Post-authorisatiannexon Safety Study Protocol: Besremi-PASS

fa

Title	A Prospective, Multicentre, Non-interventional, Observational, Post-authorisation Safety Study of Ropeginterferon alfa-2b in Polycythaemia Vera Patients
Protocol version identifier	Besremi-PASS
Date of last version of protocol	25APR2019
EU PAS register number	EUPAS29462
Active substance	Active substance: Ropeginterferon alfa-2b Pharmacotherapeutic group: Immunostimulants, interferons, ATC code: L03AB15
Medicinal product	Besremi 250 micrograms/0.5 mL solution for injection in pre-filled pen Besremi 500 micrograms/0.5 mL solution for injection in pre-filled pen
Product reference	EU/1/18/1352/001 EU/1/18/1352/002
Procedure number	EMEA/H/C/004128/0000
Marketing authorisation holder	AOP Orphan Pharmaceuticals AG Wilhelminenstraße 91/II f 1160 Vienna Austria
Joint PASS	No
Research question and objectives	The objective of the study is to provide further data to characterize the safety and tolerability of ropeginterferon alfa-2b by monitoring the hepatic and cardiovascular safety in patients with polycythaemia vera treated with ropeginterferon alfa-2b in routine post-authorisation use.
Countries of study	Austria (approx. 10 sites) and Germany (approx. 15 sites)
Author & MAH contact person	[redacted]

1. Table of contents

2. List of abbreviations

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ATC	Anatomical Therapeutic Chemical
AST	Aspartate Aminotransferase
CA	Competent Authority
CI	Confidence Interval
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug Induced Liver Injury
DM	Data Management
EC	Ethics Committee
CRF	Case Report Form
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FAS	Full Analysis Data Set
GCP	Good Clinical Practice
GDocP	Good Document Practice
GGT	Gamma-Glutamyl Transferase
GVP	Guideline on Good Pharmacovigilance Practice
Hb	Haemoglobin
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFN	Interferon
IME	Important Medical Event
ISF	Investigator Site File
MACE	Major Adverse Cardiac Events
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MP	Medicinal Product
PIC	Patient Identification Code
PIL	Patient Information Leaflet
PPS	Per Protocol Dataset
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Polycythaemia Vera
PASS	Post-authorisation Safety Study
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STATA	Validated statistical analysis software by Stata Corporation
SOC	System Organ Class
SmPC	Summary of Product Characteristics
ULN	Upper Limit of Normal
WHO	World Health Organisation

3. Responsible parties

3.1. Authorized Representative (Signatory) / Responsible party

Representative for the Sponsor

[redacted]

Contract Research Organization

[redacted]

3.2. Investigator(s)

Coordinating Investigator Austria

[redacted]

Coordinating Investigator Germany

[redacted]

The name and contact information of all of the individuals involved with the study (e.g. coordinating Investigator for each country, a full list of all participating Investigators, medical director, authorized representative(s) of the MAH) will be maintained separately from the study protocol and be made available upon request.

4. Abstract

Title

A Prospective, Multicentre, Non-interventional, Observational, Post-authorisation Safety Study of Ropeginterferon alfa-2b in Polycythaemia Vera Patients

Protocol Version 2.0, dated 13SEP2019

Rationale and background

Ropeginterferon alfa-2b is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly.

AOP Orphan Pharmaceuticals AG committed to the European Medicines Agency (EMA) to conduct this post-authorisation observational safety study to gain additional information on the safety and tolerability of ropeginterferon alfa-2b in patients with polycythaemia vera, specifically to address the effectiveness of the risk minimisation measures for hepatotoxicity and to evaluate the cardiovascular safety.

Research question and objectives

"What is the incidence rate of the important, identified risk “hepatotoxicity” in PV patients newly treated with ropeginterferon alfa-2b in routine post-authorization use?”

