CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology

Integrated Review

BLA Number	761166
Link to EDR	\\CDSESUB1\evsprod\BLA761166\0001
Submission Date	3/13/2020
Submission Type	Section 351(a), Standard Review
Brand Name	BESREMi™
Generic Name	Ropeginterferon alfa-2b
Dosage Form and Strength	500 µg/1.0 mL solution for injection in a (b) (4) prefilled syringe
Proposed Indication	For the treatment of polycythemia vera in adults without symptomatic splenomegaly
Applicant	PharmaEssentia Corporation
Associated IND	119047
OCP Review Team	Li Wang, Ph.D., Eliford Kitabi, Ph.D., Justin Earp, Ph.D., Sudharshan Hariharan, Ph.D.
OCP Final Signatory	Doanh Tran, Ph. D. Deputy Division Director Division of Cardiometabolic and Endocrine Pharmacology (DCEP)

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1. EXECUTIVE SUMMARY

This clinical pharmacology review is for an original Biologics License Application (BLA), submitted by PharmaEssentia Corporation to the Division of Non-malignant Hematology (DNH). The Applicant is seeking approval for BESREMi® (BESREMi) for the treatment of polycythemia vera (PV) in adults without symptomatic splenomegaly. BESREMi is a covalent conjugate of the protein proline-interferon alfa-2b, produced in *Escherichia coli* cells by recombinant DNA technology, with methoxypolyethylene glycol moiety. It is a long-acting monopegylated interferon analog. Compared to other pegylated interferon alfa drug products, which have a relatively short half-life, BESREMi is a more stable third-generation pegylated interferon. BESREMi is marketed in the European Union as BESREMi® (marketing authorization granted on February 15, 2019). The interferon alfa-2b moiety of the drug product exhibits its cellular effects by binding to the transmembrane interferon alfa receptor, resulting in its antiproliferative, proapoptotic, antiangiogenic, and immunomodulatory effects. These actions may be involved in the therapeutic effects of interferon alfa in PV. Furthermore, interferon alfa is able to decrease the mutated JAK2 V617F allele burden, with the fact that this mutation is found in 65-97% of patients with PV. There have been several pegylated interferon drugs including PEGASYS® (PEG-IFN-α2a), PEGINTRO® (PEG-IFN-α2b), and PLEGRIDY® (PEG-IFN-β1) approved in the U.S. for different indications (PEGASYS® and PEGINTRON®: Treatment of chronic hepatitis C; PLEGRIDY®: Treatment of relapsing forms of multiple sclerosis).

The clinical program for BESREMi consisted of a Phase 1 single- and multiple-ascending dose study A09-102-P1101 in healthy adult male subjects, a Phase 1/2 study PEGINVERA in patients with PV, one Phase 3 study, PROUD-PV, and its extension study, CONTINUATION-PV, for long-term evaluation in patients with PV. During the review, it was determined that results from PEGINVERA would form the primary basis for effectiveness and studies PROUD-PV and CONTINUATION-PV will provide supportive evidence (Refer to Clinical Review). There is also a Phase 3 study, PEN-PV, to assess self-administration of BESREMi using a pre-filled pen. In addition to these studies, the Applicant also provided population pharmacokinetic (popPK), PK/PD, PK-safety, and PK-efficacy modeling reports for review.

Key issues discussed in this review are exposure-response (E-R) analyses from PEGINVERA and PROUD-PV/CONTINUATION studies, dosing recommendations in patients with renal and hepatic impairment and adequacy of bridge between drug product used in clinical trials to the to-be-marketed product.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) review team has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in BLA 761166 to support an approval of BESREMi.

Key review issues with specific recommendations and comments are summarized below:

Review Issues	Acceptable to OCP	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	☑Yes ☐No ☐N/A	Supportive evidence of effectiveness is demonstrated by the exposure-response (E-R) analyses between ropeginterferon concentration/AUC and CHR/CHRP from PEGINVERA (primary) and PROUD-PV/CONTINUATION (secondary) studies. See Section 3.3.1 for details. For effect on primary efficacy endpoint (CHR/CHRP), refer to Clinical and Statistical reviews.
General dosing instructions	☑Yes ☐No ☐N/A	The dose is titrated individually with a recommended starting dose of 100 µg (b) (4)) as subcutaneous injection. The dose should be gradually increased by 50 µg every two weeks (b) (4) until stabilization of the hematological parameters is achieved (hematocrit <45%, platelets <400 × 10^9/L and leukocytes <10 × 10^9/L). The maximum recommended single dose is 500 µg injected every two weeks. The dose at which stabilization of the hematological parameters is achieved should be maintained in a two-week administration interval for at least (b) (4) After that, the dose may be adapted and/or the administration interval prolonged up to every four weeks, as appropriate for the patient.
Dosing in patient subgroups (intrinsic	☑Yes ☐No ☐N/A	• In general, no dose adjustment is necessary in patients based on

and extrinsic factors)		gender, body weight, race and ethnicity. • No dose adjustment is necessary in patients with estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m^2. Due to observed renal toxicity, use of BESREMi in patients with eGFR (b) (4) <30 mL/min/1.73m^2 is not recommended. (b) (4) • BESREMi is contraindicated in patients with hepatic impairment (Child-Pugh B or C). Increases in ALT (≥3 times the upper limit of normal), AST (≥3 times the upper limit of normal), GGT (≥3 times the upper limit of normal) and bilirubin (>2 times the upper limit of normal) levels have been observed in patients treated with BESREMi. When the increase in liver enzyme levels is progressive and persistent, the dose of BESREMi should be reduced. If the increase in liver enzymes is progressive and clinically significant despite dose reduction, or if there is evidence of hepatic decompensation, therapy should be discontinued. • In vitro studies demonstrate that drug interaction potential for BESREMi is low. No clinical drug interaction studies were done. However, certain proinflammatory cytokines, including interferons, can suppress CYP450 enzymes

		resulting in increased exposures of some CYP substrates. Therefore, patients on BESREMi who are receiving concomitant drugs which are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs.
Labeling	☑Yes ☐No ☐N/A	Pending satisfactory agreement with the Applicant
Bridge between the to-be-marketed and clinical trial formulations	☑Yes ☐No ☐N/A	The drug substance from (b) (4) that were used during clinical development were comparable and there was no negative impact on the process performance and product quality as a result of any modifications. Vial for injection and pre-filled-pen (PFP) were used during clinical development. The to-be-marketed product is a 0.5 mg/mL in 1 mL pre-filled syringe (PFS). The inactive ingredients are in the same proportion among the 0.5 mg/mL vial, cartridge (PFP), and PFS. Clinical pharmacokinetic bridging is not needed. Early part of study PEGINVERA used a lower strength product, namely 0.18 mg/mL, but the inactive ingredients are the same. Since the majority of the clinical development program used the 0.5 mg/mL strength, bridging study to the lower strength is not warranted.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action

Interferon alfa belongs to the class of type I interferons which exhibit their cellular effects by binding to a transmembrane receptor termed interferon alfa receptor (IFNAR). Binding to IFNAR initiates a downstream signaling cascade through the activation of kinases, in particular Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) and signal transducer and activator of transcription (STAT) proteins. Nuclear translocation of STAT proteins controls distinct gene-expression programs and exhibit various cellular effects. Interferon alfa was shown to have an inhibitory effect on the proliferation of hematopoietic and bone marrow fibroblast progenitor cells and antagonized the action of growth factors and other cytokines that have a role in the development of myelofibrosis. These actions may be involved in the therapeutic effects of interferon alfa in polycythemia vera (PV). Further, it was demonstrated that interferon alfa is able to decrease the mutated JAK2V617F allele burden in patients with PV (a V617F point mutation in the JAK2 kinase is a hallmark of PV and is present in approximately 65-97% of patients).

Absorption

The estimated geometric mean (CV%) absorption rate constant of BESREMi is 0.12 day^{-1} (27%) in patients with PV. The time to reach maximum plasma concentration is approximately 3-6 days.

Distribution

The estimated geometric mean (CV%) apparent volume of distribution of BESREMi is 4.8 L (21%) in patients with PV.

Elimination

BESREMi undergoes receptor independent degradation/excretion and receptor binding and subsequent degradation of the drug-receptor complex. The half-life and clearance of BESREMi is approximately 7 days and 1.7-2.5 L/h, respectively, in patients with PV over dose range of 100 µg to 500 µg.

Intrinsic factors

No clinically significant differences in the pharmacokinetics of BESREMi were observed based on age, sex, body surface area, and JAK2_V617F mutation.

The impact of renal impairment on BESREMi clearance was evaluated using a popPK approach. The analysis demonstrated that there was no significant impact on BESREMi with eGFR $\geq$ 30 mL/min/1.73m^2. The effect of eGFR <30 mL/min, or hepatic impairment (Child-Pugh A, B, and C) on BESREMi pharmacokinetics has not been studied. Evaluation of ALT/AST as PK covariates indicated no impact of these time varying biomarkers on ropeginterferon alfa-2b PK.

Drug Interaction Studies

Clinical Studies

No studies were performed.

In Vitro Studies

Cytochrome P450 (CYP) enzymes: BESREMi is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4, and is not an inducer of CYP1A2, 2B6 or 3A4. BESREMi is a time-dependent inhibitor of CYP2A6. There was a 37.3% inhibition on CYP2A6 actively when human liver microsome was incubated with BESREMi at 50 ng/mL (mean C_{max} at the dose of 450 µg is 44 ng/mL) for 30 min.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Single-Agent Therapy:

- The recommended starting dosage for single-agent therapy is 100 µg by subcutaneous injection every two weeks.
- Gradually increase the dose by 50 µg every two weeks until the hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 × 10^9/L, and leukocytes less than 10 × 10^9/L).
- The maximum dose is 500 µg every two weeks.

(b) (4)

Maintain the dose level at which hematological stability is achieved for (b) (4) After that time, the dose may be adapted and/or the dosing interval may be expanded to every 4 weeks.

2.2.2 Therapeutic individualization

- No dose adjustment is needed in patients based on age, body weight, gender, or race/ethnicity.
- No dose adjustment is necessary in patients with estimated glomerular filtration rate (eGFR) of ≥30 mL/min/1.73 m^2. Use of BESREMi in patients with eGFR (b) (4) <30 mL/min/1.73m^2 is not recommended. (b) (4) BESREMi is contraindicated in patients with hepatic impairment (Child-Pugh B or C).
- Certain proinflammatory cytokines, including interferons, can suppress CYP450 enzymes resulting in increased exposures of some CYP substrates. Therefore, patients on BESREMi who are receiving concomitant drugs which are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The clinical pharmacology section of the proposed label was updated to reflect the current Guidance on Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products.

The following edits are suggested in Sections 7, 8, and 12:

- Drug Interaction Studies: Include a paragraph to note the potential interaction of certain proinflammatory cytokines, including interferons with CYP450 enzymes which may result in increased exposures of some CYP substrates.
- Pharmacokinetics: Provide pharmacokinetic parameters in patients with PV derived from post-hoc empirical Bayes estimates.
- Pharmacodynamics: Included time course of pharmacodynamic response (including short-term clinical response) that was predicted from longitudinal exposure-response modelling.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

BESREMi is a covalent conjugate of the protein proline-interferon alfa-2b, produced in *Escherichia coli* cells by recombinant DNA technology, with methoxypolyethylene glycol moiety. It is a long-acting monopegylated interferon analog. Compared to other pegylated interferon alfa drug products, which have a relatively short half-life, BESREMi is a more stable third-generation pegylated interferon. BESREMi is marketed in the European Union as BESREMi® (marketing authorization granted on February 15, 2019).

The initial IND was received on June 17, 2014. This indication was granted Orphan Drug Designation by the Agency on April 2, 2012. The NDA was submitted in March 2020 and was granted standard review status.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Interferon alfa exhibits its cellular effects by binding to the transmembrane interferon alfa receptor, resulting in its antiproliferative, proapoptotic, antiangiogenic, and immunomodulatory effects. These actions may be involved in the therapeutic effects of interferon alfa in PV. Furthermore, it was demonstrated that interferon alfa is able to decrease the mutated JAK2V617F allele burden in patients with PV (a V617F point mutation in the JAK2 kinase is a hallmark of PV and is present in approximately 65-97% of patients).

Cardiac Electrophysiology	Not applicable, as the risk for QT prolongation for large therapeutic proteins is low.
General Information	
Bioanalysis	BESREMi concentrations in serum samples were determined using a validated bioanalytical assay (Refer Appendix 4.1). The samples were analyzed using an enzyme linked immunosorbent assay (ELISA) with a lower limit of quantification of 0.347 ng/mL.
Dose proportionality	Following administration of single subcutaneous doses to healthy subjects, BESREMi apparent clearance decreases from 70.7 to 46.4 mL/h and the area under the serum concentration-time curve (AUC) increased in a greater than dose proportional manner over the dose range of 24 to 270 µg. In patients with PV, C_{max}, C_{min}, and AUC increased in a dose related manner over the dose range of 50-80 to 540 µg.
Accumulation	Not measured.
Drug exposure (variability) at steady state following the therapeutic dosing regimen	The mean ± SD steady state C_{max}, C_{min}, and AUC are 11.0±1.0/48.6±22.7 ng/mL, 6.48±2.14/25.4±12.7 ng/mL, and 118±11/553±264 ng×day/mL at the dose of 150/450 µg every two weeks, respectively.
Absorption	
T_{max}	The median T_{max} of BESREMi is 3-6 days over dose range of 100 to 540 µg with two-week dosing interval. The median (range) T_{max} of BESREMi is 4 (3-6) days at the dose of 150 µg with two-week dosing interval.
Bioavailability	Absolute bioavailability is not known
Food effect	NA
Distribution	
Volume of distribution	The geometric mean (CV%) of apparent volume of distribution of BESREMi is 4.8 L (21%) in patients with PV.
Protein binding	Not available because BESREMi is a biotechnology pharmaceutical
Substrate of transporter systems	NA

Elimination	
Half-life and clearance	The mean half-life of BESREMi is 6-10 days over dose range of 100 to 540 µg with two-week dosing interval. The half-life (Mean±SD) of BESREMi is 10.0±6.72 days at the dose of 150 µg with two-week dosing interval. The steady state clearance (Mean±SD) based on population PK analysis are 3.04±3.26/1.95±1.47 L/h at the dose of 150/450 µg every two weeks, respectively.
Metabolism	
Primary metabolizing enzymes	NA.
Inhibitor/Inducer	CYP450 enzymes: BESREMi is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4 and is not an inducer of CYP1A2, 2B6 or 3A4. BESREMi is a time-dependent inhibitor of CYP2A6. There was a 37.3% inhibition on CYP2A6 actively when human liver microsome was incubated with BESREMi at 50 ng/mL (mean C_{max} at the dose of 450 µg is 44 ng/mL) for 30 min.
Excretion	
Primary excretion pathways	No human studies were done to evaluate metabolism or metabolic pathways of BESREMi. There is evidence that pegylated proteins can be susceptible to hydrolysis with the release of interferon and PEG moieties. Although, the PEG moiety may undergo uptake by macrophages and Kupffer cells by pinocytosis, biliary excretion only plays a minor role in the clearance of PEG; whereas, urinary clearance predominates.

3.3 Clinical Pharmacology Questions

3.3.1. To what extent does the available clinical pharmacology program provide supportive evidence of effectiveness?

During the review cycle, it was determined that the primary evidence of effectiveness for BESREMi will be based on the results from the Phase 1/2 study, PEGINVERA, which was an open-label dose finding study conducted in two stages. The primary objective of stage I was to identify the maximum tolerated dose and Stage II evaluated efficacy, safety and tolerability. Supportive evidence of effectiveness is based on results from PROUD-PV and CONTINUATION-PV studies. PROUD-PV investigated the safety and efficacy of BESREMi during 12 months of treatment compared to patients receiving treatment with hydroxyurea (HU). CONTINUATION-PV is an open-label extension study of PROUD-PV which assessed the long-term (at least 36 months and up to 48 months) efficacy of BESREMi versus standard first line

treatment (HU or other best available treatment). The primary efficacy endpoint in PEGINVERA, PROUD-PV and CONTINUATION-PV studies is complete hematological response which is a composite of hematocrit (HCT), platelet (PLT) and white blood cell (WBC) count responses and normal spleen size. Please refer to Clinical and Statistical reviews for interpretation of primary efficacy endpoint results.

From a clinical pharmacology perspective, supportive evidence of effectiveness is demonstrated by 3 exposure-response (E-R) analyses. The first E-R analysis evaluated the influence of increasing ropeginterferon concentration on levels of pharmacodynamic biomarkers (HCT, PLT, and WBC) overtime. Data for this analysis was pooled from PEGINVERA and PROUD-PV/CONTINUATION-PV clinical studies. In this analysis, ropeginterferon effect is characterized by an I_{max} model, whereby increasing concentrations are associated with decline of biomarker levels in a diminishing manner until a plateau is reached. The results of this analysis indicated that the IC_{50} for I_{max} models of HCT, PLT and WBC (0.719, 1.46, and 0.482 ng/mL, respectively) were below or comparable to the 5th percentile of observed ropeginterferon concentration (approx. 1 ng/mL, see Figure 3. Prediction Corrected VPC for the Applicant's Final Model. Blue shared area represents the 95% prediction interval, blue solid line = median of the simulated data, black dashed line = median of the observed data, black circles = observed data, lower and upper black dashed lines represent 5th and 95th percentiles of the observed data in the appendix). Simulation from the models indicate increasing proportions of subjects with complete hematological response regardless of phlebotomy (CHR) overtime. Subjects were deemed to have attained CHR if they had platelet count < 400 $\times 10^9$/L, WBC count < 10 $\times 10^9$/L, and hematocrit < 0.45. These results imply that ropeginterferon treatment is associated with concentration dependent decline in hematological parameters overtime and that the selected dosage provides exposures at the plateau of the exposure-response curve.

