CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761166Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	November 3, 2021
From	Tanya Wroblewski, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	BLA 761166
Applicant	PharmaEssentia US
Date of Submission	May 12, 2021
PDUFA Goal Date	November 13, 2021
Proprietary Name	Ropeginterferon alfa-2b-njft
Established or Proper Name	BESREMi
Dosage Form(s)	Subcutaneous
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with polycythemia vera without symptomatic splenomegaly
Applicant Proposed Dosing Regimen	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 500 mcg [redacted (b) (4)] until the hematological parameters are stabilized (HCT <45%, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L). [redacted (b) (4)]
Recommendation on Regulatory Action	*Approval*
Recommended Indication/Population	For the treatment of adults with Polycythemia Vera
Recommended Proposed Dosing Regimen	The recommended starting dosage for patients not on hydroxyurea is 100 mcg by subcutaneous injection every two weeks. Gradually increase the dose by 50 mcg every two weeks (to a maximum dose of 500 mcg) until the hematological parameters are stabilized (HCT <45%, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L). When transitioning to ropeginterferon-alfa-2b-njft from hydroxyurea start ropeginterferon alfa-2b 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 ropeginterferon alfa-2b-njft by 50 mcg every two weeks (up to a maximum dose of 500 mcg) while gradually decreasing the hydroxyurea dose, until the hematological parameters are stabilized (HCT <45%, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L). Discontinue hydroxyurea by Week 13.

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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
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-CTCA	National Cancer Institute-Common Terminology Criteria for Adverse Event
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. Introduction

The Applicant submitted a Biologics License 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. During the initial review cycle of the application, all disciplines recommended approval except for the Division of Medication Error and Prevention Analysis (DMEPA) and the Office of Pharmaceutical Quality (OPQ). DMEPA identified Human Factor validation deficiencies which precluded approval and FDA's assessment of drug substance manufacturing and testing facilities could not be conducted due to travel restrictions related to the COVID-19 public health emergency. The Applicant received a Complete Response Letter (CRL) on March 12, 2021.

The Applicant submitted a response to the CRL on May 12, 2021. This review of the response to the Complete Response focuses only on the deficiencies (OPQ, Human Factors), updated safety and outstanding labeling issues that were not resolved in the first review cycle.

2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Polycythemia Vera (PV) is a rare, myeloproliferative neoplasm that causes erythrocytosis, leukocytosis, thrombocytosis, bone marrow hypercellularity and/or fibrosis, and splenomegaly. The prevalence is approximately 50 per 100,000 in the United States. Median survival is 13.7 years. 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. Treatment is risk-stratified based on age and history of prior thrombosis and cytoreduction is the main goal of treatment. There are no FDA approved cytoreductive therapies for first-line, treatment-naïve patients or for the initial treatment period for patients with PV. Most treatment involves phlebotomy, off-label aspirin, off-label hydroxyurea (HU) or off-label interferon. 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 and does not have an indication for first-line treatment of PV as the ruxolitinib trial (NCT01243944) only enrolled patients with inadequate response to hydroxyurea, who required phlebotomy and exhibited splenomegaly. When patients stop treatment for PV, disease signs and symptoms recur. Physicians treating patients with PV assess response to treatment using laboratory parameters.

Ropeginterferon alfa-2b-njft (hereafter referred to as ropeginterferon alfa-2b) is a mono-pegylated proline-interferon alfa-2b, and with this approval is the first interferon specifically indicated for the treatment of PV. Interferon alfa belongs to the class of type I interferons that exhibit their cellular effects by binding to a transmembrane receptor termed interferon alfa receptor (IFNAR). Binding to IFNAR initiates a downstream signaling cascade through the

activation of kinases, in particular Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) and activator of transcription (STAT) proteins. Nuclear translocation of STAT proteins controls distinct gene-expression programs and exhibits various cellular effects. The mechanism of action of interferon alfa has not been fully elucidated; however, nonclinical studies indicate that the therapeutic effects of interferons are most likely related to stimulation of the immune system and depletion and/or elimination of mutant hematopoietic stem cell lineages.

The Applicant established substantial evidence of effectiveness for PV, a rare, serious disease with limited treatment options, using an adequate and well-controlled study (PEGINVERA) and confirmatory evidence from another study (PROUD-PV).

The PEGINVERA study is a single-arm, open-label trial that treated 51 adult patients who had confirmed PV plus JAK2 mutation positivity with ropeginterferon alfa-2b for a median of 5.2 years. The population enrolled newly diagnosed untreated patients and those previously treated with HU but not a population with refractory or resistant disease. Patients were phlebotomized until hematocrit (HCT) levels reached <45% prior to first administration of ropeginterferon alfa-2b.

The mean age was 59 years, 61% of patients were male, and 98% were Caucasian. Sixteen percent of patients were newly diagnosed; 84% had prior disease. At baseline, mean HCT, platelet count (PLTs), and white blood cell count (WBCs) were 45.1%, 458 x 10^9/L, and 11.8 x 10^9/L, respectively.

Complete hematological response (CHR) was defined as HCT < 45% without phlebotomy in the previous 2 months, PLT < 400 x 10^9/L, WBC < 10 x 10^9/L, normal spleen size, and no new thrombosis. The overall CHR was 60.8%; [95% confidence interval (CI): 46.1%, 74.2%] with a median response duration of 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 80.4% (95% CI: 66.9%, 90.2%) with median duration of response of 20.8 months (95% CI: 13, 43.8).

Similarly, ropeginterferon alfa-2b clearly and persistently reduced WBCs and PLTs and normalized these parameters in a significant proportion of patients in the PROUD-PV trial.

There are numerous published natural history studies in patients with PV demonstrating that without aggressive cytoreductive control, WBC, PLTs and HCT increase with ongoing thrombotic and cardiovascular risks. Therefore, these laboratory abnormalities do not resolve spontaneously in PV, and the findings from the PEGINVERA and PROUD-PV trials establish compelling evidence of a drug effect. Thromboses and malignancies are the 2 main causes of morbidity and mortality in patients with PV. While no drug has been shown to lower the risk of hematologic transformation to myelofibrosis or cancer, multiple lines of evidence establish a reduced thrombotic risk in PV with hematologic control, establishing clinical benefit with this approach in this rare disease.

In general, the safety profile of ropeginterferon alfa-2b is acceptable in a population with a rare life-threatening disease with a significant unmet medical need. There were 65 serious adverse events reported among 55% patients in the PEGINVERA study. Serious adverse events reported in ≥ 4% of patients included urinary tract infections (8%), transient ischemic attack (6%) and depression (4%). Adverse reactions requiring permanent discontinuation in > 2% of patients included depression (8%), arthralgia (4%), fatigue (4%), and general physical health deterioration (4%).

Common adverse reactions (>40%) reported in the PEGINVERA study included influenza-like illness, arthralgia, fatigue, pruritis, nasopharyngitis and musculoskeletal pain. The lack of a control arm for the safety assessment 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 that include neuropsychiatric events, hepatoxicity and elevation of liver enzymes, bone marrow toxicity (leukopenia and thrombocytopenia), cardiovascular toxicity, cerebrovascular toxicity, including thrombosis, hypersensitivity reactions, endocrine toxicity, including development of thyroid dysfunction, renal toxicity, colitis, pulmonary toxicity, ophthalmologic toxicities, dental and periodontal disorders, pancreatitis and elevated triglycerides.

A box warning will be required for the neuropsychiatric, autoimmune, ischemic and infectious-conditions consistent with other approved interferons. The remaining significant adverse effects will be described in the Warnings and Precautions section of the labeling, which is also consistent with the approach with other approved interferons. In addition, there will be a Medication Guide each time the prescription is dispensed, informing patients of the serious risks.

There may be a persistent thrombosis risk in the titration period due to the prolonged titration phase for ropeginterferon alfa-2b when patients have not yet reached their optimal dose. 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.

The pre-filled syringe requires users to correctly measure the prescribed dose, which poses an inherent risk for dosing errors (e.g., a patient may unintentionally administer the entire contents or the wrong dose). The potential for medication dosing errors will be monitored in the post-approval setting with enhanced pharmacovigilance for 3-years from the date of approval.

We are issuing a postmarketing requirement (PMR) to further evaluate specific safety outcomes of interest which includes hepatotoxicity, cardiovascular and thromboembolic events in the Applicant's ongoing observational safety study of ropeginterferon alfa-2b in PV.

In summary, we have concluded that the benefits of ropeginterferon alfa-2b outweigh the risks for the treatment of PV when used according to the labeling.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Polycythemia Vera 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 treated patients with PV greater than 65 years of age is 13.7 years, with longer median survival for younger patients. 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 The median survival of untreated symptomatic patients with PV is 6 to 18 months whereas median survival of treated patients over the age of 65 years is 13.7 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 therapy, treatment-naïve patients, or initial treatment. • Low risk patients (<60 years of age, no history of thrombosis): phlebotomy, low-dose aspirin • High risk patients (≥ 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 radioactive phosphorus (32P) are rarely used for treatment for PV. 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.	There are no FDA-approved therapies for patients with newly diagnosed PV 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 established in one adequate and well-controlled trial (PEGINVERA) with confirmatory evidence from another trial (PROUD-PV). In PEGINVERA, 51 patients with PV, including patients who were newly diagnosed, pre-treated and on cytoreductive therapy were treated with ropeginterferon alfa-2b for a median of 5.2 years. About 61% (95% CI: 46%, 74%) achieved a CHR defined as HCT ≤45% without phlebotomy in the previous 2 months, PLTs ≤ 400 x 10^9/L, WBC count ≤ 10 x 10^9/L, normal spleen size (≤ 12 cm females and ≤ 13 cm males) and without thrombotic events, 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 the previous two months, platelet count ≤ 400 x 10^9/L, WBC count ≤ 10 x 10^9/L) was observed in 41/51 patients [(80.4%) 95% CI: 66.9%, 90.2%], with a median duration of response of 20.8 months (95% CI: 13, 43.8). Similarly, ropeginterferon alfa-2b clearly and persistently reduced WBCs and PLTs and normalized these parameters in a significant proportion of patients in the PROUD-PV trial. The natural history of PV is well understood; erythrocytosis, leukocytosis and thrombocytosis do not resolve spontaneously; therefore, the findings from these trials establish compelling evidence of a drug effect.	Ropeginterferon alfa-2b leads to a durable cytoreductive improvement in patients with PV, which would not occur spontaneously in this disease. While no drug has been shown to lower the risk of hematologic transformation to myelofibrosis or cancer, multiple lines of evidence establish a reduced thrombotic risk in PV with hematologic control, establishing clinical benefit with this approach in this rare disease.
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 reported in ≥ 4% of patients included urinary tract infections (8%), transient ischemic attack (6%) and depression (4%). Adverse reactions requiring permanent discontinuation in > 2% of patients included depression (8%), arthralgia (4%), fatigue (4%), and general physical health deterioration (4%).	Consistent with the approach used with other interferons for other diseases, the risks of ropeginterferon alfa-2b can be sufficiently mitigated with labeling, which includes: • A box warning pertaining to neuropsychiatric,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Common adverse reactions (>40%) reported in the PEGINVERA study included influenza-like illness, arthralgia, fatigue, pruritis, nasopharyngitis and musculoskeletal pain. 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 the disease and its comorbidities. Ropeginterferon alfa-2b is an interferon and there are known class side effects and several adverse events of interest, including neuropsychiatric events, elevation of liver enzymes and hepatotoxicity, bone marrow toxicity (leukopenia and thrombocytopenia), cardiovascular toxicity, cerebrovascular toxicity including thrombosis, hypersensitivity reactions, endocrine toxicity including development of thyroid dysfunction, renal toxicity, colitis, pulmonary toxicity, ophthalmologic toxicities, dental and periodontal disorders, pancreatitis and elevated triglycerides. The pre-filled syringe requires users to correctly measure the prescribed dose, which poses an inherent risk for dosing errors (e.g., a patient may unintentionally administer the entire contents or the wrong dose).	autoimmune, ischemic and infectious conditions. • Warnings and Precautions for other significant risks. • A Medication Guide that must be dispensed to patients with each prescription alerting them to the serious risks. The potential for medication dosing errors will be monitored in the post-approval setting with enhanced pharmacovigilance for 3-years from the date of approval. To further evaluate specific safety outcomes of interest: hepatotoxicity, cardiovascular and thromboembolic events in treated patients, we are issuing a Post Marketing Requirement for the applicant to complete the ongoing observational study of ropeginterferon alfa-2b.

3. Background

3.1.1. Product Information

Ropeginterferon alfa-2b is an interferon alfa-2b analog and is comprised of recombination interferon alfa-2b conjugated with a two-arm methoxypolyethylene glycol (mPEG) (b) (4) and is considered a long-acting mono-pegylated interferon alfa-2b analog.

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 and exhibits various cellular effects. Interferons and pegylated interferons have been used off-label for the treatment of Polycythemia Vera; however, the exact mechanism of action in this disease has not been fully elucidated. Non-clinical studies indicate that the therapeutic effects of interferons are most likely related to stimulation of the immune system and depletion and/or elimination of mutant hematopoietic stem cell lineages.

Pegylation of interferon reduces the elimination of the molecule and facilitates a prolongation of the plasma half-life. Conventional pegylated interferons currently approved for other indications in the United States are administered once per week, compared to 3-times per week for unmodified interferon alfas. Ropeginterferon alfa-2b is a third-generation mono-pegylated INF that is administered on an every 2-week schedule.

3.1.2. Therapeutic Context

Polycythemia Vera was first described in the medical literature in 1892. Polycythemia Vera 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, and 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 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. Population-based epidemiological studies

done in Rochester, MN, have suggested a stable incidence of PV of approximately 2.3/100,000. The median survival of patients with symptomatic untreated 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.

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: 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, and microvascular symptoms (e.g., headaches, lightheadedness, visual disturbances, atypical chest pain, erythromelalgia, paresthesia). The most serious complications include thrombotic events and bleeding, and the risks of leukemic transformation and 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 or JAK2 exon 12 mutations. The laboratory detection of JAK2V617F is highly sensitive (97% sensitivity) and highly specific (100%) for distinguishing PV from other causes of increased HCT.

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, which has been widely adopted for initial pharmacological treatment of PV despite lack of approval for this indication. Hydroxyurea toxicities frequently require either drug reduction or drug discontinuation resulting in inadequate management of the disease. Additionally, because of 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. Additional off-label cytoreductive therapies for treatment of PV include pegylated and non-pegylated interferons as well as alkylating agents such as busulfan.

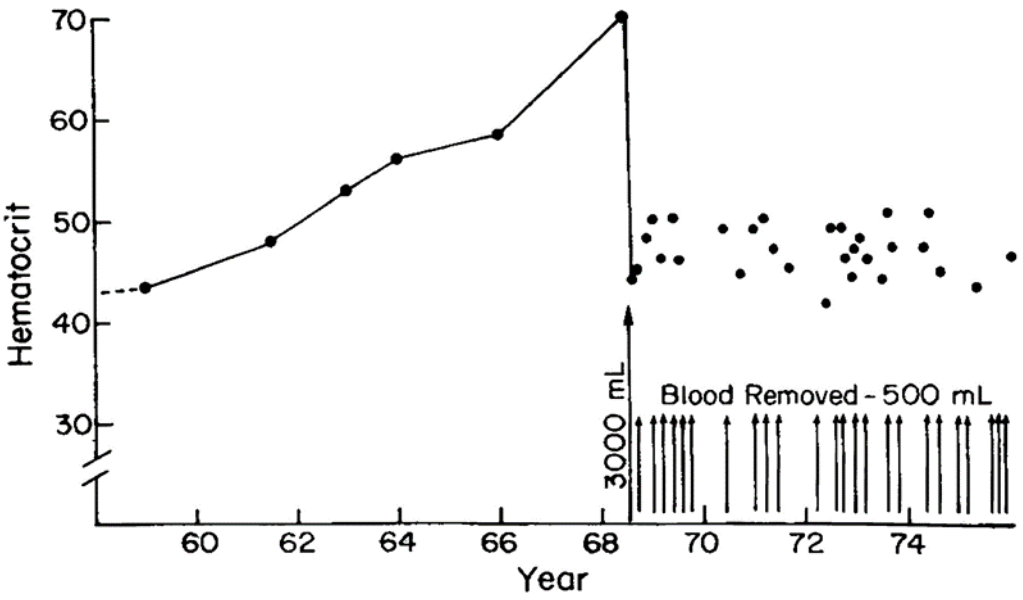
Interferons have been used for the treatment of PV and other myeloproliferative diseases for the past 30 years. A review of the literature from nonrandomized long-term studies suggest that interferon may provide better control of splenomegaly, thrombocytosis, pruritus, and thrombohemorrhagic complications compared to phlebotomy alone or phlebotomy plus HU. An objective response of approximately 80% including complete freedom from phlebotomies in approximately 60% of patients was reported. In addition, interferon alfa was reported to reduce PV-associated pruritus in many cases. (*Kiladijian JJ, 2008*).

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.

3.2. Natural History of PV

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

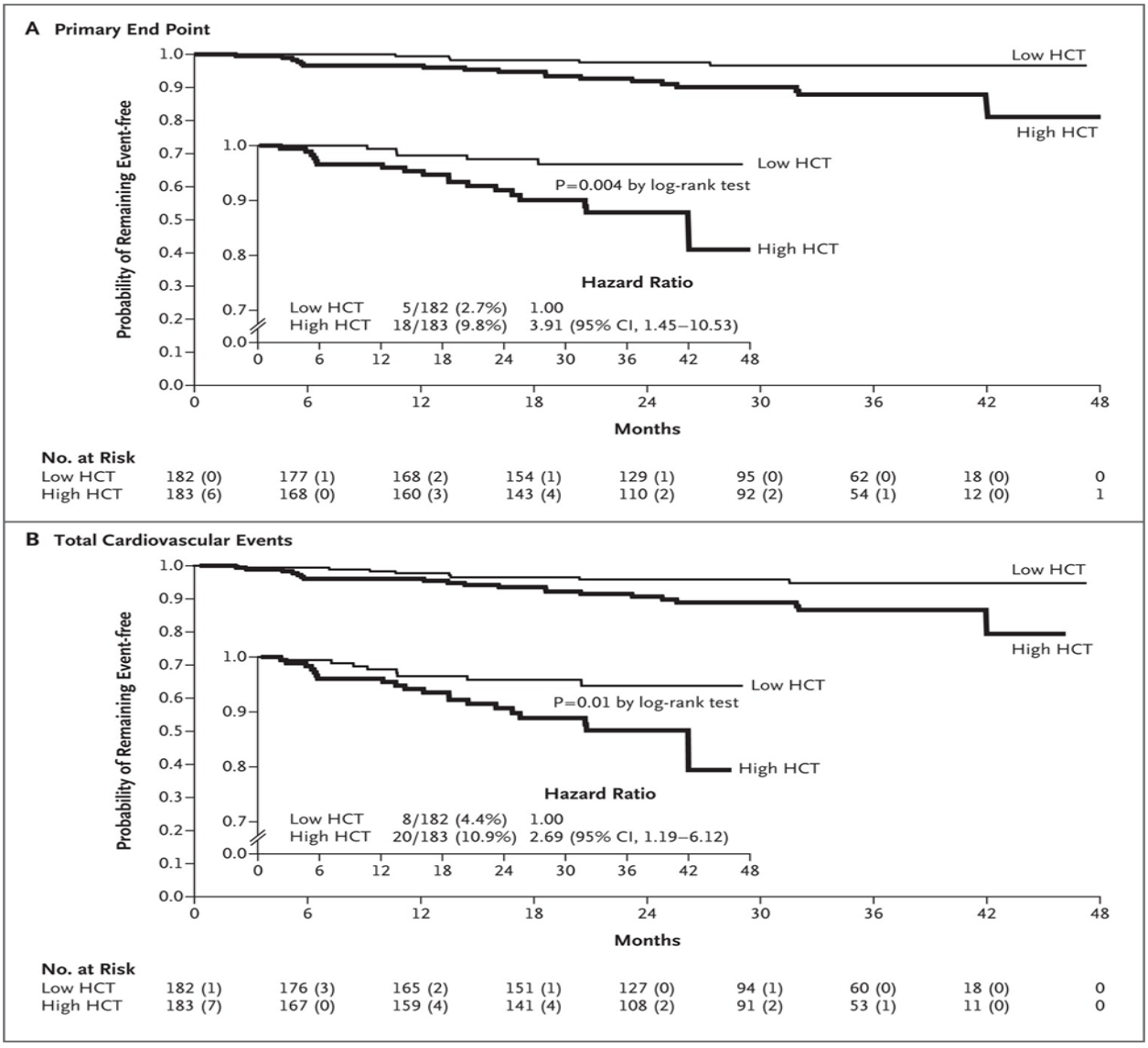
Figure 1 Increased HCT in Untreated PV Patient



(Source: CL Conley Polycythemia Vera, Diagnosis and Treatment. Hosp Pract (Off Ed). 1987

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 treated with HU, phlebotomy or both were randomized to either a low HCT target (<45%) or high HCT target (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 figures are Kaplan-Meier Curves 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

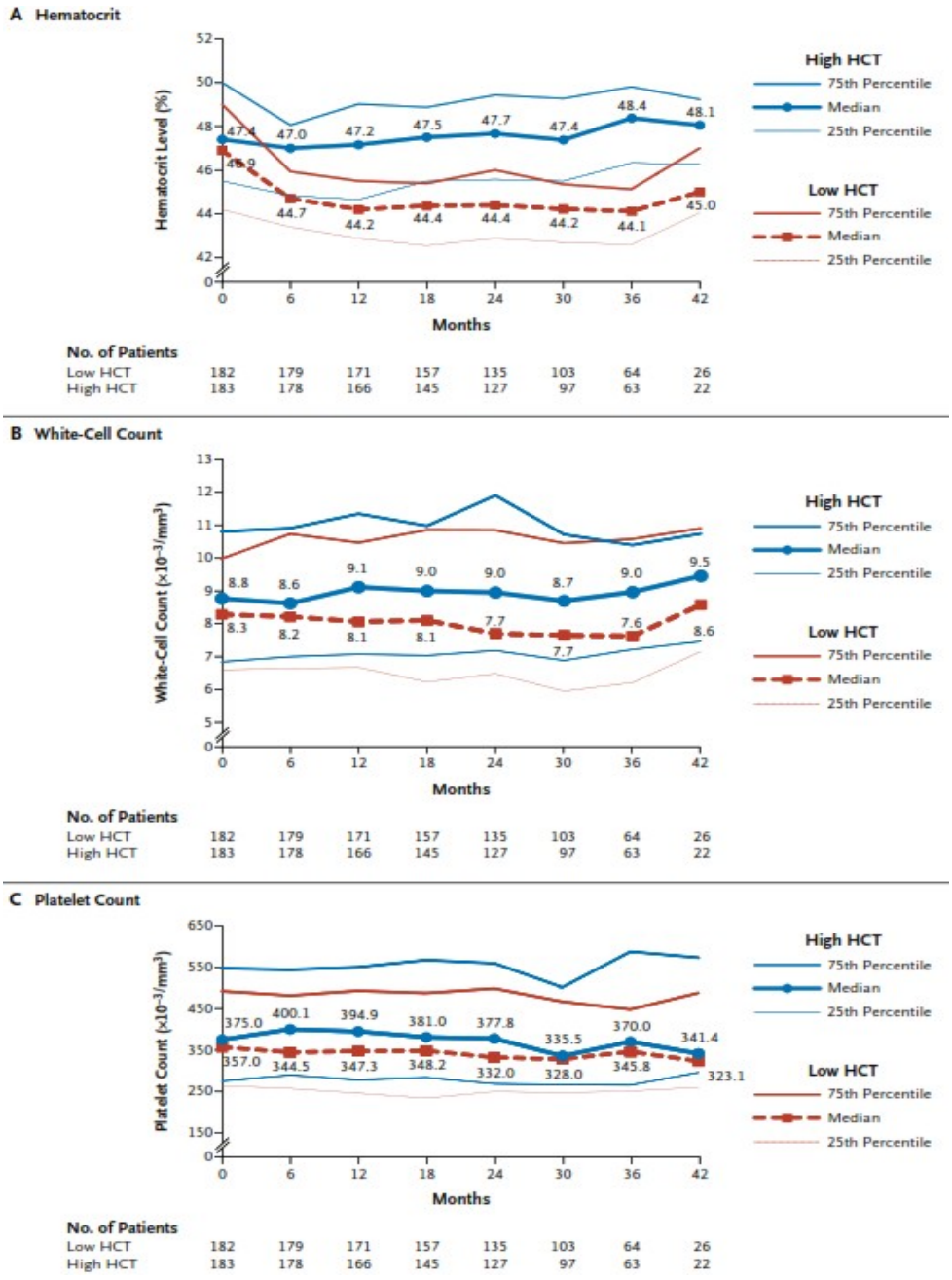


Source: Marchioli R et al. N Engl J Med 2013

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%) 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). This finding was driven by cardiovascular and thrombosis events.

