CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761166Orig1s000

CLINICAL REVIEW(S)

Division of Non-Malignant Hematology
Medical Officer's Review and Evaluation

Application Type	BLA *(Resubmission)*
Application Number(s)	761166
Priority or Standard	Standard
Submit Date(s)	May 12, 2021
Received Date(s)	May 13, 2021
PDUFA Goal Date	November 13, 2021
Division/Office	CDER/OND/OCHEN/DNH
Reviewer Name(s)	Patricia Oneal, MD
Review Completion Date	November 12, 2021
Established/Proper Name	Ropeginterferon alfa-2b-njft
(Proposed) Trade Name	BESREMi™
Applicant	PharmaEssentia US
Dosage Form(s)	Subcutaneous
Applicant Proposed Dosing Regimen(s)	The recommended starting dose for single-agent therapy is 100 mcg by subcutaneous injection every two weeks . Gradually increase the dose up by 50 mcg every 2 weeks(up to maximum of 500 mcg) until hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 x 10^9/L and leukocytes less than 10 x 10^9/L). When transitioning to BESREMi from hydroxyurea, start BESREMi at 50 mcg by subcutaneous injection every two weeks in combination with hydroxyurea. Gradually increase the dose by 50 mcg every two weeks while gradually decreasing the hydroxyurea dose until the hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 x 10^9/L and leukocytes less than 10 x 10^9/L).
Applicant Proposed Indication(s)/Population(s)	For the treatment of adults with Polycythemia Vera without symptomatic splenomegaly
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adults with Polycythemia Vera
Recommended Proposed Dosing Regimen	<u>Patients Not Already on Hydroxyurea:</u> •The recommended BESREMi starting dosage for patients not on hydroxyurea is 100 mcg by subcutaneous injection every two weeks. •Increase the dose by 50 mcg every two weeks (up to a maximum of 500 mcg), until the hematological parameters are

	stabilized (hematocrit less than 45%, platelets less than 400 x 109/L, and leukocytes less than 10 x 109/L). <u>Patients Transitioning from Hydroxyurea:</u> •When transitioning to BESREMi from hydroxyurea, start BESREMi at 50 mcg by subcutaneous injection every two weeks in combination with hydroxyurea. •Gradually taper off the hydroxyurea by reducing the total biweekly dose by 20-40% every two weeks during Weeks 3-12. •Increase the dose of BESREMi by 50 mcg every two weeks (up to a maximum of 500 mcg), until the hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 x 109/L, and leukocytes less than 10 x 109/L). •Discontinue hydroxyurea by Week 13. BESREMiBESREMi

Executive Summary and Recommended Regulatory Action
PharmaEssentia US submitted their Biologic LLicensing Application (BLA) on March 6, 2020 for the marketing approval of ropeginterferon alfa-2b-njft for the treatment of polycythemia vera (PV) in adults without symptomatic splenomegaly. The Application received a Complete Response (CR) on March 12, 2021-.

Ropeginterferon alfa-2b-njft (BESEMRi) (PEG-Proline-Interferon alpha-2b, PEG-P-IFNα-2b, AOP2014 or P1101, ropeginterferon alfa-2b-njft) is a pegylated, recombinant human interferon alpha-2b, (b) (4)

The review team recommended regular approval of ropeginterferon alfa-2b-njft under 21 CFR 314.105 for the indication treatment of polycythemia vera (PV) in adult patients without symptomatic splenomegaly. The deficiencies identified by the Office of Pharmaceutical Quality were the pending final determinations of the compliance status of two manufacturing and testing facilities to ensure that these facilities conducted manufacturing operations in compliance with current good manufacturing practice. Pre-license inspections were delayed secondary to travel restrictions related to the Coronavirus public health emergency. The Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology recommended a Complete Response action because of deficiencies in human factors validation.

To support approval of this application, the applicant submitted three studies: a phase III study (PROUD-PV), an extension study (CONTINAUTION-PV) and a phase I/II study (PEGINVERA) to demonstrate effectiveness of ropeginterferon alfa-2b-njft. The PROUD-PV study was a randomized, open-label, multicenter, active-controlled, parallel arm study to assess the efficacy and safety of ropeginterferon alfa-2b in patients with PV. After review of the phase III study, it was determined that PROUD-PV had several statistical issues with the design and analysis: lack of a prospectively planned endpoint for non-inferiority, margin not adequately justified and failure to show non-inferiority of ropeginterferon to hydroxyurea. The CONTINUATION-PV study also lacked statistical rigor and was subject to selection bias and confounders thus the results were exploratory only.

Given the understanding of the natural history of polycythemia vera and that spontaneous remissions do not occur randomly in PV, the unmet medical need for treatment of PV and rarity of the disease, the review team evaluated the effectiveness of ropeginterferon alfa-2b-njft from the PEGINVERA study and published studies on the natural history of polycythemia vera. In addition, the review team evaluated the objective change from baseline hematology laboratory parameters from the active treatment group from the PROUD-PV as mechanistic and confirmatory evidence to establish substantial evidence of effectiveness of ropeginterferon alfa-2b-njft in the treatment of patients with polycythemia vera without symptomatic splenomegaly (*see the Clinical Review dated 12 March 2021 for details on efficacy and safety*).

Response to the Complete Response
This review focuses on the submission material included in the response, submitted on May 12, 2021, to the CR letter and address the safety update and labeling issues that were unresolved during the first review cycle.

The resubmission includes a safety update. At the time of data cutoff for this original BLA submission (November 8, 2018), the overall number of patients enrolled in the PEGINVERA (n = 51) and PROUD-PV (n = 257) had completed enrollment. Among the patients in the PROUD-PV study, a total of 127 were treated with ropeginterferon alfa-2b-njft and 127 patients were treated with hydroxyurea (HU). In the original BLA, the safety data for the pooled PEGINVERA/PROUD-PV/CONTINUATION-PV (n = 178) included the first 24 months of the extension study, CONTINUATION-PV as well as the 12 months of study of the PROUD-PV study.

The new safety data includes the pooled PEGINVERA/PROUD-PV/ongoing CONTINUATION-PV safety data (up to 60 months of observation) from November 8, 2018 through May 29, 2020. There were no new individual safety datasets from either the PEGINVERA study or the PROUD-PV study submitted with the response to the complete response. Study completion of the PEGINVERA study was January 25, 2018 and had 90 months of follow-up. Study completion of the PROUD-PV ended on April 8, 2016.

There were no new safety signals identified and the safety profile of ropeginterferon alfa-2b-njft remains unchanged from initial safety assessment. Updates to the United States Prescribing Information (USPI) were completed during this review where efficacy and safety findings from the PEGINVERA study were incorporated into the USPI (*see specific details in Labeling; Page 10*).

Safety Update
The updated safety data provides for 60 month safety data from the CONTINUATION-PV Study (up to 60 months of observation) whose data base lock was May 29, 2020 which was pooled with the PEGINVERA/PROUD-PV/CONTINUATION-PV studies. The number of patients in both studies remained the same (n = 178) for comparison.

Baseline Demographics
The baseline demographic information is provided in the table below to provide context although no update information was added.

Table 1: Baseline Demographics and Disease Characteristics of Safety Population

	PROUD-PV*		PEGINVERA	
	Ropeginterferon alfa-2b n=127	HU n=127	Extension Cohort n=26	MTD Cohort n=25
Age (years)				
Mean ± SD	58.46 [10.80]	57.87 [13.11]	57.85 [11.99]	59.52 [11.06]

	PROUD-PV*		PEGINVERA	
	Ropeginterferon alfa-2b n=127	HU n=127	Extension Cohort n=26	MTD Cohort n=25
Range	30-85	21-81	35-78	40-82
Pooled Age Groups (years)				
18-<65	90 (70.9%)	84 (66.1%)	17 (65.4%)	17 (68.0%)
>=65	37 (29.1%)	43 (33.9%)	9 (34.6%)	8 (32.0%)
Sex				
Female	68 (53.5%)	67 (52.8%)	13 (50.0%)	7 (28.0%)
Male	59 (46.5%)	60 (47.2%)	13 (50.0%)	18 (72.0%)
Spleen Diameter at Baseline (cm)				
Mean ± SD	13.38 [3.16]	13.55 [3.32]	14.12 [3.24]	14.12 [3.24]
Range	7-25	7.5-24.5	8.0-22.	8.0-22.0
JAK2 Allelic Burden at Baseline				
Mean ± SD	41.91 [23.49]	42.83 [24.14]	42.19 [26.23]	46.61 [31.41]
Range	0-94.94	0-89.81	0-91.5	7-99
HCT Baseline by Central Lab				
Mean ± SD	49.54 [5.43]	49.79 [5.49]	45.05 [4.13]	45.05 [4.13]
Range	37.7-65.8	38.5-70.8	36.9-53.8	36.9-53.8

Source: FDA Reviewer Analysis
**Inclusive of the subjects who continued in the CONTINUATION-PV Study*

Subject Disposition in PEGINVERA/PROUD-PV/ongoing CONTINUATION-PV Studies

A summary of the disposition of all subjects enrolled in the original PEGINVERA/PROUD-PV/CONTINUATION-PV studies are shown in the table below as well as the updated results from the pooled studies at Month 60.

Table 11 Overview of Subject Disposition (All Enrolled Subjects)

Category	PEG (N=51)	PR (N=127)	PEG+PR (N=178)	PEG+ PR/CONTI (1-3 yrs)* (N=178)	PEG+ PR/CONTI (1-5 yrs)** (N=178)
Enrolled: n	51	127	178	178	178
Treated: n	51	127	178	178	178
Completed study: n	25	106	131	131	131
Discontinued early from study: n	26	21	47	67	72
Ongoing in study: n	0	0	0	75	70

Source: Sponsor's Safety Update Report, Module 5.3.5.3
PEG: PEGINVERA Study; PR: PROUD-PV Study; PEG+PR/CONTI: PEGINVERA + PROUD-PV/CONTINUATION-PV Studies

Reviewer's Comment: There were no significant concerns about the disposition of patients in the PEG+PR/CONTI trials at Years 1-3 (original safety analysis) compared to Years 3-5 (updated safety analysis). As per the updated review of subjects' disposition, five patients discontinued early from study.

Exposure and Treatment Modifications/Discontinuations

Across all of the clinical studies with ropeginterferon alfa-2b-njft, patients were exposed to ropeginterferon alfa-2b-njft for a mean of 38 months; constituting 548.8 patient-years in the original BLA. The update for exposure time for patients treated with ropeginterferon alfa-2b-njft increased to a mean of 45 months; constituting 674.8 patient-years.

Table 2: Duration of Exposure of Ropeginterferon alfa-2b in PEGINVERA, PROUD-PV, CONTINUATION-PV Studies at the time of Original BLA Submission compared to updated Duration of Exposure of All Studies.

	ALL STUDIES (ropeginterferon alfa-2b-njft)	ALL STUDIES (ropeginterferon alfa-2b-njft)
N	178	178
Mean (SD) (Range) (months)	38 (22.6) (0.5, 85.4)	45 (27.7) (0.5,85.4)
Patient-years	548.8 years	674.8 years

Source: FDA reviewer analysis and Sponsor Table from Module 5.3.5.3
All STUDIES: PEGINVERA + PROUD-PV/CONTINUATION-PV Studies

In the original BLA submission, the most common reason for discontinuation in all studies was due to adverse events. Those adverse reactions in > 4% of patients who received BESREMi included arthralgia (4%), fatigue (4%), general physical health deterioration (4%) depression (8%). Adverse events remained the primary reason for discontinuation in all studies at Month 60 (*see table below*).

Table 12 Reasons for Early Discontinuation from Study (All Enrolled Subjects)

Reason for early discontinuation from study: n (%)* (a, b)	PEG (N=51)	PR (N=127)	PEG+PR (N=178)	PEG+ PR/CONTI (1-3 yrs)** (N=178)		PEG+ PR/CONTI (1-5 yrs)*** (N=178)	
				PEG+PR (N=178)	CONTI (N=95)	PEG+PR (N=178)	CONTI (N=95)
Total: N	**26**	**21**	**47**	**47**	**20**	**47**	**25**
Adverse event	19 (37.3)	11 (8.7)	30 (16.9)	30 (16.9)	7 (7.4)	30 (16.9)	11 (11.6)
As per PI and Sponsor decision; patient does not tolerate a higher dosage of AOP2014	0	0	0	0	1 (1.1)	0	1 (1.1)
Death	0	0	0	0	1 (1.1)	0	1 (1.1)
Investigator's decision due to continuation of medical conditions unrelated to the underlying disease	0	0	0	0	1 (1.1)	0	1 (1.1)
Lack of efficacy	0	0	0	0	3 (3.2)	0	3 (3.2)
Lost to follow-up	0	4 (3.1)	4 (2.2)	4 (2.2)	3 (3.2)	4 (2.2)	3 (3.2)
Missing	6 (11.8)	0	6 (3.4)	6 (3.4)	0	6 (3.4)	0
Prolonged period of drug interruption due to the extended time of hepatic enzyme elevation	0	0	0	0	0	0	1 (1.1)
SI decision, PI was involved	0	0	0	0	1 (1.1)	0	1 (1.1)
Withdrawal by subject	0	6 (4.7)	6 (3.4)	6 (3.4)	3 (3.2)	6 (3.4)	3 (3.2)
Withdrawal of consent (this field is only meant for patients who are not prepared to state reason)	1 (2.0)	0	1 (0.6)	1 (0.6)	0	1 (0.6)	0

CONTI = CONTINUATION-PV; PEG = PEGINVERA; PR = PROUD-PV; Yrs = years.
* Percentage is based on the number of subjects in Safety Set in relevant group.
** Original BLA data
*** Updated safety data

Source: Sponsor's Safety Update Report, Module 5.3.5.3

Reviewer's Comment: As in the original safety analysis, adverse events was the leading reason for discontinuation of ropeginterferon alfa-2b-njft in Years 3-5 as well. An additional three subjects withdrew from the study due to adverse events during the safety update (i.e splenomegaly, non-acute porphyria, post-procedural hemorrhage, muscle weakness and rectal adenocarcinoma).

Major Safety Results

In the original BLA submission, there were three deaths in the PEGINVERA study and two deaths in the PROUD-PV and CONTINUATION-PV studies in the ropeginterferon alfa-2b-njft arm and 2 deaths in the HU arm. There were no additional deaths reported in the updated safety data.

Serious Adverse Events

In the original BLA submission, the serious adverse reactions in > 4% of patients who received BESREMi included depression (4%) and transient ischemic attack (6%) during the PEGINVERA study. There were no thrombotic adverse reactions observed over the study duration.

An updated summary of the severe adverse reactions in the PEGINVERA and PROUD-PV studies and the pooled PEGINVERA + PROUD-PV study study is provided in the table below (Table 1).

Table 1: Serious Adverse Events in PEGINVERA and PROUD-PV Studies and pooled PEGINVERA + PROUD-PV Studies

Table 3 Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term and System Organ Class (PEGINVERA and PROUD-PV Studies: Safety Population)

System Organ Class Preferred Term	PEGINVERA (N=51) n (%)	PROUD-PV (N=127) n (%)	PEGINVERA + PROUD-PV (N=178) n (%)
Overall	**28 (54.9)**	**14 (11.0)**	**42 (23.6)**
Blood and Lymphatic System Disorders	**1 (2.0)**	**0**	**1 (0.6)**
Splenic Infarction	1 (2.0)	0	1 (0.6)
Cardiac Disorders	**2 (3.9)**	**3 (2.4)**	**5 (2.8)**
Atrial fibrillation	1 (2.0)	1 (0.8)	2 (1.1)
Acute myocardial infarction	1 (2.0)	0	1 (0.6)
Atrial flutter	0	1 (0.8)	1 (0.6)
Sinus tachycardia	0	1 (0.8)	1 (0.6)
Supraventricular tachycardia	0	1 (0.8)	1 (0.6)
Ear and Labyrinth Disorders	**1 (2.0)**	**0**	**1 (0.6)**
Sudden hearing loss	1 (2.0)	0	1 (0.6)
Eye Disorders	**1 (2.0)**	**0**	**1 (0.6)**
Diplopia	1 (2.0)	0	1 (0.6)
Gastrointestinal Disorders	**5 (9.8)**	**0**	**5 (2.8)**
Anal fistula	1 (2.0)	0	1 (0.6)
Diarrhoea	1 (2.0)	0	1 (0.6)
Duodenal ulcer haemorrhage	1 (2.0)	0	1 (0.6)
Dysphagia	1 (2.0)	0	1 (0.6)
Gastrointestinal ulcer haemorrhage	1 (2.0)	0	1 (0.6)
Large intestine polyp	1 (2.0)	0	1 (0.6)
General Disorders and Administration Site Conditions	**3 (5.9)**	**1 (0.8)**	**4 (2.2)**
Fatigue	1 (2.0)	0	1 (0.6)
General physical health deterioration	1 (2.0)	0	1 (0.6)
Influenza like illness	1 (2.0)	0	1 (0.6)
Multi-organ failure	0	1 (0.8)	1 (0.6)
Pyrexia	1 (2.0)	0	1 (0.6)
Hepatobiliary Disorders	**0**	**1 (0.8)**	**1 (0.6)**
Cholecystitis acute	0	1 (0.8)	1 (0.6)
Infections and Infestations	**6 (11.8)**	**3 (2.4)**	**9 (5.1)**
Urinary tract infection	4 (7.8)	0	4 (2.2)
Diverticulitis	1 (2.0)	1 (0.8)	2 (1.1)
Appendicitis	0	1 (0.8)	1 (0.6)
Endocarditis	1 (2.0)	0	1 (0.6)
Gastroenteritis norovirus	1 (2.0)	0	1 (0.6)
Pilonidal cyst	1 (2.0)	0	1 (0.6)

System Organ Class Preferred Term	PEGINVERA (N=51) n (%)	PROUD-PV (N=127) n (%)	PEGINVERA + PROUD-PV (N=178) n (%)
Pyelonephritis	1 (2.0)	0	1 (0.6)
Sepsis	1 (2.0)	0	1 (0.6)
Septic shock	0	1 (0.8)	1 (0.6)
Wound infection	1 (2.0)	0	1 (0.6)
Injury, Poisoning and Procedural Complications	**6 (11.8)**	**0**	**6 (3.4)**
Chest injury	2 (3.9)	0	2 (1.1)
Clavicle fracture	1 (2.0)	0	1 (0.6)
Eye injury	1 (2.0)	0	1 (0.6)
Lower limb fracture	1 (2.0)	0	1 (0.6)
Rib fracture	1 (2.0)	0	1 (0.6)
Spinal compression fracture	1 (2.0)	0	1 (0.6)
Splenic rupture	1 (2.0)	0	1 (0.6)
Tibia fracture	1 (2.0)	0	1 (0.6)
Investigations	**2 (3.9)**	**0**	**2 (1.1)**
Anti-thyroid antibody positive	1 (2.0)	0	1 (0.6)
Antinuclear antibody increased	1 (2.0)	0	1 (0.6)
Transaminases increased	1 (2.0)	0	1 (0.6)
Musculoskeletal and Connective Tissue Disorders	**2 (3.9)**	**1 (0.8)**	**3 (1.7)**
Arthralgia	1 (2.0)	0	1 (0.6)
Osteoarthritis	1 (2.0)	0	1 (0.6)
Rheumatoid arthritis	0	1 (0.8)	1 (0.6)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**2 (3.9)**	**2 (1.6)**	**4 (2.2)**
Glioblastoma	1 (2.0)	1 (0.8)	2 (1.1)
Basal cell carcinoma	1 (2.0)	0	1 (0.6)
Spermatocytic seminoma	0	1 (0.8)	1 (0.6)
Squamous cell carcinoma of skin	1 (2.0)	0	1 (0.6)
Nervous System Disorders	**6 (11.8)**	**2 (1.6)**	**8 (4.5)**
Transient ischaemic attack	3 (5.9)	0	3 (1.7)
Dementia with Lewy Bodies	1 (2.0)	0	1 (0.6)
Haemorrhagic transformation stroke	0	1 (0.8)	1 (0.6)
Ischaemic stroke	0	1 (0.8)	1 (0.6)
Ophthalmic Herpes Zoster	1 (2.0)	0	1 (0.6)
Status epilepticus	1 (2.0)	0	1 (0.6)
Subarachnoid haemorrhage	1 (2.0)	0	1 (0.6)
Psychiatric Disorders	**5 (9.8)**	**0**	**5 (2.8)**
Depression	2 (3.9)	0	2 (1.1)
Acute stress disorder	1 (2.0)	0	1 (0.6)
Adjustment disorder	1 (2.0)	0	1 (0.6)
Completed suicide	1 (2.0)	0	1 (0.6)
Renal and Urinary Disorders	**2 (3.9)**	**1 (0.8)**	**3 (1.7)**
Acute kidney injury	0	1 (0.8)	1 (0.6)
Calculus ureteric	1 (2.0)	0	1 (0.6)
Cystitis haemorrhagic	1 (2.0)	0	1 (0.6)
Reproductive System and Breast Disorders	**1 (2.0)**	**1 (0.8)**	**2 (1.1)**
Prostatitis	1 (2.0)	0	1 (0.6)
Uterine polyp	0	1 (0.8)	1 (0.6)

System Organ Class Preferred Term	PEGINVERA (N=51) n (%)	PROUD-PV (N=127) n (%)	PEGINVERA + PROUD-PV (N=178) n (%)
Respiratory, Thoracic and Mediastinal Disorders	**1 (2.0)**	**0**	**1 (0.6)**
Pulmonary embolism	1 (2.0)	0	1 (0.6)
Surgical and Medical Procedures	**0**	**1 (0.8)**	**1 (0.6)**
Renal cyst excision	0	1 (0.8)	1 (0.6)
Vascular Disorders	**2 (3.9)**	**2 (1.6)**	**4 (2.2)**
Deep vein thrombosis	1 (2.0)	0	1 (0.6)
Hypertension	0	1 (0.8)	1 (0.6)
Hypertensive crisis	1 (2.0)	0	1 (0.6)
Peripheral arterial occlusive disease	0	1 (0.8)	1 (0.6)

Source: Sponsor's Safety Update Report, Module 5.3.5.3

In the safety update, a total of 5 additional patients experienced a serious adverse event that was not previously reported in the original BLA submission. These serious adverse events included chronic cardiac failure, non-acute porphyria, gastroesophageal reflux, peripheral edema, pneumonia, sepsis, bursitis, interverterbral disc protrusion, colon cancer, and cholecystectomy.

Reviewer's Comment: Among these newly reported serious adverse events, there is little evidence to suggest a causal relationship with ropeginterferon-alfa 2b. .

Treatment Emergent Adverse Events (TEAEs)

In quantifying the treatment-emergent adverse events in the PEGINVERA, PROUD-PV and CONTINUATION-PV studies, all potential safety signals were assessed using all levels of MedDRA terms, standardized MedDRA query (SMQ) and FDA MedDRA Query (FMQ). Hence, there is a noted difference in the listing of of TEAEs which are identified by system organ class (SOC) and preferred term (PT) by the Applicant. We are providing our listing of the treatment emergent adverse events by preferred term that will be included in the USPI in *Table 3 of Section 6 Adverse Reactions*.

Table 3 Adverse Reactions in > 10% of Subjects with Polycythemia Vera in the PEGINVERA Study.

Adverse Reactions	BESREMi N=51 %
Influenza-like illness [a]	59
Arthralgia	47
Fatigue [b]	47
Pruritis	45
Nasopharyngitis [c]	43
Musculoskeletal pain [d]	41
Headache [e]	39
Diarrhea	33
Hyperhidrosis [f]	29
Nausea	28
Upper respiratory tract infection [g]	27
Local administration site reactions	26
Dizziness	22
Abdominal Pain [h]	20
Depression	20
Sleep disorder [i]	20
Leukopenia	18
Decreased appetite	18
Alopecia	16
Edema [j]	16
Hypertension [k]	16
Muscle spasms	16
Neutropenia	16
Rash [l]	16
Transaminase elevations [m]	16
Urinary tract infection	16
Thrombocytopenia	12
Vertigo	12

Source: FDA reviewer analysis

Grouped Term Definitions

a Includes pyrexia, chills, and influenza-like illness.

b Includes asthenia, malaise, and fatigue.

c Includes pharyngitis and nasopharyngitis.

d Includes musculoskeletal pain, back pain, pain in extremity, bone pain, flank pain, and spinal pain.

e Includes headache, migraine, and head pain.

f Includes night sweats and hyperhidrosis.

g Includes upper respiratory tract infection, rhinitis, bronchitis, and respiratory tract infection.

h Includes abdominal pain upper, abdominal pain lower, and abdominal pain.

i Includes insomnia, sleep disorder, and abnormal dreams.

j Includes peripheral edema and generalized edema.

k Includes hypertension and hypertensive crisis.

l Includes rash, maculopapular rash, and pruritic rash.

m Includes transaminase increase, hepatic enzyme increase, GGT increase, AST increase, and ALT increase.

Reviewer's Comments: The treatment emergent emergent adverse events are consistent with the class-effect adverse events associated with other interferon-alfa products.

Labeling
The table below summarizes the revisions that FDA made to the submitted labeling.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
Indication and Usage	BESREMi is indicated for the treatment of Polycythemia Vera in adults without symptomatic splenomegaly	BESREMi is an interferon alfa-2b analog indicated for the treatment of Polycythemia Vera in adults.
Dosage and Administration	The recommended starting dose for single-agent therapy is 100 mcg by subcutaneous injection every two weeks. Titrate dose up by 50 mcg every 2 weeks until hematological parameters are stabilized. (b) (4)	Patients Not Already on Hydroxyurea: •The recommended BESREMi starting dosage for patients not on hydroxyurea is 100 mcg by subcutaneous injection every two weeks. •Increase the dose by 50 mcg every two weeks (up to a maximum of 500 mcg), until the hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 x 109/L, and leukocytes less than 10 x 109/L). Patients Transitioning from Hydroxyurea:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
		•When transitioning to BESREMi from hydroxyurea, start BESREMi at 50 mcg by subcutaneous injection every two weeks in combination with hydroxyurea. •Gradually taper off the hydroxyurea by reducing the total biweekly dose by 20-40% every two weeks during Weeks 3-12. •Increase the dose of BESREMi by 50 mcg every two weeks (up to a maximum of 500 mcg), until the hematological parameters are stabilized (hematocrit less than 45%, platelets less than 400 x 109/L, and leukocytes less than 10 x 109/L). • Discontinue hydroxyurea by Week 13. BESREMi
Contraindications	Included the contradications associated with other inteferons	Updated the contradications to include: •Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt •Hypersensitivity to interferons including interferon alfa-2b or any of the inactive ingredients of BESREMi. •Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment •History or presence of active serious or untreated autoimmune disease

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
		•Immunosuppressed transplant recipientsBESREMi
Warnings and Precautions	Warnings and Precautions did not include all potential adverse events of special interest reported with other interferon-alfa agents.	Additional warnings and precautions were included consistent with interferon alfa products, including BESREMi and listed in decreasing order or importance
Adverse Reactions	Adverse reactions were on the basis (b) (4)	Adverse reactions were on the basis of > 10% of Subjects with Polycythemia Vera in the PEGINVERA Study Over 7.5 Years.
Clinical Studies	Efficacy results were based (b) (4)	The efficacy and safety of BESREMi were evaluated in the PEGINVERA study, a prospective, multicenter, single-arm trial of 7.5 years duration.

Update from Office of Pharmaceutical Quality (OPQ)
The OPQ Executive Summary noted that the recommendation on approvability of STN 761166 for BESREMi manufactured by PharmaEssentia was pending final determinations of compliance status of the PharmaEssentia Corporation (PEC) Taichung Plant drug substance manufacturing and testing facility and PharmaEssentia Corporation Taipei (b) (4) manufacturing and testing facility. The Complete Response (CR) Letter forwarded to the Sponsor on March 12, 2021 indicated that inspections of PharmaEssentia Corporation, FEI 2000012832, Taichung, Taiwan and PharmaEssentia Corporation, FEI 3005182038, Taipei, Taiwan are required before this application can be approved. Upon resubmission of BLA 761166 on May 13, 2021, it was determined that inspection of the PEC Taichung facility was still required. Inspection of the PEC Taipei facility that manufactures the (b) (4) was waived. A pre-license inspection of the PEC Taichung facility was conducted September 20-28, 2021, which resulted in issuance of a 5-item FDA Form 483. The compliance status of the PEC Taichung facility was determined to be 'Approve'.
In response to the Agency's information request (IR) based on observations made during the prelicense inspection of the PEC Taichung facility, three testing sites were added to the BLA (IR response received October 5, 2021). These testing sites were used to support the Process Performance Qualification (PPQ) in the BLA but will not be used for quality control testing of

commercial BESREMi (ropeginterferon alfa-2b-njft) intermediate, drug substance, or drug product samples. The method transfer and qualification information from these testing sites was deemed acceptable. The inspections of these testing sites were waived.
OPQ determined that the data submitted in this application were adequate to support the conclusion that the manufacture of BESREMi is well-controlled and leads to a product that is pure and potent. It has also been recommended that this product be approved for human use under conditions specified in the package insert.

Update from Human Factors (HF) Validation Study
The Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology has identified the following concerns about dosing errors associated with the prefilled syringe design and provided corrective measures.

1. Requesting an enhanced pharmacovigilance requirement for this product specifically to ensure that all postmarket medication errors are reported to FDA for this particular product. Based on the single-dose prefilled syringe (PFS) design, we remain concerned about the inherent risk for dosing errors associated with the PFS design. Based on our postmarket experience with other similar products, we remain concerned that BESREMi end users prescribed doses less than 500 mcg may unintentionally administer the entire contents of the PFS.

Hence, the Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management has requested from the Applicant to conduct an enhanced pharmacovigilance (EPV) for all U.S. cases of wrong dose medication errors associated with BESREMi (ropeginterferon alfa-2b-njft) injection for a period of 3 years from product launch date. The Applicant must submit an EPV report to their BLA on a quarterly basis for 1 year from the product launch date and then every 6 months for an additional 2 years, for a total of 3 years.

For the purposes of this EPV, a wrong dose medication error is defined as a dose (underdose or overdose) that was unintentionally administered orcould have been administered (including near misses).

The detailed analyses in the EPV report wil linclude:

- The reporting interval and cumulative data relative to the product launch date for BESREMi (ropeginterferon alfa-2b-njft)
- A summary of the cases along with a line listing of the cases in an excel file format that includes patient demographics, narrative description, contributing factors for the error, adverse events, and outcome
- A root cause analysis of any reported medication errors
- Your strategy or reporter suggestions to mitigate the reported wrong dose medication errors
- A medical literature review for case reports/case series of wrong dose medication errors associated with BESREMi (ropeginterferon alfa-2b-njft) injection.

Risk Evaluation and Mitigation Strategies (REMS)
A REMS is not necessary for this application. No safety issues were identified that would require a REMS.

Post Marketing Requirement
Post-marketing requirement (PMR) has been submitted to the Applicant.

PMR-1: The requirement is for the completion of Study EUPAS29462 "A Prospective, Multicenter, Non-interventional, Observational, Post-authorization Safety Study of Ropeginterferon alfa-2b in Polycythemia Vera Patients" . This study will evaluate safety and tolerability during the titration phase of ropeginterferon alfa-2b-njft administration in patients with Polycythemia Vera. Specific safety outcomes of interest will include hepatotoxicity, cardiovascular and thromboembolic events in treated patients. Here are the dates of the scheduled milestones:

Schedule Milestones:

Start Date of Data Analysis:	03/31/2023
Interim Report 1:	03/31/2022
Study Completion:	06/30/2023
Final Report Submission:	09/29/2023

Summary of Safety Findings
The Applicant has provided new safety information from the pooled PEGINVERA/PROUD-PV/ongoing CONTINUATION-PV safety data (up to 60 months of observation) from November 8, 2018 through May 29, 2020. Upon review, the new safety findings were consistent with the safety data previously reviewed in the initial application. As in the original safety analysis, adverse events was the leading reason for led to the discontinuation of ropeginterferon alfa-2b-njft in the safety update. Given the known safety concern with the use of alpha interferons, a box warning has been recommended in the USPI prescribing information to be consistent with currently approved alpha interferons including BESREMi. The adverse events of special interest

(i.e. thromboembolic, neuropsychiatric, cerebrovascular and endocrine events) in the safety update remained unchanged. There were no significant new treatment emergent safety signals reported as well.
The isssues raised from the final recommendations of DMEPA does warrant the Applicant to conduct an enhanced pharmacovigilance for all US cases of wrong dose medication errors associated with the BESREMi injection for a period of 3 years from product launch date.

Regulatory Recommendation: Regular Approval

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PATRICIA A ONEAL
11/12/2021 04:28:53 PM

TANYA M WROBLEWSKI
11/15/2021 12:50:59 PM

ANN T FARRELL
11/15/2021 12:52:29 PM

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	761166
Priority or Standard	Standard
Submit Date(s)	March 6, 2020
Received Date(s)	March 13, 2020
PDUFA Goal Date	March 13, 2021
Division/Office	CDER/OND/OCHEN/DNH
Reviewer Name(s)	Patricia Oneal, MD, Tanya Wroblewski, MD
Review Completion Date	March 11, 2021
Established/Proper Name	Ropeginterferon alfa-2b-njft
(Proposed) Trade Name	BESREMi
Applicant	PharmaEssentia US
Dosage Form(s)	Subcutaneous
Applicant Proposed Dosing Regimen(s)	Single-Agent Therapy: The recommended starting dosage for single-agent therapy is 100 mcg by subcutaneous injection every two weeks. Gradually increase the dose by 50 mcg every two weeks (to a maximum dose of (b) (4)) until the hematological parameters are stabilized (HCT <45%, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L). (b) (4)
Applicant Proposed Indication(s)/Population(s)	For the treatment of adults with Polycythemia Vera without symptomatic splenomegaly
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adults with Polycythemia Vera without symptomatic splenomegaly.