The second E-R analysis evaluated the relationship between steady state AUC and probability of CHR and complete hematological response without phlebotomy for at least 3 months (CHRP) at 36 months after treatment. Subjects were deemed to have attained CHRP if, in addition to meeting CHR criteria, they did not undergo phlebotomy for at least 3 months previously. Data for this analysis was also pooled from the PEGINVERA and PROUD-PV/CONTINUATION-PV. For subjects who dropped out or with no follow-up data at month 36, last observed response was used for analysis (last observation carried forward (LOCF)). The results indicated an E_{max} relationship between ropeginterferon exposure and probability of CHR or CHRP at month 36 after treatment. At the range of POPPK model predicted steady state $AUC_{0\text{-}672h}$ (50 h*ng/mL – 550 h*ng/mL), the model predicted probability of CHR or CHRP range between 30% – 55%.

In a third E-R analysis, relationship between ropeginterferon concentration and probability of biweekly CHRP (without LOCF) was explored in both PEGINVERA and PROUD-PV studies separately. In these analyses, ropeginterferon effect was characterized by an E_{max} model and the delay of drug effect was modelled through an effect compartment. Model predicted probabilities of CHRP, overtime, were consistent with observed biweekly proportion of subjects with CHRP. In the PROUD-PV (CONTI) study, the predicted probabilities (95% CI) were: 11% (6 -17%), 21% (14 - 28%), 28% (21 - 36%), 62% (53 - 70%) and 83% (75 - 91%) at weeks 0, 12, 20, 52 and 104, respectively. In the PEGINVERA study, the predicted probabilities (95% CI) were: 22% (11 - 34%), 40% (28 - 53%), 50% (38 - 62%), 64% (47 - 78%), 70% (55 - 88%) at weeks 0, 12, 20, 52 and 104, respectively. The increasing proportion of CHRP overtime reflects both the

protracted dose titration and the delayed drug effect in PV. Results from these E-R analyses further support the evidence of effectiveness of BESREMi for treatment of PV.

Lastly, the effect of ropeginterferon on classical interferon-inducible biological markers, neopterin and 2' 5'-oligoadenylate synthase (OAS), which are widely used as indicators of interferon pharmacodynamic action is described below. In Study A09-102-P1101, the effect of single doses of BESREMi (24 µg to 270 µg) or 180 µg of PEGASYS® (peginterferon alfa-2a) on serum concentrations of OAS and neopterin were investigated in healthy adult male subjects. Furthermore, the PD effects between BESREMi and PEGASYS were compared at the 180-µg dose. A summary of PD parameters is presented in Table 1.

Table 1. Summary Statistics for PD Parameters Following SC Administration of BESREMi or PEGASYS® in Study A09-102-P1101.

PD Parameter	**Ropeginterferon Alfa-2b Dose**						**PEGASYS®**
Statistic	**24 µg (N=6)**	**48 µg (N=6)**	**90 µg (N=6)**	**180 µg (N=6)**	**225 µg (N=6)**	**270 µg (N=6)**	**180 µg (N=12)**
OAS							
E_{max} (pmol/dL) Mean (SD)	268.96 (125.53)	265.71 (96.83)	487.53 (194.42)	430.81 (210.51)	360.69 (135.25)	567.94 (378.40)	541.02 (580.47)
T_{max} (day) Mean (SD)	7.36 (4.63)	7.17 (3.67)	6.68 (3.72)	8.84 (6.68)	9.27 (5.32)	6.83 (3.97)	5.09 (2.80)
AUC_{0-t} (pmol•h/dL) Mean (SD)	51970 (24942)	89552 (45279)	117122 (73455)	122506 (49366)	106759 (55986)	175233 (107138)	119272 (43689)
Neopterin							
E_{max} (pmol/L) Mean (SD)	14.65 (4.25)	17.87 (7.11)	14.03 (1.53)	18.14 (5.33)	20.47 (3.51)	18.69 (6.46)	21.21 (4.85)
T_{max} (day) Mean (SD)	4.34 (4.80)	2.50 (0.84)	3.00 (2.01)	2.01 (0.004)	2.50 (0.84)	2.17 (0.41)	2.11 (0.29)
AUC_{0-t} (pmol•h/L) Mean (SD)	1624 (420)	2424 (1437)	1213 (970)	2224 (1087)	2783 (407)	3328 (1392)	2453 (1482)

Source: Summary of Clinical Pharmacology studies (Table 2.7.2-7; Pages 37)

NOTE: Mean (SD) AUC0-t values were rounded up or down.
Mean (SD) Tmax (day) was calculated by dividing Mean (SD) Tmax (h) by 24 hours.
PEGASYS® = peginterferon alfa-2a.
Abbreviations: µg – microgram; AUC0-t – area under the curve from time 0 to the time of last quantifiable concentration; dL – deciliter; Emax – maximum observed concentration; CSR – clinical study report; h – hour; L – liter; N – number of subjects; pmol – picomole;
OAS – 2', 5'–oligoadenylate synthetase; PD – pharmacodynamic; SC – subcutaneous; SD – standard deviation; Tmax – time to Emax

BESREMi induced elevation of OAS levels. Mean OAS E_{max} increased in a dose related manner with BESREMi dose and occurred at mean T_{max} of approximately 7 to 9 days. Likewise, mean OAS AUC_{0-t} showed a trend for increase with BESREMi dose. Similar trends were observed for neopterin E_{max} and AUC_{0-t}. However, T_{max} occurred earlier for neopterin (approximately 2 to 4 days) compared to T_{max} for OAS. Due to the high inter-subject PD variability, the power model analysis of dose proportionality of PD parameters for BESREMi was not explored. However, both PD parameters (E_{max} and AUC_{0-t}) appeared to be linearly related to dose. BESREMi had similar bioactivity as PEGASYS based on PD parameters as OAS and neopterin at the 180 µg

dose. However, a statistical analysis is compromised by the large variability and small sample size.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed titration dosing regimen includes a starting dose of 100 µg (single-agent therapy) (b) (4) by subcutaneous injection every two weeks and the dose will gradually increase by 50 µg every two weeks (b) (4) until the hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 × 10^9/L, and leukocytes less than 10 × 10^9/L) with the maximum dose as 500 µg. The proposed dosing regimen was evaluated in PROUD-PV study. PEGINVERA (Stage 2) employed a similar dosing strategy but with a starting dose of 150 µg and titrated to a maximum allowed dose of 450 µg using the following 6 dose levels: 100 µg, 150 µg, 225 µg, 300 µg, 400 µg, and 450 µg. Because the proposed and similar dosing regimens have been evaluated in clinical studies that are deemed effective, the review team agrees that the dosing regimen is acceptable for the treatment of adults with PV without symptomatic splenomegaly.

The maximum tolerated dose (MTD) for BESREMi in patients with PV was explored in study PEGINVERA, which consisted of two stages (Stage 1: To identify the MTD of BESREMi; Stage 2: Long term efficacy and safety evaluation). At Stage 1, determination of the MTD was based on a 3 + 3 dose escalation design with three patients per cohort, with seven dose levels including 50 µg, 100 µg, 150 µg, 200 µg, 250 µg, 300 µg, 360 µg, 450 µg, and 540 µg. The MTD was determined to be 540 µg as the highest dose administered since no dose-limiting toxicity or other safety signals were observed for any of the dosing groups. The mean duration of treatment in Stage 2 was approximately 33 months. The individual complete hematological response (defined as hematocrit < 45% without phlebotomy (at least 3 months since last phlebotomy), platelets count ≤ 400 × 10^9/L, and leukocyte count ≤ 10×10^9 cells/L) was observed in 62.8% of patients, and a partial response, which is defined as hematocrit < 45% without phlebotomy but with persistent splenomegaly or elevated (>400 ×10^9/L) platelets count, or reduction of phlebotomy requirements by at least 50%, was observed in 34.9% of patients over 162-week treatment. In addition, the efficacy was maintained after the switch to the 4-week regimen from the maintained 2-week regimen in terms of maintenance of best hematological response, maintenance of best molecular response, hematological parameters (hematocrit), spleen size, and need of phlebotomy. Most treatment-emergent adverse events were mild or moderate in intensity and resolved without sequelae. Based on the results from Study PEGINVERA, the maximum dose was set as 500 µg in the Phase 3 study, PROUD-PV.

Dose Confirmation through Modelling and Simulations

Although body surface area (BSA) and JAK_V617F allele were identified as PK covariates they have no impact on clinical response since ropeginterferon dosage will be titrated to individually effective and tolerable levels. The exposure-response (E-R) analysis identified statistically significant relationships between ropeginterferon concentration and hematological endpoints (HCT, PLT and WBC). Simulation from the model indicated that proportion of subjects with CHR or CHRP increased overtime approaching a maximal response at week 104 in subjects naïve to hydroxyurea treatment. Similarly, simulations from a statistically significant ropeginterferon versus CHRP model indicated that proportion of patients with CHRP increased overtime approaching a maximal response by about week 56 in the PEGINVERA study and week 104 in the PROUD-PV/CONTINUATION study. Taken together, the results from E-R analyses indicate that despite all patients reaching maximum dose by week 20 and steady-state exposure at around 24 weeks, response to ropeginterferon treatment is delayed in some patients. Further simulations assessing alternative dose regimens (with higher starting and increment doses) determined that the proposed ropeginterferon dosage, as studied in the phase 3 trial, was optimal for efficacy and conservative for safety (see Section 4.2.2. Exposure-vs-efficacy Analysis).

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. Dose adjustment is not necessary based on intrinsic factors such as age, body weight, gender, or race/ethnicity.

Body weight: Population PK analysis identified body surface area (mean = 1.92 m^2, range: 1.47 – 2.52 m^2) to be a statistically significant contributor to between subject variation in non-specific clearance of ropeginterferon. Due to strong correlation between BSA and body weight (mean = 76.7 kg, range: 48.6 – 125 kg), subsequent post-hoc analyses indicated statistically significant differences in ropeginterferon exposures (C_{min} and AUC) among quartiles of body weight with subjects in the lowest weight quartile (Q1) having higher exposure than subjects in higher quartiles (See Figure 1). Despite these differences, a body weight-based dosing is not needed due to individualized dose titration scheme and the final dose for each subject will be tailored based on effectiveness and tolerability.

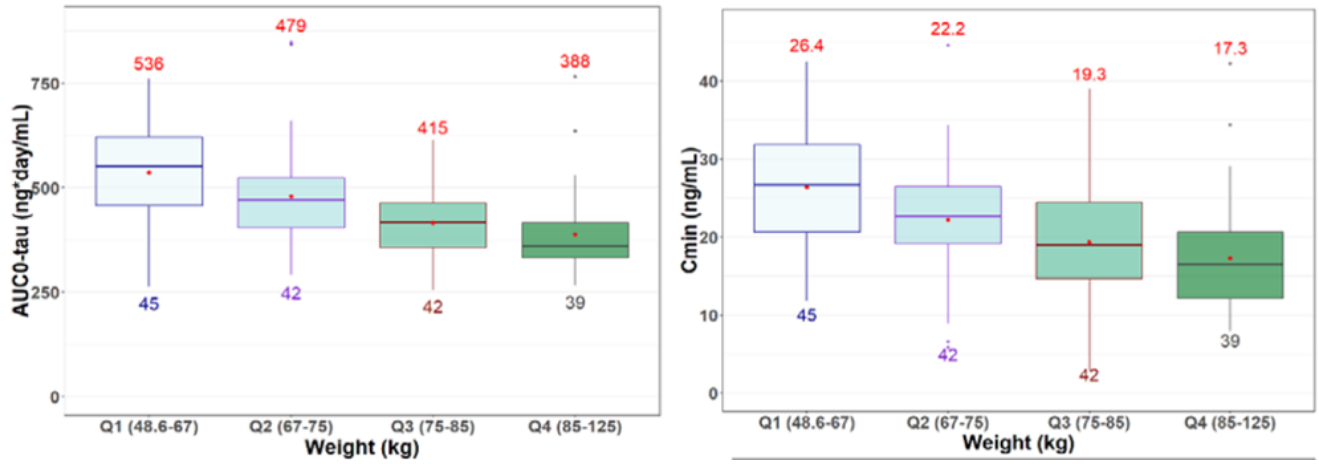


Figure 1. Boxplots of the steady state post-hoc PK exposures versus quartiles of body weight in PV patients receiving 500 µg of ropeginterferon.

Source: Applicant's PKPD safety report (#0165, page 101)

Race: The impact of race on PK and response to ropeginterferon treatment could not be assessed as the study population in both PROUD-PV and PEGINVERA comprised of mostly Caucasians (99.4%) patients and only 1 Asian patient.

Age: Population PK analysis identified age (mean = 54.3 years, range: 20 – 85 years) to have statistically significant contribution to variation in ropeginterferon absorption rate constant (Ka) with subjects ≥ 65 years old having lower Ka than < 65 years old. However, the impact did not warrant dose adjustment based on age as there was no significant difference in AUC and C_{max} between the two patient groups.

In the analysis to determine predictors of CHRP at 36 months (±4months), ropeginterferon AUC and age were determined to be statistically significant predictors of CHRP with the likelihood for CHRP decreasing by 0.96 folds for each one-year increase in age. However, this also does not warrant alternative dosing since ropeginterferon dose is individually titrated to effective and tolerable doses.

Gender: In the population PK analysis, sex (41% female) was not a contributor to between subject differences in PK parameters. However, sex was identified as a significant predictor of CHRP being a covariate on both E_{max} and intercept parameters in the longitudinal logistic regression model of ropeginterferon vs CHRP. Based on the model, female subjects have 16% - 24% higher E_{max} than male subjects and 25% to 40% lower intercept than male patients.

Renal Impairment: Creatinine clearance normalized to BSA, CLCR (mean = 75.5 ml/min/1.73m^2, range: 23.9 – 152 ml/min/1.73m^2) was assessed for contribution to between subject variation in non-specific clearance of ropeginterferon (CL/F). Most of the studied subjects had CLCR > 30 ml/min/1.73m^2. Only one subject had CLCR < 29 ml/min/1.73m^2. Population PK analysis did not find CLCR to be a covariate to CL/F or any other PK covariate.

Subsequent post-hoc analysis also indicated no difference in ropeginterferon exposure among different CLCR quartiles. Therefore, no dose-adjustment of BESREMi is needed in patients with eGFR > 30 ml/min/1.73m^2. However, renal toxicity as evidenced by increased serum creatinine occurred in BESREMi-treated patients. The Applicant proposed discontinuation of BESREMi use if severe renal impairment develops during treatment. Therefore, the review team agrees to not recommend use of BESREMi in patients with eGFR (b) (4) < 30 mL/min/1.73m^2 (b) (4)

Hepatic Impairment

Population PK analysis did not identify the time varying ALT and AST to be covariates on PK of ropeginterferon alfa-2b. No dose adjustment is needed in patients with hepatic impairment (Child-Pugh A).

BESREMi is contraindicated in patients with hepatic impairment (Child-Pugh B or C). Increases in ALT (≥3 times the upper limit of normal), AST (≥3 times the upper limit of normal), GGT (≥3 times the upper limit of normal) and bilirubin (>2 times the upper limit of normal) levels have been observed in patients treated with BESREMi. The Applicant recommends reducing the dose of BESREMi when the increase in liver enzyme levels is progressive and persistent. If the increase in liver enzymes is progressive and clinically significant despite dose reduction, or if there is evidence of hepatic decompensation, therapy should be discontinued.

3.3.4 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

Drug-drug interaction potential for BESREMi has been conducted by *in vitro* assessment. BESREMi does not inhibit the activity of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4 and is not an inducer of CYP1A2, 2B6 or 3A4. However, BESREMi is a time-dependent inhibitor of CYP2A6. There was a 37.3% inhibition on CYP2A6 activity when human liver microsome was incubated with BESREMi at 50 ng/mL (which is close to mean C_{max} at the dose of 450 µg) for 30 min. Given that there are virtually no reported drugs metabolized primarily by CYP2A6, no further clinical assessment is required.

Certain proinflammatory cytokines, including interferons, can suppress CYP450 enzymes resulting in increased exposures of some CYP substrates. This influence needs more time to take effect and administration of multiple dose of test drug is commonly required for drug-drug interaction assessment. As the Applicant has not conducted clinical DDI studies, as a precaution, patients on BESREMi who are receiving concomitant drugs which are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs.

3.1.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be marketed formulation?

Ropeginterferon alfa-2b is a covalent conjugate of the protein proline-interferon alfa-2b, produced in *Escherichia coli* cells by recombinant DNA technology, with mPEG moiety. (b) (4) were used in the development of the BESREMi drug substance. Based on the data obtained from the batches produced by all processes, it was concluded that the drug substance from the (b) (4) were comparable and there was no negative impact on the process performance and product quality as a result of any modifications. Therefore, drug substance from these processes were used in the clinical development program, including the Phase 3 trials.

