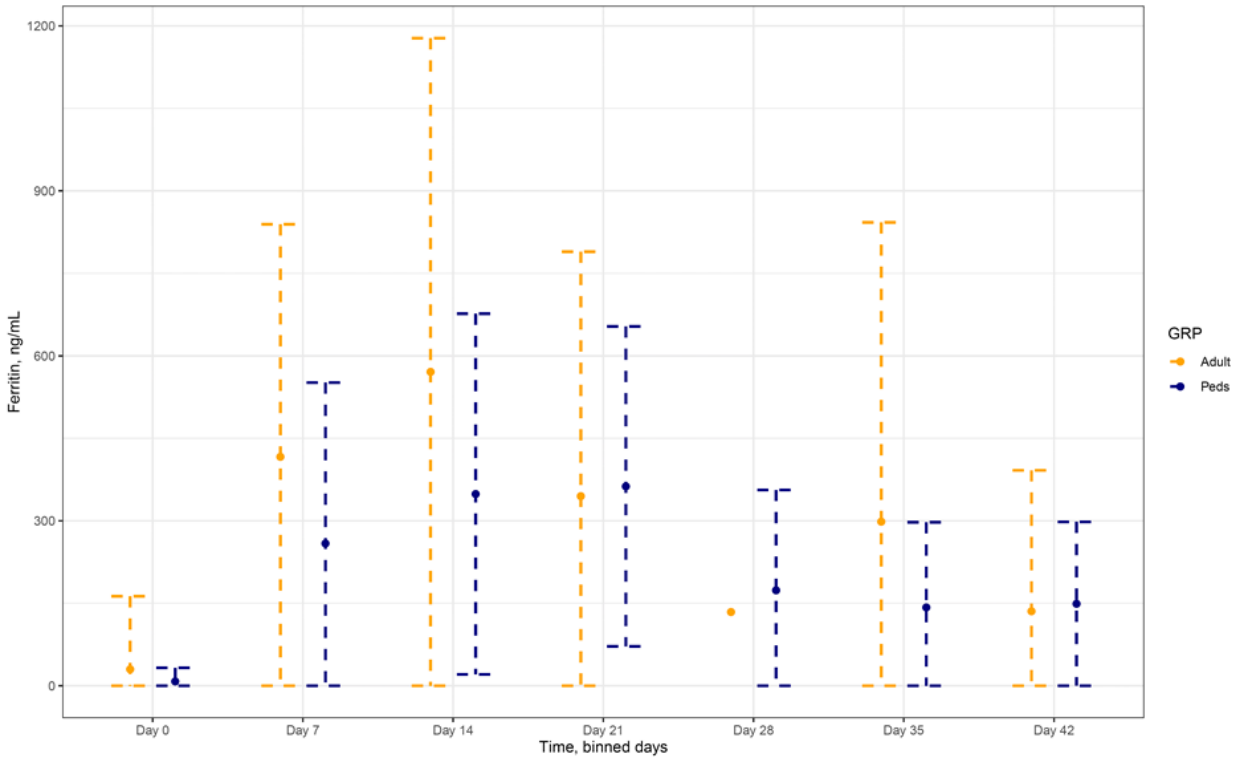


As shown in Figures 14-15, the comparability of TSI exposure (i.e., 0-72h AUC) presented significant challenges. Some possible explanation could be: 1) underlying differences in IDA etiology despite being categorically classified as IDA, 2) subject level comorbidity not captured in current dataset, and 3) demographics differences in relation to the IDA etiology. Collectively, these factors may explain the varying TSI concentrations observed between adult and pediatric subjects. As such, the reviewer performed independent analyses on PD response as an alternative path.

