OFFICE OF CLINICAL PHARMACOLOGY REVIEW

BLA	BLA 103964/ S-5270
Type of submission	Pediatric efficacy supplement
Applicant	Hoffman-La Roche
Name	PEGASYS (peginterferon alpha-2a)
Submission date	12/15/2016
Indication	Treatment of chronic hepatitis B infection
Dosage form	Solution for injection
Dosage and administration	180 mcg once weekly in adults
Clinical pharmacology reviewer	Su-Young Choi, Pharm.D., Ph.D.
Clinical pharmacology team leader	Shirley Seo, Ph.D.
Pharmacometrics reviewer	Simbarashe Zvada, Ph.D.
Pharmacometrics team leader	Jeffry Florian, Ph.D.

Executive summary

This supplemental BLA was submitted in response to PREA PMR 2322-1 established with the approval of PEGASYS for the treatment of chronic hepatitis B (CHB) in adults (103964/5037 on May 13, 2005).

> *PREA PMR 2322-1: To assess the safety and efficacy of Peginterferon alfa-2a versus a no-treatment control in 110 pediatric HBeAg positive patients chronically infected with the hepatitis B virus, who have compensated liver disease*

To fulfill the PMR, the sponsor conducted a clinical trial entitled "A Phase IIIb Parallel Group, Open Label Study of Pegylated Interferon alfa-2a Monotherapy (PEG-IFN) Compared to Untreated Control in Children with HBeAg Positive Chronic Hepatitis B in the Immune Active Phase".

In the trial, pediatric patients with HBV infection but without advanced fibrosis were randomized in a 2:1 ratio to PEG-IFN (Group A; n=101) or untreated control (Group B; n=50). Patients with advanced fibrosis (n=10) were assigned to PEG-IFN (Group C). Patients in Group A and C received once weekly PEGASYS for 48 weeks. The primary endpoint was hepatitis B e-antigen (HBeAg) seroconversion between a group treated with PEGASYS monotherapy and an untreated control group at Week 24 after the end of treatment period. Twenty six patients (26%) in Group A had HBeAg seroconversion while

three patients (6%) in group B had seroconversion. The overall safety profiles (fever, fatigue, flu-like illness, and negative impacts on growth) were consistent with the safety profile of PEGASYS in adult CHB patients as well as pediatric patients with chronic hepatitis C (CHC).

The basis of approval for this submission is the clinical efficacy data. Although the pharmacokinetic data were not considered critical for this trial, sparse samples for pharmacokinetic analysis were collected throughout the study. Based on the population pharmacokinetic analysis PEG-IFN, AUC was 3494 ng/mL·hr, which is comparable to the AUC observed in adults with HCV or HBV infection.

Detailed labeling recommendations (clinical pharmacology relevant sections only)

The labeling language is under negotiation. The following information will be added to the PEGASYS USPI.

- Section 2
  - Use of PEGASYS for the treatment of CHB in pediatric patients 3 years of age and older
- Section 12, Specific population
  - In pediatric patients with CHB receiving PEGASYS 180 mcg/1.73 m^2 X BSA, AUC values were comparable to those observed in adults receiving 180 mcg dosing.

Reviewer comments
The approved dose of PEGASYS for pediatric patients with CHC is 180 mcg/1.73 m^2 X BSA in the US.

(b) (4)

(b) (4) *Therefore, the review team has concluded that 180 mcg/1.73 m^2 X BSA is recommended in pediatric patients with CHB to avoid confusion.*

Population PK Analyses of Pediatric Efficacy Supplement PEGASYS (BLA 103964) for Chronic Hepatitis B virus (HBV) infection in pediatrics

1.1 Applicant's analysis

The applicant performed popPK analysis of PEG-IFN using the data collected from 5 clinical studies to:

- Characterize the population pharmacokinetics of PEG-IFN in children dosed according to BSA
- Compare PEG-IFN exposures achieved in children with those in adults

1.1.1 Pediatric study design

This was a randomized, parallel group, open-label, multinational study of PEG-IFN alfa-2a treatment compared with an untreated control. The study population was male and female children aged 3 to < 18 years of age with chronic hepatitis B in the immune-active phase.