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BAT	best available therapy
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CALR	Calreticulin
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHR	complete hematological response
CLD	chronic liver disease
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EoT	end of treatment
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FMQ	Food and Drug Administration Medical Query(ies)
GCP	good clinical practice
GRMP	good review management practice
HADS	Hospital Anxiety and Depression Scale
HCT	Hematocrit
HU	hydroxyurea

ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PLT	platelet
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PV	Polycythemia Vera
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
STAT	activator of transcription protein
TEAE	treatment emergent adverse event
TYK	tyrosine kinase
WBC	white blood cell; total leukocyte count

1. Executive Summary

1.1. Product Introduction

Ropeginterferon alfa-2b-njft (BESEMRi) (PEG-Proline-Interferon alpha-2b, PEG-P-IFNα-2b, AOP2014, P1101 or ropeginterferon alfa-2b) is a pegylated, recombinant human interferon alpha-2b, (b) (4)

Interferon alfa belongs to the class of type I interferons that exhibit their cellular effects by binding to a transmembrane 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 activation of transcription (STAT) proteins. Nuclear translocation of STAT proteins controls distinct gene-expression programs that exhibit various cellular effects. Interferon alfa may have direct effects on hematopoietic stem cell proliferation and differentiation; however, its precise mechanism of action has not been fully elucidated.

The applicant's proposed indication is for the treatment of PV in adults without symptomatic splenomegaly. For patients currently not on treatment, the recommended ropeginterferon alfa-2b starting dose is 100 mcg by subcutaneous injection every two weeks. For patients currently on other cytoreductive treatment, the recommended starting dose is 50 mcg every two weeks and in parallel, other cytoreductive therapy should be decreased gradually. The recommended ropeginterferon alfa-2b dose titration in 50 mcg increments every 2 weeks until hematological parameters are stabilized (HCT <45% without phlebotomy for at least 2 months since last phlebotomy, platelet count (PLTs) <400 x 10^9/L, and total leukocyte count (WBCs) <10 x 10^9/L) .

For the purpose of this review, ropeginterferon alfa-2b-njft will be referred to as ropeginterferon alfa-2b.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends approval of ropeginterferon alfa-2b under 21 CFR 314.105 for the indication "treatment of polycythemia vera in adult patients without symptomatic splenomegaly," based upon the efficacy findings from the PEGINVERA study. PEGINVERA was a single-arm, dose-escalation study that collected safety, tolerability, and response data for ropeginterferon alfa-2b. The study demonstrated a durable complete hematological response (CHR), defined as hematocrit (HCT) <45% without phlebotomy for at least 2 months since last phlebotomy, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L, normal spleen and no thrombosis, of 31 of 51 patients [60.8%; 95% confidence interval (CI): 46.1%, 74.2%] with median response duration of 14.3 months (95% CI: 5.5, 30.1).

The applicant submitted two additional studies: a phase 3 study (PROUD-PV) and its extension (CONTINUATION-PV). PROUD-PV was a randomized, open-label, multicenter, active-controlled, parallel arm study to assess the efficacy and safety of ropeginterferon alfa-2b in patients with PV. CONTINUATION-PV was an extension study designed to collect long term efficacy and safety data. PROUD-PV was originally intended to show superiority of ropeginterferon alfa-2b to hydroxyurea. Importantly, the primary analysis was changed from a superiority comparison to a non-inferiority comparison. This change was highly problematic: the scheme was changed post hoc with data in hand, there was no justification for the change, there was no agreement on the actual non-inferiority margin, and despite these critical concerns, the study failed on its primary endpoint. non-inferiority. The CONTINUATION-PV study also lacked statistical rigor and was subject to selection bias and confounding; therefore, the results were exploratory only.

Despite the application's trials' issues, the Agency acknowledges that there are clinical circumstances where regulatory flexibility may be warranted. In the Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, the statutory standard of "substantial evidence" contains both a statement of what kind of evidence must exist and also an element of expert judgment. The standard requires that the investigations be such that "it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of the use prescribed, recommended…" and permits approval on the basis of all the evidence presented in this application. In general, FDA has interpreted the law as generally requiring at least two adequate and well-controlled clinical investigations. However, there are circumstances where substantial evidence of effectiveness can be provided outside the setting of two adequate and well-controlled clinical investigations. In certain scenarios, FDA experts may "fairly and responsibly" rely on one adequate and well-controlled trial plus confirmatory evidence.

Therefore, given the natural history of PV , the fact that spontaneous remissions do not occur randomly in PV, the unmet medical need for treatment of PV, and rarity of the disease, the review team evaluated the effectiveness of ropeginterferon alfa-2b from the PEGINVERA study and published studies on the natural history of PV. In addition, the review team evaluated the

objective change from baseline for the hematology laboratory parameters in the active treatment group from the PROUD-PV as mechanistic and confirmatory evidence to establish substantial evidence of effectiveness of ropeginterferon alfa-2b in the treatment of patients with PV without symptomatic splenomegaly.

The benefit assessment is based primarily on the adequate and well-controlled PEGINVERA study, a single-arm, open-label study with supportive evidence from the natural history of the disease and confirmatory evidence from the objective change from baseline in the hematology parameters from the PROUD-PV study. The PEGINVERA study demonstrated a durable complete hematological response (CHR), defined as HCT <45% without phlebotomy for at least 2 months since last phlebotomy, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L, normal spleen and no thrombosis, of 31/51 [60.8% (95% CI: 46.1%, 74.2%)] with median duration of response of 14.3 months (95% CI: 5.5, 30.1). The primary efficacy data demonstrates a response that is a departure from the natural history of the diseases because in PV there are no spontaneous remissions nor random improvements in HCT, WBC or PLTs. This response is confirmed by the demonstration of improvement in the objective laboratory measurements from the PROUD-PV study as these improvements would not occur by chance alone in this disease. Flexibility is appropriate in the setting of this rare, serious and chronic neoplasm, especially because there are no FDA approved therapies for the treatment of PV in the initial management phase of the neoplasm.

In summary, given the natural history of PV, the lack of spontaneous remissions, rarity of the disease, and the adequate and well-controlled clinical investigation with confirmatory evidence permits a finding of substantial evidence. However, the Division of Medical Error and Prevention Analysis (DMEPA) has found that the human factors (HF) validation study protocol is not acceptable. Several areas of concern that may lead to medication errors were identified. The overall assessment of the HF validation study protocol is that the protocol requires revisions to ensure that adequate data regarding the safe and effective use of this product is collected. The Division of Medial Policy Programs (DMPP) has made recommendations for the study and the instructions for use (IFU) and that these recommendations should be implemented before commencing a new HF validation study. If there had been no approval issues other than the facilities inspections, the action would have been delayed (beyond the PDUFA goal date) until the inspections were satisfactorily completed. Because of the deficiencies with the HF protocol, this application cannot be approved at the present time, and a Complete Response will be issued.

2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Polycythemia Vera (PV) is a myeloproliferative neoplasm that displays terminal myeloid cell expansion in the peripheral blood resulting in erythrocytosis, leukocytosis, thrombocytosis, bone marrow hypercellularity and/or fibrosis, and splenomegaly. The median age of diagnosis is approximately 60 years and approximately 25% of the cases present before age 50. The prevalence is approximately 50 per 100,000 in the United States. Median survival for patients with PV is 13.7 years. Treatment is risk-stratified based on age and history of prior thrombosis. Cytoreduction is the main goal of treatment. There are no FDA approved cytoreductive therapies for first-line, treatment-naïve or in the initial treatment period for patients with PV.

Polycythemia Vera is a neoplasm with no spontaneous remissions. Thrombosis and thromboembolic events are reported in 39-41% of patients with PV with highest rates of thrombosis typically occurring shortly before diagnosis. Without treatment or with minimal intervention there is high rate of cardiovascular events and/or major thrombosis leading to increased morbidity and mortality.

To support this application, the applicant submitted three well-designed and well-conducted studies (Phase3 studies: PROUD-PV, CONTINUATION-PV, Phase 1/2 study: PEGINVERA) to demonstrate effectiveness of ropeginterferon alfa-2b. After review of the phase III study, it was determined that PROUD-PV had several statistical issues with the design and analysis: lack of a prospectively planned analysis for non-inferiority, inadequate margin justification and the failure to show non-inferiority of ropeginterferon alfa-2b to hydroxyurea. The CONTINUATION-PV study also lacked statistical rigor and was subject to selection bias and confounders thus the results were exploratory only.

Considering the unmet medical need for treatment of PV, rarity of the disease and the natural history of disease with no spontaneous responses, the review team evaluated the effectiveness of ropeginterferon alfa-2b from the adequate and well-controlled PEGINVERA study, published studies on the natural history of PV and the objective change from baseline for hematology laboratory parameters from active control from the PROUD-PV study to establish substantial evidence of effectiveness of ropeginterferon alfa-2b in the treatment of patients with PV without symptomatic splenomegaly.

Benefit-risk information for the treatment of PV in adult patients is derived primarily from the results of the PEGINVERA study. The PEGINVERA study was a single-arm, multi-center, open-label trial that included 51 adult patients with PV diagnosed by the World Health Organization (WHO) criteria or PV Study Group (PSVG) criteria plus JAK2 mutation positivity. The primary endpoint was complete hematologic response (CHR). The baseline hematological parameters were defined as the last observed non-missing value prior to first dose and baseline levels were scheduled to be assessed as visit 0: Day -28/-1 with treatment on visit 1, Day 0.

The complete hematological response (CHR) was determined at 12 months and defined as HCT <45% without phlebotomy for at least 2 months since last phlebotomy, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L, normal spleen and no thrombosis. CHR was 31/51 (60.8%) (95% CI: 46.1%, 74.2%). The median duration of response for CHR was 14.3 months (95% CI: 5.5, 30.1). The CHR based on laboratory parameters only (HCT <45% without phlebotomy for at least 2 months since last phlebotomy, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L) was 41/51 (80.4%) (95% CI: 66.9%, 90.2%) with median duration of response of 20.8 months (95% CI: 13, 43.8).

Supporting evidence comes from the natural history of the disease. The natural history of PV in the absence of treatment or minimally treated disease demonstrates an ongoing risk of thrombosis and continued increase in peripheral blood counts. Without aggressive cytoreductive control (HCT <45%), there is an increased risk of cardiovascular death and major thrombosis. Additional natural history studies demonstrate that the highest rate of thrombosis occurs shortly before diagnosis and decreases in time due to the effects of cytoreductive treatments that are initiated in patients. Thrombotic risk is not only related to HCT levels but also to the elevated WBC and platelet counts. Additional natural history studies demonstrate an elevated white blood count and platelet count at time of diagnosis as well as evidence of a rebound effect in peripheral blood counts when cytoreductive therapy is stopped in patients with PV. The objective laboratory measurements demonstrating decreases in PLTs and WBC counts from baseline from the single arm experience in the PROUD-PV/CONTINUATION-PV studies provide additional objective mechanistic confirmatory evidence.

In summary, PEGINVERA results with the prospectively planned endpoint of CHR demonstrated a clinically meaningful response rate. The CHR based on laboratory parameters only provides objective mechanistic evidence as improvements in hematological parameters do not occur spontaneously in this disease. Additional supportive evidence comes from the objective laboratory measurements from the hematology parameters from the active treatment arm in the PROUD-PV study which demonstrate an improvement (decrease) in PLTs and WBCs. Because of the well understood natural history of PV, decreases in the HCT, PLTs and WBCs are not going to occur spontaneously and represent a clinically meaningful improvement for patients with PV.

The primary safety database consisted of 51 patients with PV from the PEGINVERA study and the pooled safety population of 178 patients (PEGINVERA and PROUD-PV/CONTINUATION-PV). In general, the safety profile of ropeginterferon alfa-2b is acceptable in a population with rare life-threatening disease with a significant unmet medical need. There were 65 serious adverse events reported for 28/51 (54.9%) patients in the PEGINVERA study. Serious adverse events were notable for depression, completed suicide, transient ischemic attack (TIA), subarachnoid hemorrhage, anti-thyroid antibody positivity, acute stress disorder, arthralgia, atrial fibrillation, fatigue, influenza-like illness, transaminase increased, and pyrexia.

Common adverse reactions (>20%) reported in the PEGINVERA study included infections, fatigue, pruritus nasopharyngitis, arthralgia, upper respiratory tract infection (URI) cold, rhinitis, headache, diarrhea, back pain, dizziness, nausea, pyrexia, influenza-like illness, local administration reactions, leukopenia, rash, erythema, eye disorders, depression, insomnia and sleep disorders, and decreased appetite. The lack of a control arm for the safety assessment in the PEGINVERA limits the extent to which these events can be attributed to the drug versus disease and its comorbidities. All these risks can be adequately mitigated through labeling and further evaluated during routine pharmacovigilance.

Ropeginterferon alfa-2b is an interferon and there are known class side effects associated with interferons to include the following adverse events of special interest: neuropsychiatric events, hepatoxicity to include elevation of liver enzymes, bone marrow toxicity (leukopenia and thrombocytopenia), cardiovascular toxicity, cerebrovascular toxicity to include thrombosis, hypersensitivity reactions, endocrine toxicity to include development of anti-thyroid antibodies, renal toxicity, colitis, pulmonary toxicity, ophthalmologic toxicities, dental and periodontal disorders,

pancreatitis and elevated triglycerides.

A box warning is recommended for the neuropsychiatric, autoimmune, ischemic and infectious-conditions consistent with other approved interferons. A description of the remainder of the adverse events in the warning and precautions of the labeling is recommended.

There may be a persistent thrombosis risk in the titration period due to the prolonged titration phase for ropeginterferon alfa-2b. The risks of thromboembolic events with ropeginterferon alfa-2b in the titration phase can be sufficiently controlled with phlebotomies and cardiovascular risk mitigation and will be described in the prescribing information.

In summary, the baseline-controlled PEGINVERA study is an adequate and well-controlled trial that demonstrated substantial evidence of effectiveness given the improvement in CHR with supportive evidence from the natural history of the disease. Confirmatory evidence from the objective laboratory improvements from the active treatment arm in PROUD-PV provides additional evidence that ropeginterferon alfa-2b confers benefit in patients with PV and represents a departure from the norm for this neoplasm. The safety profile is acceptable, and risks can be mitigated with appropriate labeling to include a box warning for neuropsychiatric, autoimmune, ischemic and infectious disorders. Flexibility is appropriate in the setting of this rare, serious and chronic neoplasm, especially because there are no FDA approved therapies for the treatment of PV in the initial management phase of the neoplasm.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	PV is a myeloproliferative neoplasms that displays terminal myeloid cell expansion in the peripheral blood resulting in erythrocytosis, leukocytosis, thrombocytosis, bone marrow hypercellularity and/or fibrosis, and splenomegaly. The median age of diagnosis is approximately 60 years and approximately 25% of the cases present before age 50. The prevalence is approximately 50 per 100,000 in the United States. Median survival for patients with PV is 13.7 years. PV is a neoplasm with no spontaneous remissions. Thrombosis and thromboembolic events are reported in 39-41% of patients with PV with highest rates of thrombosis typically occurring shortly before diagnosis. Without treatment or with minimal intervention there is high rate of cardiovascular events and/or major thrombosis leading to increased morbidity and mortality.	PV is a rare, long-term debilitating disease with significant morbidity and mortality. The median survival of untreated symptomatic patients with PV is 6 to 18 months whereas survival of treated patients is more than 10 years. There are no spontaneous remissions and worsening of the disease is the norm during the clinical course of patients with PV.
Current Treatment Options	Treatment is risk-stratified based on age and history of prior thrombosis. Cytoreduction is the main goal of treatment. There are no approved cytoreductive therapies for first-line, treatment-naïve or in the initial treatment period. • Low risk patients (<60 years of age, no history of thrombosis): phlebotomy, low-dose aspirin • High risk (≥ 60 years of age, prior history of thrombosis): ▪ Treatment guidelines recommend hydroxyurea (HU) (off-label), interferon (off-label), and phlebotomy along with low-dose aspirin. Busulfan and 32P are rarely used for treatment for PV. Ruxolitinib, a JAK2 inhibitor, is FDA approved for the treatment of patients with PV who disease is resistant to or who are intolerant of hydroxyurea.	There are no FDA approved therapies for patients with PV with newly diagnosed disease or during the initial treatment period. There is an unmet medical need for treatments for patients with PV.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	The effectiveness of ropeginterferon alfa-2b in patients with PV was evaluated in PEGINVERA, an open-label, prospective, multicenter, phase I/II dose-escalation study to determine the maximum tolerated dose and to assess the efficacy and safety of ropeginterferon alfa-2b in patients with PV. The study population included 51 patients diagnosed with PV confirmed per the WHO criteria or PV Study Group (PVSG) criteria plus JAK2V617F mutation positivity including newly diagnosed, pre-treated and on cytoreductive therapy. CHR defined as HCT ≤45% without phlebotomy in previous 2 months, PLTs ≤ 400 x 10^9/L, WBC count ≤ 10 x 10^9/L, normal spleen size of ≤12 cm females and ≤ 13 cm males) and without thrombosis events was 31/51 [60.8% (95% CI: 46.1%, 74.2%)] with median duration of response of 14.3 months (95% CI: 5.5, 30.1). CHR based on laboratory parameters only (HCT < 45% without phlebotomy in previous two months, platelet count ≤ 400 x 10^9/L, WBC count ≤ 10 x 10^9/L) was 41/51 [(80.4%) 95% CI: 66.9%, 90.2%] with median duration of response of 20.8 months (95% CI: 13, 43.8). Supportive efficacy data comes from the natural history of the PV and the objective laboratory data from the active treatment arm from the PROUD-PV study for change from baseline for WBCs and PLTs. Patients demonstrated objective improvements from baseline in PLTs and WBCs in the PROUD-PV/CONTINUATION-PV studies.	The PEGINVERA study demonstrates that ropeginterferon alfa-2b confers substantial benefit in terms of a durable cytoreductive improvement in CHR in patients with PV. Improvements (decreases) in the PLTs, WBCs, and HCT levels from baseline in the PEGINVERA study and from the active treatment arm from the PROUD-PV study provides important, objective, mechanistic support for the efficacy findings. The natural history of PV is such that there are no spontaneous remissions and the natural history of PV provides supportive evidence as the responses observed are a deviation from the norm for this disease and are only explained by effective treatment. In summary, the application contains substantial evidence of effectiveness given the robust improvements in objective laboratory parameters that would be extremely unlikely to occur spontaneously in an untreated population with this disease. Flexibility

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		is appropriate in this setting of this rare, serious and chronic neoplasm, especially because there are no FDA-approved therapies at this time for this indication.
Risk and Risk Management	The primary safety database consisted of 51 patients with PV and the pooled safety population of 178 patients (PEGINVERA and PROUD-PV/CONTINUATION-PV). There were 65 serious adverse events reported for 28/51 (54.9%) patients in the PEGINVERA study. Serious adverse events were notable for depression, completed suicide, TIA, subarachnoid hemorrhage, anti-thyroid antibody positivity, acute stress disorder, arthralgia, atrial fibrillation, fatigue, influenza-like illness, transaminase increased and pyrexia. Common adverse reactions (>20%) reported in the PEGINVERA study included infections, fatigue, pruritus, nasopharyngitis, arthralgia, URI, cold, rhinitis, headache, diarrhea, back pain, dizziness, nausea, pyrexia, influenza-like illness, local administration reactions, leukopenia, rash, erythema, eye disorders, depression, insomnia and sleep disorders and decreased appetite. The lack of a control arm for the safety assessment in the PEGINVERA limits the extent to which these events can be attributed to the drug versus disease and its comorbidities. Ropeginterferon alfa-2b is an interferon and there are known class side effects and several adverse events of special interest which include neuropsychiatric events, hepatoxicity to include elevation of liver enzymes, bone marrow toxicity (leukopenia and thrombocytopenia), cardiovascular toxicity, cerebrovascular toxicity to include thrombosis, hypersensitivity reactions, endocrine toxicity to include development of anti-thyroid antibodies, renal toxicity, colitis, pulmonary toxicity, ophthalmologic toxicities, dental and periodontal disorders, pancreatitis and elevated triglycerides.	Overall, acceptable risk benefit profile Risks of ropeginterferon alfa-2b can be sufficiently addressed through Box Warning, Warnings and Precautions in the United States Prescribing Information (USPI). A box warning is recommended for the neuropsychiatric, autoimmune, ischemic and infectious conditions consistent with other approved interferons. A description of the remainder of the adverse events in the warning and precautions of the labeling is warranted.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Thrombosis is a known risk in patients with PV. There may be a persistent thrombosis risk in the titration period due to the prolonged titration phase for ropeginterferon alfa-2b. Ropeginterferon alfa-2b has a deliberate conservative dose titration for toxicities and tolerability. The risks of thromboembolic events with ropeginterferon alfa-2b in the titration phase can be sufficiently controlled with phlebotomies and cardiovascular risk mitigation and will be described in the prescribing information.	

2.1. Patient Experience Data

There was no patient experience data collected in the single arm PEGINVERA study.

Patients enrolled into the PROUD-PV and CONTINUATION-PV studies were administered the following questionnaires to assess quality of life measures such as mobility, self-care, usual activities, pain/discomfort and anxiety/depression using the Quality of Life Questionnaire (EQ-5D-3L), ECOG Performance Status and the Hospital Anxiety and Depression Scale (HADS) for evaluation for anxiety and depression at baseline and at end of treatment.

Results: The change from baseline for the visual analogue score and total score of EQ-5D-3L was comparable between the BESREMi and HU treatment arms at EoT (for VAS: 1.3 (±12.56) and 1.8 (±13.09) respectively; for total score: 0.2 (±1.08) and 0.1 (±1.17) respectively.

Because of study design and statistical issues the patient reported outcome data are considered as descriptive findings only.

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☒	Observational survey studies designed to capture patient experience data • Quality of Life EQ-5D-3L Questionnaire • ECOG Performance Status • Hospital Anxiety and Depression Scale (HADS)		See comments above.
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

3. Therapeutic Context

3.1. Analysis of Condition

First recognized in 1892, PV is the most common of the myeloproliferative neoplasms (MPN)

but is still considered a rare disorder. Polycythemia Vera results in clonal expansion of transformed hematopoietic progenitor cells in the bone marrow leading to abnormalities in the peripheral blood: erythrocytosis, leukocytosis, thrombocytosis as well as bone marrow hypercellularity/fibrosis, and splenomegaly. The increase of peripheral cells in circulation contributes to the increased the risk of thrombosis and cardiovascular events.

Polycythemia Vera is a very rare disease and usually develops in late adulthood. Population-based epidemiological studies done in Rochester, MN, have suggested a stable incidence trend for PV of approximately 2.3/100,000. The median survival of untreated symptomatic patients with PV is 6 to 18 months with cardiovascular events or thrombosis as the main cause of death. In patients with adequate treatment survival may extend beyond 10 years or more.

Polycythemia Vera can occur at any age and its frequency increases exponentially after the age of 60 years with a male predominance. Approximately 7% of patients are diagnosed before age 40 years and children are rarely diagnosed with PV.

The incidence and outcome of myeloproliferative neoplasms (MPNs) across different races and ethnicities has not been extensively explored. In a SEER registry retrospective study *(Price GL et al. PLoS One 2014)* showed that outcomes were inferior despite the fact that non-Caucasian patients represent only 11% of patients with PV. In a retrospective single institution study *(Khan I et al. Clinical Lymphoma, Myeloma and Leukemia 2016)*, a total of 127 adult patients with MPNs were reviewed. Regression models were used to demonstrate a relationship between ethno-racial background, vascular complications and disease transformation. It was shown that there was an increased risk of vascular complications including cardiovascular thrombosis and hemorrhagic events among non-Caucasian patients with PV while Caucasian patients with PV and ET had a higher risk of progression to myelofibrosis. In a Cox proportional hazard regression analysis, Caucasian race emerged as an independent prognostic factor protective against cardiovascular thrombosis in patients with PV (HR, 0.2; 95% CI, 0.03-0.9; P = .04) while age > 60 years and prior thrombosis were significant risk factors in univariate analysis (unadjusted HR, 3.7; 95% CI, 1.1-12.4; P = .04 and (unadjusted HR, 3.5; 95% CI, 1.1-11.7; P = .04, respectively).

Major progress in better understanding the affected genes was made in 2005, with the identification of the JAK2V617F mutation. Nearly all patients with PV will harbor a JAK2 mutation where 97% have somatic activating mutations in exon 14 (JAK2V617F) and 3% have a mutation in exon 12.

The key clinical features of PV include symptoms due to increased red blood cell mass, increased white blood cell (WBC) and platelet counts in peripheral blood as well as splenomegaly in advanced disease or any combination of these. Clinical symptoms include mild-to-moderate constitutional symptoms (e.g. fatigue and pruritus), symptoms of hyperviscosity, microvascular symptoms (e.g., headaches, lightheadedness, visual disturbances, atypical chest

pain, erythromelalgia, paresthesia). The most serious complications include thrombotic and bleeding complications, and risk of leukemic transformation or fibrotic progression. Arterial and venous thrombosis are significant risks in patients with PV with thrombotic risks occurring in 39-41% of patients *(Griesshammer M, et al.* 2019).

The diagnosis of PV is based on a composite assessment of clinical and laboratory features according to the 2016 World Health Organization (WHO) criteria of hemoglobin/HCT (>16.5 g/dL (49%) for males and >16 g/dL (48%) for females), bone marrow hypercellularity with trilineage growth and JAK2V617F positivity or JAK2 exon 12 mutation.

Table 3 2016 WHO Diagnostic Criteria for Diagnosis of Polycythemia Vera

Major criteria [a] 1. Hemoglobin >16.5 g/dL in men, >16.0 g/dL in women or Hematocrit >49% in men, >48% in women or Increased red cell mass (more than 25% above mean normal predicted value) 2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size) 3. Presence of *JAK2 V617F* or JAK2 exon 12 mutation
Minor criterion Subnormal serum erythropoietin level
Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion [a]

a Criterion number 2 (bone marrow biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a bone marrow biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

Source: [Arber et al., 2016]

(Taken from Arber et al., Blood. 2016)

The laboratory detection of JAK2V617F is highly sensitive (97% sensitivity) and highly specific (100%) for distinguishing PV from other causes of increased HCT.

3.2. Analysis of Current Treatment Options

Most patients with PV require life-long treatment and the goal of treatment is cytoreduction to help prevent and reduce thrombosis and bleeding. Cytoreduction can include either phlebotomy and/or cytoreductive therapeutic drugs. Additional goals of treatment include reduction in disease associated symptoms such as headache, pruritus and spleen enlargement. Overall, disease treatment goals are geared to reduce risk of arterial and venous thrombosis and prevent progression to myelofibrosis and acute myeloid leukemia.

Current therapeutic recommendations for PV stratify risk according to age and thrombosis history. Phlebotomy (*keeping the HCT level below 45% in men and below 42% in women*) and aspirin are recommended in low-risk patients <60 years of age. In patients ≥ 60 years of age, patients with persistent hematological abnormalities, poor compliance with phlebotomy and those with high risk of thrombosis, cytoreductive therapy is recommended.

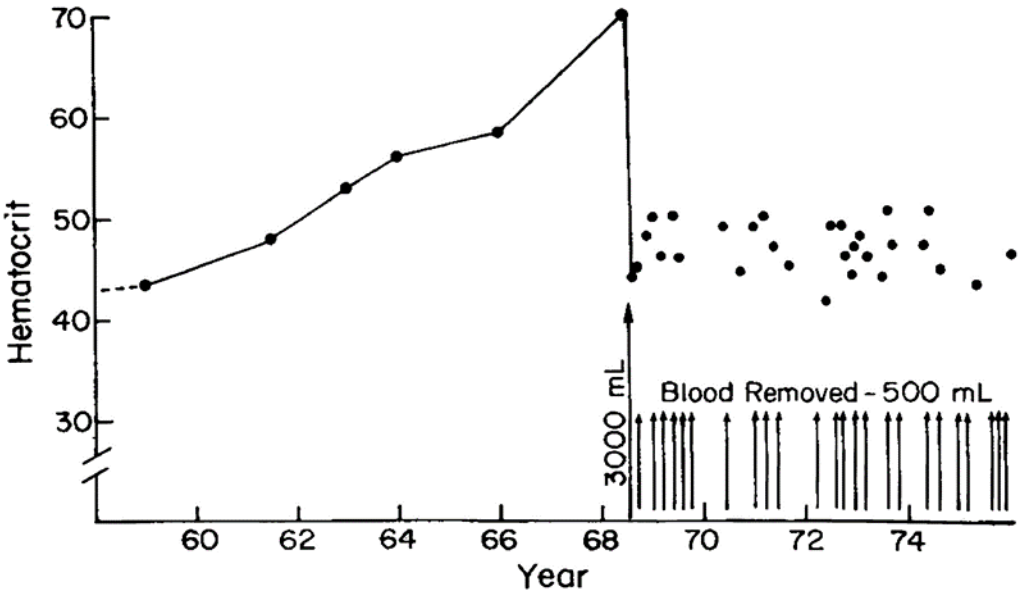
First-line cytoreductive therapies include off-label use of HU; however, HU toxicities frequently require either drug reduction or drug discontinuation resulting in inadequate management of the disease. Additionally, due to HU's mechanism of action, the theoretical possibility of HU to be mutagenic has been raised and there is controversy as to whether HU use is associated with an increased risk of leukemic transformation after long-term use in patients with PV. Additional off-label cytoreductive therapies for initial therapy of PV include pegylated and non-pegylated interferons as well as alkylating agents such as busulfan.

Ruxolitinib, a JAK2 inhibitor, is FDA-approved for the treatment of patients with PV, whose disease is resistant to or who are intolerant of hydroxyurea. Allogeneic hematopoietic stem cell transplantation is a potentially curative option for patients with end-stage PV progressing to myelofibrosis or acute myeloid leukemia.

3.3. Natural History of PV without Intervention

There are no spontaneous remissions in this neoplasm. In minimally treated or untreated patients with PV, the disease continues to progress. The following figure demonstrates the continued increase in HCT in a patient with untreated PV.

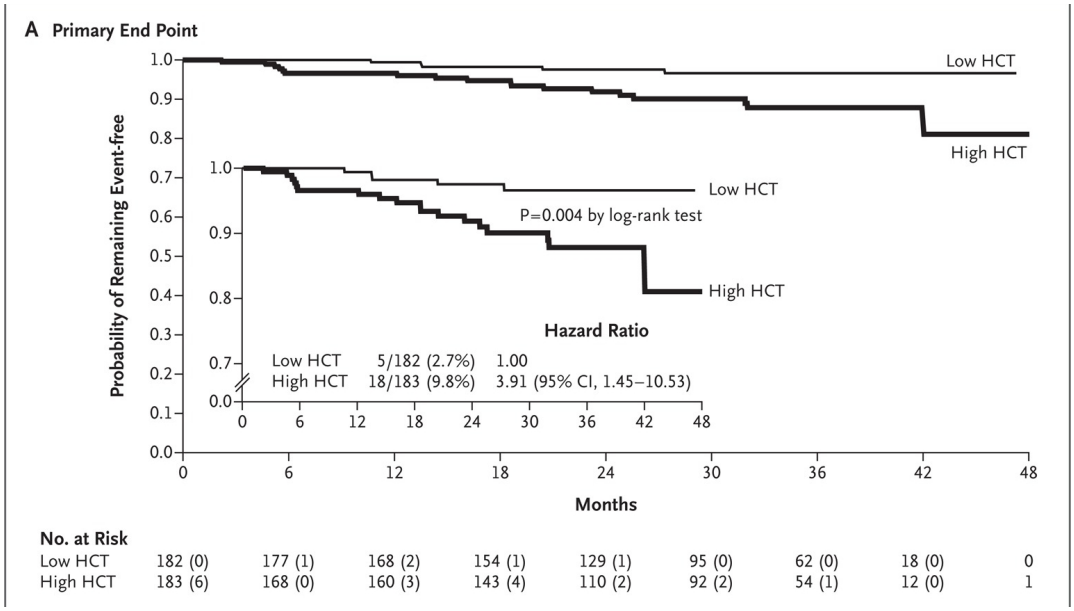
Figure 1: Increased HCT in Untreated PV Patient



(Taken from CL Conley - Hospital practice (Office ed.), Polycythemia Vera, Diagnosis and Treatment. Hosp Pract (Off Ed). 1987 Mar15;22(3):181-5, 189-200, 205-10.)

Suboptimal or minimal treatment of patients with PV results in continued and increased risk of thromboembolic disease. A prospective study in 365 adults with JAK2 positive PV randomized patients to either a low target HCT (<45%) or high target HCT (45-50%). *(Marchioli R et al. N Engl J Med 2013).* The primary composite endpoint was time until death from cardiovascular events (CV), CV hospitalizations, incidence of cancer, progression of myelofibrosis, myelodysplastic disease (MDS), leukemic transformation or, hemorrhage. The following figure is a Kaplan-Meier Curve for death from CV causes or thrombotic events for the primary endpoint demonstrating an improvement in the primary endpoint for the lower HCT group.

Figure 2: Kaplan-Meier Curve for Primary Endpoint



(Taken from Marchioli R et al. N Engl J Med 2013;368:22-23)

After a median follow-up of 31 months, the primary endpoint was observed in 5/182 (2.7%) patients in the low HCT group and 18/183(9.8%) patients in the high-HCT group (hazard ratio in the high-HCT group 3.91; 95% confidence interval [CI] 1.45 to 10.43, p=0.007).

