Clinical Trial Protocol

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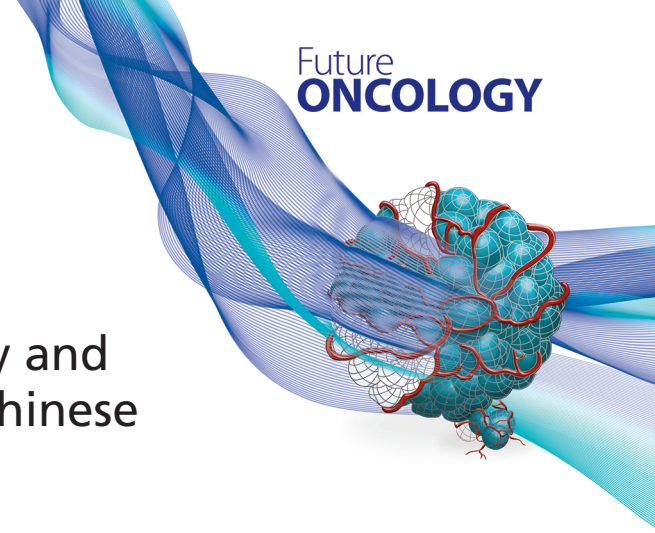

A phase II trial to assess the efficacy and safety of ropeginterferon α-2b in Chinese patients with polycythemia vera

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Ropeginterferon α-2b is a mono-PEGylated proline-interferon for the treatment of polycythemia vera. This drug is used biweekly with a starting dose of 100 μg (50 μg if patients receiving hydroxyurea) and 50 μg increments up to a maximum dose of 500 μg. Increasing evidence indicates that patients can tolerate higher starting doses of ropeginterferon α-2b. This phase II trial utilizes 250 μg as the starting dose, 350 μg at week 2 and 500 μg at week 4 as the target dose. Doses can be adjusted according to tolerability. This study assesses the safety, efficacy and molecular response of ropeginterferon α-2b in Chinese patients with PV utilizing the 250–350–500 μg dosing schema. This study will be used to support the application of a biologics license for polycythemia vera treatment in China.

Plain language summary: Polycythemia vera (PV) is a slow-growing blood neoplasm (cells that grow and divide more than they should or do not die when they should). PV often has a mutation in the gene called *JAK2*, which causes changes in the DNA of genes that cause cells to become cancerous. PV is associated with an increased number of blood cells, debilitating symptoms, risks of thrombosis (blood clot) and bleeding and can progress to other diseases, including myelofibrosis and acute myeloid leukemia. Ropeginterferon α-2b is a new product with favorable properties, allowing a convenient dosing schedule of every 2–4 weeks. This drug has demonstrated good tolerability, safety and efficacy for PV treatment and has been approved for the treatment of PV in Europe and the USA. This article discusses the design of an ongoing study that looks at the safety and efficacy of ropeginterferon α-2b for the treatment of PV. The study follows a specific dosing schedule, with the aim of controlling the neoplasm faster, and plans to include 49 patients from 12–15 major hospitals in China.

Clinical Trial Registration: This trial is registered at ClinicalTrials.gov (identifier: NCT05485948) and in China (China National Medical Products Administration Clinical Trial Registration Number: CTR20211664).

Tweetable abstract: New #phaseII #trial to assess ropeginterferon α-2b in Chinese patients with polycythemia vera.

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Keywords: Chinese patients • dosing schema • hydroxyurea • molecular response • polycythemia vera • ropeginterferon α-2b

Background & rationale

Polycythemia vera (PV) is a common subtype of myeloproliferative neoplasm (MPN), characterized by the presence of a *JAK2* gene mutation in most cases, increased blood cell counts, symptom burdens that can be debilitating over time, risks of thrombosis and bleeding and transformation to myelofibrosis or acute myeloid leukemia [1–