Patients without advanced fibrosis were randomized in a 2:1 ratio to PEG-IFN (Group A; n=101) or untreated control (Group B; n=50). Patients with advanced fibrosis (n=10) were assigned to PEG-IFN (Group C). Figure 1 below shows the study design. Patients received PEG-IFN for 48 weeks.

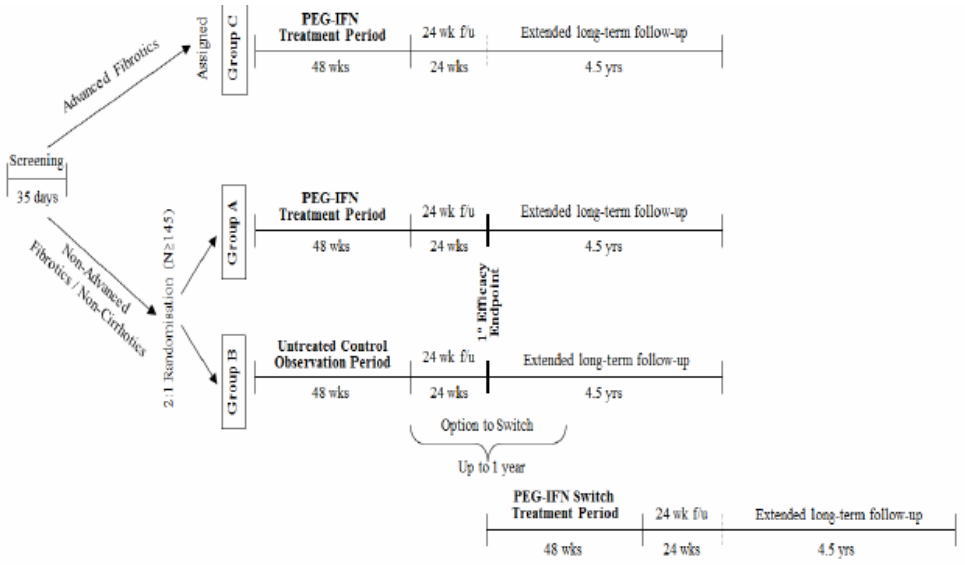

Figure 1. Illustration of YV25718 study design

The primary endpoint was HBeAg seroconversion at 24 weeks after the end of 48 weeks of treatment.

Dosing

In the US, the approved dose of PEG-IFN for pediatric patients with HCV is 180 mcg/1.73 m^2 multiplied by BSA. (b) (4) , the following doses shown in Table 1 were evaluated by the applicant in study YV25718 (5 doses based on BSA ranges). The distribution of children with respect to age and BSA-category is summarized in Table 2.

Table 1. Dosing regimen based on BSA category for study YV25718

Dose (µg)	Sample size	BSA range (m^2)	Dose equivalent
45	0	0.51-0.53	147-153 mcg/1.73m^2 X BSA
65	5	0.54-0.74	152-208 mcg/1.73m^2 X BSA
90	11	0.75-1.08	144-207 mcg/1.73m^2 X BSA
135	7	1.09-1.51	155-214 mcg/1.73m^2 X BSA
180	7	> 1.51	Adult dose

Table 2. Summary of the number of pediatric subjects per group, subcategorized by age and BSA for study YV25718

	Group A	**Group B**	**Group C**	**Overall**
Median (range) age (yrs)	7 (3-17)	8 (4-15)	8 (3-12)	7 (3-17)
BSA group (m^2)				
0.51-0.53	0	0	0	0
0.54-0.74	2	2	1	5
0.75-1.08	7	3	2	11
1.09-1.51	4	2	1	7
>1.51	4	2	1	7

Blood Sampling and Bioanalysis

For participating patients, PK samples were collected at Week 1 and Week 24 predose, and 24-48, 72-96, and 168 hours after administration of PEG-IFN. Pre-dose samples were also collected at Weeks 4, 8, and 12 within 6 hours prior to PEG-IFN administration. The concentrations of PEG-IFN were determined using a validated ELISA method. The method utilized a sandwich

ELISA, in which rabbit anti-PEG-IFN was coated onto microtiter plates. Primary antibody was mouse AGP3 and the secondary antibody was peroxidase conjugated goat anti-mouse IgM. SureBlue ™TMB was added for color development and quantitation.