Thus, targeting HCTs <45% results in lower rate of cardiovascular death and major thrombosis in patients with PV and the group with the higher HCT target reflects a less intensive disease control group and demonstrates disease outcome in PV when minimal intervention is provided supporting the premise of no spontaneous remissions.

Additional support for the natural history of the disease and lack of spontaneous remissions is highlighted in a study by the Gruppo Italiano Studio Policitemia *(Gruppo Italiano Studio Policitemia. Ann Int Med 1995)* in which 1213 patients were followed for up to 20 years. In this group of patients, 64% of thrombotic events occurred shortly before or at diagnosis with most events occurring 2 years preceding diagnosis. Similar findings were seen in the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) study *(Landolfi R, Marchioli R. Semin Thromb Hemost. 1997)* and in the real-world analysis of the MPN registry of the Study Alliance Leukemia *(Kaifie, A et al. J Hematol Oncol 2016)* in which two-thirds of event occurred shortly before or at time of diagnosis. In general, arterial thrombotic events are more common than venous thromboembolic events before diagnosis.

The highest rates of thrombosis typically occur shortly before diagnosis and decreases over time due to the effects of treatment. The Gruppo Italiano reported that the incidence of thrombosis after diagnosis was 3.4% per year and additional analyses from the CYTO-PV and the International Working Group for Myelofibrosis Research and Treatment report rates of

2.7% and 2.6% *(Marchioli R et al. Thrombosis. 2011 and Kaifie, A et al. J Hematol Oncol 2016).* Without treatment, there would be no reduction in thrombotic risk and the lower rate of thromboses after diagnosis are likely due to advances in treatment options as well as management of cardiovascular risk factors. Without these interventions, there would not be a spontaneous improvement in thrombotic outcomes.

Further evidence for the lack of spontaneous remissions in patients with PV comes from a natural history study of approximately 70 patients less than the age of 50 who were followed between 1975 and 2000. The untreated mean % HCT was 60, mean WBC was 12 x 10^9/L and mean PLTs were 544 x 10^9/L. The following table taken from the study shows the baseline characteristics of patients with PV *(Passamonti F et al. Haematologica 2003).*

Table 1: Baseline Characteristics of Patients with PV from Natural History Study

Table 1. Baseline characteristics of 70 young patients with polycythemia vera.

	N.	*%*
Patients	70	–
Male/female	49/21	–
Median follow-up, years (range)	14 (2-26)	–
Median age, years (range)	42 (18-49)	–
Mean hemoglobin (g/dL)±SD	21±2	–
Mean hematocrit (%)±SD	60±5	–
Mean white cell count (×10^9/L)±SD	12±3	–
Mean platelet count (×10^9/L)±SD	544±186	–
Splenomegaly	29	41
Hepatomegaly	28	40
Vascular accidents before diagnosis		
Arterial thrombosis	9	13
Venous thrombosis	3	4
Vascular accidents at diagnosis		
Arterial thrombosis	3	4
Venous thrombosis	2	3
Hemorrhage	3	4
Minor neurological disturbances	11	15
No clinical symptoms	33	47

Untreated PV results in elevated hematology parameters, thrombosis, cardiovascular events and eventual death. This observation is further supported by the occurrence of thromboembolic events decreasing over time due to treatments being initiated in patients with PV.

The Low-PV study was recently published and is a multicenter, open-label, two arm, parallel-group, investigator-initiated, phase 2 randomized study (1:1) in which patients receive phlebotomy and low dose aspirin (standard group) or ropeginterferon alfa-2b plus standard therapy (experimental group). Patients in the standard group were treated with phlebotomy (300mL for each phlebotomy to maintain HCT values lower than 45%) and low dose aspirin. Patients in the experimental group received ropeginterferon alfa-2b subcutaneously every 2 weeks in a fixed dose of 100 mcg on top of the phlebotomy-only regimen. Primary endpoint was treatment response defined as maintenance of median HCT values of 45% or lower without progressive disease during the 12 months. At the second pre-planned interim analysis, a higher response rate in the experimental group was observed 42/50 (84%) patients than in the standard group 30/50 (60%) patients. Because the standard group did not receive pharmacological intervention, the clinical course is representative for PV in patients treated with aspirin and phlebotomy alone. The standard group of patients did not demonstrate decreases in WBC and PLTs and these parameters increased over the observation period *(Barbui T et al. The Lancet Hematology 2021).*

Lastly, evidence for demonstrating that spontaneous remissions do not occur without intervention in patients with PV is through the observation that after cessation of cytoreductive therapy there is a rebound increase in blood counts with the risk of thrombosis and other morbidities.

Table 2: Summary of Treatment Armamentarium Relevant to PV

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
FDA Approved Treatments						

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
Ruxolitinib (Jakafi®)	PV in adults who have had an inadequate response to or are intolerant of hydroxyurea.	2011	10 mg twice daily	42% of patients achieved a 35% or greater reduction of spleen volume and 46% of patients achieved a 50% or greater reduction in total symptom score by Week 24	Anemia and thrombocytopenia, dizziness, constipation and shingles	Increased rate of herpes zoster infection and nonmelanoma skin cancer
Other Treatments – Non-FDA Approved						
Hydroxyurea (HU)	Cytoreductive agent	N/A	500 mg (15 mg/kg) twice a day orally	Fewer thrombotic events (10 versus 33 percent) in 51 patients treated with HU compared with 134 historical controls treated with phlebotomy alone	Anemia, neutropenia oral and skin ulcers, hyperpigmentation ,nail changes and potential teratogenicity	10% of patients develop resistance to HU
Interferon α	Cytoreductive agent	N/A	5 million unit three times a week 45 mcg/week subcutaneously and up to 180 mcg/week (PEG IFN alfa-2a)	Control of erythrocytosis, leukocytosis and thrombocytosis, reduction of spleen size, and relief from intractable pruritus in 80% of patients	Flu like symptoms, fatigue, anorexia, weight loss, alopecia, abnormal liver function tests, anemia, thrombocytopenia	Possibility of achieving cytogenetic remission with an interferon (IFN)
Phlebotomy	HCT control; Recommended in patients <60 years of age with PV	N/A	Men: removal of 1.5 to 2 units per week, Women, older adults, and those with low body mass (e.g., <50 kg) or cardiopulmonary disease:	Shorter time to death from cardiovascular causes or major thrombotic events (Hazard ratio 3.9 [95% CI 1.5-10.5]) among patients whose target HCT was	Maintain hydration and avoid vigorous exercise within 24 hours of phlebotomy	To keep the HCT level below 45% (used singularly or in combination with cytoreductive agents)

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
			removal of 0.5 units per week	45 to 50%		
Aspirin	Administered to high- and low- risk patients for thrombosis prevention	N/A	40-100 mg orally once or twice daily	Effective treatment for preventing thrombosis in PV and for relieving microvascular symptoms	Gastrointestinal hemorrhage	Patients with platelet > 1 million/µL should be tested for acquired von Willebrand syndrome
Busulfan	Second-line cytoreductive treatment for older adults with HU intolerance or resistance	N/A	2 to 4 mg orally daily	Efficacy is limited	Cytopenias, marrow aplasia, skin pigmentation, pulmonary fibrosis, and/or leukemia	Leukemogenic only when used in combination with other agents
Pipobroman*	Alkylating agent available in Europe	N/A	1 mg/kg per day orally subcutaneously	Efficacy is limited	Delayed cytopenia	Shorter median survival (15 versus 20 years) and doubling of the incidence of transformation to AML/MDS

*Not available in the United States but widely used in Europe

4. Regulatory Background

Ropeginterferon alfa-2b is a new molecular entity that is not currently marketed in the United States.

It was granted orphan drug designation for the treatment of PV by the Food and Drug Administration on April 2, 2012.

4.1. Summary of Presubmission/Submission Regulatory Activity

For the PV indication developed under IND 119047, the pertinent regulatory history is described in table 3.

Table 3: Submission Regulatory Activity

Date	Regulatory Interaction
July 26, 2013	Pre-IND submitted to the FDA.
June 28, 2014	IND submitted to the FDA for phase 3 study (PROUD-PV) study.
	(b) (4)
Feb 17, 2017	Type B Meeting request to discuss PROUD-PV study
April 20, 2019	Type B meeting- applicant sought guidance on results of PROUD-PV study (pre-BLA meeting).
August 28, 2019	CMC meeting
September 4, 2019	Pre-BLA meeting

4.2. Foreign Regulatory Actions and Marketing History

Ropeginterferon alfa-2b received marketing approval in Europe on February 15, 2019 as monotherapy in adults for the treatment of PV independent of previous hydroxyurea exposure.

5. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

5.1. Office of Scientific Investigations (OSI)

PharmaEssentia US (applicant) and Brightech International LLC (CRO) were inspected for a single study and its continuation trial, Study 2012-005259-18 in support of BLA 761166. Based on the results of the above inspections, PharmaEssentia US and Brightech International LLC are in compliance with Good Clinical Practice, and the two supportive studies in support of this application appears to have been conducted adequately. A form FDA 483 was not issued at the end of the study inspection. In general, the applicant appeared to be in compliance with good clinical practice. PharmaEssentia US maintained adequate oversight of clinical trials.

Please refer to the review by in DARRTS dated July 22, 2020 by Kassa Ayalew, MD, MPH.

Table 4: OSI Inspections

Site	Principal Investigator	Inspection Dates	Findings
Brightech International, LLC 285 Davidson Avenue, Suite 504 Somerset, NJ 08873	Tailiang Xie	June 17-19, 2020	NAI (No Action Indicated)
PharmaEssentia Corporation 35 Corporate Drive, Suite 325 Burlington, MA 01803	Meredith Manning	June 29-July 7, 2020	NAI (No Action Indicated)

5.2. Product Quality

The chemistry reviewer in the Office of Pharmaceutical Quality (OPQ) is Dr. Phillip Angart. His final recommendation on approvability of STN 761166 for ropeginterferon alfa-2b is pending final determinations of compliance status of the PharmaEssentia Corporation (PEC) Taichung Plant drug substance manufacturing and testing facility and PharmaEssentia (PEC) (b) (4) manufacturing and testing facility. FDA assessment of the ability of these facilities to conduct manufacturing operations in compliance with CGMP is required to support approval of the application. Pre-license inspections are delayed due to travel restrictions related to COVID-19 public health emergency. From the product quality and product quality microbiology and sterility assurance perspectives, OPQ, does not note any product quality deficiencies what would preclude approval of STN 761166 for ropeginterferon alfa-2b manufactured by PharmaEsssentia at this time.

5.3. Clinical Microbiology

There were no product quality microbiology nor sterility assurance deficiencies that would preclude approval of this product. Please refer to the product quality review for more details.

5.4. Nonclinical Pharmacology/Toxicology

Please refer to Drs. Jeffery Quinn's (non-clinical reviewer) and Todd Bourcier's (non-clinical team leader) nonclinical pharmacology review for ropeginterferon alfa-2b. Toxicology data used to support approval of ropeginterferon alfa-2b was derived predominately from pivotal one-month cynomolgus monkey study as animal studies exceeding 1 month in duration were not deemed feasible and would not provide additional information with regards to the safety assessment of the drug product.

Ropeginterferon alfa-2b was found to be negative for inducing chromosomal aberrations in vitro without metabolic activation, but equivocal with metabolic activation at concentrations where increased cytotoxicity was observed. Ropeginterferon alfa-2b is produced by covalent attachment of PET to the N-terminal proline residue of recombination proline-interferon alfa-2b (b) (4). No separate chemical linker is employed (direct conjugation). Considering the reactive linker molecule does not represent a toxicological concern and ropeginterferon alfa-2b will be metabolized by proteases (not CYPs) the genotoxicity assessment is likely uninformative with regards to assessing the safety of ropeginterferon alfa-2b.

Reproductive and development toxicity studies were not conducted with ropeginterferon alfa-2b as IFNs are known to be abortifacient in primates. Long term carcinogenicity studies were not conducted due to the lack of pharmacological activity of ropeginterferon alfa-2b in rodents.

There were no deficiencies in the nonclinical data that would preclude approval of BLA 761166.

5.5. Clinical Pharmacology

The Office of Clinical Pharmacology reviewers were Li Wang, Ph.D., Eliford Kitabi, Ph.D., Justin Earp, Ph.D., and Sudharshan Hariharan, Ph.D. They recommend approval of ropeginterferon alfa-2b for the treatment of polycythemia vera in patients without symptomatic splenomegaly. The summary below is taken from their review.

- Ropeginterferon alfa-2b undergoes receptor independent degradation/excretion and receptor binding and subsequent degradation of the drug-receptor complex. The half-life and clearance of ropeginterferon alfa-2b is approximately 7 days and 1.7-2.5L/h, respectively in patients with PV over dose range of 100 mcg to 500 mcg.

- No clinically significant differences in the pharmacokinetics of ropeginterferon alfa-2b alfa were observed based on age, sex, body surface area, and JAK2V617F mutation. The impact of renal impairment on ropeginterferon alfa-2b clearance was evaluated using a popPK approach. The analysis demonstrated that there were no significant impact on ropeginterferon alfa-2b with eGFR > 30 mL/min/1.73m2. The effect of eGFR < 30mL/min, or hepatic impairment *Childs-Pugh A, B, and C) on ropeginterferon alfa-2b pharmacokinetics has not been studies. Evaluation of ALT/AST as PK covariates indicated no impact on these time varying biomarkers on ropeginterferon alfa-2b PK.

- No drug-drug interaction studies were performed. Ropeginterferon is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 and is not an inducer of CYP1A2, 2B6, or 3A4. Ropeginterferon is a time-dependent inhibitor of CYP2A6.

- Cardiac electrophysiology is not applicable as the risk for the QT prolongation for the large therapeutic proteins is low.

5.6. Devices and Companion Diagnostic Issues

There are no companion diagnostic devices required for the use of ropeginterferon alfa-2b.

5.7. Consumer Study Reviews

Ropeginterferon alfa-2b is a combination product proposed to be supplied as a pack containing one single-dose prefilled syringe (PFS) and one injection needle.

The Division of Medication Error Prevention and Analysis (DMEPA), Office of Medication Error Prevention and Risk Management (OMEPRM) reviewed the human factors (HF) validation study

protocol and data submitted under BLA 761166 for ropeginterferon alfa-2b. DMEPA has found that the HF validation study protocol is not acceptable. Several areas of concern that may lead to medication errors were identified. The overall assessment of the HF validation study protocol is that the protocol requires revisions to ensure that adequate data regarding the safe and effective use of this product is collected. Division of Medial Policy Programs (DMPP) has made recommendations for the study and the instructions for use (IFU) and that these recommendations should be implemented before commencing a new HF validation study.

Please refer to the review by Stephanie De Graw, Ph.D. for additional details.

6. Sources of Clinical Data and Review Strategy

6.1. Table of Clinical Studies

The studies are listed separately to provide information on where each study was conducted. All participants were ex-US.

PEGINVERA Study
This study was conducted and completed at 6 sites exclusively in Austria. Among the six sites, 51 patients were enrolled.

PROUD-PV Study
This study was conducted and completed at 48 sites in 13 countries; Austria enrolled 6 patients, Hungary, Poland, Russia and Ukraine enrolled 5 patients each, Bulgaria, Czech Republic and Romania enrolled 4 patients each, France and Germany enrolled 3 patients each, Slovakia enrolled 2 patients and Italy and Spain enrolled one patient each.

CONTINUATION-PV Study
This study was conducted and completed at 41 sites in 12 countries. Russia and Ukraine enrolled five patients each. Austria, Bulgaria, Hungary and Poland enrolled four patients each. Czech Republic, France, Germany and Romania enrolled three patients each. Slovakia enrolled two patients and Spain enrolled one patient.

PEN-PV Study
This study was conducted and completed at 18 sites in 8 countries. Bulgaria and Ukraine enrolled (b) (4) patients each. Austria, Czech Republic, Hungary, and Poland enrolled (b) (4) patients each. France and Slovakia enrolled (b) (4) patients each. Patients who participated in the PEN-PV Study (estimated patient participation was approximately 12 weeks), were allowed to continue their treatment using the pen in the CONTINUATION-PV Study.

Table 5: Listing of Clinical Trials Relevant to BLA 761166

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
Controlled Studies to Support Efficacy and Safety							
2010-018768-18 (PEGINVERA)	NCT01193699	An open-label, prospective, multicenter, Phase I/II Dose Escalation Study to determine the maximum tolerated dose and to access the safety and efficacy of ropeginterferon alfa-2b in patients with PV	Ropeginterferon alfa-2b dose levels up to 540 mcg	Stage 1: Determination of maximum tolerated dose (MTD) Stage 2: Efficacy and Safety for complete hematological response	Stage 1: 14 (± 3 days) Stage 2: Up to 7.5 years	Enrolled: 51 Analyzed: 46	Patients with diagnosis of PV based on either 2008 WHO or PV Study Group (PVSG) criteria with presence of the JAK2 V617F mutation.
2012-005259-18 (PROUD-PV Study)	NCT01949805	A randomized, open-label, multicenter, controlled, parallel arm, phase III study assessing the efficacy and safety of ropeginterferon alfa-2b vs. Hydroxyurea in	Ropeginterferon alfa-2b administered, subcutaneously. at the starting dose of 100 mcg every 2 weeks for up to 12 months of treatment; 50 mcg every 2	<u>Primary efficacy endpoint:</u> Disease response rate at 12 months defined as Hct <45% without phlebotomy (at least 3 months since last phlebotomy), PLTs	Approx. 13 months per patient.	Enrolled: 257 patients. Analyzed: 254 patients	Patients must have a PV diagnosis based on the 2008 WHO criteria with the presence of the JAK2 V617F mutation.

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
		patients with PV	weeks if on concurrent HU (titrated off at 12 weeks) • HU, administered at the starting dose of 500 mg daily for up to 12 months of treatment Low dose aspirin (100 mg/day) was given to patients in both groups, during the 12 months of study treatment, unless contraindicated.	<400 x 10^9/L, WBCs <10 x 10^9/L, and normal spleen size (by imaging, central, blinded assessment, defined (per protocol) as ≤12 cm for females and ≤13 cm for males			
2014-001357-17 (CONTINUATION-PV Study)	NCT02218047	An open-label, multicenter, phase IIIb study assessing the long-term efficacy and safety of ropeginterferon alfa-2band	Ropeginterferon alfa-2b Low dose aspirin (acetylsalicylic acid) (100 mg/day); and Patients in the	<u>Co-primary efficacy endpoints:</u> 1. Disease response defined as hematologic response: Hct<45% without	24 months and 36 months	Enrolled: 171 patients (95 patients in ropeginterferon alfa-2b arm and 76	Patients must have a PV diagnosis based on the 2008 WHO criteria with the presence of the JAK2 V617F mutation.

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
		standard first line treatment (BAT) in patients with PV who previously participated in the PROUD-PV Study.	BAT arm receive standard first line treatment for treatment of PV disease	phlebotomy (at least 3 months since the last phlebotomy), PLTs<400 x 10^9/L, WBCs<10 x 10^9/L, and normal spleen size, and 2. Disease response defined as hematologic response (Hct<45% without phlebotomy (at least 3 months since the last phlebotomy), PLTs<400 x 10^9/L, WBCs<10 x 10^9/L), resolution and/or clinically (clinically significant splenomegaly) and disease-related symptoms (e.g., microvascular disturbances,		patients in control arm) Analyzed: 171 patients	

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
				pruritus, headache)			
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
2014-001356-31 (PEN-PV Study)	NCT02523638	An open-label, single-arm, Phase III study to assess the self-administration of ropeginterferon alfa-2b using a pre-filled pen, developed for the treatment of PV patients.	Ropeginterferon alfa-2b subcutaneous (s.c.) at the optimal dosing determined during the PROUD-PV study and maintained during the PROUD-PV/CONTINUATION-PV study.	Evaluation of ease of self-administration based on questionnaires	12 weeks	Enrolled: 36 Analyzed: 36	Patients with PV who were enrolled into the PROUD-PV/CONTINUATION-PV study.

6.2. Review Strategy

The application was submitted electronically. The statistical reviewers Lola Luo, Ph. D. and Yeh-Fong Chen, Ph.D. completed their review separately from the clinical review. Patricia Oneal, MD was the clinical reviewer. Comments are identified individually.

This clinical reviewer's strategy included:

- Review of regulatory histories of BLA 761166 and IND 119047;
- Examination of all clinical study reports and amendments
- Subjecting datasets to queries using JReview and JMP;
- Examination of approximately 300 CRFs, selected at random;
- Studying the applicant's presentation to the FDA on 12 May 2020;
- Searching published literature relative to PV and acute/chronic complications of PV as well as patient experiences related to all treatment modalities used in this setting;
- Consulting the FDA Division of Scientific Investigation;
- Review of the Periodic Safety Update Reports and Annual Reports ;
- Review and analysis of raw data conducted throughout studies for responders on the treatment arm;
- Review of pooled safety data from the aforementioned trials to detect additional safety signals.

Analyses by Dr. Oneal were performed using JReview 13.1 (SAS Institute, Inc) and JMP Version 11 and FDA FMQ queries using JMP. Unless specifically referenced, all analyses and presentation of findings are the work of the FDA reviewer. The clinical evaluation was based on data from PEGINVERA and the active treatment arm PROUD-PV and CONTINUATION-PV studies.

7. Review of Relevant Individual Trials Used to Support Efficacy

7.1. PEGINVERA STUDY

7.1.1. Study Design

Overview and Objective

The primary objective of PEGINVERA study was to identify the maximum tolerated dose of ropeginterferon alfa-2b in the phase 1 portion of the study. The primary objectives of phase 2 portion of the study included assessment of efficacy and safety of ropeginterferon alfa-2b. No formal hypothesis testing was planned.

Trial Design

The PEGINVERA study was an open-label, multicenter, phase 1/2 study conducted in two stages. Stage 1 (n = 25) was designed to determine the MTD using a 3+3 design in patients with PV. The MTD was determined to be 540 mcg, the highest dose administered in the first treatment cycle as no dose limiting toxicity (per protocol definition) or any other safety signals were observed for any of the dosing groups (dose range 50 to 540 mcg).

In Stage 2 (n=26), doses were escalated (from 100 – 450 mcg) as long as treatment was effective and tolerable. The starting dose was 150 mcg with increases every two weeks to 150 mcg, 225 mcg, 300 mcg, 400 mcg, until a maximum dose of 450 mcg. The dosing rules for patients who were concomitantly using hydroxyurea while being titrated to the next dose of ropeginterferon alfa-2b included dose reductions of hydroxyurea by 20-40% of the previous hydroxyurea dose weekly depending on blood parameters. Full discontinuation of hydroxyurea occurred by the end of Week 12. Patients were initially followed every 2 weeks (increased to every 3 to 4 weeks following 1 year of treatment) and remained in the study and were followed if the treatment was effective, safe and tolerable.

After meeting inclusion criteria, all patients were phlebotomized until HCT levels reached ≤ 45% prior to the first administration of ropeginterferon alfa-2b. Phlebotomies were only allowed as a rescue therapy if the HCT level was > 45%. Patients who participated in the first 12 months of treatment were eligible for administration of ropeginterferon alfa-2b every 4 weeks. The study's planned duration of 3 years was revised for a total of 7.5 years for some patients.

A revision of the treatment schedule to once every 4 weeks (28 days) was allowed. The schedule switch required the study participation of at least 12 months for each patient on the once every 14-day schedule.

Inclusion Criteria (summarized)
The key inclusion criteria included patients age greater than or equal to 18 years of age with confirmed diagnosis of PV according to the World Health Organization (WHO) criteria 2008 or the PVSG criteria plus JAK2 mutation positivity, including newly diagnosed, pre-treated patients and those on cytoreductive therapy. Additional inclusion criteria required Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2.

Key Exclusion Criteria (summarized)
Key exclusion criteria included the diagnosis of any other myeloproliferative disorder, any clinically significant illness or surgery within 4 weeks prior to dosing, systemic infections, uncontrolled hypertension, previous treatment with IFN for PV, concurrent treatment with cytoreductive agents other than HU and investigational agents of any type, history of malignant disease (except basal and squamous cell carcinomas of the skin and carcinoma in-situ of the cervix that have been completely excised and are considered cured) within the last 3 years,

history of severe allergic or hypersensitivity reactions, clinical significant history of known presence of psychiatric disorders, organ transplant, inadequate liver function defined by serum total bilirubin > 2.5 x ULN and AST or ALT > 2.5x ULN, clinically significant ECG findings, history of renal disease requiring dialysis, seizure disorder requiring anticonvulsant therapy, acute or chronic infections or autoimmune diseases.

Study Endpoints

Determination of the maximum tolerated dose (MTD) was the primary efficacy endpoint in Stage 1 of the study. The primary efficacy endpoint of Stage 2 was the achievement of complete hematological response.

- Complete hematological response (HCT <45% without phlebotomy in the previous two months, platelet count ≤400 x 10^9/L, WBC count ≤10 x 10^9/L, normal spleen size measured by ultrasound (longitudinal diameter ≤ 12 cm for females and ≤ 13 cm for males) and absence of thromboembolic events). In case of concomitant HU, the patient was considered as a complete responder once 2 weeks after the last HU administration had elapsed.
- Partial hematological response (HCT < 45% without phlebotomy but with persistent splenomegaly or elevated platelet count (>400 x 10^9/L) or reduction of phlebotomy requirements by at least 50%

Molecular response:

- Complete molecular response: reduction of any molecular abnormality to undetectable levels.
- Partial molecular response: reduction ≥ 50% in patients with < 50% mutant allele burden, or a reduction ≥ 25% in patients with > 50% mutant allele burden.

Splenomegaly: Evaluated as absolute reduction and dichotomized as reduction of spleen size of at least 30%, both measured via ultrasound (longitudinal diameter).

Additional hematological endpoints: HCT, platelet count, WBCs count, molecular reaction (defined by reduction of molecular abnormality) and number of phlebotomies.

Sample Size Determination

The 3 + 3 dose escalation design allowed a maximum 18 patients for determination of MTD at the 5 dose levels investigated. A single cohort of 26 additional patients was enrolled without formal size calculation after the MTD finding was completed to further investigate the drug efficacy and safety of ropeginterferon alfa-2b.

Analysis Plan

The MTD was determined per the standard procedure of the 3 x 3 dose escalation design. All study data were analyzed using descriptive statistical procedures including confidence intervals when appropriate. There was no formal hypothesis testing.

Analysis Population

Twenty-five patients completed Stage 1 and 26 additional newly enrolled patients participated in Stage 2 of the study for a total of 51 patients. The ITT population includes the 51 enrolled and treated patients. The FAS population includes 46 patients and excluded 5 patients due to violations of inclusion and exclusion criteria.

Analysis Methods

All study data were analyzed using descriptive statistical procedures including confidence intervals when appropriate on the bases of scheduled time-points.

7.1.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that all clinical studies were conducted with respect for the individual participants in accordance with the study protocol, Good Clinical Practice (GCP) guidelines, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (E6), and local regulatory requirements.

Financial Disclosure

Financial disclosure forms were collected for the PEGINVERA. No principal investigators or sub-investigators in this study were or are a full-time or part-time employee of PharmaEssentia US. One principal investigator reported disclosable financial compensation for conducting the study interests/arrangements in the PEGINVERA as well as the PROUD-PV/CONTINUATION-PV studies.

Reviewer's Comment:
The Agency agrees with the Applicant's comment on compliance with good clinical practice and financial disclosures. Explanation of financial compensation was provided and reviewed. Refer to appendix 12.2 for financial disclosure information.

Data Quality and Integrity

Data quality was satisfactory for clinical review. A review of data quality was undertaken by the reviewer and included assessment of laboratory values by site at selected study time point

assessments. The following table shows the median and range of the individual hematology parameters of the laboratory component of the CHR endpoint by study site.

Table 6: Hematology Parameters by Site and EOT Treatment Visit

	PLTs $x10^9$/L median (range)	WBC x 10^9/L median (range)	HCT percentage (%) median (range)
Site 1 EOT Visit 26 (WK50)	320 (94,686)	6.96 (3.72,16.56)	43.4 (35.9, 49.4)
Site 2 EOT Visit 26 (WK50)	144 (105,1044)	3.95 (3.5,18)	44 (40,51)
Site 3 EOT Visit 26 (WK50)	280 (168, 360)	4.44 (3.26,8.86)	42.5 (36.5,43.1)
Site 4 EOT Visit 26 (WK50)	265 (167,587)	5.2 (3.1,17.1)	41.6 (38,45.1)
Site 5 EOT Visit 26 (WK50)	207 (154,641)	4.75 (3.8,12.7)	43 (35.7,50)
Site 6 EOT Visit 26 (WK50)	223 (115,371)	7.2 (3.5,14.7)	42.9 (38.2,45.5)

Source: FDA Analysis

Data was also reviewed for Visit 14 (Week 25) by site and the values by visit. In review of the data, the individual hematology parameters differed by site and subject identification number.

Patient Disposition

Fifty-one (51) patients were screened, enrolled and treated. All were included in the safety-analysis set. Of these, 46 patients (92.2%) were considered in the full-analysis set (FAS).

Table 7: Disposition of Study Patients in PEGINVERA Study

	MTD cohort	Extension cohort	All Patients
Patients (enrolled) n, (%)	25	26	51
Patients (treated) n, (%)	25 (100%)	26 (100%)	51 (100%)
Full Analysis Set (FAS) n, (%)	22 (88%)	24 (92.3 %)	46 (90.2 %)

	MTD cohort	Extension cohort	All Patients
Safety Set n, (%)	25 (100%)	26 (100%)	51 (100%)
Completion of Treatment Period n,(%)			
1 year (Week 50)	20 (80%)	16 (61.5%)	36 (71%)
3 year (Week 146)	17 (68%)	15 (58%)	32 (63%)
5 year (Week 242)	15 (60%)	12 (46%)	27 (53%)
6 year (Week 290)	13 (52%)	3 (12%)	16 (32%)
Premature Discontinuation from PEGINVERA n, (%)			
Any reason (all discontinued patients)	12 (48%)	14 (53.8%)	26 (51%)
Adverse Event	10 (40%)	11 (42.3 %)	21 (41%)
Withdrawal of consent	2 (8%)	0 (0%)	2 (3.9%)
A treatment cycle delayed for more than four weeks	0 (0%)	1 (3.8%)	1 (2.0%)
Lack of Efficacy	0 (0%)	1 (3.8%)	1 (2%)
Other*	0 (0%)	1 (3.8%)	1 (2%)

Source: FDA reviewer analysis
Other: Concurrent cytoreductive agent*

Fifty-one (51) patients received the study drug. The median study duration (from screening to last visit or discontinuation) for all patients was approximately 5.2 years (62 months; range 1-88 months). The median duration of exposure to ropeginterferon alfa-2b (period between first and last study drug administration) was approximately 5.1 years (61 months; range 0-87). Thirty-six patients (70.6%) completed one year of treatment. Twenty-seven patients (52.9%) completed at least 60 months of treatment.

Protocol Violations

Five subjects were excluded from the efficacy analysis (FAS; N=46) due to two deviations from exclusion criterion (clinically significant history or known presence of psychiatric disorders and concurrent treatment with cytoreductive agents other than HU and investigational agents). Three patients were excluded because they had > 6 weeks between two consecutive administration of the study drug. Three patients were excluded from the per-protocol set because they exceeded maximum treatment interval of 6 weeks for a given visit.

Demographic Characteristics

Table 8: Baseline Demographics Characteristics for the PEGINVERA Study

	Ropeginterferon alfa-2b n=51
Age	
Mean (SD)	59 (11)
Median	56
Range	35-82
Pooled Age Group - n and %	
18-<65 years	30 (58.8%)
>=65 years	21 (42%)
Sex - n and %	
Female	20 (39.2%)
Male	31 (60.8%)
Race - n and %	
Caucasian	50 (98%)
Asian	1 (2%)
Ethnicity - n and %	
Not Hispanic or Latino	51 (100%)
Country Description - n and %	
Austria	51 (100%)

In the PEGINVERA Study, the median age was 56 years. Seventeen percent of subjects were over the age of 60 years old. There was a male predominance in this study (male: 60.8%) and fifty patients were Caucasian and one non-Caucasian patient of Asian origin was enrolled. All participants were from Austria.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 9: Other Demographic Characteristics of the PEGINVERA Study All-treated population

	Ropeginterferon alfa-2bn=51
Weight at Baseline kg – Mean (SD)	77.82 (13.41)
Height at Baseline cm - Mean (SD)	172.4 (9.17)
Body Mass Index Baseline (kg/m^2)	
Mean (SD)	26.13 (3.69)
Median	25.30
Range	21.0-36.7
Disease History	
Known Disease	43 (84.3%)
Newly Diagnosed	8 (15.7%)

	Ropeginterferon alfa-2bn=51
Duration of PV (months) from Diagnosis at screening - mean (SD)	51.21 (57.12)
JAK 2 Allelic Burden at Baseline	
Count Subjects with Data	51
Mean (SD)	44.35 (8.67)
Median	42.0
Range	0-99
JAK 2 Mutation Present at Baseline - n and %	N=51
Present	51 (100%)
Absent	0 (0%)
Normal Spleen Size at Baseline - n and %	N=50
No	16 (31.4%)
Yes	30 (58.8%)
(missing)	4 (7.8%)
Spleen Size at Baseline (males) - n and % - ≤ 13 cm	N=31
Normal	13 (41.9 %)
Enlarged	16 (51.6 %)
(missing)	2 (6.5 %)
Spleen Size at Baseline (females) - n and % - ≤ 12 cm	N=20
Normal	6 (30 %)
Enlarged	12 (60 %)
(missing)	2 (10 %)
Treatment with Hydroxyurea at Screening	N=51
No	34 (66.7 %)
Yes	17 (33.3 %)
Number of Phlebotomies in last 3 months prior to screening (mean ± SD)	1.5 ± 1.9
Number of Phlebotomies from screening to baseline – n and % (N=51)	0: 27 (52.9%) 1: 14 (27.5%) 2: 5 (9.8%) 3: 4 (7.8%) 6: 1 (2.0%)
HCT percentage (mean)(SD) at Baseline (%)	45.1 (+/-4)
PLTs x 10^9/L (mean)(SD) at Baseline (10^9/L)	457.9 +/- 186.5
WBCs x 10^9/L (mean)(SD) at Baseline (10^9/L)	11.8 +/-5.2

Source: FDA Analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study treatment was administered to patients in a clinic setting and study product accountability was conducted during monitoring visit. Investigators were responsible for ensuring completion of study product accountability logs. All doses were recorded in the CRF.

