PharmaEssentia
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Pegylated Proline-Interferon Alfa-2b (P1101)

Clinical Study Protocol: P1101 in Japanese PV

Study Title: Phase 2 single arm study of efficacy and safety of P1101 for polycythemia vera (PV) patients for whom the current standard of treatment is difficult to apply.

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SPONSOR CONTACT INFORMATION

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1 SYNOPSIS

Name of Sponsor/Company:

PharmaEssentia Japan

Name of Investigational Product:

P1101 (ropeginterferon alfa-2b)

Name of Active Ingredient:

Ropeginterferon (P1101) is a mono-pegylated form of the P1040 drug intermediate (Proline-IFNα-2b) that has been reacted with a 40 kDa branched PEG-aldehyde. The pegylation site is predominantly at the N-terminal proline of the P1040 drug intermediate; more precisely, the drug substance P1101 is an N-terminally mono-pegylated drug intermediate of P1040.

Title of Study:

Phase 2 single arm study of efficacy and safety of P1101 for polycythemia vera (PV) patients for whom the current standard of treatment is difficult to apply.

Study Countries and Center(s): Japan

Coordinating Investigator:

Prof. Keita KIRITO (Yamanashi University)

Planned Studied Period:	**Phase of development:**
September 2019 to August 2021	Phase 2

Objective:

The primary objective is to demonstrate safety and efficacy of P1101 in terms of complete hematologic response (CHR) without phlebotomy with Japanese patients diagnosed with PV for whom the current standard of treatment is difficult to apply.

The primary endpoint "complete phlebotomy-free hematologic response (CHR)" is defined as a condition that meets the following hematological criteria, hematocrit (<45%), WBC (≤10 x 10^9/L), platelets (≤400 x 10^9/L) and require no phlebotomy at month 9 and month 12.

The secondary objective is to demonstrate safety and efficacy of P1101 in terms of changes in Hct, WBC, PLT, spleen size, molecular and cytogenetic response from baseline, time to requiring no phlebotomy, numbers of phlebotomy required, time to response, duration of response maintenance, ratio of CHR rates of subjects with/without prior treatment with HU and Proportion of subjects without thrombotic events.

Study Design:

This is a Phase 2 single arm study to investigate efficacy and safety of P1101 for adult Japanese patients with PV. Eligible patients will be treated with P1101, starting at 100 µg (or 50 µg in patients under another cytoreductive therapy). The dose should be gradually increased by 50 µg every two weeks (in parallel, other cytoreductive therapy should be decreased gradually, as appropriate) until stabilization of the hematological parameters is achieved (hematocrit <45%, platelets <400 x 10^9/L and leukocytes <10 x 10^9/L). The maximum recommended single dose is 500 µg injected every two weeks.

At week 36 (month 9) and week 52 (month 12), the primary study endpoint, phlebotomy-free CHR, will be analyzed. After completion of the 52-week study duration, provision and administration of P1101, collection of the long-term follow up information (blood parameters, molecular and

cytogenetic data, safety parameters and as also the optional bone marrow data) will be continued until the drug becomes commercially available for all study subjects..

Number of Patients (planned):

30 patients (all recruited in Japan)

Diagnosis and Main Criteria for Inclusion and Exclusion:

- **Inclusion Criteria**

1. Male or female patients ≥20 years old at the time of informed consent
2. Patients diagnosed with PV according to the WHO 2008 or WHO 2016 criteria
3. PV patients for whom the current standard of treatment is difficult to apply. Patients with a documented history of refractory to HU are excluded (see Appendix 6; modified ELN criteria based on "Barosi et al, 2010 ELN criteria", (Barosi et al. 2010)).
   - Younger patients (long-term treatment is anticipated)
   - Patients who are categorized as low risk, but cytoreduction is recommended due to disease-related signs and symptoms (headache, dizziness, pruritus, night sweats, fatigue, erythromelalgia, vision disorders, scintillating scotoma, early satiety, abdominal distension).
   - Patients with HU intolerance (see Appendix 6; modified ELN criteria based on "Barosi et al, 2010 ELN criteria", (Barosi et al. 2010))
4. Total HU treatment duration shorter than 3 years (cumulatively) at screening
5. For cytoreduction naïve patients only: PV in need of cytoreductive treatment, defined by fulfilling as one or more of the following criteria at baseline:
   - at least one previous well documented major cardiovascular PV-related event in the medical history
   - poor tolerance of phlebotomy (defined as a phlebotomy/ procedure-related adverse event causing significant adverse impact on the patient and limiting ability to apply phlebotomy with the intention to keep Hct <45%)
   - frequent need of phlebotomy (more than one phlebotomy within last month prior entering the study)
   - platelet counts greater than 1000 x 10^9/L (for two measurements within the month prior treatment start)
   - leukocytosis (WBC>10 x 10^9/L for two measurements within the month prior treatment start)
   - manifestation of disease-related signs and symptoms (headache, dizziness, pruritus, night sweats, fatigue, erythromelalgia, vision disorders, scintillating scotoma, early satiety, abdominal distension)
6. Adequate hepatic function defined as total bilirubin ≤1.5 x upper limit normal (ULN), international normalized ratio (INR) ≤1.5 x ULN, albumin >3.5 g/dL, alanine aminotransferase (ALT) ≤2.0 x ULN, aspartate aminotransferase (AST) ≤2.0 x ULN at screening
7. Hemoglobin (HGB) ≥10 g/dL at screening
8. Neutrophil count ≥1.5 x 10^9/L at screening
9. Serum creatinine ≤1.5 x ULN at screening
10. Hospital Anxiety and Depression Scale (HADS) score 0-7 on both subscales (Appendix 8).

(Patients with a borderline of HADS score (score 7 but <10) or patients with necessity (expected

benefits are higher than the risks) based on investigators' discretion are required to receive following assessment by psychiatric specialist to confirm the eligibility for IFNα therapy.).

11. Males and females of childbearing potential, as well as all women <2 years after the onset of menopause, must agree to use an acceptable form of birth control until 28 days following the last dose of the study drug
12. Written informed consent obtained from the patient or the patient's legal representative, and ability for the patient to comply with the requirements of the study

- **Exclusion Criteria**

1. Patients with symptomatic splenomegaly
2. Previous use of IFNα for any indication
3. Any contraindications or hypersensitivity to interferon-alfa
4. Co-morbidity with severe or serious conditions which may impact patient participation in the study in investigator's opinion
5. History of major organ transplantation
6. Pregnant or lactating females (Breastfeeding women are not allowed to enter this study by discontinuing breastfeeding)
7. Patients with any other medical conditions, which in the opinion of the Investigator would compromise the results of the study or may impair compliance with the requirements of the protocol, including but not limited to:
   - 7.1. History or presence of thyroid dysfunction (clinical symptoms of hyper- or hypo-thyroidism) of the autoimmune origin, except late stages cases on the oral thyroid substitution therapy, where potential exacerbation under interferon therapy will not constitute any further harm to the patient
   - 7.2. Documented autoimmune disease (e.g., hepatitis, idiopathic thrombocytopenic purpura [ITP], scleroderma, psoriasis, or any autoimmune arthritis)
   - 7.3. Clinically relevant pulmonary infiltrates and pneumonitis at screening, patients with a history of interstitial pulmonary disease
   - 7.4. Active infections with systemic manifestations (e.g., bacterial, fungal, hepatitis B [HBV], hepatitis C [HCV], or human immunodeficiency virus [HIV]) at screening)
   - 7.5. Evidence of severe retinopathy (e.g., cytomegalovirus retinitis [CMV], macular degeneration) or clinically relevant ophthalmological disorder (due to diabetes mellitus or hypertension) based on the ophthalmological assessment by specialists.
   - 7.6. Uncontrolled depression
   - 7.7. Previous suicide attempts or at any risk of suicide at screening
8. Uncontrolled diabetes mellitus (HbA1c level of > 7% at baseline)
9. History of any malignancy within for the past 5 years (except Stage 0 chronic lymphocytic leukemia [CLL], basal cell, squamous cell, and superficial melanoma believed to be cured)
10. History of alcohol or drug abuse within the last year
11. History or evidence of post polycythemia vera-myelofibrosis (PPV-MF), essential thrombocythemia, or any non-PV MPN;
12. Presence of circulating blasts in the peripheral blood within the last 3 months
13. Use of any investigational drug(s), or investigational drug combinations <4 weeks prior to the first dose of study drug or not recovered from effects of prior administration of any investigational agent

With regard to acetylsalicylic acid, which will be considered as the background treatment in the

study unless contraindicated, the following contraindications are known for low-dose acetylsalicylic acid: history of hypersensitivity to Bayaspirin or any salicylic acid preparation, peptic ulceration, bleeding tendency, aspirin-induced asthma (asthma attack induced by NSAID etc.) ant its history, pregnant women within 12 weeks of estimated date of confinement, baby with a low birth weight/newborn infant/ suckling infant. If any of the contraindications are observed, the patient may still participate in the study without being administered acetylsalicylic acid.

Investigational Product and Reference Therapy, Dosage, and Mode of Administration:

Patients who meet the inclusion criteria and who do not meet the exclusion criteria will start therapy with P1101 (ropeginterferon alfa-2b). The investigational product will be administered subcutaneously every 2 weeks at the starting dose of 100 μg every two weeks (or 50 micrograms in patients under another cytoreductive therapy). The dose should be gradually increased by 50 μg every two weeks (in parallel, other cytoreductive therapy should be decreased gradually, as appropriate) until stabilization of the hematological parameters is achieved (hematocrit <45%, platelets <400 x 10^9/L and leukocytes <10 x 10^9/L). The maximum recommended single dose is 500 μg injected every two weeks. The dose will be maintained at the highest level which can be tolerated and delivers best possible disease response.

Low-dose aspirin (acetylsalicylic acid) (75-150 mg/day per local practice) will be given during the 12 months of study treatment, unless contraindicated.

Phlebotomy is performed aiming at a hematocrit < 45%. When the hematocrit value is 45% or higher, phlebotomy is performed. The volume of phlebotomy per procedure should be 200 to 400 mL per one phlebotomy while monitoring the circulatory dynamics such as blood pressure and pulse. In the elderly and patients with cardiovascular disorders, a small volume (100 to 200 mL) should be considered to avoid rapid changes in hemodynamics.

Disease Progression

For this study, disease progression will be defined as:

- Death due to any cause
- Development of secondary MF, as evidenced e.g. by bone marrow biopsy
- Transformation into acute myeloid leukemia or myelodysplastic syndrome, as evidenced by bone marrow biopsy

Withdrawal Criteria

Discontinuation from the study may occur for the following reasons:

- Disease progression;
- Screening failure;
- Withdrawal of patient consent;
- Severe Noncompliance;
- Worsening of the underlying disease in cases when the further participation (with dose adjustment) is not expected to provide sufficient medical care to the patient;
- Study drug-related adverse event (AE) not recovering within the pre-specified period;
- Medical condition unrelated to the underlying disease or study treatment (study drug-unrelated AE);
- Lost to follow-up.

Study Procedures:

For eligibility purposes, local lab data and local evaluations (incl. mutational status, bone marrow) will be accepted if properly documented in the source data.

Patient visits will be scheduled every 2 weeks: at regular visits, safety and AE data collection with

the basic lab investigations will be performed, while every three months (month 3, 6, 9 and 12) extended assessment visits will be scheduled. A safety follow-up visit will take place 28 days after the end of the last treatment visit.

Study procedures are detailed in the study flowchart (Appendix 1).

Pharmacokinetic (PK) samples will be collected once every 2 weeks at a timing prior to drug administration (at steady state), four consecutively at Week 0 (at first dose) and Week 28 (Appendix 2), at the end of treatment visit, and at the safety follow-up visit.

Assessment of safety will be determined by vital sign measurements, clinical laboratory tests, physical examinations, spleen size measurement by ultrasound, electrocardiogram (ECG) evaluation, lung X-ray, Eastern Cooperative Oncology Group (ECOG) performance status, ophthalmologic investigations, and the incidence and severity of treatment-emergent AEs (TEAEs).

At screening, month 9 and 12, central lab will be testing Hct, WBC and platelets for the purposes of primary endpoint analysis.

Also, a central lab will be in charge of the quantitative allelic burden measurement, as also will perform all further evaluations.

Local labs will be used for other measurement in the study.

Due to the lack of experience of administration of the study drug over 300 μg in Japanese subjects, Sponsor introduce careful observation of all the subject after the administrations over 300 μg to ensure subjects safety and to respond quickly and appropriately in emergency situations. More specifically, all the subjects will be hospitalized for the first 2 days (incl. the date of administration) when they receive the study drug over 300 μg (350, 400, 450 and 500 μg). Two days after the administration, the subjects can be discharged if there is no evidence of clinically significant adverse reactions based on the assessment by the institutional Principal Investigators at each site. All safety data up to Day 15 (from previous dose to next dose) will be collected and reviewed by Principal Investigators at each site, to determine if any of the criteria for stopping dose escalation has been met. Increase to the next higher planned dose level will only occur if the previous dose level was deemed to be safe and well-tolerated following review by Principal Investigators at each site. For the safety confirmation after administration of 500 μg, the time to dose increase to 500 μg should not exceed 32 weeks. In addition, as with the administration of 350 μg, 400 μg, and 450 μg, the Principal Investigators and sub-investigators at each medical institution assess that no drug-related adverse events requiring dose reduction/interruption/discontinuation occur within 2 weeks after dose increase (by Day 15 after the next visit) according to the protocol criteria. If the safety profile of the 500 μg dosing level for the 5 subjects in the first 6 evaluable subjects is confirmed by Coordinating Principal Investigator, Principal Investigators at each site and Sponsor's Medical Monitor, the observation based on the hospitalization for two days after administration will be deactivated and the rest of study subjects will receive the predefined higher dose level of the study drug (over 300 μg) without hospitalization. If two or more of the first six evaluable subjects fail to meet the criteria for tolerability, the Coordinating Principal Investigator, the Principal Investigators at each site and the sponsor's Medical Monitor will perform a comprehensive assessment of continuation of the study.

Study Duration:

Study duration is approximately 14 months for the core treatment phase with 12 months duration.

Study Endpoints:

- **Primary efficacy endpoint (month 9 and month 12):**

The primary efficacy endpoint is the phlebotomy-free complete hematologic responder rate (CHR) at month 9 and month 12.

The phlebotomy-free responder rate is defined as the proportion of patients with complete hematologic response (CHR) and with no phlebotomies during the previous 3 months.

A responder in sense of a primary endpoint is a patient who has met all of the following criteria at

month 9 and month 12:

- Hematocrit <45% phlebotomy-free (absence of phlebotomy during the previous 3 months)
- Platelet count ≤400 x 10^9/L,
- WBC count ≤10 x 10^9/L,

- **Secondary efficacy endpoints:**
  - Changes in Hct, WBC, PLT and spleen size from baseline
  - Time to requiring no phlebotomy
  - Time to first response
  - Duration of response maintenance
  - Proportion of subjects without thrombotic or hemorrhagic events
  - Change of *JAK2* mutant allelic burden over time vs. baseline
  - PK of P1101
- **Exploratory evaluation:**
  - Bone marrow histological remission defined as the disappearance of hypercellularity, trilineage growth (panmyelosis) and absence of >grade 1 reticulin fibrosis (optional)
- **Safety evaluation:**
  - Incidence, causality, and severity of AEs, according to common terminology criteria for AEs (CTCAE 5.0)
  - Incidence, causality, and severity of AEs of special interest (e.g., cardiovascular events [Appendix 5])
  - Events leading to dose reduction or permanent treatment discontinuation

Statistical Methods:

Sample size is calculated, based on the following assumptions;

- The target population of the Japanese local study: Japanese PV patients for whom the current standard of treatment is difficult to apply.
- Study design: P1101 single arm no controlled study (previous proposal was designed as a historical control study using PROUD-PV study).
- Primary study objective: To evaluate the safety and efficacy of P1101 for Japanese PV patients for whom the current standard of treatment is difficult to apply.
- Primary efficacy variable: Complete Hematological Response (CHR)
- Study period and evaluation visits: 3, 6, 9 and 12 months. The safety follow-up will be continued to 12 months and the major efficacy data will be obtained at 12 months.
- The primary analysis of the primary endpoint: The lower limit of the 95% confidence interval of CHR rate is greater than 11%, and also the slope of the linear regression model of the CHR rate time course is greater than 0 (positive trend):
- The rationale: the natural healing rate (placebo response) of CHR rate of PV patients is 0%, thus if the lower limit of 95% confidence interval of the CHR rate exceed 11%, the efficacy of P1101 can be confirmed. The rationale to set the CHR rate limit as 11% is, (1) 11% is the minimum CHR rate value of P1101 obtained in the PROUD-PV study, (2) and the trend of the CHR rate is positive, thus 11% can be considered as a limit of the acceptable clinical risks.