The assay was conducted using 100 µL of 5-fold diluted human serum. The range of quantitation ranged from 250 to 5000 pg/mL in undiluted matrix. The standard curve and QC data (750, 2000, and 4000 pg/mL) indicated that assays were precise (inter-day % CV: 5.4 to 9.9%) and accurate (inter-day % accuracy: -4.9 to -1.5%). All samples were stored and processed in the time frame supported by the stability data (1722 days at – 70 ºC).

1.1.2 Population PK materials and methods

The applicant developed a population PK model of PEG-IFN in pediatric patients based on data from study YV25718 pooled together with data from adults originating from four clinical studies: NP17354, NP17355, PP22512 and PP22612. The data from adults were used to first develop the structural population PK model of PEG-IFN including covariates, and the data from study YV25718 were then added to develop a population PK model of PEG-IFN in pediatric patients and adults. Clinical studies were selected for this analysis if they had been conducted over the last 10 years, included multiple doses, and had intensive PK samples collected. The adult studies included data from adult patients with chronic hepatitis B (CHB), as well as chronic hepatitis C (CHC).

In brief, Study NP17354 investigated the influence of ethnicity on the PK of PEG-IFN, in patients with CHC; Study NP17355 was undertaken to investigate the PK of PEG-IFN in CHC patients with moderate and severe renal impairment and end-stage renal disease patients undergoing hemodialysis; Study PP22512 evaluated the acute immunologic response in Asian subjects with HBeAg-positive following therapy with either PEG-IFN, nucleoside analogues or both; Study PP22612 was an open-label extension study of CHB study PP22512. A summary of the clinical studies is listed in Table 3, and a summary of patient characteristics is listed in Table 4 below. The doses of PEG-INF used for study YV25718 are summarized above in Table 1.

Table 3. Summary of studies used in the population PK analysis *(Source: Applicant's summary of clinical pharmacology studies, Table 2, Page 9)*

Study	Population	Patients	Design	Relevant treatment	Collection time
NP17354	CHC	N = 46	Open-label, parallel group	180 µg PEG-IFN once weekly for 8 weeks plus ribavirin	Profiles at week 1 and week 8
NP17355	CHC with renal disease	N = 63	Non-randomized, parallel group	180 µg and 135 µg (ESRD) PEG-IFN once weekly for 12 weeks plus ribavirin	Profiles at week 1 and week 12
PP22512	CHB	N = 13	Open-label, randomized	360 µg PEG-IFN once weekly for 2 weeks	Profiles at week 1
PP22612	CHB	N = 8	Open-label, randomized	180 µg PEG-IFN once weekly for 48 weeks	Samples every 8 weeks
YV25718	pediatric patients with CHB	N = 31[a]	Open-label, randomized	PEG-IFN once weekly for 48 weeks based on BSA categories:	Profiles at week 1 and week 24 Samples every 4 weeks

BSA = body surface area, CHB = chronic hepatitis B, CHC = chronic hepatitis C, ESRD = end-stage renal disease, N = Number of patients, PEG-IFN = Pegylated interferon α-2a

[a] Thirty-one is the total number of patients included in the PK substudy who were enrolled in Group A (n=17), Group C (n=5), and Switch arm (n=9).

[b] No pediatric patients were enrolled in the 0.51-0.53 m^2 BSA category in study YV25718.

Table 4. Summary of characteristics of patients *(Source: Applicant's summary of clinical pharmacology studies, Table 3, Page 10)*

Study	Mean (Min. – Max.)							
	Age (Years)	Weight (kg)	Sex (F/M)	Race	BMI (kg/cm^2)	BSA (m^2)	LBW (kg)	CL_{CR} (mL/min)
NP17354	48 24-64	85 52-130	19F 27M	White:25 Black:17 Other: 4	28.6 19.6-43.6	2.00 1.52-2.50	55.1 39.0-71.8	121 59-217
NP17355	51 23-65	83 52-136	20F 43M	White:35 Black:27 Other:1	27.9 19.0-47.7	1.99 1.49-2.76	55.3 36.9-83.3	45.8 8.0-162
PP22512	27 23-32	70 54-87	13M	Asian:13	23.3 18.7-29.2	1.83 1.59-2.08	52.0 45.3-59.7	121 89-167
PP22612	30 24-43	75 58-94	8M	Asian:8	25.3 19.6-31.6	1.88 1.66-2.11	53.3 47.8-59.5	124 96-155
YV25718	8 3-17	36 15-88	11F 20M	White:5 Black:1 Asian:25	17.7 13.5-28.6	1.14 0.62-2.06	26.5 3.6-58.6	113 48-292