The objective of this study is to provide further data to characterize the safety and tolerability of ropeginterferon alfa-2b by monitoring the hepatic and cardiovascular safety in patients with polycythaemia vera treated with ropeginterferon alfa-2b in routine post-authorisation use.

Study design

This is a prospective, multicentre, non-interventional, observational, post-authorisation safety study of ropeginterferon alfa-2b (250 micrograms or 500 micrograms solution for injection in pre-filled pen) in adult polycythaemia vera patients.

The study will be conducted in two parts for the assessment of safety:

- Part A: observation of patients during the first 6 months of ropeginterferon alfa-2b treatment for the evaluation of hepatotoxicity and major cardiovascular adverse events (interim analysis after 6 months)
- Part B: follow-up observation of patients for an additional 12 months of ropeginterferon alfa-2b treatment for further evaluation of hepatotoxicity and major cardiovascular adverse events

Patients who will be monitored in this study will receive ropeginterferon alfa-2b in the course of routine clinical practice. To be eligible for study inclusion, patients must meet all inclusion and none of the exclusion criteria.

The estimated study duration is approximately 3.5 years, from the first patient receiving ropeginterferon alfa-2b treatment (baseline) until the end of the observation time of the last patient within the study.

The observation time per patient in the study will be

- 6 months in Part A
- 12 months in Part B

The maximum study duration per patient will be 18 months.

Population

The study population will be adult polycythaemia vera patients. Ropeginterferon alfa-2b therapy will be in accordance with the physician´s routine clinical practice (who is experienced in the management of polycythaemia vera) and with the recommendations in the current product information for ropeginterferon alfa-2b (Annex 1).

Variables

Parameters of the standard assessments will be monitored which include the collection of cardiovascular events [i.e. thromboembolic adverse events and major adverse cardiac events [MACE], treatment-emergent hepatobiliary adverse drug reactions, other treatment-emergent adverse events and clinical laboratory parameters (i.e. liver enzymes/bilirubin; haematocrit).

Data sources

Data will be collected from the medical records of the patients in the study.

Study size

Approximately 228 adult polycythaemia vera patients.

Data analysis

The safety dataset will contain all patients who were enrolled in this study, received ropeginterferon alfa-2b treatment at least once during routine medical setting and from whom data are available.

Milestones

The planned milestones are the final study protocol, start and end of data collection, interim and final report.

5. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	13SEP2019	3, 4, 5, 6, 7, 8, 9, 11, 12	Specification of study objectives; specification of evaluation of risk minimization measures; change to duration of patient observation	PRAC Assessment report

6. Milestones

Milestone	Planned date
Study protocol	Q1/Q2 2019
Start of data collection (first patient in)	Q3 2019
End of data collection (last patient out)	Q1 2023
Interim report	Q1 2022
Final report of study results	Q3 2023

7. Rationale and background

Polycythaemia vera (PV), a myeloproliferative neoplasm, is a very rare disease and typically develops in late adulthood. It is an acquired form of primary erythrocytosis which is characterized by an excess production of erythrocytes, leukocytes and platelets.

Ropeginterferon alfa-2b belongs to the pharmacotherapeutic group of antineoplastic and immunostimulating agents, immunostimulants; interferons (IFNs). Ropeginterferon alfa-2b is the first IFN indicated as monotherapy in adults for the treatment of PV without symptomatic splenomegaly.

The general safety profile of ropeginterferon alfa-2b can be seen as well characterized and safety data provided for ropeginterferon alfa-2b can be compared with that of already approved IFN products.

Hepatic safety

Hepatotoxicity is a well-known safety class effect of IFNs[1] (including cases of drug-induced liver injury [DILI]) characterized by potentially significant increases in liver enzymes. Hepatotoxicity has to be considered as the most clinically relevant toxicity of IFNs, including also ropeginterferon alfa-2b.

[1] Hepatotoxicity is included as important, identified safety concern in the EMA approved Risk Management Plan for ropeginterferon alfa-2b (Version 1.0, dated 13DEC2018).