Assuming the above conditions, the power of the study at 9 months will be about 85% with 25 cases (CHR rate of the PROUD-PV study at 3, 6, 9 and 12 months are 11%, 27%, 36% and 43%, respectively). Considering the uncertainty of maximum 5 patients who are different background

from PROUD-PV, a total of 30 cases will be reasonable to evaluate both efficacy and safety.

2 SIGNATURE PAGE FOR SPONSOR

Protocol P1101 in Japanese PV

Title Phase 2 single arm study of efficacy and safety of P1101 for polycythemia vera (PV) patients for whom the current standard of treatment is difficult to apply.

Approved by the following:

		September 14th, 2020
Hiroaki Kawase, *Head, Clinical Operation*		*Date*

		September 14th, 2020
Toshiaki Sato, *Head, Medical Monitor*		*Date*

3 SIGNATURE PAGE FOR INVESTIGATORS

Protocol P1101 in Japanese PV

Title Phase 2 single arm study of efficacy and safety of P1101 for polycythemia vera (PV) patients for whom the current standard of treatment is difficult to apply.

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

I will use only the informed consent approved by the Institutional Review Board (IRB) and will fulfill all responsibilities for submitting pertinent information to the IRB responsible for this study.

I agree that the Sponsor (PharmaEssentia Japan) or its representatives shall have access to any source documents from which case report form information may have been generated.

I further agree not to originate or use the name of PharmaEssentia Japan or study drug code P1101 in any publicity, news release, or other public announcement, written or oral, whether to the public, press, or otherwise, relating to this protocol, to any amendment to the protocol, or to the performance of this protocol, without the prior written consent of PharmaEssentia Japan.

Investigator Name		*Signature*		*Date*

4 ABBREVIATIONS AND TERMS

Abbreviation	Term
ADA	Anti-Drug Antibody
AE	Adverse events
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
aPTT	Activated partial thrombin time
AST	Aspartate transaminase
AUC	Area under the drug concentration-time curve
BAT	Best available therapy
BNP	Brain natriuretic peptide
BUN	Blood urea nitrogen
CIOMS	Council for International Organizations of Medical Sciences
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum plasma concentration
CMV	Cytomegalovirus
CP	Conditional power
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for AEs
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eCRF	Electronic case report form
ELN	European Leukemia Net
EoS	End of study
EoT	End of treatment
ET	Essential thrombocythemia
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimation Equation
GGT	Gamma-glutamyl transferase
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
HDL	High-density lipoprotein
hERG	Human Ether-a-go-go-Related Gene
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HU	Hydroxyurea
IB	Investigator's brochure
IC_{50}	Median inhibition concentration
ICH	International Conference on Harmonisation
IFN	Interferon
IFN-α	Interferon-α

INR	International normalized ratio
IRB	Institutional Review Board
ITP	Idiopathic thrombocytopenic purpura
ITT	Intent-to-treat
IV	Intravenous
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
JAK2	Janus kinase 2
LDL	Low-density lipoprotein
LDH	Lactate hydrogenase
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MI	Myocardial infarction
MPL	Myeloproliferative leukemia
MPN	Myeloproliferative neoplasm
MPN-SAF TSS	Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NR	Not reported
NSAID	Nonsteroidal anti-inflammatory drug
NT-proBNP	N-terminal portion of proBNP
NYHA	New York Heart Association
OR	Odds ratio
P1101	Ropeginterferon-interferon-α-2b
PD	Pharmacodynamic
PEG	Pegylated
peg-IFNα-2a	Peginterferon-α-2a
PET-MF	Post-ET myelofibrosis
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PPP	Per Protocol
PT	Prothrombin time
PV	Polycythemia vera
QoL	Quality of life
QT	Time corresponding to the beginning of depolarization to repolarization of the ventricles
QTc	Time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
sAML	Secondary acute myeloid fibrosis
sMF	Secondary myelofibrosis
SOHO	Society of Hematologic Oncology
SOP	Standard Operating Procedures
TSH	Thyroid stimulating hormone
TSS	Total Symptom Score
ULN	Upper limit of normal

US	United States
WBC	White blood cell
WHO	World Health Organization

5 INTRODUCTION AND RATIONALE

5.1 Background

Polycythemia Vera (PV) is the most common type of chronic myeloproliferative neoplasms with reported annual incidence rates up to 2.6 per 100.000, and a prevalence rate of approx. 2.0 per 10,000 (Moulard et al. 2014; Titmarsh et al. 2014; Choi et al. 2015; Stein et al. 2015). It is a long-term debilitating and life-threatening condition as it is associated with the risk of thrombosis, hemorrhage, and a long term propensity to develop myelofibrosis (MF) and secondary acute myeloid leukemia (sAML) (Stein et al. 2015; Griesshammer, Gisslinger, and Mesa 2015). Therapeutic options for PV are limited and no cure is available. Currently, most PV patients are treated with phlebotomy and low-dose aspirin as front-line therapy to correct abnormal blood viscosity and to control the risk of vascular events, whereas high-risk patients receive cytoreductive treatment (Barbui et al. 2011; Vannucchi et al. 2009; Vannucchi 2014; Tefferi and Barbui 2015). Until recently, hydroxyurea (HU) was the only first-line therapy licensed in the European Union (EU) for patients requiring cytoreductive treatment. The JAK2 inhibitor ruxolitinib has been approved in 2014 as a second-line treatment of PV restricted to patients who are resistant to or intolerant of HU (EMA 2015; Vannucchi et al. 2015; Tefferi and Pardanani 2015).

The PharmaEssentia Corporation (PEC) develop ropeginterferon, PEG-Pro-IFNα-2b (P1101) for the treatment of PV and other MPNs.

Ropeginterferon alfa-2b, a novel, long-acting, mono-pegylated proline interferon, uniquely administered once every two weeks and contains an additional N-terminal Proline, which is covalently modified by a 40 kDa Polyethylene glycol (PEG) moiety. Because of the site specific mono-pegylation Ropeginterferon alpha-2b represents a long-acting interferon with only one major isoform as opposed to the 8-14 isoforms of randomly pegylated interferon products approved for indications different than PV. Commercially, Ropeginterferon alfa-2b will be provided in pre-filled syringe.

The non-clinical pharmacology program of Ropeginterferon alfa-2b includes the in vivo evaluation of 2',5'-oligoadenylate synthase (2'-5'-OAS) activity induced by Ropeginterferon alfa-2b in monkeys, as well as safety pharmacology studies of the effects on the cardiovascular system in vitro (human Ether-a-go-go-Related-Gene [hERG] assay) and in monkeys, and on the central nervous system (CNS) and respiratory systems in rats.

The pharmacokinetics (PK) and pharmacodynamics (PD) of Ropeginterferon alfa-2b versus Pegasys were evaluated in a study in monkeys. Toxicology assessment includes single-dose toxicity studies in rats and monkeys, and repeat-dose toxicity studies of up to 7-days, 14-days, and 4-weeks (with 4-week recovery) in monkeys with toxicokinetic and immunogenicity evaluations. Genotoxicity was evaluated using a bacterial reverse mutation assay and a chromosome aberration assay in Chinese Hamster Ovary (CHO) cells. No toxicities different from other licensed pegylated interferons were found in these studies.

The clinical development program for Ropeginterferon alfa-2b in PV includes a Phase I/II open-label dose escalation study to determine the maximum tolerated dose (MTD), safety and efficacy of Ropeginterferon alfa-2b in 51 PV patients (PEGINVERA Study) and a pivotal Phase III program comprising (1) PROUD-PV Study, a randomized, open-label, controlled parallel-arm non-inferiority study of Ropeginterferon alfa-2b versus HU in 254 patients with PV, (2) CONTINUATION-PV Study, an open-label, Phase IIIb extension study assessing the long-term efficacy and safety of Ropeginterferon alfa-2b in PV patients who completed the Ropeginterferon alfa-2b arm of the PROUD-PV Study in comparison to patients who completed the HU arm of PROUD-PV Study and are managed according to standard of care/best available treatment (BAT), and (3) PEN-PV Study, an open-label, single-arm Phase III study to assess the self-administration of Ropeginterferon alfa-2b using the pre-filled pen intended for commercial use in 36 patients with PV.

P1101 has been approved by EMA in February 2019 to treat PV without symptomatic splenomegaly (EMA 2019). In addition to being approved in EU, Ropeginterferon alfa-2b has Orphan Drug designation in the United States of America to treat PV, but also ET and MF.

The PharmaEssentia Corporation develops Ropeginterferon alfa-2b (P1101) also for Japanese patients. The Phase 1 study in Japanese healthy subjects in compliance with the Japanese Pharmaceutical and Medical Devices Agency (PMDA) regulations has been completed recently.

The planned study by this protocol will collect efficacy and safety data of treating Japanese PV patients with P1101.

5.2 Overview of Nonclinical Studies

Detailed summaries on the nonclinical studies conducted with P1101 are included in the Investigator's Brochure (IB). The studies and the key results are briefly summarized in the following sections.

5.2.1 Safety Pharmacology

In a study with rats, activity, behavior, and body temperature were observed after administration of a single subcutaneous (SC) dose of P1101. Four groups of rats (n=6) received either placebo or a dose of 0.2, 2.0, or 20 mg/kg of P1101. Six Irwin observations were performed post dose and no behavioral, physiological, or body temperature changes were observed.

The in vitro effects of P1101 on human ether-a-go-go-related gene (hERG) channel current were observed. P1101 significantly inhibited the hERG current by 10.8% and 49.9% at concentrations of 0.3 and 2.5 µM, respectively, compared to 0.4% in the control group. The inhibitory concentration (IC_{50}) for the inhibitory effect of P1101 on the hERG potassium current was not determined since inhibition was <50%.

Six male cynomolgus monkeys were pre-instrumented for single-lead telemetry recordings following intravenous (IV) infusion of P1101. Each animal received vehicle or test item using adjusted Latin square design in doses of 0, 60, and 600 µg/kg. The changes measured indicated generally dose-related increases in body temperature and heart rate with consequent time corresponding to the beginning of depolarization to repolarization of the ventricles (QT) and QT corrected for heart rate (QTc) shortening at doses of 60 and 600 µg/kg. It is important to note that no significant effects on body temperature, heart rate, electrocardiograms (ECGs), or QT duration were observed with multiple dosing in the monkey toxicity studies with P1101.

Four groups of rats (N=6) were placed in whole body plethysmograph boxes and initial respiratory parameters (tidal volume, respiration rate, and minute volume) were recorded. Each group then received either no treatment or was inoculated intravenously with 0.1, 1.0, or 10 mg/kg of P1101 and respiratory parameters were recorded for a 6-hour period. Intravenous administration of P1101 did not elicit any statistically significant changes in respiratory parameters in the conscious rat during a 6-hour period when compared to the vehicle control group.

5.2.2 Nonclinical Pharmacokinetics and Pharmacodynamics

The pharmacokinetic (PK) and pharmacodynamic (PD) profile of P1101 has been investigated in a study in cynomolgus monkeys (n=4/group). In the first phase, the PK and PD profiles of P1101 were compared with Pegasys® when administered subcutaneously (30 µg/kg). P1101 exhibited a PK profile similar to Pegasys. In the second phase, the PK and PD profiles of P1101 were evaluated following IV (30 µg/kg) and SC (300 µg/kg) administration.

Intravenous administration of P1101 at the same dose resulted in greater serum concentration of P1101 from 2 to 96 hours in comparison to SC administration in Phase 1. Relative bioavailability of P1101 was calculated to be 80%.

5.2.3 Toxicology

In an active-controlled single- and repeated-dose toxicity study in rats, P1101 was evaluated in 48 rats assigned to 8 groups (n=6 / group). Group 1 received a placebo control and Groups 2, 3, and 4 were inoculated with a single dose of P1101 at 200, 2000, and 20000 μg/kg, respectively. Group 5 received 3 separate doses of a placebo control article and Groups 6, 7, and 8 received doses of P1101 at 200, 2000, and 20000 μg/kg, respectively, on Days 1, 4, 8, and 11. No treatment-related clinical signs, unscheduled deaths, changes in mean body weight or treatment-related clinical pathology or macroscopic findings were observed after single or multiple doses. Based on these findings, the no observed effect level (NOEL) was ≥20000 μg/kg.

The toxicity of P1101 was evaluated after administration of escalating doses via SC injection to cynomolgus monkeys. Phase 1 consisted of 2 monkeys receiving an escalating dose (0.675, 2.0, and 6.75 mg/kg) of P1101 on Days 1, 5, and 9, respectively. Phase 2 involved 3 groups (n=2) receiving a repeat dose of either 0.0, 2.0, or 6.75 mg/kg of P1101 on Days 1, 4, 8, and 11. During Phase 1, all animals survived until the scheduled termination, and there were no treatment-related effects on clinical observations, food consumption, or body weights. In Phase 2, all animals survived, but decreased body weight and food consumption were observed in the 2 mg/kg and 6.75 mg/kg groups. No macroscopic changes were observed during either phase of the study. Based on these findings, the no observed adverse effect level (NOAEL) was determined to be <2 mg/kg. A maximum tolerated dose (MTD) was not achieved in this study.

In a placebo-controlled study, 32 cynomolgus monkeys were assigned to 4 groups to evaluate the toxicity of P1101. Group 1 (n=10) received a control article. Groups 2 (n=6), 3 (n=6), and 4 (n=10) received 0.675, 2.0, and 6.75 mg/kg of P1101, respectively, on Days 1, 4, 8, 11, 15, 18, 22, and 24. No deaths were observed, and treatment-related changes observed were generally minor and reversed during the recovery period. Most of these treatment-related changes were observed in males and females treated with the highest dose of 6.75 mg/kg and were resolved by the end of the 29-day recovery period. The maximum plasma concentration (C_{max}) and area under the concentration curve (AUC) values increased in a linear manner in proportion to dose in the P1101 treatment groups. Pharmacokinetic parameters decreased after the 8th dose (Day 24), which indicated the development of neutralizing antibodies. P1101 sera concentrations decreased after the 5th dose, indicating that neutralizing antibodies were developed by Day 17. Because the treatment-related effects were not considered to be adverse, the NOAEL was determined to be 6.75 mg/kg.

5.3 Overview of Clinical Studies

P1101 (also known as ropeginterferon alfa-2b) is being developed in the field of MPNs for the indication polycythemia vera (PV). The clinical development program for ropeginterferon alfa-2b in PV includes a Phase 1/2 study to determine the MTD, safety, and efficacy of ropeginterferon alfa-2b. Two-hundred and fifty-four (254) PV patients have been studied over 3 years under 3 protocols; the first year under the PROUD-PV protocol, and the second and third year under the CONTINUATION-PV protocol to assess the long-term efficacy and safety of ropeginterferon alfa-2b.