BMI = body mass index, BSA = body surface area, Cl_{CR} = creatinine clearance, F = female, LBW = lean body weight, M = male, Max = maximum, Min = minimum

The final population PK model included data from 158 subjects, including data from 30 pediatric patients enrolled in study YV25718 (one of the 31 participating patients from study YV25718 was deemed non-evaluable due to high interference peak at baseline and excluded from PK analyses), with a total of 2563 concentration-time records. The structural model was developed based on the adult data, followed by assessment of covariates and subsequently the pediatric data were added to the model. As PK data from a renal impairment study were included, the effect of creatinine clearance (CLcr) on clearance (CL) was incorporated into the model from the beginning of model development. The effect of body weight on CL and volume of distribution (V) were also included in the model from the beginning, since it was planned to use the adult model to describe the pharmacokinetics in pediatric patients.

1.1.3 Results

The structural population PK model of PEG-IFN in adults consisted of a one-compartment disposition model with a sequential zero-first order absorption and an endogenous IFN level. CLcr and body weight were identified as covariates on clearance. Body weight was also identified as a covariate for V. Similar to the model in adults, fixed effects parameters of the model were precisely estimated with the exception of the impact of CLcr on CL. Furthermore, a body weight-dependent allometric exponent of 0.75 on clearance was found to adequately describe the adult and pediatric clearance. The results from the final model are shown in Table 5.

Table 5. Parameter estimates of final popPK PEG-INF model *(Source: Applicant's summary of clinical pharmacology studies, Table 4, Page 12)*

Thetas (Fixed effects)		Estimate	SE	SE (%)	95 % CI	
θ1	Central volume (L)*	14.8	1.53	10	11.8	17.8
θ2	Clearance (L/h)**	0.0733	0.00415	6	0.065	0.081
θ3	Lag time (h)	0 FIX				
θ4	0 order absorption duration (h)	6.61	0.894	14	4.9	8.4
θ5	Absorption rate constant (h-1)	0.0228	0.00262	11	0.018	0.028
θ8	Creatinin clearance impact on θ2**	0.0698	0.0697	100	-0.067	0.206
θ9	Endogeneous INF (ng/ml)	0.253	0.0408	16	0.173	0.333
θ10	Weigth impact on θ1*	1.52	0.181	12	1.165	1.87
θ11	Weigth impact on θ2**	0.75 FIX				

Etas (Random effects)		Estimate	SE	SE (%)	IIV (%)
η1	Central volume (L)	0.575	0.120	21	76
η2	Clearance (L/h)	0.135	0.0323	24	37
η3	Lag time (h)	0 FIX			
η4	0 order absorption duration (h)	1.24	0.224	18	111
η5	Absorption rate constant (h-1)	0.811	0.247	30	90
η13	Endogeneous INF (ng/ml)	0.441	0.135	31	66

Etas (Random effects)		Estimate	SE	SE (%)	IOV (%)
η6-8	Bioavailability	0.255	0.0327	13	50
η9-10	0 order absorption duration (h)	0 FIX			
η11-12	Absorption rate constant (h-1)	0.833	0.132	16	91

Sigmas (Residual error)		Estimate	SE	SE (%)	Residual variability
θ6	Additive	0.158	0.00155	1	0.16 (ng/ml)
θ7	Proportional	0.193	0.00338	2	19 (%)

* V for typical subject = θ1*((WT/84)**θ10)

** CL for typical subject = θ2*((CRCL/114.8)**θ8)*((WT/84)**θ11)

Comparison of efficacy

The applicant did a comparison of PEG-IFN exposures observed in the studies included in the model, and the results are shown in Figure 2 below.