Five different drug product (DP) presentations were used throughout the development program: (i & ii) (b) (4) ready-to-use vials, (iii) (b) (4) ready-to-use vial, and (iv & v) (b) (4) pre-filled pens (PFP). PEGINVERA study used 0.18 mg/mL solution for injection in (b) (4) vials initially, but later transitioned to (b) (4) vial to reduce the number of injection sites during subcutaneous administration. As the clinical development transitioned from Phase 1/2 to Phase 3, the (b) (4) 0.5 mg/mL vial was further investigated in the PROUD-PV and CONTINUATION-PV studies. The (b) (4) 0.5 mg/mL (b) (4) glass cartridges (PFP) were also introduced in the CONTINUATION-PV and PEN-PV studies.

The PEN-PV study was conducted to assess the self-administration of BESREMi using a PFP. The enrolled patients either entered the study after completion of PROUD-PV or from the on-going CONTINUATION-PV study. During the 12-week treatment period, these patients switched from vial drug product administered by healthcare providers to self-administered PFP. Since the drug product formulation was the same between vial and PFP and there was no change in individualized dose of BESREMi, PK assessment was not conducted in PEN-PV study. (b) (4) . Additionally, the rate of responders (hematological response with and without spleen size) was maintained during study participation, showing no significant difference between the vial and PFP. Finally, there were no safety concerns arising from the administration of BESREMi using the pre-filled pen.

The to-be-marketed DP presentation is 0.5 mg/mL in 1 mL pre-filled syringe (PFS) and has the same inactive ingredients, in the same proportion as the 0.5 mg/mL vial and cartridge (PFP). Analytical comparability studies are considered sufficient to support the transition from the clinical DPs, 0.5 mg/mL in ready-to-use vials and PFP to the proposed to-be-marketed 0.5 mg/mL, 1 mL, glass PFS. There are some differences in the container closure systems between PFP and PFS, but the basic operation and method of use are similar. Although the needle for PFS (30G x 12.7mm) is thinner and longer than the needle of PFP (b) (4) the injection

force of PFS is not an issue because the BESREMi DP is not a viscous liquid (close to the viscosity of water). Early part of study PEGINVERA used a lower strength product, namely 0.18 mg/mL, but the inactive ingredients are the same as the 0.5 mg/mL strength. Since the majority of the clinical development program used the 0.5 mg/mL strength, bridging study to the lower strength is not warranted.

Based on the information summarized above, the review team concludes that an adequate bridge has been established across all different DP presentations used in the clinical development program. This supports the use and approval of 0.5 mg/mL in 1 mL PFS.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation

The Applicant used an enzyme linked immunosorbent assay (ELISA) procedure (double-antibody sandwich electrochemiluminescence method) to determine plasma BESREMi concentrations. MSD Human IFN-α Ultra-Sensitive Kit was used. Anti-human IFNa-2a antibodies are precoated on the plate. 50 µL of HSC assay diluent (Diluent 2) / Triton 0.6 % is added to each well and incubated for 30 min at RT. Then 10 µL of samples, standards or quality controls are added to the well and incubated for 2 hours at room temperature. The plate is washed and 25 µL of an antibody conjugated with Ruthenium(ll)-tris(bipyridyl)$^{2+}$ are added to the well. After 2 hours of incubation at room temperature, the plate is washed again and 150 µL 2X Read Buffer containing 12-O-tetradecanoylphorbol-13-acetate (TPA) are added per well. After connecting to voltage, the TPA releases electrons becoming a positively charged TPA radical. [Ru(bpy3)]$^{2+}$ is oxidized to [Ru(bpy3)]$^{3+}$. This molecule binds the free electron and is thereby reduced to [Ru(bpy3]$^{2+}$ switching to an energic high level. Emitting photons at 620 nm, the molecule reaches a lower energetic level. The intensity of the emitted chemiluminescence signal is directly proportional to the concentration of the analyte in the sample. The chemiluminescence signal is measured using a QuickPlex (Meso Scale Discovery). The bioanalytical methods were developed and validated by (b) (4) The ELISA methods were validated in compliance with the standards set forth in the FDA Bioanalytical Method Validation guidance. Summary of the validation parameters are presented in Table 2.

Table 2. Summary Review of BESREMi plasma assays

	BESREMi
Bioanalytical method validation reports	6780.012511
Validation assay range (ng/mL)	0.347-44.4
QCs (ng/mL)	0.347, 1.11, 3.33, and 44.4
Inter-day precision (% CV)	≤ 11.5
Inter-day accuracy (% Bias)	-1.3 to 10.2
Intra-day precision (% CV)	≤ 4.5
Intra-day accuracy (% Bias)	-1.3 to 10.2
Reference standard	08DPL-B002
Specificity	No significant interference observed in the blank matrix
Freeze/thaw stability	4 freeze (-20/-80°C)-thaw (room temperature) cycles
Stock stability	15 months at 4°C in formulation solution

Bench-top stability	24 hours at room temperature in human serum
Processed stability	18 hours at room temperature in formulation solution
Long-term storage stability	23 days at -80°C in human serum

4.2 PHARMACOMETRIC ASSESSMENT

4.2.1. Population PK Analysis

4.2.1.1. Review Summary

The applicant's population PK analysis is acceptable for characterizing sources of PK variability and for exposure-response analyses to support the proposed dosage of ropeginterferon in patients with polycythemia vera. The goodness-of-fit (GOF) plots and the prediction-corrected visual predictive check (PcVPC) indicate that the final population PK model is adequate in characterizing the PK profile of ropeginterferon in health subjects and subjects with polycythemia vera.

The final population PK model has 3 submodels: a one-absorption compartment model parameterized in first order absorption rate constant (Ka) and absorption lag time (Tlag); a non-specific one-compartment disposition model parameterized in clearance (CL/F) and volume of the central compartment (Vc/F); and a specific target-mediated disposition (TMDD) model parameterized in receptor decay constant (Kdec), drug-receptor complex decay constant (Kint), drug and drug-receptor complex equilibrium rate constant (KD), baseline receptor amount (Rtot0), and steady state receptor amount (Rtotss). An assumption was made that, due to treatment, Rtot0 decreased from baseline value at day 7 and continued to decrease to a steady state value (Rtotss).

Identified sources of variability for CL/F were body surface area (BSA) and JAK2_V617 allele burden. CL/F increased exponentially with increasing BSA and linearly with increasing JAK2_V617 allele burden. The only source of Vc/F variability was polycythemia vera disease; subjects with polycythemia vera had 89% higher Vc/F compared to healthy subjects. Ka decreased exponentially with increasing age.

Inter-individual variabilities were estimated for CL/F, Vc/F, Ka, Rtot0, and Kint. The estimated IIV were small for CL/F (25%) but large for the rest of the parameters (> 40%). Eta Shrinkages for CL/F (22%), Vc/F (44%), and Ka (34%) support evaluation of covariates. The estimated PK parameters appear reasonable. The applicant's analyses were verified by the reviewer and no significant discordance was identified.

***The developed model was used to support labeling of ropeginterferon in the current submission as outlined in* Table 3.**

Table 3. Reviewer's Comments on the Population PK model.

Utility of the final model			Reviewer's Comments
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	ropeginterferon dosing is individualized based on response and tolerability. Therefore, dosing based on identified PK covariates in not necessary	A statistically and clinically meaningful exposure-efficacy relationship for complete hematological response without phlebotomy (CHRP) was identified supporting rogeginterferone dose titration based on response and tolerability Furthermore, shallow exposures versus safety relationships (thrombocytopenia and GGT elevation) were identified, supporting the practice of safety monitoring during dose up-titrations
	Extrinsic factor	No extrinsic covariates were identified.	
Derive exposure metrics for Exposure-response analyses	Post-hoc PK parameters were used in exposure-efficacy/safety analyses		The use of post-hoc PK parameters in E-R analyses is acceptable since the model performance was reasonable as indicated by GOF and PcVPC
Predict exposures at alternative dosing regimen			The model was not used to assess predicted exposures at other doses

4.2.1.2. Introduction

The primary objectives of this analysis were to:

- Develop the population pharmacokinetic model of ropeginterferon.
- Identify sources of PK variability that may impact exposure to ropeginterferon.
- Generate post-hoc PK parameters for subsequent exposure-response analyses.

4.2.1.3. Model development

Data

The analyses were based on PK data from 3 studies. The study design, study population, and timing of blood samples varied among the 3 clinical studies. Brief descriptions of the studies included are presented in Table 4.

The final NONMEM data file for analysis contained 1538 PK observations from 200 subjects. Table 5 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 4. Summary of Studies with PK Sampling Included in Population PK Analysis.

Study No.	Population	Study design	Dosage	PK sampling
A09-102	Healthy adult male subjects	Phase I, randomized, double-blind, active control, single dose escalation, PK and safety study	Six dosing groups received the following dose levels; 24ug, 48ug, 90ug, 180ug, 225ug, and 270ug	PK samples collected at 1 hour prior and at 1, 3, 6, 9, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 240, 288, 336, 504, and 672 hours after admininstration
PEGINVERA	Male and female subjects with PV	Open label, prospective, phase I/II, 3+3 dose escalation to maximum tolerated dose (MTD) and maintenance of MTD for as long as it was effective, PK, safety and efficacy were assessed	Tested dose levels in 3+3 dose escalation part were; 50, 100, 150, 250, 300, 360, 450, and 540: In intrapatient dose escaltion part dose was titrated in levels (100, 150, 225, 300, 400, and 450) until response or untolerated, maximum dose was 540	PK sample collected at trough, and at 72, 120, 144, 192, 240, and 288 after bi-weekly dose administrations. After reaching individual MTD, trough samples were collected for 5 successive same dose levels
PROUD-PV	Male and female Subjects with PV	Phase III, randomized, open label, controlled, parallel arm, efficacy and safety study	Dose titration from 50ug or 100ug up to individually tolerated doses or response, maximum being 500	Sparse PK samples collected at trough, and every 3 months

Source: Reviewer's summary of data from Applicant's POP PK report (#0158-1) and Clinical study report (p11012010)

Table 5. Summary of Baseline Demographic Covariates.

Variable		N (%)	Mean	SD	Median	Min	Max
Age (yr)		200	54.3	14.3	56.0	20	85
Weight (kg)		200	76.7	13.1	76.6	48.6	125
Height (cm)		200	171	8.89	171	149	190
BSA (m^2)		200	1.92	0.197	1.93	1.47	2.52
BMI (kg/m^2)		200	26.2	3.63	25.6	17.2	40
CLcr ($mL/min/1.73\ m^2$)		200	75.5	25.7	71.7	23.9	152
ALT (U/L)		200	26.3	15.1	22.0	4.00	107
AST (U/L)		200	24.2	7.46	23.0	2.00	49.0
JAK2_V617F allele burden (%)		200	35.3	27.4	30.5	0	98.5
HCT (%)		200	46.6	4.84	46.0	36.8	61.7
WBC ($10^9/L$)		200	10.8	5.02	10.3	4.00	30.9
Platelets ($10^9/L$)		200	480	257	430	115	1500
Sex	Male	118 (59.0)	—	—	—	—	—
	Female	82 (41.0)	—	—	—	—	—
Race	Caucasian	196 (98.0)	—	—	—	—	—
	Black	3 (1.50)	—	—	—	—	—
	Asian	1 (0.50)	—	—	—	—	—
Population	Healthy Subject	41 (16)	—	—	—	—	—
	PV Patient	168 (84.0)	—	—	—	—	—
ECOG Score	0	155 (77.5)	—	—	—	—	—
	1	42 (21.0)					
	2	3 (1.50)	—	—	—	—	—

Source: Applicant's population PK report (#0158-1) at page 32

Base Model

The final base model was comprised of 3 submodels as follows: a non-specific one-compartment disposition model parameterized in clearance (CL/F) and volume of the central compartment (Vc/F); a specific target-mediated disposition (TMDD) model parameterized in receptor decay constant (Kdec), drug and drug-receptor equilibrium constant (KD), drug-receptor decay constant (Kint), baseline receptor amount (Rtot0), and steady state receptor amount (Rtotss); and an absorption compartment model parameterized in first order absorption rate constant (Ka) and absorption lag time (Tlag). An assumption was made that, due to treatment, Rtot0 decreased overtime from the baseline value at day 7 to a steady-state value (Rtotss). Inter-individual variabilities were estimated for 5 structural model parameters, namely CL/F, Vc/F, Ka, Rtot0, and Kint. The parameters were assumed to be log-normally distributed and therefore IIV values were estimated using exponential error models. Residual variability of the observed data was modeled using combined additive and proportional residual error models. Data below the limit of quantification (BLQ) were excluded from analysis. Outlying data points (defined as data points with absolute conditional weighted residuals CWRES > 4) were also excluded from further model development steps. Model evaluation and selection of the base model were based on standard statistical criteria of

goodness-of-fit (GOF) such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic GOF plots.

Covariate Analysis

Graphical exploration of ETA-vs-covariate plots were used for selection of covariates to include in univariate analysis of parameter-covariate relationships. The following covariates were assessed: patient demographics (baseline age, weight, height, body mass index, body surface area (BSA), sex, or race), clinical laboratory measures for hepatic injury (time-varying AST and ALT), calculated baseline CLcr as a measure of renal function, or other disease-related indices (baseline JAK2_V617F allele burden, ECOG performance status, WBC count, platelet count, and HCT).

Covariates identified through graphical explorations were included in the model in a stepwise, univariate, forward inclusion step. Parameter-covariate relationships were retained in the model if all of the following retention criteria were met: (1) significant decrease in OFV ($\Delta\ OFV \geq 6.635$) (2) the model converged and minimized successfully (3) decrease in variance of the parameter on which the covariate was added (4) no compensatory increase in variance of other parameters or residuals.
After each covariate inclusion, graphical exploration was used to identify remaining parameter-covariate relationships. Collinearity between covariates were also investigated. The identified non-collinear covariates were added to the covariate model. After conclusion of the stepwise forward step, covariance between variance parameters were investigated. In a final step, covariates were removed from the model in a stepwise backward covariate elimination step. During this step, covariates were to be permanently excluded from the model if removing them resulted in increase in OFV < 10.83.

Continuous covariates were evaluated using a power function and categorical covariates were parameterized as a fractional change.

Final Model

The stepwise covariate model building included the following relationships in the forward inclusion step: BSA and JAK2_V617F allele burden as covariate on CL/F; Healthy status as covariate on Vc/F; and age as covariate on Ka. The parameter estimates for the final covariate model are listed in Table 6. The goodness-of-fit plots for the final covariate model for all data are shown in **Figure 2**. The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in **Figure 3**.

Table 6. Parameter estimates from the Applicant's final population PK model.