PEGINVERA is an open-label, prospective, multicenter, Phase 1/2 dose escalation study, conducted in Austria with the primary objective to identify the MTD of P1101 in subjects diagnosed with PV. Safety and tolerability are assessed and an exploratory analysis of efficacy and biomarker modulation is performed in this study. Fifty-one subjects were enrolled into the study and received study medication (recruitment between Sep 2010 and Dec 2012, and study is now completed). No dose-limiting toxicities (DLTs) were observed at the dose levels up to 540 μg infused every two weeks, and efficacy and safety were assessed during the whole study period for each subject. Results of the study revealed that efficacy of P1101 in PV: more than 90% of the subjects were either complete or partial responders (20-50% of subjects, depending on time period for assessment were complete responders). Study drug-related AEs that occurred in >10% of the subjects (listed from most to less frequent): included pyrexia, arthralgia, influenza like illness, infection site reaction, fatigue, leukopenia, myalgia, pain in extremity, chills, thrombocytopenia, nausea, pruritus, alopecia, headache, and neutropenia.

PROUD-PV is a randomized, open-label, multicenter, controlled, parallel-arm Phase 3 study assessing the efficacy and safety of P1101 versus HU in subjects with PV. The primary objective of the study is to compare the efficacy of P1101 versus HU in terms of disease response rate in both HU naïve and currently treated subjects, diagnosed with PV. Secondary objectives include assessments of efficacy, safety, quality of life (QoL) and change of Janus kinase2 (JAK2) allelic burden in the two treatment arms. A total of 254 subjects were randomized and received study medication, and 217 completed the study. Overall, 36 serious adverse events (SAEs) occurred in this study, 4 of them rated as related to study drug: one case of atrial fibrillation and one case of rheumatoid arthritis (study treatment P1101), and two cases of basal cell carcinoma (both occurred in subjects receiving HU).

PROUD-CONTINUATION-PV is an open-label, multicenter study assessing the long-term efficacy and safety of P1101 and standard first-line best available treatment (BAT) in subjects with PV who previously participated in the PROUD-PV study. The primary objective is to assess the long-term efficacy of P1101 or BAT. Secondary objectives further assess the long-term efficacy, safety, QoL, and change of JAK2 allelic burden. A total of 171 subjects were enrolled (95 in the P1101 treatment arm, 76 in the BAT arm [HU arm in previous PROUD-PV study]). Two cases of acute leukemia were assessed as related to BAT (subject received HU). No treatment-emergent SAEs were observed in the study.

PEN-PV is an open-label, single arm study to assess the self-administration of P1101 using a pre-filled auto-injection pen, developed for the treatment of PV subjects. Primary objective was to assess the ease of P1101 self-administration using dedicated questionnaires. Secondary objectives include the assessment of safety and tolerability, the assessment of maintenance of the blood efficacy parameters (hematological response) as well as the feasibility of P1101 self-administration (defined as the ability of the subjects to use the auto-injection pen as a self-administration tool). The study was conducted in 8 countries and 36 subjects were enrolled from subjects who completed the P1101 arm of the PROUD-PV study (N=5), or participated in the CONTINUATION-PV study (N=31). Overall, 1 SAE (atrial fibrillation) occurred in this study and was assessed as unrelated to P1101. No treatment-emergent SAEs were observed in the study.

Single doses of P1101 were investigated in a dose escalation clinical study at doses of 24 (n=5), 48 (n=6), 90 (n=6), 180 (n=6), 225 (n=6), and 270 (n=5) µg (IB) in healthy adult male subjects. The exposure to P1101 was dose-related, and the mean half-life ranged from 68 hours to 117 hours (approximately 3 to 5 days). P1101 reached maximal plasma concentrations (1.8 to 21.3 ng/mL) after 75 to 90 hours (Tmax) when 24 to 225 µg single doses were administered subcutaneously (n = 4 to 5). The Tmax values observed did not show any dose dependency. However, after SC administration of 270 µg dose, maximal levels (24.8 ng/mL) were seen after 116 hours (n=5). With SC doses of 24 to 225 µg, the elimination half-life was determined as 61 to 92 hours with no obvious dose dependency (n=4 to 5). However, after a SC dose of 270 µg the elimination half-life was 118 hours (n=5).

Another single doses of P1101 were investigated in a dose escalation clinical study at doses of 100 (n=12), 200 (n=12), and 300 (n=12) μg in healthy adult male subjects (Six Caucasian subjects and 6 Japanese subjects at each dose level). The first dose of 100 μg (cohort 1) was administered on May 30, 2018. To date, one serious adverse event has been observed in 1 subject at the dose of 100 μg (cohort 1). A 22-year-old Caucasian healthy subject developed neutropenia (ANC 0.8 x 109) on day 2 (June 1, 2018) after a single dose. Subjects remained healthy without fever, and neutropenia resolved spontaneously after 1 week without therapeutic intervention. Because neutropenia was considered a significant safety issue per protocol, this event was reported to the Australian Government, Department of Health, The Therapeutic Goods Administration (TGA) on July 18, 2018. The adverse event corresponded to the original study stopping criteria, so the study was temporarily on hold. However, as a result of discussion at the SRC held on June 15, 2018, the study stopping criteria were modified, and at the beginning of the new cohort, the study site's Medical Monitor judged whether to administer the drug to the remaining subjects after confirming safety and tolerability during the first week after administration in sentinel subjects (sentinel subject: precautionary subjects for careful and early detection of potentially safety-related events). Administration of the remaining subjects with 100 μg dose (cohort 1) were resumed on October 3, 2018 and ended on November 22, 2018 (Day 35 after administration for the last subject in cohort 1). Evaluation of PK, PD, and safety data up to the Day 15 after administration of the 100 μg dose (cohort 1) was discussed at the SRC on November 13, 2018, and it was agreed to proceed to the next dosing level of 200 μg (cohort 2) administration to sentinel subjects. In the 100 μg dose (cohort 1), 3 other subjects reported 6 AEs. All the AEs were mild and resolved spontaneously. Reported AEs were injection site tenderness, phlebitis, inattention, neutropenia, headache, and urinary tract infection. Administration of 200 μg dose (Cohort 2) to sentinel subjects started on November 15, 2018 and ended on February 11, 2019 (Day 35 of administration for the last subject in Cohort 2). Evaluation of PK, PD, and safety data up to the Day 15 of administration at the 200 μg dose (Cohort 2) was discussed at the SRC on February 12, 2019, and it was agreed to proceed to the next dosing level of 300 μg (Cohort 3) administration to sentinel subjects. No serious adverse events were reported in this cohort. No safety issue was identified in vital signs and ECG data from any of the subjects. Compared to cohort 1, there was no remarkable trend in cases of neutropenia. Forty-nine adverse events were reported in 12 patients, but all adverse events were mild to moderate in intensity and resolved. Notable adverse events were: Mild injection site reactions/erythema, neutropenia, lymphopenia, headache, influenza-like illness, arthralgia, elevated amylase, mild ALT and AST elevations, myalgia, urticaria, hyperesthesia, fatigue, fever, chest tightness were noted. Subjects receiving 300 μg (Cohort 3) started receiving treatment as of February 14, 2019, and ended treatment as of April 29, 2019 (on Day 35 of treatment in last subject in Cohort 2). No SAE was reported in this cohort. Among 12 subjects, 37 AEs occurred in 11 subjects; all of which were mild to moderate, and resolved in the end. AEs of special interest included mild injection site reaction/erythema (4 subjects), mild arthralgia/muscle pain (3 subjects), neutrophil count decreased of D3 to D4 (3 subjects), mild pruritus and eruption (2 subjects), and mild to moderate fever of D1 (38.1°C, 38.5°C, and 39.5°C) and cold chill (4 subjects). Neutropenia occurred in 3 subjects, all of which were reported to be mild to moderate, and resolved by Day 12 of treatment. Other AEs included headache (6 subjects), diarrhoea, nausea, convulsion, pharyngeal pain, and urine odour fouls. On Day 15 and thereafter, 1 subject had AST increase of ≤2 fold of the reference value, and ALT increase of ≥2 fold of the reference value, which peaked on Day 17 (April 11, 2019). The events were resolved and became normal by July 5, 2019. This event was considered to be clinically not important. Also, there was no clinically-relevant ECG finding.

This Study was initially designed to allow for dose up to 450 μg; however, a dose greater than that was considered to be inappropriate for healthy adults, and thus, 450 μg dose cohort was omitted, and the study was terminated.

Additional safety details on these clinical studies are included in the IB.

5.4 Study Rationale

P1101 has been approved in Europe to treat PV, and regulatory discussions in the USA are on the way. To make P1101 accessible also to the Japanese patients and hematologists, PEJ plans to conduct the necessary studies of P1101 in Japanese (healthy volunteers, PV patients). Healthy volunteers study has been recently completed, while this study will provide efficacy and safety data of P1101 in Japanese PV patients. This single arm design is sufficient is complementary to the completed development program of P1101 vs HU in PV in Europe.

5.5 Risks and Benefits

Pegylation confers upon P1101 special PK and PD properties that optimize its therapeutic utility. Specifically, P1101 is expected to an improved safety and tolerability profile compared to other existing PV therapies, which may lead to better adherence to treatment and ultimately, better drug efficacy. In addition, a reduction in the frequency of phlebotomies should be achieved. It is expected that the reduced intake frequency of P1101 will contribute to higher compliance rates than existing IFN therapy.

The safety profile of IFN-α is well-characterized after nearly 30 years of clinical experience. The effects of IFNα-2b (the active moiety of P1101) are also well-characterized in humans based on the clinical data supporting the marketing authorization applications for the approved PEG IFN products: Pegasys, PegIntron™, and Intron®A. Because P1101 belongs to the same therapeutic class as Pegasys, PegIntron, and IntronA, similar warnings and precautions as for the authorized drugs are expected to be applied to P1101, as reflected in the IB and in the EU label of P1101 (trade name Besremi®) (EMA 2019).

To minimize safety risks, subject data will be carefully monitored throughout the study, and subjects will be discontinued from study treatment if necessitated for safety reasons. Safety assessments (e.g., autoantibody measurements, ophthalmologic investigations, ECGs) will be implemented to detect any clinical meaningful changes in subject health conditions at the earliest possible time point. Subjects with any significant medical conditions at screening, which in the opinion of the Investigator may compromise their safety, will not be allowed to enter the study.

5.6 Justification of Study Drug Route of Administration, Dosage, Dosage Regimen, and Treatment Duration

The aim of this study is to provide long-term safety and efficacy of P1101 in Japanese PV subjects in a single arm setting. The study will be used to complement the regulatory dossier in Japan to apply for marketing authorization of P1101 in subjects with PV in Japan.

In a Phase 1 study with P1101, single SC doses of P1101 from 24 µg to 270 µg were safe and well-tolerated (Study A09-102). In a Phase 1/2 study (PEGINVERA), the MTD for subjects diagnosed with PV was defined at the level of 540 µg every 2 weeks.

Assessment of the available data (animal studies with the highest tested strength of 3.375 mg/mL administered, and also review of the relevant literature; refer to the IB for more details) concluded that no differences in absorption, systemic tolerability, or differences in local tolerability were observed, and no substantial risks are expected to occur following the repeated administration of P1101 doses ranging from 50 µg to 350 µg.

In the development program in viral hepatitis, P1101 dose up to 450 µg was well-tolerated in subjects with chronic hepatitis C genotype 1, genotype 2, and chronic hepatitis B. P1101 showed comparable safety profiles to their active comparator, Pegasys. Almost all subjects reported AEs during treatment that were mostly mild or moderate. Grade 3 and 4 toxicities were uncommon and were managed effectively with dose reduction or discontinuation. The most common AEs were those that have been previously reported for other PEG IFNs, such as anemia, rash, leukopenia, pruritus, myalgia, insomnia, and neutropenia. No unexpected safety signal of P1101 up to 450 µg was noted in these studies.

In the development program in PV, specifically in the PROUD-CONTINUATION-PV study, the dropout rate was low, and there were no new safety concerns observed with subjects receiving 500 µg of P1101 in the maintenance period while the drug was effective in term of controlling elevated blood parameters. In fact, 40.18% subjects received the plateau dosage of 500 µg, and 60.53% subjects received the plateau dosages of 350 µg or higher.

The dose, used in the PV studies (PROUD-CONTI) and approved by the EMA will be used in this study. Treatment will continue beyond the one year of therapy, since PV therapy is chronic to keep the blood counts controlled and prevent long term disease complications (cardiovascular, transformations).

5.7 Justification of Study Target Subject Population

The study will include patients with PV for whom the current standard therapy is difficult to apply. Specifically, it is planned to include younger patients considering the long-term treatment, patients who are classified as low risk of thrombosis but are considered to be candidates for cytoreductive therapy based on disease-related symptoms, etc., and patients who are intolerant of first-line therapy (hydroxyurea) as the standard therapy at present.

IFN-α is established as the treatment of choice in both first-line and second-line settings for PV. This has been reflected by the European approval of P1101, with the indication "PV without symptomatic splenomegaly". The medical and clinical rationale supports the use of P1101 in early stage of the disease, when the immune function is still preserved and long-lasting, immune mediated remission can be induced. Younger, early stage PV patients can also better tolerate P1101 as known also for other representatives of the IFN-a class of drugs.

6 STUDY OBJECTIVES

6.1 Primary Objective

The primary objective is to demonstrate safety and efficacy of P1101 in terms of complete hematologic response (CHR) without phlebotomy with Japanese PV patients for whom the current standard therapy is difficult to apply. The primary endpoint "complete phlebotomy-free hematologic response (CHR)" is composed of freedom of phlebotomy with normal defined as a condition that meets the following hematological criteria, hematocrit (<45%), and normalization of WBC (≤10 x 10^9/L), and platelets (≤400 x 10^9/L) and require no phlebotomy at month 9 and month 12.

6.2 Secondary Objectives:

The secondary objective is:

- to demonstrate safety and efficacy of P1101 in terms of changes in Hct, WBC, PLT, spleen size, molecular and cytogenetic response from baseline, time to requiring no phlebotomy, numbers of phlebotomy required, time to response, duration of response maintenance, ratio of CHR rates of subjects with/without prior treatment with HU and Proportion of subjects without thrombotic events.
- to assess the pharmacokinetics (PK) of P1101 and population PK (PPK) analysis
- to assess the relationship between exposure and key efficacy and safety endpoint using exposure-response (E-R) analysis
- to assess the immunogenicity of P1101

7 STUDY ENDPOINTS

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the phlebotomy-free complete hematologic responder rate (CHR) at month 9 and month 12.

The phlebotomy-free responder rate is defined as the proportion of patients with complete hematologic response (CHR) and with no phlebotomies during the previous 3 months.

A responder in sense of a primary endpoint is a patient who has met all of the following criteria at month 9 and month 12:

- Hematocrit <45% phlebotomy-free (absence of phlebotomy during the previous 3 months)
- Platelet count ≤400 x 10^9/L,

- WBC count ≤10 x 10^9/L

7.2 Secondary Endpoints

The secondary endpoints include:

- Changes in Hct, WBC, PLT and spleen size from baseline
- Time to requiring no phlebotomy
- Time to first response
- Duration of response maintenance
- Proportion of subjects without thrombotic or hemorrhagic events
- Change of *JAK2* mutant allelic burden over time from baseline
- PK of P1101

7.3 Exploratory Endpoint

Bone marrow histological remission defined as the disappearance of hypercellularity, trilineage growth (panmyelosis) and absence of >grade 1 reticulin fibrosis (optional)

7.4 Safety Endpoints

Incidence, causality, and severity of AEs, according to Common Terminology Criteria for Adverse Events (CTCAE; version 5.0)

Incidence, causality, and severity of AEs of special interest (AESIs; e.g., cardiovascular events, hemorrhagic, thrombotic events, psychiatric events)

Events leading to dose reduction or permanent treatment discontinuation

7.5 PPK and E-R Endpoints

PK parameters of P1101, including (but not limited to) C_{min}, T_{max}, C_{max}, and AUC_{0-t}, will be derived using PPK analysis and the relationship between exposure and efficacy and safety endpoints will be examined using E-R analysis

7.6 Immunogenicity endpoints

Proportion of subjects who are ADA positive and negative will be determined

8 OVERVIEW OF STUDY DESIGN

This is a Phase 2 open-label, multicenter, single arm study designed to evaluate the efficacy and safety and tolerability of P1101 in Japanese PV patients for 12 months of treatment for subjects with PV for whom the current standard therapy is difficult to apply. Specifically, it is planned to include younger patients considering the long-term treatment, patients who are classified as low risk of thrombosis but are considered to be candidates for cytoreductive therapy based on disease-related symptoms, etc., and patients who are intolerant of first-line therapy (hydroxyurea) as the standard therapy at present.