HCT decreased within the ranges directed by the protocol, however, the low HCT intervention had modest effects on WBCs and both groups had similar PLT counts – therefore, WBCs and PLTs remained elevated for a not insignificant proportion of patients in both treatment groups during the study (see figure; panels B and C). Note that WBCs (middle panel, B) remained in the 10 to 11 X 10^9/L range and PLTs (lower panel, C) remained in the 400 to 500 X 10^9/L range throughout the study.

Figure 3 HCT, WBC, PLT changes during CYTO-PV Study



(Source: Marchioli R. et al. N Engl J Med 2013)

Thus, targeting HCT <45% results in lower rates of cardiovascular death and major thrombosis, and the WBC and PLT counts in the higher HCT target group, reflecting less intensive disease control, support the premise that there are 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 all the reported thrombotic events over these years occurred shortly

before or at diagnosis with most events occurring within 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 events 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 decrease over time during treatment (e.g., phlebotomy). 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).* The lower rates of thromboses after diagnosis are likely due to advances in treatment as well as better management of cardiovascular risk factors. Without these interventions, there would not be a spontaneous improvement in hematologic parameters and 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. At baseline, 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 ($\times 10^9$/L)±SD	12±3	–
Mean platelet count ($\times 10^9$/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

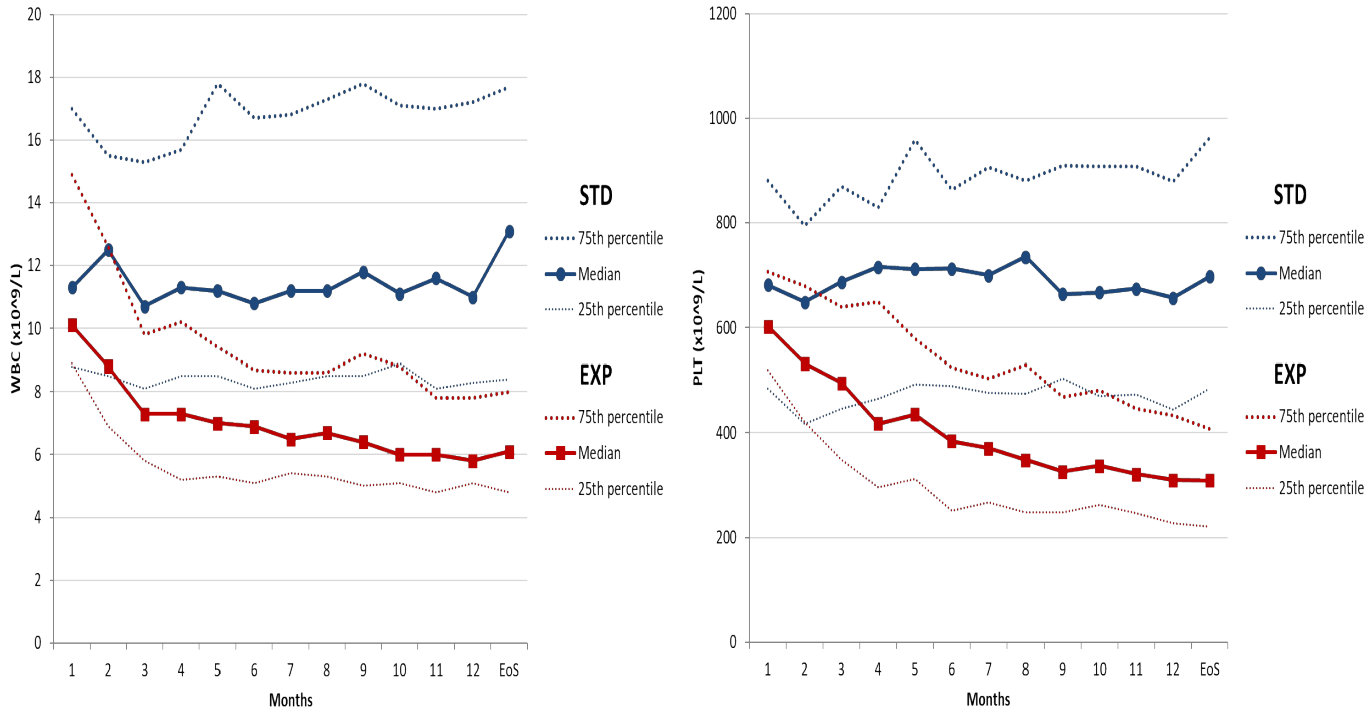
Source: *Passamonti F. et al. Haematologica 2003*

In summary, untreated PV results in elevation of hematology parameters (WBC, PLT, HCT), thrombosis, cardiovascular events and eventual death. The occurrence of thromboembolic events decreases after treatments are initiated in patients with PV.

The Low-PV study (NCT03003325) is an investigator-initiated, industry-funded, multicenter, open-label, two arm, parallel-group, randomized study (1:1) in which patients received phlebotomy and low dose aspirin (standard group) or ropeginterferon alfa-2b plus phlebotomy plus low dose aspirin (experimental group). Patients in both groups had 300 mL of blood removed with each phlebotomy to maintain HCT values lower than 45%. Patients in the experimental group received ropeginterferon alfa-2b subcutaneously every 2 weeks at a fixed dose of 100 mcg. The primary endpoint was treatment response defined as maintenance of median HCT values of 45% or lower without progressive disease during 12 months. At the second pre-planned interim analysis, a higher response rate in the experimental group was observed: 42/50 (84%) patients in the experimental group vs. 30/50 (60%) in the standard

group (95% CI 7-41%, p=0.0075). Since the trial crossed the threshold for statistical significance, there will be no additional analyses of the primary endpoint as the second pre-planned interim analysis of primary endpoint is the final analyses. Because the standard group did not receive pharmacological intervention, the clinical course is representative of patients with PV 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. The total number of phlebotomies needed in the standard group was 189 (57%) and 140 (43%) in the experimental group. The following figure shows the 25th, 50th (median) and 75th percentiles for WBC and PLT count at various time points in the two study groups. *(Barbui T et al. The Lancet Hematology 2021)*

Figure 4 Low-PV Study: White blood cell and platelet counts over time, by arm



Source: *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.

4. Product Quality

The Office of Pharmaceutical Quality (OPQ), recommends approval of STN [redacted] (b) (4) for BESREMi

manufactured by Pharma Essential Corporation. The data submitted in the response to the CRL are adequate to support the conclusion that the manufacture of BESREMi is well-controlled and leads to a product that is pure and potent.

The OPQ Executive Summary during the initial review cycle (finalized in Panorama on February 26, 2021) 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 Letter issued to the Applicant 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 (Refer to the Facilities memorandum finalized in Panorama on October 29, 2021). 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 and a Voluntary Action Indicated (VAI) classification. Upon review of these findings, OPQ determined the compliance status of the PEC Taichung facility 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. For additional details, refer to the Facilities memorandum finalized in Panorama on October 29, 2021 and the Office of Biotechnology Products (OBP) memorandum finalized in Panorama on October 5, 2021.

Additional product quality issues that were not approvability issues listed on the March 12, 2021 CR Letter were addressed by the Applicant in this resubmission. The response was deemed to be satisfactory by the Office of Pharmaceutical Manufacturing Assessment (OPMA). For additional details, refer to the drug product microbiology technical assessment memorandum finalized in Panorama on October 29, 2021.

5. Nonclinical Pharmacology/Toxicology

The February 2, 2021 nonclinical pharmacology review was performed by Jeffrey Quinn, Ph.D. and Todd Bourcier, Ph.D. There are no new updates to this assessment. The non-clinical reviewers concluded that there are no deficiencies in the nonclinical data that would preclude approval of BLA 761166, and they recommend approval.

6. 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. There are no new updates for clinical pharmacology. Please refer to the initial review dated March 3, 2021 for pertinent details.

7. Clinical Microbiology

From the product quality microbiology and sterility assurance perspectives, there were no concerns for this product. There are no new updates for this review.

8. Division of Medical Error Prevention and Analysis

The Division of Medication Error Prevention and Analysis, Office of Medication Error Prevention and Risk Management (OMEPRM) reviewed the human factors (HF) validation study results and data in the original BLA submission. DMEPA found that the HF validation study demonstrated several failures, close calls, and use difficulties associated with the critical task of setting and administering doses that may result in harm to the patient, leading to a complete response on March 12, 2021. The Applicant submitted a response to the CRL on May 12, 2021 and the resubmission includes the results of the additional requested HF validation study for the revised user interface.

DMEPA's review of the updated results of the HF validation study in the CRL response identified use errors with critical tasks. However, taking into consideration the review of the subjective feedback, root cause analysis, and their independent review of the proposed user interface, they found the residual risks associated with these use errors acceptable. Thus, DMEPA accepted the simulated HF validation study results.

DMEPA's evaluation of the proposed BESREMi medication guide and Instructions for Use received on May 13, 2021 did not identify areas of vulnerability that may lead to medication errors. The revised container label received on October 4, 2021, carton labeling insert received on October 12, 2021, and carton labeling received on October 26, 2021 are acceptable from a medication error perspective.

DMEPA stated that the submitted HF validation study supports that the proposed user interface and has been optimized to the extent possible with residual risks at an acceptable level; however, they state there are limitations to an HF validation study. From DMEPA's postmarketing experience with similar products, they find the proposed pre-filled syringe (PFS), requiring users to adjust the doses less than 500 mcg, poses an inherent risk for dosing errors that can lead to compromised care (e.g., BESREMi end users prescribed doses less than 500 mcg may unintentionally administer the entire contents of the PFS). The review team recommends that the Applicant conduct 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. This will be a reporting requirement but not a post marketing requirement.

DMEPA also recommends requesting that the Applicant explore and develop other designs or presentations post-approval that further facilitate the recommended dosing for BESREMi (e.g., consider the most common dose for patients to maintain hematological stabilization). DMEPA describes that while dosing flexibility is necessary with injectable drug products, applicants should determine the appropriate fill sizes, considering how the presentations are likely to be used. Even when appropriately labeled, single-dose prefilled syringes that contain significantly more drug than is required for a single dose may result in the misuse of the leftover drug product. Nonetheless, DMEPA has found the HF protocol to be adequate and acceptable and did not find any other areas of vulnerability that may lead to medication error and the development of an alternative presentation is only a recommendation that can be conveyed to the Applicant in the postmarketing setting in an advice letter.

Please refer to the reviews by Stephanie De Graw, Ph.D. for additional details dated October 27, 2021 and February 26, 2021.

9. Clinical- Efficacy

Efficacy was previously established and there are no new updates to this assessment. The clinical reviewer and the statistical reviewers were Patricia Oneal M.D. and Lola Luo Ph.D., respectively. Please refer to the original clinical review dated March 12, 2021 and the statistical review dated February 26, 2021 in DARRTs.

Efficacy was based on the intent-to-treat population which included 4 patients who were treated and enrolled in trial but had protocol violations due to not meeting exclusion criteria. Three of these patients had a history of depression and one patient received anagrelide (used off-label for treatment of myeloproliferative disorders but does not have an effect on WBCs or HCT). We included these patients in the assessment of efficacy as the protocol violations would not impact the primary efficacy responder analysis.

Note that the dosing regimen in the PEGINVERA trial is different from the approved dosing regimen in the prescribing information. In stage I of the PEGINVERA trial, the maximum tolerated dose (MTD), defined as highest administered dose without dose-limiting toxicities (DLT) was determined to be 540 mcg. No dose-limiting toxicities (DLT) or any other safety signals were observed for any of the dosing cohorts (dose range 50 to 540 mcg). In stage II, an intra-patient dose escalation began at 150 mcg, or 100 mcg if titrating from HU, or at the highest dose achieved in those patients enrolled during stage I. Titration with BESREMi occurred every two-weeks at doses of 225 mcg, 300 mcg, 400 mcg and 450 mcg with dose escalation stopping when hematological parameters were stabilized. Because of formulation changes, the prescribing information for starting dose, titration amounts, and maximum dose of BESREMi differ slightly from those used in the PEGINVERA trial.

Another potential clinical benefit to patients could be a delay in the time to requiring phlebotomy while consistently maintaining HCT <45%. The Sponsor's phlebotomy analyses for the PEGINVERA study are limited as phlebotomy is not analyzed only when HCT < 45%. In addition, not all patients are evaluable at visits and the reasons for not being evaluable are not provided. (b) (4)

10. Safety

The safety of ropeginterferon alfa-2b-njft was evaluated and discussed in the original clinical review and CDTL reviews both dated March 12, 2021. The PEGINVERA study serves as the primary source of the safety data. All patients in the PEGINVERA study received ropeginterferon alfa-2b-njft and were followed for up to 90 months. The supportive safety population consisted of the pooled safety data from the patients who received ropeginterferon alfa-2b-njft and included the PROUD-PV/CONTINUATION-PV studies. The pooled safety database including the PEGINVERA study involves 178 patients.

The original application included safety data for the pooled PROUD/CONTINUATION-PV data for 24-months which consisted of the first 12 months of the PROUD-PV and 24 months of the CONTINUATION-PV study for a total of 3 years for these two studies. The new safety data consists of 60 months of safety data from the CONTINUATION study from November 8, 2018 through May 29, 2020. There were no new individual datasets from the PEGINVERA (closed January 25, 2018) or the PROUD-V study (database lock January 23, 2017) in the CRL response.

There is no evidence of a substantial change in the incidence of common, but less serious adverse events between the original safety data and updated safety data submitted. Common adverse reactions (>40%) reported in the PEGINVERA study included influenza-like illness, arthralgia, fatigue, pruritis, nasopharyngitis and musculoskeletal pain. All these risks can be adequately mitigated through labeling and further evaluated during routine pharmacovigilance. Table 4 describes the common adverse reactions > 10% in the PEGINVERA study. In the prescribing information, adverse reactions are presented by preferred term with removal of the SOC. Preferred terms that represent similar clinical concepts are presented as grouped terms.

Table 2: PEGINVERA: Common Adverse Events by System Organ Class and Preferred Terms >10%.

Adverse Reactions SOC/Preferred Terms	Ropeginterferon alfa-2b N=51 n (%)
Infection and Infestations	
Nasopharyngitis, pharyngitis	22 (43%)
*URI, cold, rhinitis upper resp tract infection, bronchitis	14 (27%)

Adverse Reactions SOC/Preferred Terms	Ropeginterferon alfa-2b N=51 n (%)
UTI	8 (16%)
General Disorders and Administration Site Conditions	
*Fatigue, asthenia, malaise	24 (47%)
Pyrexia	12 (24%)
*Influenza like illness, pyrexia, chills	30 (59%)
Local administration reactions	13 (26%)
Chest pain (non-cardiac or unknown)	6 (12%)
*Peripheral edema, general edema	8 (16%)
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	24 (47%)
*Musculoskeletal pain, back pain, pain in extremity, bone pain, flank pain, spinal pain	21 (41%)
Muscle spasms	8 (16%)
Myalgia	10 (20%)
Gastrointestinal Disorders	
Diarrhea	17 (33%)
Nausea	14 (28%)
*Abdominal pain, abdominal pain upper, lower	10 (20%)
Dyspepsia	6 (12%)
Nervous System Disorders	
*Headache, migraine, head pain	20 (39%)
Dizziness	11 (22%)
Vertigo	6 (12%)
Blood and Lymphatic Disorders	
Leukopenia	9 (18%)
Thrombocytopenia	6 (18%)
Neutropenia	8 (16%)
Skin and Subcutaneous Disorders	
Pruritus	23 (45%)
*Rash, maculopapular rash, pruritic rash	8 (16%)
*Night sweats/hyperhidrosis	15 (29%)
Erythema	11 (22%)
Alopecia	8 (16%)
Eye Disorders	
Eye other	11 (23%)
Psychiatric Disorders	
*Insomnia, sleep disturbance, abnormal dreams	10 (20%)
Depression, depressed mood,	10 (20%)

Adverse Reactions SOC/Preferred Terms	Ropeginterferon alfa-2b N=51 n (%)
Endocrine Disorders	
*Hyper/hypo thyroid, thyroiditis, goiter	9 (18%)
Metabolism and Nutrition Disorders	
Decreased appetite	9 (18%)
Investigations	
*AST, ALT, GGT, Hepatic Enzyme, Transaminases	8 (16%)
Ear and Labyrinth Disorders	
Vertigo	6 (12%)
Cardiac Disorders	
Arrhythmia	8 (16%)
Vascular Disorders	
Systemic hypertension	8 (16%)

** Includes terms that represent similar clinical concepts*
Source: FDA reviewer analysis
Abbreviations: N, number of subjects, n number of subjects with adverse event

There were 65 serious adverse events reported for 38/51 (54.9%) in the PEGINVERA study. The most common serious adverse reactions in ≥ 4% included depression (4%), urinary tract infection (8%), transient ischemic attack (6%), glioblastoma multiforme (4%), chest injury (4%) and depression (4%). The chest injury and occurrences of GBMs are likely not treatment related and will not be included in the prescribing information. Adverse reactions requiring permanent discontinuation in > 2% of the patients included depression (8%), arthralgia (4%), fatigue (4%), and general physical health deterioration (4%).

Overall, no new significant safety findings arose from the additional two years of follow-up of safety data in the CONTINUATION-PV study in the pooled analysis. There were no new deaths. The occurrence of the rate of atrial fibrillation and atrial flutter [11 (6.1%)] remained stable with no new events. There were three new endocrine events observed (hyperthyroidism, hypothyroidism, and autoimmune thyroiditis) with the additional 5 year safety follow-up for a total of 10.7% of endocrine disorders compared to 9% with 3 years of safety follow-up. The frequency of leukopenia, thrombocytopenia, anemia, and neutropenia remained unchanged. There were no new cases of depression, acute stress disorder or suicide and no new vascular events with the additional safety data.

In general, the safety profile of ropeginterferon alfa-2b is acceptable in a population with this rare life-threatening disease with a significant unmet medical need. The risks of ropeginterferon alfa-2b-njft can be mitigated with appropriate labeling to include a box warning for neuropsychiatric, autoimmune, ischemic and infectious disorders, which is consistent with the labeling of other interferon products for other diseases.

10.1.1. Pediatrics and Assessment of Effects on Growth

There was no pediatric data submitted with this application.

10.2. Advisory Committee Meeting and Other External Consultations

Neither an Advisory Committee Meeting nor an 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 that required external discussion.

11. Labeling Recommendations

11.1.1. 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	Ropeginterferon alfa-2b is an interferon alfa-2b analog indicated for the treatment of PV in adults. Revised indication to all patients with PV as patients with splenomegaly were included in the study and there were no exclusion criteria for patients with symptomatic splenomegaly. The main concern is a delay in improvement in symptomatic splenomegaly (e.g., pain) in patients with an enlarged spleen who are being titrated on BESREMi and have not reached their optimal dose. Providers understand the disease and can manage with phlebotomy during the titration phase if clinically indicated. We have added language about this to the labeling.
Dosage and Administration	The recommended starting dose for single-agent therapy is 100 mcg by subcutaneous	The recommended starting dosage for patients not already on hydroxyurea is

	injection every two weeks. Titrate dose up by 50 mcg every 2 weeks until hematological parameters are stabilized. (b) (4) [redacted]	100 mcg by subcutaneous injection every two weeks. Gradually increase the dose by 50 mcg every two weeks (to a maximum dose of 500 mcg) until the hematological parameters are stabilized (HCT <45%, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L). When transitioning to ropeginterferon-alfa-2b-njft from hydroxyurea start ropeginterferon alfa-2b at 50mcg by subcutaneous injection every two weeks in combination with hydroxyurea. Gradually taper off the hydroxyurea and increase the dose of ropeginterferon alfa-2b njft by 50mcg every two weeks (up to a maximum dose of 500mcg) while gradually decreasing the hydroxyurea dose, until the hematological parameters are stabilized (HCT <45%, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L).
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. Revised box warning.
Clinical Trials Experience	The safety evaluation was based on (b) (4) [redacted]	The Warnings and Precautions (section 5) is based on the pooled safety population (n=178) as this represents a larger safety database for detecting rarer, but serious adverse reactions. Section 6 describes the adverse reactions for the

		PEGINVERA study which is the main basis for efficacy and captures safety risks with longer term use of the product.
Clinical Studies	Efficacy results were based on (b) (4)	The efficacy of ropeginterferon alfa-2b is based on the overall Complete Hematologic Response (CHR) (hematocrit <45% without phlebotomy (at least 2 months from last phlebotomy), platelets ≤ 400 x 10^9/L and leukocytes ≤ 10 x 10^9/L, normal spleen size (longitudinal diameter ≤ 12cm for females and ≤ 13cm for males) and absence of thromboembolic events. from the PEGINVERA trial. Included CHR with exclusion of normal spleen size and thrombosis in label.

12. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary for this application. No safety issues were identified that would require a REMS. This approach to risk mitigation is consistent with that used for other approved interferon products for other diseases.

13. Postmarketing Requirements and Commitments

PMR 1: Complete Study EUPAS29462 "A Prospective, Multicenter, Non-interventional, Observational, Post-authorization Safety Study of Ropeginterferon alfa-2b in Polycythemia Vera Patients" to evaluate safety and tolerability during the titration and maintenance phase of BESREMi administration in patients with Polycythemia Vera. Specific safety outcomes of interest include hepatotoxicity, cardiovascular and thromboembolic events in treated patients.

PMR Schedule Milestones

Interim Report:	03/2022
Study/Trial Completion:	06/2023
Final Report Submission:	09/2023

14. Appendices

14.1. References

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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/

TANYA M WROBLEWSKI
11/12/2021 01:38:24 PM

ANN T FARRELL
11/12/2021 01:56:36 PM

HYLTON V JOFFE
11/12/2021 03:51:28 PM
I concur with approval. This memorandum serves as the decisional memorandum on the application.