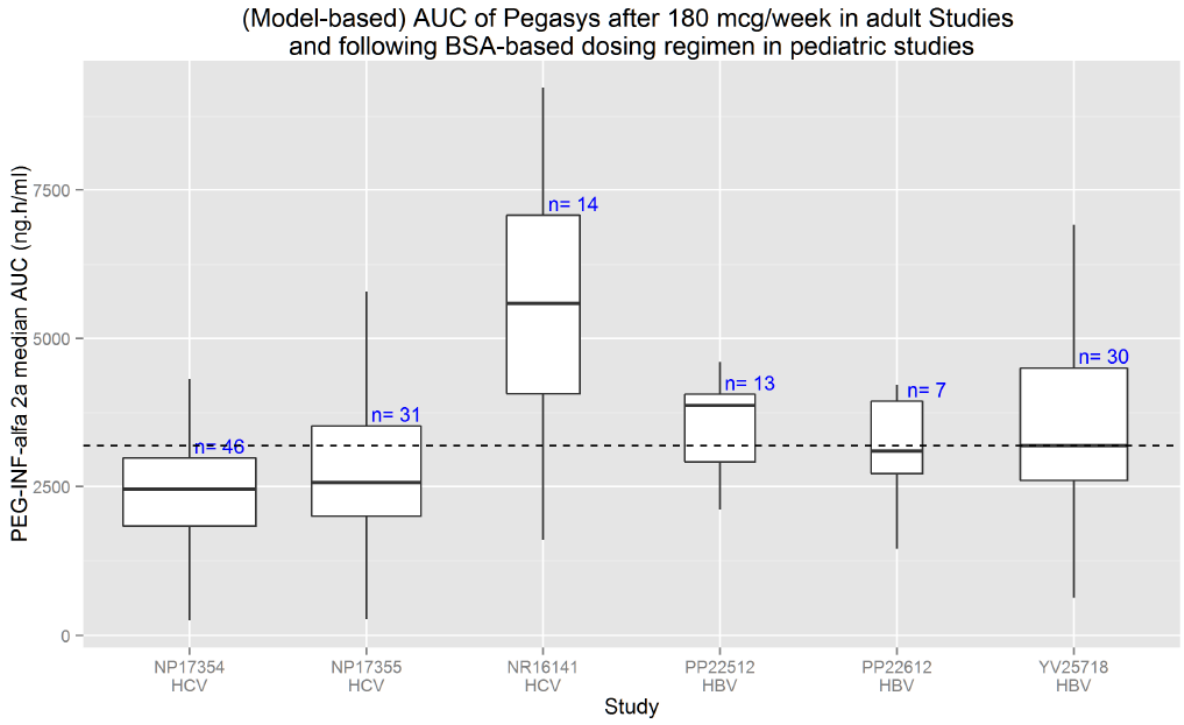

Figure 2. Box-Plot of the Predicted (Model-Based) Steady-State AUC across Several PEG-IFN PK Studies (*(Source: Applicant's summary of clinical pharmacology studies, Figure 2, Page 15)*

The applicant reported that in pediatric study NR16141 in patients with CHC, the PEG-IFN dose was also adjusted by BSA. However, unlike in pediatric patients with CHB, the BSA dosing in pediatric patients with CHC did not result in similar exposure as in adults. It is unclear why the exposure was higher than expected. Study NR16141 was conducted more than 10 years ago in a small number of patients (N=14). The higher exposure may be the result of the small sample size. To avoid the divergent PK data from study NR16141 in CHC from interfering with the analysis of the HBV pediatric PK data, this study was not included in the population PK analysis.

1.1.4 Conclusion

The applicant concluded that, the final population PK model of PEG-IFN in adults and pediatric patients described the available concentration-time data well. The applied BSA category-based dosing of PEG-IFN in pediatric patients was found to result in similar PK exposures between adults and pediatric patients, as well as similar exposures among the BSA-based dosing categories in pediatric patients

Reviewer's comment.

The reviewer agrees with the methodology undertaken by the sponsor and find the conclusions to be acceptable. Exclusion of study NR16141 from the population PK analysis was acceptable to avoid biasing of results given that the PK from that study was unexpectedly different from all other studies included in the analysis.