3]. Treatment goals include the prevention of thrombo-hemorrhagic complications [2,4]. Adequate control of hematologic parameters, including hematocrit, white blood cell and platelet levels, is crucial, as increasing evidence indicates that higher blood cell counts resulting in altered hematocrit levels, leukocytosis and thrombocytosis are correlated with thrombosis or even cardiovascular mortality [5–8]. Treatments are also aimed at alleviating the symptomatic burden and reducing the risk of progression to myelofibrosis and acute myeloid leukemia [1–4,8]. Therefore, disease-modifying agents that can selectively suppress the driver mutation-carrying hematopoietic stem or progenitor cells, control abnormal hematologic parameters, inhibit the transformation to myelofibrosis or acute myeloid leukemia and promote progression-free and overall survival are needed. Interferon-based therapies have been recognized to have disease-modifying potential [9–15].

Ropeginterferon α-2b is a novel PEGylated proline-IFN-α, generated *via* site-selective PEGylation, resulting in favorable pharmacokinetic properties and a convenient clinical dosing schema – that is, once every 2 weeks (biweekly) or once every 3 to 4 weeks [13,15–19]. Several clinical studies in PV patients have demonstrated its safety and tolerability and complete hematologic remission (CHR), including freedom from phlebotomies [13,15,19–21]. It inhibits the cells carrying *JAK2* with a driver mutation of valine to phenylalanine substitution at codon 617 (*JAK2V617F*) *in vitro* and *in vivo* [22]. Its treatment decreases the *JAK2V617F* allelic burden in patients, inducing molecular response together with durable CHR and less PV progression [13,15,19–21]. Recently, ropeginterferon α-2b was approved for the treatment of adult patients with PV in the USA. It is the first approved interferon-based therapy for PV and is approved for all adult PV patients, including those at low or high risk in the USA [23]. In addition to treating PV, ropeginterferon α-2b is under evaluation for the treatment of other indications, including essential thrombocythemia and chronic viral hepatitis [24–27].

Objectives

Current treatment options for PV in China are either low-dose aspirin with hydroxyurea (HU) or earlier-generation interferon preparations, which are associated with frequent injections or toxicities. Despite the availability of ropeginterferon α-2b in the USA, Europe and other countries or regions, including Macao of China, ropeginterferon α-2b is currently not available in mainland China. A pharmacokinetics (PK) study of ropeginterferon α-2b has been conducted in healthy Chinese volunteers [17]. After communication with the Center for Drug Evaluation of China, this phase II clinical study in Chinese patients with PV was planned. The goal of this phase II, single-arm, multicenter study is to evaluate the efficacy, safety and clinical utility of ropeginterferon α-2b to support the biologics license approval for the treatment of PV in China. This trial is registered at ClinicalTrials.gov (identifier: NCT05485948) and in China (China National Medical Products Administration registration number: CTR20211664).

Rationale for the dosing schema

In a compassionate use program, HU or anagrelide-resistant or -intolerant MPN patients were treated with ropeginterferon α-2b, mainly at a 250–350–500 μg dosing schema [28]. This schema consisted of a starting dose of 250 μg (week 0), followed by 350 μg at week 2 and 500 μg at week 4 as the target dose to be administered thereon. This starting dose of 250 μg is higher than the typical 100 μg starting dose and the schema has three intra-patient dose-up steps to the target dose of 500 μg compared with nine or ten dose titration steps used in the phase III PROUD-PV study. Dose reduction or interruption is allowed if patients experience tolerability issues. Real-world data collected from the compassionate use program demonstrated that patients tolerated the treatment well and showed a decrease in the *JAK2V617F* allelic burden and significant hematologic and clinical responses, including symptom alleviation [28].

In the ongoing phase III SURPASS study in patients with essential thrombocythemia, the same dosing schema of 250–350–500 μg with a target dose of 500 μg is used [24].