During the screening visit, after obtaining informed consent, screening evaluations will begin. Subject eligibility will be determined by the inclusion and exclusion criteria listed in Section 9.

Subject visits will be scheduled every 2 weeks. A safety follow-up visit or end of study (EoS) visit will take place 28 days after the End of Treatment (EoT) visit.

Efficacy evaluations, safety assessments, and PK and immunogenicity sampling will be performed according to the study flowcharts (Appendix 1).

Evaluation of efficacy will include clinical laboratory assessments, allelic burden measurements of *JAK2*, spleen size measurements (palpation, sonography) and bone marrow sampling (optional). HADS questionnaire (see Appendix 8) will be applied at screening and at quarterly assessment visits at month 3, 6, 9 and 12.

Evaluation of safety will include assessing vital signs, clinical safety laboratory tests, physical examinations, ECG evaluation, heart ECHO, lung X-ray, ECOG performance status, ocular examination, and AEs.

A urine pregnancy test must be performed within 7 days prior to the first administration of study drug and subsequently every 4 weeks for all women of childbearing potential, as well as for all women <2 years after the onset of menopause.

Serial PK samples (n=4 per subject) will be collected at Week 0 and Week 28, at the following time points: pre-dose (0 hr), 48 (±24) hr, 96 (±24) hr, and 168 (±24) hr. Trough PK samples (mandatory) will be collected at every visit.

Quantitative *JAK2* allelic burden measurements will be done by a central laboratory.

Total duration is approximately 14 months, with a screening period of 28 days, a treatment period of 12 months, and a follow-up period of 28 days.

8.1 Disease Progression/Withdrawal Criteria

The reason(s) for a subject discontinuing from the study will be recorded in the electronic case report form (eCRF). A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol planned schedule. The Investigator must determine the primary reason for discontinuation.

Discontinuation from the study may occur for the following reasons:

- Disease progression;

  For this study, disease progression will be defined as:

  - Death due to any cause
  - Development of secondary MF, as evidenced e.g. by bone marrow biopsy
  - Transformation into acute myeloid leukemia or myelodysplastic syndrome, as evidenced by bone marrow biopsy
- Screening failure;
- Withdrawal of patient consent;
- Severe Noncompliance;
- Worsening of the underlying disease in cases when the further participation (with dose adjustment) is not expected to provide sufficient medical care to the patient;
- Study drug-related adverse event (AE) not recovering within the pre-specified period*;
  - pre-specified period*: 8 weeks after discontinuation of IMP administration
- Medical condition unrelated to the underlying disease or study treatment (study drug-unrelated AE);
- Lost to follow-up.

The EoT visit will be performed at the time of study discontinuation.

In case of early treatment discontinuation, the subject should be invited to attend the safety follow-up visit (28 days after the EoT visit).

Subjects who discontinue study drug due to a study drug-related AE or abnormal laboratory value must be followed at least once a week for 8 weeks (and subsequently at 2-week intervals) until resolution or stabilization of the event. If a subject has not recovered from any toxicity within 8 weeks of prematurely discontinuing study drug, s/he must be discontinued from the study, but will continue to be followed for toxicity as described above. In this case, data will not be entered into the database but will be documented in the study log, which is stored at the site.

9 STUDY POPULATION

Subjects with a diagnosis of PV who meet the inclusion criteria and do not meet the exclusion criteria will be eligible for participation in this study.

9.1 Inclusion Criteria

1. Male or female patients ≥20 years old at the time of informed consent
2. Patients diagnosed with PV according to the WHO 2008 or WHO 2016 criteria
3. PV patients for whom the current standard of treatment is difficult to apply. Patients with a documented history of refractory to HU are excluded (see Appendix 6; modified ELN criteria based on "Barosi et al, 2010 ELN criteria", (Barosi et al. 2010)).
   - Younger patients (long-term treatment is anticipated)
   - Patients who are categorized as low risk, but cytoreduction is recommended due to disease-related signs and symptoms (headache, dizziness, pruritus, night sweats, fatigue, erythromelalgia, vision disorders, scintillating scotoma, early satiety, abdominal distension).
   - Patients with HU intolerance (see Appendix 6; modified ELN criteria based on "Barosi et al, 2010 ELN criteria", (Barosi et al. 2010))
4. Total HU treatment duration shorter than 3 years (cumulatively) at screening
5. For cytoreduction naïve patients only: PV in need of cytoreductive treatment, defined by fulfilling as one or more of the following criteria at baseline:
   - at least one previous well documented major cardiovascular PV-related event in the medical history
   - poor tolerance of phlebotomy (defined as a phlebotomy/ procedure-related adverse event causing significant adverse impact on the patient and limiting ability to apply phlebotomy with the intention to keep Hct <45%)
   - frequent need of phlebotomy (more than one phlebotomy within last month prior entering the study)
   - platelet counts greater than 1000 x 10^9/L (for two measurements within the month prior treatment start)
   - leukocytosis (WBC >10 x 10^9/L for two measurements within the month prior treatment start)
   - manifestation of disease-related signs and symptoms (headache, dizziness, pruritus, night sweats, fatigue, erythromelalgia, vision disorders, scintillating scotoma, early satiety, abdominal distension)
6. Adequate hepatic function defined as total bilirubin ≤1.5 x upper limit normal (ULN), international normalized ratio (INR) ≤1.5 x ULN, albumin >3.5 g/dL, alanine aminotransferase (ALT) ≤2.0 x ULN, aspartate aminotransferase (AST) ≤2.0 x ULN at screening
7. Hemoglobin (HGB) ≥10 g/dL at screening
8. Neutrophil count ≥1.5 x 10^9/L at screening
9. Serum creatinine ≤1.5 x ULN at screening
10. Hospital Anxiety and Depression Scale (HADS) score 0-7 on both subscales (Appendix 8).
    - (Patients with a borderline of HADS score (score > 7 but <10) or patients with necessity (expected benefits are higher than the risks) based on investigators' discretion are required to receive following assessment by psychiatric specialist to confirm the eligibility for IFNα therapy.)

11. Males and females of childbearing potential, as well as all women <2 years after the onset of menopause, must agree to use an acceptable form of birth control until 28 days following the last dose of the study drug
12. Written informed consent obtained from the patient or the patient's legal representative, and ability for the patient to comply with the requirements of the study

9.2 Exclusion Criteria

1. Patients with symptomatic splenomegaly
2. Previous use of IFNα for any indication
3. Any contraindications or hypersensitivity to interferon-alfa
4. Co-morbidity with severe or serious conditions which may impact patient participation in the study in investigator's opinion
5. History of major organ transplantation
6. Pregnant or lactating females (Breastfeeding women are not allowed to enter this study by discontinuing breastfeeding)
7. Patients with any other medical conditions, which in the opinion of the Investigator would compromise the results of the study or may impair compliance with the requirements of the protocol, including but not limited to:
    7.1. History or presence of thyroid dysfunction (clinical symptoms of hyper- or hypo-thyroidism) of the autoimmune origin, except late stages cases on the oral thyroid substitution therapy, where potential exacerbation under interferon therapy will not constitute any further harm to the patient
    7.2. Documented autoimmune disease (e.g., hepatitis, idiopathic thrombocytopenic purpura [ITP], scleroderma, psoriasis, or any autoimmune arthritis)
    7.3. Clinically relevant pulmonary infiltrates and pneumonitis at screening, patients with a history of interstitial pulmonary disease
    7.4. Active infections with systemic manifestations (e.g., bacterial, fungal, hepatitis B [HBV], hepatitis C [HCV], or human immunodeficiency virus [HIV]) at screening)
    7.5. Evidence of severe retinopathy (e.g., cytomegalovirus retinitis [CMV], macular degeneration) or clinically relevant ophthalmological disorder (due to diabetes mellitus or hypertension)
    7.6. Uncontrolled depression
    7.7. Previous suicide attempts or at any risk of suicide at screening
8. Uncontrolled diabetes mellitus (HbA1c level of > 7% at screening)
9. History of any malignancy within the past 5 years (except Stage 0 chronic lymphocytic leukemia [CLL], basal cell, squamous cell, and superficial melanoma believed to be cured)
10. History of alcohol or drug abuse within the last year
11. History or evidence of post polycythemia vera-myelofibrosis (PV-MF), essential thrombocythemia, or any non-PV MPN
12. Presence of circulating blasts in the peripheral blood within the last 3 months

13. Use of any investigational drug(s), or investigational drug combinations <4 weeks prior to the first dose of study drug or not recovered from effects of prior administration of any investigational agent

With regard to acetylsalicylic acid, which will be considered as the background treatment in the study unless contraindicated, the following contraindications are known for low-dose acetylsalicylic acid: active peptic ulceration or history of peptic ulceration, hemophilia, hypersensitivity to acetylsalicylic acid or any other nonsteroidal anti-inflammatory drugs (NSAIDs), including those in whom attacks of asthma, angioedema, urticaria, and rhinitis have been precipitated by acetylsalicylic acid or any other NSAID, and hypersensitivity to any of the other constituents. If any of the contraindications are observed, the patient may still participate in the study without being administered acetylsalicylic acid.

9.3 Justification of Inclusion/Exclusion Criteria

9.3.1 Justification of Inclusion Criteria

Inclusion criterion 1 was designed to allow for the participation of subjects aged 20 years or older, since this study will be conducted in Japanese adults.

Inclusion criterion 2 identifies the patient population to be enrolled to this study and is based on internationally accepted WHO diagnostic criteria guidelines.

Since the 2016 version was actually widely used after 2017, both the 2008 and 2016 versions are applicable.

Inclusion criterion 3 was established in consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) and considers the group of patients for whom treatment with drug is desired.

In general, the treatment of PV is long-term and is intended for inclusion in young people.

Inclusion criterion 4 was set to include PV patients with a history of treatment with hydroxyurea for no more than 3 years because of concerns about the effect on efficacy and safety in PV patients with a long history of cytoreductive therapy with hydroxyurea and the possibly advanced disease status.

Inclusion criterion 5 is for patients with PV who have not been treated with cytoreductive therapy.

Current national treatment guidelines recommend phlebotomy and aspirin therapy for patients with PV at low risk of thrombosis, but no cytoreductive therapy.

However, foreign NCCN guidelines consider the introduction of cytoreductive therapy in PV patients with low-risk for thrombosis who experiences frequent phlebotomy, worsening of disease-related symptoms, or increased platelets or white blood cell counts. These PV patients are considered "the current standard of treatment is difficult to be applied".

Inclusion criteria 6 and 9 are general criteria for liver function, renal function, and were set to minimize risks in subjects.

Inclusion criteria 7 and 8 were set because they are expected to decrease red blood cell count and neutrophil count due to the cytopenic effects of drug. If these values are low at the time of screening, anaemia and susceptibility to infection are expected to occur. Therefore, these values were set.

Inclusion criterion 10 was set to exclude subjects with psychiatric disorders based on the evaluation of HADS score, since interferon may exacerbate psychiatric disorders.

Inclusion criterion 11 is general criteria for contraception during the study, and were set for subjects who can comply with the clinical trial procedures to ensure consistency of safety and data.

Inclusion criteria 12 is implemented in accordance with the Guideline for Good Clinical Practice. Therefore, the inclusion criteria are set for subjects who can provide appropriate informed consent to participate in this clinical trial.

9.3.2 Justification of Exclusion Criteria

Exclusion criterion 1 was based on the indication "Besremi (trade name) is indicated as monotherapy in adults for the treatment of polycythemia vera without symptomatic splenomegaly" approved by the EMA on February 19th, 2019, and PV patients with symptomatic splenomegaly will be excluded in this study because they were not eligible for treatment according to the SmPC (EMA 2019).

Exclusion criteria 2 and 3 were set to exclude patients who had previously been treated with interferon-alpha and those who were hypersensitive to interferon-alpha.

This is because the above information may interfere with the assessment of the efficacy and/or safety of the drug in these patients.

Exclusion criteria 4, 5, and 6 were set to exclude patients with conditions that could interfere with the efficacy and/or safety assessment of this drug.

Exclusion criteria 7 (7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7.7), 8, 9, and 10 were set to exclude patients with complications such as autoimmune diseases, psychiatric disorders, ophthalmic diseases, diabetes mellitus, and cancer, and those with a history of such complications may be exacerbated by interferon therapy.

Exclusion criterion 11 was set to exclude patients with myelofibrosis progressed from PV (post polycythemia vera myelofibrosis: PPV-MF), essential thrombocythemia, or non-PV myeloproliferative neoplasms (Myeloproliferative neoplasms).

This is because the interpretation of the treatment outcome may be affected in patients other than those with PV.

Exclusion criterion 12 was set because the presence of blasts in the peripheral blood may preclude the assessment of the efficacy and/or safety of this drug in these patients, who are considered to have progressed to profibrotic status in the bone marrow.

Exclusion criterion 13 is a criterion for subjects who have recently participated in another clinical trial and/or received another investigational product.

These subjects will be excluded because they could impair an accurate assessment of the causality of the AE.

10 RANDOMIZATION AND BLINDING

Not applicable – single arm study.

11 ASSIGNMENT TO STUDY

Screening numbers will be assigned by the Principal Investigator/designee at each study site as soon as the subject has signed the informed consent. Subjects who are screened and who do not meet all entry criteria are screen failures and will be entered into a screening log; data collected on screening failures will be entered in the clinical database. Once assigned, numbers for any screening failures subjects will not be re-used.

12 STUDY DRUG

12.1 Investigational Treatment

Subjects who meet the inclusion criteria and who do not meet the exclusion criteria will be treated with investigational product P1101 (ropeginterferon alfa-2b). It will be administered subcutaneously every 2 weeks at the starting dose of 100 μg (Week 0). The dose will be elevated biweekly by 50 μg until 500 μg, or until response (as defined by primary endpoint) will be achieved. The dose then will remain fixed for the study duration. Dose adjustment to prior dose will be allowed if triggered by safety or tolerability. For transition phase from previous HU treatment to P1101 (for all patients on active HU), the rules as specified in the Appendix 7 will apply.