1.2 Reviewer's Analysis

1.2.1 Introduction

Population PK (PopPK) analysis for PEG-INF was included in this application to identify covariates which influence PEG-INF exposure. The primary objective of the reviewer's independent analysis was to evaluate whether the results from population PK analysis conducted by the sponsor are adequate and to evaluate if the exposures (AUC) achieved in pediatrics with the dosing in Table 1 are similar to those in adults.

1.2.2. Materials and Methods

The datasets and characteristics of patients used in the analyses are summarized in Table 3 and Table 4, respectively. The Table 6 below shows the link to the files and datasets used by the reviewer.

Table 6. Source for dataset and files used in the analysis

Model	File name
Pegasys base model control stream	PEGbaseCTL.txt ;
Pegasys base model list file	PEGbaseLST.txt;
Pegasys final model	PEGfinalCTL.txt
Pegasys final model list file	PEGfinalLST.txt
PKDATA	24FEB16_04.csv
Location of above files	\\CDSESUB1\evsprod\BLA103964\0235\m5\datasets\poppk-yv25718\analysis\legacy\programs
PKDATA	24FEB16_04.csv EDR Location: \\CDSESUB1\evsprod\BLA103964\0235\m5\datasets\poppk-

	yv25718\analysis\legacy\datasets

The reviewer's popPK analysis was performed in NONMEM 7.3 using a first-order conditional estimation method with ε–η interaction (FOCE INTER). In the analysis, the reviewer used a cut-off of at least 3.84 units change in objective function for inclusion of covariates. This cut-off corresponds to a p-value of 0.05 for 1 degree of freedom. Conventional allometric scaling was also applied on clearance and volume of distribution, with the exception that the exponent for volume of distribution was estimated. AUC was calculated by the reviewer as follows:

AUC =Dose·F/CL,

where Dose is the amount administered adjusted for relative changes in bioavailability (F) between occasions after subcutaneous administration in order to obtain correct individual estimates of AUC. Since all the doses were administered subcutaneously, the reason why F was accounted for was to adjust for differences that occur between occasions. F was modeled as:

F = 1·exp(IOVF),

where IOVF was the interoccasion variability in F.

1.2.3 Results

The final parameter estimates are shown in Table 7 below. The parameters were reasonably estimated except the impact of renal function (e.g., creatinine clearance (CRCL)) on PEG-IFN clearance. Removing CRCL as a covariate from the final model did not result in statistically significant changes in the model. However, PEG-IFN clearance has been proven to be affected by the stage of renal function, and PEG-IFN is dosed based on CRCL. Therefore, CRCL was kept in the final model even though the data could not reliably estimate its effect on clearance from the available data. The final model was used to obtain estimates of AUC for each individual.

Comparison of AUCs across individuals per study is shown in Figure 3. Studies NP17354HCV and NP17355HCV were conducted in adults with HCV infection. An anomaly was observed in the applicant's results. Specifically, Figure 2 presented by the applicant did not account for differences in bioavailability due to occasions after subcutaneous administration. . According to the dataset provided, PP2512HBV participants were dosed at 300 µg PEG-IFN followed by 180 µg .With regards to boxplots shown in Figure 2 and 3, only AUCs at steady state for dosing of 180 µg from study PP2512HBV were presented. Of note, the applicant did not provide the data for study for NR16141HCV, which was excluded from the analysis to avoid biasing the popPK analysis.

Table 7. Parameter estimates of the final PEG-IFN model

Parameter	Estimate [%RSE]	%IIV [%RSE]	%IOV [%RSE]
CL (L/hr)	0.0711 (6.0)	36.6 (12)	
Vc (L)	15.1 (9.8)	74.8 (11)	
Zero-order duration	6.47 (11)	110 (8.2)	
Absorption rate (1/hr)	0.0233(12)	90 (18.1)	91.9 (8.8)
Bioavailability (F)	1 (Fixed)		49.8 (6.1)
Endogenous INF2 alpha	0.246 (12)	67.3 (13.9)	
BW effect on Vc	1.53 (12)		
BW effect on CL	0.75 (Fixed)		
CRCL on CL	0.0358 (195)		
Additive error	0.197 (4.3)		
Proportional error	15.9 (1.1)		

CL-clearance; Vc – Volume of distribution in central compartment; BW – total body weight; CRCL-creatinine clearance.