Ropeginterferon α-2b has been tested in four clinical studies in patients with chronic viral hepatitis B or C [29–32]. In these studies, for the biweekly dosing schedule, ropeginterferon α-2b was administered to patients at doses ranging from 270 to 450 μg for treatment durations of 24 or 48 weeks. A biweekly dose of 450 μg as monotherapy for 48 weeks in patients with chronic viral hepatitis B was well tolerated [29]. Ropeginterferon α-2b was also well tolerated in patients with chronic viral hepatitis C genotype 1 or 2 when administered at doses ranging from 270 to 450 μg in combination with daily oral ribavirin [30–32]. Most reported adverse events (AEs) during treatment were mild or moderate. Grade 3 and 4 toxicities were uncommon and were generally managed well with dose reduction or discontinuation. In a recently completed phase III study in patients with chronic viral hepatitis C genotype 2, ropeginterferon α-2b administered at 400 μg biweekly in combination with daily ribavirin showed favorable safety

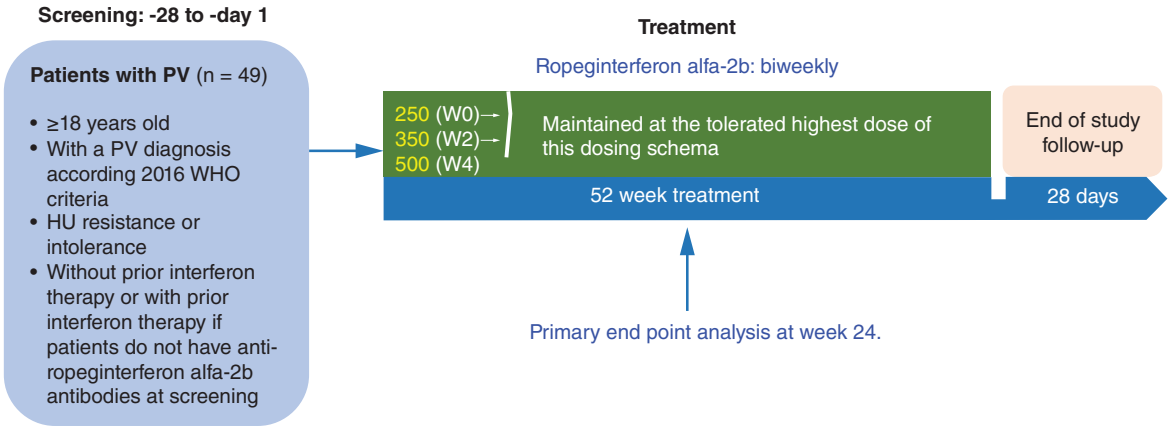

Figure 1. Study design.
HU: Hydroxyurea; PV: Polycythemia vera; W: Week.

profiles and antiviral activities compared with an earlier generation of PEGylated IFN-α-2b [32]. Therefore, patients with chronic viral hepatitis tolerated higher doses up to 450 μg of ropeginterferon α-2b.

In the phase I/II PEGINVERA study, PV patients were treated with ropeginterferon α-2b up to a dose of 540 μg without dose-limiting toxicities [19]. In the phase III PROUD-PV and its extension study, CONTINUATION-PV, good tolerability and safety were observed in patients receiving doses of ropeginterferon α-2b up to 500 μg during the maintenance period to control the hematologic parameters of PV [13].

Therefore, this phase II study utilizes the 250–350–500 μg dosing schema in Chinese patients with PV after consultation with the regulatory authority in China. The starting dose of ropeginterferon α-2b is 250 μg, followed by 350 μg at week 2 and 500 μg at week 4 onward. Dose adjustment is allowed according to tolerability.

Methods

Study population

HU is the current first-line treatment for patients with PV in China. Patients undergoing HU treatment develop hematologic or nonhematologic toxicities such as intolerable skin ulcers, leading to HU resistance or intolerance [33,34]. The need for the treatment of PV patients with HU resistance or intolerance in China is unmet. As a result, HU-resistant or -intolerant PV patients in China were enrolled in this trial.