Parameter	Final estimate	%SEM
CL/F (L/day) coefficient at mean BSA of 1.92 m^2 and CL/F-JAK2_V617F of 35.3%	1.12	2.70
CL/F-BSA power	1.15	21.9
CL/F-JAK2_V617F allele burden slope	0.000164	27.7
Vc/F (L) coefficient	2.56	12.4
Fold-increase in Vc/F for PV patient	0.892	35.5
k_a (day^{-1}) coefficient at mean age of 54.3 yr	0.120	5.73
k_a-age power	-0.655	23.7
t_{lag} (hr)	0.658	9.36
$R_{tot,0}$ (ng/mL)	0.322	17.7
$R_{tot,SS}$ (ng/mL)	0.0382	18.2
k_{int} (hr^{-1})	0.0333	12.3
k_{deg} (hr^{-1})	0.362	17.8
K_D (ng/mL)	0.181	16.9
k_{dec} (day^{-1})	0.0253	10.8
TSTART (days)	7.00[a]	FIXED
ω^2 for CL/F	0.0621 (24.9% CV)	14.1
ω^2 for Vc/F	0.276 (52.5% CV)	24.6
ω^2 for k_a	0.161 (40.1% CV)	16.5
ω^2 for $R_{tot,0}$	0.893 (94.5% CV)	32.3
ω^2 for k_{int}	0.0592 (76.9% CV)	36.8
σ^2 CCV component	0.0336 (18.3% CV)	2.64
Additive component	0.0463 (0.215 SD)	12.6

Note: Abbreviations are provided in the Abbreviation Listing.
a. Fixed to value obtained from the base structural PK model stage run in order to stabilize model and achieve successful minimization

Source: Applicant's population PK report (#0158-1, page 63)

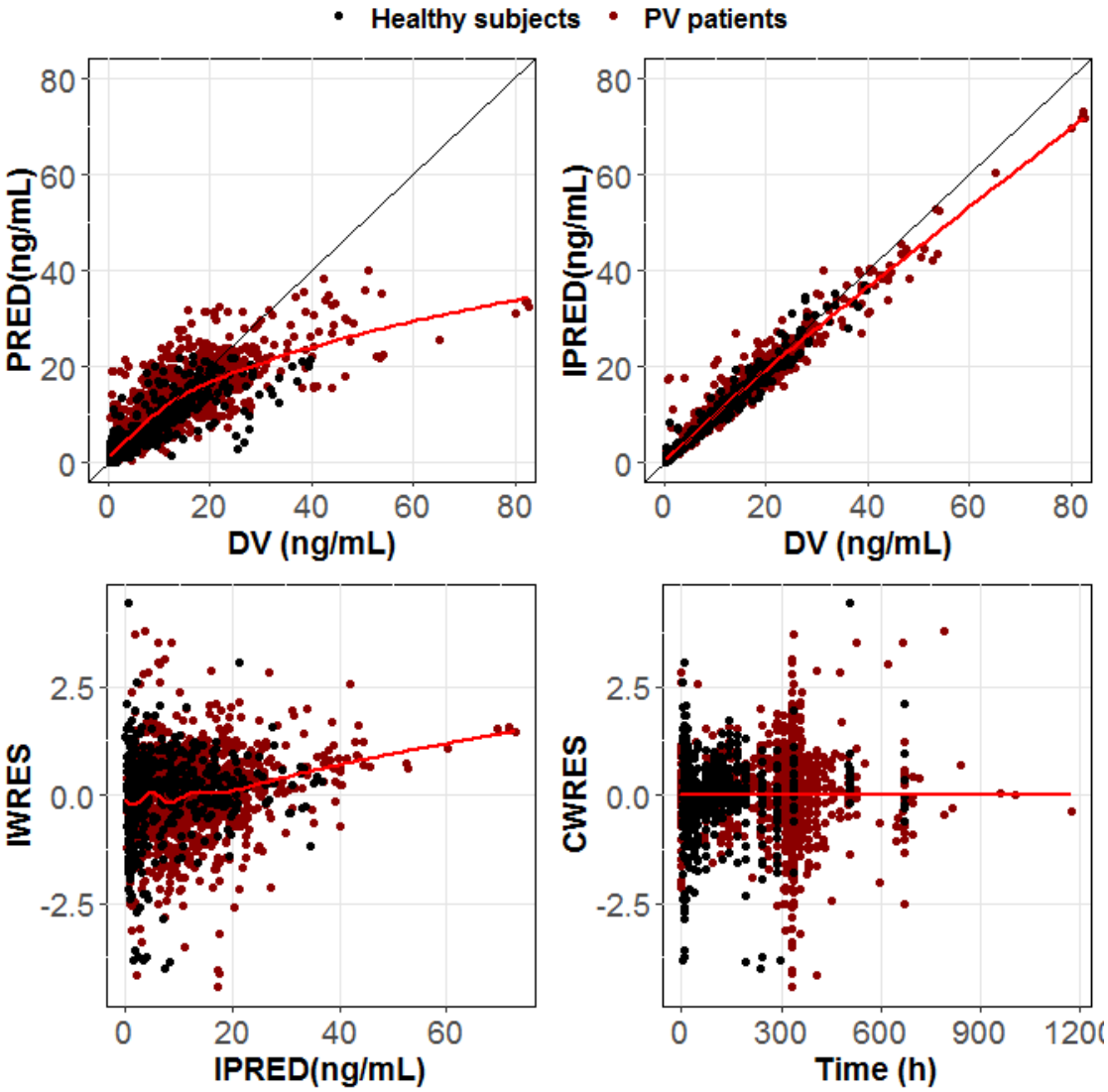


Figure 2. Goodness-of-fit plots for final covariate model.

Source: Reviewer's post-processing of NONMEM outputs of the Applicant's pop PK model

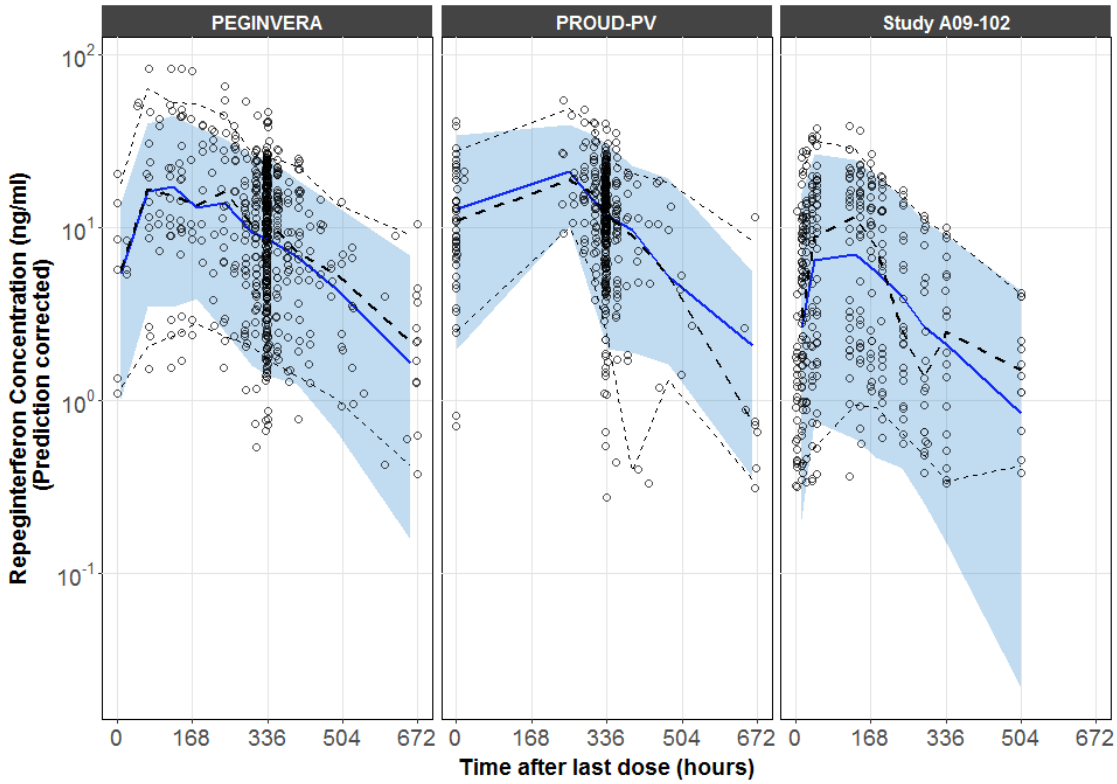


Figure 3. Prediction Corrected VPC for the Applicant's Final Model. Blue shared area represents the 95% prediction interval, blue solid line = median of the simulated data, black dashed line = median of the observed data, black circles = observed data, lower and upper black dashed lines represent 5th and 95th percentiles of the observed data

Source: Reviewer's post-processing of NONMEM outputs of the Applicant's pop PK model

4.2.1.4. Reviewer's comments

The reviewer finds the applicant's model development steps and identification of covariate effects to be acceptable. Based on simulations using the applicant's final model, ropeginterferon AUC and Cmin were dependent on body weight with subjects in the first quartile of body weight having 20% and 27% higher AUC and Cmin respectively than subjects with median weight. Similarly, the simulations indicated that subjects in first quartile of JAK2 allele burden have 23% and 25% higher AUC and Cmin respectively than subjects with median burden. However, these covariate effect will not have impact on ropeginterferon exposure since the dose will be individually titrated to an effective and tolerable amount. The reviewer repeated the applicant's analyses and found similar results as those reported by the applicant.

4.2.2. Exposure-vs-efficacy Analysis

4.2.2.1. Review Summary

The applicant's exposure-response (ER) analyses for the hematological endpoints (hematocrit (HCT), platelets (PLT), and white-blood cells (WBC)) are acceptable for characterizing the hematological profiles during treatment with ropeginterferon. The hematological profiles were described by indirect response models parameterized in baseline hematological values (HCT0, PLT0, and WBC0), first-order rate constant

of cell elimination (K_{out}), and drug effect ($DE = \frac{Imax \times Conc^{\gamma}}{IC50 + Conc^{\gamma}}$). Baseline zero-order rate constant of cell production (K_{in}) was derived as product of K_{out} and baseline hematological values. There was good agreement between model predicted and observed data. However, in these models, baseline hematological values (HCT0, PLT0, and WBC0) reflect the intensity of periodic phlebotomy that the patients received before starting ropeginterferon treatment. As a result, the derived K_{in} values may be lower than true intrinsic $K_{in'}$ values due to the PV disease without phlebotomy. With K_{in} being lower than its true value, the estimated drug effect (DE) parameters (Imax, IC50, and γ) appear to be apparent than true values. Furthermore, the estimated DE parameters appears to be apparent values than true values because, despite that some patients continued to receive phlebotomy during ropeginterferon treatment, the influence of phlebotomy on hematological profiles was not accounted for in the model.
In order to account for phlebotomies, both before and during treatment, the reviewers developed an alternative model describing the longitudinal relationship between drug exposure and probability of complete hematological response without phlebotomy within previous 3 months (CHRP). The model was used to predict the probability of CHRP overtime at different ropeginterferon dosages, and through simulations, the applicant's recommended dosage was supported. The sections below summarize the applicant's E-R analyses followed by the reviewer's independent E-R analyses.

4.2.2.2. Applicant's exposure-response analyses

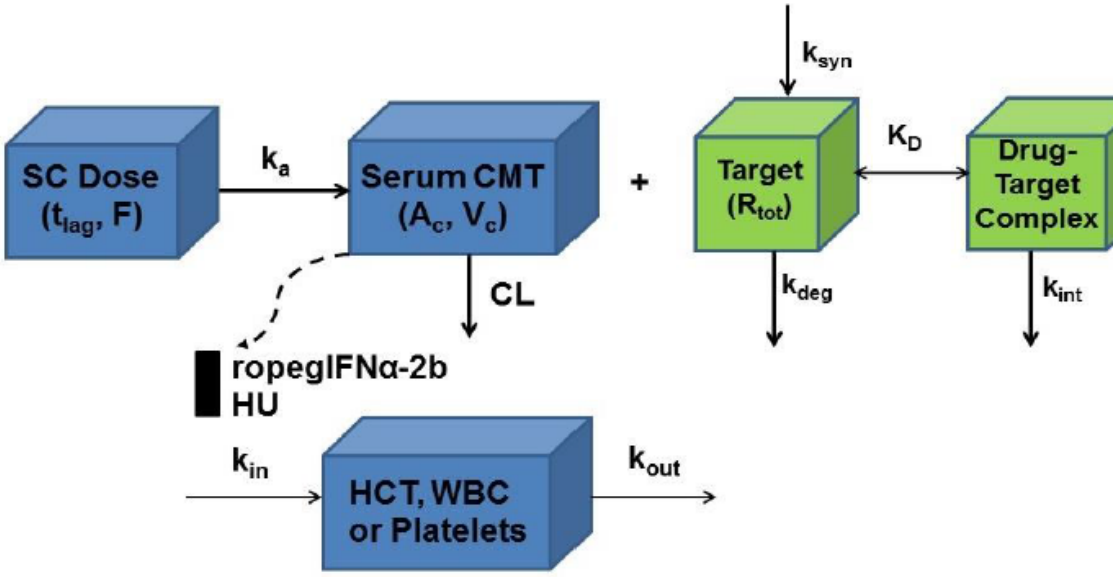
The applicant developed ER models for three hematology PD endpoints (HCT, PLT, and WBC) using pooled data from PEGINVERA, PROUD-PV, PEN-PV, and CONTINUATION-PV studies (n=178). A brief description of PEGINVERA and PROUD-PV studies is given in Table 4. The PEN-PV study assessed the ease of use and safety of a self-administration device prefilled with ropeginterferon in 36 patients from the PROUD-PV study who had completed 12 months of continuous treatment with ropeginterferon. The CONTINUATION-PV assessed long-term safety and efficacy of ropeginterferon compared to best available therapy (BAT) among patients completing the first 12 months of the PROUD-PV study. Summary statistics of baseline subject characteristics for the overall ER analysis population are given in Table 7. Mean age, weight and JAK2_V617 allele burden were 58.5 years, 76.2 Kg, and 42.5% respectively.

Table 7. Baseline characteristics of subjects included in the PKPD studies.

Variable		N (%)	Mean	SD	Median	Min	Max
Age (yr)		178	58.5	11.0	60.0	30	85
Weight (kg)		178	76.2	13.7	75.0	48.6	125
Height (cm)		178	170	8.76	170	149	188
BSA (m^2)		178	1.91	0.205	1.90	1.47	2.52
BMI (kg/m^2)		178	26.3	3.77	25.9	17.2	40
JAK2_V617F allele burden (%)		178	42.5	25	38.2	0	99
HCT (%)		178	47.1	5.03	46.8	36.8	61.7
WBC ($10^9/L$)		178	11.6	4.89	10.9	4	30.9
Platelets ($10^9/L$)		178	515	253	459	115	1500
Sex	Male	90 (50.6)	—	—	—	—	—
	Female	88 (49.4)	—	—	—	—	—
Race	Caucasian	177 (99.4)	—	—	—	—	—
	Black	0 (0)	—	—	—	—	—
	Asian	1 (0.6)	—	—	—	—	—
ECOG Score	0	131 (73.6)	—	—	—	—	—
	1	44 (24.7)	—	—	—	—	—
	2	3 (0.02)	—	—	—	—	—

Source: Applicant's population PKPD report (#0165)

The applicant tested a maturation PK-PD model and indirect response PK-PD model for the effect of ropeginterferon on hematology PD endpoints. The applicant found that the basic indirect response PK-PD model, as shown in **Figure 4**, was the most parsimonious model to characterize the joint effects of serum ropeginteferon and time-varying hydroxyurea (HU) dose on reducing HCT, PLT and WBC in PV patients.



$$\frac{dHCT}{dt} = k_{in,H} \bullet \left(1 - \frac{I_{max,H} \bullet C_S^{\gamma_H}}{IC_{50,H}^{\gamma_H} + C_S^{\gamma_H}}\right) \bullet \left(1 - \frac{I_{max,HU,H} \bullet Dose_{HU}}{Dose_{50,H} + Dose_{HU}}\right) - k_{out,H} \bullet HCT$$

$$\frac{dPLAT}{dt} = k_{in,P} \bullet \left(1 - \frac{I_{max,P} \bullet C_S^{\gamma_P}}{IC_{50,P}^{\gamma_P} + C_S^{\gamma_P}}\right) \bullet \left(1 - \frac{I_{max,HU,P} \bullet Dose_{HU}}{Dose_{50,P} + Dose_{HU}}\right) - k_{out,P} \bullet PLAT$$

$$\frac{dWBC}{dt} = k_{in,W} \bullet \left(1 - \frac{I_{max,W} \bullet C_S^{\gamma_W}}{IC_{50,W}^{\gamma_W} + C_S^{\gamma_W}}\right) \bullet \left(1 - \frac{I_{max,HU,W} \bullet Dose_{HU}}{Dose_{50,W} + Dose_{HU}}\right) - k_{out,W} \bullet WBC$$

Figure 4. Schematic diagram of the exposure response model

Source: Applicant's population PKPD report (#0165)

The indirect ER models were parameterized by rate constant of cell expiration (K_{out}) and estimated baseline fraction/amount (HCT0, PLT0, and WBC0). The baseline zero-order rate constant of cell production or generation of the PD endpoints (K_{in}) was calculated as the product of baseline fraction/amount and K_{out}. The K_{in} decreased over time due to drug effect (DE). The ropeginterferon DE model was an Emax model parameterized by Imax (maximum reduction in K_{in}), EC50 (ropeginterferon concentration at which 50% of Imax achieved), and the Hill coefficient (γ). Ropeginterferon concentration (Cs) was derived from the final population PK model and the emperical bayes parameter estimates. The hydroxyurea effect model was also an Emax model with time varying hydroxyurea dose as the driver of effect. Stepwise covariate model building (guided by graphical exploration) was used to assess covariates of the ER model parameters. Results from each of the hematology PD endpoint models are briefly described in the sub-sections below.

Ropeginterferon concentration vs hematocrit.

The parameter estimates of the final hematocrit ER model are given in Table 8. Sex was a covariate on HCT0, with female subjects estimated to have 6.49% lower baseline hematocrit than males. On the other hand, baseline observed HCT was a significant covariate on Imax, with Imax parameterized as increasing with baseline HCT using a power function.

Table 8. Parameter estimates of the final indirect ER model for effect of ropeginterferon on HCT in PV patients.

Parameter	Final estimate	%SEM
HCT_0 (fraction) for males	0.477	0.642
Proportional decrease in HCT_0 for females	-0.0622	13.5
$k_{out,H}$ (day^{-1})	0.00393	12.6
$I_{max,H}$ Coefficient at mean baseline HCT of 0.471	0.176	9.80
$I_{max,H}$-Baseline HCT power	2.31	31.8
$IC_{50,H}$ (ng/mL)	0.719	23.2
γ_H	2.08	5.91
$I_{max,HU,H}$	1	FIXED
$Dose_{50,H}$ (mg)	984	58.9
ω^2 for HCT_0	0.00331 (5.75% CV)	11.6
ω^2 for $k_{out,H}$	2.19 (148% CV)	15.9
Covariance($\eta k_{out,H}$,$\eta I_{max,H}$)	-0.848 (r^2 = 0.278)	25.9
ω^2 for $I_{max,H}$	1.18 (1.09 SD)	12.3
ω^2 for $IC_{50,H}$	9.23 (304% CV)	14.8
ω^2 for $Dose_{50,H}$	8.34 (289% CV)	50.0
σ^2 CCV	0.00253 (5.03% CV)	0.50

Note: Abbreviations are provided in the Abbreviation Listing
Note: $k_{in,H}$ was calculated as $HCT_0 \cdot k_{out,H}$

Source: Applicant's population PKPD report (#0165, pages 55)

The PC-VPC of the final ER model for HCT is shown in **Figure 5**. The median of the simulated HCT profiles is higher than the median of the observed data for the first 3 months of treatment indicating that the model overpredicts HCT profiles for the first 3 months.