Office of Drug Evaluation-I: Decisional Memorandum

Date	March 12, 2021
From	Ellis F. Unger, MD Director Office of Cardiology, Hematology, Endocrinology, and Nephrology Office of New Drugs Center for Drug Evaluation and Research
Subject	Office Director Decisional Memo
New Drug Application (BLA) #	761166
Applicant Name	PharmaEssentia US
Date of Submission	March 13, 2020
PDUFA Goal Date	March 13, 2021
Proprietary Name/ Established (USAN) Name	Besremi Ropeginterferon alfa-2b
Dosage Forms/ Strengths	(b) (4)
Final Indication	For the treatment of adults with polycythemia vera without symptomatic splenomegaly
Action:	*Complete Response*

Material Reviewed/Consulted - Action Package, including:	
Project Manager	Carleveva Thompson
Clinical Reviewer	Patricia Oneal
Clinical Pharmacology/Pharmacometrics	Li Wang; Eliford Kitabi; Justin Earp; Sudharshan Hariharan
Office of Biostatistics	Lola Luo; Yeh-Fong Chen; Thomas Gwise
Pharmacology Toxicology	Jeffrey A Quinn; Todd Bourcier
Office of Biotechnology Products	Phillip Angart, Patrick Lynch
Office of Pharmaceutical Quality	Vicky Borders-Hemphill, Phillip Angart, Richard Ledwidge, Peter Qiu, Patrick Lynch
Office of Scientific Investigations	Kassa Ayalew
Pharmacometrics	Eliford Kitabi, Justin Earp
Human Factors	Stephanie DeGraw; Hinta Mehta; Colleen Little; Lolita White; Alice Tu
Office of Prescription Drug Promotion	Rebecca Falter
Division of Medication Error Prevention and Analysis	Stephanie DeGraw; Hinta Mehta; Colleen Little; Lolita White; Alice Tu
Division of Risk Management	Till Olickal; Naomi Boston
Associate Director for Labeling	Virginia Kwitkowski
Patient Labeling	Sharon R. Mills; LaShawn Griffiths; Barbara Fuller
Cross-Discipline Team Leader	Tanya Wroblewski
Director, Division of Non-malignant Hematology	Ann Farrell

1. Background

The applicant is seeking marketing approval of ropeginterferon alfa-2b: "for the treatment of polycythemia vera in adults without symptomatic splenomegaly." Ropeginterferon alfa-2b is a new molecular entity that has not been approved in the US. The drug received marketing authorization from the European Medicines Agency on February 15, 2019 "as monotherapy in adults for the treatment of PV without symptomatic splenomegaly" (independent of previous hydroxyurea exposure).

The application has been carefully considered by the review team. All review disciplines are recommending approval, with two exceptions:

- Final recommendations by the Office of Pharmaceutical Quality are pending final determinations of the compliance status of two manufacturing and testing facilities, to ensure that these facilities conduct manufacturing operations in compliance with CGMP. 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 recommends a Complete Response action because of deficiencies in human factors validation.

I agree with the assessments and conclusions of all review disciplines; therefore, the BLA will receive a Complete Response action, consistent with the human factors deficiency. Had there been no approval issues other than the facilities inspections, we would have delayed our action (beyond the PDUFA goal date) until the inspections were satisfactorily completed.

Polycythemia Vera

Polycythemia vera (PV) belongs to the group of Philadelphia chromosome–negative myeloproliferative neoplasms, characterized by clonal proliferation of transformed hematopoietic progenitor cells with variable maturity. The overwhelming majority of patients with PV have a gain of function mutation in the tyrosine kinase Janus-activated kinase-2 (JAK2V617F) (~97% of patients), although other mutations have been described as well (~3% of patients have a mutation in exon 12). These JAK2 mutations cause the enzyme to be constitutively active, leading to an "always on" signal for cell propagation, with overproduction of cell lines that express erythropoietin receptors. Clinical manifestations of PV include pruritus, particularly following a warm bath or shower, erythromelalgia (burning pain in the feet or hands), and splenomegaly. Common laboratory manifestations of the disease include erythrocytosis, leukocytosis, thrombocytosis, elevated serum lactate dehydrogenase (LDH), and low serum erythropoietin levels. Patients typically present on the basis of an abnormal CBC, or reach medical attention because of symptoms or following a thrombotic or thromboembolic event.

Polycythemia vera is a long-term debilitating and life-threatening condition, causing thrombosis, hemorrhage, significant symptoms, and in the long-term, the possibility of developing myelofibrosis and secondary acute myeloid leukemia. Arterial and venous thrombotic events are the major contributor to morbidity in patients with PV; estimates of the annual incidence of thrombosis range from 1.8% in patients <40 years of age to 5.1% in those above 70 years. The disease is not known to remit spontaneously.

Current Treatments

Patients are classified as low- and high-risk. Low-risk patients (age ≤ 60 years and no history of thrombosis) are managed with therapeutic phlebotomy (which is the mainstay of therapy; leads to iron deficiency), low-dose aspirin to prevent thrombotic events, and management of cardiovascular risk factors. Patients with low-risk PV generally do not receive cytoreductive therapy, because the absolute risk reduction afforded by these agents does not justify their toxicities. In contrast, cytoreductive agents are recommended for high-risk patients with PV (age > 60 or history of thrombotic event); in these patients, the absolute risk reduction is higher, which justifies the risk.

Cytoreductive treatment is recommended for low-risk patients in selected circumstances, generally when there is progressive leukocytosis, thrombocytosis, splenomegaly, poor tolerability of phlebotomies, or poorly controlled symptoms, even though there are no prospective clinical trials to support these recommendations. Several approved cytoreductive drugs are used on- and off-label for the treatment of PV.

Hydroxyurea (HU) has been widely adopted for initial pharmacologic treatment of PV despite limited evidence of effectiveness and lack of approval for this indication. Most data supporting use of HU have been obtained from randomized controlled trials in essential thrombocythemia. Notable adverse reactions include myelosuppression/immunosuppression, malignancies, e.g., skin cancer, embryo-fetal toxicity, and cutaneous vasculitis. Approximately 10% of patients develop HU resistance.

Ruxolitinib is a Janus kinase inhibitor—the only drug approved for the treatment of PV. Because of its toxicity, however, it is approved for treatment of PV in HU-resistant or HU-intolerant patients. Important adverse reactions limit its use and include cytopenias, immunosuppression with serious opportunistic viral, bacterial, mycobacterial, and fungal infections (e.g., tuberculosis, herpes zoster, hepatitis B, and progressive multifocal leukoencephalopathy [PML]), non-melanoma skin cancer, diarrhea, dyspnea, and fatigue. Sudden withdrawal of ruxolitinib can cause relapses and/or findings suggestive of systemic inflammatory response syndrome (SIRS, e.g., fever, hypotension, hypoxia) that may require resumption of ruxolitinib and other management.

Interferons

Interferons (IFNs) are cytokines capable of exerting multiple biologic effects through the expression of over 30 genes encoding proteins with antiviral, antiproliferative and immunomodulatory functions. First described 60 years ago as potent antiviral agents, their specific immunomodulatory activities are dependent upon the type of interferon and the particular biological system. Several pegylated interferon drugs have been approved in the U.S. for different indications, including treatment of chronic hepatitis C and treatment of relapsing forms of multiple sclerosis.

Interferon-α belongs to the class of type I interferons that exhibits their cellular effects by binding to a transmembrane interferon alfa receptor. When bound to its receptor, IFN-α 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-α may have direct effects on hematopoietic stem cell proliferation and differentiation; however, its precise mechanism of action has not been fully elucidated.

Pegylated IFN-α is recommended as an alternative for HU for the treatment of PV, based on nonrandomized long-term studies, and such use is also off-label. Generally, IFN is less well tolerated than HU, with many patients discontinuing because of side effects such as fever, malaise, nausea, and vomiting. A number of studies have shown that Interferon-α can decrease hematocrit (HCT), platelet count (PLTs), and total leukocyte count (WBCs), thus reducing the need for phlebotomy. More recent studies suggest that long-term treatment with interferon-α can lead to molecular responses as well.

In summary, although HU and IFNs are widely used in the treatment of PV, the only drug approved for the treatment of PV is ruxolitinib, and it is approved only for PV that is resistant to HU, itself an unapproved drug for the PV indication.

Ropeginterferon alfa-2b

The original non-pegylated preparations of IFN-α had short half-lives, limiting their use. Pegylated interferons provided an advance, in that they prolonged half-life, allowing weekly administration. Ropeginterferon alfa-2b is a long-acting recombinant interferon α-2b analog conjugated to a two-arm branched methoxypolyethylene glycol (mPEG) moiety attached at the N-terminal proline residue. This structure further prolongs the functional half-life of the molecule, permitting less frequent administration.

The drug substance is produced by recombinant DNA technology in cultures of *Escherichia coli* cells (b) (4) The final drug product is formulated as a colorless solution for injection, provided in a pre-filled syringe.

2. Nonclinical Pharmacology/Toxicology

The Division of Pharmacology and Toxicology, OCHEN, found no deficiencies in the nonclinical data that would preclude approval. Refer the review by Drs. Jeffrey Quinn and Todd Bourcier for details.

3. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the BLA to support approval. See the review by Drs. Li Wang, Eliford Kitabi, Justin Earp, and Sudharshan Hariharan (final signatory Dr. Doanh Tran) for details.

4. Clinical Microbiology

Refer to Cross-Discipline Team Leader Review. There are no outstanding issues.

5. Clinical/Statistical – Efficacy

Refer to Cross-Discipline Team Leader Review for details, and see below.

6. Safety

Refer to Cross-Discipline Team Leader Review for information.

7. Regulatory Basis for Approval

One Adequate and Well-controlled Trial Plus Confirmatory Evidence

FDA has issued a pair of critical guidance documents on demonstrating substantial evidence of effectiveness: the 1998 Guidance "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" and the 2019 Draft Guidance "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biologic Products." One of the scenarios described for meeting the substantial evidence standard is one adequate and well-controlled (AWC) trial plus confirmatory evidence, as described in section 115(a) of FDAMA, which amended the 21 U.S.C. § 355(d), to state:

> "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence."

In this setting, the confirmatory evidence provides substantiation of the results of the single AWC trial, and such evidence is stronger if it is independent. Confirmatory evidence can arise from one or more sources, including clinical data sources and translational animal research.

When considering the feasibility of establishing substantial evidence of effectiveness based on a single AWC trial plus confirmatory evidence, the 2019 Draft Guidance cites the seriousness of a disease, the size of the patient population, and the presence of unmet need as factors for consideration. With respect to PV, the disease is unquestionably serious, causing thrombotic events and premature death, and rare, with a prevalence of ~50/100,000, i.e., fewer than 200,000 individuals in the US are thought to have the disease.

As noted above, several approved drugs are used off-label for the treatment of PV; only one drug, ruxolitinib, is approved. Hydroxyurea (HU) has been widely adopted for initial pharmacologic treatment of PV despite limited evidence of effectiveness and lack of approval for this indication. Most of the data supporting HU for the treatment of PV have been obtained from randomized controlled trials in essential thrombocythemia. Notable adverse reactions include myelosuppression/immunosuppression, malignancies, e.g., skin cancer, embryo-fetal toxicity, and cutaneous vasculitis. Approximately 10% of patients develop HU resistance.

Pegylated interferon (IFN) is an alternative to HU for the treatment of PV, based on nonrandomized long-term studies. Its use is also off-label. Generally, IFN is less well tolerated than HU, with many patients discontinuing because of side effects such as fever, malaise, nausea, and vomiting.

Ruxolitinib is a Janus kinase inhibitor—the only drug approved for the treatment of PV. Because of its toxicity, however, it is approved for use only in HU-resistant or HU-intolerant patients. Important adverse reactions limit its use and include cytopenias, immunosuppression with serious opportunistic viral, bacterial, mycobacterial, and fungal infections (e.g., tuberculosis, herpes zoster, hepatitis B, and progressive multifocal leukoencephalopathy [PML]), non-melanoma skin cancer, diarrhea, dyspnea, and fatigue. Sudden withdrawal of ruxolitinib can cause relapses and/or findings suggestive of systemic inflammatory response syndrome (SIRS, e.g., fever, hypotension, hypoxia) that may require resumption of ruxolitinib and other management.

In summary, although HU and IFNs are widely used in the treatment of PV, they are unapproved for this indication. Ruxolitinib is approved for PV that is resistant to HU, and for patients who cannot tolerate HU. No drugs are approved for PV that is responsive to HU.

Thus, based on the severity of the disease, its rarity, and the unmet need for effective treatments, the application warrants flexibility in the amount and type of evidence needed to meet the substantial evidence standard, and approval based on a single AWC trial plus confirmatory evidence is appropriate.

Nature of Confirmatory Evidence for PV

A pharmacodynamic (PD) biomarker that demonstrates salient biological effects can provide confirmatory evidence to support a single AWC study. Generally, PD biomarkers do not provide evidence of effectiveness, but are aimed at supporting a drug's mechanism of action and aiding in dose selection. For PV, however, the principal disease manifestations (e.g., thrombosis, pruritis) are thought to be directly caused by elevated biomarkers (hemoglobin, platelet count, WBC count), parameters that can be accurately and reliably assessed. (Spleen size is also used, though its assessment is less straightforward than the hematologic parameters.) For example, the approval of ruxolitinib for patients with PV who are refractory to hydroxyurea was based on control of HCT and spleen volume reduction, both PD biomarkers. Thus, for PV, the use of reliable, quantitative data on hemoglobin, platelet count, and WBC count, all directly relevant to the pathophysiology and clinical manifestations of the disease, are deemed appropriate to provide confirmatory evidence.

A Single Adequate and Well-controlled Trial

PROUD-PV
The applicant's intent was to submit PROUD-PV as an AWC trial to provide substantial evidence of effectiveness. This study was designed with a "high bar," however, in that its aim was to demonstrate superiority of ropeginterferon alfa-2b over HU for the treatment of PV. As noted above, although HU is not approved for this indication, it is generally considered to be effective and widely prescribed by the hematology community. As explained in the various reviews, it is not possible to consider PROUD-PV as an AWC study. The analytical plan was changed from a superiority analysis to a non-inferiority analysis, without agreement of the Agency. The change was made prior to database lock; however, because PROUD-PV was an open-label study, there are concerns that knowledge obtained from the study could have biased the investigation by influencing the change in the 1° endpoint. And even with this change, the study did not demonstrate non-inferiority. Nevertheless, the study does provide significant data on hematologic parameters and change in JAK2 allelic burden (discussed later).

PEGINVERA
PEGINVERA was an open-label, single-arm, dose-escalation study designed to assess the tolerability and safety of escalating doses of ropeginterferon alfa-2b. The study enrolled 51 patients at 6 sites in Austria. No formal hypothesis testing was planned.

Stage 1 (n = 25) was designed to determine the maximally tolerated ropeginterferon alfa-2b dose, which was detremined to be 540 µg, the highest dose tested.

In Stage 2 (n=26), patients were initially followed every 2 weeks, with less frequent follow-up (every 3 to 4 weeks) after one year. Ropeginterferon alfa-2b doses were escalated from 100 to 450 µg, as tolerated. For patients on HU, the HU dose was reduced in increments of 20-40%, depending on blood counts, and full discontinuation was to occur by Week 12.

The study enrolled adult patients with a PV diagnosis confirmed according to the World Health Organization criteria 2008 or the PVSG criteria plus JAK2 mutation positivity. Patients were newly diagnosed or pre-treated with HU. Prior use of other cytoreductive therapies was not permitted.

Patients were phlebotomized until HCT levels reached $\leq$ 45% prior to the first administration of ropeginterferon alfa-2b. Phlebotomy was allowed as a rescue therapy when the HCT exceeded 45%.

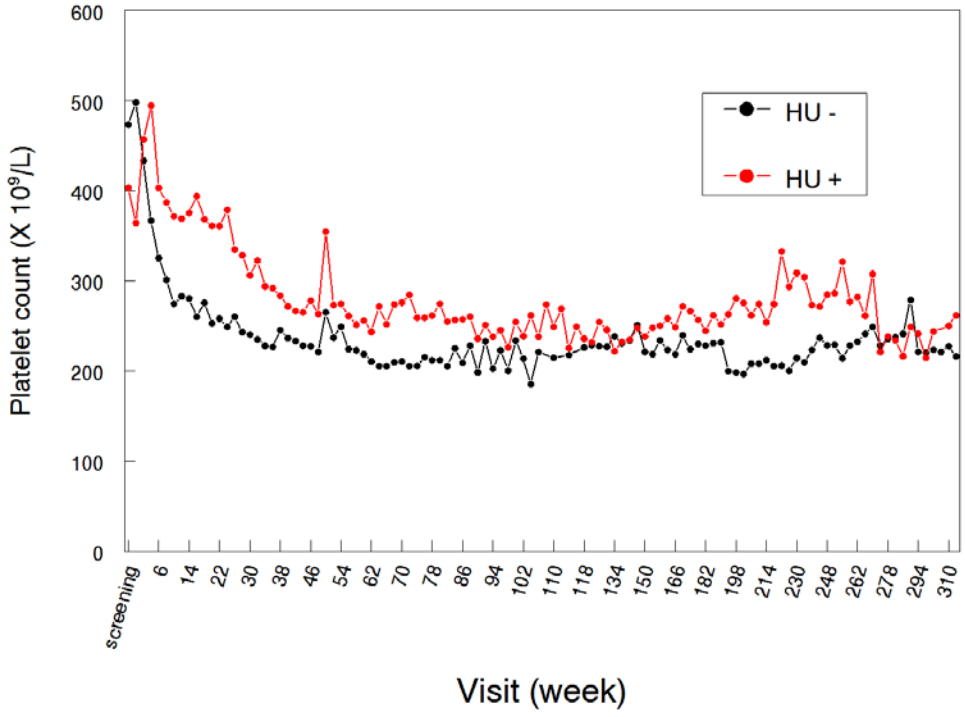
The 1° endpoint for Stage 1 of the study was the determination of the maximum tolerated dose. The 1° efficacy endpoint for Stage 2 was complete hematological response, defined as HCT < 45% without phlebotomy in the previous 2 months, platelet count $\leq$ 400 x 10^9/L, WBC count $\leq$ 10 x 10^9/L, and normal spleen size. Other endpoints included partial hematological response, molecular response, spleen size, and number of phlebotomies. For patients using concomitant HU, responsiveness could not be determined until 2 weeks after the last HU dose.

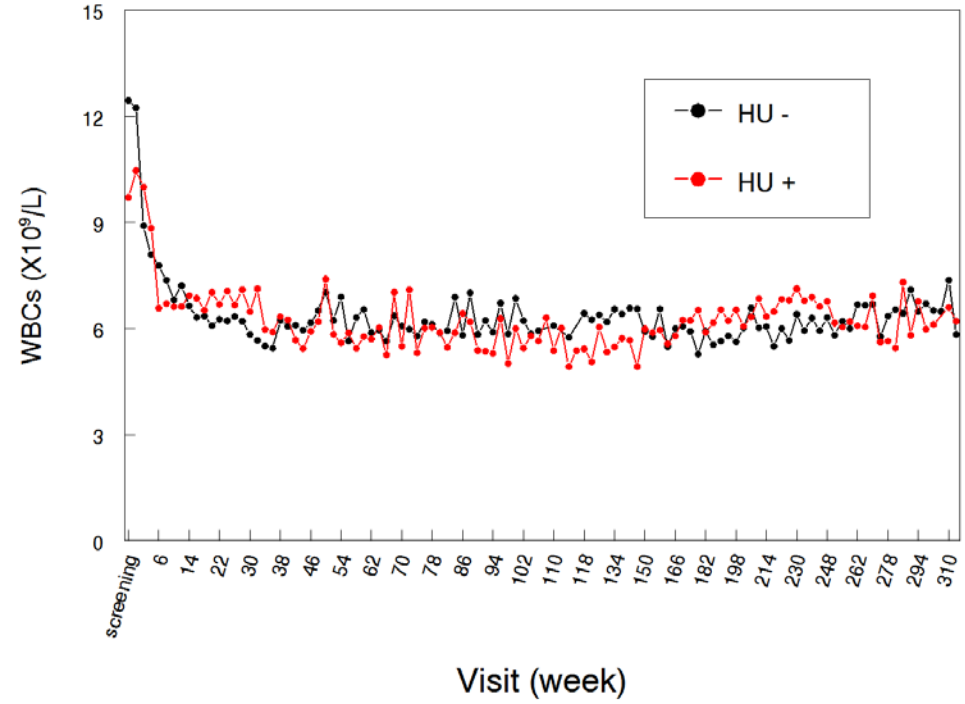
With 51 enrolled patients, the median study duration was 5.1 years. Mean age was 59 years, 61% of patients were male, and 98% were Caucasian. Sixteen percent of patients were newly diagnosed; 84% had prior disease. At baseline, mean HCT, PLTs, and WBCs were 45.1%, 458 x 10^9/L, and 11.8 x 10^9/L, respectively. All patients were JAK 2 allelic-positive at baseline.

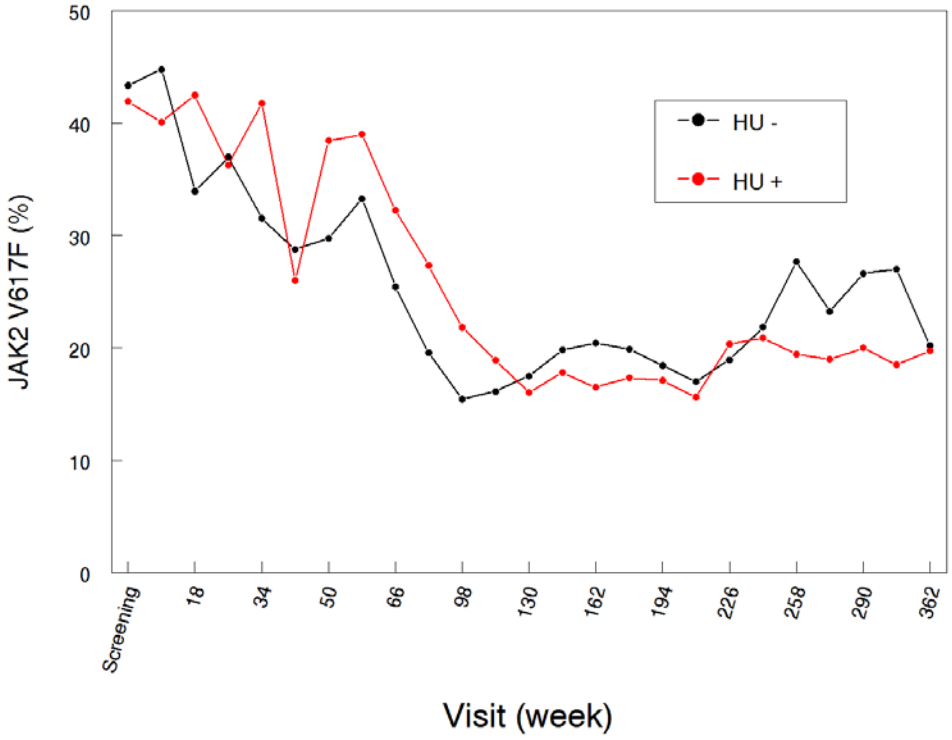
The overall rate of complete hematological response was 60.8%, with a median duration of response of 14.3 months. For patients who had been receiving HU, the response rate was 84.6%. A JAK 2 molecular response was observed in 29% of patients. Response rates were similar across the 6 study centers.