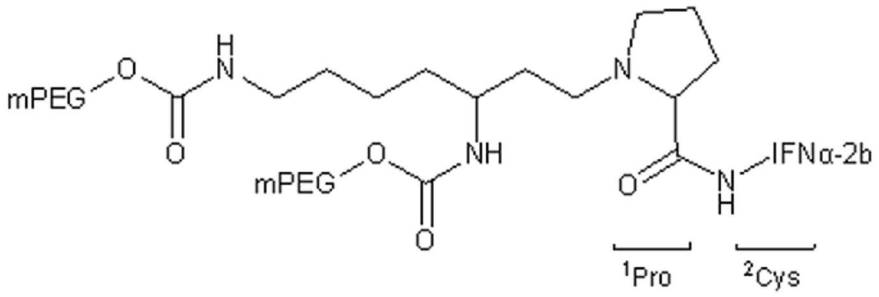
Due to the lack of experience of administration of the study drug over 300 μg in Japanese subjects, Sponsor introduce careful observation of all the subject after the administrations over 300 μg to ensure subjects safety and to respond quickly and appropriately in emergency situations. More specifically, all the subjects will be hospitalized for the first 2 days (incl. the date of administration) when they receive the study drug over 300 μg (350, 400, 450 and 500 μg). Two days after the administration, the subjects can be discharged if there is no evidence of clinically significant adverse reactions based on the assessment by the institutional Principal Investigatos at each site. All safety data up to Day 15 (from previous dose to next dose) will be collected and reviewed by Principal Investigators at each site, to determine if any of the criteria for stopping dose escalation has been met. Increase to the next higher planned dose level will only occur if the previous dose level was deemed to be safe and well-tolerated following review by Principal Investigator at each site. For the safety confirmation after administration of 500 μg, the time to dose increase to 500 μg should not exceed 32 weeks. In addition, as with the administration of 350 μg, 400 μg, and 450 μg, the Principal Investigators and sub-investigators at each medical institution assess that no drug-related adverse events requiring dose reduction/interruption/discontinuation occur within 2 weeks after dose increase (by Day 15 after the next visit) according to the protocol criteria. If the safety profile of the 500 μg dosing level for the 5 subjects in the first 6 evaluable subjects is confirmed by Coordinating Principal Investigator, Principal Investigators at each site and Sponsor's Medical Monitor, the observation based on the hospitalization for two days after administration will be deactivated and the rest of study subjects will receive the predefined higher dose level of the study drug (over 300 μg) without hospitalization. If two or more of the first six evaluable subjects fail to meet the criteria for tolerability, the Coordinating Principal Investigator, the Principal Investigators at each site and the sponsor's Medical Monitor will perform a comprehensive assessment of continuation of the study.

12.2 Physical, Chemical, Pharmaceutical Properties, and Formulations

The chemical name of P1101 is poly(oxy-1,2-ethanediyl), α-hydro-ω-methoxy-,1,1-diester with interferon α-2b [1-[1-[3,7-bis(carboxyamino) heptyl] proline].

P1101 is available as a solution containing P1101, sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate anhydrous, acetic acid, sodium hydroxide, hydrochloride acid, and water for injection. The solution is colorless to light yellow. P1101 will be supplied in pre-filled syringes.

The structural formula and amino acid sequence for P1101 is provided in Figure 12-1.



PCDLPQTHSL GSRRTLMLLA QMRRISLFSC LKDRHDFGFP QEEFGNQFQK
AETIPVLHEM IQQIFNLFST KDSSAAWDET LLDKFYTELY QQLNDLEACV
IQGVGVTETP LMKEDSILAV RKYFQRITLY LKEKKYSPCA WEVVRAEIMR
SFSLSTNLQE SLRSKE

Figure 12-1 P1101 Structural Formula and Amino Acid Sequence

Due to innovative pegylation technology, P1101 is composed of a single isoform. Recombinant IFNs as well as pegylated recombinant IFNs have been approved in several countries in various indications based on their antiviral, antiproliferative, and immunoregulatory properties.

12.3 Packaging, Labeling and Storage

The study drug will be labelled in the local language and comply with the legal requirements of each country. The study drug will include the following labeling: "For Clinical Trial Use Only," "To be administered at a dose according to the physician's instructions," and "Keep out of reach of children." The labels will include storage conditions for the study drug and the study drug number, but no information about the subject.

Additionally, aspirin (aspirin) 75 to 150 mg per day as background therapy (provided locally) will be prescribed to all subjects (unless contraindicated). In this case, other prophylactic antithrombotic agents may be used.

Table 12-1 Packaging and Labeling

Study drugs	Packaging
P1101	Pre-filled syringes with 500 µg per syringe

P1101 pre-filled syringes will be shipped in cooled containers. Pre-filled syringes must be refrigerated immediately upon receipt to ensure optimal retention of physical and biochemical integrity and should remain refrigerated until just prior to use. Study drug should be stored by the study site at controlled room temperature of 2 to 8ºC. Temperature logs must be maintained to ensure proper storage conditions. Do not freeze or shake the pre-filled syringes. Do not use medication beyond the expiration date stamped on the PFS. PFS must be kept in their outer carton to protect them from the light.

If the temperature of study drug storage in the clinic/pharmacy exceeds or falls below the 2ºC to 8ºC range, this should be reported to the Sponsor/designee and captured as a temperature excursion. Additional details on study drug storage requirements and related information will be provided in the pharmacy manual.

12.4 Supply of Study Drug at Site

The Sponsor/designee will ship the study drug to the investigational sites. The initial study drug shipment will be authorized by the Sponsor/designee after all required regulatory documentation for a particular site has been received. Subsequent study drug shipments will be made after site request for resupply. Details will be included in the pharmacy manual.

The study drug must be received by the study pharmacist or designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the study pharmacist and designated assistants have access. Upon receipt, the study drug should be stored according to the instructions specified on the drug labels. All drug product must be accounted for in accordance with the standard practice at each study center and in compliance with applicable regulations. The site must use an appropriate dispensing log/accountability form provided by the sponsor, or an acceptable substitute approved by the sponsor. Each time study medication is dispensed for a subject, the following information must be recorded: the subject's unique identifying number, the dose strength, the number of units (syringe) with the corresponding lot number, and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study and will be periodically verified by a representative of the sponsor.

12.5 Dosage and Dosing Schedule

P1101 will be administered SC during the study visits every 2 weeks. Subjects will receive an initial dose of 100 µg at Week 0, 150 µg at Week 2, and then 200 µg at Week 4, etc., i.e. dose escalation by 50 µg biweekly until 500 µg, or until response will be achieved. The dose can be further adjusted to prior dose for safety and tolerability reasons, but should preferably remain fixed for the treatment period.

The study drug should be administered SC into the abdominal skin around but not within 5 cm of the navel. If the abdomen appears inappropriate or unfavorable for injection according to the Investigator's judgment, study drug can be injected SC into the thigh. At the time of dispensing, the person administering the study drug will note the date and time of administration, both of which are then to be documented into the subject's eCRF.

A standardized dosing paradigm will be used to determine dose adjustments for safety and tolerability so that each subject will receive their most appropriate dose (Section 12.5.2).

12.5.1 Aspirin

All subjects should receive low-dose aspirin (75-150 mg/day) as background therapy unless medically contraindicated. In this case, other prophylactic antithrombotic agents may be used. Higher doses of aspirin (>150 mg/day) should not be used except when medically indicated.

12.5.2 Dose Reduction and Dose Interruption

Dose reduction or interruption for P1101 are recommended in subjects experiencing AEs until the AE abates. If intolerance persists after dose reduction or interruption, therapy should be discontinued. These dose changes must be recorded on the Dosage Administration Record and Adverse Event eCRF page.

Dose reduction of the study drugs should be driven exclusively by the safety and tolerability of the drugs under study. If a certain dose is poorly-tolerated and drug-related toxicities arise, the dose has to be reduced to the prior dose, or interrupted, following the scenarios below:

If a subject has a severe (Grade 3 or 4) toxicity, or a drop in absolute neutrophil count (ANC) to below 0.5×10^9/L, temporary interruption has to be implemented until recovery to the condition, which allows treatment continuation (e.g., Grade 1 mild intensity). Treatment re-initiation has to occur from the prior lower dose than those that caused the toxicity. For example, if Grade 3 AE occurs at 500 µg, treatment re-initiation will occur with 450 µg.

If a subject has a Grade 2 toxicity, or a drop in ANC to below 0.75×10^9/L but higher than 0.5×10^9/L, dose decrease without treatment interruption should be considered.

Grade 1 toxicity should not lead to dose reduction or interruption.

Dose re-escalation may be omitted in those subjects who do not recover from previous toxicity.

13 COMPLIANCE

P1101 will be supplied by the Sponsor. The study drug is to be prescribed only by the Principal Investigator or the designee. Under no circumstances will the Principal Investigator allow the study drug to be used in any settings other than those specified and directed by this protocol.

The Principal Investigator or designee is responsible for ensuring that all drug supplies are kept under lock and key, with access limited to the study team. The Investigator or designated study personnel will maintain accountability of all study drugs received, dispensed, and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. The pharmacist/designated person must maintain accurate records of the receipt of all study drugs shipped by the Sponsor, including date received, lot number, expiration date, amount received, and the disposition of all study drugs. If any damage in the clinical drug supply shipments occurs, the Investigator should contact the Sponsor/designee immediately. The inventory will be made available to the monitor to verify drug accountability during the study.

Compliance with the dosing regimens will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee (injection counts).

Drug administration will also be recorded in each subject's eCRF. An accountability log will be kept, indicating disposition of study drug; this log will be kept in the On-Site Study File.

14 PRIOR AND CONCOMITANT THERAPY

All medications (i.e., over-the-counter drugs and blood products) taken within 3 months (12 weeks) prior to the administration of the study drug, as well as, all concurrent therapies will be recorded in the relevant eCRF pages. All prior nondrug therapies, as well as, all surgeries will be recorded in the relevant eCRF pages. Dose, route, unit frequency of administration, indication for administration, and dates of medication will be captured. Any concomitant medications or changes thereof must be recorded at each visit. If the change influences the subjects' eligibility to continue in the trial, the Sponsor must be informed.

14.1 Allowed Concomitant Therapy

All subjects should receive low-dose aspirin (75-150 mg/day), unless medically contraindicated. In this case, other prophylactic antithrombotic agents may be used.

Paracetamol (acetaminophen), chlorphenamine (chlorpheniramine), and other antihistamines (used as monotherapy or combination preparations) can be used according to local clinical practice, for the prevention and treatment of injection site reactions associated with peg-interferon.

Moreover, paracetamol (e.g., 500 mg by mouth) or an appropriate dose of another NSAID is recommended to be administered 8 to 10 hours, 24 hours, and 48 hours after the first administration of P1101 in order to avoid potential flu-like symptoms. No prophylaxis will be administered until Visit 2 in order to assess the necessity of prophylaxis and to assess the true rate of IFN-induced flu-like symptoms.

Anti-coagulation therapy: subjects who experience thromboembolic events during the study treatment are permitted to receive full-dose anticoagulants and remain on the study drug based on the judgement of the treating Investigator, except for severe thromboembolic events. All details regarding anticoagulant treatment should be collected and recorded in the Concomitant eCRF page. Details regarding discontinuation due to severe thromboembolic events should be reported on the AEs and discontinuation eCRF page. Severe thromboembolic events are defined as Grade 3 and related AEs. On the Discontinuation eCRF page, the reason for discontinuation would be thromboembolic event.

Phlebotomy is performed aiming at a hematocrit < 45%. When the hematocrit value is 45% or higher, phlebotomy is performed. The volume of phlebotomy per procedure should be 200 to 400 mL per one phlebotomy while monitoring the circulatory dynamics such as blood pressure and pulse. In the elderly and patients with cardiovascular disorders, a small volume (100 to 200 mL) should be considered to avoid rapid changes in hemodynamics.

14.2 Prohibited Concomitant Therapy

Except for the investigational and reference drugs, no other cytoreductive (i.e., leading to decrease of cell counts in peripheral blood) therapy, JAK inhibitors, nor any other drugs leading to a decrease of peripheral blood cell counts are allowed in this study. Investigational medications, other than the study drugs used in this study, are not allowed in this study.

In addition, interstitial pneumonitis associated with the concomitant use of interferon-α preparations and Sho-sai-ko-to (or xiao-chai-hu-tang, herbal medicine) has been reported as safety data common to interferon-α 2a and interferon-α 2b products. Therefore, the concomitant use of Sho-sai-ko-to is contraindicated from a safety standpoint.

The contraindicated concomitant therapy period is set as from obtaining informed consent to the safety follow-up visit after completion of the administration period.

14.3 Contraception Use

Females of childbearing potential will be required to use oral, injectable, or implanted contraceptives. Use of hormonal contraception will be determined by the Investigator, taking into account the therapy used, the manufacturer's instructions, labeling, and accepted medical practice.

Male subjects will use an appropriate method of contraception, such as vasectomy (confirmed to be azoospermia) or condom use.

In this study, contraception is required from the start of the study to 28 days after the last dose of the investigational product, regardless of gender.

15 STUDY EVALUATIONS

15.1 Study Procedures by Visit

15.1.1 Overview

The study is divided into 2 phases with associated evaluations and procedures that must be performed at specific time points, as described in the following sections. The study flowchart (Appendix 1) summarizes the frequency and timing of study events.

As soon as the subject is considered for this study, and prior to any other study procedures, the subject will have the nature of the study explained to them, and will be asked to give written informed consent. Informed consent must be obtained prior to any procedures during the course of a clinical trial.

Subjects who are prematurely discontinued from the study should attend the safety follow-up visit 28 days after the last study drug administration.

15.1.2 Screening (-28 days/-1 day)

Subjects who might meet the inclusion criteria will be contacted and asked for their interest in participating in the study. If they agree to participate in the study, all subjects must provide written informed consent before any study-specific assessments or procedures are performed.

Subjects who are considered for study entry but fail to meet one or more of the eligibility criteria should not be reported in the eCRF. A detailed reason for ineligibility should be reported in the screening log.

An eCRF should be completed for all subjects fulfilling all of the entry criteria.

The site notifies the Sponsor when a subject eligible according to all inclusion and exclusion criteria is to be enrolled into the study. Study entry (enrollment) is defined by the subject's, or their legally authorized representative's, signature on the informed consent form. All subjects enrolled will be assigned a subject ID number.

The following assessments will be completed according to the study flowchart (Appendix 1).

- Informed consent - verification of personally signed and dated informed consent of the subject, or their legally authorized representative, prior to any study-related examinations performed
- Inclusion and exclusion criteria - Subjects who meet all inclusion criteria and none of the exclusion criteria will be invited to participate in the study
- Demographic information (e.g., age, sex, and race) will be recorded at screening in the appropriate eCRF. Relevant medical history, including history of prior and current disease(s), and information regarding underlying diseases will also be recorded at screening. Included will be the usage of any and all drugs used to treat PV.
- Standard 12-lead ECG
- A urine pregnancy test must be performed within 7 days prior to the first administration of study drug and subsequently every 4 weeks for all women of childbearing potential (no hysterectomy or bilateral oophorectomy, or at least 12 consecutive months without spontaneous menopause [i.e., menstruation occurred sometime in the past 12 consecutive months], or amenorrhea due to medical treatment such as antineoplastic drugs) as well as for all women <2 years from the onset of presumed menopause (the time point of completion of the last menstruation was considered as menopause, when the next menstruation has not started for more than 2 years)
- Complete physical examination
- Vital signs (pulse rate, blood pressure, and body temperature)
- Blood chemistry
- Blood coagulation

- Serology to exclude systemic infections; the tests commonly used in the local setting for diagnosing current infections (with HIV and HCV, as well as hepatitis B surface antigen [HBsAg] to detect HBV infection) are to be performed for eligibility assessment purposes
- Hematology
- Autoimmune markers (blood)
- Urine test
- Urine beta 2 microglobulin test
- ECOG performance status
- Spleen size measurement: Spleen size will be measured by palpation and, for palpable spleen, subsequently by ultrasound with local review of the images
- Genetic test sample including JAK-2 allelic burden (data collected according to WHO criteria)
- Bone marrow sampling (optional). Bone marrow biopsy collected within 6 months of Screening could be used to replace the Screening sample. If a sample was taken within 6 months, but since then the patient was treated with HU and failed, the sample needs to be retaken.
- AEs
- Concomitant treatment
- Ocular examination
- Lung X-ray: Will be accepted if they are not older than 12 weeks prior to the date of the screening visit
- Heart ECHO: Will be accepted if they are not older than 12 weeks prior to the date of the screening visit
- HADS (Appendix 8)
- After having successfully completed the screening period and if found eligible for the study, the subjects will receive the study treatment.