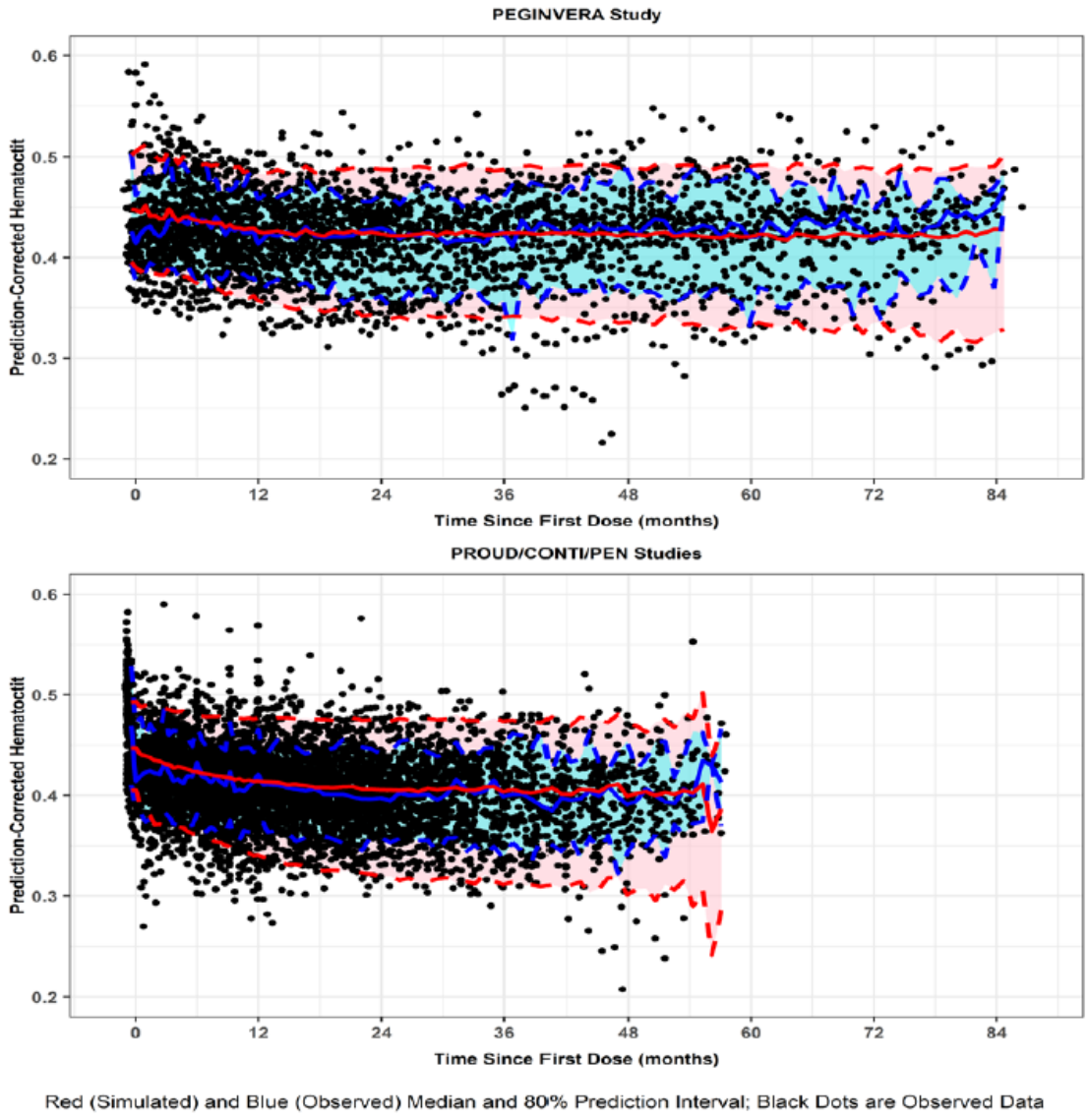


Figure 5. PC-VPC of the final indirect-response ER model for HCT in PV patients. Red solid lines represent model predictions of the median while blue solid line represent median of the observed data. Red shaded area represents 95% prediction interval while blue shaded area represents 95%CI of the observed data.

Source: Applicant's population PKPD report (#0165, pages 58)

Ropeginterferon concentration vs platelets.

The parameter estimates for the final indirect-response ER model for PLT are given in Table 9. Covariate analysis identified baseline PLT count to be a statistically significant covariate on Imax, with Imax parameterized as increasing with the observed baseline PLT count using a power function.

Table 9. Parameter estimates of the final indirect ER model for effect of ropeginterferon on PLT in PV patients.

Parameter	Final estimate	%SEM
PLT_0 (10^9/L)	471	3.36
$k_{out,P}$ (day^{-1})	0.0119	8.05
$I_{max,P}$ Coefficient at mean baseline platelet count of 515	0.667	2.00
$I_{max,P}$-Baseline platelet count power	0.151	23.3
$IC_{50,P}$ (ng/mL)	1.46	8.18
γ_P	1.64	3.07
$I_{max,HU,P}$	1	FIXED
$Dose_{50,P}$ (mg)	2064	26.0
ω^2 for PLT_0	0.179 (42.3% CV)	11.4
ω^2 for $k_{out,P}$	1.31 (114% CV)	14.5
Covariance($\eta k_{out,P}$,$\eta I_{max,P}$)	-0.380 (r^2 = 0.230)	24.5
ω^2 for $I_{max,P}$	0.480 (0.692 SD)	11.0
ω^2 for $IC_{50,P}$	2.37 (154% CV)	16.7
ω^2 for $Dose_{50,P}$	2.51 (158% CV)	71.2
σ^2 CCV	0.0288 (17.0% CV)	0.25

Note: Abbreviations are provided in the Abbreviation Listing
Note: $k_{in,P}$ was calculated as $PLT_0 \bullet k_{out,P}$

Source: Applicant's population PKPD report (#0165, pages 60)

Unlike the HCT model, the PLT model has no overprediction of the median PLT profiles overtime (See **Figure 6**)

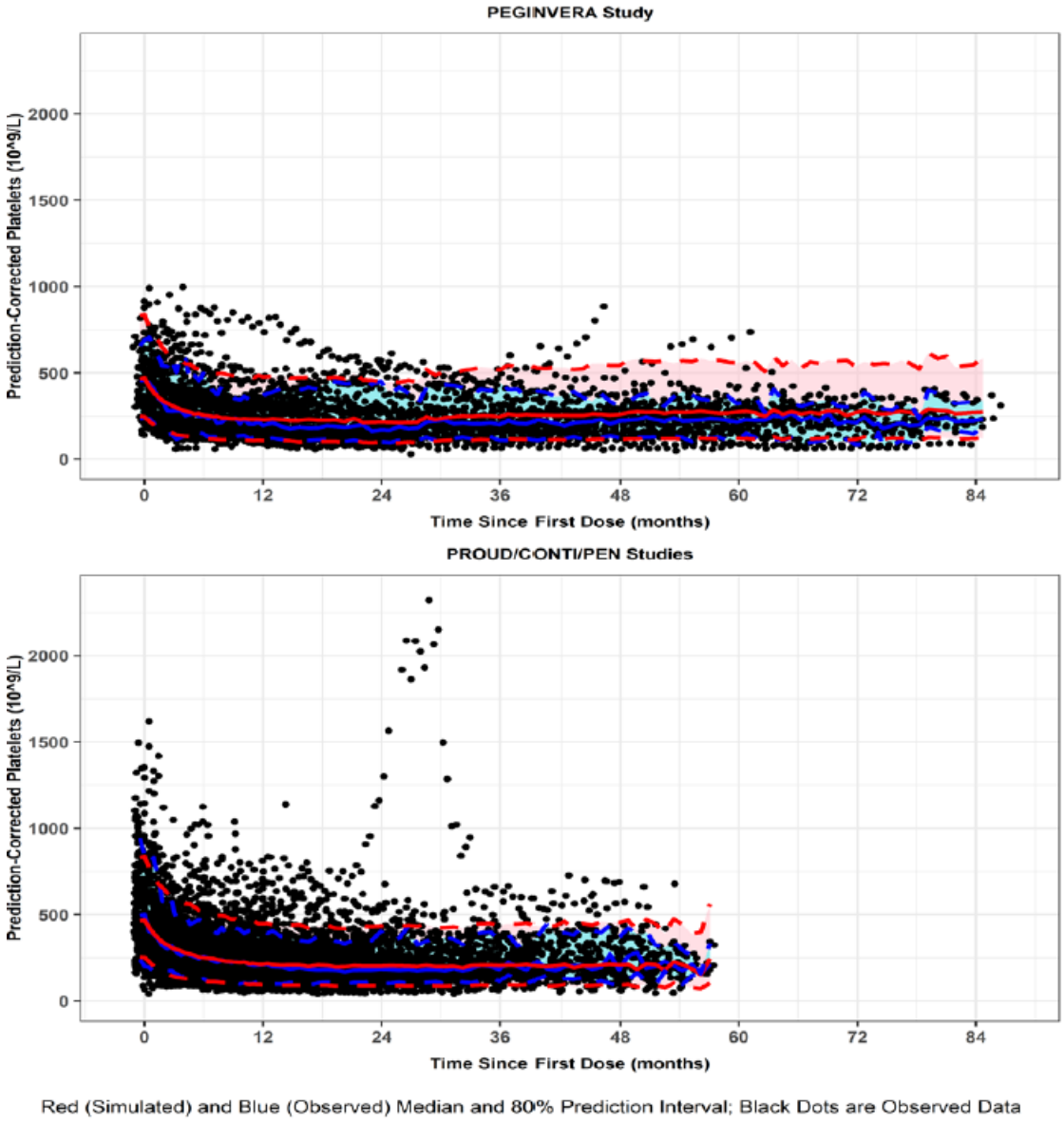


Figure 6. PC-VPC of the final indirect-response ER model for PLT in PV patients. Red solid lines represent model predictions of the median while blue solid line represent median of the observed data. Red shaded area represents 95% prediction interval while blue shaded area represents 95%CI of the observed data.

Source: Applicant's population PKPD report (#0165, pages 63)

Ropeginterferon concentration vs white-blood cells.

The parameter estimates of the final indirect-response model for WBC in PV patients are given in Table 10. Covariate analysis identified JAK2_V617F allele burden to be a covariate for both WBC0 and Imax. Baseline WBC was identified as a covariate for Imax, with Imax parameterized as increasing with baseline WBC using a power function.

Table 10. Parameter estimates of the final indirect ER model for effect of ropeginterferon on WBC in PV patients.

Parameter	Final estimate	%SEM
WBC_0 (10^9/L) Coefficient at JAK2_V617F allele burden of 42.5%	10.6	2.63
WBC_0-JAK2_V617F allele burden slope	0.0691	16.7
$k_{out,W}$ (day^{-1})	0.0222	13.0
$I_{max,W}$ Coefficient at JAK2_V617F allele burden of 42.5% and observed baseline WBC count of 11.6 10^9/L	0.592	2.66
$I_{max,W}$-JAK2_V617F allele burden slope	0.00262	28.7
$I_{max,W}$-Baseline WBC count power	0.173	35.8
$IC_{50,W}$ (ng/mL)	0.482	28.0
γ_W	0.861	4.69
$I_{max,HU,W}$	1	FIXED
$Dose_{50,W}$ (mg)	2331	5.56
ω^2 for WBC_0	0.0992 (31.5% CV)	12.8
ω^2 for $k_{out,W}$	2.60 (161% CV)	16.3
ω^2 for $I_{max,W}$	0.414 (0.643 SD)	16.0
ω^2 for $IC_{50,W}$	6.77 (260% CV)	12.2
ω^2 for $Dose_{50,W}$	1.21 (110% CV)	45.5
σ^2 CCV	0.0313 (17.7% CV)	0.49

Note: Abbreviations are provided in the Abbreviation Listing
Note: $k_{in,W}$ was calculated as $WBC_0 \bullet k_{out,W}$

source: Applicant's population PKPD report (#0165, pages 65)

Unlike the HCT model, the WBC model has no overprediction of WBC profiles overtime (See **Figure 7**)

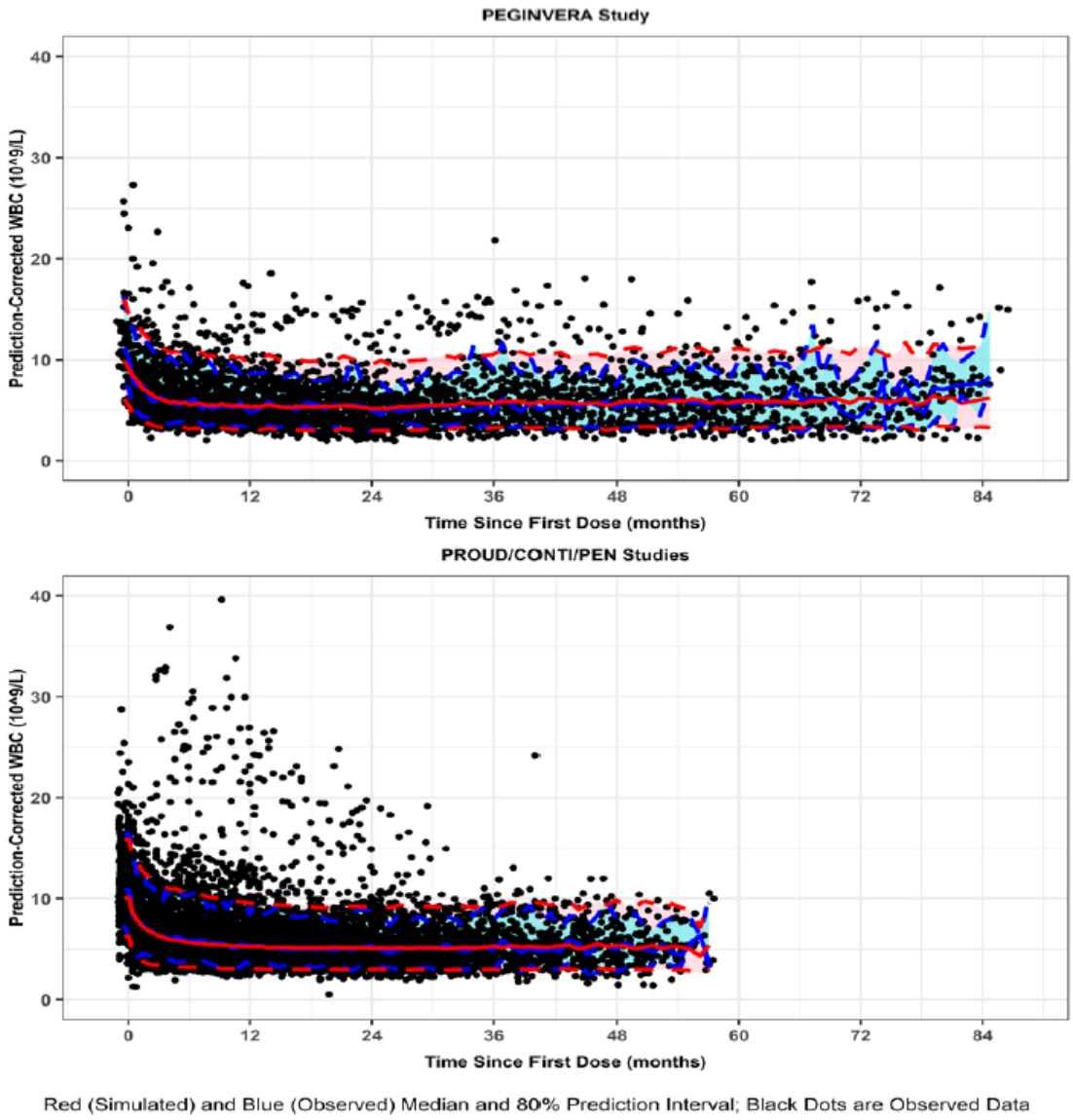


Figure 7. PC-VPC of the final indirect-response ER model for PLT in PV patients. Red solid lines represent model predictions of the median while blue solid line represent median of the observed data. Red shaded area represents 95% prediction interval while blue shaded area represents 95%CI of the observed data.

Source: Applicant's population PKPD report (#0165, pages 68)

Steady state ropeginterferon exposure vs probability of complete hematological response at 3 years

The applicant also assessed the relationship between steady-state ropeginterferon exposures (Cmin_ss, Cmax_ss, and AUC0-tau_ss) versus the probability of complete hematological responses. Several complete hematological response endpoints were assessed, but only two of them will be reviewed here: (1) Complete hematological response regardless of phelobotomy (CHR). For this endpoint, the following hematological

criteria were to be met at 36 months (± 4) after start of treatment; platelet count < $400 \times 10^9/L$, WBC counts < $10 \times 10^9/L$, and hematocrit < 0.45. (2) Complete hematological response without phlebotomy (CHRP). For this endpoint, subjects had CHRP if in addition to meeting criteria for CHR, they did dot undergo phlebotomy within the previous 3 months. For every patient, steady-state exposure measures were generated based on the structural PK model, the actual dosing histories, and individual post-hoc PK parameters. All patients recruited in PEGINVERA (n=51) and PROUD-PV (n=127) study were included in these analyses. For patients who did not receive dose at or past 35 months, the last available hematological data was used to calculate CHR or CHRP (Last observation carried forward). Exploratory graphical analysis of proportions with CHR/CHRP versus 10 quantiles of Cmin_ss, Cmax_ss, and AUC0-tau_ss were used to determine plausible relationships to take further into logistic regression analysis.