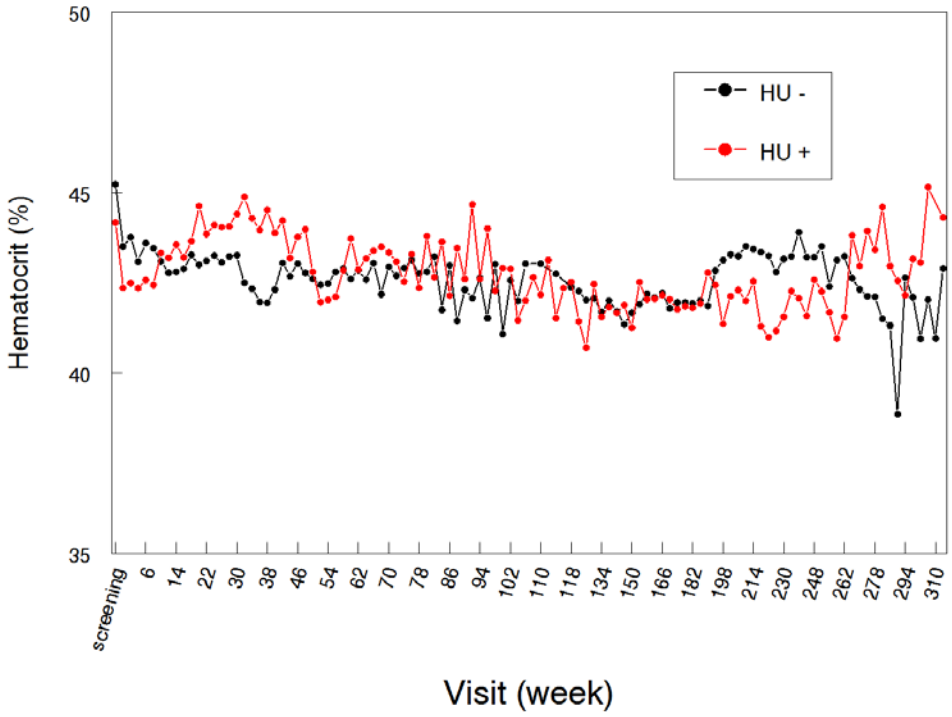
The following figures show mean values for PLTs, WBCs, JAK2 V617F, and HCT throughout the study. Patients who were taking HU prior to the study are shown by the red markers; those who were HU-naïve are shown by the black markers. In HU-naïve subjects, there is a striking decrease in PLTs and WBCs once ropeginterferon alfa-2b is initiated (first two figures). For patients previously on HU, the screening values trend slightly lower, and the decrease in platelet count is more gradual, presumably because HU is being withdrawn as the ropeginterferon alfa-2b dose is increased. The decrease in JAK2 V617F is evident in patients who were previously on HU and those who were HU-naïve (third figure). Changes in HCT are difficult to interpret, because therapeutic phlebotomy was used when HCT exceeded 45%.

Of note, discontinuation of ropeginterferon alfa-2b led to mean increases of 17% and 22% in WBCs and PLTs, respectively (data not shown).


Platelet count (X 10⁹/L)
600
500
400
300
200
100
0
HU -
HU +
screening
6
14
22
30
38
46
54
62
70
78
86
94
102
110
118
134
150
166
182
198
214
230
248
262
278
294
310
Visit (week)


WBCs (X10⁹/L)
15
12
9
6
3
0
HU -
HU +
screening
6
14
22
30
38
46
54
62
70
78
86
94
102
110
118
134
150
166
182
198
214
230
248
262
278
294
310
Visit (week)


JAK2 V617F (%)
50
40
30
20
10
0
HU -
HU +
Screening
18
34
50
66
98
130
162
194
226
258
290
362
Visit (week)


Hematocrit (%)
50
45
40
35
HU -
HU +
screening
6
14
22
30
38
46
54
62
70
78
86
94
102
110
118
134
150
166
182
198
214
230
248
262
278
294
310
Visit (week)

FDA regulations at 21 CFR 314.126 state that characteristics of an AWC study include "…a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results. In addition, the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used."

The PEGINERVA study objectives and planned methods of analysis were clearly described in the study protocol and the clinical study report. Although PEGINVERA lacked a parallel control group, the study was otherwise well planned, executed, and conducted, and demonstrated clinically meaningful decreases in PLTs, WBCs, and JAK2 V617F. Importantly, the counts increased when ropeginterferon alfa-2b was discontinued.

In discussing acceptable types of control groups, regulations at 21 CFR 314.126 state that a historical control may be appropriate for AWC studies under special circumstances, e.g., for diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident; "The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations." Because the striking decreases in WBCs and PLTs are extremely unlikely to have occurred spontaneously or by chance, because these hematological abnormalities constitute the pathophysiological underpinnings of the disease, and because these parameters can be measured with great precision, the review team believes that comparison of these patients to an external control group is valid. Thus, PEGINVERA can be considered an AWC study when its treatment group is compared to a historical control.

Natural History of Untreated PV

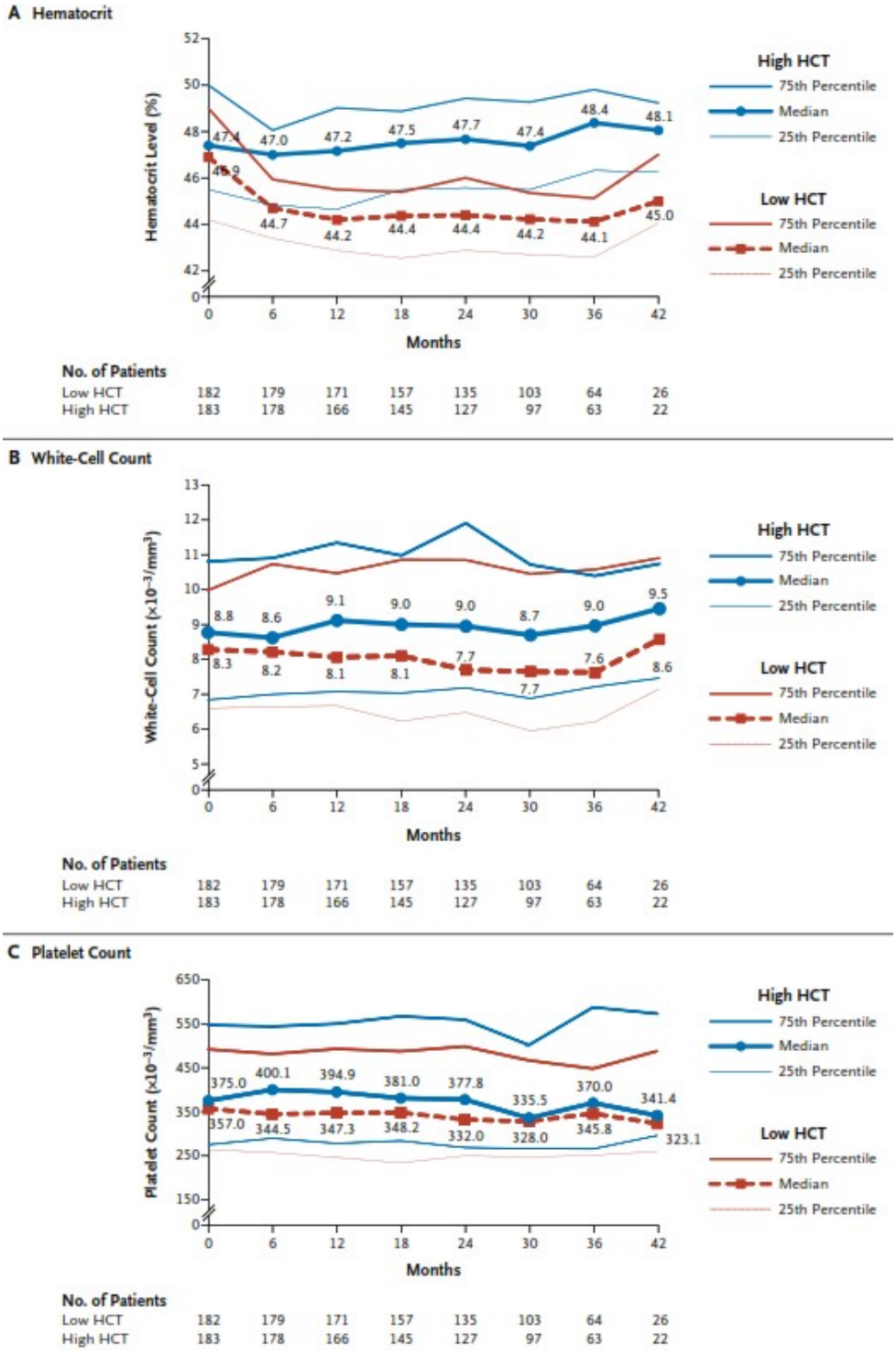
PV does not remit spontaneously.

The CYTO-PV Study, a multicenter, randomized trial conducted in Italy, compared the efficacy of conventional treatment (phlebotomy, HU [~50% of patients], or both) aimed at maintaining a HCT of < 45%, to a strategy designed to maintain HCT between 45 and 50%, with respect to the prevention of thrombotic events in patients with PV.[1] Three hundred sixty-five patients with a confirmed JAK2 V617F or exon 12 mutation were randomly assigned to two treatment strategies: a HCT of < 45% was targeted in the "low-hematocrit" group and a HCT of 45 to 50% was targeted in the "high hematocrit" group. The 1° composite endpoint was the time until cardiovascular death or a major thrombotic event. After a median follow-up of 31 months, a 1° endpoint event occurred in 5/182 patients in the low-hematocrit group (2.7%) and 18/183 patients in the high-hematocrit group (9.8%) (hazard ratio 3.91; 95% confidence interval [CI], 1.45 to 10.53; P=0.007).

Importantly with respect to this discussion, although HCT was shown to decrease and stay within the protocol-directed ranges for both treatment groups, WBCs and PLTs remained elevated throughout the study (see figure; panels B and C). The high hematocrit group, receiving less intensive phlebotomy, is reflective of disease sequalae when minimal intervention is provided over the course of disease. Note

[1] Marchioli R, et al. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med* 2013;368:22-33.

that WBCs (middle panel, B) remained in the 10 to 11 X 10^9/L range and PLTs (lower panel, C) remained in the 400 to 500 X 10^9/L range throughout the study.



Low-PV Study

Results of the Low-PV Study (NCT03003325) were only recently published online in *Lancet Heamatology*.[2] The study was not conducted under IND and the data have not been submitted to FDA. This was an investigator-initiated, industry-funded, randomized, open-label trial to examine the efficacy and safety of ropeginterferon alfa-2b, added to standard phlebotomy, vs. standard phlebotomy alone. The study was conducted at 21 sites in Italy and enrolled adult subjects with PV based on 2008–16 WHO criteria. All subjects had a JAK2*V617F or exon 12 mutation, HCT < 45%, and need for phlebotomy. All met the definition of low-risk PV (< 60 years of age and no history of thrombotic event).

Subjects were randomized 1:1 to receive either low-dose aspirin with phlebotomy (300 mL) to maintain HCT < 45% (standard group) or to receive ropeginterferon alfa-2b, 100 µg every other week, in addition to the above conventional therapy. The 1° endpoint was treatment response, defined as maintenance of median HCT values < 45% without disease progression; there were multiple 2° endpoints.

The study enrolled 127 subjects, but accrual stopped at the second planned interim analysis when the stopping rule was met for efficacy, demonstrating superiority of ropeginterferon alfa-2b. One hundred subjects were included in the second interim analysis (50 in both groups), as directed by the statistical analytical plan.

The composite 1° endpoint, treatment response, occurred in 42 of 50 subjects (84%) in the ropeginterferon alfa-2b group and 30 of 50 subjects (60%) in the control group. The authors analyzed the 1° endpoint using a logistic regression model, and estimated the treatment effect as an odds ratio with 95% CIs based on maximum likelihood. The publication states that the odds ratio is 3.5, 95% CI 1.3, 10.4; p=0.0075. A simple test of proportions yields a relative risk (RR) of 1.4, 95% CI 1.08, 1.81, which would also be nominally statistically significant.

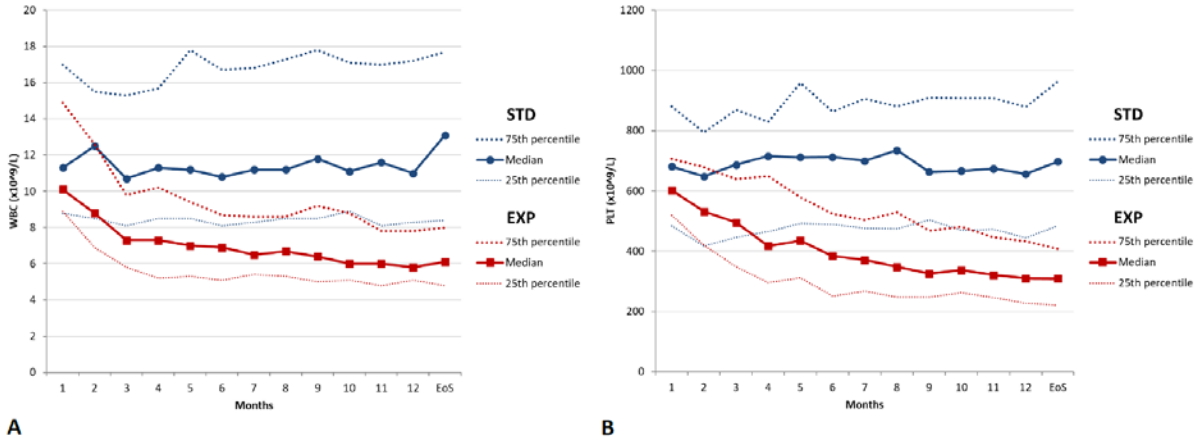
Not surprisingly, most of this difference was driven by maintenance of median HCT values < 45% (66% in the control group and 84% in the ropeginterferon alfa-2b group). Disease progression was reported in only 4 of 50 subjects (8%) in the control group and in no subjects in the ropeginterferon alfa-2b group.

Secondary endpoints included the need for phlebotomy; mean numbers of phlebotomies per patient were 2.8 per and 3.8 in the ropeginterferon alfa-2b and control groups, respectively. Eight of 50 subjects (16%) in the ropeginterferon alfa-2b group remained phlebotomy-free throughout the 12-month period, vs. none in the control group. Only one thromboembolic event (splenic vein) occurred in the study (in the control group), and no bleeding events or transformations to myelofibrosis or leukemia were reported in either group. Not surprisingly, neutropenia was reported in the ropeginterferon alfa-2b group (18% of subjects vs. none in the control group). Hypertransaminasemia was also reported in 6% vs. 0% of subjects in the ropeginterferon alfa-2b and control groups, respectively, and flu-like symptoms were reported in 16% vs. 0%, respectively. Night sweats and pruritis were reported at lower frequencies in the ropeginterferon alfa-2b group than in the control group.

The following figure, reprinted from page 13 of the study appendix, shows WBC and PLT counts for the ropeginterferon alfa-2b group (in red) and the control group (in blue).

[2] Published Online January 18, 2021: https://doi.org/10.1016/S2352-3026(20)30373-2

Figure S2. White blood cell and platelet counts over time, by arm



Legend. *In figure are shown the 25th, 50th (median), and 75th percentiles for white-cell count (Panel A), and platelet count (Panel B) at various time points in the two study groups.*

Abbreviations. WBC=White blood cells, PLT=platelets, STD=Standard arm, EXP=Experimental arm, EoS=End of Study

Note that WBCs remain persistently increased in the control (standard treatment) group, in the 11 to 12 X 10^9/L-range (left panel). For PLTs, the count remains ~700 X 10^9/L throughout the 12-month study in the control group (right panel). These data show lack of overall spontaneous change in WBCs and PLTs in patients with low-risk PV throughout a 12-month period, despite therapeutic phlebotomy. The data also suggest that ropeginterferon alfa-2b decreases WBCs and PLTs when used in conjunction with therapeutic phlebotomy.

Given the persistence of increased WBC and PLT counts in the high hematocrit group of the CYTO-PV Study and in the control group of the Low-PV Study, and given what is widely accepted with respect to the natural history of PV, I conclude that the striking reductions in WBCs and PLTs observed in the PEGINVERA study could not have occurred by chance. Thus, PEGINVERA can be viewed as an AWC study with an external control.

Confirmatory Evidence for this Application

The PROUD-PV study provides independent confirmatory evidence for this application. The study design and results are discussed in detail in the statistical and clinical reviews. Given the striking decreases in WBCs and PLTs coincident with the initiation of therapy, and considering that these parameters were assessed repeatedly at intervals approximately 2 weeks apart, there is virtually no possibility that these values represent regression to the mean, a spurious finding, a chance finding, or a spontaneous occurrence.

Discussion

As noted, the PEGINVERA Study can be interpreted as an AWC study, with a historical control. In essence, we are able to reach this conclusion because we recognize that the leukocytosis and thrombocytosis of PV do not resolve spontaneously. In the PEGINERVA Study, however, marked reductions in WBCs and PLTs coincided with initiation of ropeginterferon alfa-2b. Because these parameters were assessed on a frequent basis (every 2 weeks), there is virtual certainty that these

results were neither spurious nor the result of error, leaving open only two possibilities: that the decreases in WBCs and PLTs occurred spontaneously, or that they resulted from drug treatment. Recognizing that the normalization of these laboratory parameters was not limited to a few patients, i.e., the WBC and PLT counts in the figures represent *mean* effects, and given that such changes do not occur spontaneously in PV, we infer, with high confidence, that these changes represent true drug effects. The study was well designed and executed, with good retention of subjects. The sole missing factor was pre-specification of the objective (comparison to an external control).

Importantly, an independent study, PROUD-PV, similarly demonstrated dramatic decreases in WBCs and PLTs coincident with initiation of ropeginterferon alfa-2b. The results from these two independent studies are mutually reinforcing and substantiating, and together provide substantial evidence of effectiveness.

Recognizing that this paradigm does not provide a straightforward path to approval, it is important to state that this action is consistent with our approval standards. In essence, we can draw an analogy to oncology, where, not infrequently, uncontrolled single-arm trials are used to provide substantial evidence of effectiveness: just as tumors do not shrink spontaneously, the leukocytosis and thrombocytosis of PV do not resolve spontaneously.

8. Human Factors

Review of the Human Factors (HF) validation study results concluded that the

> "…study demonstrated several failures, close calls, and use difficulties associated with the critical task of setting and administering doses that may result in harm to the patient." Recommendations were provided to the applicant to conduct another HF validation study to demonstrate that the product can be used safely and effectively.?

The applicant submitted their revised labels and labeling on December 22, 2020, and the protocol for an additional HF validation study on December 29, 2020. The review team found the protocol unacceptable for a number of reasons (see review for details). Lacking satisfactory HF data, a *Complete Response* action is recommended.

The Division of Medication Error Prevention and Analysis reviewer has made the following recommendation for regulatory action based on the submission:

> "Based on the results of the human factors validation study data, root cause analysis, and participants' subjective feedback, the proposed product design and user interface does not support safe and effective use of Besremi (ropeginterferon alfa-2b-njft) injection. We recommend that you implement our HF protocol recommendations prior to commencing your HF validation study, consider additional design modifications and labeling changes, and submit the results of another human factor validation study to demonstrate that the product can be used safely and effectively."

9. Postmarketing Recommendations

Recommendations for postmarketing commitments and requirements are pending, based on the applicant's response to the issues in the Complete Response letter.

10. REMS

In light of the human factors deficiency, evaluation of the need for REMS will be undertaken after the applicant addresses the deficiencies in the Complete Response letter.

11. Advisory Committee Meeting

This application was not referred for review to an advisory committee, based on the strength of the efficacy findings, and the lack of safety issues for which the advice of an advisory committee would be necessary.

12. Product Quality

A final recommendation by the Office of Pharmaceutical Quality (OPQ) is pending final determinations of compliance status of the PhamaEssentia Corporation (PEC) Taichung Plant drug substance manufacturing and testing facility and the PharmaEssentia (PEC) (b) (4) manufacturing and testing facility. FDA's assessment of the ability of these facilities to conduct manufacturing operations in compliance with CGMP is required to support approval. Pre-license inspections were delayed secondary to travel restrictions related to the Coronavirus Disease 2019 (COVID-19) public health emergency.

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/s/

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Cross-Discipline Team Leader Review

Date	March 13, 2021
From	Tanya Wroblewski, M.D.
Subject	Cross-Discipline Team Leader Review
BLA #	BLA 761166
Applicant	PharmaEssentia US
Date of Submission	March 6, 2020
PDUFA Goal Date	March 13, 2021
Proprietary Name	Ropeginterferon alfa-2b-njft
Established or Proper Name	BESREMi
Dosage Form(s)	Subcutaneous
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with polycythemia vera without symptomatic splenomegaly
Applicant Proposed Dosing Regimen	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 500 mcg [redacted] (b) (4) until the hematological parameters are stabilized (HCT <45%, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L). [redacted] (b) (4)
Recommendation on Regulatory Action	*Complete Response*
Recommended Indication/Population	For the treatment of adults with Polycythemia Vera without symptomatic splenomegaly
Recommended Proposed Dosing Regimen	The recommended starting dosage for 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 500 mcg every two weeks) until the hematological parameters are stabilized (HCT <45%, PLTs <400 x 10^9/L, and WBCs <10 x 10^9/L). [redacted] (b) (4)

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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-CTCA	National Cancer Institute-Common Terminology Criteria for Adverse Event
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. 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 the age of 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 and 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.

Ropeginterferon alfa-2b-njft (hereafter referred to as ropeginterferon alfa-2b) is a mono-pegylated proline-interferon alfa-2b. Interferon alfa belongs to the class of type I interferons that exhibit their cellular effects by binding to a transmembrane receptor termed interferon alfa receptor (IFNAR). Binding to IFNAR initiates a downstream signaling cascade through the activation of kinases, in particular Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) and activator of transcription (STAT) proteins. Nuclear translocation of STAT proteins controls distinct gene-expression programs and exhibits various cellular effects. The mechanism of action of interferon alfa has not been fully elucidated; however, nonclinical studies indicate that the therapeutic effects of interferons are most likely related to stimulation of the immune system and depletion and/or elimination of mutant hematopoietic stem cell lineages.

The applicant submitted three studies as part of this application: PROUD-PV, CONTINUATION-PV, PEGINVERA. The PROUD-PV study was intended to be an adequate and well-controlled (AWC) study to provide substantial evidence of effectiveness. The PROUD-PV was a randomized, open-label, multicenter, active-controlled study to assess the efficacy and safety of ropeginterferon alfa-2b in patients with PV. The 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, there was no justification for the change, and there was no agreement on the actual non-inferiority margin. Although this change was made prior to database lock, because PROUD-PV was an open-label study, there are concerns that the knowledge obtained from study could have biased the investigation by influencing the primary endpoint analysis. Despite these critical concerns, the study failed on its primary endpoint. The CONTINUATION-PV was an extension study designed to collect long term efficacy and safety data. The

CONTINUATION-PV study also lacked statistical rigor and was subject to selection bias and potential confounders; therefore, the results were exploratory only.

The applicant also submitted the PEGINERA study. The PEGINVERA study was an open-label, single-arm, dose-escalation study designed to assess the tolerability and safety of escalating doses of ropeginterferon alfa-2b. The study enrolled 51 patients from 6 sites in Austria.

The Agency acknowledges that there are circumstances where regulatory flexibility may be warranted. FDA has issued two guidance documents on demonstrating substantial evidence of effectiveness: the 1998 Guidance, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products " and the 2019 Guidance "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.

One of the scenarios described for meeting the substantial evidence standard is one adequate and well-controlled (AWC) trial plus confirmatory evidence, as described in section 115(a) of FDAMA, which amended the 21 U.S.C. § 355(d), to state: "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence."

In this setting, the confirmatory evidence provides substantiation of the results of the single AWC trial, and such evidence is stronger if it is independent. Confirmatory evidence can arise from one or more sources, including clinical data sources and translational animal research. In addition, the seriousness of the disease, the size of patient population, and presence of unmet medical need are factors for consideration when considering the feasibility of establishing substantial evidence of effectiveness based on a single AWC. Therefore, given the natural history of PV, the unmet medical need and rarity of the disease, flexibility is warranted for the amount and type of evidence needed to meet the substantial evidence standard. Approval based on a single AWC plus confirmatory evidence is appropriate for this proposed indication.

The review team evaluated the effectiveness of ropeginterferon alfa-2b from a single adequate and well-controlled study, the PEGINVERA study. FDA Regulations at 21 CFR 314.126 state that characteristics of an AWC study include "…a clear statement of the objectives of the investigation and summary of the proposed or actual methods of analysis in the protocol for the study and in the report for its results. In addition, the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods if analyses ultimately used." The PEGINVERA study objectives and planned methods of analysis were clearly described in the study protocol and clinical study report.