15.1.3 Treatment Period Week 0 to Week 52

The first dose of study drug will be administered at 0 hours on Day 1.

All assessments, including local laboratory samples, are to be completed prior to the study drug administration at each visit.

Note: If hematology and/or blood chemistry are done within 7 days prior to Visit 1, they do not have to be repeated.

Please refer to the study flowchart and others (Appendix 1, Appendix 2, Appendix 3) for specific assessments at each visit.

15.1.4 Safety Follow-up or End of Study Visit

Subjects who discontinue study drug prematurely will return for a follow-up visit 28 days after the last dose. Please refer to the study flowchart and others (Appendix 1, Appendix 2, Appendix 3) for visit-specific assessments.

If subjects will participate in extension study of A19-201, safety follow-up will not be performed.

Subjects who discontinue study drug due to a suspected study drug-related AE must be followed at least once a week for 8 weeks and subsequently at 2-week intervals until resolution or stabilization of the event.

If a subject has not recovered from any toxicity within 8 weeks of prematurely discontinuing study drug, s/he must be discontinued from the study, but will continue to be followed for toxicity as described above.

Subjects who discontinue study drug due to a severe thromboembolic event will have an AE reported as the reason for discontinuation, and "severe thromboembolic event" indicated in the specific field.

If a subject has not recovered from any toxicity within 8 weeks of prematurely discontinuing study drug, s/he must be discontinued from the study, but will continue to be followed for toxicity as described above. In this case, data may not be entered into the database but will be documented in the study log, and stored at the site.

There may be a post-study care opportunity for study subjects who benefit from P1101 therapy. Further details will be provided as a separate protocol or amendment to this protocol at a later stage.

15.2 Pharmacokinetic and Immunogenicity Evaluations

Pharmacokinetic Evaluation

- The PK samples will be collected for population PK analysis of P1101.
- Serial PK samples (n=4 per subject) will be collected at Week 0 and Week 28, at the following time points: pre-dose (0 hr), 48 (±24) hr, 96 (±24) hr, and 168 (±24) hr. At Weeks 0 and 24, subjects must administer their P1101 dose in the clinic.
- Trough PK samples will be collected at every visit.
- The PK sampling schedule is provided in Appendix 2. The actual date and time of dose and PK sample collection must be recorded on the CRF.
- All P1101 treated subjects will have their blood samples collected for the analysis of serum concentrations of P1101 according to the study flowchart (Appendix 1, Appendix 2). Population PK/PD models will be updated with the PK and PD data from Week 0 to Week 12 of the first 15 subjects in the P1101 arm.
- Detailed instructions will be provided in a laboratory manual and stored in the investigator site file.

Immunogenicity Evaluation

- The immunogenicity samples will be collected for anti-drug antibody assessment for P1101.
- Blood samples will be collected from the subject confirmed positive for P1101 ADA at EoS visit every three months until ADAs return to baseline levels or up to 12 months.
- The immunogenicity sampling schedule is provided in Appendix 3. The actual date and time of dose and immunogenicity sample collection must be recorded on the CRF.
- All P1101 treated subjects will have their blood samples collected for the analysis of serum anti-drug antibody against P1101 according to the study flowchart (Appendix 3).
- Detailed instructions will be provided in a laboratory manual and stored in the investigator site file.

15.3 Assessment of Efficacy

15.3.1 Efficacy Measurements and Time Points

15.3.1.1 Primary Efficacy Measurements – Peripheral Blood Count Remission

The primary efficacy endpoint is the phlebotomy-free complete hematologic responder rate (CHR) at month 9 and month 12.

The phlebotomy-free responder rate is defined as the proportion of patients with complete hematologic response (CHR) and with no phlebotomies during the previous 3 months.

A responder in sense of a primary endpoint is a patient who has met all of the following criteria at month 9 and month 12:

- • Hematocrit <45% phlebotomy-free (absence of phlebotomy during the previous 3 months)

- • Platelet count ≤ 400 x 10^9/L,
- • WBC count ≤ 10 x 10^9/L

Scheduled hematological assessments will occur as indicated in Appendix 1. Samples for hematology assessments will be prepared using standard procedures. For the hematologic parameters of Hct, platelets and WBCs, central laboratory assessments at Weeks 0, 12, 24, 36, and 52 will be used for determination of responder. Detailed specifications for hematology sample handling, shipping, and processing will be provided in a laboratory manual.

15.3.1.2 Other Efficacy Measurements

There will be disease response assessments at Weeks 0, 12, 24, 36, and 52 of treatment with P1101. During these times, changes in Hct, WBC, PLT, spleen size, molecular response from baseline, time to requiring no phlebotomy, numbers of phlebotomy required, time to response, duration of response maintenance, ratio of CHR rates of subjects with/without prior treatment with HU and Proportion of subjects without thrombotic events will be assessed.

15.3.1.3 Genetic Assessment of *JAK2*

Genetic assessments will consist of screening tests for PV diagnosis purposes and quantitative *JAK2* measurements at screening, Weeks 0, 12, 24, 36 and 52 (central laboratory). Change of *JAK2* allelic burden over time will be assessed (by ELN 2013 criteria; (Barosi et al. 2013)).

Whole blood samples, collected from all subjects prior to study drug administration, will be centrally assessed. Detailed instructions for sample handling, labeling, and storage will be provided in the laboratory manual.

Handling of samples for JAK2 mutation assessment and disclosure of assay results to subjects are as follows.

- Storage period, storage method and disposal of samples

  DNA samples are extracted from whole blood at a central laboratory and stored in a locked and manageable refrigerator.

  The DNA samples are handed over to the company handing industrial waste as industrial wastes 6 months after the end of the determination.

- Volume of blood samples collected

  Three mL of whole blood is collected from vein at each sampling

- Disclosure plan of genetic test results to subjects and the reason

  The genetic test results will be disclosed to the subject or the subject's legally acceptable representative, only if the subject or the subject's legally acceptable representative desire to know the results.

- Handling of blood samples if the consent is withdrawn the use of blood samples during the study

  If a subject withdraws consent to the genetic mutation test during the study period, the genetic test will be discontinued, and the sample will be discarded.

15.3.1.4 Spleen Size Assessment

Spleen size will be measured by ultrasound. The captured images are recorded and assessed, according to the clinic’s routine criteria. Detailed instructions for procedures will be provided in the laboratory manual.

15.3.1.5 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) will be used. HADS is a self-report questionnaire commonly used by doctors and therapists to assess levels of anxiety and depression in patients. The HADS comprises 14 statements which the patient rates based on their experience over the past week. Each question has 4 possible responses. Responses are scored on a scale from 3 to 0. The maximum score is 21 for depression and 21 for anxiety. A score of 11 or higher indicates the probable presence of mood disorder, with a score of 8 to 10 being just suggestive of the presence of the respective state. The HADS is divided into four ranges: normal (0-7), mild (8-10), moderate (11-15) and severe (16-21) (Snaith 2003). HADS was found to perform well in assessing the symptom severity and identifying cases of anxiety disorders and depression in both somatic, psychiatric and primary care patients and in the general population (Bjelland et al. 2002). HADS is being used and confirmed to be a valid tool for assessment of psychiatric side effects of interferon alpha (Kraus et al. 2005). Furthermore, the HADS can be administered by non-psychiatrist physicians (Olsson, Mykletun, and Dahl 2005). For HADS see Appendix 8.

15.3.2 Assessment of Safety

Assessment of safety will be determined by vital signs, clinical laboratory tests, physical examinations, ECGs, heart ECHOs, lung X-rays, ECOG performance status, ocular examinations, and AEs.

15.3.3 Subject Demographics and Medical History

Demographic information (e.g., age, sex, race) will be recorded at screening in the appropriate eCRF. Relevant medical history, including history of prior and current disease(s), and information regarding underlying diseases will also be recorded at screening. Included will be the usage of any and all drugs used to treat PV.

At screening, in-depth medical history data will be collected, including thrombosis/hemorrhage history, *JAK2* mutation status, acquired von Willebrand disease in the past, presence of progressive/symptomatic splenomegaly, symptomatic thrombocytosis, progressive leukocytosis, progressive disease-related symptoms, and vasomotor/microvascular disturbances not responsive to aspirin.

15.3.4 Physical Examination

Information about the physical examination must be present in the source documentation at the study site. The physical examination will include general status, lungs, cardiovascular system, abdomen, musculoskeletal system, skin, lymph nodes, and central nervous system. Any significant findings associated with clinical signs or symptoms, or requiring therapy before the screening visit should be recorded. Clinically significant findings made after the start of the study drug that meet the definition of an AE must be recorded as AEs.

15.3.5 Vital Signs

Body temperature, blood pressure, and pulse rate will be measured after resting in a supine position for 5 minutes at all visits.

15.3.6 Electrocardiograms

In accordance with the study flowchart (Appendix 1), standard 12-lead ECGs will be performed at screening, and prior to study drug administration (0 hr) at Weeks 0, 2, 4, 12, 24, 28, 36, and 52 , as well as at early withdrawal and the safety follow-up visit. At Weeks 0 and 28, an additional ECG assessment will be performed at 96 (±24) hr after study drug administration. The ECG should be performed following the subject is in a supine position for 5 minutes and prior to the collection of any PK samples.

The QT/QTcF interval will be determined from at least 3 to 5 cardiac cycles (heart beats).

Any abnormal findings assessed by the Investigator as clinically significant should be recorded in the relevant eCRF modules (e.g., AE, medical history).

15.3.7 Bone Marrow Assessment

Bone marrow sampling is optional. However, if bone marrow is collected, the following process will be followed. The bone marrow samples should be centrally assessed. Two bone marrow samplings (one at the first study drug dose [Week 0] and one at Week 52) will be taken and sent for central evaluation.

The definition of bone marrow histological remission is disappearance of hypercellularity, trilineage growth (panmyelosis) and absence of > grade 1 reticulin fibrosis.

15.3.8 Ocular Examination

All subjects will have an ocular examination at screening and at the EoT visit. The examination will consist of visual acuity assessment, slit lamp examination, tonometry, and fundus examination. Clinically relevant ophthalmological disorder (due to diabetes mellitus or hypertension) at screening will be an exclusion criterion. In addition to scheduled examinations, an ophthalmologist consultation is mandatory for all subjects reporting worsening vision or visual symptoms. P1101 treatment will be discontinued in subjects who develop a new ophthalmologic disorder during the study.

15.3.9 Lung X-Ray and Heart ECHO

All subjects will have a lung X-ray and heart ECHO at screening and at the EoT visit. For screening, lung X-rays will be accepted which are not older than 12 weeks prior to the date of screening visit. In case of premature discontinuation, no X-ray examination (but the heart ECHO only) will be performed (to reduce the burden from exposure to radiation) unless necessary for safety follow-up purposes.

Subjects with clinically relevant pulmonary infiltrates, pneumonia, and pneumonitis at screening will not be eligible for the study. In cases of persistent or unexplained pulmonary infiltrates or pulmonary function impairment, treatment will be discontinued as a precautionary measure if deemed necessary in the judgement of the Investigator or sponsor.

15.3.10 ECOG Performance Status

The ECOG Performance Status are scales and criteria used by doctors and researchers to assess how a subject's disease is progressing, assess how the disease affects the daily living abilities of the subject, and determine appropriate treatment and prognosis.

The performance status will be assessed according to the ECOG performance status scale as noted in Appendix 4. The ECOG performance status is graded on a 6-point scale (range 0 to 5): 0=Asymptomatic (fully active, able to carry on all pre-disease activities without restriction); 1=Symptomatic but completely ambulatory (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work); 2=Symptomatic, <50% in bed during the day (ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours); 3=Symptomatic, >50% in bed, but not bedbound (capable of only limited self-care, confined to bed or chair 50% or more of waking hours); 4=Bedbound (completely disabled, cannot carry on any self-care, totally confined to bed or chair); and 5=Death.

In accordance with the study flowchart (Appendix 1), the ECOG will be performed at screening, and Weeks 0, 12, 24, 36, and 52 following first study drug administration, as well as at early withdrawal/EoT and the safety follow-up visit.

15.3.11 Adverse Events

Information regarding occurrence of AEs will be captured throughout the study. Duration (start and stop dates and times), seriousness, severity/grade, outcome, concomitant medication use, action taken, and relation to study drug will be recorded in the eCRF. For more information on safety reporting, see Section 16.

15.3.12 Laboratory Evaluations

Table 15-1 presents the list of clinical laboratory measurements that will be performed. A local laboratory will be used for analysis of all specimens. Hematology specimens for baseline (Visit 1) and Months 3, 6, 9, and 12 will also be evaluated by the central laboratory. Details on the collection, shipment of samples, and reporting of results will be provided to Investigators in the laboratory manual. For the schedule of the laboratory assessments, refer to Appendix 1, Appendix 2 and Appendix 3.

Table 15-1 Clinical Laboratory Measurements

Hematology Panel	Blood Chemistry Panel	Others
HGB HCT Red blood cell (RBC) count Platelet count White blood cell (WBC) count WBC differential （neutrophils, lymphocytes, monocytes, eosinophils, basophils and reticulocytes) MCV	ALT, AST Gamma-glutamyl transferase (GGT) NT-proBNP or BNP Alkaline phosphatase (ALP) Amylase Lipase Total bilirubin Albumin Total protein Electrolytes (Potassium, Sodium, Calcium, Chloride) Lactate dehydrogenase (LDH) Blood urea nitrogen (BUN) Creatinine Glucose Iron Transferrin Thyroid stimulating hormone (TSH), FT4 Uric acid Low-density lipoprotein (LDL) High-density lipoprotein (HDL) Total cholesterol Triglycerides	Coagulation tests: PT-INR, aPTT, Fibrinogen Urinalysis (pH, blood, protein, glucose, WBC, nitrite) Urine beta 2 microglobulin Pregnancy test (urine) Serology: HBsAg, HCV antibody, HIV antibody Autoimmune markers: Antinuclear antibodies, TgAb, TPOAb Genetic test: JAK-2

Increases in liver enzyme levels in blood serum have been observed in subjects treated with pegylated IFNs. Therefore, liver enzyme levels (ALT, AST, and GGT) and total bilirubin will be measured at screening and subsequently, every 2 weeks in the treatment period of the trial, as well as at early withdrawal/EoT and the safety follow-up visit (if applicable). If the increase of liver enzyme levels is progressive and clinically significant, despite dose reduction, or is accompanied by increased total bilirubin, the subject will be withdrawn from the study.

Immunogenicity assessment of anti-P1101 antibodies (anti-drug antibodies; ADA) will be measured before the first dose (Week 0), 7 days (168 (±24) hr) after the initial P1101 dose, Week 4, 12, 24, 36, and at End of Treatment (EoT; Week 52), and at the EoS/Follow-up visit (28 days after the final P1101 drug administration at the EoT visit). Presence of anti-PEG antibodies will be measured. A multi-tiered ADA testing approach will include assays for the following: anti-P1101 binding antibodies and a confirmatory assay, antibody titers, and P1101 neutralizing antibodies. Blood samples will be collected from the subject confirmed positive for P1101 ADA at EoS visit every three months (Week 64, 76, and 88) until ADAs return to baseline levels or up to 12 months (Week 104). (Appendix 3)

15.4 Appropriateness of Measurements

Platelets and WBCs at baseline (Visit 1), Months 3, 6, 9, and 12 will be evaluated by a central laboratory.

Quantitative JAK2 allelic burden measurements will be also done by a central laboratory, every 3 months including baseline (Visit 1; Day 0).

16 SAFETY REPORTING

Clinical events occurring before starting study treatment but after signing the informed consent are recorded on the Medical History/Current Medical Conditions eCRF page.