Logistic regression analyses identified AUC_{0-tau} to be the best predictor of CHR and CHRP. Additional predictors were age, and baseline platelet count. Table 11 shows the structure of the final logistic regression model and the estimated parameters. **Figure 8 and Figure 9** are validation plots showing good agreement between observed and predicted probabilities of CHR and CHRP at 36 months (± 4) after treatment.

Table 11. Parameter estimates of the final logistic regression models of ropeginterferon AUC0-tau versus CHR and CHRP.

CHR Definition	Logit Model	COV_1	COV_2	θ_1 (SE)	θ_2 (SE)	θ_3 (SE)	θ_4 (SE)	θ_5 (SE)
CHR	$CHR \sim \theta_1+\theta_2*\frac{AUC_{0-tau}}{\theta_3+AUC_{0-tau}}+\theta_4*COV_1+\theta_5*COV_2$	AGE	$PLAT_0$	-7.00 FIXED	10.7 (1.03)	5.30 (2.94)	-0.0452 (0.0152)	-0.00133 (0.000661)
CHRP	$CHR \sim \theta_1+\theta_2*\frac{AUC_{0-tau}}{\theta_3+AUC_{0-tau}}+\theta_4*COV_1$	AGE	-	-7.00 FIXED	9.88 (0.913)	5.04 (3.10)	-0.0447 (0.0151)	-

Source: Applicant's population PKPD report (#0165, pages 82)

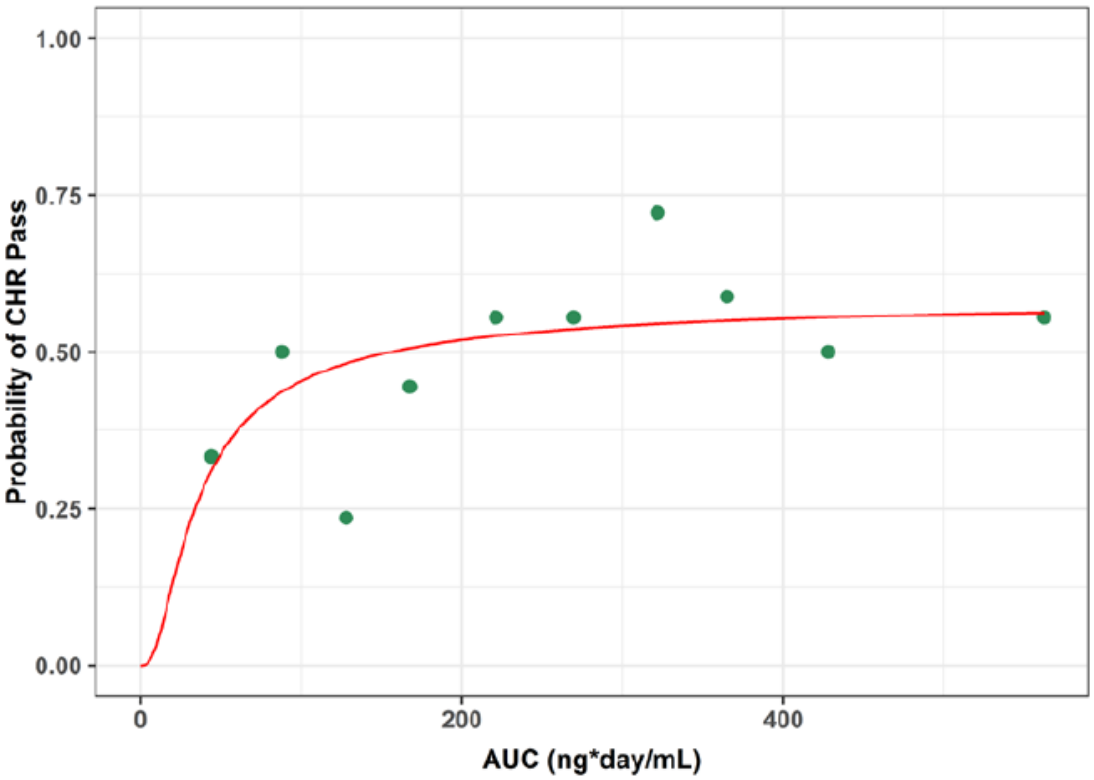


Figure 8. Observed and Predicted probability of CHR versus quantiles of steady state $AUC_{0\text{-}tau}$.

Source: Applicant's population PKPD report (#0165, pages 83)

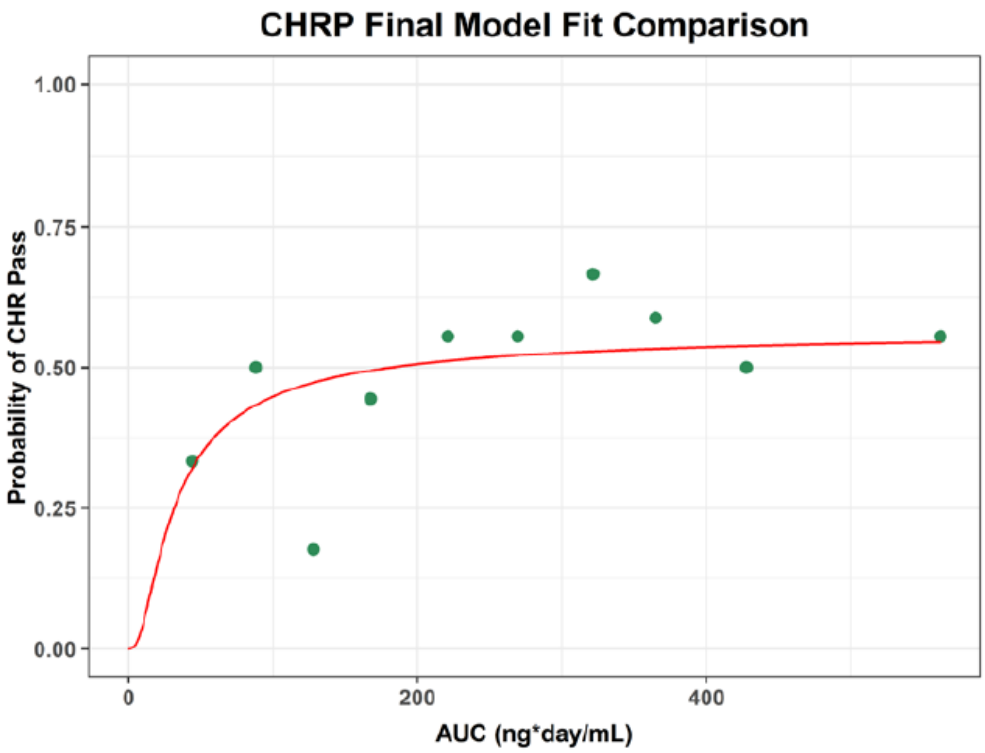


Figure 9. Observed and Predicted probability of CHRP versus quantiles of steady state $AUC_{0\text{-}tau}$.

source: Applicant's population PKPD report (#0165, pages 84)

Simulation of hematological endpoints and derivation of CHR overtime

The applicant used parameters from the final PKPD models of hematocrit, platelet, and WBC count to simulate time profiles for these hematological endpoints in a virtual population of patients having the same demographic and disease related characteristics as the patients in PEGINVERA and PROUD-PV studies. Individual PKPD models of hematocrit, platelet, and WBC count were merged into one full model which was subsequently used to simulate the profiles of hematocrit, platelet, and WBC count simultaneously. The full model ensured covariance between variance parameters of the individual models. The aim of the simulations were to support the recommended ropeginterferon dosage and therefore the following dosages were used during the simulations: For patients naive to hydroxyurea, ropeginterferon was initiated at 100μg , and titrated by 50μg every 2 weeks until a maximum dose of 500 μg; For patients switching from hydroxyurea, the starting dose was 50μg, tritrated by 50μg every 2 weeks until a maximum dose of 500 μg, in these patients, hydroxyurea dose was reduced from 1000 mg to 600 mg after 6 weeks of treatment and finally stopped at week 12. The simulated hematocrit, platelets, and WBC counts were used to derive CHR at 12, 26, 38, 52, 64, 78, 90, 104, 116, 130, 142, and 156 weeks after treatment. **Figure 10** shows the derived CHR overtime. Since the individual models did not account for phlebotomy, it was not possible to simulate phlebotomy and derive CHRP overtime.

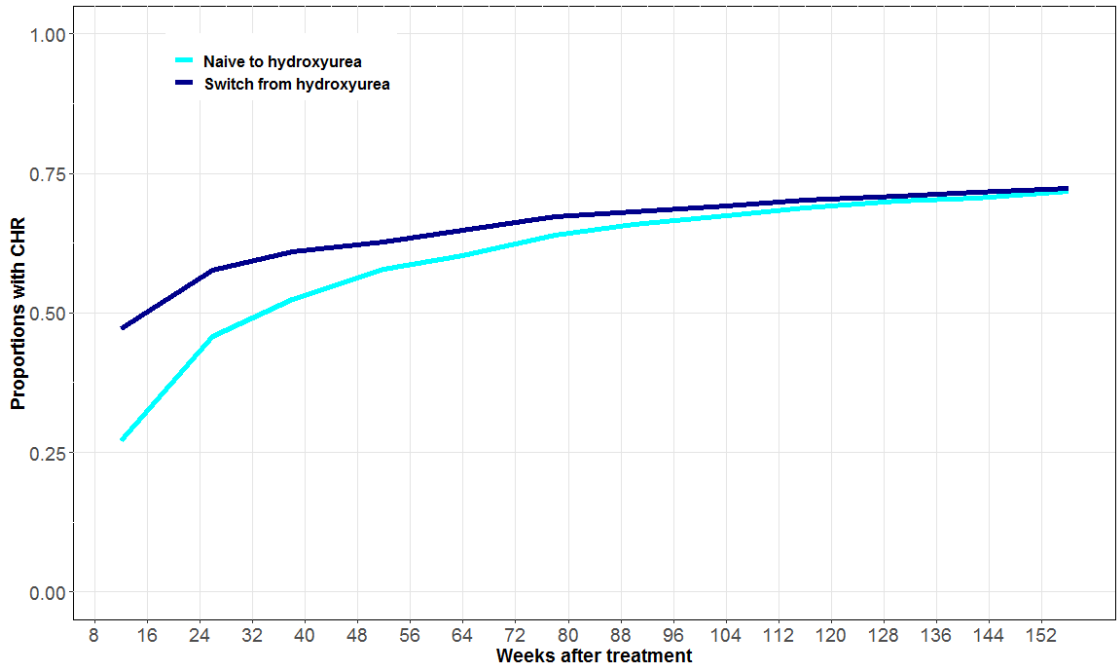


Figure 10. Predicted proportions of CHR overtime (Derived from hematological endpoints (HCT, PLT, and WBC) profiles) based on the final HCT, PLT, and WBC exposure-response models.

Source: Reviewer's analyses of the derived CHR data

4.2.2.3. Reviewer's comments

The applicant's analyses are acceptable for making conclusions on exposure-response relationships for HCT, PLT, WBC and CHR. They should not however be used to establish CHRP profile over the course of treatment. This is because the models do not account for effect of phlebotomies before and during treatment on the hematological endpoints. On the other hand, CHRP is an endpoint that account for influence of phlebotomy on the wellbeing of patients. For this reason, the reviewer developed an exposure-response model to describe the relationship between ropeginterferon exposure and CHRP overtime (0 - 24 months). The sections below describe the methods and results from the reviewer's independent analyses.

4.2.2.4. Reviewer's exposure-response analyses

Introduction

The applicant's E-R analyses do not account for the effect of phlebotomies on the hematological endpoints. A clinical endpoint that account for the effect of phlebotomy could be useful at establishing the course of clinical response overtime. CHRP is an endpoint that account for influence of phlebotomy on the wellbeing of patients. Bi-weekly CHRP data were available since the start of treatment and could be used to establish the bi-weekly clinical response overtime. The effect of ropeginterferon exposure on the bi-weekly response was investigated by the reviewer in a longitudinal exposure-response analysis.

Objectives

The objective of this exposure-response modeling was to describe the relationship between ropeginterferon exposure and CHRP overtime (0 - 24 months). Other objectives were to obtain post-hoc estimates of clinical responses overtime in both PEGINVERA and PROUD-PV/CONTINUATION-PV study, and to test the impact of different dosage algorithms (varying starting, increment and maximum doses) on the predicted time course of clinical response.

Methods

Longitudinal modeling of ropeginterferon exposure vs CHRP response

The bi-weekly rate of CHRP for patients in the PEGINVERA and PROUD-PV studies are shown in **Figure 11** and **Figure 12**, respectively. The figures show that the rate of CHRP increased overtime and was different between males and female after treatment, being slightly higher in female subjects.

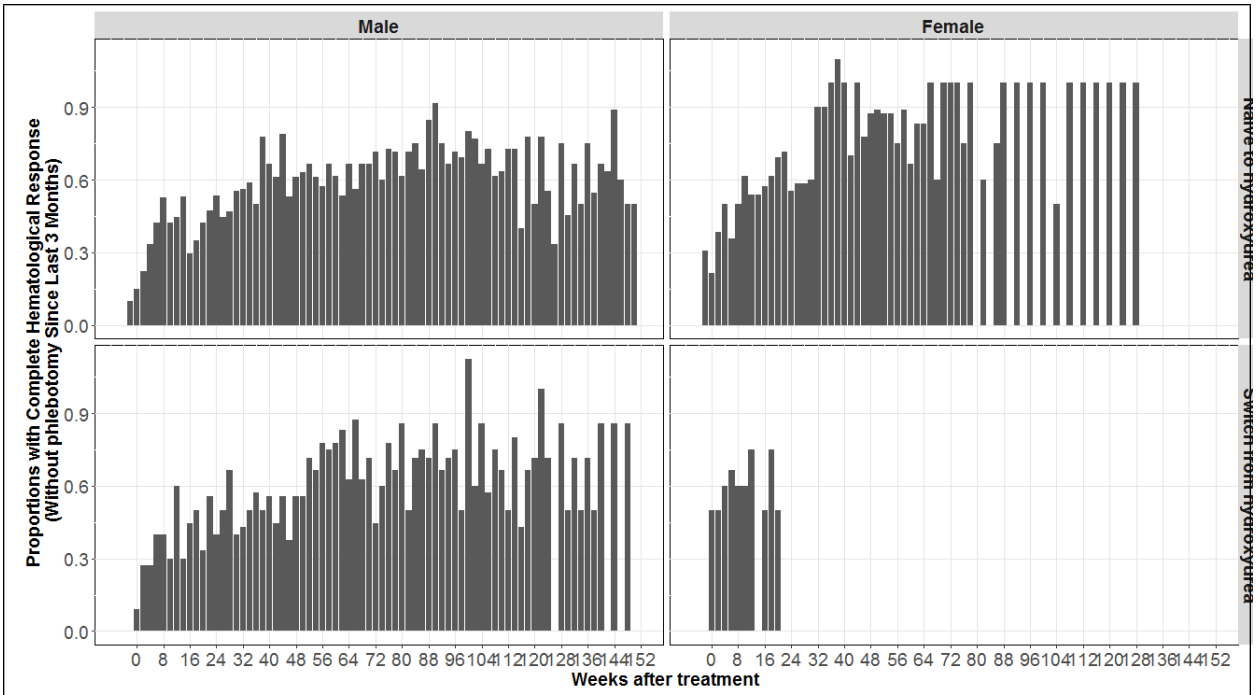


Figure 11. Bi-Weekly rate of CHRP in the PEGINVERA study.