The confirmatory evidence is based on pharmacodynamic biomarkers and natural history of the disease (historical control group). The nature of the confirmatory evidence is such that PD biomarkers that demonstrate salient

biological effects can provide confirmatory evidence. In PV, the use of quantitative data of hemoglobin, platelet, and WBC counts are directly relevant to pathophysiology and clinical manifestations of the disease and are appropriate to provide confirmatory evidence.

The PEGINVERA study enrolled 51 adult patients with PV diagnosed by the World Health Organization (WHO) criteria or PV Study Group (PSVG) criteria plus JAK2 mutation positivity. Patients were newly diagnosed or pre-treated with HU. Patients were phlebotomized until HCT levels reached <45% prior to first administration of ropeginterferon alfa-2b.

The primary endpoint for Stage 1 of the study was the determination of the maximum tolerated dose. The primary endpoint for Stage 2 was complete hematological response (CHR), defined as HCT < 45% without phlebotomy in the previous 2 months, platelet count < 400 x 10^9/L, WBC count < 10 x 10^9/L, and normal spleen size and no thrombosis. For patients using concomitant HU, responsiveness could not be determined until 2 weeks after the last HU dose.

The mean age was 59 years, 61% of patients were male, and 98% were Caucasian. Sixteen percent of patients were newly diagnosed; 84% had prior disease. At baseline, mean HCT, PLTs, and WBCs were 45.1%, 458 x 10^9/L, and 11.8 x 10^9/L, respectively. All patients were JAK2 mutation positive at baseline.

The study demonstrated an overall complete hematological response rate of 60.8%; [95% confidence interval (CI): 46.1%, 74.2%] with a median response duration of 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). Of note, discontinuation of ropeginterferon alfa-2b led to mean increases of 17% and 22% in WBCs and PLTs.

In summary, PEGINVERA was a well-planned, executed and conducted study demonstrating clinically meaningful decreases in PLTS and WBC as demonstrated by the CHR rate. Importantly, when the drug was discontinued, the counts increased. These responses are unlikely to have occurred spontaneously or by chance alone as the laboratory parameters are measured with precision and reflect changes directly related to pathophysiology of the disease. The comparison of these changes to a valid external control group is acceptable and PEGINVERA can be considered an adequate and well controlled study when its treatment group is compared to a historical control.

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. There are numerous published natural history studies in patients with PV demonstrating that without aggressive cytoreductive control, WBC, PLTs and HCT increase with ongoing thrombotic and cardiovascular risks.

The CYTO-PV study, a multicenter, randomized trial that compared the efficacy of conventional treatment (phlebotomy, HU [~50% of patients], or both) to either a low HCT target (<45%) or high HCT target (45-50%) with respect to the prevention of thrombotic events in patients with PV. Three hundred sixty-five patients with a confirmed JAK2 V617F or exon 12 mutation were randomly assigned to two treatment strategies: a HCT of < 45% was targeted in the "low-hematocrit" group and a HCT of 45 to 50% was targeted in the "high hematocrit" group. The primary composite endpoint was the time to cardiovascular death or a major thrombotic event. After a median follow-up of 31 months, the primary endpoint event occurred in 5/182 patients in the low-hematocrit group (2.7%)

and 18/183 (9.8%) patients in the high-hematocrit group (hazard ratio 3.91; 95% confidence interval [CI], 1.45 to 10.53; P=0.007). The HCT decreased and remained within the protocol-directed ranges for each treatment group however the WBCs and PLTs remained elevated throughout the study and the high HCT group is reflective of disease sequalae when minimal intervention is provided over the course of the disease.

The Low-PV Study (NCT03003325) is an investigator initiated, industry-funded, randomized, open-label multicenter center study in which patients received standard therapy, phlebotomy and low dose aspirin (standard group), or ropeginterferon alfa-2b plus standard therapy (experimental group). Patients were randomized (1:1) to the standard group and treated with phlebotomy (300mL for each phlebotomy to maintain HCT values lower than 45%) and low dose aspirin or to the experimental group which received ropeginterferon alfa-2b subcutaneously every 2 weeks at a fixed dose of 100 mcg on top of the phlebotomy-only regimen. The primary endpoint was treatment response defined as maintenance of median HCT values of 45% or lower without progressive disease during 12 months. At the second pre-planned interim analysis, a higher response rate was observed in the experimental group 42/50 (84%) than in the standard group 30/50 (60%) (95% CI: 7-41%, p=0.0075). Because the standard group did not receive pharmacological intervention, the clinical course and lack of spontaneous changes in WBCs and PLTs are representative of patients with PV treated with aspirin and phlebotomy alone. There were no spontaneous remissions of WBCs and platelets in the group who received phlebotomy and aspirin alone.

Regulations at 21 CFR 314.126 state that a historical control may be appropriate for AWC studies under special circumstances, e.g. for diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident; "The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations." The persistent elevation of PLTs and WBCs in the high HCT group of the CYTO-PV study and the control group in the LOW-PV study provide validity to the well understood natural history of PV. The review team concludes that the reductions in the WBC and PLTs observed in the PEGINVERA study did not occur by chance alone and the PEGINVERA study can be considered an AWC study when the treatment group is compared to a historical control.

Additional confirmatory evidence comes from the PROUD-PV study. There was a meaningful reduction in WBCs and PLTs in the ropeginterferon alfa-2b arm. These values were measured objectively and the likelihood that the responses observed represent a regression to the mean, chance findings or a spontaneous occurrence is implausible.

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 that include these adverse events of special interest: neuropsychiatric events, hepatoxicity to include elevation of liver enzymes, bone marrow toxicity (leukopenia and thrombocytopenia), cardiovascular toxicity, cerebrovascular toxicity, including thrombosis, hypersensitivity reactions, endocrine toxicity, including 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 PEGINVERA study can be considered an AWC study with a historical control. This conclusion can be reached because of the well described and understood natural history of PV and because leukocytosis and thrombocytosis observed in PV do not resolve spontaneously. The reductions of WBCs and PLTs in the PEGINVERA occurred in response to ropeginterferon alfa-2b and the objective measurement of these parameters provide certainity that these changes did not occur randomly or by chance. 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.

The approvability of STN 761166 for ropeginterferon alfa-2b-njft 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.

Finally, 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 is that an additional study will be necessary prior to approval. A protocol for a new HF validation study was submitted, but was deemed inadequate. The Division of Medial Policy Programs (DMPP) has made recommendations for the study and the instructions for use (IFU), and these recommendations should be implemented before initiating 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.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Polycythemia Vera 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 therapy, treatment-naïve patients, or initial treatment. • Low risk patients (<60 years of age, no history of thrombosis): phlebotomy, low-dose aspirin • High risk patients (≥ 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 whose 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 the previous 2 months, PLTs ≤ 400 x 10^9/L, WBC count ≤ 10 x 10^9/L, normal spleen size (≤ 12 cm females and ≤ 13 cm males) and without thrombotic events was observed in 31/51 patients [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 the previous two months, platelet count ≤ 400 x 10^9/L, WBC count ≤ 10 x 10^9/L) was observed in 41/51 patients [(80.4%) 95% CI: 66.9%, 90.2%], with a median duration of response of 20.8 months (95% CI: 13, 43.8). Confirmatory efficacy data comes from the natural history of 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 study. The natural history of PV is well understood and leukocytosis and thrombocytosis in PV do not resolve spontaneously. The PEGINVERA study can be interpreted as an AWC study with an external control in light of the natural history of PV. The reductions in the WBC and PLTS in the PEGINVERA study and PROUD-PV study did not occur due to change or randomly, but reflect a response to treatment.	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 provide 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 is

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		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. Notable serious adverse events were 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, 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 the disease and its comorbidities. Ropeginterferon alfa-2b is an interferon and there are known class side effects and several adverse events of special interest, including neuropsychiatric events, elevation of liver enzymes, bone marrow toxicity (leukopenia and thrombocytopenia), cardiovascular toxicity, cerebrovascular toxicity including thrombosis, hypersensitivity reactions, endocrine toxicity including 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 a Box Warning and the Warnings and Precautions section of 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.

2. Background

2.1.1. Product Information

PharmaEssentia submitted a Biological License Application (BLA 761166) for ropeginterferon alfa-2b (P1101, AOP2014) Injection (0.5mg/1 mL in a pre-filled syringe). Ropeginterferon alfa-2b is an interferon alfa-2b analog. Ropeginterferon alfa-2b is comprised of recombination interferon alfa-2b conjugated with a two-arm methoxypolyethyleneglycol (mPEG) (b) (4) and is considered a long-acting mono-pegylated interferon alfa-2b analog.

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 and exhibit various cellular effects. Interferons and pegylated interferons have been used for the treatment of Polycythemia Vera; however the exact mechanism of action has not been fully elucidated. Non-clinical studies indicate that the therapeutic effects of interferons are most likely related to stimulation of the immune system and depletion and/or elimination of mutant hematopoietic stem cell lineages.

Pegylation of interferon reduces the elimination of the molecule and facilitates a prolongation of the plasma half-life. Conventional pegylated interferons currently approved in the United States are administered once per week, compared to 3-times per week for unmodified interferon alfas. Ropeginterferon alfa-2b is a third-generation mono-pegylated INF that is administered on an every 2-week schedule.

2.1.2. Therapeutic Context

Polycythemia Vera was first described in the medical literature in 1892. Polycythemia Vera 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, and 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 of 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.

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: 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 events and bleeding, and the risks of leukemic transformation and 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 or JAK2 exon 12 mutations. The laboratory detection of JAK2V617F is highly sensitive (97% sensitivity) and highly specific (100%) for distinguishing PV from other causes of increased HCT.

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, which has been widely adopted for initial pharmacological treatment of PV despite lack of approval for this indication. Hydroxyurea toxicities frequently require either drug reduction or drug discontinuation

resulting in inadequate management of the disease. Additionally, because of 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. Additional off-label cytoreductive therapies for treatment of PV include pegylated and non-pegylated interferons as well as alkylating agents such as busulfan.

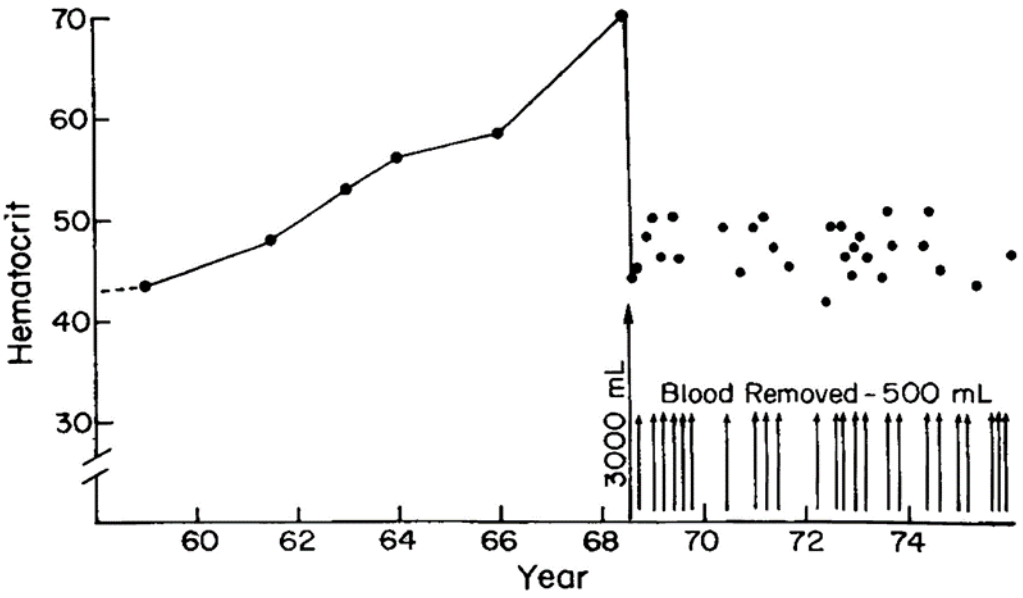
Interferons have been used for the treatment of PV and other myeloproliferative diseases for the past 30 years. A review of the literature from nonrandomized long-term studies suggest that interferon may provide better control of splenomegaly, thrombocytosis, pruritus, and thrombohemorrhagic complications compared to phlebotomy alone or phlebotomy plus HU. An objective response of approximately 80% including complete freedom from phlebotomies in approximately 60% of patients was reported. In addition, interferon alfa was able to reduce PV-associated pruritus in many cases. (Kiladijian JJ, 2008).

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.

2.2. Natural History of PV

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

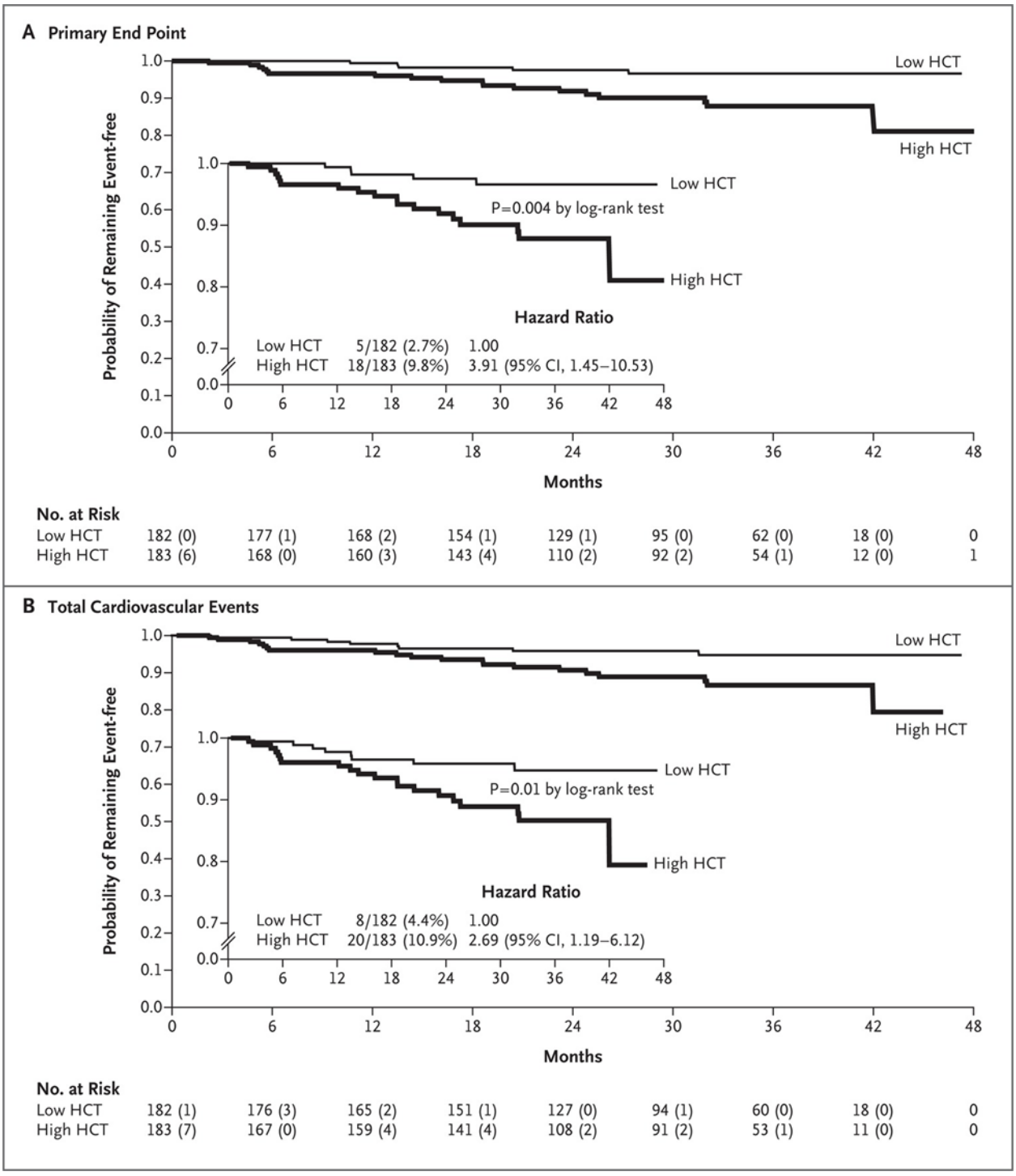
Figure 1 Increased HCT in Untreated PV Patient



(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, randomized study in 365 adults with JAK2-positive PV randomized patients to either a low HCT target (<45%) or high HCT target (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

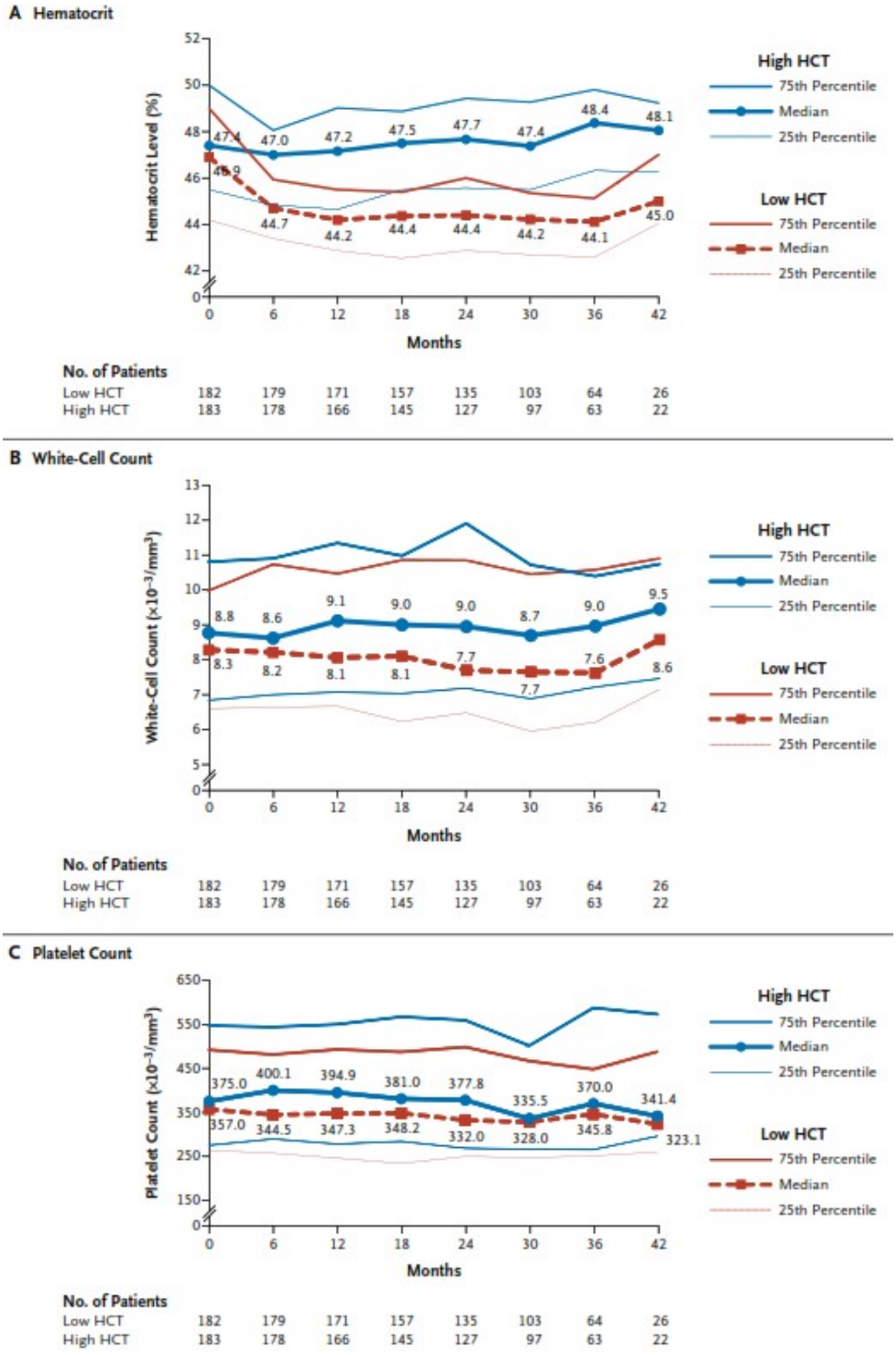

A Primary End Point
Probability of Remaining Event-free
Low HCT
High HCT
P=0.004 by log-rank test
Hazard Ratio
Low HCT 5/182 (2.7%) 1.00
High HCT 18/183 (9.8%) 3.91 (95% CI, 1.45–10.53)
Months
No. at Risk
Low HCT 182 (0) 177 (1) 168 (2) 154 (1) 129 (1) 95 (0) 62 (0) 18 (0) 0
High HCT 183 (6) 168 (0) 160 (3) 143 (4) 110 (2) 92 (2) 54 (1) 12 (0) 1
B Total Cardiovascular Events
Probability of Remaining Event-free
Low HCT
High HCT
P=0.01 by log-rank test
Hazard Ratio
Low HCT 8/182 (4.4%) 1.00
High HCT 20/183 (10.9%) 2.69 (95% CI, 1.19–6.12)
Months
No. at Risk
Low HCT 182 (1) 176 (3) 165 (2) 151 (1) 127 (0) 94 (1) 60 (0) 18 (0) 0
High HCT 183 (7) 167 (0) 159 (4) 141 (4) 108 (2) 91 (2) 53 (1) 11 (0) 0

(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%) 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).

Interestingly, HCT was decreased within the ranges directed by the protocol, but the WBC and PLTs remained elevated during the study (see figure; panels B and C). Note that WBCs (middle panel, B) remained in the 10 to 11 X 10^9/L range and PLTs (lower panel, C) remained in the 400 to 500 X 10^9/L range throughout the study.

Figure 3 HCT, WBC, PLT changes during CYTO-PV Study



Thus, targeting HCT <45% results in lower rates of cardiovascular death and major thrombosis, and the WBC and PLT counts in the higher HCT target group, reflecting less intensive disease control, support the premise that there are 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 events 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 decrease 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 rates of thromboses after diagnosis are likely due to advances in treatment as well as better 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.