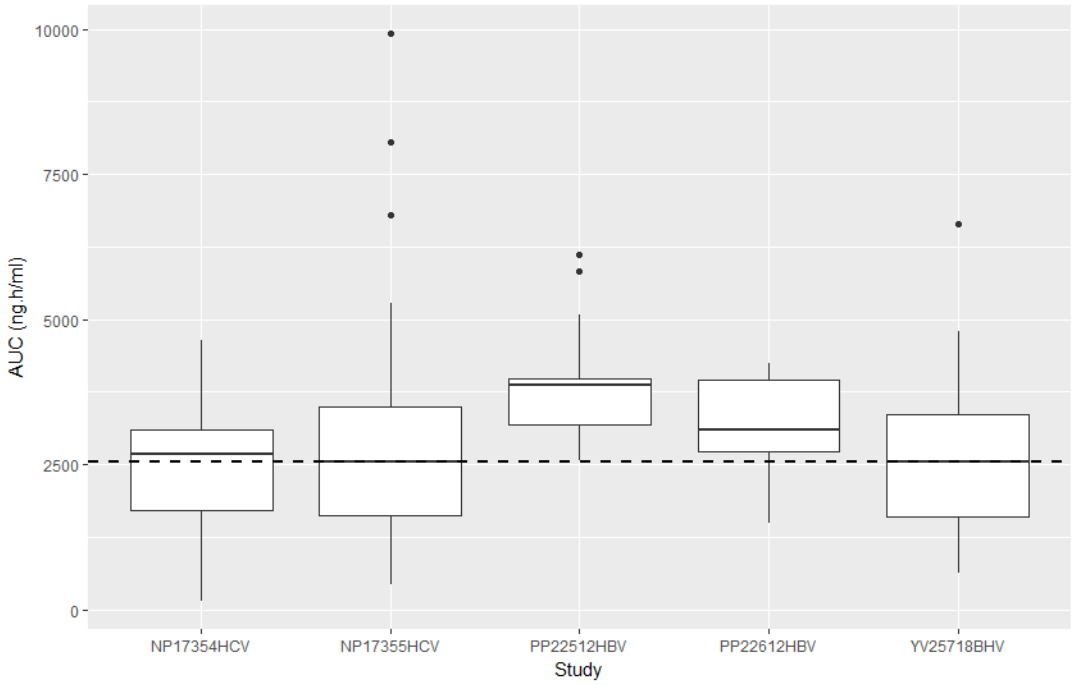

Figure 3. Comparison of steady state AUCs for 180 µg PEG-IGN across different studies included in the popPK analysis. AUC values are based on the popPK analysis conducted by the reviewer.

Final model diagnostics

The model diagnostics are shown in Figure 4 below.