Source: Reviewer's independent analyses

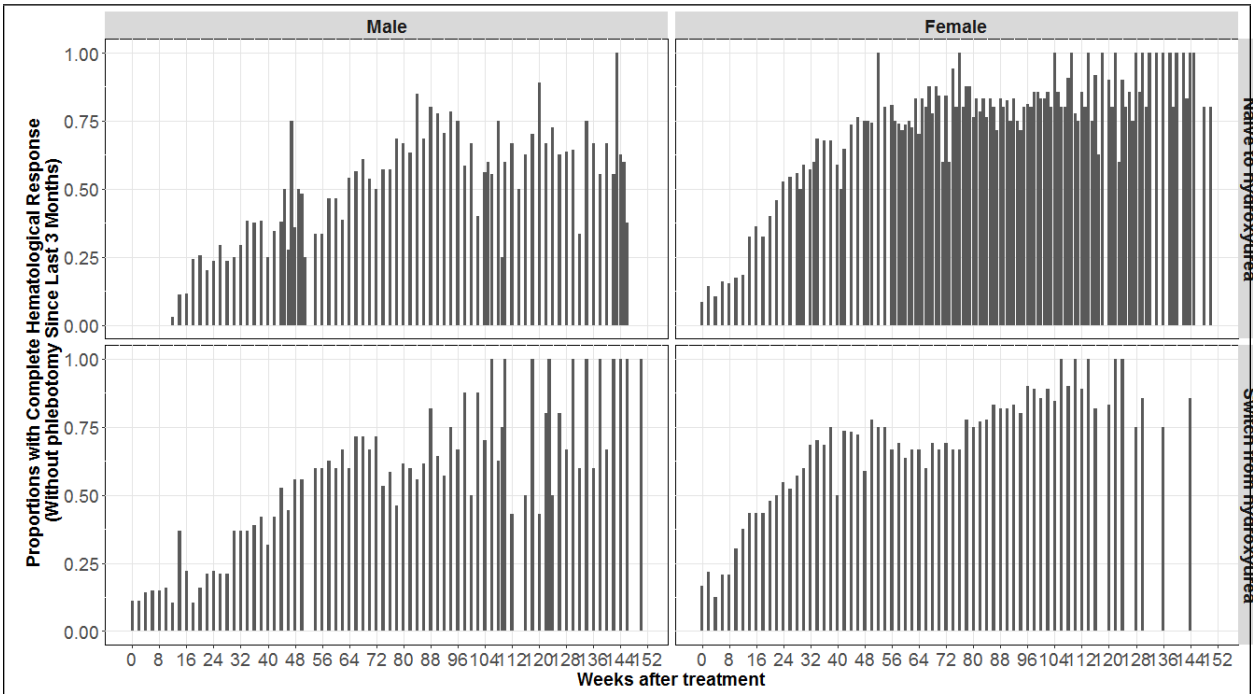


Figure 12. Bi-Weekly rate of CHRP in the PROUD-PV and CONTINUATION study

Source: Reviewer's independent analyses

The bi-weekly proportions of patients receiving different ropeginterferon doses in the PEGINVERA and PROUD-PV studies are shown in **Figure 13 and Figure 14** respectively. **Figure 14** shows increasing proportions of subjects on higher dose levels overtime. This is due to the implementation of the dose escalation protocol in the PROUD-PV study. The dose titration protocol was also implemented in the PEGINVERA study, but this is not clearly reflected in **Figure 13** because the figure represents doses taken during the part II of the PEGINVERA study. In this part of the study about 25 subjects, who had participated in part I of the study, were already on their tolerable and effective doses.

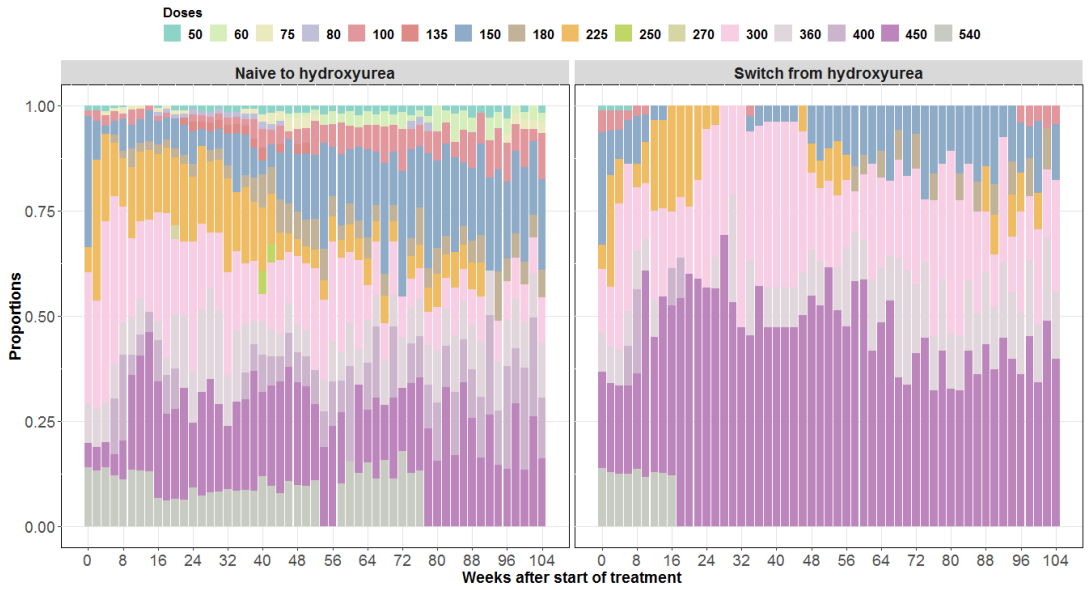


Figure 13. Proportions of Patients at Different Dose Levels Over Time in the PEGINVERA Study.

Source: Reviewer's independent analyses

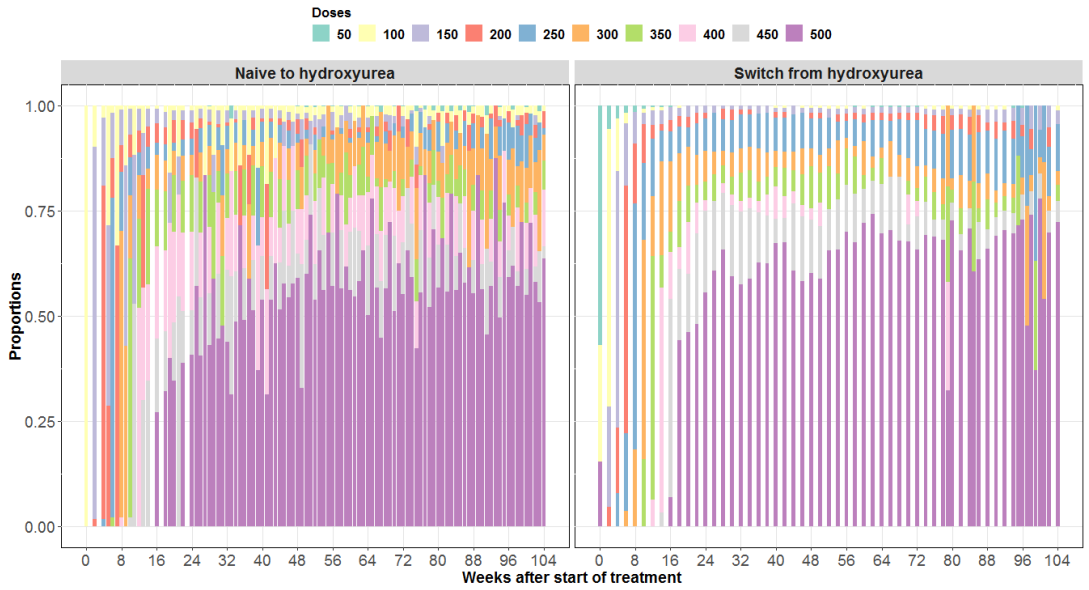


Figure 14. Proportions of Patients at Different Dose Levels Over Time in the PROUD-PV and CONTINUATION-PV Studies.

Source: Reviewer's independent analyses

The response dataset consisted of the subject identifiers, time, CHRP as a dependent variable (DV), and baseline covariate characteristics (demographic, laboratory and clinical). The exposure-response dataset was created by adding post-hoc PK parameter estimates from the final population PK model. Finally, since consecutive CHRP responses are correlated, an additional variable with CHRP lagged by 2 weeks (LAGDV) was added to the dataset as an additional predictor of CHRP.

The final logistic regression model expressed the relationship between the logit of CHRP, and drug effect and lagged CHRP as predictors (equation (1)). The drug effect was expressed as an Emax model parameterized in Emax, EC50 and HILL coefficient. The driver of drug effect was the ropeginteferon concentration in a hypothetical effect compartment that models the delay in drug effects. The concentration in the hypothetical effect compartment was determined by the rate constant of transfer to the hypothetical compartment from the central PK compartment (KEF).

$$logit(CHRP) = INTERCEPT + DRUGEFFECT + \beta \times LAGDV + \eta$$

$$Whereby:$$

$$logit(CHRP) = log\left(\frac{proportion\ of\ CHRP}{1 - proportion\ of\ CHRP}\right)$$

$$DRUGEFFECT = \frac{EMAX \times CONC^{\gamma}}{(EC50^{\gamma} + CONC^{\gamma})} \quad (1)$$

$$LAGDV = Lagged\ CHRP\ record$$

$$\beta = correlation\ coefficient\ between\ consecutive\ CHRP\ records$$

$$\eta = between\ subject\ residuals$$

$$\gamma = Hill\ coefficient\ (steepness\ of\ exposure\ vs\ drug\ effect\ relationship)$$

The identified covariates for the PKPD model parameters were sex on INTERCEPT and EMAX and Hydroxyurea use on INTERCEPT. Parameter estimates and diagnostic VPC plots for the final model fit to PEGINVERA and PROUD-PV data are given in the following sub-sections.

Results

Parameter estimates and VPC of the E-R model of the CHRP data from the PEGINVERA study

The parameter estimates of the longitudinal logistic regression model of CHRP data from the PEGINVERA study are given in Table 12. The corresponding visual predictive check of the model is shown in **Figure 15.**

Table 12. Parameter estimates of the final model fitted to CHRP data from the PEGINVERA trial.

Parameter	Description	Estimates (RSE)
Intercept_Naive	Intercept for subjects naive to hydroxyurea	-2.832(17%)
Intercept_HU	Intercept for subjects switching from hydroxyurea	1.083(27%)
Emax	Maximum drug effect	4.354(18%)
EC50 (ng/mL)	Concentration required to reach 50% of Emax	0.001564(21%)
Hill	Steepness of exposure-vs-drug effect relationship	1(FIXED)
Beta	Correlation coefficient between consecutive CHRP records	1.272(23%)
KEF	Rate constant of transfer to effect compartment	2.702e-08(52%)
Sex_Emax	Fold increase in Emax for female compared to male subjects	1.244(26%)
Sex_Int	Fractional decrease in intercept for female compared to male	0.6184(43%)
ETA	Standard deviation of the residual variability	2.121(12%)

Source: Reviewer's independent analyses

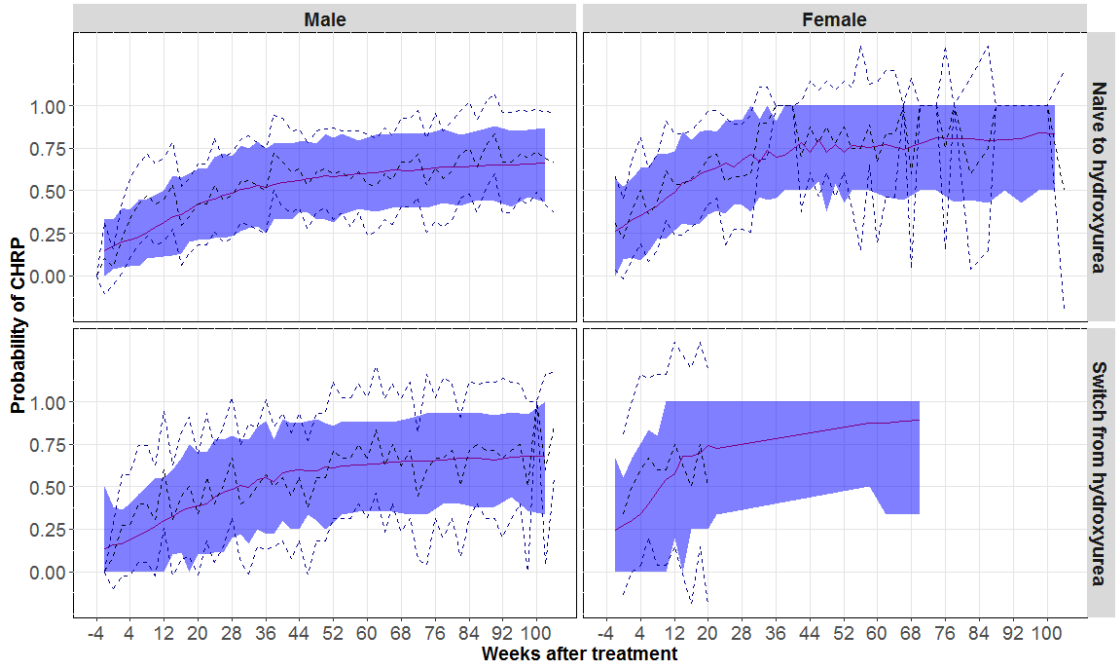


Figure 15. Visual Predictive Check of the final E-R model of CHRP using PEGINVERA data. Black dashed lines represent median and 95% confidence interval of the observed data while the red line and shaded area represent the median and 95% prediction intervals.

Source: Reviewer's independent analyses

Parameter estimates and VPC of the E-R model of the CHRP data from the PROUD-PV and CONTINUATION study

The parameter estimates of the longitudinal logistic regression model of CHRP data from the PROUD-PV study are given in Table 13. The corresponding visual predictive check of the model is shown in **Figure 16**.

Table 13. Parameter estimates of the final model fitted to CHRP data from the PROUD-PV and CONTINUATION studies.

Parameter	Description	Estimates (RSE)
Intercept_Naive	Intercept for subjects naive to hydroxyurea	-4.379(11%)
Intercept_HU	Intercept for subjects switching from hydroxyurea	0.9206(10%)
Emax	Maximum drug effect	6.456(20%)
EC50 (ng/mL)	Concentration required to reach 50% of Emax	0.002882(25%)
Hill	Steepness of exposure-vs-drug effect relationship	1(FIXED)
Beta	Correlation coefficient between consecutive CHRP records	3.532(5%)
KEF	Rate constant of transfer to effect compartment	1.305e-08(27%)
Sex_Emax	Fold increase in Emax for female compared to male subjects	1.156(19%)
Sex_Int	Fractional decrease in intercept for female compared to male	0.7509(13%)
ETA	Standard deviation of the residual variability	1.712(13%)

source: Reviewer's independent analyses

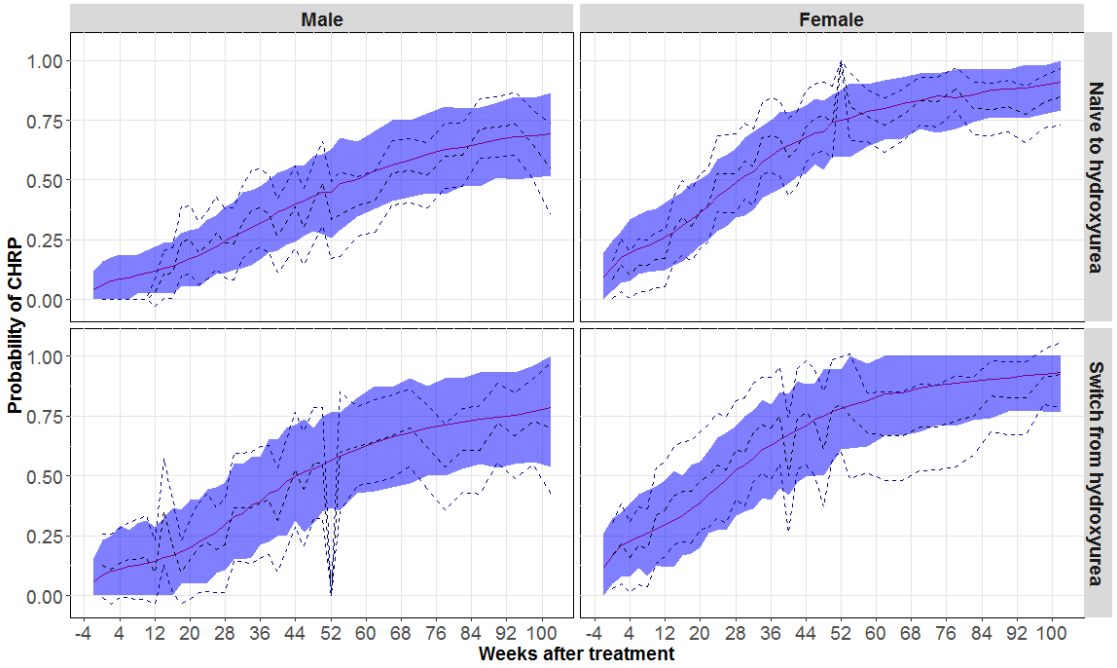


Figure 16. Visual Predictive Check of the final E-R model of CHRP using PROUD-PV and CONTINUATION data. Black dashed lines represent median and 95% confidence interval of the observed data while the red line and shaded area represent the median and 95% prediction.

Source: Reviewer's independent analyses

The stochastic simulations used for the VPCs of the final models were also used to derive the overall predicted probabilities of CHRP over-time in the PEGINVERA and PROUD-PV/CONTINUATION studies. The results of the derivation are shown in in Table 14.

Table 14. Predicted probability of CHRP over-time based on final models and datasets from the PROUD-PV/CONTINUATION and PEGINVERA studies.

	Probability of CHRP (95% CI)	
Weeks	PROUD-PV	PEGINVERA
0	11 (6 - 17)	22 (11 - 34)
12	21 (14 - 28)	40 (28 - 53)
20	28 (21 - 36)	50 (38 - 62)
52	62 (53 - 70)	64 (47 - 78)
104	83 (75 - 91)	70 (55 - 88)

Source: Reviewer's independent analyses

Investigation of alternative ropeginterferon dosage regimens

The observed and model predicted probabilities of CHRP indicates that response to ropeginterferon response is delayed. Using the final models and a virtual population of patients, the reviewer tested different alternative dosages to determine a dosage that would provide relatively early response to treatment. The

results of these investigation using the PEGINVERA and PROUD-PV models are given in **Figure 17 and Figure 18** respectively. They are also summarized in Table 15.