In the PEGINVERA Study, all patients were on concomitant medications. The most common concomitant medications are of the following:

- Analgesics/Anilides: 72.5% (37/51)
- Antithrombotic agents/Platelet aggregation inhibitors excl. heparin: 86.3% (44/51)
- Drugs for acid related disorders: 51% (26/51)
- Antineoplastic agents: 29.4% (15/51)
- Thyroid therapy: 23.5% (12/51)

Efficacy Results – Primary Endpoint

The efficacy criteria are based on complete hematological response defined as: HCT < 45% (without phlebotomy in previous two months), platelet count ≤ 400 $x10^9$/L, WBC ≤10 x 10^9/L, normal spleen size (longitudinal diameter ≤ 12 cm for females and ≤ 13 cm for males), and absence of thromboembolic events.

The best observed complete hematological response for patients in the all-treated population group was 60.8% (31/51) (95% CI: 46.1, 74.2). The median duration of response was 14.26 months (95% CI: 5.5, 30.1).

In the subgroup analysis, the HU-pretreated patients, 11/13 (84.6%) of patients achieved a complete hematologic response (spleen assessment and absence of thrombosis) and 2/13 (15.4%) of patients achieved a partial response.

Among the all-treated population who achieved a complete hematological response, the median time to response was 7.8 months of treatment with ropeginterferon alfa-2b and the median time on treatment required to achieve any hematological response was 10 weeks. It required 1.2 years for 50% of patients (HU-naïve) to achieve CHR and 1.4 years for 50% of patients (with prior HU use) to achieve CHR.

With the exclusion of normal spleen size and thrombosis, a complete hematological response (CHR based on objective laboratory parameters only) was achieved among 41/51 patients (80.4%, 95% CI: 66.9, 90.2). The median duration of response is 20.75 months (95% CI: 13, 43.8).

A total of 29 patients were eligible to switch dosing to once every 4 weeks. The median duration of treatment at the time of the switch was 104 weeks.

Efficacy Results – Secondary and other relevant endpoints

Secondary endpoints included the change in JAK2 mutant allele burden from baseline and molecular response. Additional secondary endpoints explored by the review team included the individual change from baseline for the laboratory parameters.

Further evaluation of the individual components of CHR (WBC, HCT, and PLTs) demonstrated a reduction from baseline for all three components.

- The mean baseline absolute WBC count was 11.8 x 10^9/L (SD 5.2) and by week 50, the mean WBC count was 5.8 x 10^9/L (SD 2.3).
- The mean baseline HCT percentage was 45.1% (SD 4.0) and by week 50, the mean HCT percentage had decreased to 43.05% (SD 3.67). Please note that the mean baseline HCT was close to 45% as patients were receiving phlebotomies prior to enrollment to help control HCT counts.
- The mean baseline PLT count was 455.9 x 10^9/L (SD 186.5) and by week 50, the mean PLT count had decreased to 246.6 x 10^9/L (SD 118.9).

The median differences from baseline for HCT (median, 43.3%; Day 0) ranged from −7.5% (Week 358) to 3.2% (Week 334). The median differences in PLT counts compared to baseline (median, 404.5 x 10^9/L; Day 0) ranged from −344.00 x 10^9/L (Week 136) to 169.00 x 10^9/L (Week 342). The median differences in WBC values from baseline (median, 10.9 x 10^9 cells/L; Day 0) ranged from 11.30 x 10^9 cells/L (Week 358) to 2.27x 10^9 cells/L (Week 370).

In the PEGINVERA study, mutant allelic burden for JAK2 was present in 98% of patients and over the course of the study the allelic burden decreased from baseline. The best observed individual complete molecular response was 12/42 (28.6%) and partial response of 19/42 (45.2%).

Table 10: JAK2 Molecular Response in PEGINVERA Study

	Complete Response n (%)
FAS	12/42 (28.6%)
HU-pretreated group	4/13 (30.8%)
HU-naïve group	8/29 (27.6%)

n = Responders
Source: FDA reviewer analysis

Dose/Dose Response

In the PEGINVERA Study the MTD was set to 540 mcg. There was no dose limiting toxicity was observed. The mean dose received by any patient was 236.6 mcg (+/- 110) during the treatment period. The median exposure to study drug was 155 weeks for all patients (range: 2-

258).

Durability of Response

For CHR [HCT < 45% (without phlebotomy in previous two months), platelet count ≤ 400 x10^9/L, WBC ≤10 x 10^9/L, normal spleen size (longitudinal diameter ≤ 12 cm for females and ≤ 13 cm for males, absence of thromboembolic events]. The median duration of response was 14.3 months.

Table 11: Duration of Response for CHR

	Total N=51
Subjects with response, n (%)	31 (60.8%)
Duration of longest response, months	
Events, n (%)	21 (67.7%)
Censored, n (%)	10 (32.3%)
No progressive disease (PD), No Death	8 (25.8%)
PD/Death after 2 or more missed assessments	2 (6.5%)
25th Percentile (95% CI)	3.70 (2.10, 8.52)
Median (95% CI)	14.26 (5.54, 30.10)
75th percentile (95% CI)	43.87 (16.56,NC)
Min, max	61.25

Source: FDA reviewer analysis

For CHR based on laboratory response only (HCT < 45%, PLTs ≤400 x 10^9/L, WBC count ≤10 x 10^9/L) the responses were durable with duration of response of 20.8 months for CHR (range 12.6, 43.9).

Table 12: Duration of Response in PEGINVERA for CHR based on laboratory parameters

	Total N=51
Subjects with response, n (%)	41 (80.4)
Duration of longest response, months	
Events, n (%)	24 (58.5)
Censored, n (%)	17 (41.5)
Reason for censoring, n (%)	
No PD, No death	16 (39.0)
PD/Death after 2 or more missed assessments	1 (2.4)
25th percentile (95% CI)	9.93 (2.23, 13.11)
Median (95% CI)	**20.75 (12.95, 43.87)**
75th percentile (95% CI)	NC (30.10, NC)
Min, Max	0.03, 73.41

Source: Information Request from PharmaEssentia dated 11 January 2021

The Kaplan-Meier point estimate for 50% of patients to record a CHR was 1.4 years [521 days (95% CI 242-992)].

Persistence of Effect

Not applicable as there were no protocol driven periods of discontinuation in the studies.

Additional Analyses Conducted on the Individual Trial

Change in blood counts during dosing delays for the PEGINVERA study was evaluated. For patients who had a drug interruption of greater than 42 days, the blood value (WBC, PLT, HCT) of each patient at visit before the interruption and after the re-introduction of ropeginterferon alfa-2b were analyzed.

In the PEGINVERA study, study drug interruption led to a mean 17% increase and median increase of 21% for WBC, mean 22% increase in PLTs and median increase of 14% in PLTs and mean 0.65% increase of HCT. The HCT did not display a significant change as therapeutic phlebotomy was required for all patients with HCT > 45%.

Table 13: Mean and Median Changes in Counts during Drug Interruption > 42 days

	Statistics	Value (N=25, Nx=57)
	n	57
WBC Count (10^9/L)	Mean	6.22

before Interruption	Median (min, max)	5.20 (2.9, 18.4)
WBC Count (10^9/L) after Interruption	Mean Median (min, max)	6.92 6.30 (3.7, 14.6)
PLTs (10^9/L) before Interruption	Mean Median (min, max)	254 244 (114,599)
PLTs (10^9/L) after Interruption	Mean Median (min, max)	298 287 (132,570)

Source: Sponsor Response to IR 21 Feb 2021
N- number of enrolled patients with evaluable interruptions
Nx= number of evaluable interruptions
N=number of laboratory rests results immediately before/after exposure interruptions. Patients with multiple exposure interruptions are counted multiple times.

The following table provides the response rates by CHR (spleen assessment and no thrombosis) for the six sites in Austria for PEGINVERA study.

Table 14: CHR by Site for PEGINVERA Study

Site	Number of Responses (n/N) %	Number of Evaluable Patients N
Site 1	15/19 (78.9%)	19
Site 2	3/4 (75%)	4
Site 3	7/7 (100%)	7
Site 4	4/5 (80%)	5
Site 5	7/10 (70%)	10
Site 6	5/6 (83%)	6

Source: FDA reviewer analysis

7.2. PROUD-PV STUDY

7.2.1. Study Design

Overview and Objective

The original objective of the PROUD-PV study was to demonstrate superiority of

ropeginterferon alfa-2b versus HU in disease response rate in patients with PV who were either naïve to treatment or currently treated with hydroxyurea.

The objective was changed to non-inferiority analysis in a protocol amendment (version 4.0) with a prespecified non-inferiority margin of 10.5%. The final analysis of this study included 12-month response data with one formal interim analysis planned on 6-month response data.

The secondary study objectives were to evaluate safety, quality of life (QoL) and change of JAK2 allelic burden in PV patients treated with ropeginterferon alfa-2b vs HU. A double-blind design was not an option due to differences in route of administration (subcutaneous vs. oral) and toxicity between the regimens.

The study started on October 4, 2013 and ended April 8, 2016.

Trial Design PROUD-PV

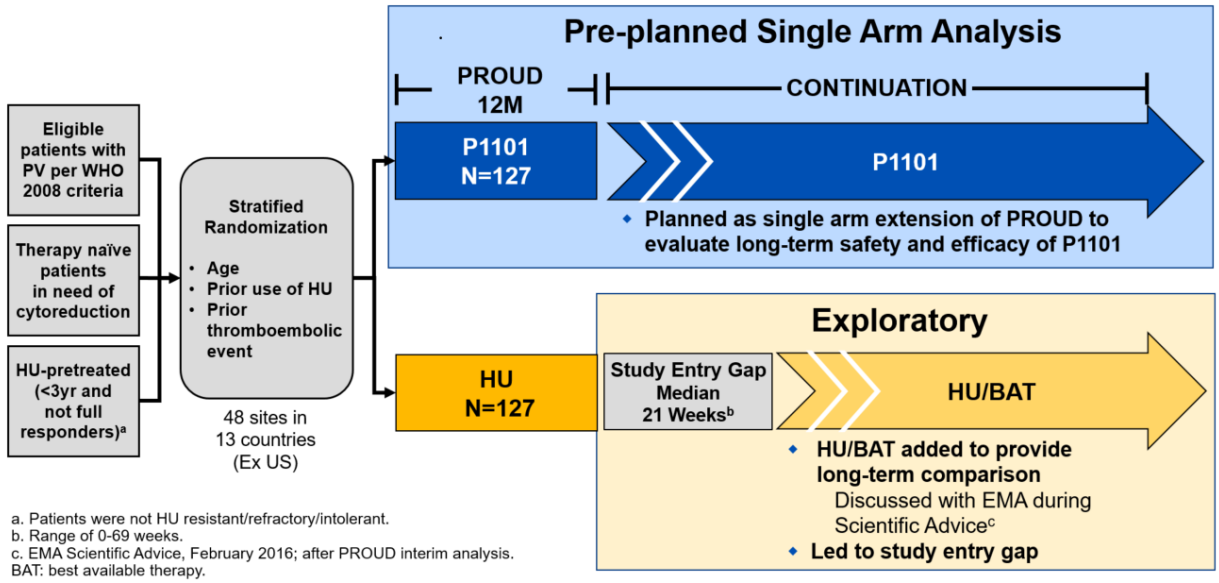
The PROUD-PV study was a randomized, open-label, Phase 3, randomized, active-controlled, parallel group, non-inferiority study (ropeginterferon alfa-2b compared to hydroxyurea). Patients diagnosed with PV, either HU naïve or currently being treated with HU, and fulfilling other eligibility criteria were randomized to either ropeginterferon alfa-2b or HU treatment arms. Stratification was by: HU exposure (yes/no), age at screening (≤60 or >60) and presence of thromboembolic events in the past (yes/no). Relevant blood values at different timepoints were measured by central laboratory and blinded to treatment assignment. Observer-independent imaging (CT/MRI) with blinded radiological assessment were used for spleen size.

During the initial treatment phase (first 12 weeks following randomization), the initial dose of ropeginterferon alfa-2b was 50 mcg for patients switching from HU to ropeginterferon alfa-2b. Patients (HU naïve) received a starting dose of 100 mcg for the ropeginterferon alfa-2b treatment arm. Ropeginterferon alfa-2b was administered subcutaneously at clinic visits every 2 weeks and titrated by 50 mcg for up to 12 months of treatment. The highest dose administered did not exceed 500 mcg every two weeks. Patients concurrently receiving HU who were randomized into the ropeginterferon alfa-2b had their HU dose decreased to the next lower level until they completely discontinued HU. This weaning period was over a twelve-week period.

The starting dose of hydroxyurea was 500 mg orally daily for first two weeks with evaluation for dose change every 2 weeks, increasing from 500 mg up to 3000 mg or individual MTD for up to 12 months of treatment.

Low dose aspirin (acetylsalicylic acid) (100 mg/day) was given to all patients for the duration of study treatment, unless contraindicated.

Figure 3: Schema for PROUD-PV/CONTINUATION-PV Study



(Schema of both trials taken from Applicant's Late Cycle meeting package, January 2021)

Study Endpoints

The primary endpoint of the PROUD-PV study was disease response rate after 12 months which was defined by the number of patients who met all four components in the PROUD-PV study:

- HCT < 45% without phlebotomy (at least 3 months since last phlebotomy)
- PLTs < 400 x 10^9/L
- WBCs < 10 x 10^9/L (all three hematological parameters will be measured by the blinded central lab)
- Normal spleen size (by imaging, central, blinded assessment where the spleen length < 12 cm for females and < 13 cm for males).

Additional secondary endpoints included the disease response rate at 12 months (complete hematological response only, without normal spleen size). The endpoint, "complete hematological response" at Month 12 (excluding spleen normalization) was not pre-specified in the protocol. This endpoint was defined after data lock date.

The secondary efficacy endpoints include the following:

- Change in hematological parameters, HCT, WBCs, PLTs and red blood cells (RBCs), from baseline (i.e. "EoT visit" in the PROUD-PV Study) over time up to last patient visit.
- Change in spleen size from baseline (i.e. "EoT visit" in the PROUD-PV Study) over time up to last patient visit.

- Duration of response maintenance.
- Phlebotomy need
- Change in QoL (EQ-5D-3L) from baseline ("EoT visit" of the PROUD-PV Study) over time up to last patient visit.
- Change in JAK2 allelic burden and other molecular and genetic abnormalities from baseline ("EoT visit" of the PROUD-PV Study) over time up to last patient visit.

Selection of Study Population
Inclusion Criteria (summarized):

1. Male or female, 18 years or older
2. Diagnosis of PV per the World Health Organization (WHO) 2008 criteria with the mandatory presence of JAK2V617F mutation as the major disease criterion.
3. For previously cytoreduced untreated patients- documented need for cytoreductive treatment (one or more of the following criteria):
    - Age > 60 years at planned day of first drug administration
    - At least one previous well documented major cardiovascular PV-related event, except bleeding and PV-related thromboembolic complications in the abdominal area
    - Poor tolerance or frequent need for phlebotomy
    - Progressive splenomegaly
    - Platelet counts greater than 1000 x 10^9/L
    - Leukocytosis (WBC > 10 x 10^9/L)
4. For patients currently treated or pre-treated with HU, all of the following criteria: being non-responders (defined by the response criteria for primary endpoint in this protocol, total HU treatment duration shorter than 3 years, no documented resistance or intolerance as defined by modified Barosi et al 2009 criteria.
5. HADS score 0-7 on both subscales
6. Signed written informed consent

Exclusion Criteria (summarized)
A patient who met any of the following criteria did not qualify for entry into this trial:

1. Any systemic cytoreduction for PV in the medical history prior to study entry with exception of HU for shorter than 3 years (see respective inclusion criterion).
2. Any contraindication to any of the investigational medicinal products (IMPs) (pegylated IFN or HU) or their excipients
3. Any systemic exposure to a non-pegylated or pegylated IFN-α in the medical history. Documented autoimmune disease at screening or in the medical history
4. Clinically relevant pulmonary infiltrates, pneumonia, and pneumonitis at screening.
5. Infections with systemic manifestations, e.g., hepatitis B, hepatitis C, or human
    - immunodeficiency virus (HIV) at screening.

- Known, PV-related thromboembolic complications in the abdominal area (e.g. portal vein thrombosis (Budd-Chiari syndrome) and/or splenectomy in the medical history.

6. Any investigational drug less than 6 weeks prior to the first dose of study drug or not recovered from effects of prior administration of any investigational agent
7. History or presence of depression requiring treatment with antidepressant.
8. HADS score equal to or above 11 on either or both of the subscales.
9. Any risk of suicide at screening or previous suicide attempts.
10. Any significant morbidity or abnormality which may interfere with the study participation.
11. Pregnancy and breast-feeding females of reproductive potential and males not using effective means of contraception. Note: women of childbearing potential not using effective contraceptive methods were not eligible for the study. A woman of childbearing potential was defined as any female having experienced menarche and who is not postmenopausal or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy).
12. History of active substance or alcohol abuse within the last year.
13. Evidence of severe retinopathy (e.g. cytomegalovirus retinitis, macular degeneration) or clinically relevant ophthalmological disorder (due to diabetes mellitus or hypertension).
14. Thyroid dysfunction (clinical symptoms of thyroid hyper or hypofunction) not adequately controlled.
15. Patients tested positively to thyroglobulin (TgAb) autoantibodies and / or thyroid peroxidase (TPOAb) autoantibodies at screening.
16. History of major organ transplantation.
17. History of uncontrolled severe seizure disorder.
18. Leukocytopenia at the time of screening (WBCs below the lower limit of normal).
19. Thrombocytopenia at the time of screening (PLTs below the lower limit of normal).
20. History of malignant disease, including solid tumors and hematological malignancies (except basal cell and squamous cell carcinomas of the skin and carcinoma *in situ* of the cervix that have been completely excised and are considered cured) within the last 3 years.

Statistical Analysis Plan and Amendments

The statistical analysis plan of PROUD-PV study was initially designed to demonstrate superiority of ropeginterferon alfa-2b versus HU based on disease response at 12 months. The applicant changed the primary efficacy endpoint to non-inferiority of ropeginterferon alfa-2b vs HU based on disease response at 12 months with a pre-specified non-inferiority margin of 10.5%. The statistical analysis plan (SAP) finalized on 10 September 2019.

Sample Size Determination

The PROUD-PV was originally designed as superiority study and sample size was calculated based on superiority comparison of ropeginterferon alfa-2b to HU with anticipated size of treatment effect that was at least 25%. The assumed rate of responses in patients treated with HU was 15% and 40% in patients treated with ropeginterferon alfa-2b and the projected drop-out rate was approximately 20%. The plan stated that patients who dropped out would be considered non-responders decreasing assumed rate of responders to 12% and 32%. Based on these assumptions, 126 patients per group (252 total) would be needed to detect the difference in response rate between groups at 1% (two-sided) significance level with 90% power using standard chi-square test. Taking into account 8 strata, 128 patients per treatment arm (256) were planned to be enrolled. Later, the applicant changed the primary objective from superiority to non-inferiority comparison with NI margin of 10.5% and statistical power for non-inferiority hypothesis was retrospectively calculated.

Analysis Population

The intent-to-treat (ITT) population included all randomized patients, irrespective of any protocol violations, subsequent therapies taken (n=127). The full analysis set (FAS) was defined as randomized patients without those with no study medication or no post-randomization data. The applicant used FAS as the primary analysis population. The Per Protocol Set (PPS) consisted of patients included in the FAS who complete a certain pre-specified minimal exposure to the treatment regimen.

Analysis Methods

The primary analysis was conducted using a weighted Cochran-Mantel-Haenszel framework for estimation. Corresponding response rate difference between the two treatment arms (test/reference) and its 95% confidence interval was calculated. The stratification factors used in the randomization scheme are: age groups ≤60 years/ >60 years, presence/absence of previous thrombotic event, and previous HU exposure. Noninferiority was intended if the lower limit of the 95% two-sided CI of the Mantel-Haenszel common estimate of response rate difference exceeds -0.1050 for both the full analysis set (FAS) and the per protocol set (PPS).

The analysis of the primary endpoint was disease response rate at 12 months and the null hypothesis for the non-inferiority comparison was that the difference in response rate (ropeginterferon alfa-2b– HU arm) is less than or equal to the NI margin of -10.5%. The non-inferiority of ropeginterferon alfa-2b to HU was based on disease response rate and demonstrated if the lower bound of the 95% CI of this difference is greater than -10.5%. The one-sided null hypothesis was tested against the alternative hypothesis at a one-sided significance level of 2.5%. The secondary efficacy analyses were performed for explorative purposes using descriptive analysis and standard statistical tests.

Sensitivity Analyses

The Per Protocol Set (PPS) was used for efficacy sensitivity analysis in the PROUD-PV study.

Protocol Amendments

The major amendment to the protocol occurred on June 15, 2016 in which the applicant changed the primary endpoint from a demonstrate superiority of ropeginterferon alfa-2b compared to HU to non-inferiority comparison with a NI margin of 10.5%. This change was made 2 months after completion of the study (PROUD-PV, 8 April 2016).

7.2.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that all clinical studies were conducted with respect for the individual participants in accordance with the study protocol, Good Clinical Practice (GCP) guidelines, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (E6), and local regulatory requirements.

Financial Disclosure

Financial disclosure forms were collected for the Phase 3 Studies, PROUD-PV, CONTINUATION-PV (b) (4) No principal investigators or sub-investigators in these studies were or are a full-time or part-time employee of PharmaEssentia US. One investigator reported disclosable financial interests or arrangements as described in 21 CFR § 54.4(a)(3).

Data Quality and Integrity

Data quality was satisfactory for clinical review.

Patient Disposition

Table 15: Disposition of Study Patients in PROUD-PV Study

	Ropeginterferon	Hydroxyurea	All Patients
Randomized but not treated	127	130	257
Patients participated in PROUD-PV (FAS)	127	127	254
Premature Discontinuation from PROUD-PV, n (%)	21/127 (16.5%)	16/127 (12.6%)	37 (14.6%)

	Ropeginterferon	Hydroxyurea	All Patients
Adverse Event	11 (8.7%)	3 (2.4%)	14 (5.5%)
Lack of Efficacy	0 (0%)	2 (1.6%)	2 (0.8%)
Lost to follow-up	4 (3.1%)	1 (0.8%)	5 (2.0%)
Withdrawal by Subject	6 (4.7%)	5 (3.9%)	11 (4.3%)
Other	0 (0%)	5 (3.9%)	5 (2.0%)
Completed PROUD-PV (FAS), n (%)	106 (83.5%)	111 (87.4%)	217 (85.4%)

BAT: Best available therapy
Source: FDA reviewer analysis

Protocol Violations/Deviations

There were 14 major protocol deviations which occurred in 11 patients (5 in the ropeginterferon alfa-2b, and 6 in the HU arm). Eleven of the major protocol deviations led to exclusion from the protocol analysis set in 9 patients (4 in AOP arm and 5 in HU arm). The major protocol deviations leading to exclusion from the per protocol set included: 6 major deviations as a result in violation of the eligibility criteria: (disclosure of malignant disease in two patients, positive TPO Ab in two patients, low hemoglobin value in one patient and positive Hospital Anxiety and Depression Scale without psychiatric assessment in one patient).

There were 5 major protocol deviations due to a dose reduction or interruption following an adverse events not related to the study drug in 4 patients or due to missed visits in 1 patient.

There were 3 major safety deviations were observed in two patients (1 in each treatment arm): included two cases of study drug continuation despite a Grade 3 Adverse event (in 1 patient) and an accidental overdose of the ropeginterferon alfa-2b study drug (in 1 patient).

Demographics

Table 16: Baseline Demographic Characteristics for PROUD-PV ITT Population

	Ropeginterferon alfa-2b n=127 n (%)	HU n=127 n (%)
Age		
Subjects	127	127
Mean (SD)	58.46 (10.80)	57.87 (13.11)
Median	60	60
Range	30-85	21-81
Pooled Age Group - n and %		
18-<65 years	90 (70.9%)	84 (66.1%)
>=65 years	37 (29.1%)	43 (33.9%)
Stratification by Age - n and %		
<=60 years	67 (52.8%)	65 (51.2%)
>60 years	60 (47.2%)	62 (48.8%)
Sex - n and %		
Female	68 (53.5%)	67 (52.8%)
Male	59 (46.5%)	60 (47.2%)
Race - n and %		
Caucasian	127 (100%)	127 (100%)
Ethnicity - n and %		
Not Hispanic or Latino	123 (96.9%)	120 (94.5%)
Not Reported	2 (1.6%)	3 (2.4%)
Unknown	0 (0%)	3 (2.4%)
Hispanic or Latino	2 (1.6%)	1 (0.8%)
Country Description - n and %		
Bulgaria	25 (19.7%)	20 (15.7%)
Hungary	14 (11.0%)	20 (15.7%)
Poland	12 (9.4%)	15 (11.8%)
Russian Federation	16 (12.6%)	17 (13.4%)
Ukraine	17 (13.4%)	13 (10.2%)
Czech Republic	14 (11.0%)	12 (9.4%)
Austria	11 (8.7%)	8 (6.3%)
France	5 (3.9%)	8 (6.3%)
Romania	3 (2.4%)	6 (4.7%)
Slovakia	6 (4.7%)	4 (3.1%)
Germany	3 (2.4%)	3 (2.4%)
Spain	1 (0.8%)	0 (0%)

	Ropeginterferon alfa-2b n=127 n (%)	HU n=127 n (%)
Italy	0 (0%)	1 (0.8%)

Source: FDA reviewer analysis

Although PV is described in all age ranges, the median age at presentation was 60 years with a slight female predominance noted in both arms in the PROUD-PV study. Based on the stratification factors, forty-eight percent were over the age of 60 years. All 254 participants were Caucasian, and none were recruited from the US. Retrospective studies have demonstrated racial disparities in myeloproliferative outcomes and attributed this to differences in access to health care. The majority of participants were from Eastern Europe (214/257, 84%). The remaining participants were from Western Europe (43/257, 17%).

Table 17: Other Demographics for PROUD-PV ITT Population

	Ropeginterferon alfa-2b n=127	HU n=127
Body Mass Index Baseline (kg/m2)		
Subjects	127	127
Mean (SD)	26.40 (3.82)	26.50 (3.80)
Median	25.90	26.30
Range	17.2-40	18-38.4
Baseline ECOG Status - n and %		
Grade 0	87 (68.5%)	79 (62.2%)
Grade 1	38 (29.9%)	47 (37.0%)
Grade ≥2	2 (1.6%)	1 (0.8%)
Duration of PV (months) from Diagnosis - median and range	1.9 [0-146]	3.6 [0-126]
Duration of PV (months) from Diagnosis of HU pre-treated patients – n and median/range	45 10.2 [0.9-34]	37 7.9 [1-36]
Spleen Diameter at Baseline (cm)		
Subjects	127	127
Mean (SD)	13.38 (3.16)	13.55 (3.32)
Median	13.10	13

	Ropeginterferon alfa-2b n=127	HU n=127
Range	7-25	7.5-24.5
Clinic Sig Splenomegaly at Baseline - n and %		
No	115 (90.6%)	112 (88.2%)
Yes	12 (9.4%)	15 (11.8%)
Normal Spleen Size at Baseline - n and %		
No	68 (53.5%)	68 (53.5%)
Yes	59 (46.5%)	59 (46.5%)
Disease Related Symptoms at Baseline - n and %		
No	125 (98.4%)	124 (97.6%)
Yes	2 (1.6%)	3 (2.4%)
JAK2 Allelic Burden at Baseline		
Subjects	126	125
Mean (SD)	41.91 (23.49)	42.83 (24.14)
Median	37.11	36.98
Range	0-94.94	0-89.81
JAK2 Allelic Burden Finding at Baseline - n and %		
POSITIVE	126 (99.2%)	125 (98.4%)
(missing)	1 (0.8%)	2 (1.6%)
HCT at Baseline (%)		
Subjects	124	126
Mean (SD)	49.54 (5.43)	49.79 (5.49)
Median	49.40	49.40
Range	37.7-65.8	38.5-70.8
WBCs at Baseline (10^9/L)		
Subjects	127	126
Mean (SD)	11.36 (4.7)	12.09 (5.1)
Median	10.8	11.4
Range	8.4-13.5	8.1-15.4
PLTs at Baseline (10^9/L)		
Subjects	127	126
Mean (SD)	524.7 (275.4)	519.5 (253.3)
Median	478	455

	Ropeginterferon alfa-2b n=127	HU n=127
Range	69-1353	117-1389
Stratification Description - n and %		
S1: Age<=60, HU+, TE+	4 (3.1%)	5 (3.9%)
S2: Age>60, HU+, TE+	5 (3.9%)	4 (3.1%)
S3: Age<=60, HU-, TE+	7 (5.5%)	5 (3.9%)
S4: Age>60, HU-, TE+	9 (7.1%)	9 (7.1%)
S5: Age<=60, HU-, TE-	33 (26.0%)	34 (26.8%)
S6: Age>60, HU-, TE-	31 (24.4%)	32 (25.2%)
S7: Age<=60, HU+, TE-	23 (18.1%)	21 (16.5%)
S8: Age>60, HU+, TE-	15 (11.8%)	17 (13.4%)

HU+/-: Hydroxyurea use/No Hydroxyurea use, TE+/-: Thrombosis event
Source: FDA reviewer analysis

The median duration of PV was 1.9 months (range 0-146 months) in the ropeginterferon alfa-2b treatment arm and 3.6 months (range 0-126 months) in the HU treatment arm indicating that patients were diagnosed in an early stage of the disease. At baseline, ninety-eight percent of patients were JAK2V617 positive and the JAK2V617 allelic burden was similar in both arms (ropeginterferon alfa-2b: 41.91 ± 23.49; HU: 42.83 ± 24.14). Among the stratification groups, the largest enrolled group were patients 60 years or less and not previously treated with hydroxyurea and had no thrombotic event (ropeginterferon alfa-2b 26%; HU 26.8%) and patients older than 60 and not previously treated with hydroxyurea and had no thrombotic event (ropeginterferon alfa-2b: 24.4%; HU: 25.2%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study treatment was administered to all patients in a clinic setting. Study product accountability was conducted during monitoring visits and investigators were responsible for ensuring completion of study product accountability log. All doses were recorded in the CR.

In the PROUD-PV study, most of the patients 98.4% (250/254) were on concomitant medication during the study. The following agents were identified:

- Antithrombotic agents/platelet-aggregation inhibitors: 89.8% (228/254),
- Beta blocking agents: 32.3% (82/254),
- Uricosuric agents: 21.7% (55/254),
- Angiotensin converting enzyme inhibitors: 20.5% (52/254) and
- Analgesics: 16.1% (41/254).

Efficacy Results – Primary Endpoint PROUD-PV

In the PROUD-PV Study, the primary endpoint of disease response rate was defined by the normalization of all hematological parameters (CHR) and normalization of the size of the spleen (responder) at Month 12. The results were 20.4% (26/127) in the ropeginterferon alfa-2b arm and 26.8% (34/127) in the HU arm (-6.57; 95% CI: -17.23 to 4.09). This pre-specified primary endpoint was not achieved in the PROUD-PV Study.