Study design & methods

This study is an open-label, single-arm, multicenter trial in Chinese PV patients with HU resistance or intolerance. Ropeginterferon α-2b is administered every 2 weeks as a subcutaneous injection during the study visits. Patients who have received prior interferon-based therapies are allowed to be enrolled if no binding antibodies against ropeginterferon α-2b are detected. Subsequently, patients are treated with ropeginterferon α-2b at the 250–350–500 μg dosing schema (Figure 1). Dose reduction or interruption is allowed if patients experience intolerance. Specifically, if a patient experiences a severe (grade 3 or above) toxicity or a decrease in absolute neutrophil count to below 0.5×10^9/l, temporary dosing interruption has to be implemented until recovery of the condition (e.g., recovering to grade 0 or 1). Treatment re-initiation must begin at a dose lower than the dose that caused the toxicity. For example, if a grade 3 AE occurs at the dose of 500 μg, treatment re-initiation will occur at 350 μg. If there is an absence of response (i.e., failure to keep hematocrit <45%) after 1 month of treatment at this reduced dose, the dose will be increased back to the level before the dose reduction. If a patient experiences a grade 2 toxicity or a decrease in absolute neutrophil count to below 0.75×10^9/l but higher than 0.5×10^9/l, dose reduction without treatment interruption should be considered. Grade 1 toxicity will not lead to dose reduction or dose interruption.

For patients currently receiving HU treatment, the HU dose is gradually reduced during the screening period (adjusted by the investigator based on clinical practice). HU treatment ends within 4 weeks of ropeginterferon α-2b treatment and is prohibited thereafter.

Table 1. Eligibility criteria for the study.

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years	• Symptomatic splenomegaly
• Diagnosis with PV (2016 WHO criteria)	• Any contraindications or hypersensitivity to IFN-α
• HU-resistant or -intolerant PV patients meeting at least one of the following criteria: a. Drug resistance: 3 months of treatment at HU doses >2 g/d – Phlebotomy still required to maintain hematocrit <45% – Failure to control bone marrow proliferation (e.g., as platelet count >400 × 10^9/l and white blood cell count >10 × 10^9/l) – Spleen shrinkage of <50% b. Intolerance – At the minimum dose of HU required to achieve complete or partial clinical hematologic response: absolute neutrophil count <1.0 × 10^9/l, platelets <100 × 10^9/l or hemoglobin <100 g/l – At any dose of HU treatment, the patient develops lower limb ulcers or other intolerable nonhematologic toxicity, such as skin mucosal manifestations (dark skin, teeth or nails; oral ulcers; mucositis; skin ulcers; rash; and other symptoms), gastrointestinal complaints (nausea, loss of appetite, indigestion, vomiting, abdominal pain, constipation and other symptoms), pneumonia, fever etc.	• Patients with any other diseases that the investigator determines will affect the study results or may weaken compliance to the protocol, including but not limited to – Prior or current autoimmune thyroid disease (clinical symptoms of hyper- or hypothyroidism), but patients with oral thyroxine replacement therapy could be enrolled – Other documented autoimmune diseases (e.g., hepatitis, immune thrombocytopenia, scleroderma, psoriasis or any autoimmune arthritis) – Clinically significant pulmonary infiltration, infectious and noninfectious pneumonia or a past history of interstitial pneumonia at screening – Active infection with systemic manifestations (e.g., presence of bacteria, fungi or HIV, excluding hepatitis B virus and/or hepatitis C virus at screening) – Evidence of severe retinopathy (e.g., cytomegalovirus-induced retinitis or macular degeneration) or clinically significant eye diseases (due to diabetes or hypertension) – Clinically significant depression or a history of depression – Previous suicide attempts or any risk for suicidal tendency at screening
• Patients who have not received interferon therapy previously or have negative antiropeginterferon α-2b binding antibody at screening	• History of major organ transplantation
• Good liver function at screening, defined as total bilirubin ≤1.5 × ULN, international normalized ratio ≤1.5 × ULN, albumin >3.5 g/dl, alanine aminotransferase ≤2.0 × ULN and aspartate aminotransferase ≤2.0 × ULN	• Pregnant or breastfeeding women
• Hemoglobin ≥10 g/dl for females and ≥11 g/dl for males at screening	• Severe or serious diseases that the investigator determines may affect the patient's participation in this study
• Neutrophil count ≥1.5 × 10^9/l at screening	• Poorly controlled diabetes
• Creatinine clearance rate ≥40 ml/min at screening (according to the Cockcroft–Gault formula)	• Thromboembolic complications caused by PV and active abdominal hemorrhage
• Males and females of childbearing potential, as well as all of the females with a menopause duration of less than 2 years, must consent to use acceptable contraceptive methods within 28 days after the last dose of the study drug	• History of any malignant tumors (except stage 0 chronic lymphocytic leukemia, cured basal cell carcinoma, squamous cell carcinoma and superficial melanoma) in the past 5 years
• The patient or the patient's guardian signed the written informed consent, and the patient is able to comply with the study requirements	• History of alcohol or drug abuse in the past year
	• History or evidence of post PV-myelofibrosis, essential thrombocythemia or any non-PV myeloproliferative neoplasm
	• Presence of blast cells in the peripheral blood in the past 3 months
	• Use of any investigational drugs or investigational drug combinations within 4 weeks before the first dose of the study drug, or no recovery from the effects caused by any previously administered investigational drug