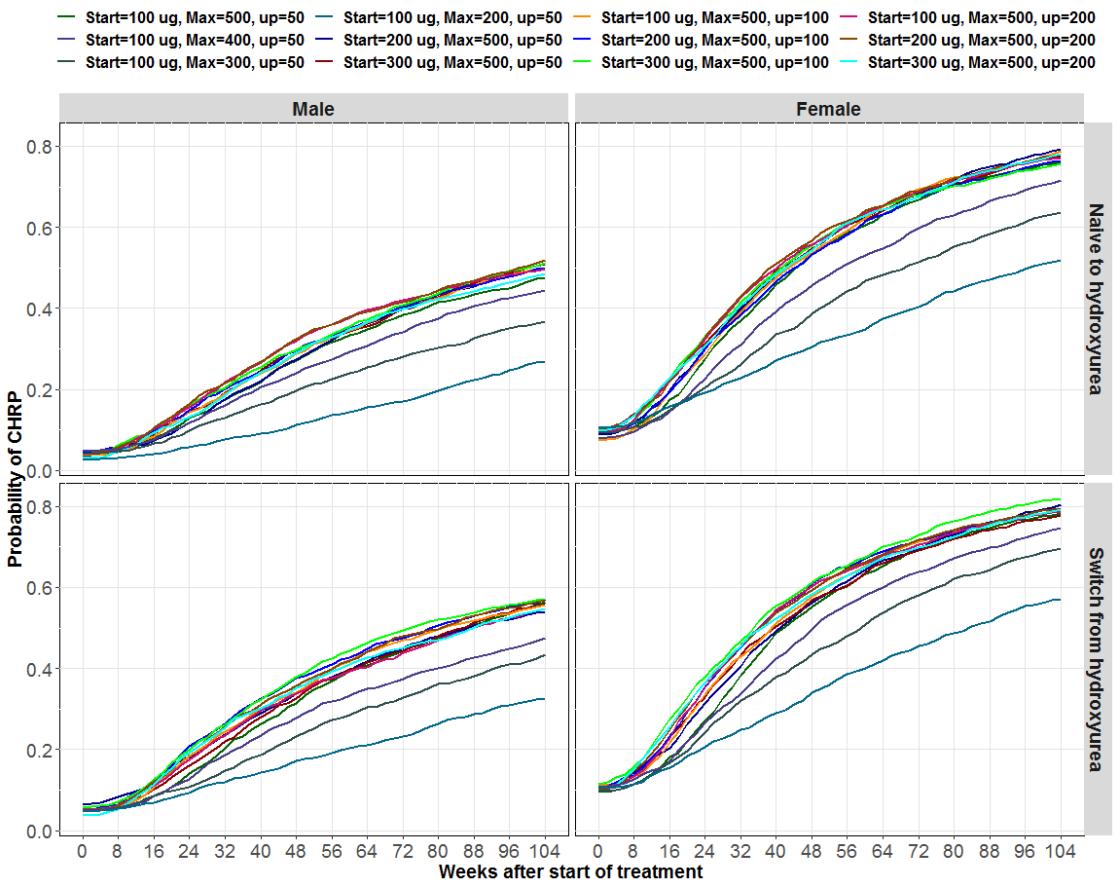


Figure 17. Predicted probabilities of CHRP over-time at different dosage of ropeginterferon using the model parameters obtained using the PROUD-PV dataset.

Source: Reviewer's independent analyses

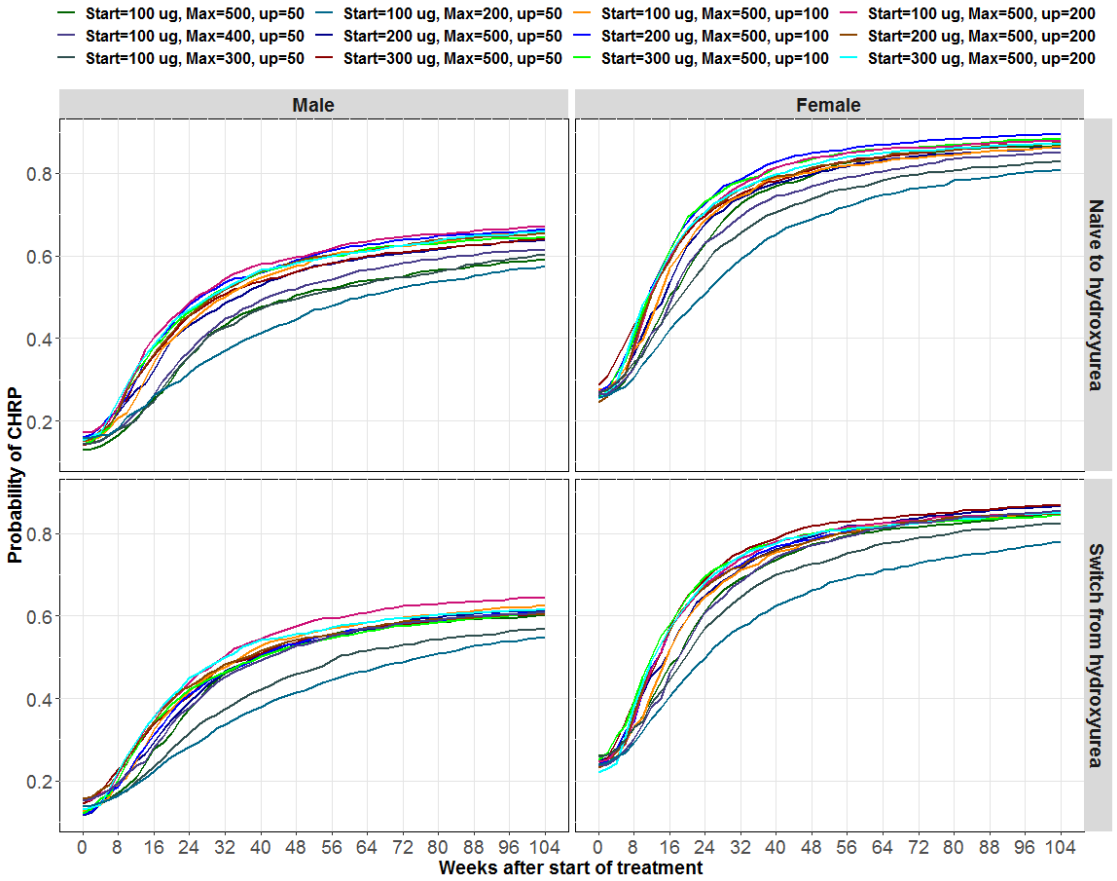


Figure 18. Predicted probabilities of CHRP over-time at different dosage of ropeginterferon using the model parameters obtained using the PEGINVERA dataset

Source: Reviewer's independent analyses

Table 15 . Predicted probability of CHRP at maximum ropeginterferon doses after 2 years of treatment.

	Probability of CHRP (95% CI)	
Maximum dose (ug)	PROUD-PV	PEGINVERA
200	52 (49 - 54)	80 (77 - 82)
300	64 (61 - 67)	84 (81 - 85)
400	71 (68 - 74)	85 (83 - 88)
500	76 (73 - 79)	86 (84 - 88)

Source: Reviewer's independent analyses

Conclusions from the reviewer's analyses

The following conclusions can be made from longitudinal logistic regression modeling and simulation of the PEGINVERA and PROUD-PV/CONTINUATION studies:

1. The proportion of patients with CHRP at the beginning of part II in the PEGINVERA study is higher (about 20%) than in PROUDPV (about 10%).

2. Observed data shows that females had higher proportions of CHRP over time compared to male subjects.

3. There is no difference in proportions of responders by age groups (<=65 Years vs > 65 years).

4. Compared to the model developed using PROUD-PV/CONTINUATION data, the model developed with PEGINVERA data shows:

    I. Higher baseline CHR,
    II. Higher ropeginterferon potency (Lower EC50),
    III. Lower maximum effect (Emax), and
    IV. Higher influence of sex on CHRP (female have 24% higher Emax than male in PEGINVERA compared to having 16% higher Emax in PROUDPV).

5. The observed and predicted effect of sex on CHRP in the PEGINVERA study is consistent with that observed in the PROUD-PV study.

6. The maximum probability of CHRP is reached earlier in patients participating in the PEGINVERA compared those in the PROUD-PV study.

7. The predicted probabilities of CHRP at week 52 are comparable between PEGINVERA and PROUDPV models, but at week 104, predicted CHRP is lower in PEGINVERA compared to PROUD PV. This may be due to differences in maximum dose levels reached by individuals in the PEGINVERA compared to that in PROUD-PV study.

8. Due to the estimated higher potency (EC50) using PEGINVERA data, the predictions using PEGINVERA model shows > 80% probability of CHRP at maximum dose levels of 200ug and higher. The PROUDPV model predicts lower probabilities of CHRP at the same maximum dose levels.

LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	**Description**	**Location in \\cdsnas\pharmacometrics**
Pharmacometrics_Review.Rmd	Draft of pharmacometrics review including codes for tables and figures	Reviews\Ongoing PM Reviews\Ropeginterferon_BLA761166_EK\FDA Reviews\Notebook
Run03.mod	Nonmem script for E-R modelling of CHRP data from PEGINVERA	Reviews\Ongoing PM Reviews\Ropeginterferon_BLA761166_EK\ER Analyses\modeling\reviewer
Run31.mod	Nonmem script for E-R modelling of CHRP data from PROUD-PV	Reviews\Ongoing PM Reviews\Ropeginterferon_BLA761166_EK\ER Analyses\modeling\reviewer

4.2.3. Exposure-vs-Safety Analysis

4.2.3.1 Review Summary

The applicant's exposure-vs-safety analyses are acceptable for describing relationships between ropeginterferon exposures and adverse thrombocytopenia and GGT elevation events. Using post-hoc ropeginterferon trough concentration (Cmin) at the time of occurrence of adverse events, the applicant assessed the relationship between ropeginterferon exposure and the following safety end points: treatment

related adverse event (AE) of thrombocytopenia of any grade, and treatment related AE of gamma glutamyl-transferase (GGT) elevation of any grade. Linear logistic regression analyses determined statistically significant associations between Cmin and the AEs of thrombocytopenia and GGT elevation. In addition to ropeginterferon exposure, additional predictors of thrombocytopenia were baseline platelet count and JAK2_v617F allele burden. Probability of thrombocytopenia increased with increasing Cmin and JAK2_V617F_allele burden and decreased with increasing baseline platelet count. Similarly, an additional predictor of GGT elevation was sex. Female subjects had less probability of GGT elevation than males. The following section summarizes results from these logistic regression analyses. As titration is based on both efficacy and tolerability, these relationships for AEs do not suggest the need for lower doses.

4.2.3.2. Applicant's exposure-safety analyses

Ropeginterferon CMIN vs Thrombocytopenia and GGT elevation.

Assessments of ropeginterferon Cmin vs probability of thrombocytopenia and GGT elevation was based on pooled data from PEGINVERA, PROUD-PV, PEN-PV, and CONTINUATION-PV studies. For each endpoint, post-hoc estimate of ropeginterferon Cmin was determined at the time of occurrence of the adverse event for everyone. For subjects without adverse event, post-hoc Cmin at steady state of the maximal dose was used. The Cmin vs probability of thrombocytopenia and GGT elevation relationships were best described by linear logistic regression model. Stepwise model building was used to determine additional predictors of the adverse events. Results are summarized in **Table 16** and **Figure 19 and Figure 20**.

Table 16. Final parameter estimates of linear logistic regression models for predictors of thrombocytopenia and GGT elevation.

AE No.	Logit Model	COV_1	COV_2	θ_1 (SE)	θ_2 (SE)	θ_3 (SE)	θ_4 (SE)
Treatment-related AE of thrombocytopenia of any grade	$AE \sim \theta_1+\theta_2*C_{min}+\theta_3*COV_1+\theta_4*COV_2$	$PLAT_0$	JAK2	-1.83 (0.740)	0.0807 (0.0248)	-0.00354 (0.00120)	0.0248 (0.00861)
Treatment-related AE of GGT elevation of any grade	$AE \sim \theta_1+\theta_2*C_{min}+\theta_3*COV_1$	SEXF	-	-2.44 (0.429)	0.0793 (0.0285)	-1.29 (0.570)	-

Note: Abbreviations are provided in the Abbreviation Listing

Source: Applicant's PKPD safety report (#0165, pages 95)

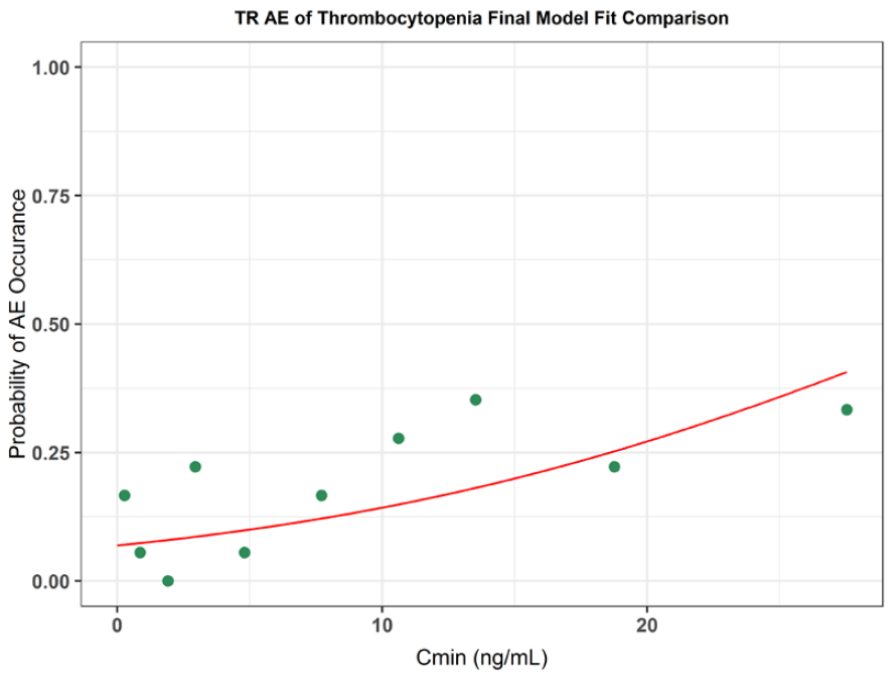


Figure 19. Observed (points) and predicted (red line) probabilities of thrombocytopenia versus Cmin of ropeginterferon.

Source: Applicant's PKPD safety report (#0165, pages 96)

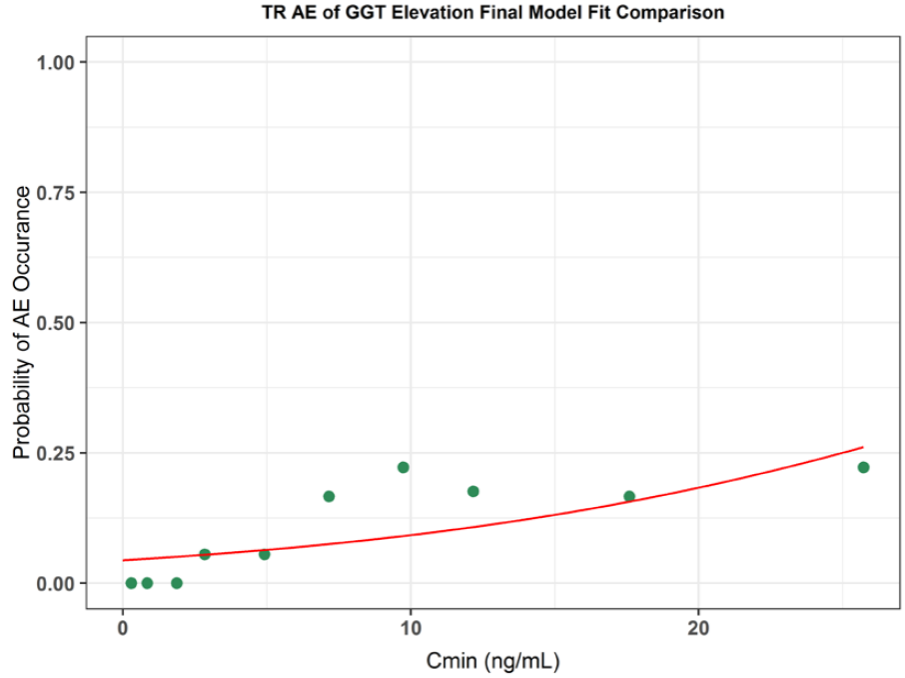


Figure 20. Observed (points) and predicted (red line) probabilities of GGT elevation versus Cmin of ropeginterferon.

Source: Applicant's PKPD safety report (#0165, pages 97)

4.2.3.3. Reviewer's comments

The applicant's analyses are acceptable for making conclusions on exposure-safety relationships at the recommended ropeginterferon doses. Although significant relationships are identified by these analyses, the side effects were tolerated by most patients, and did not lead to drug discontinuations. The results support the recommended dose individualization for ropeginterferon.

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/s/

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