FCM PD endpoints in pediatric data and historic adult data

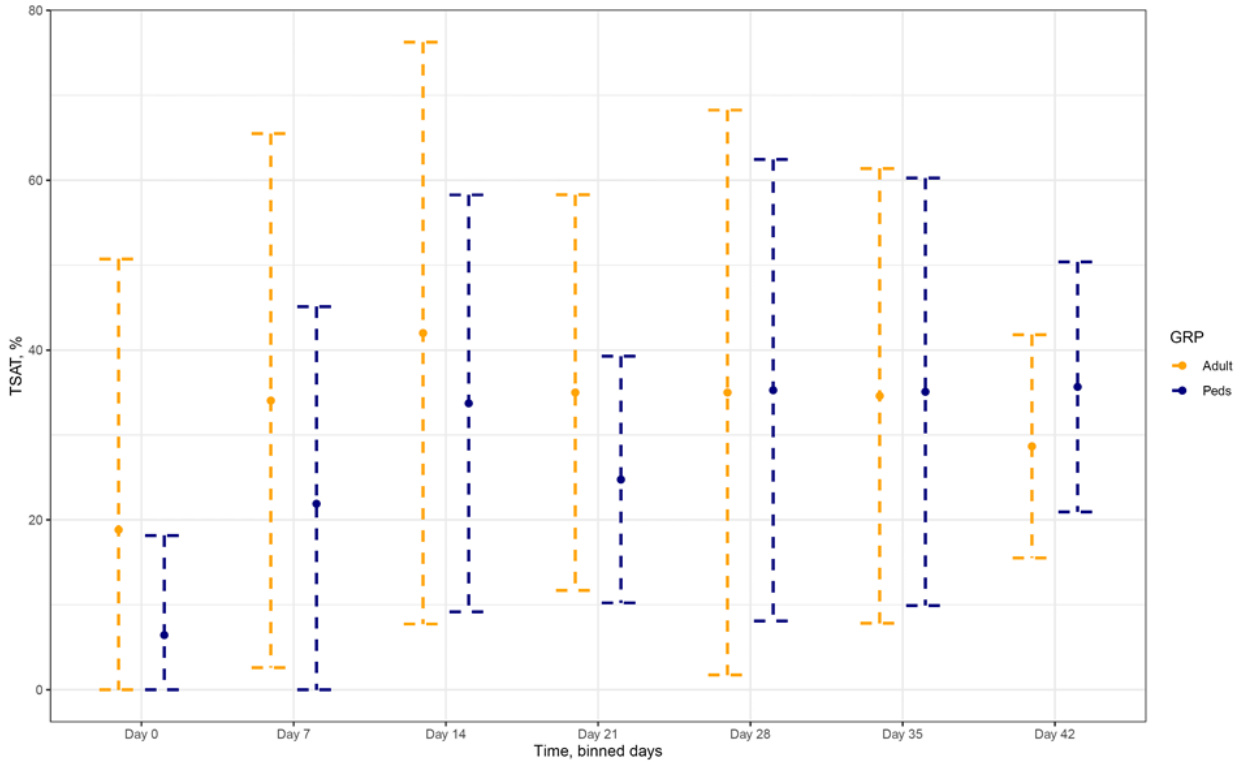
A total of 249 adult subjects from 1VIT09031 (Cohort 1, Group A) contributed ferritin, TSAT, and Hgb data for this analysis. For pediatric subjects, ferritin and TSAT data were available from 40 subjects (1VIT17044); Hgb data was available from 56 subjects receiving 15 mg/kg (pooled data from 1VIT13036 and 1VIT07044). Figures 15-17 showed respective comparisons of available data between adult and pediatric subjects. Overall, the PD response are similar between pediatric and historic adult subjects.