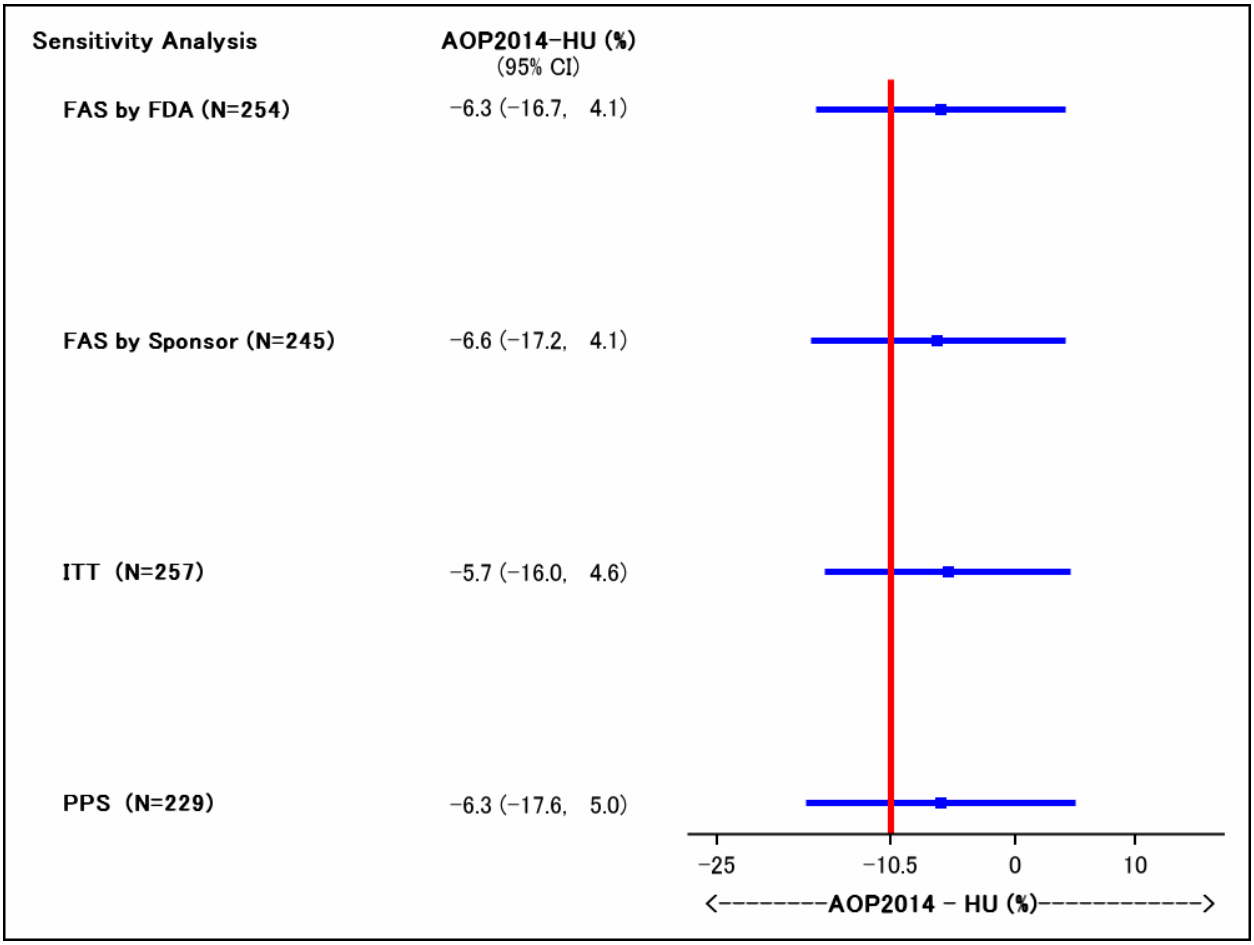
Table 18: Primary Endpoint for PROUD-PV

Treatment Group	Ropeginterferon N=127	HU N=127
Responders	26 (20.47%)	34 (26.8%)
Difference (%) in disease response (Ropeginterferon-alfa -HU and 95% CI stratified CMH (95% CI)	-6.3 (-16.7, 4.1)	
NI margin	-10.5%	

(Taken from Statistical FDA review by Lola Luo, Ph.D.)

The statistical team conducted sensitivity analysis of the primary endpoint with different analysis population for the PROUD-PV study. The following plot displays the analysis.

Figure 4: Sensitivity Analysis for Primary Endpoint for Different Populations (PROUD-PV)



Source: FDA Statistical Review Team

Efficacy Results – Secondary and other relevant endpoints

The different secondary endpoints were evaluated and described in the table below.

Table 19: Secondary Endpoints of PROUD-PV Study

	Ropeginterferon alfa-2b (n = 127)	Hydroxyurea (n = 127)
Key Secondary Endpoint *(post-hoc analysis)* CHR at Month 12 (excluding spleen)	53 (41.7%)	57 (44.9%)
Other Secondary Endpoints		
Hct < 45% at least 3 months from last phlebotomy	68 (53.5%)	75 (59.0%)
WBCs < 10 x 10^9/L	118 (92.9%)	112 (88.1%)

	Ropeginterferon alfa-2b (n = 127)	Hydroxyurea (n = 127)
PLTs < 400 x 10^9/L	114 (89.8%)	103 (81.1%)
Normal Spleen Size	61 (48.0%)	70 (55.1%)

Source: FDA reviewer analysis

Table 20: JAK2 Molecular Response in PROUD-PV

	PROUD-PV 12 months (n/total) %
Ropeginterferon alfa-2b	42/123 (34.1%)
HU	52/123 (42.2%)

n = Responders
Source: FDA reviewer analysis

Reviewer's Comments: Passamonti et al (Haematologica 2009) highlights how the JAK2 mutant allelic burden may impact disease phenotype and complications associated with PV. In the paper, it reported that patients with a higher JAK2 mutant allelic burden have been correlated with a more severe phenotype and that the JAK2 burden predicts which cell line would be most dominant during the disease course. The full understanding of decrease in JAK2 allelic burden in PV in terms of mortality is not fully known.

Dose/Dose Response

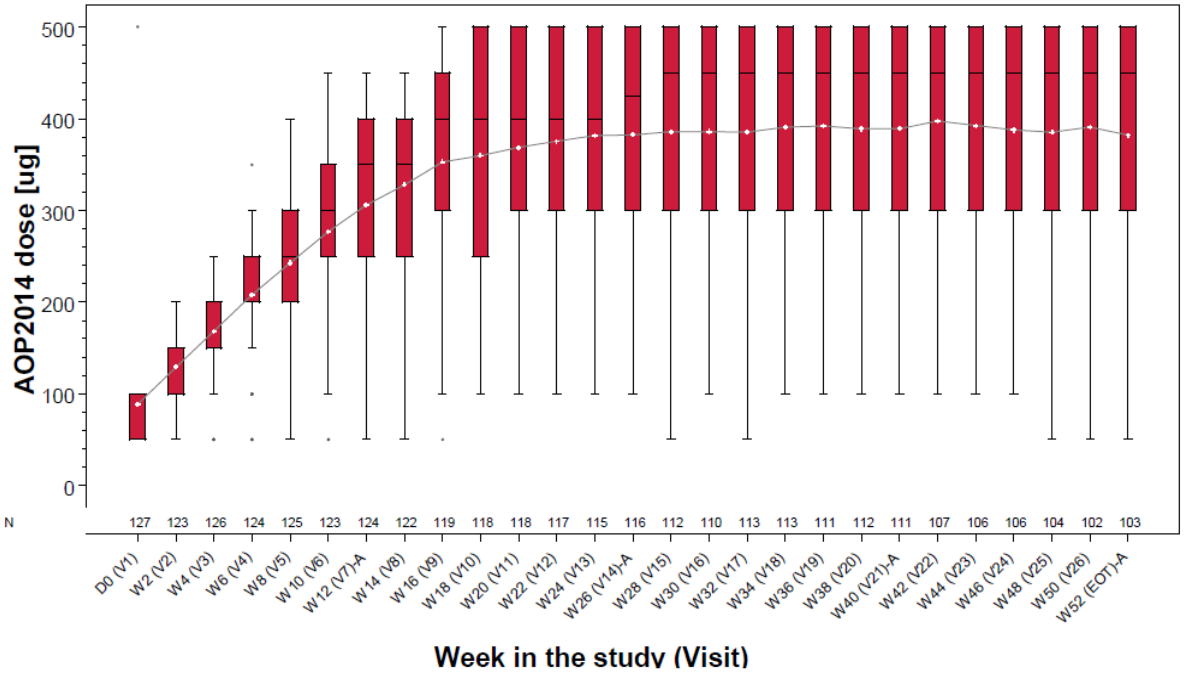
In the PROUD-PV Study, the mean dose of ropeginterferon alfa-2b at EOT was 382 mcg (±141); the median dose was 450 mcg administered every two weeks. At 24 months, the mean dose was 377 (±142) mcg, and the median was 450 (range: 50-500) mcg. At 36 months, the mean dose of ropeginterferon alfa-2b administered by assessment visit was 363 (±149) mcg; the median dose was 425 (range: 35 - 500) mcg.

Dose Administration during the PROUD-PV Study

The dose titration for ropeginterferon alfa-2b was conservative which was done for tolerability. The following graphs are representative of the dose titration for both ropeginterferon alfa-2b and hydroxyurea in the PROUD-PV Study. In Figure 5, the starting dose of ropeginterferon alfa-2b was 100 mcg and increased by 50 mcg increments to attain a maximum targeted dose of 500 mcg. Due to the slow titration of ropeginterferon alfa-2b, it took 28 weeks to reach a maximum dose level. In Figure 6, patients randomized to hydroxyurea started at 500 mg and were titrated towards the known maximum tolerated dose of 3000 mg. It took 8 weeks to reach the maximum tolerated dose. Hence, there was a 20 week delay in time to reach maximum dose level compared to the HU arm.

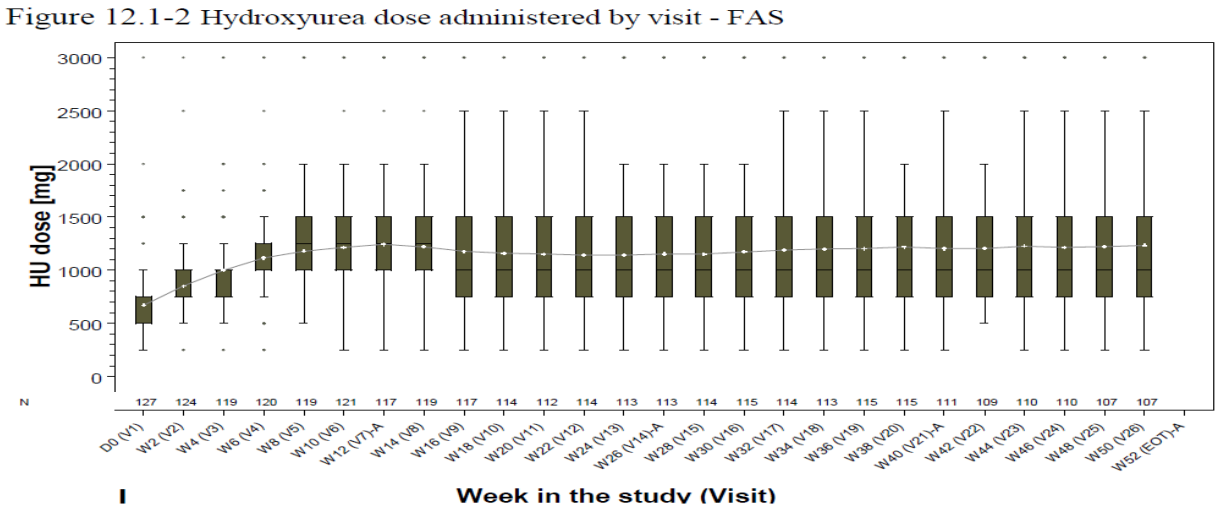
Figure 5: Ropeginterferon Alfa-2b Dose Administered by Visit - FAS Population

Figure 12.1-1 AOP2014 dose administered by visit - FAS



Source: Figure 14.2.1.1

Figure 6: Hydroxyurea Dose Administered by Visit - FAS Population



Source: Figure 14.2.1.2

Durability of Response

The study endpoint was assessed at 12 months and is captured in the primary endpoint.

Persistence of Effect

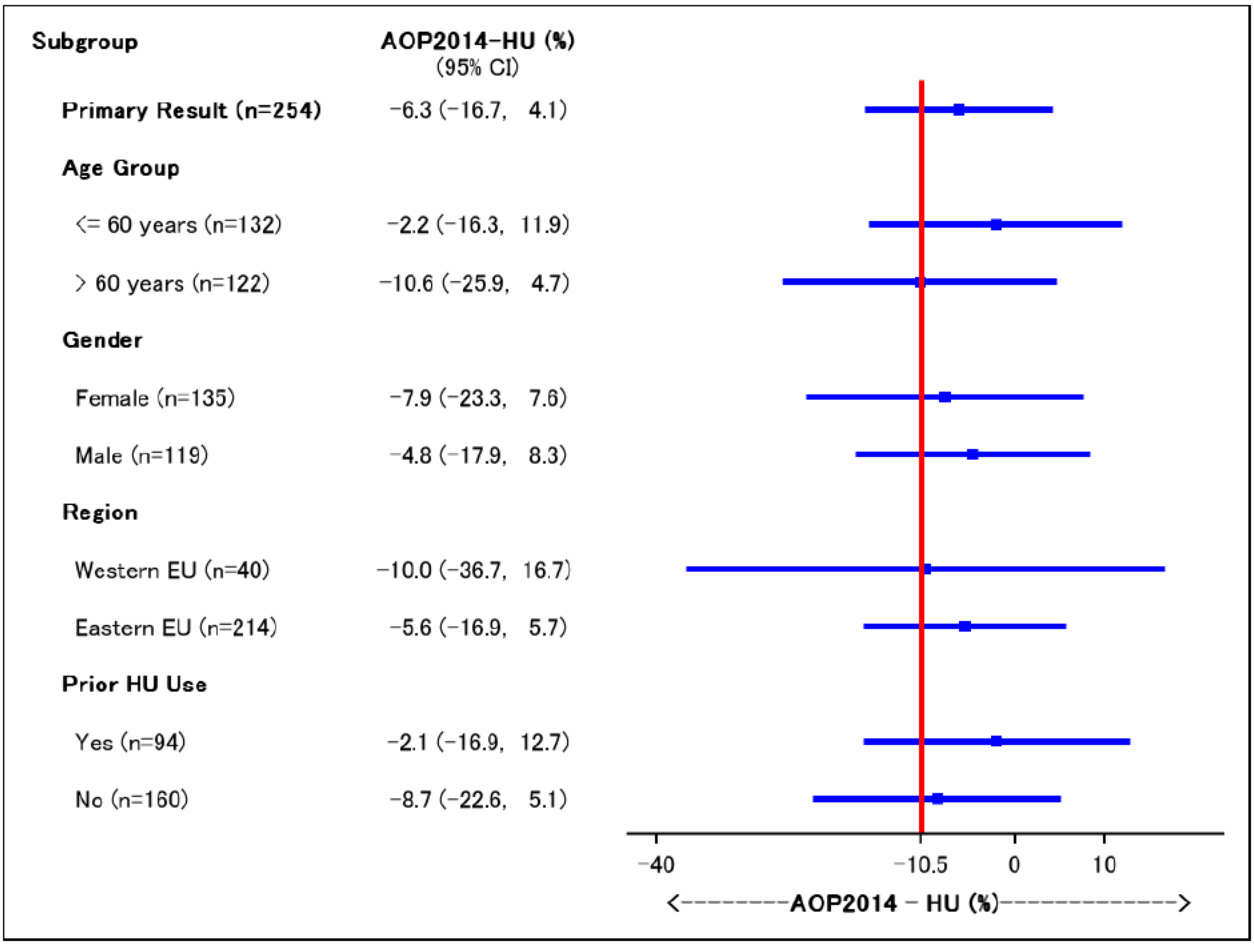
Not applicable as there were no protocol driven periods of discontinuation in the studies.

Additional Analyses Conducted on the Individual Trial

Subpopulations

Subgroup analysis of the primary endpoint by age group, sex, region and prior HU were assessed and results agreed with the primary analysis result. No outlier subgroups observed.

Figure 7: Sensitivity Analysis for Primary Endpoint for Subgroups



Source: FDA Statistical Review Team

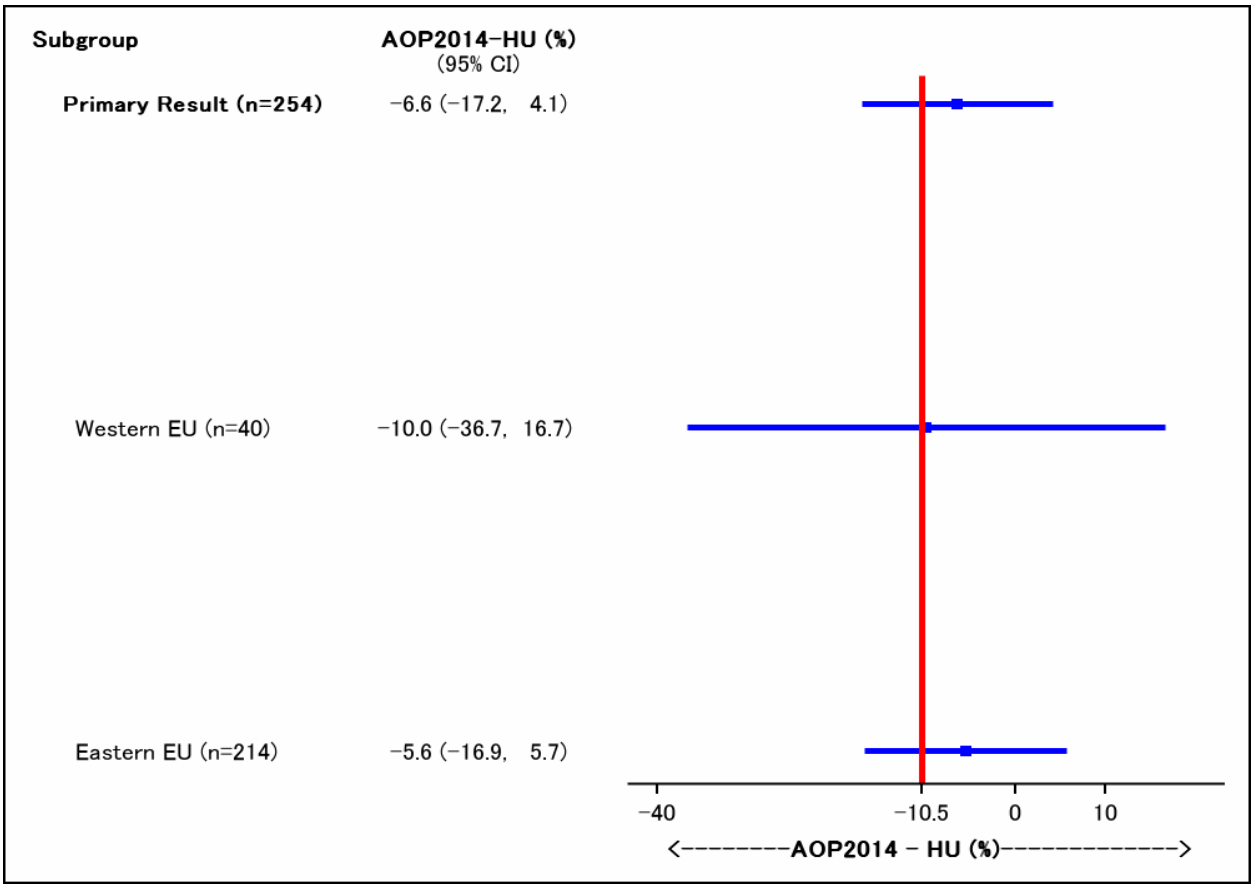
Baseline laboratory parameters were evaluated between the Eastern and Western European patients enrolled in these trials. Overall, the baseline hematology parameters appear comparable between regions.

Table 21: Baseline Hematology Parameters in Eastern and Western Europe Patient Population in PROUD-PV

	All Countries N=127	Eastern Europe N=107	Western Europe N=20
HCT Percentage Median (range)	43 (36.8, 54.9)	43 (31, 50.9)	43.5 (38.6, 54.9)
WBC X 10^9/L Median (range)	10.8 (5.7, 25.6)	10.3 (4, 18.3)	13.1 (7.8, 24.3)
PLT Count x 10^9/L, Median (range)	478 (138, 1293)	503 (138, 1293)	602.5 (69, 1242)

Source: FDA reviewer analysis

Figure 8: Subgroup Analysis for Primary Endpoint for European Region



Source: FDA Statistical Review Team

Subgroup analysis for primary endpoint was performed by the statistical team. There does not appear to be any heterogeneity in terms of response by Eastern or Western Europe. This information did not demonstrate any relevant differences between Eastern and Western Europe and was applicable to the US population.

7.3. CONTINUATION-PV STUDY

7.3.1. Study Design

Overview and Objectives

The primary objective of the CONTINUATION-PV study was to assess the long-term efficacy of ropeginterferon alfa-2b in terms of disease response rate in patients diagnosed with PV, who were previously treated with ropeginterferon alfa-2b in the PROUD-PV study. The secondary objectives included assessment of long-term efficacy, safety, quality of life (QoL), and change of JAK2 allelic burden.

Study Design

The CONTINUATION-PV study is an open-label, multicenter study assessing the long-term efficacy and safety of ropeginterferon alfa-2b. It was originally designed as a single-arm extension study. Treatment could be continued as long as it was effective and safe or until ropeginterferon alfa-2b becomes otherwise available. The HU/BAT arm was started approximately 9 months after initiation of study following an amendment to the initial study protocol. Low dose aspirin (acetylsalicylic acid) (100 mg/day) was given to all patients for the duration of study treatment, unless contraindicated.

The first ropeginterferon alfa-2b patient in the CONTINUATION-PV study enrolled Nov 25, 2014 and protocol version 5.1 (November 2016) added the HU/BAT group. The first patient enrolled in the HU/BAT group completed the PROUD study October 19, 2015 and enrolled in CONTINUATION the same day resulting in a gap of ~ 11 months between starting date of ropeginterferon alfa-2b group and the HU/PROUD-PV group. Thus by the time the HU/BAT group began enrollment some patients in the HU group may have completed the PROUD-PV study and been treated by own physician for periods of up to one year or more.

Selection of Study Population
Patients who had completed the 12 months in the PROUD-PV Study and who fulfilled at least one of the following criteria:

a) Normalization of at least two out of three main blood parameters (HCT, PLTs and WBCs) if these parameters were moderately increased (HCT<50%, WBC<20 x 10^9/L, PLTs<600 x 10^9/L) at baseline of the PROUD-PV Study, OR
b) >35% decrease of at least two out of three main blood parameters (HCT, PLTs and WBCs) if these parameters were massively increased (Hct>50%, WBCs>20 x 10^9/L, PLTs >600x 10^9/L), at baseline of the PROUD-PV Study, OR
c) Normalization of spleen size, if spleen was enlarged at baseline of the PROUD-PV Study, OR
d) Otherwise a clear, medically verified benefit from treatment (e.g. normalization of
e) disease-related micro-vasculatory symptoms, substantial decrease of JAK2 allelic burden)

Exclusion Criteria:

a) Non-recovery from the ropeginterferon alfa-2b related toxicities to the grade (usually, grade I) which allowed continuation of the treatment.
b) HADS score of 11 or higher on either or both of the subscales, and /or development or worsening of the clinically significant depression or suicidal thoughts.
c) Progressive and clinically significant increase of liver enzyme levels despite dose reduction ,or if such increase was accompanied by increased bilirubin level or any signs.
d) Symptoms of a clinically significant autoimmune disease.
e) Clinically significant development of a new ophthalmologic disorder, or worsening of a preexisting one, during the study.
f) Ropeginterferon alfa-2b arm only: Loss of efficacy of ropeginterferon alfa-2b or any comparable situation where no further benefits of treatment continuation were expected by the Investigator.

Co Primary Efficacy Endpoints

- HCT <45% without phlebotomy (at least 3 months since the last phlebotomy),
- PLTs <400 x 10^9/L,
- WBCs <10 x 10^9/L,
- normal spleen size, and

- HCT <45% without phlebotomy (at least 3 months since the last phlebotomy),
- PLTs <400 x 10^9/L,
- WBCs <10 x 10^9/L,
- Resolution and/or clinically improvement of disease related signs (clinically significant splenomegaly) and disease-related symptoms (microvascular disturbances, pruritus, headache).

Patients were classified as a responder only if all disease response criteria were met. Normal spleen size was defined as < 12 cm in females and < 13cm in males. Normality of spleen size evaluated by investigator was used for the analysis in the CONTINUATION-PV study.

Statistical Methods

Sample Size Calculation

No formal hypothesis was planned to be tested in CONTINUATION-PV study, therefore no power calculation or sample size calculations were performed. Efficacy analysis included all enrolled patients.

7.3.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that all clinical studies were conducted with respect for the individual participants in accordance with the study protocol, Good Clinical Practice (GCP) guidelines, the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (E6), and local regulatory requirements.

Financial Disclosure

Financial disclosure forms were collected for the Phase 3 Studies, PROUD-PV, CONTINUATION-PV (b) (4) No principal investigators or sub-investigators in these studies were or are a full-time or part-time employee of PharmaEssentia US. One investigator reported disclosable financial interests or arrangements as described in 21 CFR § 54.4(a)(3).

Data Quality and Integrity

Data quality was satisfactory for clinical review.

Patient Disposition

Table 22: Patient Disposition in CONTINUATION-PV Study

	Ropeginterferon alfa-2b	HU	Total
Completed PROUD-PV (FAS), n (%)	106 (83.5%)	111 (87.4%)	217 (85.4%)
Patients enrolled in CONTINUATION-PV, n/N(%)	95/127 (74.8%)	76/127 (59.8%)	171/254 (67.3%)
Completed PROUD and enrolled into CONTINUATION-PV, n/N(%)	95/106 (89.6%)	76/111 (31.5%)	171/217 (78.8%)
Premature Discontinuation from CONTINUATION, n/N (%)	17/95 (17%)	7/76 (9.2%)	27/171 (15.8%)
Adverse Event	7 (7.4%)	2 (2.6%)	9 (5.3%)
Lack of Efficacy	3 (3.2%)	0 (0%)	3 (1.8%)
Lost to follow-up	3 (3.2%)	0 (0%)	3 (1.8%)
Withdrawal by Subject	3 (3.2%)	3 (3.9%)	6 (3.5%)
Other	4 (4.2%)	2 (2.6%)	6 (3.5%)

Ninety-five patients (89.6%) entered the ropeginterferon alfa-2b -treated arm and seventy-six patients (68.5%) participated in the HU- treated arm. In the CONTINUATION-PV Study, patients entered CONTINUATION-PV Study after a median of 14 days (range 0-122 days) in the

ropeginterferon alfa-2b arm, and after a median of 148 days (range 69-481 days) in the Best Available Therapy (BAT) arm.

Table 23: Other Demographic Characteristics for CONTINUATION-PV Study ITT Population

	Ropeginterferon alfa-2b n=95	Best Available Therapy (BAT) n=76
Weight at Baseline kg - Mean [SD]	75.01 [14.32]	77.76 [15.04]
Height at Baseline cm - Mean [SD]	169.25 [8.16]	169.93 [9.39]
Baseline ECOG Status – n and %		
Grade 0	74 (77.9%)	51 (67.1%)
Grade 1	19 (20%)	23 (30.3%)
Grade >=2	2 (2.1%)	2 (2.6%)
Duration of PV (months) from Diagnosis to EOT- mean [SD]	24.73 [25.85]	22.80 [17.33]
Duration of PV (years) from Diagnosis to EOT - mean [SD]	2.07 [2.16]	1.90 [1.45]
JAK 2 Allelic Burden at Baseline		
Subjects	94	74
Mean [SD]	42.81 [23.40]	42.94 [23.01]
Median	37.11	38.12
Range	2.58-94.94	2.52-86.61
JAK 2 Allelic Burden at Baseline - n and %		
POSITIVE	94 (98.9%)	74 (97.4%)
(missing)	1 (1.1%)	2 (2.6%)
JAK 2 Allelic Burden at EOT		
Subjects	92	74
Mean [SD]	30.06 [23.03]	24.40 [20.56]
Median	22.67	18.20
Range	1.42-93.23	0.31-74.55
JAK 2 Allelic Burden at EOT - n and %		
POSITIVE	92 (96.8%)	74 (97.4%)
(missing)	3 (3.2%)	2 (2.6%)
HCT at Baseline (%)		
Subjects	93	75
Mean [SD]	49.87 [5.49]	51.03 [5.92]
Median	49.60	50.90
Range	38.3-65.8	40.5-70.8
HCT at EOT (%)		

	Ropeginterferon alfa-2b n=95	Best Available Therapy (BAT) n=76
Subjects	92	76
Mean [SD]	43.63 [3.98]	42.04 [4.17]
Median	44	42.60
Range	32.3-53.5	29-51.4
Normal Spleen Size at Baseline - n and %		
No	55 (57.9%)	40 (52.6%)
Yes	39 (41.1%)	35 (46.1%)
(missing)	1 (1.1%)	1 (1.3%)
Normal Spleen Size at EOT - n and %		
No	53 (55.8%)	32 (42.1%)
Yes	37 (38.9%)	40 (52.6%)
(missing)	5 (5.3%)	4 (5.3%)

Source: FDA reviewer analysis

In the CONTINUATION-PV Study, the median age at presentation was 59 years in the ropeginterferon alfa-2b arm and 60.5 years in the BAT arm. There was a slight female predominance noted in both arms. The percentage of women was slightly lower than the percentage of women enrolled in the PROUD-PV study.

Reviewer's Comment: The baseline characteristics seen in the CONTINUATION study were similar to the findings in the PROUD-PV.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Once an optimal disease response was reached, the dose was to remain stable as a maintenance dose throughout both the PROUD and the CONTINUATION-PV studies. Study treatment was administered to all patients in a clinic setting. Study product accountability was conducted during monitoring visits and investigators were responsible for ensuring completion of study product accountability log. All doses were recorded in the CR.

The most common concomitant medications in the CONTINUATION-PV study (>20%) fell within the following categories:

- Antithrombotic agents/Platelet aggregation inhibitors excl. heparin: 92.4% (158/171).
- Beta blocking agents/Beta blocking agents, selective: 32.2% (55/171).

- Anti-gout preparations/Preparations inhibiting uric acid production: 22.2% (38/171).
- Agents acting on the renin-angiotensin system/ACE inhibitors, plain: 21.1% (36/171).

There was no evidence that any concomitant medications had any potential to affect the efficacy results.

The results for the co-primary endpoints for the CONTINUATION-PV study are displayed in the table and were confirmed by the statistical reviewer.

Table 24: Results for the Co-Primary Endpoints (CONTINUATION-PV)

	Ropeginterferon alfa-2b (N=95)	**BAT (N=76)**
CHR and Normal Spleen Size		
Month 24 Responder, n (%)	35 (36.8)	23 (30.3)
Relative Risk (95% CI)	1.2 (0.7, 1.7)	
Month 36 Responder, n (%)	38 (40)	21 (27.6)
Relative Risk (95% CI)	1.4 (0.9, 2.1)	
CHR and Improvement in Disease Burden		
Month 24 Responder, n (%)	47 (49.5)	26 (34.2)
Relative Risk (95% CI)	1.4 (0.9, 1.9)	
Month 36 Responder, n (%)	50 (52.6)	28 (36.8)
Relative Risk (95% CI)	1.4 (1.0, 2.0)	

Source: FDA Analysis

7.4. Active-Control Efficacy Review from PROUD-PV/CONTINUATION-PV

The active-control experience from the PROUD-PV and CONTINUATION-PV were evaluated given the failure of the randomized trials. The single-arm was evaluated because the natural history of PV is such that there are no spontaneous remissions and reviewing the objective laboratory assessments can provide supportive efficacy data. In this combined exploratory analysis, 127 patients were considered the as treated population and could also be considered as an intent-to-treat population.

Evaluation of complete hematological response based on laboratory components is important because a key component in response assessment of cytoreductive therapy in PV is a reduction in HCT, WBC and platelets that has a confirmed predictive value for clinically relevant outcomes. Additionally, spleen normality has limitations related to the baseline measurements of spleen and the early stage of disease in patient.

In the PROUD-PV/CONTINUATION-PV study components of complete hematological response (laboratory measures) were objectively measured . The single arm data from PROUD-PV/CONTINUATION-PV allows for assessment of response beyond 12 months for CHR defined as HCT < 45 %, PLTs < 400 x 10^9/L and WBCs < 10 x 10^9/L. Using the population of 127 patients, CHR was evaluated at 12, 24 and 36 months.