16.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. All AEs occurring during the course of the clinical trial (i.e., from signing the informed consent form onwards through the treatment phase until the safety follow-up visit) will be collected, documented, and reported by the Investigator. Details on AE collection will be available in the eCRF collection guideline.

All AEs, serious and non-serious, will be fully documented on the appropriate eCRFs. For each AE, the Investigator will provide the onset, end, intensity, treatment required, outcome, seriousness, and action taken with the study drug. The Investigator will determine the relationship of the investigational drug to all AEs and record it in the eCRF. When assessing whether an AE is causally related to the study drug, the Investigator should consult the IB and use his/her clinical judgement and the subject's underlying disease before rendering an assessment.

All collected AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). AEs and laboratory parameters will be graded according to CTCAE Version 5.0, (http://ctep.cancer.gov).

Adverse event monitoring should be continued until the safety follow-up visit/EoS or until AE resolution/stabilization, whichever occurs first. Safety follow-up visit is 28 days after end of treatment visit. AEs will be regarded as treatment-emergent if the time of onset or worsening is after or on the first intake of study drug.

Disease progression of PV should not be regarded or reported as an AE unless it is associated with a separate AE. Relationship will be assessed with not related, unlikely related, possibly related, probably and definitely related. Action taken will be described as dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn, and unknown.

16.2 Abnormal Clinical Laboratory Test Results

All clinically significant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to baseline or to a level deemed acceptable by the Investigator and the Sponsor's clinical monitor (or his/her designated representative), or until the abnormality is explained by an appropriate diagnosis. Clinically significant abnormal laboratory tests that result in a change in study drug dosage, discontinuation of the drug, or require intervention or diagnostic evaluation to assess the risk to the subject, or are otherwise clinically relevant, should be recorded as AEs in the eCRF. Clinical diagnosis should be provided whenever possible. If no clinical diagnosis is available, the increase/decrease in the laboratory parameter may be recorded as an AE term. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 event (severe), as per CTCAE, does not automatically indicate an SAE unless it meets the definition of serious as defined in the protocol and/or as per Investigator's discretion. A dose modification or medication for the laboratory abnormality may be required by the protocol in Section 12.5.2 and should not contribute to the designation of a laboratory parameter abnormality as an SAE.

16.3 Abnormal Physical Examination Findings

Clinically significant changes, in the judgment of the Investigator, in physical examination findings (abnormalities) will be recorded as AEs and followed up until resolved or considered stable. Physical examination AEs should be followed up and reported in the same way as for the laboratory findings. Clinical diagnosis should be provided whenever possible. If no clinical diagnosis is available, the finding may be recorded as an AE term.

16.4 Pregnancy

In female subjects of childbearing potential, as well as all women <2 years after the onset of menopause, appropriate contraceptive measures are mandatory during the study (e.g., barrier method such as condoms or diaphragms; intrauterine devices; surgical methods; contraceptives of hormone preparations alone or in combination; or sexual abstinence).

Male subjects will use an appropriate method of contraception, such as vasectomy (confirmed to be azoospermia) or condom use.

In this study, contraception is required from the start of the study to 28 days after the last dose of the investigational product, regardless of gender.

Pregnancy itself is not an AE, but pregnancy-related AEs should be captured for study subjects and female partners of male study subjects who may become pregnant during the study. Pregnancies should be reported and followed up within the timelines specified for SAEs. Relevant risk factors as well as outcome should be recorded. Subjects should be advised to discontinue study treatment at the first suspicion of pregnancy.

16.5 Adverse Events of Special Interest

According to the Council for International Organizations of Medical Sciences (CIOMS VI) definition, an AESI is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. Such an event (serious or non-serious) might warrant further investigation in order to characterize and understand it.

Such events should be reported within the timelines and according to the procedures defined for SAEs.

Protocol-specific AESIs, e.g., psychiatric AEs, will be described in the statistical analysis plan (SAP). For cardiovascular disease-related AESIs, the diagnostic criteria are pre-specified in Appendix 5 of this protocol with conditions to ensure adherence to the diagnostic criteria standards across all centers in the study.

16.6 Serious Adverse Events

Information about all SAEs will be collected and recorded on the AE eCRF page. To ensure subject safety, each SAE must also be reported to the Sponsor within 24 hours of learning of its occurrence. All SAE will be followed until resolution or up to 30 days following the last infusion / last dose of study drug. An SAE is defined in general as an untoward (unfavorable) event that is serious and has the following outcome(s):

- Death
- Life-threatening: The study subject's life was in an immediate danger due to the event.
- Hospitalization: The study subject had to be hospitalized due to the event.
- Prolongation of hospitalization: The existing hospital stay had to be prolonged due to the event.
- Persistent/significant disability/incapacity: The event resulted in persistent/ significant disability/incapacity having caused long-term changes (either anatomical, physiological, or psychic) affecting the study subject's life.
- Congenital anomaly/birth defect: Any abnormalities in features or functions of the offspring of the study subject who has been exposed to study drug treatment during pregnancy.

- Important medical event: The event is considered medically significant, but none of the above categories are applicable (e.g., the study subject required medical intervention to prevent the event to become life-threatening). Important medical events are those which may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Hospitalizations occurring under the following circumstances are not considered SAEs: admission to a hospice for respite care; hospitalizations planned before entry into the clinical study; hospitalization for elective treatment of a condition unrelated to the studied indication or its treatment; hospitalization on an emergency, out-subject basis that does not result in admission (unless fulfilling the criteria above); hospitalization as a part of the normal treatment or monitoring of the studied indication; and hospitalization not associated with any deterioration in condition.

16.7 Instructions for Expedited Notification of Serious Adverse Events

16.7.1 Reporting Responsibility

Any SAE occurring in a subject after providing informed consent and until completion of the last visit for subjects, e.g., completing EoS form must be reported to the sponsor. The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated. All SAEs must also be reported for the period in which the study protocol interferes with the standard medical treatment given to a subject.

Each SAE must be reported by the Investigator to the Sponsor within 24 hours of learning of its occurrence, even if it is not considered to be treatment-related. Follow-up information about a previously reported SAE must also be reported to the Safety Desk within 24 hours of receiving it. The Safety Desk may contact the Investigator to obtain further information on a reported SAE. If warranted, an Investigator alert may be issued, to inform all Investigators involved in any study with the same drug that this SAE has been reported.

16.7.2 Reporting Procedures

If the investigator becomes aware of a serious adverse event or malfunction of device, the investigator must report it to the point of contact described in “4) Contact Information for serious adverse event” in the Attachment 1 of the protocol by telephone, fax or e-mail, etc. within 24 hours.

If additional information such as follow-up information is collected, it should be reported immediately to the sponsor. All the reports will be filed in the Trial Master File.

17 STATISTICAL ANALYSIS

17.1 General Consideration

Categorical variables will be summarized using frequency counts and percentages. Percentages will be presented to 1 decimal point, unless otherwise specified. Continuous variables will be summarized by total number (n), mean, standard deviation, median, minimum, and maximum.

17.2 Sample Size Estimation

Sample size is calculated, based on the following assumptions;

- The target population of the Japanese local study: Japanese PV patients for whom the current standard of treatment is difficult to apply.
- Study design: P1101 single arm no controlled study (previous proposal was designed as a historical control study using PROUD-PV study).
- Primary study objective: To evaluate the safety and efficacy of P1101 for Japanese PV patients for whom the current standard of treatment is difficult to apply.
- Primary efficacy variable: Complete Hematological Response (CHR)

- Study period and evaluation visits: 3 month, 6 month, 9 month and 12 months. The safety follow-up will be continued to 12 months and the major efficacy data will be obtained at 12 months.
- The primary analysis of the primary endpoint: The lower limit of the 95% confidence interval of CHR rate is greater than 11%, and also the slope of the linear regression model of the CHR rate time course is greater than 0 (positive trend):
- The rationale: the natural healing rate (placebo response) of CHR rate of PV patients is 0%, thus if the lower limit of 95% confidence interval of the CHR rate exceed 11%, the efficacy of P1101 can be confirmed. The rationale to set the CHR rate limit as 11% is, (1) 11% is the minimum CHR rate value of P1101 obtained in the PROUD-PV study, (2) and the trend of the CHR rate is positive, thus 11% can be considered as a limit of the acceptable clinical risks.
- Assuming the above conditions, the power of the study at 9 months will be about 85% with 25 cases (CHR rate of the PROUD-PV study at 3, 6, 9, and 12 months are 11%, 27%, 36% and 43%, respectively). Considering the uncertainty of maximum 5 patients who are different background from PROUD-PV, a total of 30 cases will be reasonable to evaluate both efficacy and safety.

17.3 Populations for Analysis

17.3.1 Enrolled Population

The enrolled population will include subjects who signed informed consent form.

17.3.2 Intent-to-Treat (ITT) Population

The intent-to-treat (ITT) population will include all treated subjects. Analysis based on ITT population will be based on the treatment to which they are treated.

17.3.3 Per Protocol Population (PPP)

The PPP will consist of subjects included in the ITT who are exposed to treatment and have all measurements needed for assessment of the primary endpoint for at least 1 post-baseline visit, and do not have a major protocol deviation.

17.3.4 Protocol Deviations

The following are considered potential protocol deviations:

- No diagnosis of PV.
- Prior therapy does not match with protocol requirements in terms of types of previous therapy regimens.
- No baseline spleen size measurement in the protocol-specified time windows.
- Subjects who take <80% of the prescribed dose over the total duration of study drug dosing as calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee.

Other observations made during the study will also be considered. All potential protocol deviations will be reviewed prior to any interim analysis or database lock. For every potential protocol deviation, a general decision will be made whether to regard it as major or minor, and approved by the Sponsor before database lock. The PPP will be used for efficacy sensitivity analysis.

17.3.5 Safety Population

The Safety Population will include all subjects who have received at least one dose of study drug. For analysis, it will assign subjects to the treatment actually received.

17.4 Efficacy Endpoints Analysis

17.4.1 Primary Efficacy Endpoint Analysis

This study will enroll 30 Japanese PV subjects and collect laboratory and clinical data on each subject every 3 months after baseline through 12 months. Primary endpoint analysis will be based on all the evaluable subjects. For each subject at each time point of 3 months, response will be assessed.

The primary efficacy endpoint is the phlebotomy-free complete hematologic responder rate (CHR) at month 9 and month 12.

The phlebotomy-free responder rate is defined as the proportion of patients with complete hematologic response (CHR) and with no phlebotomies during the previous 3 months.

A responder in sense of a primary endpoint is a patient who has met all of the following criteria at month 9 and month 12:

- Hematocrit <45% phlebotomy-free (absence of phlebotomy during the previous 3 months)
- Platelet count $\leq 400 \times 10^9$/L,
- WBC count $\leq 10 \times 10^9$/L,

17.4.2 Secondary Efficacy Endpoints Analyses

The secondary efficacy endpoints are for providing additional supportive evidence of efficacy of the treatment.

- Changes in Hct, WBC, PLT and spleen size from baseline
- Time to requiring no phlebotomy
- Numbers of phlebotomy
- Time to first peripheral blood count response: Cox regression will be performed with treatment, age and baseline factors as the covariates.
- Duration of peripheral blood count response maintenance: Only subjects with response will be included. Mean duration of response will be compared between the two arms using appropriate parametric t-test or non-parametric rank-based test.
- Change from baseline of *JAK2* allelic burden over time: Longitudinal evaluation using repeated measures will be performed.
- Spleen size measurements by sonography will be summarized by scheduled time points, as appropriate.
- Difference in CHR rate between subject with or without of treatment with HU
- Proportion of subjects without thrombotic or hemorrhagic events

Frequencies of disease-related symptoms will be presented in frequency table and compared between treatment arms using chi-square test (or logistic regression with the same factors as used in the primary endpoint analysis).

Additional analyses to those proposed below that may be performed after the completion of the clinical study report (CSR) will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies, or the analysis of biomarkers generated from samples collected during the study but analyzed after database lock and completion of the CSR. In addition, the relationship between biomarker endpoints and safety and efficacy endpoints may be explored. Such data analysis will be described in the SAP.

17.5 Exploratory Analysis

The exploratory analysis consists of bone marrow histological remission. Bone marrow histological remission defined as the disappearance of hypercellularity, trilineage growth (panmyelosis) and absence of >grade 1 reticulin fibrosis (optional).

17.6 PPK, E-R, and Immunogenicity Endpoints Analyses

- PPK Analysis
- PK analyses will be performed using the PPK approach and summarized in a separate report where PK parameters, including but not limited to AUC, C_{max}, T_{max}, and half-life, will be summarized with mean, median, SD, and 95% confidence intervals. The effects of covariates on the PK of P1101 will be investigated.
- E-R Analysis
- The relationship between exposure and key efficacy and safety endpoints will be explored using E-R analysis. The effects of covariates on E-R will be investigated.
- Immunogenicity Analysis
- The proportion of subjects who are positive or negative to anti-P1101 antibody will be summarized.

17.7 Safety Endpoints Analysis

Safety data, including ECOG performance status, vital signs, ECGs, heart ECHOs, clinical laboratory tests, physical examinations, lung X-rays, AEs, and ocular examinations, will be summarized by treatment arms and scheduled visits, as appropriate. Change from baseline will be included in summary tables for laboratory, ECG, and vital sign parameters. AEs will be coded by MedDRA and then summarized by system organ class and preferred term for each treatment.

17.8 Handling of Missing Data

Missing data will not be imputed, unless otherwise specified. See details in the SAP on the general issue of handling intercurrent events and sensitivity analysis for the primary endpoint.

18 ETHICAL AND REGULATORY ASPECTS

18.1 Ethics and Good Clinical Practice

This study will be conducted in accordance with the ethical principles laid down in the Declaration of Helsinki. The study protocol and any subsequent amendment(s) will be submitted for approval to an Institutional Review Board (IRB). The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) regulations and applicable regulatory requirements. The regulatory application or submission for regulatory approval will be made by the Sponsor or its delegate as required by national law.

18.2 Institutional Review Board

Before implementing this study, the proposed informed consent, and other information given to subjects must be reviewed by an IRB, and a signed/subscribed and dated statement that the informed consent have been approved by the IRB must be given to Sponsor before study initiation. The IRB membership roster must be provided to the Sponsor. The IRB will review any amendments to the protocol that require formal review and approval. The IRB may be notified for all other amendments (i.e., administrative changes) in accordance with applicable regulatory requirements.

18.3 Subject Information and Informed Consent

The Investigator (or a properly trained specialty physician, allocated with this task by the Investigator), should obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study that is relevant to the subject's decision to participate. The informed consent form must be signed, with name and date noted by the subject or their legally authorized representative, if applicable, before the subject is exposed to any study-related procedures, including screening tests for eligibility.

The Investigator will explain that the subject is completely free to refuse to enter the study or to withdraw from the study at any time, without any consequences to their current or future care and without the need to justify their decision.

Each subject will be informed that his/her source records may be reviewed by the study monitor, IRB, or a regulatory authority inspector, in accordance with applicable regulations, and that these persons are bound by confidentiality obligations.

18.4 Confidentiality

The Investigator will ensure that the confidentiality of the subjects' data will be preserved. In the eCRF or any other documents submitted to the Sponsor, the subjects will not be identified by their names, but by an identification system.

The Investigator will maintain documents not meant for submission to the Sponsor, e.g., the confidential subject identification code and the signed informed consent forms, in strict confidence.

Each subject will be informed that a monitor or a regulatory authority inspector, in accordance with applicable regulatory requirements, may review portions of their source records and source data related to the study. Data protection and confidentiality will be handled in compliance with applicable local, regional, and/or international requirements.

19 QUALITY CONTROL AND QUALITY ASSURANCE

19.1 Source Data and Records

Source data are defined as all the information related to clinical findings, observations, or other activities in the study, added to the original records allowing reconstruction and evaluation of the study.