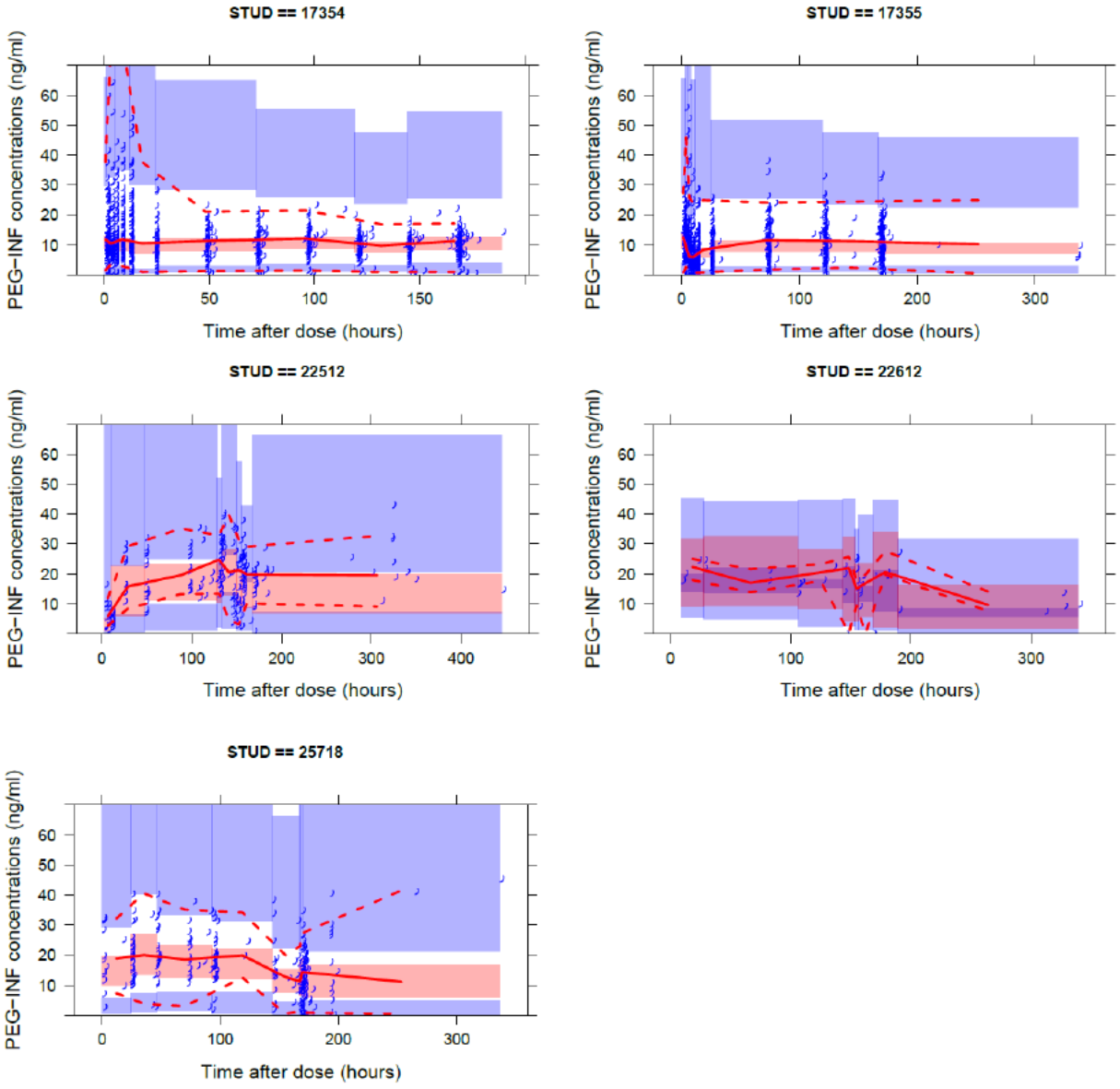

Figure 4. Prediction corrected visual predictive check for PEG-IFN final model stratified by study. The shaded areas represent the 90% prediction interval of the 5th, 50th and 95th percentiles of simulated PEG-IFN concentrations, the solid red line represents median of concentrations and dashed red lines represent the 5th and 95th percentile of the prediction corrected observed PEG-IFN concentrations. The open blue circles represent the observed PEG-IFN concentrations.

Reviewer's comments:

The reviewer agrees with the modeling approach taken by the applicant. The exposures in children are comparable with those observed in adults with HCV following BSA based dosing in children. The reviewer agrees with the labelling claim that the exposures in children following BSA dosing are comparable to those achieved in adults.

With regards to model performance, the diagnostic plots provide reasonable evidence to conclude adequate performance of the model. However, even though the applicant reached a similar conclusion, the results provided for by the sponsor comparing AUCs did not appear to account for bioavailability changes between occasions following subcutaneous administration. In other words, the sponsor calculated AUC based on the typical patient clearance without accounting for IOV values from different assessments. The reviewer's summary provided about calculates the mean for each subject based on all occasions, then uses that value for generating the box plots. Using this approach, the reviewer still agrees with the sponsor that the evaluated dosing results in exposures (AUC) in children that matches that in adults with HCV. These exposures were lower compared with adults with HBV, as shown in Figure 2.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SU-YOUNG CHOI
09/07/2017

SIMBARASHE P ZVADA
09/07/2017

JEFFRY FLORIAN
09/07/2017

SHIRLEY K SEO
09/08/2017