Table 25: Complete Hematological Response for PROUD-PV/CONTINUATION-PV Study (ITT Population; N = 127)

CHR (WBC, HCT, PLT)	N (%)	95%CI
Month 12	66 (52.0)	(43.3, 60.7)
Month 24	67 (52.8)	(44.1, 61.4)
Month 36	67 (52.8)	(44.1, 61.4)
CHR plus Normal Spleen Size		
Month 12	31 (24.4)	(16.9, 31.9)
Month 24	34 (26.8)	(19.1, 34.5)
Month 36	38 (29.9)	(22.0, 37.9)

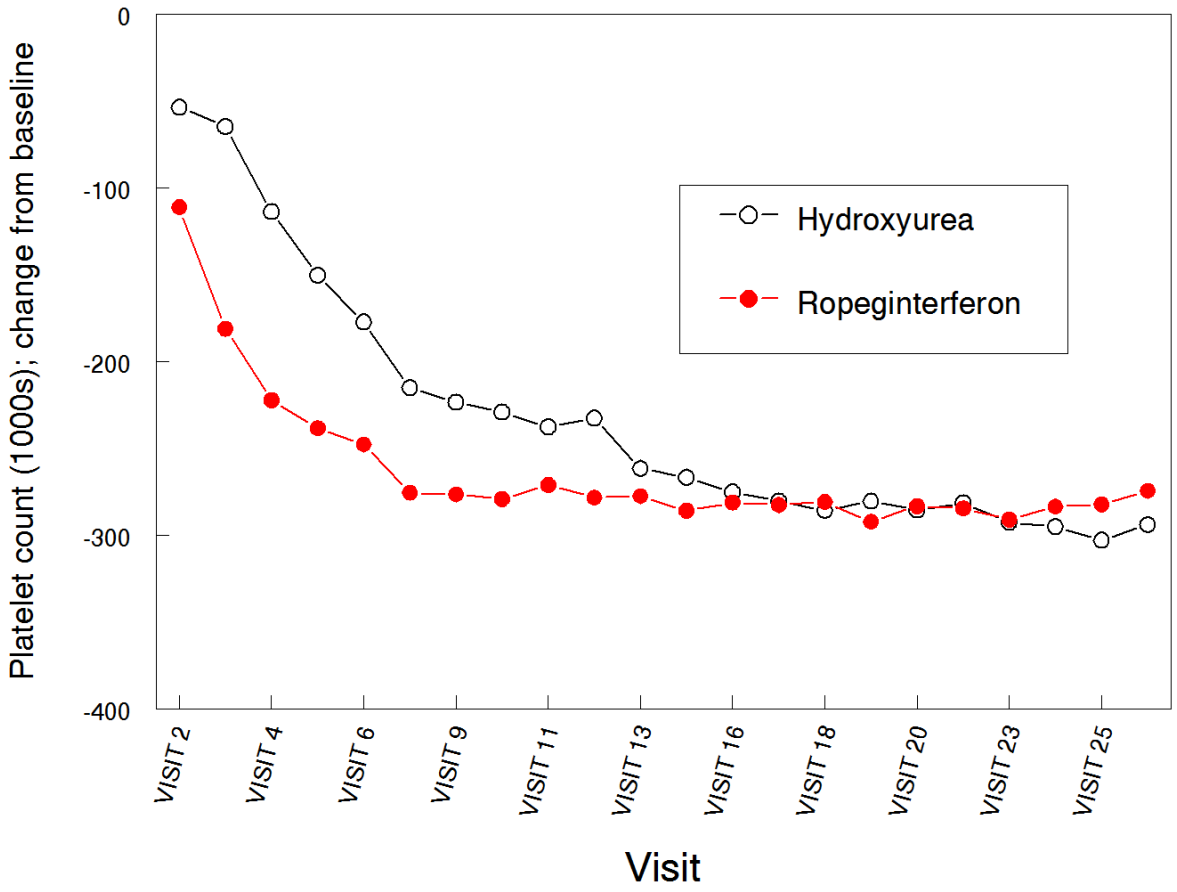
Source: Table 1 of Applicant's FDA IR Response Final_20201015.docx

Additional Endpoints

Change from Baseline for PLTs and WBCs in PROUD-PV

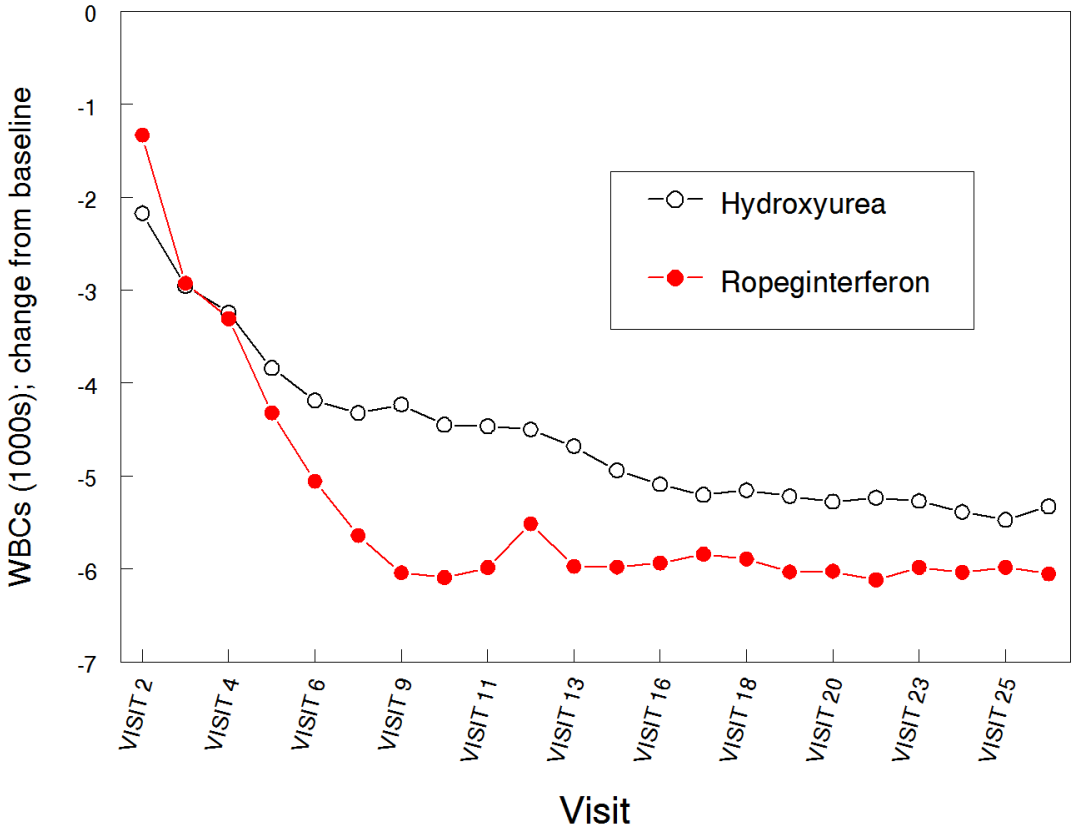
Evaluation of the change from baseline for PLTs and WBCs for ropeginterferon alfa-2b was evaluated up to visit 25 (12 months). There was a demonstratable decrease in PLTs and WBCs from baseline/visit 2 until visit 25. These changes would not occur by chance alone with this disease. In addition, with cessation of cytoreductive therapy, there is an increase in counts. Please note that the change in HCT was not as dramatic as all patients required to have HCT < 45% before administration of ropeginterferon alfa-2b. Figure 9 displays these changes.

Figure 9: Change from Baseline for PLTs in the PROUD-PV Study



Source: FDA Analysis

Figure 10: Change from Baseline for WBC Count for PROUD-PV Study



Source: FDA Analysis

The mean values over time for HCT, WBCs and PLTs shows how these values decreased over time. Ninety percent of patients were able to achieve normalization of WBCs and PLTs by the end of treatment at Month 24 and Month 36. The difference in HCT values was not as robust because all patients were required to obtain a HCT level < 45% before administration of ropeginterferon alfa-2b.

Table 26: Change from Baseline for Hematology Parameters in PROUD-PV/CONTINUATION-PV Study

Secondary Endpoints Change in Hematologic Parameters from Baseline	Ropeginterferon alfa-2b at Month 24 Value ± SD	Ropeginterferon alfa-2b at Month 36 Value ± SD
HCT < 45% at least 3 months from last phlebotomy	40.5 ±3.9 (88/95)	42.3± 4.0 (83/95)
HCT mean ± SD from Baseline to EoT	42.35 (±3.085) 40.45 (±3.875)	42.35 (±3.085) 40.34 (±4.003)

Secondary Endpoints Change in Hematologic Parameters from Baseline	Ropeginterferon alfa-2b at Month 24 Value ± SD	Ropeginterferon alfa-2b at Month 36 Value ± SD
WBCs < 10 x 10^9/L	5.53±2.12 (88/95)	7.22±3.56 (64/76)
WBCs mean ± SD from Baseline to EoT	11.47 (±4.690) 5.53 (±2.120)	11.47 (±4.690) 5.27 (±2.448)
PLTs < 400 x 10^9/L	221.5±128.74 (88/95)	208.9±100.25 (83/95)
PLTs mean ± SD from Baseline to EoT	529.2 (±281.11) 221.5 (±128.74)	529.2 (±281.11) 222.3 (±149.48)

Source: FDA Analysis

In the CONTINUATION study, the mean values over time for HCT, WBCs and PLTs were consistent with the results from PROUD-PV study. All patients with a HCT >45% at screening were phlebotomized until sustained HCT of ≤45% was achieved prior to the first administration of ropeginterferon alfa-2b. The need for phlebotomies decreased with ongoing treatment duration. The number of phlebotomies performed, per protocol in the PROUD-PV study, was 400 among 94/127 (74%) patients assigned to the ropeginterferon alfa-2b arm. At 24 months of treatment, the proportion of patients in CONTINUATION-PV study needing phlebotomy decreased to 16.7% among 9/95 patients remaining on the ropeginterferon alfa-2b arm.

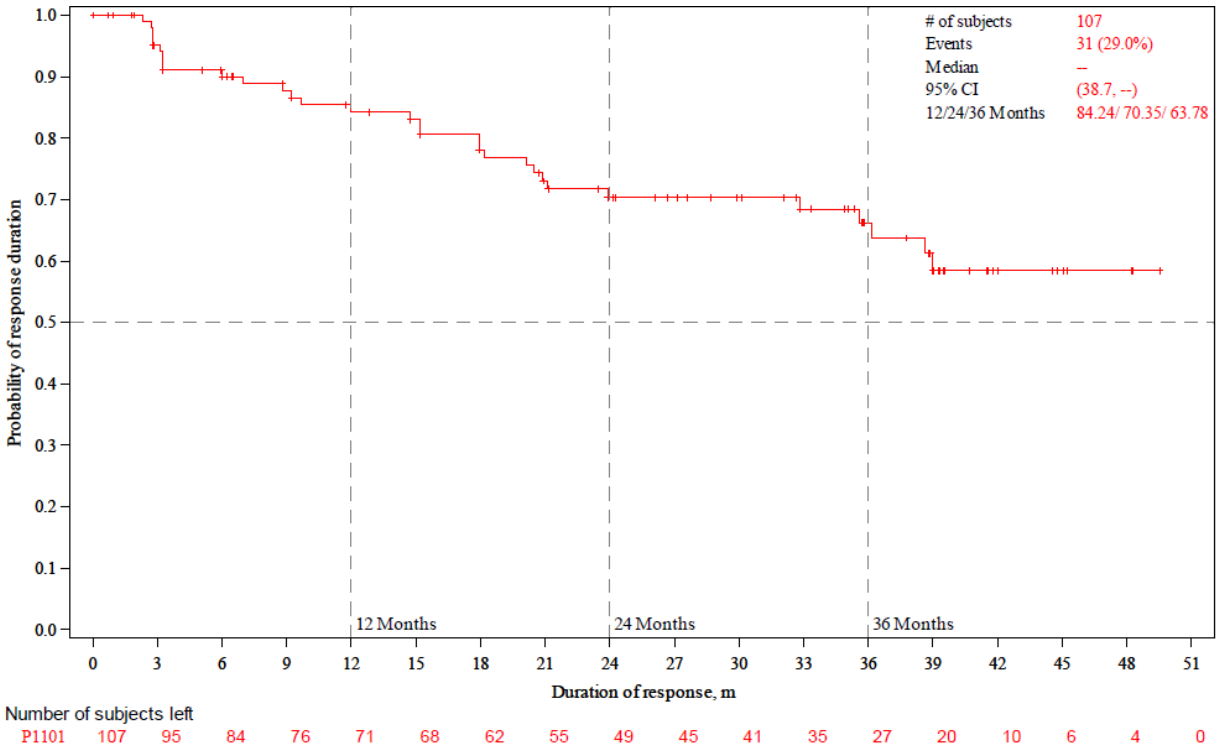
JAK2 Allelic Burden

The JAK2 allelic burden was followed from baseline to the end of the CONTINUATION-PV study, no patient achieved a complete molecular response. The median absolute levels of the JAK2 allelic burden ranged from 23.7% (Month 12), 14.3% (Month 24) to 9.49% (Month 36).

Duration of Response

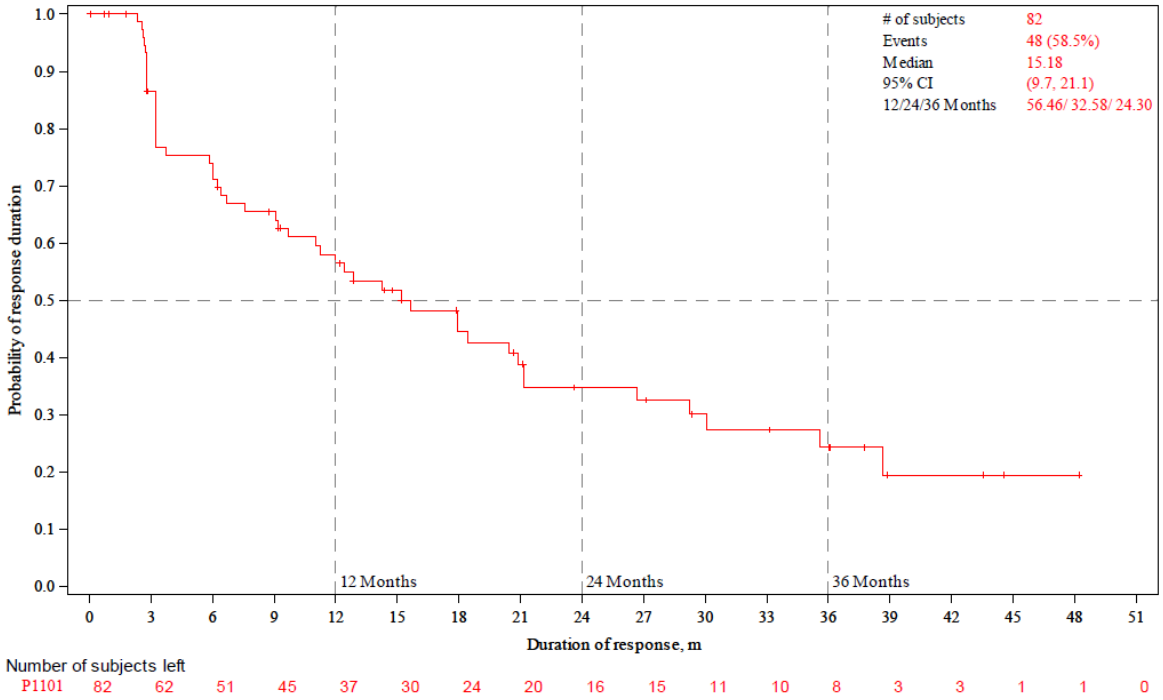
Duration of response for endpoints CHR and CHR plus normal spleen size are displayed in the figures below. For the endpoint CHR, median duration of the 107 patients who reported responses was not reached. For endpoint CHR plus normal spleen size, the median duration was 15 months with 95% CI (9.7, 21.1).

Figure 11: Kaplan-Meier Plot of Duration of Longest CHR (by hematology parameters) - As Treated Population (Single Arm)



Source: Figure 1 of Sponsor's FDA IR Response Final 20201015.docx

Figure 12: Kaplan-Meier Plot of Duration of Longest CHR with Normal Spleen Size - As Treated Population (Single Arm)



Source: Figure 3 of Sponsor's FDA IR Response Final_20201015.docx

7.5. Key Review Issues for Efficacy

- PROUD-PV study was initially designed as a superiority trial but changed to a non-inferiority study after study completion (last patient out, prior to database lock). Sample size calculations based on assumptions for superiority and could not be changed. Additionally, the change of analysis was made 2 months after completion of the PROUD-PV and one cannot completely exclude the possibility that applicant had access to unblinded data during the study.
- The PROUD-PV study failed to show non-inferiority of ropeginterferon alfa-2b to HU as the lower bound of the 95% CI of the difference in disease response rate (ropeginterferon alfa-2b-HU) was -17.2% which is less than the NI margin of -10.5% in the full analysis population (primary analysis result).
- Neither statistical nor clinical justification of the -10.5% margin was provided, and the margin was never agreed upon by the statistical team or adequately justified.
- The patient population in the CONTINUATION-PV consisted of a subgroup of patients who completed PROUD-PV and met certain outcome dependent eligibility criteria and

the study was not properly randomized. Selection bias may exist (known and unknown) which could undermine the study results.

- There was a lack of formal hypothesis testing for inferential comparison between ropeginterferon alfa-2b and BAT arms in the CONTINUATION study.

A possible reason for the PROUD-PV trial failure includes the different dose titration between the two arms. The two arms in the study had different dose titrations with a very conservative dose titration for ropeginterferon alfa-2b. The dose escalation for ropeginterferon alfa-2b was deliberately conservative to avoid toxicities and for tolerability. The difference in dose titration resulted in a 20 week delay in reaching the maximum dose for ropeginterferon alfa-2b. The PROUD-PV study duration was too short and assessment of efficacy planned too early at 12 months.

The active-treatment experience of the PROUD-PV was evaluated for supportive evidence only for this application.

The primary evidence for effectiveness is derived from the following:

- The complete hematological response from the PEGINVERA study. defined as HCT <45% without phlebotomy for at least 2 months since last phlebotomy, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L, normal spleen and no thrombosis).The overall response rate for CHR was 31/51 (60.8%) (95% CI: 46.1%, 74.2%). The median duration of response for CHR was 14.3 months (95% CI: 5.5, 30.1). The CHR for laboratory parameters only (HCT <45% without phlebotomy for at least 2 months since last phlebotomy, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L) is 41/51 (80.4%) (95% CI: 66.9%, 90.2%) with median duration of response of 20.8 months (95% CI: 13, 43.8).

- Supporting evidence comes from the natural history of the disease. The natural history of PV in the absence of treatment or minimally treated disease demonstrates an ongoing risk of thrombosis and continued increase in peripheral blood counts. Without aggressive cytoreductive control (HCT <45%), there is an increased risk of cardiovascular death and major thrombosis. Additional natural history studies demonstrate that the highest rate of thrombosis occurs shortly before diagnosis and decreases in time due to the effects of cytoreductive treatments that are initiated in patients. Thrombosis risk is not only related to HCT levels but also to the elevated WBC and platelet counts. Additional natural history studies demonstrate an elevated white blood count and platelet count at time of diagnosis as well as evidence of a rebound effect in peripheral blood counts when cytoreductive therapy is stopped in patients with PV.

- The objective laboratory measurements from the active treatment group which demonstrate decreases in PLTs and WBC counts from baseline PROUD-PV study provide additional objective confirmatory evidence.

7.6. Additional Efficacy Considerations

7.6.1. Other Relevant Benefits

Not applicable

7.7. Integrated Assessment of Effectiveness

The single, multicenter PEGINVERA study was the principle source of data supporting the efficacy of ropeginterferon alfa-2b for treatment of patients with PV. There were no integrated efficacy datasets reviewed for this application.

8. Review of Safety

8.1. Safety Review Approach

The PEGINVERA study (N=51) serves as the primary source of safety data. The pooled safety population of the PEGINVERA and PROUD-PV/CONTINUATION-PV studies (N=178) serve as supportive safety data for the proposed indication in patients with PV.

Primary Safety Analysis

The primary safety analyses included the all treated population (patients who received at least one dose of study drug) for the PEGINVERA study and includes adverse events collected up to 28 days after discontinuation of the study drug. Pooled analysis of PROUD-PV/CONTINUATION-PV studies and individual safety analysis of these studies were also performed. The applicant proposed several adverse events of special interest (AESI) based on findings from the ropeginterferon alfa-2b program and class safety effects of interferon products. The data cut-off date for the PEGINVERA study was March 30, 2018 and May 29, 2018 for the PROUD-PV/CONTINUATION-PV studies.

Other potential safety signals were assessed by searching treatment-emergent adverse event (TEAES) using all levels of MedDRA terms, standardized MedDRA query (SMQ). Other safety assessments of laboratory evaluations, vital signs and ECGs were also performed.

The safety analysis included a review of the following:

- Data quality
- Baseline characteristics and concomitant medications
- Incidence and severity of AEs, hepatic-related AEs, psychiatric-related AEs and thrombosis-related AEs
- Incidence of TEAEs, SAEs and adverse drug reactions (ADRs)
- Incidence of discontinuation, dose interruptions and dose delays
- Assessment of other adverse events of special interest including ocular events, immunological reactions (development of anti-thyroid antibodies or hypersensitivity issues), major cardiovascular events
- Laboratory tests, vital signs and electrocardiogram results
- Analysis of deaths.
- Summary of clinical safety
- Patient narratives and case report forms

A 120-Day safety update was submitted on July 9, 2020 date. This safety update includes additional safety data in studies from May 29, 2019 through June 30, 2020.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Total patient exposures were consistent with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and sufficient to assess the safety of ropeginterferon alfa-2b for the proposed indication, dosage regimen, duration and patient population.

Table 27: Duration of Exposure of Ropeginterferon alfa-2b in PEGINVERA, PROUD-PV, CONTINUATION-PV Studies and Pooled Safety Database

	PROUD-PV	PEGINVERA	PROUD-PV/CONTINUATION-PV	ALL STUDIES
N	127	51	127	178
Exposure (days) Median (range)	399 (28,336)	1816 (14, 2604)	1201 (43, 1568)	1237 (14, 2604)

	PROUD-PV	PEGINVERA	PROUD-PV/CONTINUATION-PV	ALL STUDIES
Mean (SD)	336 (74.97)	1379 (962.2)	1024 (489.3)	1125 (676.6)
Exposure (weeks) Median (range) Mean (SD)	52 (4, 57) 48 (10.7)	259 (2,372) 197 (137.5)	172 (6, 224) 146 (69.9)	177 (2, 372) 161 (96.7)
Exposure (months) Median (range) Mean (SD)	13 (1, 14) 12 (2.5)	61 (1, 87) 46 (32.1)	40 (1, 52) 43 (16.3)	41 (0.5, 85.4) 38 (22.6)

Source: FDA reviewer analysis

Across all of the clinical studies with ropeginterferon alfa-2b, patients were exposed to ropeginterferon alfa-2b for a mean of 41 months; constituting 548.8 patient-years.

The median duration of treatment in the PEGINVERA-PV was 62 months (range: 1 to 87 months) for ropeginterferon alfa-2b. In the PEGINVERA study, the majority (52.9%) of patients completed 5 years of treatment and 16 (31.4%) completed 6 years of treatment before discontinuing or completing the study.

8.2.2. Relevant characteristics of the safety population:

The safety populations in the PEGINVERA and pooled safety population are similar and the demographics (age and sex) and baseline characteristics such as spleen size, HCT, and JAK2 allelic burden are similar between the populations.

Table 28: Relevant Characteristics of all Patients in Safety Population in all Clinical Trials

	PROUD-PV		CONTINUATION		PEGINVERA	
	Ropeginterferon alfa-2b n=127	HU n=127	Ropeginterferon alfa-2b n=95	HU/BAT n=76	Extension Cohort n=26	MTD Cohort n=25
Age						
Mean [SD]	58.46 [10.80]	57.87 [13.11]	58.45 [10.63]	58.58 [11.45]	57.85 [11.99]	59.52 [11.06]

	PROUD-PV		CONTINUATION		PEGINVERA	
	Ropeginterferon alfa-2b n=127	HU n=127	Ropeginterferon alfa-2b n=95	HU/BAT n=76	Extension Cohort n=26	MTD Cohort n=25
Median	60	60	59	60.50	57	62
Range	30-85	21-81	31-86	33-80	35-78	40-82
Pooled Age Groups						
18-<65	90 (70.9%)	84 (66.1%)	67 (70.5%)	50 (65.8%)	17 (65.4%)	17 (68.0%)
>=65	37 (29.1%)	43 (33.9%)	28 (29.5%)	26 (34.2%)	9 (34.6%)	8 (32.0%)
Sex						
Female	68 (53.5%)	67 (52.8%)	48 (50.5%)	40 (52.6%)	13 (50%)	7 (28.0%)
Male	59 (46.5%)	60 (47.2%)	47 (49.5%)	36 (47.4%)	13 (50%)	18 (72.0%)
Race						
White	127 (100%)	127 (100%)	95 (100%)	76 (100%)	25 (96.2%)	25 (100%)
Asian					1 (3.8%)	0 (0%)
Ethnicity						
Not Hispanic or Latino	123 (96.9%)	120 (94.5%)	91 (95.8%)	72 (94.7%)	26 (100%)	25 (100%)
Not Reported	2 1.6%)	3 (2.4%)	2 (2.1%)	3 (3.9%)	0	0
Unknown	0 (0%)	3 (2.4%)		0	0	0
Hispanic or Latino	2 1.6%)	1 (0.8%)	2 (2.1%)	1 (1.3%)	0	0
Spleen Diameter at Baseline (cm)						
Mean [SD]	13.38	13.55	13.72	13.29	14.12	14.12

	PROUD-PV		CONTINUATION		PEGINVERA	
	Ropeginterferon alfa-2b n=127	HU n=127	Ropeginterferon alfa-2b n=95	HU/BAT n=76	Extension Cohort n=26	MTD Cohort n=25
	[3.16]	[3.32]	[3.15]	[2.98]	[3.24]	[3.24]
Median	13.10	13.50	13.5	12.8	13.2	13.2
Range	7-25	7.5-24.5	8.5-25.0	7.5-22.0	8.0-22.0	8.0-22.0
JAK2 Allelic Burden at Baseline						
Mean [SD]	41.91 [23.49]	42.83 [24.14]	42.81 [23.40]	42.94 [23.01]	42.19 [26.23]	46.61 [31.41]
Median	37.11	37.37	37.11	38.12	41.50	43
Range	0-94.94	0-89.81	2.58-94.94	2.52-86.61	0-91.5	7-99
HCT Baseline by Central Lab						
Mean [SD]	49.54 [5.43]	49.79 [5.49]	49.87 [5.49]	51.03 [5.92]	45.05 [4.13]	45.05 [4.13]
Median	49.40	49.50	49.60	50.90	44.5	44.5
Range	37.7-65.8	38.5-70.8	38.3-65.8	40.5-70.8	36.9-53.8	36.9-53.8

Demographics and disease characteristics of the safety population included patients with PV representative of patients with the disease in the US and adequately representative of the target population of patients with PV likely to be treated in clinical practice. This highlights the need for greater representation of non-Caucasians in studies investigating polycythemia vera.

8.2.3. Adequacy of the safety database

The size of the safety database is acceptable and the characteristics of patients in the PEGINVERA study and pooled safety database are generally similar to indicated US population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The submission was of adequate quality to enable a clinical review. Overall, it was well organized with appropriate analyses and detailed reports and summaries. The review team did not identify any major data quality or integrity issues that precluded performing a safety issue. No major issues were identified with respect to recording, coding and categorizing AEs. The applicant's translations of verbatim terms to MedDRA preferred terms for the events reported in PEGINVERA and PROUD-PV/CONTINUATION-PV were reviewed and found to be acceptable.

8.3.2. Categorization of Adverse Events

Adverse events were analyzed using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 and reported down to the investigator's verbatim term. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTAE, version 4.0) in the PROUD-PV/CONTINUATION-PV trial and graded per mild, moderate, severe categorization in the PEGINVERA trial. The applicant used standard procedures to collect and analyze AE data. AEs (both serious and non-serious) were recorded as all subject visits from the first dose through the last subject's last visit. TEAE is defined as an event which begins after start of treatment or which worsens during course of study until the last dose + 28 days.

8.3.3. Routine Clinical Tests

Safety assessments included physical examinations including vital signs, laboratory test measurements, spleen size assessment by ultrasound, CT or MRI at baseline and at month 12, Heart ECHO or MUGA, assessment of JAK2 at baseline and every 6 months, bone marrow assessment, administration of phlebotomies which are used to sustain a HCT of < 45%, and the assessment of Quality of Life using the EQ-5D-3L questionnaire.

The components and scheduling of safety monitoring was appropriate to capture the known AEs for that are associated with interferons to include elevated transaminases. The schedule of monitoring for all trials are presented in Tables 29-31.

Table 29: Schedule of Monitoring for PEGINVERA Study

Table 9-6: Clinical Assessments and Procedures for Patients

d = day w = week	Screening	Initial treatment phase						Maintenance treatment phase		End of Treatment visit
		d0	d14	d28	d42	d56	d70	every 2 weeks (w12)	every 8 weeks (first visit w18, w26, w34, w42)	
		w0	w2	w4	w6	w8	w10			w50
	-28/-1d Visit 0[a]	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Assessment visit (Visit 6)	Visits 7, 8, 9, 11, 12, 13, 15, 16, 17, 19, 20, 21, 23, 24, 25	Assessment visit (Visits 10, 14, 18,22)	Final assessment visit Visit 26
	(all visits within -3/+1 days of schedule)									
Informed consent	X									
Inclusion and exclusion criteria	X									
Demographics & medical history	X									
Pregnancy test[b]	X	X		X		X		X	X	X
Standard 12-lead ECG	X									X
Physical examination	X	X	X	X	X	X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X
Blood chemistry [1,2,3]	*1,2,3*	*1*	*1*	1	1	1	1,2	1	1,2	1,2
Coagulation[f]	X						X		X	X
Virology[e]	X									
Haematology[d]	X	X	X	X	X	X	X	X	X	X
O_2-saturation	X									
Immunological parameters[g]	X						X		X	X
ECOG performance status		X					X		X	X
Ultrasonography[i]	X						X		X	X
JAK2-V617F mutation	X								X[h]	X
PEGInterferon administration		X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X
Concomitant treatment	X	X	X	X	X	X	X	X	X	X
PK/PD sampling		X						Please see Table 2 of the Study Protocol Version 13.0		
Immunogenicity		X					X		X	X

(Taken from Applicant's Application Package, Module 5, page 57)

Table 30: Schedule of Monitoring for PROUD-PV

w = week	Screening	Initial treatment phase							Maintenance treatment phase		End of Treatment / Premature discontinuation visit	Safety follow-up visit
		w0	w2	w4	w6	w8	w10	w12	every 2 weeks, except visits co-incident to the assessment visits	every 12 weeks (month 6 and 9)	month 12	28 days after the EoT visit
											w52	
	-28/-1d Screening Visit *	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Assessment visit (visit 7)	Visits 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26	Assessment visit (visits 14 and 21)	Final assessment visit 27	
	(all visits within -3/+2 days of schedule)											
Informed consent	X											
Inclusion and exclusion criteria	X											
Demographics & medical history	X											
Pregnancy test (urine)	X	X		X		X		X	X (every other visit, i.e. every 4 weeks)	X	X	X
LVEF measurement (heart ECHO or MUGA) and the standard 12-lead ECG**	X							X		X	X	X
Physical examination	X	X			X					X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry [1,2] (blood)	1,2	1,2	1	1	1,2	1	1	1,2	1	1,2	1,2	1,2
Coagulation (blood)	X				X			X		X	X	X
Virology (blood)	X											
Hematology [1,2] (blood)	2[c]	2	1	1	2	1	1	2[c]	1	2[c]	2[c]	1,2
Immunological parameters (blood)	X							X		X	X	X
Urine test	X	X	X	X	X	X	X	X	X	X	X	X
Urine beta 2 microglobulin test	X									X	X	X
ECOG performance status	X	X						X		X	X	X
Spleen size measurement*	X							X		X	X	
Genetic test sample (incl. JAK2 allelic burden) (blood)	X									X (month 6 only)	X	
Bone marrow sampling (OPTIONAL)	X										X	
AOP2014 administration/ HU distribution		X	X	X	X	X	X	X	X	X	X[b]	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
HADS	X	X			X			X		X	X	X
Concomitant treatment	X	X	X	X	X	X	X	X	X	X	X	
Immunogenicity[a]and PK[a] (blood)	X[3,4]			X[a]				X[3,4]		X[3,4]	X[3,4]	X[3,4]
QoL	X	X			X			X		X	X	
Ocular examination	X										X	
Lung X-ray	X										X[d]	

(Taken from Applicant's Application Package, Module 5, page 68)

Table 31: Schedule of Monitoring for CONTINUATION-PV and PEN-PV Studies

	AOP2014 Arm and BAT Arm	AOP2014 Arm only Administration via Vials or Pen		AOP2014 Arm and BAT Arm				
	Visit 1*	Treatment visits at site (vial or pen)	Treatment at home (pen only)	Phone visits (pen and BAT)	Assessment visits	End of Treatment (EoT)/ Premature discontinuation visit	Safety follow-up visit****	End of Trial
		Every 2, 3 or 4 weeks		Every 4 weeks	Every 3 months		28 days after the EoT visit	
		-3/+2 days		-3/+2 days	+/- 2 weeks		-3/+2 days	
Informed consent	X							
Inclusion and exclusion criteria	X							
Demographics	X							
Medical History	X							
Pregnancy test (urine)	X				X	X	X	
Standard 12-lead ECG	X				X (every 6 months)	X	X	
Heart ECHO	X				X (every 6 months)	X		
Complete physical examination	X				X	X	X	
Vital signs	X	X§			X	X	X	
Coagulation (blood)	X				X	X	X	
Hematology [1,2] (blood)	X[2]	X[1 §]			X[2]	X[2]	X[1]	
Blood Chemistry [1,2] (blood)	X[2]	X[1 §]			X[2]	X[2]	X[1]	
Immunological parameters (blood)	X				X	X		
Urine test	X	X§			X	X	X	
Urine beta 2 microglobulin test	X							
ECOG performance status	X				X	X	X	
Spleen size measurement	X				X	X		
JAK2 allelic burden testing (blood) [a]	X[a]				X[a] (every 6 months)	X[a]		
Genetic testing (optional) (blood) #, [a, d]	X[a]				X[a] (every 6 months)	X[a]		X[d]
Bone marrow histology (optional) #, [a]	X[a]					X[a]		
AOP2014 administration**	X	X	X		X***	X		
Adverse events ##	X	X			X	X	X	
HADS	X				X	X	X	
Concomitant treatment	X						X	
Immunogenicity (blood)*** [a]	X[a §§]				X[a §§]	X[a §§]	X[a §§]	
Immunogenicity (optional) (blood)*** [a, d]								X[d]
Patient memory card [b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]		
QoL	X				X	X		
Ocular examination	X				X[c]	X[c]		
Lung X-ray	X				X[c]	X[c]		

(Taken from Applicant's Application Package, Module 5, page 14)

8.4. Safety Results

8.4.1. Deaths

There were three deaths in the PEGINVERA study and two deaths in the PROUD-PV and CONTINUATION-PV studies in the ropeginterferon alfa-2b arm and 2 deaths in the HU arm. In the PEGINVERA study, one death was due to sepsis/endocarditis, one death due to suicide and one death due to glioblastoma multiforme. In the ropeginterferon alfa-2b arm in the PROUD-PV/CONTINUATION-PV study, there was one death due to glioblastoma multiforme and one death due to an unknown cause.