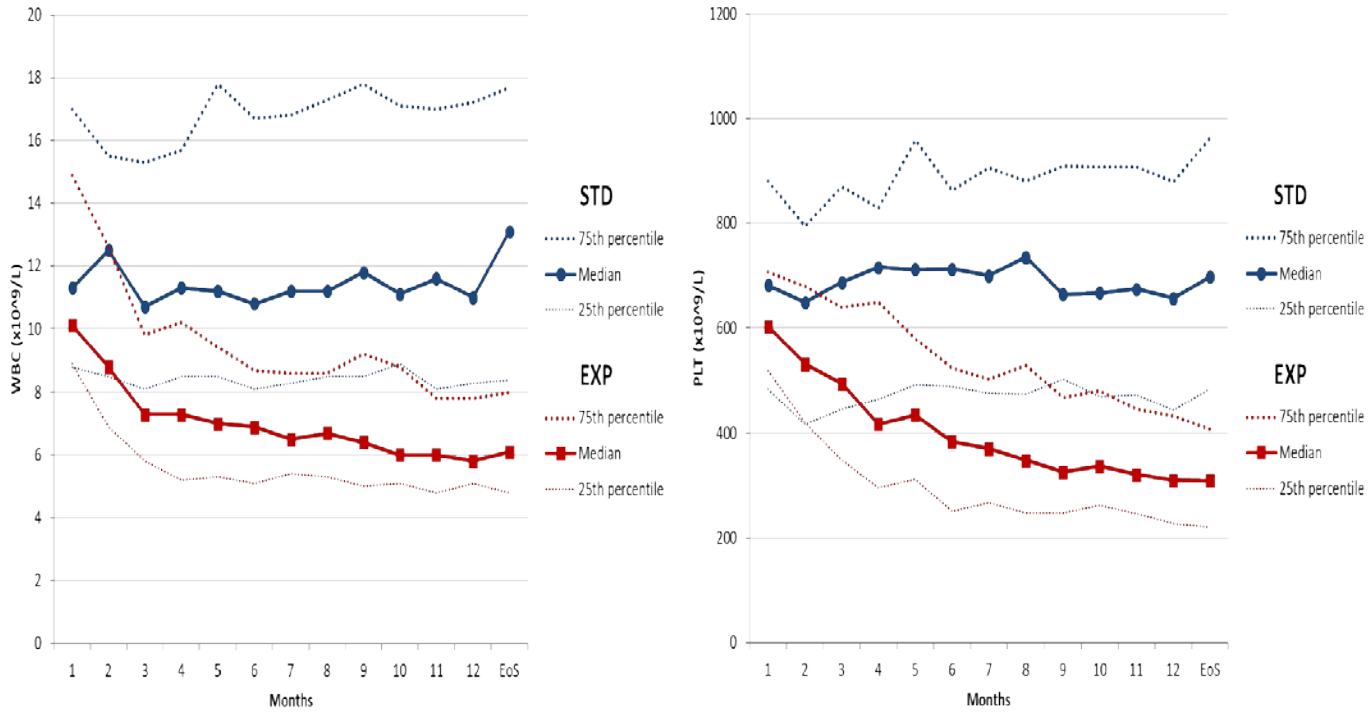
	N.	%
Patients	70	–
Male/female	49/21	–
Median follow-up, years (range)	14 (2-26)	–
Median age, years (range)	42 (18-49)	–
Mean hemoglobin (g/dL)±SD	21±2	–
Mean hematocrit (%)±SD	60±5	–
Mean white cell count ($\times 10^9$/L)±SD	12±3	–
Mean platelet count ($\times 10^9$/L)±SD	544±186	–
Splenomegaly	29	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 elevation of hematology parameters (WBC, PLT, HCT), 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 (NCT03003325) is an investigator-initiated, industry funded, multicenter, open-label, two arm, parallel-group, randomized study (1:1) in which patients received 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 at a fixed dose of 100 mcg in addition to the phlebotomy-only regimen. The primary endpoint was treatment response defined as maintenance of median HCT values of 45% or lower without progressive disease during 12 months. At the second pre-planned interim analysis, a higher response rate in the experimental group was observed: 42/50 (84%) patients

in the experimental group vs. 30/50 (60%) in the standard group (95% CI 7-41%, p=0.0075). Because the standard group did not receive pharmacological intervention, the clinical course is representative of patients with PV 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. The following figure shows the 25th, 50th (median) and 75th percentiles for WBC and PLT count at various time points in the two study groups. *(Barbui T et al. The Lancet Hematology 2021)*

Figure 4 Low-PV Study: White blood cell and platelet counts over time, by arm



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.

Key Events in the Regulatory History of Submission

The following table was taken and modified slightly from the clinical review by Dr. Patricia Oneal and describes the regulatory interactions between the Agency and applicant.

Table 2 Key Regulatory Interactions

Date	Regulatory Interaction
July 26, 2013	Pre-IND submitted to the FDA

Date	Regulatory Interaction
June 28, 2014	IND submitted to the FDA for phase 3 study(PROUD-PV) study
[redacted] (b) (4)	
February 17, 2017	Type B Meeting request to PROUD-PV study
April 20, 2019	Type B meeting- Sponsor sought guidance on results of PROUD-PV study (pre-BLA meeting)
August 28, 2019	CMC meeting
September 4, 2019	Pre-BLA meeting

3. Product Quality

Dr. Phillip Angart is the chemistry Reviewer in the Office of Pharmaceutical Quality (OPQ). His final recommendation on approvability of STN 761166 for ropeginterferon alfa-2b-njft 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-njft manufactured by PharmaEsssentia at this time.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology review was performed by Jeffrey Quinn, Ph.D. and Todd Bourcier, Ph.D. They recommended approval. The summary below is taken from their review.

The toxicological evaluation of ropeginterferon alfa-2b was limited to studies of < 1 month in duration due to the production of neutralizing antibodies (ADAs) in cynomolgus monkeys (4-Weeks) and the lack of biologic activity in Sprague Dawley rats (14-Days).

PEG accumulation and vacuolation of cells in the nervous system were not observed during the pivotal 1-month monkey toxicity study of ropeginterferon; however, the results were confounded by the presence of ADAs and the short study duration. Mononuclear perivascular infiltrates in the brain and an increase in the incidence and severity of atrophy of the thymus

and mild necrosis of the epithelium in the stomach were observed in a 14 _Day monkey bridging study, however the non-clinical reviewer considered these findings attributable to the animal source (China) as similar results were not observed in monkey studies (2-weeks and 4-weeks) that employed US-sourced monkeys. Based on comparable toxically (versus conventionally PEGylated IFNs) and clinical experience a nonclinical assessment of cytokine release was not deemed necessary.

Drug-related effects noted during the pivotal 4-Week monkey toxicity study (US sourced) were consistent with the known effects of administration of human IFN to cynomolgus monkeys. P1101 caused significant thrombocytopenia at the HD in monkeys and is consistent with the known effects of PEGylated IFN use in human subjects. Hence, the MD is considered the most clinically relevant NOAEL and is associated with Day 1 (due to ADAs) exposure margins (sex averaged)of 533x (Cmax) and 2790x (AUC0-t).

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.

- The pharmacokinetics, pharmacodynamics and biological activity of ropeginterferon alfa-2b are comparable to those of marketed pegylated IFN alfa products.

- Ropeginterferon alfa-2b is a weak inhibitor of hERG channels in vitro (decrease 49.9% at 2.5 uM-HD) and in vivo correlates (i.e., QT prolongation or ECG morphology changes) were not observed in monkey studies. The mean serum Cmax (49nng/mL) of ropeginterferon alfa-2b achieved in patients with Polycythemia Vera at the MRHD(0.5mg) represents a concentration that is 1000-fold lower than the approximated hERG IC_{50} (2.5uM=50ug/mL).

- Ropeginterferon alfa-2b exhibited time-dependent inhibition of CYP2A6 at a concentration equivalent to the observed Cmax at the MRHD in patients with Polycythemia Vera. Drugs with a narrow therapeutic index metabolized by CYP2A6 (letrozole, tegafur, coumarin, valproic acid, methoxyflurane, artesunate, disulfiram, halothane and fadrozole) should be used with caution when co-administered with ropeginterferon alfa-2b. This is of particular relevance to patients undergoing cytoreductive therapy who may be administered coumarin.

- 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 PEG to the N-terminal proline residue of recombination proline-interferon alfa-2b [redacted] (b) (4) [redacted] No separate chemical linker is employed (direct conjugation). Considering the reactive linker molecule does not represent a toxicological

concern and ropeginterferon alfa-2bwill 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.

PEG accumulation and vacuolation of cells in the nervous system were not observed during the pivotal 1-month toxicity study of ropeginterferon, however the results were confounded by the presence of ADAs and the short study duration. Mononuclear perivascular infiltrates in the brain and an increase in the incidence and severity of atrophy of the thymus and mild necrosis of the epithelium in the stomach were observed in a 14-Day monkey bridging study (study 44103-08-300); however the non-clinical reviewer considers these findings attributable to the animal source (China), as similar results were not observed in monkey studies (2-weeks and 4-weeks) that employed US-sourced monkeys. Based on the comparable toxicology (vs conventionally PEGylated IFNs) and clinical experience a nonclinical assessment of cytokine release was not deemed necessary.

Drug-related effects noted during the pivotal 4-Week monkey toxicity study (US sourced) were consistent with the known effects of administration of human IFN to cynomolgus monkey. Ropeginterferon alfa-2b caused significant thrombocytopenia at the HD in monkeys and is consistent with the known effects of PEGylated IFN use in human subjects. Hence, the MD is considered the most clinically relevant NOAEL and is associated with Day 1 (due to ADAs) exposure margins (sex-averaged of 533x (Cmax) and 2790 (AUC0-t).

These findings are reflected in the agreed-upon labeling. The non-clinical reviewers concluded that there are no deficiencies in the nonclinical data that would preclude approval of BLA 761166.

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.

Interferon alfa belongs to class of type I interferons that exhibit their cellular effects by binding to a transmembrane receptor termed interferon alfa receptor (IFNAR). Binding to IFNAR initiates a downstream signaling cascade through activation of kinases, in particular Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2) and signal transducer and activator of transcription (STAT) proteins. Interferon alfa was shown to have an inhibitory effect on the proliferation of hematopoietic and bone marrow fibroblast progenitor cells and antagonized the action of

growth factors and other cytokines that have a role in development of myelofibrosis. These actions may be involved in the therapeutic effects of interferon alfa in polycythemia vera.

Absorption

- The estimated geometric mean (CV%) absorption rate constant of ropeginterferon alfa-2b is 0.12 day^{-1} (27%) in patients with PV. The time to reach maximum plasma concentration is approximately 3-6 days.

Distribution

- The estimated geometric mean (CV%) apparent volume of distribution of ropeginterferon alfa-2b is 4.8 L (21%) in patients with PV.

Elimination

- 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.

Intrinsic Factors

- No clinically significant differences in the pharmacokinetics of ropeginterferon alfa-2b 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 with eGFR ≥30 mL/min/1.73m^2. The effect of eGFR < 30mL/min, or hepatic impairment (Child-Pugh A, B, and C) on ropeginterferon alfa-2b pharmacokinetics has not been studied. Evaluation of ALT/AST as PK covariates indicated no impact on these time varying biomarkers on ropeginterferon alfa-2b PK.

Drug Interaction Studies

- No clinical drug-drug interaction studies were performed. Ropeginterferon alfa-2b is not a direct inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 and is not an inducer of CYP1A2, 2B6, or 3A4. Ropeginterferon alfa-2b is a time-dependent inhibitor of CYP2A6 and there was a 37.3% inhibition on CYP2A6 actively when human liver microsome was incubated with ropeginterferon alfa-2b at 50ng/mL (mean Cmax at the dose of 450ug us 44ng/mL) for 30 minutes.

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

6. Clinical Microbiology

From the product quality microbiology and sterility assurance perspectives, there were no concerns for this product.

7. Division of Medical Error Prevention and Analysis (DMEPA)

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 results and data submitted under BLA 761166 for ropeginterferon alfa-2b. DMEPA found that the HF validation study demonstrated several failures, close calls, and use difficulties associated with the critical task of setting and administering doses that may result in harm to the patient. DMEPA recommended that the applicant conduct another HF validation study to demonstrate that the product can be used safely and effectively. The applicant then submitted a protocol for a new HF study to review. After assessment of the HF validation study protocol, it was determined that the protocol requires revisions to ensure that adequate data regarding the safe and effective use of this product are collected. The Division of Medial Policy Programs (DMPP) has made recommendations for the study and the instructions for use (IFU); 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.

8. Clinical- Efficacy

The clinical reviewer and the statistical reviewers were Patricia Oneal M.D. and Lola Luo Ph.D., respectively. The summary below borrows heavily from their reviews.

8.1. PEGINVERA Study

8.1.1. Study Design

Overview and Objective

The primary objective of the 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 the phase 2 portion of the study included assessments of efficacy and safety of ropeginterferon alfa-2b. There was no formal hypothesis testing 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 as long as treatment was effective and tolerable. The starting dose was 150 mcg with increases by 50 mcg every 2 weeks 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.

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.

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 first 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 or seizure disorder requiring anticonvulsant therapy, acute or chronic infections or autoimmune diseases.

Study Endpoints

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 sound measured by ultrasound (longitudinal diameter ≤ 12 cm for females and ≤ 13 cm for males) and absence of thromboembolic events). In case of concomitant hydroxyurea, 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.

8.1.2. 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. One investigator received payments, [redacted] (b) (4) exceeding US $25,000 for [redacted] (b) (4) in the PROUD-PV/COINTINUATION-PV and PEGINVERA studies.

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 3 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 4: 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 %)
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-PV 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, concurrent treatment with cytoreductive agents other than HU and investigational agents) and three patients were excluded because they had > 6 weeks between two consecutive administration of the study drug.

Demographic Characteristics

Table 5: Baseline Demographic Characteristics for the PEGINERVA 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 6: Other Demographic Characteristics of the PEGINVERA Study All-treated Population

	Ropeginterferon alfa-2b n=51
Weight at Baseline kg – Mean (SD)	77.82 (13.41)
Height at Baseline cm - Mean (SD)	172.4 (9.17)
Disease History	
Known Disease	43 (84.3%)
Newly Diagnosed	8 (15.7%)
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

	Ropeginterferon alfa-2b n=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 Baseline	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

In the initial listing, the data for JAK2 positivity was reported using collection method measurement method allele-specific PCR (detection limit of 1%). One patient was first analyzed as negative. Using next-generation sequencing (NGS), with 10-fold higher detection limit of 0.1%, this patient was identified has having a characteristic JAK2 mutation (single G to T missense mutation in the gene for the JAK2 tyrosine kinase leads to a V617F amino acid substitution).

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 achieved CHR of 70.6% (12/17)and in the HU Naïve 55.9% (19/34) achieved CHR. When evaluating using the denominator of the all-treated population, 12/51 (23.5%) and 19/51 (37.2%) achieved CHR.

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 had decreased to 246.6 x 10^9/L (SD 118.9).

In the PEGINVERA study, mutant allelic burden for JAK2 was present in 100% 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 7: 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 8 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 9 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

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 dose 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 WBCs, mean 22% increase 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%.

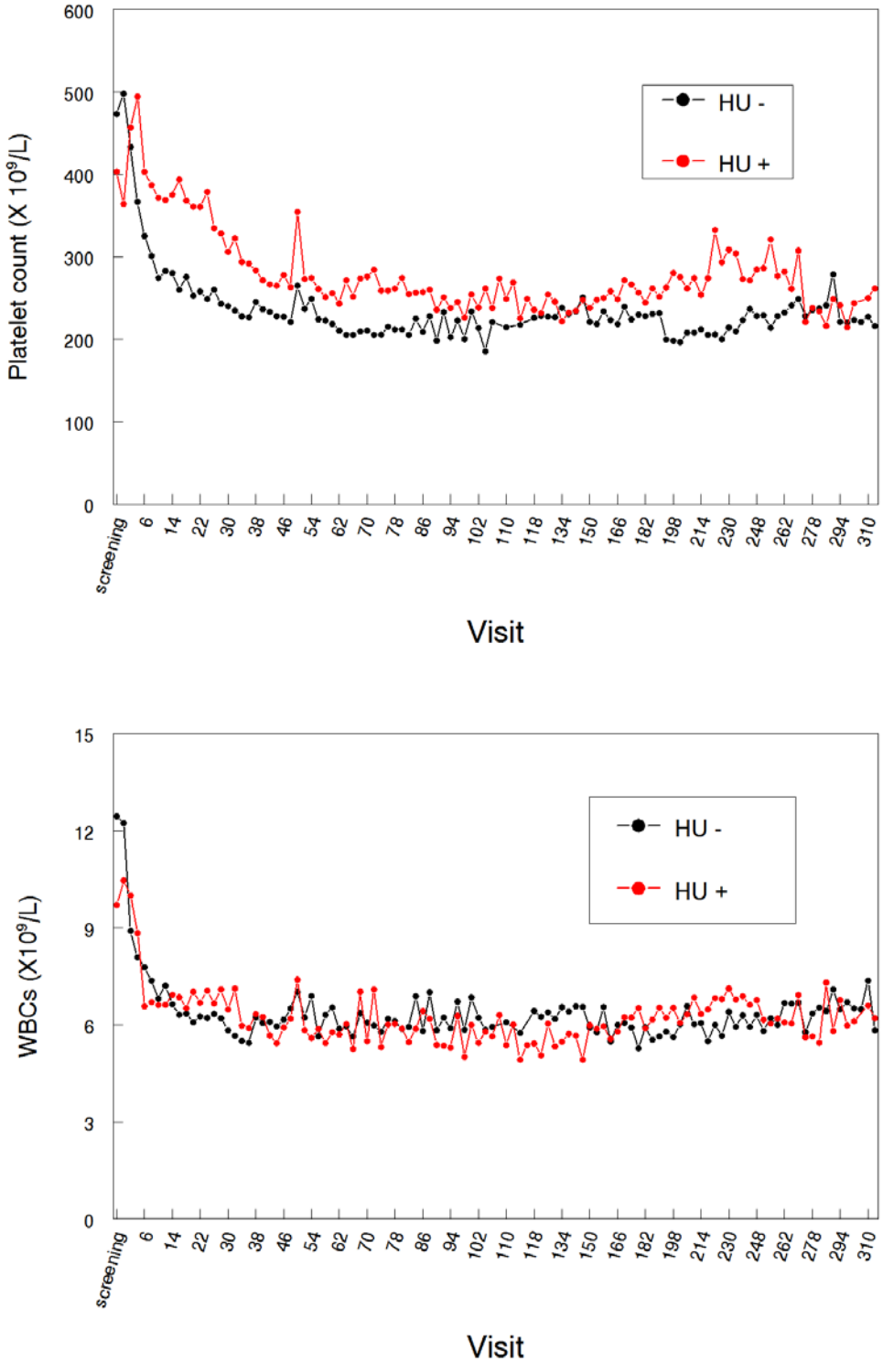
Table 10 Mean and Median Changes in Counts during Drug Interruption > 42 days

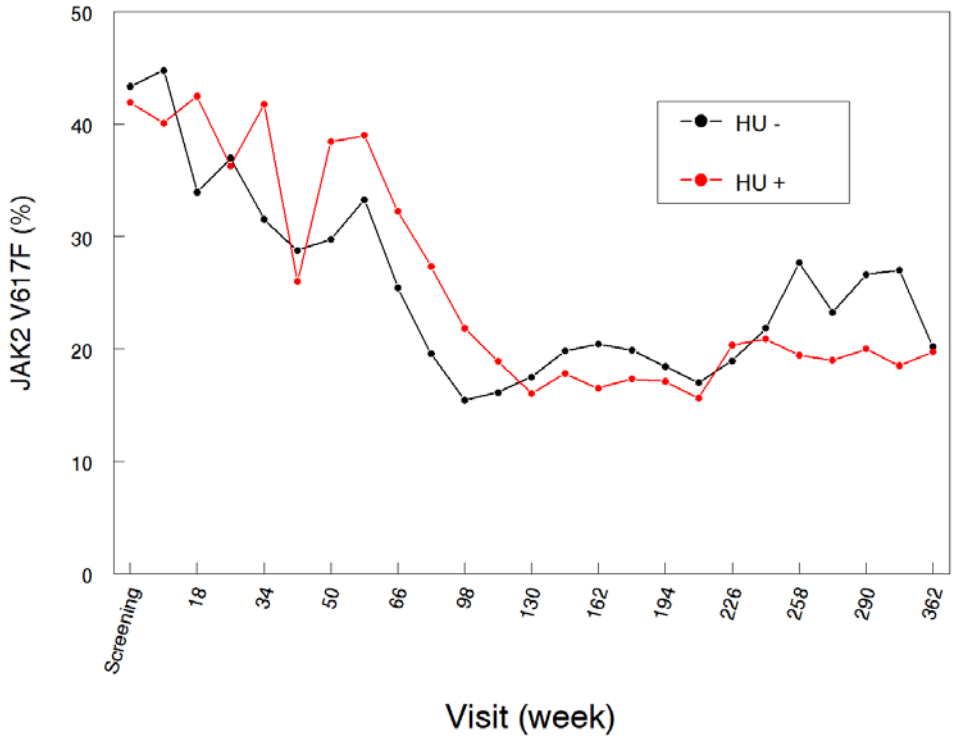
	Statistics	**Value (N=25, Nx=57)**
	n	57
WBC Count (10^9/L) before Interruption	Mean Median (min, max)	6.22 5.20 (2.9, 18.4)
WBC Count (10^9/L) after Interruption	Mean Median (min, max)	6.92 6.30 (3.7, 14.6)
PLTs (10^9/L) before Interruption	Mean Median (min, max)	254 244 (114,599)
PLTs (10^9/L) after Interruption	Mean Median (min, max)	298 287 (132,570)

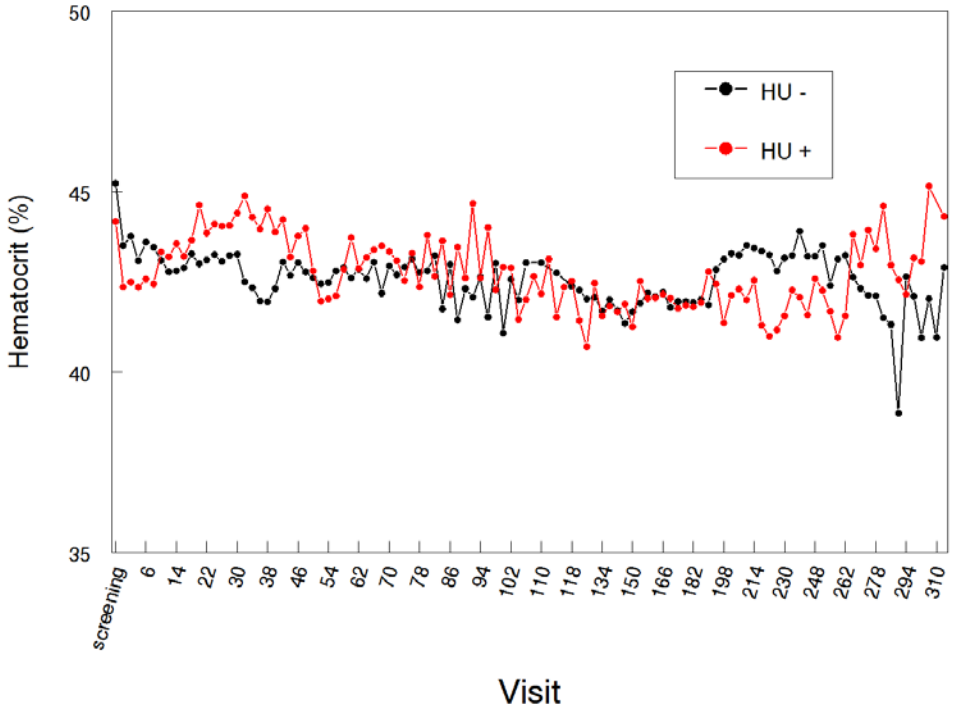
Source: Applicant Response to Agency IR 21 Feb 2021
N=number of enrolled patients with evaluable interruptions
Nx- number of evaluable interruptions
N= number of laboratory test results immediately before/after exposure interruption. Patients with multiple exposure interruptions are counted multiple times in the summary.

The following figures show mean values for PLTs, WBCs, JAK2 V617F, and HCT throughout the study. Patients who were taking HU prior to the study are shown by the red markers; those who were HU-naïve are shown by the black markers. In HU-naïve subjects, there is a striking decrease in PLTs and WBCs once ropeginterferon alfa-2b is initiated (top two figures). For patients previously on HU, the screening values trend slightly lower, and the decrease in platelet count is more gradual, presumably because HU is being withdrawn as the ropeginterferon alfa-2b dose is increased. The decrease in JAK2 V617F is evident in patients who were previously on HU and those who were HU-naïve. Changes in HCT are difficult to interpret, because therapeutic phlebotomy was used when HCT exceeded 45%.

Figure 5 Mean values for PLTS, WBC, JAK2V617F, and HCT




JAK2 V617F (%)
50
40
30
20
10
0
HU -
HU +
Screening
18
34
50
66
98
130
162
194
226
258
290
362
Visit (week)



There was a decrease in JAK2 mutation allelic burden over time in the PEGINVERA study. There is a evidence that the presence of a higher V617F allele burden is associated with clinical phenotype of PV with hematological and clinical markers associated with more aggressive phenotype. The correlation between allele burden reductions and clinical benefits has not been fully evaluated in trials in patients with PV.