HU: Hydroxyurea; PV: Polycythemia vera; ULN: Upper limit of normal.

Efficacy evaluation includes assessments of CHR, disease progression, bleeding or thrombotic events, quality of life according to EuroQoL 5-Dimension 3-Level and *JAK2V617F* allele burden. The quantitative determinations of *JAK2V617F* allele burden and hematologic parameters for CHR are completed by the central laboratory.

The study duration for each patient will be approximately 14 months, including a 28-day screening, 52-week treatment (12 months) and 28-day safety follow-up period. The primary end point (CHR) is measured at 24 weeks (6 months). During the treatment period, biweekly patient visits will be scheduled. The end-of-treatment visit is to be performed at week 52 of treatment or upon early termination of the study. The end-of-study visit is to occur 28 days after the end-of-treatment visit. Data analyses will be performed after all patients complete 24 weeks of treatment, and a clinical trial study report will be written. New drug application is planned for submission with the report. A statistical analysis will be performed after all patients have completed all visits, as per the protocol. Patients who complete the entire trial (i.e., the 52-week treatment period and the end-of-study follow-up visit) may have the opportunity to receive additional ropeginterferon α-2b treatment under the direction of the investigator for up to 12 months. The study plans to enroll a total of 49 patients from 12–15 major hospitals in China.

Patient eligibility criteria

A complete list of the key inclusion and exclusion criteria is provided in Table 1. The major eligibility criteria include male or female patients aged ≥18 years with a diagnosis of PV according to the 2016 WHO criteria [35]. Additionally,

patients with HU intolerance or resistance according to the modified European LeukemiaNet criteria [36] are enrolled.

Study end points

As the dosing schema used in the trial has a higher starting dose and quicker intra-patient dose-up steps, CHR is anticipated to be achieved sooner than in PROUD-PV. The primary end point of PROUD-PV was measured after 12 months of treatment. The primary end point of this study is the proportion of patients who reach CHR at 6 months (week 24). CHR is defined by the following hematologic criteria: hematocrit <45% without phlebotomy or erythrocyte apheresis in the preceding 3 months, platelet count $\leq 400 \times 10^9$/l and leukocyte count $<10 \times 10^9$/l [36]. The secondary end points include CHR rates at weeks 12, 36 and 52. Other secondary end points are the time trend in the CHR rate; changes from baseline in hematocrit, white blood cell and platelet levels; time to first hematocrit, white blood cell and platelet response; duration of CHR; progression-free remission rates at weeks 12, 24, 36 and 52; improvement in quality of life as assessed by the EQ-5D-3L questionnaire; proportion of patients without thrombotic or hemorrhagic events; and change from baseline in the *JAK2V617F* allele burden over time. Safety assessments include the incidence, causality and severity of AEs assessed according to the Common Terminology Criteria for Adverse Events 5.0 (CTCAE 5.0); the incidence, causality and severity of AEs of special interest; and the events leading to dose reduction or permanent termination of treatment. In addition, PK, population PK, the relationship between exposure and key efficacy and safety end points will be evaluated using exposure-response analysis.