Table 32: Deaths in the Ropeginterferon alfa-2b Development Program

Patient/ARM/Country	Age/Sex/Race	Time (days) from date of last study drug to date of death	Summary of Death Narrative
PEGINVERA - (b) (6) (ropeginterferon alfa-2b arm)	72 y/o male Caucasian	*Start Date:* (b) (6) *Last Dose:* (b) (6)	Enrolled in PEGINVERA study. Patient's medical history

Patient/ARM/Country	Age/Sex/Race	Time (days) from date of last study drug to date of death	Summary of Death Narrative
		(b) (6) *Date of Death* (b) (6)	of hypertension. Patient was hospitalized for Grade 2 UTI, Grade 3 T12 compression fracture due to fall and Grade 5 subarachnoid hemorrhage. Hospitalized for Grade 2 planned rectocoloscopy with polypectomy. Hospitalized again with Grade 5 endocarditis, sepsis and status epilepticus resulting in fatal outcome. Autopsy not performed. *Grade 5 endocarditis, sepsis and status epilepticus not related to ropeginterferon alfa-2b- or PV*
PEGINVERA - (b) (6) (ropeginterferon alfa-2b arm-	59 y/o male Caucasian	*Start Date:* Unknown *Last Dose:* (b) (6) *Date of Death:* (b) (6) (b) (6)	Enrolled in PEGINVERA study. Did not receive IMP due to behavior (i.e. depression). Patient was withdrawn from study on (b) (6) by investigator. Patient experienced left hemianopsia, hemineglect, hemiparesis. CT scan on (b) (6) revealed brain tumor. Biopsy revealed Grade IV Glioblastoma on (b) (6) Patient underwent localized radiotherapy and chemotherapy,

Patient/ARM/Country	Age/Sex/Race	Time (days) from date of last study drug to date of death	Summary of Death Narrative
			Temozolomide. Patient died on (b) (6) *Grade 4 Glioblastoma not related to ropeginterferon alfa-2b or PV*
PEGINVERA - (b) (6) (ropeginterferon alfa-2b arm-	81 y/o female Caucasian	*Start Date:* (b) (6) *Last Dose:* (b) (6) *Date of Death:* (b) (6) (b) (6)	Enrolled in PEGINVERA. History of hypertension, hyperuricemia, hepatic steatosis, dyspnea, prostate hypertrophy. Hospitalized for macrohematuria. No medical history of psychological disorder. *Grade 5 completed suicide*
(b) (6) (ropeginterferon alfa-2b arm-PROUD-PV)- (b) (6)	67 y/o female Caucasian	*Start Date*: (b) (6) *Last Dose:* (b) (6) (b) (6) *Date of Death:* (b) (6)	Experienced a non-epileptic seizure (NES) on (b) (6) and discharged on Valproic acid. Experienced a second NES on (b) (6) CT scan revealed a temporal lesion; Valproic acid dose increased. MRI on (b) (6) concluded the diagnosis of Glioma/Glioblastoma. Removal of the Glioma occurred on (b) (6) Patient died on 09 June 2016 from sequelae associated with Glioma. *Grade 4 Glioblastoma not related to ropeginterferon alfa-2b or PV*
Patient # (b) (6) (HU/BAT arm-CONTINUATION-PV)	67 y/o male Caucasian	*Start Date:* (b) (6) *Last Dose:* (b) (6)	Received her first dose of HU on (b) (6) and treated with HU in

Patient/ARM/Country	Age/Sex/Race	Time (days) from date of last study drug to date of death	Summary of Death Narrative
Austria		(b) (6) *Date of Death:* (b) (6) (b) (6)	PROUD-PV and CONTINUATION-PV studies. Start of the adverse event (Acute Leukemia) on (b) (6) Discontinued study on (b) (6) *Grade 3 pneumonia and septicemia due to Grade 5 Acute Leukemia resulting in death on* (b) (6) *and related to HU and PV*
Patient # (b) (6) (ropeginterferon alfa-2b arm-CONTINUATION-PV) Bulgaria	65 y/o female Caucasian	*Start Date:* (b) (6) (b) (6) *Last Dose:* (b) (6) *Date of Death:* (b) (6)	Enrolled in PROUD-PV and CONTINUATION-PV Studies. Patient unexpectedly died on (b) (6). No autopsy of death *Unknown cause of death.*
Patient # (b) (6) (HU/BAT arm-CONTINUATION-PV) Hungary	63 y/o female Caucasian	*Start Date* (b) (6) *Last Dose:* (b) (6) (b) (6) *Date of Death:* (b) (6)	Enrolled in PROUD-PV and CONTINUATION-PV studies. Found to have increase in spleen size and platelet count. Experienced sudden death and found dead in nursing home. *Cause of death unknown; no autopsy performed.*

UTI: Urinary Tract Infection; IMP: Investigational Medical Product

Reviewer's Comments: There is not a known risk of ropeginterferon alfa-2b and development of Glioblastoma Multiforme. There is likely a higher risk of developing acute leukemia in patients with PV, but no definitive literature describing an increased risk of solid tumors. Interferons are associated with adverse reactions of depression and suicidal ideation and the one death to suicide may very well be associated with the use of ropeginterferon alfa-2b. Recommend box

warning for potential depression and suicidal ideation with the use of ropeginterferon alfa-2b similar to current labeling for interferons.

8.4.2. Serious Adverse Events

There were 65 serious adverse events (SAE) reported for 28/51 (54.9%) patients in the PEGINVERA study. Six of the SAEs resulted in death in three of the 51 patients (5.9%) and 49 SAES resulted in hospitalization or prolongation of hospitalization in 22/51 (43%) of patients. Serious adverse events were notable for depression, transient ischemic attack (TIA), subarachnoid hemorrhage, anti-thyroid antibody positivity, acute stress disorder, arthralgia, atrial fibrillation, fatigue, influenza-like illness, transaminase increased and pyrexia.

Table 33: Serious Adverse Events in PEGINVERA Study

SOC and Preferred Term	N=51 n (%)
Infections and Infestations	6 (11.8%)
Urinary tract infection	4 (7.8%)
Diverticulitis	1 (1.9%)
Endocarditis	1 (1.9%)
Gastroenteritis norovirus	1 (1.9%)
Wound infection	1 (1.9%)
Pilonidal Cyst	1 (1.9%)
Pyelonephritis	1 (1.9%)
Sepsis	1 (1.9%)
Injury, Poisoning and Procedural Complications	
Chest injury	2 (3.9%)
Clavicle fracture	1 (1.9%)
Eye Injury	1 (1.9%)
Lower Limb Fracture	1 (1.9%)
Rib Fracture	1 (1.9%)
Spinal Compression Fracture	1 (1.9%)
Splenic Rupture	1 (1.9%)
Tibia Fracture	1 (1.9%)
Nervous System Disorders	
Transient Ischemic Attack	3 (5.8%)
Dementia with Lewy bodies	1 (1.9%)
Status epilepticus	1 (1.9%)
Ophthalmic herpes zoster	1 (1.9%)

SOC and Preferred Term	N=51 n (%)
Subarachnoid hemorrhage	1 (1.9%)
Psychiatric Disorders	
Depression	2 (3.9%)
Acute Stress Disorder	1 (1.9%)
Adjustment Disorder	1 (1.9%)
Completed Suicide	1 (1.9%)
Gastrointestinal Disorders	
Anal fistula	1 (1.9%)
Diarrhea	1 (1.9%)
Duodenal ulcer hemorrhage	1 (1.9%)
Dysphagia	1 (1.9%)
Gastrointestinal ulcer hemorrhage	1 (1.9%)
Large intestine polyp	1 (1.9%)
General Disorders and Administration Site Conditions	
Fatigue	1 (1.9%)
General physical health deterioration	1 (1.9%)
Influenza like illness	1 (1.9%)
Pyrexia	1 (1.9%)
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	1 (1.9%)
osteoarthritis	1 (1.9%)
Investigations	
Anti-thyroid antibody positive	1 (1.9%)
Antinuclear antibody increased	1 (1.9%)
Transaminase increased	1 (1.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (3.9%)
Basal Cell carcinoma	1 (1.9%)
Glioblastoma	2 (3.9%)
Squamous cell carcinoma of skin	1 (1.9%)
Vascular Disorders	2 (3.9%)
Deep Vein Thrombosis	1 (1.9%)
Hypertensive Crisis	1(1.9%)
Cardiac Disorders	
Acute Myocardial Infarction	1 (1.9%)
Atrial Fibrillation	1 (1.9%)
Renal and Urinary Disorders	2 (3.9%)

SOC and Preferred Term	N=51 n (%)
Calculus ureteric	1 (1.9%)
Cystitis hemorrhagic	1 (1.9%)
Respiratory, thoracic and mediastinal disorders	
Pulmonary Embolism	1 (1.9%)
Blood and Lymphatic System Disorders	
Splenic infraction	1 (1.9%)
Ear and Labyrinth Disorders	
Sudden Hearing loss	1 (1.9%)
Eye disorders	
Diplopia	1 (1.9%)
Reproductive System and breast Disorders	
Prostatitis	1 (1.9%)

Source: FDA reviewer analysis

Serious Adverse events in the Pooled Safety Population

In the pooled analysis, the most frequent serious adverse events occurred in the infections and infestations SOC, nervous system disorders SOC, cardiac disorders SOC, neoplasms benign, malignant and unspecified SOC, injury, poisoning and procedural SOC.

Table 34: Serious Adverse Events in Pooled Safety Population (N = 178)

PREFERRED TERM	N=178 N (%)
INFECTIONS AND INFESTATIONS	
Urinary Tract Infection	4 (2.2%)
Diverticulitis	2 (1.1%)
Septic Shock/Sepsis	2 (1.1%)
Tuberculosis	1 (0.6%)
Sinusitis	1 (0.6%)
Pilonidal Cyst	1 (0.6%)
Wound Infection	1 (0.6%)
Pyelonephritis	1 (0.6%)
Pneumonia	1 (0.6%)
Gastroenteritis Norovirus	1 (0.6%)

PREFERRED TERM	N=178 N (%)
Endocarditis	1 (0.6%)
Diverticulitis	1 (0.6%)
Cholangitis Infective	1 (0.6%)
Appendicitis	1 (0.6%)
NERVOUS SYSTEM DISORDERS	
Transient Ischemic Attack	3 (1.6%)
Ischemic Stroke	2 (1.1%)
Dementia with Lewy Bodies	1 (0.6%)
Encephalopathy	1 (0.6%)
Hemorrhagic Transformation Stroke	1 (0.6%)
Ischemic Stroke	1 (0.6%)
Ophthalmic Herpes Zoster	1 (0.6%)
Status Epilepticus	1 (0.6%)
Subarachnoid Hemorrhage	1 (0.6%)
CARDIAC DISORDERS	
Atrial Fibrillation	3 (1.6%)
Atrial Flutter	1 (0.6%)
Acute Myocardial Infarction	1 (0.6%)
Acute Stress Disorder	1 (0.6%)
Sinus Tachycardia	1 (0.6%)
Supraventricular Tachycardia	1 (0.6%)
NEOPLASMS BENING, MALIGNANT AND UNSPECIFIED	
Glioblastoma	2 (1.1%)
Adenocarcinoma Of Colon	1 (0.6%)
Adrenal Adenoma	1 (0.6%)
Basal Cell Carcinoma	1(0.6%)
Bile Duct Cancer	1 (0.6%)
Bladder Transitional Cell Carcinoma	1 (0.6%)
Rectal Adenocarcinoma	1 (0.6%)
Spermatocytic Seminoma	1 (0.6%)
Squamous Cell Carcinoma of Skin	1 (0.6%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Pyrexia	2 (1.1%)
Fatigue	1 (0.6%)
General Physical Health Deterioration	1 (0.6%)
Influenza Like Illness	1 (0.6%)
Multi-Organ Failure	1 (0.6%)

PREFERRED TERM	N=178 N (%)
Death	1 (0.6%)
PSYCHIATRIC DISORDERS	
Depression	2 (1.1%)
Completed Suicide	1 (0.6%)
Adjustment Disorder	1 (0.6%)
GASTROINTESTINAL DISORDERS/HEPATOBILIARY DISORDERS	
Diarrhea	1 (0.6%)
Diverticulum Intestinal	1 (0.6%)
Duodenal Ulcer Hemorrhage	1 (0.6%)
Dysphagia	1 (0.6%)
Gastrointestinal Ulcer Hemorrhage	1 (0.6%)
Cholecystitis Acute	1 (0.6%)
Anal Fistula	1 (0.6%)
Cholelithiasis	1 (0.6%)
Large Intestinal Polyp	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER	
Arthralgia	1 (0.6%)
Osteoarthritis	1 (0.6%)
Rheumatoid Arthritis	1 (0.6%)
GENERAL DISORDERS AND ADMINSITRATION SITE	
Chest Injury	2 (1.1%)
Clavicle Fracture	1(0.6%)
Skull Fractured Base	1(0.6%)
Eye Injury	1 (0.6%)
Fall	1 (0.6%)
Lower Limb Fracture	1 (0.6%)
Rib Fracture	1 (0.6%)
Spinal Compression Fracture	1 (0.6%)
Splenic Rupture	1 (0.6%)
Tibia Fracture	1 (0.6%)
VASCULAR DISORDERS	1 (0.6%)
Hypertension	1 (0.6%)
Hypertensive Crisis	1 (0.6%)
Peripheral Arterial Occlusive Disease	1 (0.6%)
ALL OTHERS	
Microcytic Anemia	1 (0.6%)

PREFERRED TERM	N=178 N (%)
Acute Kidney Injury	1 (0.6%)
Calculus Ureteric	1 (0.6%)
Cystitis Hemorrhagic	1 (0.6%)
Pleural Fibrosis	1 (0.6%)
Prostatitis	1(0.6%)
Pulmonary Embolism	1 (0.6%)
Renal Cyst Excision	1 (0.6%)
Shoulder Arthroplasty	1 (0.6%)
Splenic Infarction	1 (0.6%)
Sudden Hearing Loss	1 (0.6%)
Transaminases Increased	1 (0.6%)
Umbilical Hematoma	1 (0.6%)
Antinuclear Antibody Increased	1 (0.6%)
Anti-Thyroid Antibody Positive	1 (0.6%)
Uterine Polyp	1 (0.6%)
Verbatim: BLEEDING AFTER FEMORAL ENDARTERECTOMY	1 (0.6%)
Verbatim: POLYCYTHAEMIA VERA SECONDARY MYELOFIBROSIS	1 (0.6%)

Source: FDA reviewer analysis

Serious adverse events were also assessed in the PROUD-PV and CONTINUATION-PV studies.

Table 35: Serious Adverse Events in the PROUD-PV Study

	Ropeginterferon alfa-2b N=127 N (%)	HU P=127 n (%)
At least one SAE	25 (19.7%)	24 (18.9%)
Neoplasms Benign, Malignant and Unspecified	6 (4.7%)	6 (4.7%)
Acute Leukemia	0 (0%)	2 (1.6%)
Infections and Infestations	6 (4.7%)	3 (2.4%)
Pneumonia	1 (0.8%)	1 (0.8%)
Cholangitis	1 (0.8%)	0 (0%)
Diverticulitis	1 (0.8%)	0 (0%)
Acute Pyelonephritis	0 (0%)	1 (0.8%)
Sepsis/Septic Shock	1 (0.8%)	1(0.8%)

	Ropeginterferon alfa-2b N=127 N (%)	HU P=127 n (%)
Sinusitis	1 (0.8%)	0 (0%)
TB	1 (0.8%)	0 (0%)
Cardiac Disorders	6 (4.7%)	5 (3.9%)
Atrial Fibrillation/Atrial Flutter	3 (2.4%)	2 (1.6%)
Cardiac Failure/Acute Cardiac Failure	0 (0%)	2 (1.6%)
Pericardial Effusion	1 (0.8%)	1 (0.8%)
Sinus Tachycardia	1 (0.8%)	0 (0%)
Supraventricular Tachycardia	1 (0.8%)	0 (0%)
Other Disorders	7 (5.5%)	0 (0%)
Rheumatoid Arthritis	1 (0.8%)	0 (0%)
Ischemic Stroke	2 (2.4%)	0 (0%)
Hemorrhagic Transformation Stroke	1 (0.8%)	0 (0%)
Acute Cholecystitis	1 (0.8%)	0 (0%)
Multi-Organ Failure	1 (0.8%)	0 (0%)
Acute Kidney Injury	1 (0.8%)	0 (0%)

Source: FDA reviewer analysis

SAEs were evaluated in the CONTINUATION-PV study, however it is to be noted that the 95 patients in the CONTINUATION study represent same patients in the PROUD-PV study with longer duration of follow-up.

Table 36: Serious Adverse Events in the CONTINUATION-PV Study

	Ropeginterferon alfa-2b n=95	Best Available Treatment n=76
Subjects with at least 1 SAE	22 (23.5%)	20 (26.1%)
INFECTIONS AND INFESTATIONS	4 (4.2%)	1 (1.3%)
Pneumonia	1 (1.1%)	1 (1.3%)
Sinusitis	1 (1.1%)	0 (0%)
Cholangitis Infective	1 (1.1%)	0 (0%)
Tuberculosis	1 (1.1%)	0 (0%)
Sepsis	0 (0%)	1 (1.3%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	4 (4.2%)	4 (5.3%)
Rectal Adenocarcinoma	1 (1.1%)	0 (0%)
Bile Duct Cancer	1 (1.1%)	0 (0%)

	Ropeginterferon alfa-2b n=95	Best Available Treatment n=76
Adrenal Adenoma	1 (1.1%)	0 (0%)
Adenocarcinoma of Colon	1 (1.1%)	0 (0%)
Acute Leukemia	0 (0%)	2 (2.6%)
Malignant Melanoma	0 (0%)	1 (1.3%)
Neoplasm of Appendix	0 (0%)	1 (1.3%)
NERVOUS SYSTEM DISORDERS	2 (2.1%)	0 (0%)
Encephalopathy	1 (1.1%)	0 (0%)
Ischemic Stroke	1 (1.1%)	0 (0%)
AE SYSTEM ORGAN CLASS NOT CODED	2 (2.1%)	1 (1.3%)
Verbatim: Bleeding After Femoral Endarterectomy	1 (1.1%)	0 (0%)
Verbatim: PV Secondary Myelofibrosis	1 (1.1%)	0 (0%)
Verbatim: Brain Cancer	0 (0%)	1 (1.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (2.1%)	1 (1.3%)
Death	1 (1.1%)	0 (0%)
Pyrexia	1 (1.1%)	0 (0%)
Sudden Death	0 (0%)	1 (1.3%)
HEPATOBILIARY DISORDERS	1 (1.1%)	0 (0%)
Cholelithiasis	1 (1.1%)	0 (0%)
GASTROINTESTINAL DISORDERS	1 (1.1%)	1 (1.3%)
Diverticulum Intestinal	1 (1.1%)	0 (0%)
Gastritis	0 (0%)	1 (1.3%)
CARDIAC DISORDERS	1 (1.1%)	1 (1.3%)
Atrial Fibrillation	1 (1.1%)	1 (1.3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (1.1%)	2 (2.6%)
Microcytic Anemia	1 (1.1%)	0 (0%)
Anemia	1 (1.1%)	1 (1.3%)
Granulocytopenia	0 (0%)	1 (1.3%)
Leukopenia	0 (0%)	1 (1.3%)
Splenomegaly	0 (0%)	1 (1.3%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (1.1%)	3 (3.9%)
Skull Fractured Base	1 (1.1%)	0 (0%)
Fall	1 (1.1%)	0 (0%)
Upper Limb Fracture	0 (0%)	1 (1.3%)

	Ropeginterferon alfa-2b n=95	Best Available Treatment n=76
Uterine Dehiscence	0 (0%)	1 (1.3%)
Gastroenteritis Radiation	0 (0%)	1 (1.3%)
RENAL AND URINARY DISORDERS	1 (1.1%)	0 (0%)
Bladder Transitional Cell Carcinoma	1 (1.1%)	0 (0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	1 (1.1%)	1 (1.3%)
Umbilical Hematoma	1 (1.1%)	0 (0%)
Skin Ulcer	0 (0%)	1 (1.3%)
SURGICAL AND MEDICAL PROCEDURES	1 (1.1%)	2 (2.6%)
Shoulder Arthroplasty	1 (1.1%)	0 (0%)
Knee Arthroplasty	0 (0%)	1 (1.3%)
Colectomy	0 (0%)	1 (1.3%)
PSYCHIATRIC DISORDERS	0 (0%)	1 (1.3%)
Depression	0 (0%)	1 (1.3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0 (0%)	1 (1.3%)
Osteoarthritis	0 (0%)	1 (1.3%)
VASCULAR DISORDERS	0 (0%)	1 (1.3%)
Thrombophlebitis Superficial	0 (0%)	1 (1.3%)

Source: FDA reviewer analysis

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 37: Reasons for Discontinuation of Study Therapy in PEGINVERA Study

	All Patients N=51 N (%)	MTD Cohort N=25 n (%)	Extension Cohort N=26 n (%)
Reason for Discontinuation of Study Therapy			
Adverse Event	21 (41.2%)	10 (40%)	11 (42.3%)
Withdrawal by Subject	2 (3.9%)	2 (8%)	0 (0%)
Treatment Cycle Delayed for more than four weeks	1 (2%)	0 (0%)	1 (3.8%)
Other	1(2%)	0 (0%)	1 (3.8%)
Lack of Efficacy	1 (2%)	0 (0%)	1 (3.8%)

Source: FDA reviewer analysis

The most common reasons for discontinuations in the PEGINVERA study included depression, arthralgias, fatigue and general physical health deterioration.

Table 38: Reasons for Discontinuations of Study Therapy in PROUD-PV Study

	Ropeginterferon alfa-2b n=127 (n%)	HU n=127 (n%)	Totals n=254 (n%)
Reason for Discontinuation of Study Therapy	21	16	37
Adverse Event	11 (8.7%)	3 (2.4%)	14 (5.5%)
Withdrawal by Subject	6 (4.7%)	5 (3.9%)	11 (4.3%)
Lost to Follow-Up	4 (3.1%)	1 (0.8%)	5 (2.0%)
Other	0 (0%)	5 (3.9%)	5 (2.0%)
Lack of Efficacy	0 (0%)	2 (1.6%)	2 (0.8%)

Source: FDA reviewer analysis

Discontinuation in the ropeginterferon alfa-2b- arm occurred in 21/127 (16.5%) versus 16/127 (12.6%) in the HU arm in the PROUD-PV study. Withdrawals by the subject were balanced between both arms. Tables 38 and 39 describes the reasons for discontinuation of study therapy.

Table 39: Reasons for Discontinuation of Study Therapy in CONTINUATION-PV Study

	Ropeginterferon alfa-2b N=95 n (%)	BAT/HU N=76 n (%)	Totals N=171 n (%)
Reason for Discontinuation of Study Therapy	10	6	16
Adverse Event	10 (10.5%)	6 (7.9%)	16 (9.4%)

Source: FDA reviewer analysis

All of the recorded reasons for discontinuation of study therapy were due to adverse events. Each adverse events occurred only once. They included anemia, thrombocytopenia, bile duct cancer, tuberculosis, alanine and aspartate aminotransferase increased, Sjogren's syndrome, depression and nervousness.

Reviewer's Comment: Adverse events were the most common reason for discontinuation in all studies.

8.4.4. Significant Adverse Events

8.4.5. Adverse Events of Special Interest

The applicant proposed several adverse events of special interest based on findings from other interferons. The review team included several other adverse events of special interest based upon the known safety profile of FDA-approved pegylated interferons. Table 4038 describes the adverse events of special interest in the pooled safety group (N=178).

Table 40: Adverse Events of Special Interest

	Ropeginterferon alfa-2b N=178 n (%)
Endocrine Disorders	
Hyperthyroidism	7 (3.9%)
Hypothyroidism	6 (3.3%)
Autoimmune Thyroiditis/Thyroiditis	5 (2.8%)
Cardiovascular Disorders	
Atrial fibrillation/Atrial flutter/arrythmia	11 (6.1%)
Tachycardia	6 (3.3%)
Cardiac failure/cardiac insufficiency	4 (2.2%)
Palpitations	3 (1.6%)
Supraventricular extrasystoles, supraventricular tachycardia, ventricular tach	3 (1.6%)
AV Block, AV 2nd degree block, LBBB, SA block	2 (1.1%)
Bradycardia	1 (0.8%)
Acute Myocardial Infarction	1 (0.8%)
Psychiatric Disorders	
Insomnia/Sleep Disorders	18 (10%)
Depression/depressive symptoms, depressed mood, listless	17 (9.5%)
Anxiety/panic attack	7 (3.9%)
Nervousness/restlessness	5 (2.8%)
Mood Altered/Swings	4 (2.2%)
Irritability	2 (1.1%)
Completed Suicide	1 (0.8%)
Cerebrovascular Disorders	
Hemorrhagic transformation stroke	3 (1.6%)
Transient Ischemic Attack	2 (1.1%)
Ischemic Stroke	2 (1.1%)
Pulmonary Embolism	1 (0.8%)
Splenic Infarct	1 (0.8%)
Truncus Celiacus Thrombosis	1 (0.8%)
Deep Vein Thrombosis	1(0.8%)

	Ropeginterferon alfa-2b N=178 n (%)
Ophthalmologic Disorders	
Maculopathy	1 (0.8%)
Retinopathy/hypertensive retinopathy/diabetic retinopathy	5 (2.8%)
Eye pain/Eye Inflammation/Eye Irritation	3 (1.6%)
Eye hemorrhage	1 (0.8%)
Autoimmune disorders	
Sjogren's Syndrome	2 (1.1%)
Rheumatoid Arthritis	2 (1.1%)
Investigations/Labs	
GGT increased	29 (16.2%)
ALT increased	19 (10.6%)
AST increased	14 (7.8%)
Hepatic enzyme increased/transaminase increased	13 (7.3%)
Anti-thyroid antibody positive	8 (4.4%)
TSH increased	7 (3.9%)
DNA Antibody Increased	2 (1.1%)
Metabolism and Nutritional Disorders	
Hyperlipidemia, hypertriglyceridemia, dyslipidemia, hyperchloremia	6 (3.3%)
Gastrointestinal/Hepatic	
Hepatic steatosis	7 (3.9%)
Pancreatitis chronic, pancreatitis steatosis	4 (2.2%)
Toxic hepatitis/hepatoxicity/liver disorder	4 (2.2%)
Bone Marrow Toxicity	
Pancytopenia	2 (1.1%)
Grade 3 or higher thrombocytopenia	4 (2.2%)
Grade 3 or higher leukopenia	3 (1.6%)
Pulmonary	
Pneumonitis	1 (0.8%)
Hypersensitivity	0 (0%)
Colitis	0 (0%)

Source: FDA Analysis

A serious class effect observed with interferon is psychiatric disorders. In a literature review, the prevalence of these side effects ranges from 0% to 70% depending on the study and the type of psychiatric side effect reported. The conservative dose titration may help to mitigate some of these adverse effects. The clinical team recommends a box warning in the label for neuropsychiatric events.

Elevated transaminases were seen among patients who received ropeginterferon alfa-2b. Elevation of transaminases is a known class effect of interferons. In published literature, hepatoxicity of all grades is observed in 60% to include grade 3-4 toxicity in 30% of patients. Management of the enzyme disturbances usually involve dosing delay and the elevated transaminase resolve to pretreatment levels.

There was one patient who was reported to have renal insufficiency and one patient with toxic renal nephropathy. Overall, there were no increased signal detected for an increased renal toxicity in ropeginterferon alfa-2b.

Increased auto-antibody formation is a well reported interferon class effect. The frequency reported in safety population for ropeginterferon alfa-2b does not give rise to any additional safety signals. Recommend a contraindication in the label for patients at risk for immunological reactions.

Overall, the adverse events of special interest are known class effects of interferons and based on review of the safety data with ropeginterferon alfa-2b, appropriate mitigation, warnings and precautions can be provided in the prescribing information.

8.4.6. Treatment Emergent Adverse Events and Adverse Reactions

This table focuses on the adverse events seen among patients with a frequency of 7% or greater in the PEGINVERA study. The adverse reactions are FMQ narrow terms or coded as MedDRA preferred terms. Influenza (flu)-like illness is a common adverse event with reported use of interferon alfa and thus flu-like illness is represented separately from the URI, cold, rhinitis and upper respiratory tract infection term.

Table 41: Common Adverse Events by System Organ Class and Preferred Terms > 7% in PEGINVERA Study

Adverse Reactions	Ropeginterferon alfa-2b N=51 n (%)
Infection and Infestations	
Infection, all	37 (73%)
Nasopharyngitis	25 (49%)
URI, cold, rhinitis upper resp tract infection	19 (37%)
UTI	9 (18%)
Infection, viral	8 (16%)
Herpes virus	6 (12%)
Infection, fungal	6 (12%)

Adverse Reactions	Ropeginterferon alfa-2b N=51 n (%)
General Disorders and Administration Site Conditions	
Fatigue	24 (51%)
Pyrexia	14 (28%)
Influenza like illness	14 (28%)
Local administration reactions	13 (26%)
Chest pain (non-cardiac or unknown)	6 (12%)
Peripheral edema	9 (18%)
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	24 (47%)
Back pain	16 (31%)
Myalgia	10 (20%)
Arthritis	5 (10%)
Gastrointestinal Disorders	
Diarrhea	17 (33%)
Nausea	14 (28%)
Abdominal pain	10 (20%)
Dyspepsia	6 (12%)
Nervous System Disorders	
Headache	19 (37%)
Dizziness	15 (29%)
Vertigo	6 (12%)
Paresthesia	5 (10%)
Blood and Lymphatic Disorders	
Leukopenia	13 (26%)
Thrombocytopenia	9 (18%)
Skin and Subcutaneous Disorders	
Pruritus	26 (51%)
Rash	12 (24%)
Erythema	11 (22%)
Alopecia	8 (16%)
Eye Disorders	
Eye other	11 (22%)
Cataract	4 (8%)
Psychiatric Disorders	
Insomnia, sleep disturbance, abnormal dreams	10 (20%)
Depression	10 (20%)
Hepatic	

Adverse Reactions	Ropeginterferon alfa-2b N=51 n (%)
Hepatic injury	4 (8%)
Hepatic steatosis	4 (8%)
Endocrine Disorders	
Hyper/hypo thyroid, thyroiditis, goiter	9 (18%)
Metabolism and Nutrition Disorders	
Decreased appetite	10 (20%)
Investigations	
AST, ALT, GGT, Hepatic Enzyme, Transaminases	9 (18%)
Anti-thyroid antibody positive	5 (10%)
Antinuclear antibody increased/positive, DNA antibody positive	4 (8%)
Ear and Labyrinth Disorders	
Vertigo; vestibular dysfunction	8 (16%)
Cardiac Disorders	
Arrhythmia	8 (16%)
Atrial Fibrillation	5 (10%)
Vascular Disorders	
Hemorrhage	14 (28%)
Systemic hypertension	8 (16%)
Thrombosis, pulmonary embolism, retinal artery occlusion, splenic infarct	6 (12%)
Injury, Poisoning, Procedural Complications	
Fracture	7 (14%)
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnea	7 (14%)
Cough	4 (8%)

Hemorrhage included: gingival bleeding, GI ulcer hemorrhage, hemorrhagic diathesis, vaginal hemorrhage, hematochezia, umbilical hematoma, infectious hematoma, contusion, epistaxis, duodenal ulcer, spontaneous hematoma, subcutaneous hemorrhage.
Fungal included: vulvovaginal, tinea pedis, oral candidiasis, esophageal candidiasis, fungal skin, onychomycosis
Fatigue: asthenia, malaise, listless
Depression: depressive symptom, depressed mood
Source: FDA reviewer analysis
Abbreviations: N, number of subjects, n number of subjects with adverse event,

Reviewer's Comment: The most frequently reported TEAEs by SOC and PT are in accordance to the well-known adverse events related to interferons.

Additional analyses were performed for the severity of the adverse events in the PEGINVERA Study as severity was based on mild, moderate and severe grading. The following table provides the moderate and severe events in the PEGINEVERA study.

Table 42: Moderate and Severe Events in PEGINVERA Study

Preferred Term	Moderate and Severe Adverse Events in PEGINVERA study N=51
Arthralgia	11 (21.5%)
Fatigue	10 (19.6%)
Pruritus	8 (15.6%)
Diarrhea	7 (13.7%)
Depression	5 (9.8%)
Influenza Like Illness	5 (9.8%)
Leukopenia	5 (9.8%)
Urinary Tract Infection	5 (9.8%)
Gamma Glutamyl transferase Increased	4 (7.8%)
General Physical Health Deterioration	4 (7.8%)
Nasopharyngitis	4 (7.8%)
Neutropenia	4 (7.8%)
Pain in extremity	4 (7.8%)
Atrial fibrillation	3 (5.8%)
Transaminases increased	3 (5.8%)
Hypertension	3(5.8%)
Hypertensive crisis	3 (5.8%)
Transient Ischemia Attack	3 (5.8%)

Source: FDA Analysis

The FDA medical query was used to document the treatment emergent adverse events of all for the pooled analysis population and is described in the table below.