Figure 15. Comparison of Ferritin Concentrations by Nominal Days



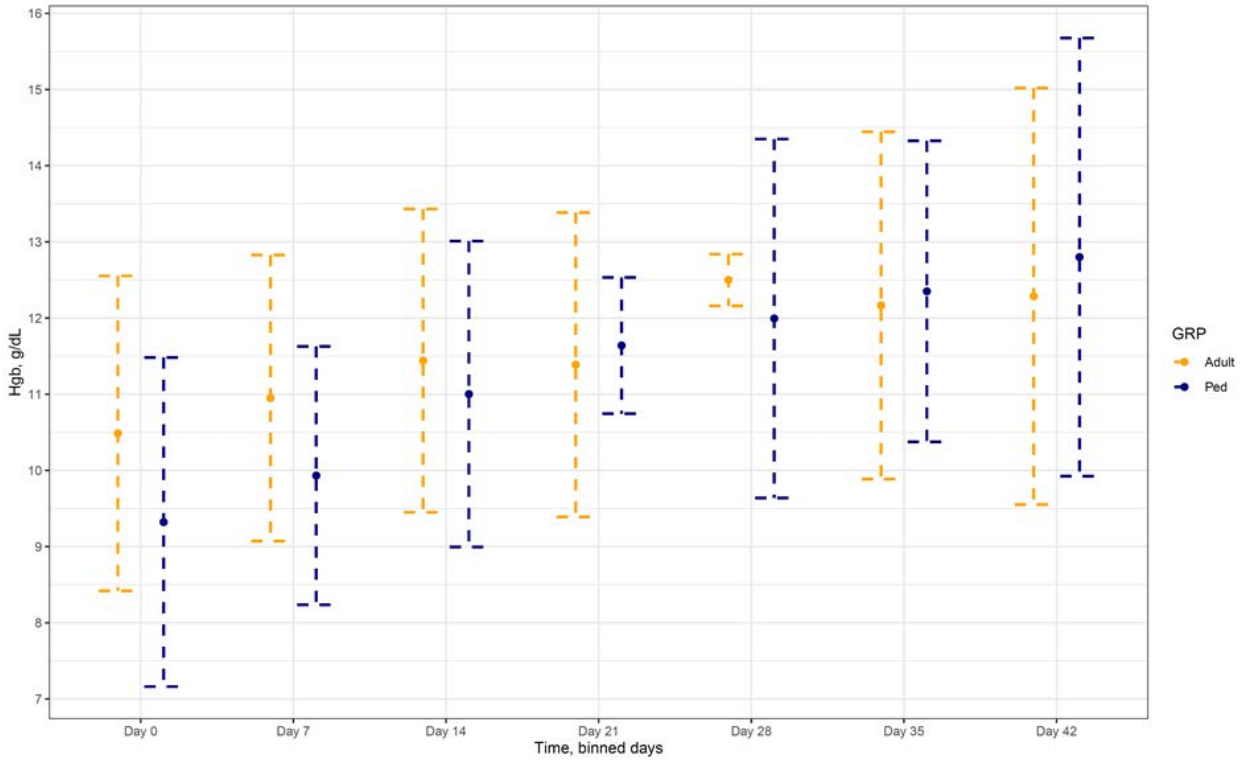
Data points on nominal days denote mean values; dashed lines and whiskers, 95% CI

Figure 16. Comparison of TSAT by Nominal Days



Data points on nominal days denote mean values; dashed lines and whiskers, 95% CI

Figure 17. Comparison of Hgb Concentrations by Nominal Days



Data points on nominal days denote mean values; dashed lines and whiskers, 95% CI

1.5.5 Listing of analyses codes and output files

Items	**Files/Description**	**Location in \\cdsnas\pharmacometrics**
NONMEM final TSI PK model	tsi.csv tsi3038.mod	…\sNDA_203565-S-16_Injectafer\PPK_Analysis\NONMEM\runs\2_TSI
NONMEM final TSI PK model	tsi_fdat.csv tsi3038_JLIU.mod To obtain exposure metrics	…\sNDA_203565-S-16_Injectafer\PPK_Analysis\NONMEM\runs\7_TSI_metrics
NONMEM final PK/PD model	hgb.csv hb2200dc.mod	…\sNDA_203565-S-16_Injectafer\PPK_Analysis\NONMEM\runs\3_HB2200dc
NONMEM final PK/PD model Sensitivity #1	Changed NITER for importance sampling	…\sNDA_203565-S-16_Injectafer\PPK_Analysis\NONMEM\runs\4_HB2200dc_JLIU
NONMEM final PK/PD model Sensitivity #2	Removed TSAT as a covariate	…\sNDA_203565-S-16_Injectafer\PPK_Analysis\NONMEM\runs\5_HB2200dc_sensitivity

R script	R script for data manipulation and graphical interpretation	…\sNDA_203565-S-16_Injectafer\PPK_Analysis\NONMEM
Adult data	Historic adult data from 09031 study	…\sNDA_203565-S-16_Injectafer\PPK_Analysis\data_adults
Pediatric data	Laboratory data for PD comparison	…\sNDA_203565-S-16_Injectafer\PPK_Analysis\data_peds\1vit17044\analysis\datasets

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