Calculation of sample size

Previous data suggested that the CHR rate of best available therapy in PV patients who were resistant or intolerant to HU was only 5% at 28 weeks and 9% at 32 weeks [37,38]. Based on PROUD-PV, it was assumed that the CHR rate of ropeginterferon α-2b in Chinese PV patients who are HU-resistant or -intolerant could reach at least 30% by week 24. With reference to historical study data in combination with current requirements for clinical practice, the drug can be determined as effective only when the lower limit of the 95% CI of the CHR rate at week 24 of treatment obtained from the trial is greater than 11% (H0: CHR ≤11%; H1: CHR >11% [assuming the true value = 30%]). Using one-sided $\alpha = 0.025$ for type I error, a power of 89% to infer the effectiveness of ropeginterferon alfa-2b can be obtained with 44 patients using the exact test. Considering a dropout rate of 10%, the authors planned to enroll 49 patients in this study.

Statistical analysis methods

For continuous variables, the descriptive statistics include the number of cases, mean, median, standard deviation, maximum and minimum. For categorical variables, the descriptive statistics include the number and percentage of patients. Statistical analyses will be performed using Statistical Analysis System (SAS®) software, version 9.4.

The primary efficacy indicator in this trial is the CHR rate at week 24, based on the evaluation of the central laboratory test results. The number and percentage of patients who achieve CHR at week 24 will be calculated, and the 95% CI of the CHR rate at week 24 will be estimated using the Clopper–Pearson method. For the secondary efficacy indicators of this trial, the CHR rates at different time points and other response rates will be described using the number and percentage of patients, and the 95% CI will be estimated using the Clopper–Pearson method. The median and 95% CI of the time-event end points will be estimated using the Kaplan–Meier method.

AEs will be described according to the system organ classes and preferred terms of the MedDRA dictionary and graded according to the CTCAE v.5.0. Descriptive statistics will be calculated for the number of occurrences, number of patients and incidence of various AEs (all AEs, treatment-emergent AEs [TEAEs], serious AEs, drug-related TEAEs, TEAEs of grade 3 and above, TEAEs leading to permanent termination of the trial and TEAEs leading to drug suspension). Immunogenicity analysis (the proportion of patients with positive or negative anti-ropeginterferon α-2b antibodies and the status of neutralizing antibodies in binding antibody-positive patients) will also be summarized.

Conclusion

Ropeginterferon α-2b is a new-generation PEGylated IFN-α with favorable PK, tolerability and safety profiles. It is approved for the treatment of adult patients with PV in the USA and Europe based on safety and efficacy data from the phase I/II PEGINVERA and phase III PROUD-PV/CONTINUATION-PV studies. On 12 November

2021, the US FDA approved ropeginterferon α-2b for the treatment of all adult patients with PV, regardless of their prior treatment history. Therefore, it was the first interferon-based product approved for PV. Recently, it was approved in Macao, China, for PV treatment (13 September 2022). However, ropeginterferon α-2b is not yet available in mainland China. Previously, a phase I clinical study in healthy Chinese volunteers was conducted to collect the required PK data for the biologics license application. This phase II study was planned after consultation with the Chinese Center for Drug Evaluation and will generate efficacy and safety data needed for the biologics license application in China.