The Investigator will maintain adequate source records (e.g., files for each enrolled subject). Source records should be preserved for the maximum period of time required by applicable regulations.

All data entered in the eCRF must be supported by source data in the subjects' records.

The Investigator will permit trial-related monitoring, audit(s), IRB review(s), and regulatory inspection(s) by local and/or regional regulatory authorities, as applicable, by providing direct access to source data/records.

The Investigator may authorize site staff (e.g., co-Investigators, nurses) to enter study data into the eCRF.

19.2 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to review all trial-related source data/records, verify the adherence to the protocol and the completeness, correctness, and accuracy of all eCRF entries compared to source data. The Investigator will cooperate with the monitor to ensure that any discrepancies identified are resolved.

The monitor must be given direct access to source documents (original documents, data, and records). Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the trial. Source data will be available for all data in the eCRFs, including all laboratory results. Data, which will be continuously monitored during drug administration, will be entered into the eCRF periodically.

19.3 Confidentiality of Subjects´ Data

The Investigator will ensure that the subject's anonymity will be preserved. On eCRFs or any other documents submitted to the Sponsor, the subjects will not be identified by their names, but by a unique subject number. Documents that are not intended for submission to the Sponsor, i.e., the original consent forms and source records, will be maintained by the Investigator in strict confidence and in accordance with regulatory requirements.

20 DATA HANDLING AND RECORDKEEPING

20.1 Responsibilities of Investigators

The Investigator is accountable for the conduct of the trial at the site. If any responsibilities are delegated, the Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated significant trial-related duties.

20.2 Case Report Forms

Electronic Case Report Forms (eCRF) are supplied by the CRO and should be handled in accordance with instructions from the Sponsor. Only the Sponsor approved version of the eCRF should be used for recording study data.

The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded to eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation.

eCRFs should be completed by the Investigator or delegate as stated in the site delegation log for all subjects who have signed informed consent.

The Investigator should complete the relevant eCRF pages as soon as possible after each visit observation or clinical laboratory test.

All data sent to the Sponsor must be endorsed by the Investigator.

The Study Monitor should verify the contents against the source data. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

20.3 Changes to Case Report Form Data

Errors occurring in eCRFs will be modified by the Investigator or designee, and all changes will be tracked in the audit trail.

20.4 Recording, Access, and Retention of Source Data and Study Documents

Source data to be reviewed during this study will include, but is not limited to: subject's medical file, subject ID code list, subject diary cards, original laboratory reports, and histology and pathology reports, investigational medicinal product inventory, 12-lead ECG printouts and echocardiograph reports.

All key data must be recorded in the subject's medical records. Original printouts of data that were generated by technical equipment, for example 12-lead ECG trace, must be labelled with the date that they were printed by the machine, and the subjects' unique identification number. The medical evaluation of such records should be documented as necessary and signed and dated.

The Investigator must permit authorized representatives of the Sponsor, the respective national, local, or foreign regulatory authorities, the IRB, and auditors to inspect facilities and records relevant to this study.

The Study Monitor (and auditors, IRB or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the Sponsor or its representatives, national or local regulatory authorities or the IRB having access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the Pharmaceuticals Medical Devices Agency, Japan [PMDA], U.S. Food and Drug Administration [FDA], European Medicines Evaluation Agency [EMEA], UK Medicines and Healthcare products Regulatory Agency [MHRA]) or an auditor.

Essential documents must be maintained according to J-GCP requirements and may not be destroyed without written permission from the Sponsor. The Investigator is required to arrange within the study site, that designated essential documents will be retained for the period as specified in GCP and local regulatory requirements. The head of the study site will designate an archive manager for each type of record to ensure appropriate archiving. The Investigator will be provided with an Investigator Site File at the start of the study. This file contains all relevant documents necessary for the conduct of the study. This file must be safely archived after termination of the study. It is the responsibility of the Investigator or the Head of the Medical Institution to ensure that the subject identification sheets (records stipulated in GCP Ordinance, Article 41 Paragraphs 1 and 2) are stored for at least 15 years (or 2 years after the last Marketing Authorization Application granted for the investigational medicinal product, whichever is longest) beyond the end of the clinical study. All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the Investigator will notify the Sponsor.

21 CHANGES IN THE CONDUCT OF THE STUDY

21.1 Protocol Amendments

Any prospective change to the protocol will be submitted to the IRB and to the competent authority in every country, as required, and should be approved before its implementation.

21.2 Premature Study Termination

Both an Investigator and the Sponsor reserve the right to terminate the study at any time. If this becomes necessary, the procedures will be arranged on an individual study basis after review and consultation by both parties. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects interests. Furthermore, the Investigator should promptly inform the IRB and provide a detailed written explanation that includes the reasons for study termination. The relevant regulatory authorities should be informed according to applicable regulatory requirements.

21.3 Publication of Results

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement. Any formal publication of the study in which input of the Sponsor's personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel. In general, the maximum number of authors allowed on any abstract/publication will be used. All screening investigators will be added to the main publication as a group.

22 LIABILITIES AND INSURANCE

In case of any damage or injury occurring to a subject in association with the trial medication or the participation in the study, PharmaEssentia Corporation, will maintain an insurance policy that meets local regulatory requirements. The Investigator is responsible for administering/dispensing the study drug according to this protocol, and for its secure storage and safe handling throughout the study.

23 REFERENCES

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24 APPENDICES

24.1 Appendix 1. Study Flowchart

	Screening	Treatment phase		End of Treatment	End of Study (Safety follow-up visit)
		every 2 weeks, except visits co-incident to the Assessment visits	Assessment visits - every 12 weeks (month 3, 6 and 9)	Month 12 / Premature discontinuation visit	28 days after the EoT visit
Informed consent	X				
Inclusion and exclusion criteria	X				
Demographics & medical history	X				
Pregnancy test (urine)	X	X (Every 4 weeks from Week 0)	X	X	X
Heart ECHO standard	X			X	X (cases with early termination only)
12-lead ECG	X	Week 0, Week 0 +96 h Week 2, Week 4, Week 28, Week 28 + 96 h	X	X	X
Physical examination	X	X	X	X	X

Vital signs	X	X	X	X	X
Blood chemistry small panel	X	X	X	X	X
Blood chemistry large panel	X		X	X	
Coagulation (blood)	X		X	X	X
Virology (blood)	X				
Hemoglobin A1c HbA1c)	X				
Hematology small panel	X	X	X	X	X
Hematology large panel	X		X	X	
Immunological parameters (blood)	X		X	X	X
Urine test	X	X	X	X	X
Urine beta 2 microglobulin test	X			X	
ECOG performance status	X	Week 0 only	X	X	X
Spleen size measurement	X	Week 0 only	X	X	
Genetic and mutation test sample (incl. *JAK2* allelic burden) (blood)	X	Week 0 only	X	X	
Bone marrow sampling (OPTIONAL)	X			X	
P1101 administration		X	X		
Adverse events	X	X	X	X	X

Concomitant treatment	X	X	X	X	X
Immunogenicity (blood)		Week 0 and Week 4 (Week 0: 0 hr. and 168 hr.) (Week 4: 0 hr.) see Appendix 3	X	X	X
PK (blood)		X (Trough value at every dosing) (4 sampling points per visit at Week 0 and Week 28, see Appendix 2)	X	X	X
HADS	X		X	X	X
Ocular examination	X			X	
Lung X-ray	X			X	

Vital signs:	Pulse rate, blood pressure and body temperature.
Blood chemistry small panel:	BUN, ALT, AST, GGT, LDH, total bilirubin.
Blood chemistry large panel:	NT-proBNP or BNP, Na^+, K^+, Ca^{++}, Cl^-, uric acid, blood glucose, alkaline phosphatase, amylase, lipase, creatinine, total protein, albumin, LDL, HDL, cholesterol, triglycerides, serum iron, transferrin, TSH and fT4.
Coagulation (Blood):	PT-INR, aPTT and fibrinogen.
Virology:	Serology: HBsAg, HCV antibody, HIV antibody
Hematology small panel:	Hemoglobin, hematocrit, platelet count, RBC, WBC.
Hematology large panel:	WBC differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and reticulocytes), MCV
Immunological parameters:	ANA, TgAb (autoantibodies to thyroglobulin), TPOAb (autoantibodies to thyroid peroxidase).
Urinalysis:	pH, blood, protein, glucose, WBC, nitrite
Spleen size measurement:	ultrasound
Lung X-ray:	For screening, X-rays will be accepted which are not older than 12 weeks prior to the date of screening visit. In case of premature discontinuation, no X-ray examination will be performed (to reduce the burden from exposure to radiation) unless necessary for safety follow-up purposes.

Necessity of Lab examination at Week 0: Week 0 tests can be omitted if the difference in the dates between screening and Week 0 is 7 days or less.

24.2 Appendix 2. Pharmacokinetic Sampling Schedule

Scheme	PK Sample Collection Times Relative to Dosing [a]		
	Sample Window	Visit 1 (Week 0)	Visit 15 (Week 28)
4 (4 samples per visit)	1	0	0
	2	48 (± 24)	48 (± 24)
	3	96 (± 24)	96 (± 24)
	4	168 (± 24)	168 (± 24)

[a]Since dosing is every 2 weeks, Day 1/Week 0 is the dosing day (first day of the dosing interval) and the trough sample will be collected before dosing. Trough samples will be collected at every visit, and ANY dose amount change thereafter.

24.3 Appendix 3. Immunogenecity Sampling

Scheme	Immunogenecity Sample Collection Times Relative to Dosing[a]							
	Visit 1 (Week 0)	Visit 3 (Week 4)	Visit 7 (Week 12)	Visit 13 (Week 24)	Visit 19 (Week 36)	Visit 27 (Week 52)	EoS (Week 56)	Week 64, 76, 88, and 104[a]
	0	0	0	0	0	0	0	0
	168 (± 24)							

[a]Immunogenicity assessment of anti-P1101 antibodies (anti-drug antibodies; ADA) will be measured at before the first dose (Week 0), 7 days (168 (±24) hr) after the initial P1101 dose, Week 4, 12, 24, 36, and at End of Treatment (EoT; Week 52), and at the EoS/Follow-up visit (28 days after the final P1101 drug administration at the EoT visit). Blood samples will be collected from the subject confirmed positive for P1101 ADA at EoS visit every three months until ADAs return to baseline levels or up to 12 months.

24.4 Appendix 4. ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: (Oken et al. 1982)

24.5 Appendix 5. Diagnosis of the PV-Related Cardiovascular Complications as Adverse Events of Special Interest

These criteria are to be used for the diagnosis of cardiovascular PV-related events as AEs of special interest (as per Section 16.5).	
ARTERIAL	
Event	**Definition/Diagnostic findings**
Stroke	A new focal neurologic deficit of presumed vascular origin which persists for >24 hours or results in death within 24 hours. Diagnostic are the following procedures: CT, magnetic resonance imaging (MRI), angiography, and transcranial Doppler.
Cerebrovascular event such as a major transient ischemic attack	Cerebral circulatory disturbance caused by the changes in the blood supply to a particular area of the brain resulting in transient neurologic dysfunction that persists, by definition, for >60 min and <24 hours. Diagnostic is a neurological examination.
Myocardial infarction	Comprising non-ST-segment elevation MIs identified by blood tests and typical MIs with additional ECG changes such as ST-segment elevation.
Unstable Angina	Acute coronary syndromes (including Prinzmetal's angina) which have to be treated as an emergency.
Acute peripheral arterial occlusive diseases	Acute limb ischemia confirmed by, e.g., ankle-brachial index, color duplex sonography, and digital subtraction angiography. Severity of the event requires either immediate surgical intervention or interventional revascularization.
Other major arterial events	Arterial events other than the events mentioned above, which led to hospitalization, were permanently disabling or life-threatening.
VENOUS	
Pulmonary infarction (pulmonary embolism)	Confirmed by plasma D-dimer measurement, lower limb compression ultrasound, V/Q lung scintigraphy, spiral CT and pulmonary angiography.
Splanchnic vein thrombosis (mesenteric infarction)	Confirmed by CT scan, MRI, and/or duplex ultrasonography of the visceral system.
Portal	Confirmed by Doppler ultrasonography, magnetic resonance

24.6 Appendix 6. HU resistance and intolerance criteria according to ELN (Barosi et al. 2010).

1. Need for phlebotomy to keep haematocrit <45% after 3 months of at least 2 g/day of Hydroxycarbamide, OR
2. Uncontrolled myeloproliferation, i.e. platelet count >400 G/L AND white blood cell count >10G/L after 3 months of at least 2 g/day of Hydroxycarbamide, OR
3. Failure to reduce massive* splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/day of Hydroxycarbamide, OR
4. Absolute neutrophil count <1 G/LOR platelet count <100G/L or haemoglobin <100 g/l at the lowest dose of Hydroxycarbamide required to achieve a complete or partial clinico-haematological response, OR
5. Presence of leg ulcers or other unacceptable Hydroxycarbamide-related non-haematological toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of Hydroxycarbamide

24.7 Appendix 7. Transition phase from previous HU treatment to P1101 (for all patients on active HU

Transition phase is the initial part of the dose finding for the patients concurrently receiving HU at the time of screening but transferred to P1101.

The following scheme will be applied:

	HU weekly dose	P1101 dose
Week 1-2	100% of the dose at baseline	50 mcg
Week 3-12 Earliest possible HU discontinuation is being encouraged	Every two weeks, decrease the HU level 250-500 mg	Every two weeks, increase the P1101 level by 50 mcg
By week 13 onwards	discontinued	Monotherapy with dose, allowing CHR

24.8 Appendix 8. Hospital Anxiety and Depression Scale

(A stays for anxiety, D stays for depression)

A	**1.** I feel tense or 'wound up'							
	3	Most of the time	2	A lot of the time	1	From time to time, occasionally	0	Not at all
D	**2.** I still enjoy the things I used to enjoy							
	0	Definitely as much	1	Not quite so much	2	Only a little	3	Hardly at all
A	**3.** I get a sort of frightened feeling as if something awful is about to happen							
	3	Very definitely and quite badly	2	Yes, but not too badly	1	A little, but it doesn't worry me	0	Not at all
D	**4.** I can laugh and see the funny side of things							
	0	As much as I always could	1	Not quite so much now	2	Definitely not so much now	3	Not at all
A	**5.** Worrying thoughts go through my mind							
	3	A great deal of the time	2	A lot of the time	1	Not too often	0	Very little
D	**6.** I feel cheerful							
	3	Never	2	Not often	1	Sometimes	0	Most of the time
A	**7.** I can sit at ease and feel relaxed							
	0	Definitely	1	Usually	2	Not often	3	Not at all
D	**8.** I feel as if I am slowed down							
	3	Nearly all the time	2	Very often	1	Sometimes	0	Not at all
A	**9.** I get a sort of frightened feeling like 'butterflies' in the stomach							
	0	Not at all	1	Occasionally	2	Quite often	3	Very often
D	**10.** I have lost interest in my appearance							
	3	Definitely	2	I don't take as much care as I should	1	I may not take quite as much care	0	I take just as much care as ever
A	**11.** I feel restless as if I have to be on the move							
	3	Very much indeed	2	Quite a lot	1	Not very much	0	Not at all
D	**12.** I look forward with enjoyment to things							
	0	As much as I ever did	1	Rather less than I used to	2	Definitely less than I used to	3	Hardly at all
	13. I get sudden feelings of panic							

A	3	Very often indeed	2	Quite often	1	Not very often	0	Not at all
D	**14.** I can enjoy a good book or radio or television programme							
	0	Often	1	Sometimes	2	Not often	3	Very seldom

Anxiety Subscale: questions 1, 3, 5, 7, 9, 11, 13

Depression Subscale: questions 2, 4, 6, 8, 10, 12, 14

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