Table 43: Treatment Emergent Adverse Events of Pooled Studies > 5%

Common TEAEs (All Studies Combined)	Ropeginterferon alfa-2b
	N=178 n (%)
Blood and Lymphatic System Disorders	
Leukopenia FDA N	44 (24.7%)

Common TEAEs (All Studies Combined)	Ropeginterferon alfa-2b
	N=178 n (%)
Thrombocytopenia FDA N	40 (22.5%)
Anemia FDA N	21 (11.8%)
Fe Deficiency	13 (7.3%)
Infections and Infestations	
Infection, All	90 (50.6%)
URI, Cold, Rhinitis, Upper Resp Tract Infection, Flu-Like Illness	73 (41%)
Nasopharyngitis FDA N	42 (23.6%)
Infection, Viral	26 (14.6%)
UTI	19 (10.7%)
Herpes Virus	13 (7.3%)
Bronchitis, Bronchiolitis, Tracheitis, Alveolitis, Bronchiectasis	8 (4.5%)
Influenza	8 (4.5%)
Investigations	
GOT, GPT, GGTP, LFTs increased	45 (25.3%)
General Disorders and Administration Site Conditions	
Fatigue FDA N	49 (27.5%)
Pyrexia FDA N	27 (15.2%)
Local Administration Reactions FDA N	17 (9.6%)
Chest Pain (Non-Cardiac or Unknown)	15 (8.4%)
Hepatic Disorders	
Hepatic Injury FDA N	27 (15.2%)
Metabolism and Nutrition Disorders	
Decreased Appetite FDA N	13 (7.3%)
Musculoskeletal and Connective Tissue Disorders	
Arthralgia FDA N	39 (21.9%)
Back Pain FDA N	29 (16.3%)
Myalgia FDA N	22 (12.4%)
Nervous System Disorders	
Headache FDA N	37 (20.8%)
Paresthesia FDA N	10 (5.6%)
Gastrointestinal Disorders	
Diarrhea FDA N	29 (16.3%)
Abdominal Pain FDA N	21 (11.8%)
Nausea FDA N	18 (10.1%)

Common TEAEs (All Studies Combined)	Ropeginterferon alfa-2b
	N=178 n (%)
Dyspepsia FDA N	12 (6.7%)
Skin and Subcutaneous Tissue Disorders	
Pruritis	34 (19.1%)
Rash FDA N	17 (9.6%)
Eye Disorders	
Eye, Other	24 (13.5%)
Retinopathy, Retinal Disorders	15 (8.4%)
Cataract	16 (9%)
Respiratory, Thoracic and Mediastinal Disorders	
Cough FDA N	15 (8.4%)
Psychiatric Disorders	
Insomnia, Sleep Disturbance, Abnormal Dreams	17 (9.6%)
Depression FDA N	14 (7.9%)
Cardiac Disorders	
Arrhythmia FDA N	19 (10.7%)
Endocrine Disorders	
Hyper/Hypo Thyroid, Thyroiditis, Goiter	21 (11.8%)
Ear and Labyrinth Disorders	
Vertigo; Vestibular Dysfunction	15 (8.4%)
Vertigo FDA N	11 (6.2%)
Vascular Disorders	
Hemorrhage FDA N	30 (16.9%)

Source: FDA Analysis

Common adverse events were also evaluated in the PROUD-PV and CONTINUATION-PV trials.

Table 44: Common Adverse Events by System Organ Class and Preferred Terms in PROUD-PV Study

Adverse Events by System Organ Class and Preferred Terms	Ropeginterferon alfa-2b N=127	HU N=127
Infections		
URI, cold, rhinitis, upper resp tract infection, flu-like illness	39 (30.7%)	30 (23.6%)
Infection, viral	18 (14.2%)	21 (16.5%)

Adverse Events by System Organ Class and Preferred Terms	Ropeginterferon alfa-2b N=127	HU N=127
Nasopharyngitis FDA N	17 (13.4%)	19 (15%)
Pneumonia FDA N	13 (10.2%)	19 (15%)
Influenza	6 (4.7%)	13 (10.2%)
UTI	10 (7.9%)	7 (5.5%)
Bronchitis, bronchiolitis, tracheitis, alveolitis, bronchiectasis	5 (3.9%)	11 (8.7%)
Herpes virus	7 (5.5%)	5 (3.9%)
Blood and Lymphatic Disorders		
Thrombocytopenia FDA N	31 (24.4%)	47 (37%)
Leukopenia FDA N	31 (24.4%)	36 (28.3%)
Anemia FDA N	18 (14.2%)	36 (28.3%)
General Disorders and Administration		
Asthenia, fatigue, malaise, weakness, narcolepsy	25 (19.7%)	21 (16.5%)
Fatigue FDA N	23 (18.1%)	21 (16.5%)
Chest pain (non-cardiac or unknown)	9 (7.1%)	2 (1.6%)
Fever, rigors	13 (10.2%)	5 (3.9%)
Pyrexia FDA N	13 (10.2%)	5 (3.9%)
Influenza Like illness	10 (7.9%)	0 (0%)
Local administration reactions FDA N	4 (3.1%)	3 (2.4%)
Investigations		
GOT, GPT, GGTP, LFTs	37 (29.1%)	7 (5.5%)
Hepatic		
Hepatic injury FDA N	23 (18.1%)	5 (3.9%)
Cholecystitis, cholelithiasis, bile duct stone	5 (3.9%)	3 (2.4%)
Central Nervous System		
Somnolence FDA N	18 (14.2%)	18 (14.2%)
Headache FDA N	18 (14.2%)	17 (13.4%)
Vertigo FDA N	5 (3.9%)	8 (6.3%)
Dizziness FDA N	17 (13.4%)	17 (13.4%)
Fall, dizziness, balance disorder, gait disturbance, difficulty walking	16 (12.6%)	11 (8.7%)

Adverse Events by System Organ Class and Preferred Terms	Ropeginterferon alfa-2b N=127	HU N=127
Dizziness, light-headedness	14 (11%)	11 (8.7%)
Paresthesia FDA N	5 (3.9%)	6 (4.7%)
Cardiac Disorders		
Syncope FDA B	17 (13.4%)	11 (8.7%)
Arrhythmia FDA N	11 (8.7%)	6 (4.7%)
Supra-ventricular	7 (5.5%)	3 (2.4%)
Musculoskeletal and Connective tissue Disorders		
Arthralgia, arthritis, arthrosis	17 (13.4%)	8 (6.3%)
Arthralgia FDA N	15 (11.8%)	5 (3.9%)
Back pain FDA N	13 (10.2%)	7 (5.5%)
Myalgia FDA N	12 (9.4%)	5 (3.9%)
Myalgia, myositis, rhabdomyolysis	12 (9.4%)	5 (3.9%)
Arthritis FDA N	8 (6.3%)	3 (2.4%)
Vascular Disorders		
Hemorrhage FDA N	16 (12.6%)	17 (13.4%)
Bleeding	13 (10.2%)	13 (10.2%)
Systemic hypertension FDA N	10 (7.9%)	14 (11%)
Endocrine		
Hyper/hypo thyroid, thyroiditis, goiter	12 (9.4%)	3 (2.4%)
Diabetes, glucose intolerance, hyperglycemia, HbA1c, glycosuria, ketones	7 (5.5%)	4 (3.1%)
Gastrointestinal Disorder		
Dyspepsia, N, V, indigestion, epigastric pain, gastritis, duodenitis	11 (8.7%)	21 (16.5%)
Abdominal pain, distension, bloating, spasm, IBS, megacolon	14 (11%)	17 (13.4%)
Diarrhea FDA N	12 (9.4%)	14 (11%)
Diarrhea, colitis, enteritis, proctitis, gastroenteritis, C-diff	13 (10.2%)	15 (11.8%)
Abdominal pain FDA N	11 (8.7%)	14 (11%)
Dyspepsia FDA N	6 (4.7%)	9 (7.1%)
Nausea FDA N	4 (3.1%)	16 (12.6%)

Adverse Events by System Organ Class and Preferred Terms	Ropeginterferon alfa-2b N=127	HU N=127
Vomiting FDA N	4 (3.1%)	5 (3.9%)
Nausea, vomiting	6 (4.7%)	18 (14.2%)
Constipation FDA N	4 (3.1%)	6 (4.7%)
Respiratory Disorders		
Cough FDA N	11 (8.7%)	9 (7.1%)
Pulmonary embolism	1 (0.8%)	2 (1.6%)
Skin Disorders		
Pruritis	10 (7.9%)	9 (7.1%)
Rash FDA N	5 (3.9%)	8 (6.3%)
Rash, eruption, dermatitis	5 (3.9%)	6 (4.7%)
Urticaria FDA B*	5 (3.9%)	6 (4.7%)
Eye Disorders		
Eye ,other	10 (7.9%)	5 (3.9%)
Cataract	7 (5.5%)	4 (3.1%)
Ear and Labyrinth Disorders		
Vertigo; vestibular dysfunction	7 (5.5%)	9 (7.1%)
Vertigo FDA N	5 (3.9%)	8 (6.3%)
Metabolism and Nutrition Disorders		
Gout, High Uric Acid	7 (5.5%)	3 (2.4%)
Psychiatric Disorders		
Insomnia FDA N	4 (3.1%)	5 (3.9%)
Depression FDA B	9 (7.1%)	3 (2.4%)
Anxiety FDA B	11 (8.7%)	6 (4.7%)
Anxiety, nervousness, panic attacks	6 (4.7%)	4 (3.1%)

Source: FDA reviewer analysis
Abbreviations: FDA N: narrow FMQ query, FDA B: broad FMQ query

Table 45: Grade 3 or Higher Treatment Adverse Events in PROUD-PV Study

Grade 3 Or 4 Adverse Events in PROUD-PV		ROPEGINTERFERON ALFA-2B N=127 n (%)	HU N=127 n (%)
Subjects		22 (17.3%)	26 (20.5%)
Primary System Organ Class	Dictionary Derived Term		
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Anemia	0 (0%)	1 (0.8%)
	Leukopenia	2 (1.6%)	4 (3.1%)
	Neutropenia	1 (0.8%)	2 (1.6%)
	Thrombocytopenia	1 (0.8%)	4 (3.1%)
CARDIAC DISORDERS	Atrial Fibrillation	0 (0%)	1 (0.8%)
	Cardiac Failure	0 (0%)	1 (0.8%)
	Cardiac Failure Acute	0 (0%)	1 (0.8%)
	Pericardial Effusion	0 (0%)	1 (0.8%)
	Sinus Tachycardia	1 (0.8%)	0 (0%)
EYE DISORDERS	Cataract	0 (0%)	1 (0.8%)
GASTROINTESTINAL DISORDERS	Abdominal Pain	0 (0%)	1 (0.8%)
	Diarrhea	0 (0%)	1 (0.8%)
	Stomatitis	0 (0%)	1 (0.8%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Asthenia	0 (0%)	1 (0.8%)
	Multi-Organ Failure	1 (0.8%)	0 (0%)
HEPATOBILIARY DISORDERS	Cholecystitis Acute	1 (0.8%)	0 (0%)
INFECTIONS AND INFESTATIONS	Appendicitis	1	0

Grade 3 Or 4 Adverse Events in PROUD-PV		ROPEGINTERFERON ALFA-2B N=127 n (%)	HU N=127 n (%)
Subjects		22 (17.3%)	26 (20.5%)
Primary System Organ Class	Dictionary Derived Term		
		(0.8%)	(0%)
	Influenza	1 (0.8%)	2 (1.6%)
	Pyelonephritis Acute	0 (0%)	1 (0.8%)
	Septic Shock	1 (0.8%)	0 (0%)
INVESTIGATIONS	Alanine Aminotransferase Increased	1 (0.8%)	0 (0%)
	Aspartate Aminotransferase Increased	1 (0.8%)	0 (0%)
	Blood Bilirubin Increased	0 (0%)	1 (0.8%)
	Gamma-Glutamyl transferase Increased	6 (4.7%)	1 (0.8%)
	Hepatic Enzyme Increased	1 (0.8%)	0 (0%)
	Platelet Count Decreased	0 (0%)	2 (1.6%)
	Platelet Count Increased	1 (0.8%)	0 (0%)
	White Blood Cell Count Decreased	0 (0%)	1 (0.8%)
METABOLISM AND NUTRITION DISORDERS	Diabetic Metabolic Decompensation	1 (0.8%)	0 (0%)
	Hypocalcemia	1 (0.8%)	0 (0%)
	Hypokalemia	1 (0.8%)	0 (0%)
	Hyponatremia	0 (0%)	1 (0.8%)

Grade 3 Or 4 Adverse Events in PROUD-PV		ROPEGINTERFERON ALFA-2B N=127 n (%)	HU N=127 n (%)
Subjects		22 (17.3%)	26 (20.5%)
Primary System Organ Class	Dictionary Derived Term		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia	1 (0.8%)	0 (0%)
	Arthritis Reactive	1 (0.8%)	0 (0%)
	Osteoarthritis	0 (0%)	1 (0.8%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	Basal Cell Carcinoma	0 (0%)	1 (0.8%)
NERVOUS SYSTEM DISORDERS	Ischemic Stroke	1 (0.8%)	0 (0%)
PSYCHIATRIC DISORDERS	Anxiety	1 (0.8%)	0 (0%)
RENAL AND URINARY DISORDERS	Acute Kidney Injury	1 (0.8%)	0 (0%)
	Calculus Urinary	0 (0%)	1 (0.8%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Psoriasis	1 (0.8%)	0 (0%)
SURGICAL AND MEDICAL PROCEDURES	Aortic Valve Replacement	0 (0%)	1 (0.8%)
	Carotid Endarterectomy	0 (0%)	1 (0.8%)
	Cataract Operation	0 (0%)	1 (0.8%)
VASCULAR DISORDERS	Femoral Artery Occlusion	0 (0%)	1 (0.8%)
	Hypertension	2 (1.6%)	4 (3.1%)
	Hypertensive Crisis	0 (0%)	1 (0.8%)
	Peripheral Arterial Occlusive Disease	1 (0.8%)	0 (0%)

Source: FDA reviewer analysis

Serious treatment emergent adverse events (TEAEs) were mostly of moderate (Grade 2) intensity (47.6%, 121/254) for all patients in the PROUD-PV study.

Incidental neoplasms (benign or malignant) were reported in the ropeginterferon alfa-2b arm at 1 case each: adenocarcinoma of the colon, adrenal adenoma, bile duct cancer, rectal adenocarcinoma, bladder transitional cell carcinoma along with one patient identified with PV secondary myelofibrosis. Acute leukemia and appendiceal cancer were listed as one case each in the HU arm.

8.4.7. Laboratory Findings

In general, analyses of the laboratory data did not raise any new major safety concerns. Laboratory parameters of interest are discussed further below.

Liver Enzymes
In the PEGINVERA study, there were elevation of liver enzymes > 3X ULN.

	AST N=2154 tests		ALT N=2156 tests		Bilirubin N=2150 tests	
	Tests	Patients	Tests	Patients	Tests	Patients
>3X ULN or higher n (%)	44 (2%)	6 (11.8%)	74 (3.4%)	11 (21.6%)	2 (0.1)	2 (3.9%)

Source: FDA reviewer analysis

There was one episode of AST or ALT > 3 X ULN and bilirubin > 2 x ULN and ALP <2 x ULN that was observed during one single visit in the study. A brief summary of the event is described below.

Patient (b) (6): 59 year-old female with no reported underlying medical disease or medication. At screening, the patient had slightly elevated AST and total bilirubin which was considered not clinically significant. Patient received first injection of ropeginterferon alfa-2b (150 mcg) on (b) (6) and second dose of 225 mcg on (b) (6) At the next regular visit, AE of transaminase elevation was registered, and the patient skipped next two doses of study drug. The next treatment was 150 mcg after a 4 week interruption. The subsequent doses were reduced to 100 mcg and then 50 mcg with periods of interruptions until (b) (6) when the patient was taken off study at week 58. The single episode of elevation occurred at visit 5/week 8 (b) (6) Patient had fluctuating bilirubin values with baseline of 23.77umol/L at baseline to highest of 116.28 at week 8 to 14 at week 10 and back to 23 at week 26. The patient continued to be treated with ropeginterferon alfa-2b after visit 8 at lower dose without a recurrence of the elevation of the laboratory values.

Amylase and Lipase and Triglycerides

Table 46: Amylase, Lipase and Triglyceride Elevations in PEGINVERA Study

Lab Parameter	Elevation Category	PEGINVERA study N=51 n (%)
Amylase	>2 x ULN	1 (1.9%)
Amylase	>3 x ULN	1 (1.9%)
Amylase	>5 x ULN	0 (0%)
Lipase	>2 x ULN	4 (7.8%)
Lipase	>3 x ULN	2 (3.9%)
Lipase	>5 x ULN	0 (0%)
Triglycerides	>2 x ULN	8 (15.7%)
Triglycerides	>3x ULN	4 (7.8%)
Triglycerides	>5x ULN	1 (1.9%)

8.4.8. Vital Signs

The applicant obtained routine vital signs including temperature, respiratory rate, pulse, systolic and diastolic blood pressure at the scheduled assessment times in the PEGINVERA study. There were no clinically relevant changes in the vital signs during the study.

In the PROUD-PV/CONTINUATION study, there were two clinically significant abnormal values of pulse rate observed in the ropeginterferon alfa-2b arm at Visit 3 and Visit 4. The median pulse rate from baseline in both arms were comparable. The median changes from baseline of abnormal values of systolic blood pressure levels was seen in 2% of patients (5/254) at the time of their screening visits. However, the median changes from baseline in both arms were comparable.

8.4.9. Electrocardiograms (ECGs)

In the PEGINVERA study, there was a single abnormal and clinically significant ECG value obtained at an end of treatment for one patient (51 y/o male) after Week 146 and the ECG reading was atrial fibrillation.

In the PROUD-PV ECGs were obtained at the screening visit and end of study visit (month 12). In addition, an echocardiogram or MUGA were obtained at baseline and at months 3, 6, 9 and 12. There was one clinically significant abnormal value of PR interval increased was observed in HU arm at Visit 14 and clinically significant abnormal value of heart rate elevation was observed

in HU arm at Visit 7.

8.4.10. QT

In the PROUD-PV/CONTINUATION studies there were three clinically significant abnormal values of QTcB and QtcF observed (two in ropeginterferon alfa-2b at visit 14 and EOT and one in the HU arm at follow-up). The median changes from baseline in QTcB for all patients ranged from -3.5 msec (V21) to 2.0 msec (EOT). The median changes from baseline in QTcF for all patients ranged from 0.0msec (visit 7) to 2.0 msec (V14 and EOT).

8.4.11. Immunogenicity

In the PEGINVERA study, there were 51 patients and in the PROUD-PV study eligible 126 patients evaluated for binding and neutralizing antibodies for a total of evaluable 177 patients. At baseline, there were 7 patients who were positive for ADA and post baseline there were 24 patients positive for ADA with the screening assay. With the confirmatory test for ADA, there was only 1 patient positive for ADA and no subjects positive for neutralizing antibodies (Nab).

There were 36 healthy subjects in the Phase 1 study (PEGINVERA study) who had evaluable anti-drug antibodies (ADA) data at baseline and post-baseline. There were 5 patients who tested positive for ADA at baseline and 11 patients who tested positive post-baseline for ADA. The confirmatory ADA test identified 2 subjects positive for ADA however no subjects tested positive for neutralizing antibodies in the healthy subject population.

In summary, there was 1 patient in the PEGINVERA/PROUD-PV studies who had a positive immunogenic response and no neutralizing antibody. No subjects developed neutralizing antibodies.

The limited immunogenicity data precludes any investigation of any clinically meaningful effects on PK, safety or efficacy of ropeginterferon alfa-2b.

8.5. Analysis of Submission-Specific Safety Issues

Hepatoxicity
Further analysis of liver enzyme elevation was conducted by the review team. Liver enzyme elevation and hepatotoxicity are known class safety effects of the interferons and in particular elevation of GGT, ALT and AST. Table 47 provides a table of the TEAEs of elevation of the liver enzymes in the pooled safety group. This table does not consider laboratory changes from the laboratory dataset.

Table 47: Liver Enzyme Elevation (by Preferred Term) in Pooled Safety Group for Ropeginterferon alfa-2b

	Ropeginterferon N=178 n(%)
TEAEs	
AST	14 (7.9%)
ALT	19 (10.6%)
GGT	29 (16.2%)
Bilirubin	0 (0%)
Hepatic enzyme increased/transaminase increased	13 (7.3%)
CTCAE Grade **≥3** elevations	
AST	4 (3%)
ALT	6 (6%)
GGT	9 (5%)
Hepatic enzyme increased	1 (0.56%)

Source: FDA Analysis
*Based on preferred term of AST or ALT increase (does not include laboratory data)

Most of the hepatotoxicity observed was mild or grade 1 or grade 2 however there were several cases of grade 3 or higher elevations of liver enzymes. There was one episode of AST or ALT > 3 ULN and bilirubin > 2 x ULN and ALP <2 x ULN, observed during one single visit in the study and is described in the laboratory data. The patient was able to resume study drug.

Thrombotic Risk

The risk of thrombosis is a known cause of morbidity and mortality associated with PV. Ropeginterferon alfa-2b requires a conservative titration schedule and maximum dose level is not reached until around week 20. During this interval of dose-escalation, patient are likely to retain their risk of thrombosis.

Two patients in the ropeginterferon alfa-2b arm had thromboembolic events during dose-titration before reaching their maximum dose in the PROUD-PV study (ischemic stroke at 13 weeks and a hemorrhagic transformation stroke at 9 weeks after starting ropeginterferon alfa-2b treatment).

Table 48 displays the thromboembolic events in the pooled safety population.

Table 48: Thromboembolic Events in the Pooled Safety Population

Thromboembolic Events	Ropeginterferon N=178 n (%)
Splenic Infarction	3 (1.6%)
Pulmonary Embolism	2 (1.1%)
Truncus Coeliacus thrombosis	1 (0.6%)
Intracardiac Thrombus	1(0.6%)
Deep Vein Thrombosis	1 (0.6%)
Ischemic Stroke	1 (0.6%)
Hemorrhagic Transformation Stroke	1(0.6%)
Transient Ischemic Attack	3 (1.7%)

Source: FDA reviewer analysis

In the pooled analysis, four of these events occurred during the first 100 days of the study duration with two events of transient ischemic attacks occurring on study day 28 and 87, and ischemic stroke and hemorrhagic stroke transformation occurring on study day 95 and 63, respectively.

In the PEGINVERA study, there were a total five thromboembolic events during the study (three TIAs and two splenic infarct) with two events occurring before study day 100 (two TIAs). The other three events of TIA, splenic infarct (2 events) and occurred on study day, 198, 365 and 1970, respectively.

Table 49: Thromboembolic Events Occurring during Titration/Maintenance Phases in the PROUD-PV Study

Thromboembolic Events	ROPEGINTERFERON ALFA-2B N=127	HU N=127
Titration Phase	2	0 (0%)
Hemorrhagic transformation stroke	1 (0.8%)	0 (0%)
Ischemic Stroke	1 (0.8%)	0 (0%)
Maintenance Phase	3 (2.4%)	2 (1.6%)
Splenic infraction	1 (0.8%)	0 (0%)
Intracardiac thrombus	1 (0.8%)	0 (0%)
Truncus Coeliacus thrombosis	1 (0.8%)	0 (0%)
Embolism	0 (0%)	1 (0.8%)
Femoral artery occlusion	0 (0%)	1 (0.8%)

Source: FDA reviewer analysis

The risk of TE in the PV population is increased compared to age matched controls and is one of the key reasons to initiate cytoreductive therapy in patients with PV. Because the treatment

intensity may be lower in the first 20 weeks of the treatment period, there may be a continued risk of thromboembolic events, although phlebotomy can help to reduce this risk , increased WBCs and PLTs may contribute to the thrombotic risk.

The number of phlebotomy visits required during the titration phase to obtain a HCT > 45% ranged from 0-27 visits in the ropeginterferon alfa-2b arm compared to 0-6 visits in the HU arm.

8.6. Safety Analyses by Demographic Subgroups

There were no demographic subgroup safety concerns identified for this application. Information regarding outcome and consistency of effects in subgroups defined by age, sex, ethnicity, organ function or genetic polymorphisms remains limited due to the small trial population.

8.7. Specific Safety Studies/Clinical Trials

No additional studies or trials were conducted to evaluate a specific safety concern.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

In the pooled analysis for ropeginterferon alfa-2b, there were three events of colon adenoma, two events of glioblastoma multiforme, and two events of basal cell carcinoma and one case of colon adenocarcinoma, once case of rectal adenocarcinoma and one case of intestinal adenocarcinoma. There were single reported events of adrenal neoplasm, bile duct cancer, prostate cancer, seminoma, thyroid neoplasm, and two cases of squamous cell (one of skin, one not identified).

There were also two events of myelofibrosis. There were no cases of acute leukemia reported in the ropeginterferon alfa-2b arm.

In review of the literature, there are no reported signals for interferons and risk of glioblastoma multiforme or increased risk of malignancy. In comparative safety analysis between HU and ropeginterferon alfa-2b, there were a similar number of neoplasms observed between arms. The observation of the two cases of glioblastoma leading to death is considered a chance finding as no similar events are documented in the literature.

8.8.2. Human Reproduction and Pregnancy

No pregnancies were reported during any of the following studies: (PEGINVERA Study, PROUD-PV Study, CONTINUATION-PV Study, (b) (4)

8.8.3. Pediatrics and Assessment of Effects on Growth

There was no pediatric data submitted with this application.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

One case of overdose was reported in a 54-year-old, female patient during participation in the PROUD-PV Study. The patient received a dose 10 times higher than the recommended starting dose. She received 1000 mcg instead of 100 mcg; the highest allowed dose in the study was 500 mcg. She developed flu-like symptoms for 3 days, which were assessed as non-serious. The patient recovered completely after paracetamol medication and temporary discontinuation of ropeginterferon alfa-2b therapy. The event was considered an administrative error by the Investigator.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

There is no postmarketing experience with ropeginterferon alfa-2b in the United States.

8.9.2. Expectations on Safety in the Postmarket Setting

The safety profile of ropeginterferon alfa-2b is similar to the known safety profile of interferon drug products.

8.9.3. Additional Safety Issues From Other Disciplines

Overall, the patient populations evaluated in the PEGINVERA study and PROUD-PV/CONTINATION study are reasonably representative of patients with PV who are expected to take ropeginterferon alfa-2b in the postmarketing setting. Although the clinical trial safety database is small due to the rare disease, the safety profile observed in the clinical development program may be generalized to the target population

8.10. Integrated Assessment of Safety

The safety data submitted with the BLA was sufficient to assess the safety of ropeginterferon alfa-2b in the proposed PV population. The safety information for ropeginterferon alfa-2b is primarily derived from the PEGINVERA study with additional safety data from the PROUD-PV/CONTINUATION study for a total of 178 subjects who received at least one dose of study drug (n=51 for PEGINVERA and N=127 for PROUD-PV/CONTINUATION).

The most common SAEs in the pooled analysis were in the infections and infestations SOC but also included depression, TIA, subarachnoid hemorrhage, anti-thyroid antibody positive, acute stress disorder, atrial fibrillation, transient ischemic attack, diverticulitis, and ischemic stroke.

Common adverse reactions (>20%) reported in the PEGINVERA study included infections, fatigue, pruritus nasopharyngitis, arthralgia, URI, cold, rhinitis, headache, diarrhea, back pain, dizziness, nausea, pyrexia, influenza-like illness, local administration reactions, leukopenia, rash, erythema, eye disorders, depression, insomnia and sleep disorders, decreased appetite. These were similar to the common treatment adverse events in the pooled safety analysis which also included elevation of liver enzymes, leukopenia and thrombocytopenia and headache.

A number of safety topics of interest were identified by the applicant and reviewer in the development program for ropeginterferon alfa-2b and are associated with the use of pegylated interferons.

- Neuropsychiatric events to include depression and suicidal ideation
- Infections
- Cardiac disease
- Ischemic or hemorrhagic cerebrovascular events to include thrombosis
- Autoimmune disorders
- Endocrine disorders to include hypothyroidism, hyperthyroidism
- Ophthalmologic disorders
- Pancytopenia (severe decreases in neutrophil or PLTs)
- Pancreatitis
- Colitis
- Pulmonary function impairment
- Triglyceridemia
- Hepatic failure and elevation of liver enzymes

Neuropsychiatric events to include depression and one completed case of suicide occurred during the development of ropeginterferon alfa-2b. Given this known safety concern with the use of interferons, a box warning is recommended for the prescribing information consistent with currently approved interferons.

Cardiac disease to include events of atrial fibrillation, tachycardia and cardiac failure were observed in pooled safety analysis for ropeginterferon alfa-2b. Given this known safety concern, inclusion of this risk in the warnings and precautions is recommended consistent with currently approved interferons.

Cerebrovascular events are reported with the use of interferons and patients with PV are at risk for developing these events due to baseline risk of thrombosis and cardiovascular events associated with PV. There may be a persistent thrombosis risk in the titration period due to the prolonged titration phase for ropeginterferon alfa-2b a. The risks of thromboembolic events with ropeginterferon alfa-2b in the titration phase can be sufficiently controlled with phlebotomies and cardiovascular risk mitigation and will be described in the prescribing information.

Liver enzyme elevation and hepatotoxicity are known class safety effects of interferons and in the pooled safety analysis, there were grade 3 or higher elevations of AST, ALT and GGT of 3%, 4% and 13%, respectively. There was one episode of laboratory values AST or ALT > 3 ULN and bilirubin > 2 x ULN and ALP <2 x ULN, observed during one single visit in the study. In this patient, the laboratory parameters improved and the patient resumed therapy. Hepatotoxicity including cases of drug-induced liver injury are a well-known class safety effect reported for all interferons. Ropeginterferon is contraindicated in patients with severe hepatic impairment and an appropriate warning will be included in the prescribing information.

Endocrine disorders to include hyperthyroidism and hypothyroidism, autoimmune thyroiditis and anti-thyroid antibodies present were reported. These safety findings are known safety concerns with the use of interferons and an appropriate warning in the prescribing information will be included as well as contraindication for patients with autoimmune disorders.

Immunological adverse events with this known side effect reported in the literature with the use of interferons. Antibodies against antinuclear antigens (ANAs), thyroid antigens were observed and identified as clinically relevant. Appropriate warnings will be included in label to include box warning for immunological reactions.

Ophthalmologic disorders, pancytopenia (severe decreases in neutrophil or PLTs), pancreatitis, colitis, pulmonary function impairment, triglyceridemia are known safety concerns with the use of interferons. Some of these to include pancytopenia, pneumonitis, maculopathy, triglyceridemia occurred in the pooled safety analysis for ropeginterferon alfa-2b. Of note, there were no cases of colitis reported. Appropriate warnings in the prescribing information are recommended.

The other cytoreductive agents used for the treatment of PV have genotoxic risk and potential risk of leukemia. There were no cases of AML in the ropeginterferon alfa-2b development program. The absence of leukogenic transformation potential is a benefit very relevant to patients considering the long duration of treatment needed, particularly in younger patients more concerned about life-long exposure and those in reproductive age.

Overall the risk/benefit profile for ropeginterferon alfa-2b in the treatment of rare serious disease such as PV is favorable, and the adverse events of special interest can be appropriately managed and mitigated with labeling.

9. Advisory Committee Meeting and Other External Consultations

Neither an Advisory Committee Meeting nor external consultation was deemed necessary because this review did not raise any significant or unexpected safety or efficacy issues for this drug class or indication. This application was not presented at an Advisory Committee.

9. Labeling Recommendations

9.1 Prescription Drug Labeling

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Proposed Labeling	Approved Labeling
Indication and Usage	Besremi is indicated for the treatment of PV in adults without symptomatic splenomegaly	Besremi is an interferon alfa-2b analog indicated for the treatment of PV in adults without symptomatic splenomegaly.
Dosage and Administration	The recommended starting dose for single-agent therapy is 100 mcg by subcutaneous injection every two weeks. Titrate dose up by 50 mcg every 2 weeks until hematological parameters are stabilized. (b) (4)	The recommended starting dose for single-agent therapy is 100 mcg by subcutaneous injection every two weeks. Titrate dose up by 50 mcg every 2 weeks until hematological parameters are stabilized. (b) (4)
Warnings and Precautions	Warnings and Precautions did not include all potential adverse events of special interest reported with other interferon-alfa agents.	Additional warnings and precautions were included consistent with other interferons.
Clinical Trials Experience	The safety evaluation was based on (b) (4)	Revise section 6.1 to base the safety evaluation on the PEGINVERA study (b) (4).
Clinical Studies	Efficacy results were based on (b) (4)	The efficacy of Besremi is based on the PEGINVERA trial (b) (4)

10. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary for this application. No safety issues were identified that would require a REMS.

11. Postmarketing Requirements and Commitments

The applicant will be required to commit to a post-marketing requirement of an observation study (PASS ropeginterferon alfa-2b: safety observational study) to investigate tolerability with a focus on hepatotoxicity and evaluation of cardiovascular and thromboembolic events during the titration phase of the administration of ropeginterferon alfa-2b.

12. Appendices

12.1. References

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12.2. Financial Disclosure

The applicant requested financial disclosures from all investigators participating in the clinical trials supporting this BLA.

Covered Clinical Study (Name and/or Number): PROUD-PV, CONTINUATION-PV, PEGINVERA [redacted] (b) (6)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 67		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: x Significant payments of other sorts: See description below. Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Applicant of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Reviewer's Comment:
The details of the clinical investigator's financial disclosure, [redacted] (b) (6) *are described below.*

1. *PROUD-PV/CONTINUATION-PV: Received or entered into an agreement to receive significant payments, grants, Honoria and/or equipment having a total monetary value exceeding US $ 25, 000. Description:* (b) (6)
    a. *Total number of patients:* (b) (6)
2. *PEGINVERA: Entered into any financial arrangement whereby the value of your compensation could be influenced by the outcome of the clinical trial. Description:* (b) (6) *AND Received or entered into an agreement to receive significant* (b) (6) *and/or equipment having a total monetary value exceeding US $ 25, 000. Description:* (b) (6)
    a. *Total number of patients:* (b) (6)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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03/12/2021 07:42:29 AM

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