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

Table 11 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

8.2. PROUD-PV Study

8.2.1. Study Design

Overview and Objective

The original objective of the PROUD-PV study was to demonstrate superiority of ropeginterferon alfa-2b versus HU for 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 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, active-controlled, parallel group, non-inferiority study (ropeginterferon alfa-2b compared to HU). 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 a central laboratory blinded to treatment assignment. Independent imaging (CT/MRI) with blinded radiological assessment was used for spleen size assessment.

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 of 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 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.

Study Endpoints

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

- 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 to a non-inferiority analysis 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) was finalized on 10 September 2019.

Sample Size Determination

The PROUD-PV trial was originally designed as superiority study design and sample size was calculated based on superiority comparison 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 with a projected drop-out rate of approximately 20%. The plan stated that patients who dropped out would be considered non-responders decreasing the assumed rate of responders to 12% and 32%, respectively. Based on these assumptions 126 patients per group (252 total) would be needed to detect the difference in response rate between groups at a 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 a non-inferiority comparison with a NI margin of 10.5% and statistical power for the non-inferiority hypothesis was retrospectively calculated.

Analysis Population

The intent-to-treat (ITT) population included all randomized patients, irrespective of any protocol violations and subsequent therapies taken (n=127). The full analysis set (FAS) included the ITT population but excluded any patients for whom it was documented that they had not received any study medication and provided no follow-up (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. Non-inferiority 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 analysis from a demonstration 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 (April 8, 2016).

8.2.2. 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 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 12: Disposition of Study Patients in PROUD-PV Studies

	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 (%) Adverse Event Lack of Efficacy Lost to follow-up Withdrawal by Subject Other	21/127 (16.5%) 11 (8.7%) 0 (0%) 4 (3.1%) 6 (4.7%) 0 (0%)	16/127 (12.6%) 3 (2.4%) 2 (1.6%) 1 (0.8%) 5 (3.9%) 5 (3.9%)	37 (14.6%) 14 (5.5%) 2 (0.8%) 5 (2.0%) 11 (4.3%) 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 ropeginterferon alfa 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 2 patients, positive TPO Ab in 2 patients, low hemoglobin value in one patient and positive HADS without psychiatric assessment in 1 patient).

There were 5 major protocol deviations due to a dose reduction or interruption following an adverse events that were considered not related to the study drug by the applicant in 4

patients or due to missed visits in 1 patient.

There were 3 major safety deviations 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 13: 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%)

	Ropeginterferon alfa-2b n=127 n (%)	HU n=127 n (%)
Slovakia	6 (4.7%)	4 (3.1%)
Germany	3 (2.4%)	3 (2.4%)
Spain	1 (0.8%)	0 (0%)
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. All 254 participants were Caucasian, and none were recruited from the US.

Table 14: Other Demographics for PROUD-PV ITT Population

	Ropeginterferon alfa-2b n=127	HU n=127
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)		
Count Subjects with Data	127	127
Mean (SD)	13.38 (3.16)	13.55 (3.32)
Median	13.10	13
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		
Count Subjects with Data	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 (%)		
Count Subjects with Data	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)		
Count Subjects with Data	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)		
Count Subjects with Data	127	126
Mean (SD)	524.7 (275.4)	519.5 (253.3)
Median	478	455
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. 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%). The second largest enrolled group included 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 CRF.

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). The pre-specified primary endpoint was not achieved in the PROUD-PV Study.

Table 15 Primary Endpoint for PROUD-PV

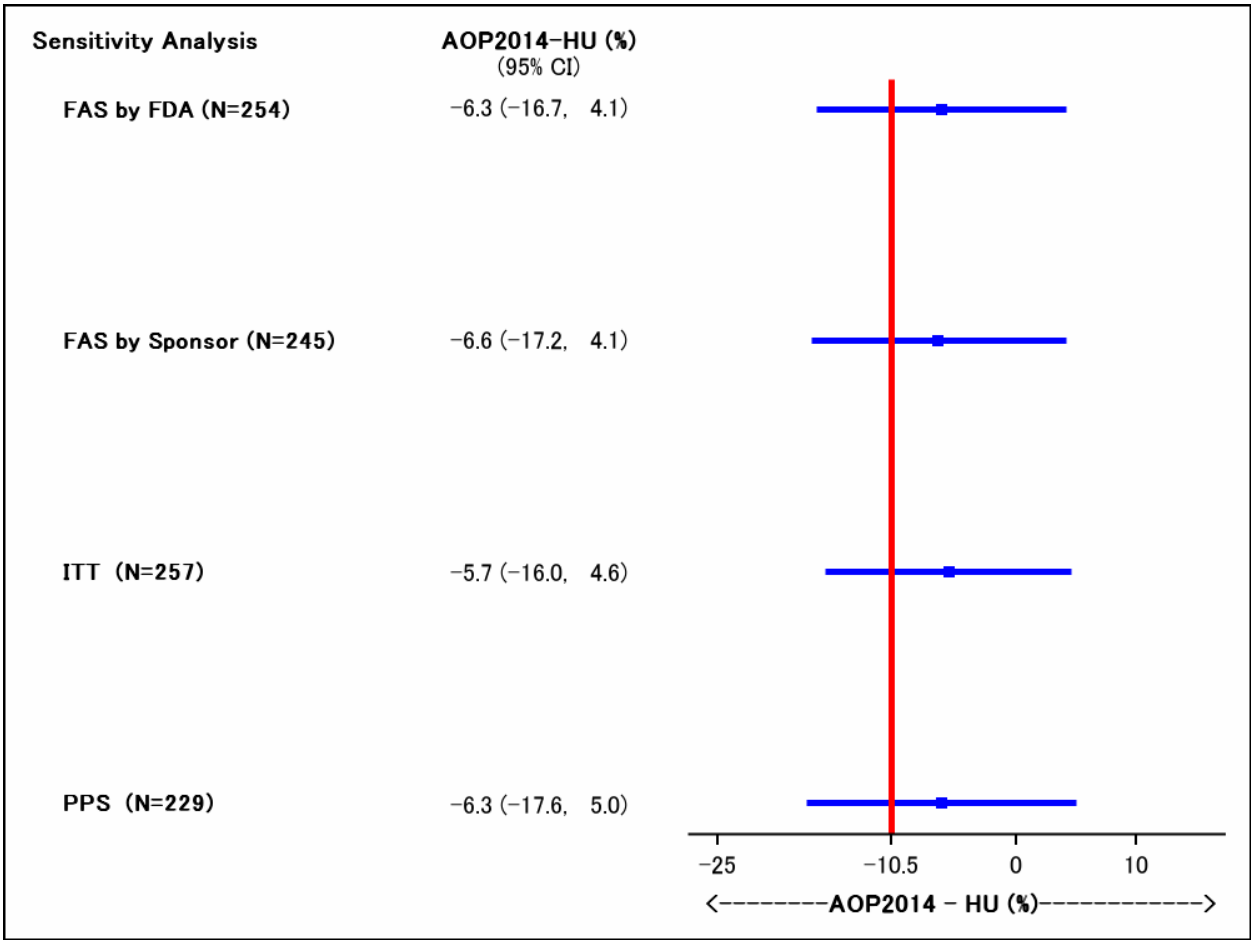
Treatment Group	**Ropeginterferon N=127**	**HU N=127**
Responders	26 (20.47%)	34 (26.8%)

Treatment Group	Ropeginterferon N=127	HU N=127
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 6 Sensitivity Analysis for Primary Endpoint for Different Populations (PROUD-PV)



Efficacy Results – Secondary and other relevant endpoints

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

Table 16: 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%)
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 17: 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

Dose/Dose Response

In the PROUD-PV Study, the mean dose of ropeginterferon alfa-2b at EOT was 382 mcg (±141), and the median dose was 450 mcg administered every two weeks. At 24 months the mean dose was 377 (±142) mcg and the median dose 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.

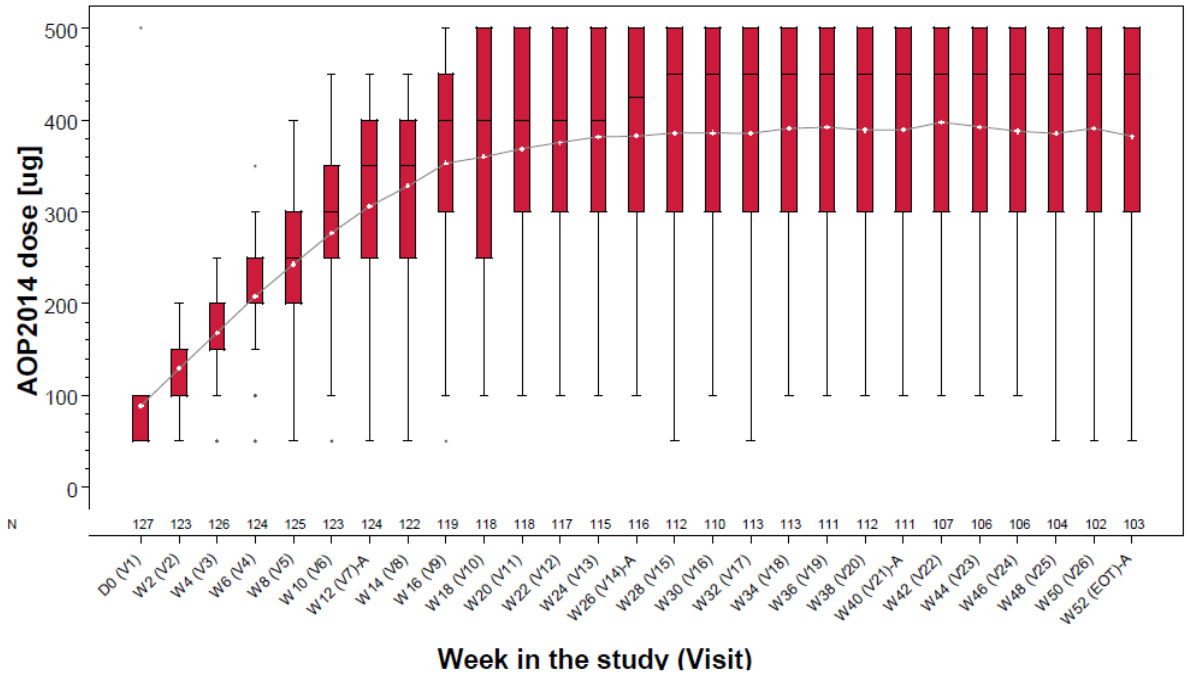
Dose Administration during the PROUD-PV Study

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 7: ROPEGINTERFERON ALFA-2B Dose Administered by Visit- FAS Population

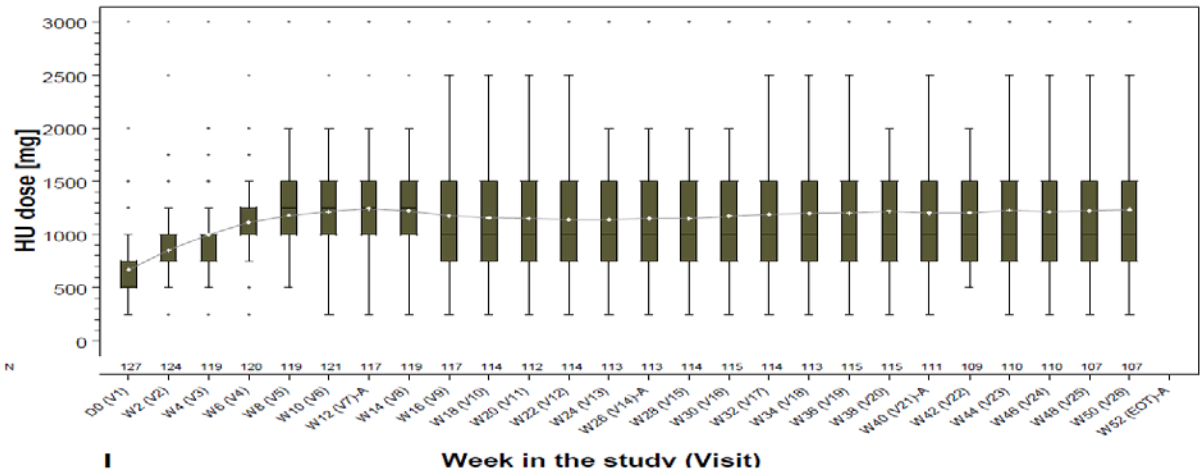
Figure 12.1-1 AOP2014 dose administered by visit - FAS



Source: Figure 14.2.1.1

Figure 8: Hydroxyurea Dose Administered by Visit –FAS Population

Figure 12.1-2 Hydroxyurea dose administered by visit - FAS



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

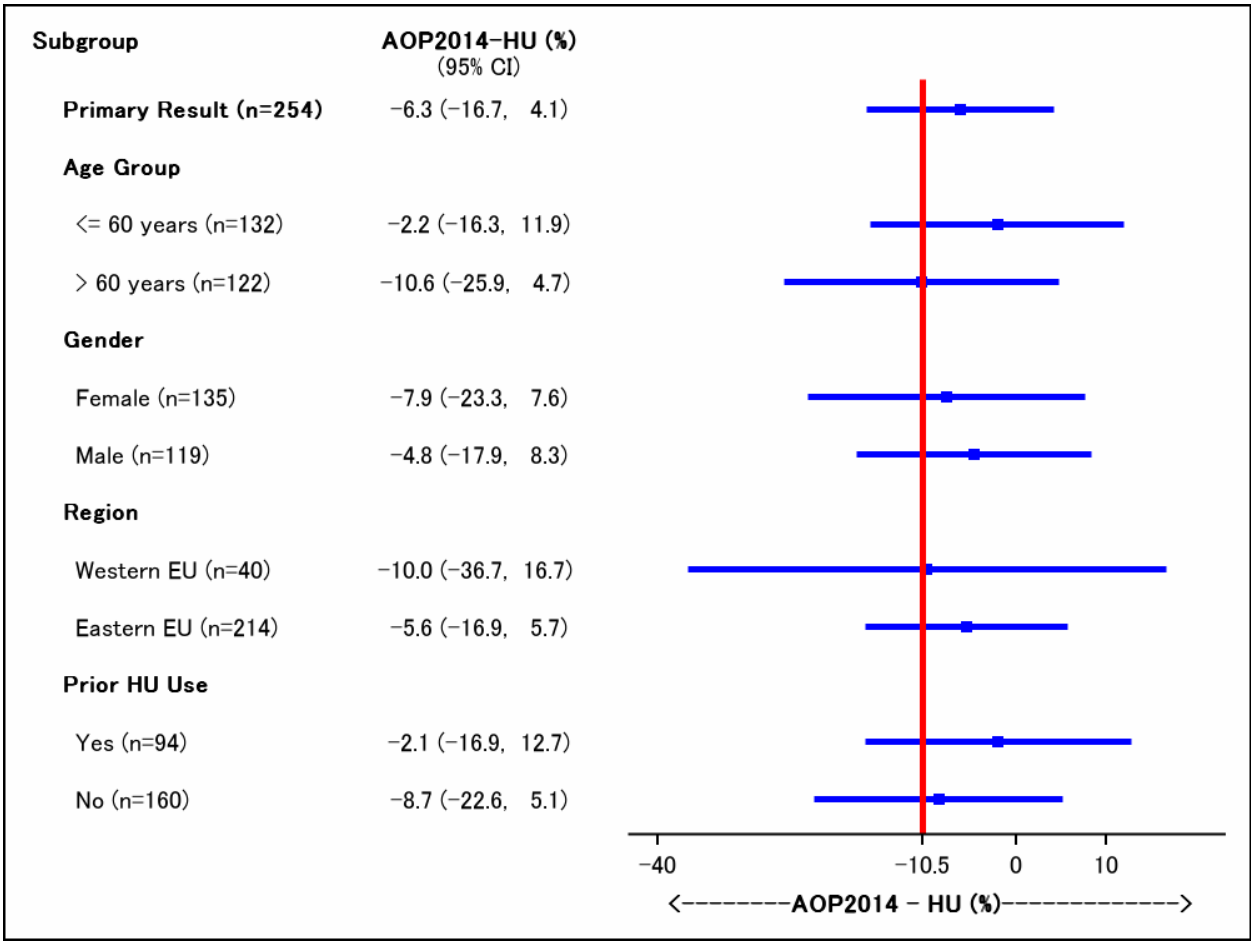
Not applicable as there were no protocol driven periods of discontinuation in the studies.

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 9 Sensitivity Analysis for Primary Endpoint for Subgroups



Source: FDA Statistical Review Team

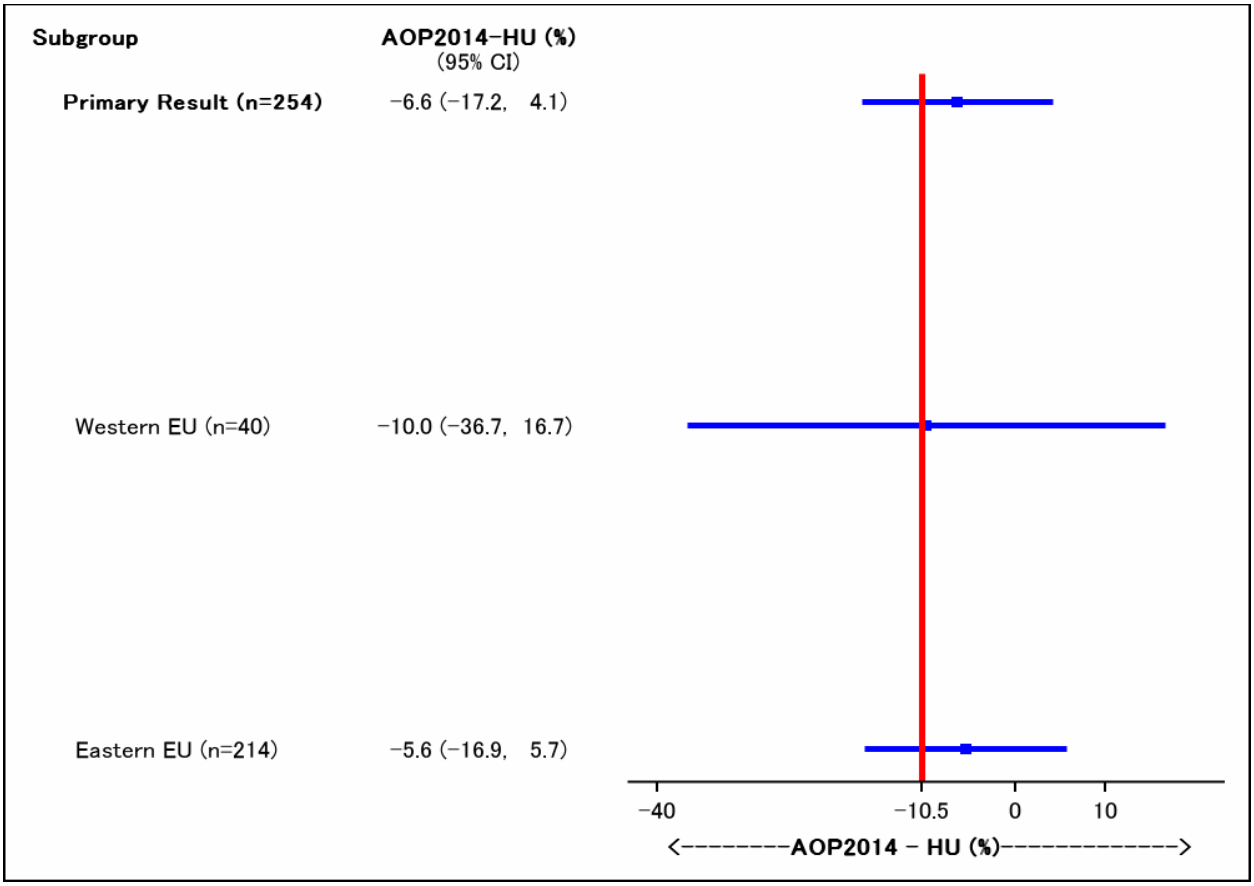
Baseline laboratory parameters were evaluated between the Eastern and Western European patients enrolled in the trials. Overall, the baseline hematology parameters appear comparable between regions.

Table 18: 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 10 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.

8.3. CONTINUATION-PV

8.3.1. Study Design

Overview and Objective

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 in patients with PV who previously participated in the PROUD-PV Study. 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 the protocol version 5.1 added the HU/BAT group was dated November 2016. 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 their own physician for periods of up to one year or more.

<u>Selection of Study Population</u>

Inclusion 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
d) Otherwise a clear, medically verified benefit from treatment (e.g. normalization of 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
d) 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.

8.3.2. 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 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 19 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 (%) **Adverse Event**	17/95 (17%) 7 (7.4%) 3 (3.2%)	7/76 (9.2%) 2 (2.6%) 0 (0%)	27/171 (15.8%) 9 (5.3%) 3 (1.8%)

	Ropeginterferon alfa-2b	HU	Total
Lack of Efficacy	3 (3.2%)	0 (0%)	3 (1.8%)
Lost to follow-up	3 (3.2%)	3 (3.9%)	6 (3.5%)
Withdrawal by Subject	4 (4.2%)	2 (2.6%)	6 (3.5%)
Other			

In the CONTINUATION-PV Study, the median age at presentation was 59 years in the ropeginterferon alfa-2barm 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. Based on the stratification factors, forty-four percent were over the age of 60 years.

Table 20: Other Demographics Characteristics for CONTINUATION 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]
Body Mass Index Baseline (kg/m²)		
Count Subjects with Data	93	76
Mean [SD]	26.08 [3.90]	26.81 [4.00]
Median	25.60	26.80
Range	17.7-39.5	17.3-36.7
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 - n and %		
POSITIVE	94 (98.9%)	74 (97.4%)
(missing)	1 (1.1%)	2 (2.6%)
JAK 2 Allelic Burden at EOT		

	Ropeginterferon alfa-2b n=95	Best Available Therapy (BAT) n=76
Count Subjects with Data	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
HCT at Baseline (%)		
Count Subjects with Data	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 (%)		
Count Subjects with Data	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

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.

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 10: 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

8.4. Active-Control Efficacy Review of Ropeginterferon from PROUD-PV/CONTINUATION

The active-control from the PROUD-PV and CONTINUATION-PV were evaluated given the failure of the randomized trials. The active-treatment 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. The all-treated population of 127 patients were used for this analysis.

Control of HCT, WBC and PLTs remains a key component in response assessment of cytoreductive therapy in PV with confirmed predictive value for clinically relevant outcomes. Therefore, CHR based on hematology parameters was assessed in addition to CHR with normal spleen. In addition, most of the patient enrolled in the PROUD-PV study did not have clinically significant splenomegaly.

Components of complete hematological response (laboratory measures) were objectively measured in the PROUD-PV. 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 24 displays CHR(hematology parameters) and CHR with normal spleen at Month 12, Month 24 and Month 36.