Because increasing evidence suggests that patients can tolerate higher starting doses of ropeginterferon α-2b treatment, the trial will also provide important efficacy and safety data to determine whether a higher starting dose and faster intra-patient dose escalation (i.e., the 250–350–500 μg dosing schema) can safely, effectively and quickly lead to CHR. This could minimize the risk of any insufficient dosing during the dose titration phase of the slow dose titration schema (starting dose of 100 μg or 50 μg for patients under cytoreductive therapy, followed by 50 μg increments biweekly up to 500 μg), which could require 20–28 weeks for the dose to reach the plateaued level, as demonstrated in the PROUD-PV study. Efficient control of abnormal hematologic parameters and elimination of malignant mutation-carrying clones at a tolerable dose may control the disease and effectively inhibit neoplastic progression in patients. The trial is ongoing and all 49 patients have been enrolled in the study.

Executive summary

Background

- Polycythemia vera (PV) is a common myeloproliferative neoplasm associated with *JAK2* gene mutations, increased blood cell counts, the symptoms and risk of thromboembolic events and transformation to myelofibrosis and acute leukemia.
- Disease-modifying agents are needed to induce a molecular response, control abnormal hematologic parameters that can lead to thromboembolic events, inhibit PV transformation to myelofibrosis and acute leukemia and promote overall survival.
- Interferon-based therapies have been shown to have disease-modifying potential in PV.
- Ropeginterferon α-2b is a novel PEGylated proline-IFN-α-2b with favorable pharmacokinetics (PK), tolerability and safety profiles. It is clinically administered once every 2–4 weeks.
- It is approved for the treatment of adult patients with PV in the USA and Europe based on safety and efficacy data from the PEGINVERA and PROUD-PV/CONTINUATION-PV studies.
- Emerging data suggest that patients can tolerate a higher starting dose and faster intra-patient dose escalation to the therapeutic target dose or a maximally recommended dose.
- Ropeginterferon α-2b is approved in Macao, China, but is not yet available in mainland China.
- Clinical data in Chinese patients with PV are needed for the approval of ropeginterferon α-2b in mainland China.

Study design

- This is an open-label, single-arm, multicenter trial in Chinese PV patients with hydroxyurea resistance or intolerance. Patients who have received prior interferon-based therapy are allowed to be enrolled if no binding antibodies against ropeginterferon α-2b are detected.
- Patients are treated with ropeginterferon α-2b subcutaneously at a starting dose of 250 μg (week 0), followed by 350 μg at week 2 and 500 μg at week 4 onward.
- The study duration for each patient is to be approximately 14 months, including a 28-day screening period, 52-week treatment period and 28-day safety follow-up period.
- The primary end point of complete hematologic remission will be measured at 6 months (24 weeks). The study has a 12-month treatment period in total, and the secondary efficacy end points include complete hematologic remission rates at weeks 12, 36 and 52.
- Quantitative determination of the genetic *JAK2V617F* allele burden and hematologic parameters for complete hematologic remission assessment will be completed by the central laboratory.
- Forty-nine patients are enrolled in the study.

Conclusion

- This trial will generate valuable data for the biologics license application for ropeginterferon α-2b in China and will provide important efficacy and safety data for an emerging dosing schema of ropeginterferon α-2b regarding whether it can safely, effectively and quickly lead to complete hematologic remission and decrease *JAK2V617F* allele burden.

Author contributions

Each author listed contributed to the work and takes responsibility for the content. All authors participated in the writing and review process of the manuscript and agreed with the publication of this article.

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Financial & competing interests disclosure

PharmaEssentia Corporation sponsored the study and supported the study drugs. J Jin, L Zhang and Z Xiao have no conflicts of interest to disclose. A Qin works for PharmaEssentia Corporation. W Shen, W Wang, J Zhang, Y Li and D Wu are employees of PharmaEssentia Biotech (Beijing) Ltd. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Editage provided editing in the production of this manuscript.

Ethical conduct of research

The study was approved by the appropriate institutional review board and followed the principles of the Declaration of Helsinki for all human experimental investigations. Informed consent was obtained from all the participating patients.

Data sharing statement

Data will be available after the trial is completed and ropeginterferon α-2b has acquired marketing approval for polycythemia vera treatment in mainland China at the request of researchers approved by PharmaEssentia.

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