Table 21: Complete Hematological Response for PROUD-PV/CONTINUATION Study (ITT population N=127)

CHR	**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)

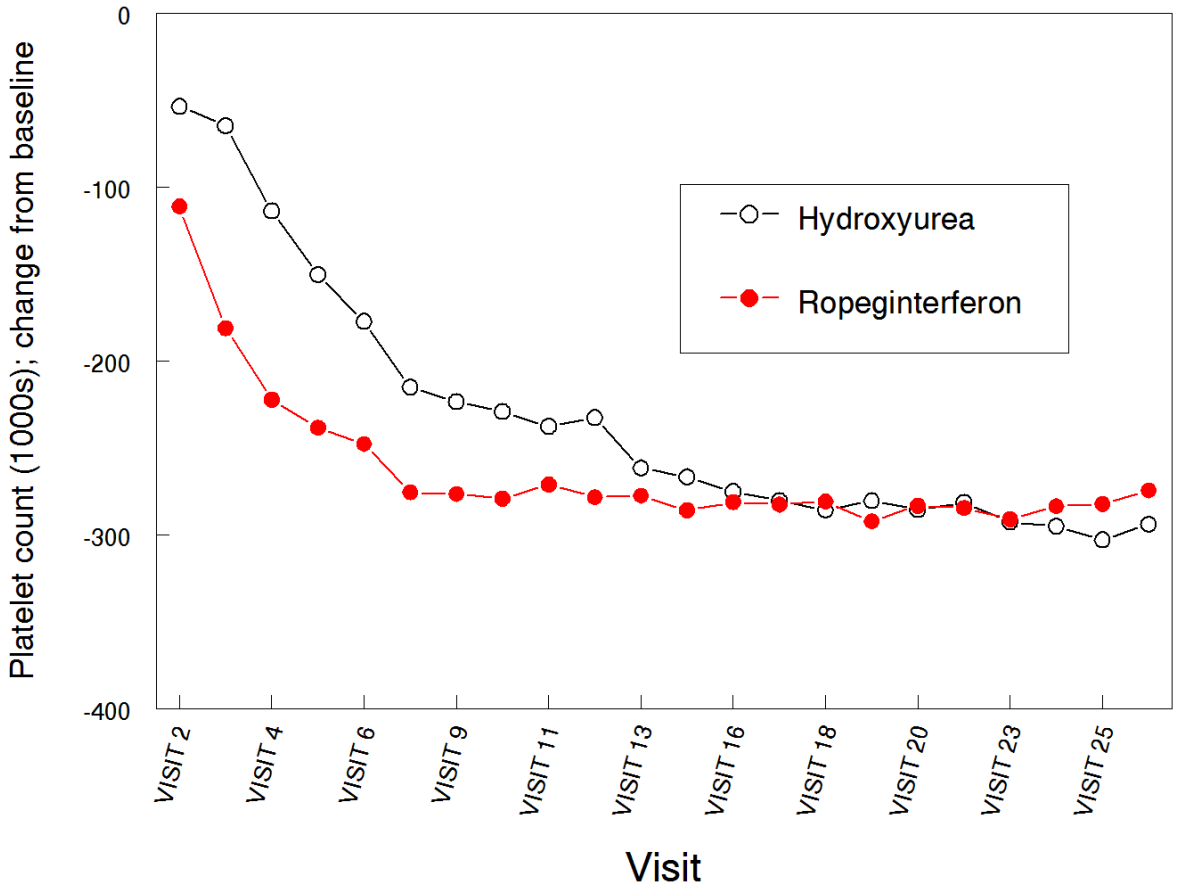
Source: Table 1 of Applicant's FDA IR Response Final_20201015.docx

Additional Endpoints

Change from Baseline for PLTs and WBCs in PROUD-PV

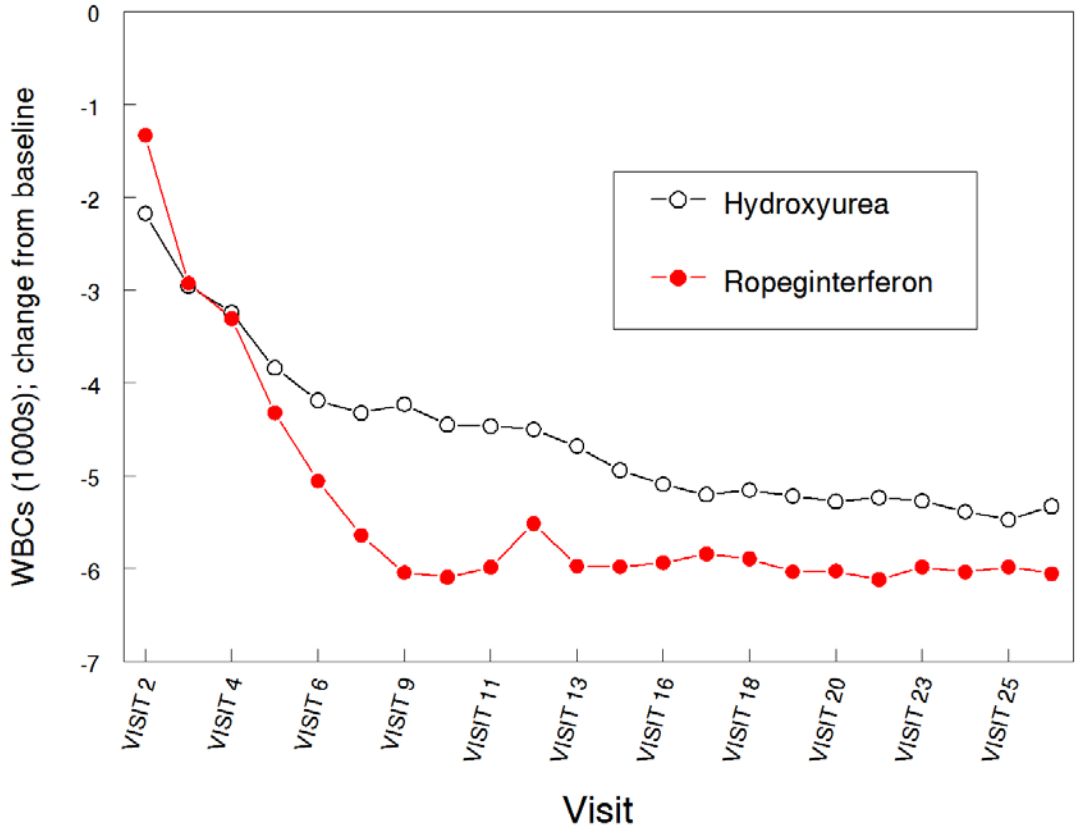
Evaluation of the change from baseline for PLTs and WBCs for ropeginterferon alfa-2b was evaluated up to visit 25 (12 months). There was a demonstratable decrease in PLTs and WBCs from baseline/visit 2 until visit 25. These changes would not occur by chance alone in this disease. In addition, with cessation 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 11 Change from Baseline for PLTs in the PROUD-PV Study



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

Figure 12 Change from Baseline for WBC Count for PEGINVERA study



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

The mean values over time for HCT, WBCs and PLTs 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 22: Change from Baseline for Hematology Parameters in PROUD-PV/CONTINUATION 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)
WBCs < 10 x 10^9/L	5.53±2.12 (88/95)	7.22±3.56 (64/76)

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 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)

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.

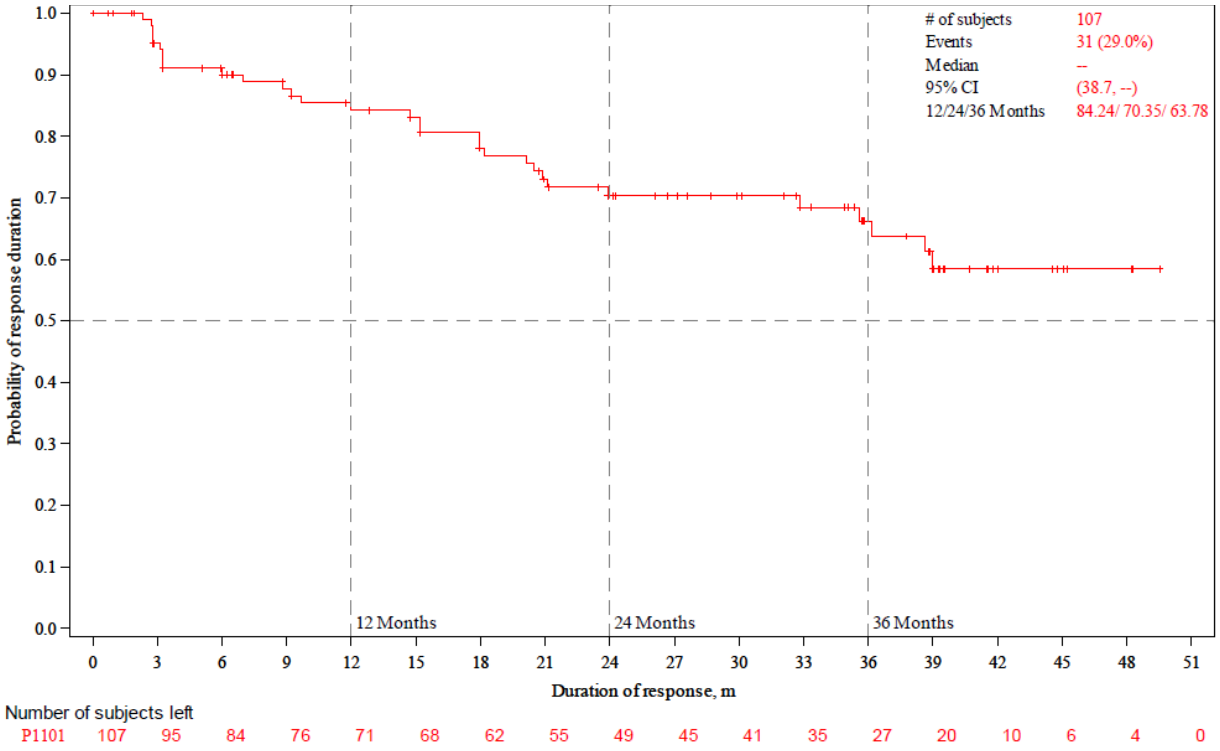
JAK2 Allelic Burden

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

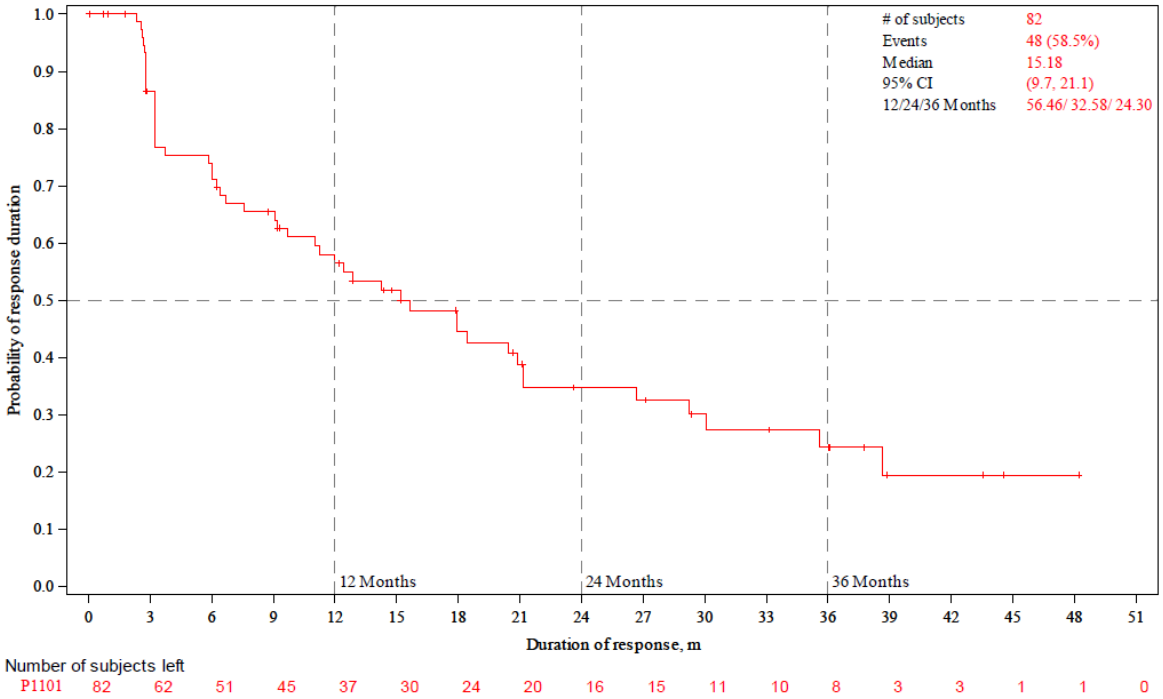
Duration of response for endpoints CHR and CHR plus normal spleen size are displayed in the figures below. For the endpoint CHR, median duration of the 107 patients who reported responses was not reached. For endpoint CHR plus normal spleen size, the median duration was 15 months with 95% CI (9.7, 21.1).

Figure 13 Kaplan-Meier Plot of Duration of Longest CHR(hematology parameters only)-As Treated Population (single arm)



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

Figure 14: 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

8.5. 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 database lock). Sample size calculations based on assumptions for superior and could not be changed. Additionally, the change was made 2 months after completion of the PROUD-PV.
- The PROUD-PV study failed to show non-inferiority of ropeginterferon to HU as the lower bound of the 95% CI of the difference in disease response rate (ropeginterferon-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 or adequately justified.
- Selection bias in the CONTINUATION-PV study was not properly randomized and selection bias may exist (known and unknown) which could undermine the study results.
- No formal hypothesis testing for inferential comparison between ropeginterferon alfa-2b and BAT arms in the CONTINUATION-PV study.

A possible reason for the PROUD-PV trial failure is the different dose titration between the two arms in the PROUD-PV study. 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 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) after 12 months of treatment in the PEGINVERA study. 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).

- 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. Thus, the PEGINVERA study can be viewed as an AWC with valid historical control because we recognize that the leukocytosis and thrombocytosis of PV do not resolve spontaneously.

- The objective laboratory measurements from the active treatment group from the independent PROUD-PV demonstrate decreases in PLTs and WBC counts from baseline provide additional objective confirmatory evidence. These parameters were assessed on a frequent basis (every 2 weeks) and were objectively measured and these parameters did not occur by chance alone.

9. Safety

9.1. 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.

9.1.1. 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 23: Duration of Exposure of Ropeginterferon alfa-2b in PEGINVERA, PROUD-PV, CONTINUATION-PV and Pooled Safety Database.

	PROUD-PV	PEGINVERA	PROUD-PV/CONTINUATION-PV	ALL STUDIES
N	127	51	95	178
Exposure (days) median (range) Mean (SD)	399 (28,336) 336 (74.97)	1816 (14, 2604) 1379 (962.2)	1201 (43, 1568) 1024 (489.3)	1237 (14, 2604) 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	13	61	40	41

	PROUD-PV	PEGINVERA	PROUD-PV/CONTINUATION-PV	ALL STUDIES
(months) median (range) Mean (SD)	(1, 14) 12 (2.5)	(1, 87) 46 (32.1)	(1, 52) 43 (16.3)	(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

The median duration of treatment in the PEGINVERA-PV was 62 months (range: 1 to 88 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.

9.2. Adequacy of Applicant's Clinical Safety Assessments

9.2.1. 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 applicants translations of verbatim terms to MedDRA preferred terms for the events reported in PEGINVERA and PROUD-PV/CONTINUATION were reviewed and found to be acceptable.

9.2.2. 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 and CONTINUATION trial-PV. In the PEGINVERA, adverse events were graded as mild, moderate, severe. 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 b begins after start of treatment or which worsens during course of study until the last dose + 28 days.

9.3. Safety Results

9.3.1. Deaths

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

Table 24: 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)	72 y/o male Caucasian	*Start Date:* (b) (6) *Last Dose:* (b) (6) *Date of Death:* (b) (6)	Enrolled in PEGINVERA-PV study. Patient's medical history 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)	59 y/o male Caucasian	*Start Date:* Unknown *Last Dose:* (b) (6) *Date of Death:* (b) (6) (b) (6)	Enrolled in PEGINVERA-PV study. Did not receive IMP due to behavior (i.e. depression). Patient was withdrawn from study on

Patient/ARM/Country	Age/Sex/Race	Time (days) from date of last study drug to date of death	Summary of Death Narrative
			(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, Temozolomide. Patient died on (b) (6) *Grade 4 Glioblastoma not related to ropeginterferon alfa-2b-njft or PV*
PEGINVERA - (b) (6) (ropeginterferon alfa-2b)	81 y/o female Caucasian	*Start Date:* (b) (6) *Last Dose:* (b) (6) *Date of Death:* (b) (6) (b) (6)	Enrolled in PEGINVERA-PV. History of hypertension, hyperuricemia, hepatic steatosis, dyspnea, prostate hypertrophy. Hospitalized for macrohematuria. No medical history of psychological disorder. *Grade 5 completed suicide*
PROUD-PV (ropeginterferon alfa-2b) (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

Patient/ARM/Country	Age/Sex/Race	Time (days) from date of last study drug to date of death	Summary of Death Narrative
			of Glioma/Glioblastoma. Removal of the Glioma occurred on (b) (6) Patient died on (b) (6) (b) (6) from sequelae associated with Glioma. *Grade 4 Glioblastoma not related to ropeginterferon alfa-2b.*
CONTINUATION-PV) (ropeginterferon alfa-2b) (b) (6)	65 y/o female Caucasian	*Start Date:* (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.*

UTI: Urinary Tract Infection; IMP: Investigational Medical Product; PV: Polycythemia Vera

9.3.2. 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 25: 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%)

SOC and Preferred Term	N=51 n (%)
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%)
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	

SOC and Preferred Term	N=51 n (%)
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%)
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 26 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%)
endocarditis	1 (0.6%)
diverticulitis	1 (0.6%)
cholangitis infective	1 (0.6%)
appendicitis	
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%)

PREFERRED TERM	N=178 N (%)
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%)
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%)

PREFERRED TERM	N=178 N (%)
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%)
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: Polycythemia Vera secondary myelofibrosis	1 (0.6%)

Source: FDA Analysis

9.3.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 27: 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.

9.3.4. Adverse Events of Special Interest

The applicant proposed several adverse events of special interest based on findings from other interferons. The Agency included several additional adverse events of special interest based upon known safety profile of FDA-approved pegylated interferons. Table 39 describes the adverse events of special interest in the pooled safety group (N=178).

Table 28 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%)

	Ropeginterferon alfa-2b N=178 n (%)
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%)
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%)

	Ropeginterferon alfa-2b N=178 n (%)
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

Neuropsychiatric events to include depression and one completed case of suicide occurred during the development of ropeginterferon alfa-2b. In a literature review, the prevalence of psychiatric 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 and review team recommends a box warning in the label for the neuropsychiatric events.

Cardiac disease to include events of atrial fibrillation, tachycardia and cardiac failure were observed in the 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. Appropriate description in the warnings and precautions of prescribing information is recommended.

Liver Enzyme Elevation and hepatotoxicity to include drug-induced liver injury are known class safety effects of interferons. In published literature, hepatoxicity of all grades is reported in approximately 60% of patients to include grade 3-4 toxicity in approximately 30% of patients. 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. Appropriate mitigation strategies to include interruption of treatment will be described 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 are reported in the literature with the use of interferons. Antibodies against antinuclear antigens (ANAs), thyroid antigens were observed and identified as clinically relevant. Appropriate warning 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 (pneumonitis), and 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.

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

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 for patients with known immunological diseases in the label.

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 are recommended in the label to address these risks.

This table focuses on the adverse events seen among patients with a frequency of 7% or greater for the PEGINVERA study. The terms 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.

Table 29: PEGINVERA: Common Adverse Events by System Organ Class and Preferred Terms >7%.

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%)
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	

Adverse Reactions	Ropeginterferon alfa-2b N=51 n (%)
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	
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	

Adverse Reactions	Ropeginterferon alfa-2b N=51 n (%)
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,

Additional analyses were performed on the based on 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 30 Moderate and Severe Events in the 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 31: 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%)
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%)

Common TEAEs (All Studies Combined)	Ropeginterferon alfa-2b
	N=178 n (%)
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%)
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

Treatment Emergent Adverse Events were also considered in the PROUD-PV study and the following table describes the TEAEs in the PROUD-PV study for the ropeginterferon alfa-2b arm and the HU arm.

Table 32 TEAEs in the PROUD-PV

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%)
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%)

Adverse Events by System Organ Class and Preferred Terms	Ropeginterferon alfa-2b N=127	HU N=127
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%)
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%)

Adverse Events by System Organ Class and Preferred Terms	Ropeginterferon alfa-2b N=127	HU N=127
Dyspepsia FDA N	6 (4.7%)	9 (7.1%)
Nausea FDA N	4 (3.1%)	16 (12.6%)
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

9.3.5. 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 elevation of liver enzymes > 3X ULN was reported.

	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 Table/ Sponsor response to Information Request by the review team.

There was one episode of AST or ALT > 3 X ULN and bilirubin > 2 x ULN and ALP <2 x ULN, 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 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, the AE of transaminase was registered and the patient skipped the next two doses of study drug. The next treatment was 150 mcg after a 4 week interruption which started on (b) (6). The next dose was reduced to 100 mcg and then reduced further to 50 mcg with periods of interruptions until (b) (6). The patient was taken off study at week 58. The single episode occurred at visit 5/week 8 (b) (6) Patient had fluctuating bilirubin levels (baseline of 23.77umol/L to highest of 116.28 umol/L during weeks 8 to 14). Bilirubin levels returned to 23umol/L at week 26. The patient continued to be treated with ropeginterferon alfa-2b after visit 8 at a lower dose without a recurrence of the elevation of the laboratory values.

Amylase and Lipase and Triglycerides

Table 33 Amylase, Lipase and Triglyceride Elevations in the 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 (0.0%)
Lipase	>2 x ULN	4 (7.8%)
Lipase	>3 x ULN	2 (3.9%)
Lipase	>5 x ULN	0 (0.0%)
Triglycerides	>2 x ULN	8 (15.7%)
Triglycerides	>3x ULN	4 (7.8%)
Triglycerides	>5x ULN	1 (1.9%)

Source: FDA Analysis based on Applicant's response to Information Request

9.3.6. 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-PV 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.

9.3.7. 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 year-old male) after Week 146. 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.

9.3.8. 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).

9.3.9. Immunogenicity

There were 51 patients from the PEGINVERA study and 126 eligible patients from the PROUD-PV study evaluated for binding and neutralizing antibodies for a total of evaluable 177 patients. At baseline, there were 7 patients who were positive for anti-drug antibodies (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.

9.4. Analysis of Submission-Specific Safety Issues

Hepatoxicity

Further analysis of hepatotoxicity 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 48 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 34 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)

The majority of the TEAES observed were grade 1 or grade 2 events 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. This event is described in section 10.3.6 in more detail.

Recommend including hepatotoxicity to include description of elevation of hepatic enzymes in the warnings and precautions of the prescribing information.

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.

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

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 49 displays the thromboembolic events in the pooled safety population.

Table 35 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%)

Thromboembolic Events	Ropeginterferon N=178 n (%)
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%)

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.

Table 36: 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%)

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, elevated WBCs and PLTs may contribute to the thrombotic risk. Recommend appropriate warning and mitigation measures in the prescribing information.

9.5. 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.

9.6. Specific Safety Studies/Clinical Trials

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

9.7. Additional Safety Explorations

9.7.1. 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 developing glioblastoma multiforme or increased risk of malignancy. In comparative safety between HU and ropeginterferon alfa-2b, there was 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.

9.7.2. Human Reproduction and Pregnancy

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

9.7.3. Pediatrics and Assessment of Effects on Growth

There was no pediatric data submitted with this application.

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

One case of overdose was reported in a 54 year-old, female patient enrolled 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 µg. 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.

9.8. Advisory Committee Meeting and Other External Consultations

Neither an Advisory Committee Meeting nor an 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.

10. Labeling Recommendations

10.1.1. 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	Ropeginterferon alfa-2b 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. Revised box warning.
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 ropeginterferon alfa-2b is based on CHR from the PEGINVERA trial.

11. Risk Evaluation and Mitigation Strategies (REMS)

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

12. Postmarketing Requirements and Commitments

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

13. Appendices

13.1. References

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