Increases in alanine aminotransferase (ALT) (≥3 times the upper limit of normal), aspartate aminotransferase (AST) (≥3 times the upper limit of normal), gamma-glutamyl transferase (GGT) (≥3 times the upper limit of normal) and bilirubin (>2 times the upper limit of normal) levels have been observed in patients treated with ropeginterferon alfa-2b. These elevations were mostly transient and occurred during the first treatment year.

Cardiovascular safety

Thromboembolic events are rare events but appear significantly more frequent in PV patients than in the healthy population and are a major risk of this disease.

The recommended posology for the titration phase of ropeginterferon alfa-2b results in a prolonged time to reach the individual optimal dose compared to hydroxycarbamide. In a phase III clinical study in PV (PROUD-PV; EudraCT number 2012-005259-18), the end of the mean individual titration phase for ropeginterferon alfa-2b was reached after approximately 3.7 months, for hydroxycarbamide after approximately 2.6 months of treatment. Thus, other products (e.g. hydroxycarbamide) may be preferred in patients for whom an early reduction in elevated blood counts is necessary to prevent thrombosis and bleeding. During the titration phase the effectiveness to reduce the cardiovascular and thromboembolic risk of the underlying disease may not be fully established.

Risk minimization measures for the important, identified risk of “hepatotoxicity”

The routine risk communication in the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) and legal status (prescription only medicine) implemented in the EMA approved Risk Management Plan for ropeginterferon alfa-2b (Version 1.0, dated 13DEC2018) are considered sufficient to manage the important identified risk “hepatotoxicity”.

Evaluation of the effectiveness of risk minimization measures for the important, identified risk “hepatotoxicity” during this post-authorization safety study will focus on the risk communication in the SmPC. Specifically, on the recommendations on hepatic enzyme monitoring during long-term treatment with ropeginterferon alfa-2b and dose adjustments (including dose changes or treatment discontinuation) in case of adverse events.

8. Research question and objectives

In addition to the routine pharmacovigilance activities, AOP Orphan Pharmaceuticals AG proposed to the EMA to conduct this post-authorization safety study to address the effectiveness of the risk minimization measures for the important, identified risk of hepatotoxicity and to evaluate the cardiovascular safety within the cohort of patients with PV and treated with ropeginterferon alfa-2b.

The main research question is: "What is the incidence rate of the important, identified risk “hepatotoxicity” in PV patients newly treated with ropeginterferon alfa-2b in routine post-authorization use?”

1. Primary objective

- To assess the incidence rate of the important, identified risk “hepatotoxicity” in PV patients newly treated with ropeginterferon alfa-2b in routine post-authorization use.

2. Secondary objectives

- To describe the baseline characteristics of PV patients newly treated with ropeginterferon alfa-2b in routine post-authorization use.
- To evaluate the effectiveness of the risk minimization measures for the important, identified risk “hepatotoxicity”.

- To further characterize the important, identified risk “hepatotoxicity” in subgroups of the patient population (i.e. with/without co-medication with nonsteroidal anti-inflammatory drugs, with/without pre-existing liver disease or baseline liver parameter elevation).
- To assess the incidence rate of thromboembolic adverse events and major adverse cardiac events (MACE) in PV patients newly treated with ropeginterferon alfa-2b in routine post-authorization use.
- To further evaluate cardiovascular safety in subgroups of the patient population (i.e. with/without cardiovascular risk factors, with/without pre-existing cardiovascular disease).

9. Research methods

9.1. Study design

This is a prospective, multicentre, non-interventional, observational, post-authorization safety study of ropeginterferon alfa-2b in adult PV patients.

The purpose of the study is to conduct analyses of safety data related to ropeginterferon alfa-2b treatment. The study will be conducted in two parts over 18 months for the assessment of safety:

- Part A: observation of patients during the first 6 months of ropeginterferon alfa-2b treatment for the evaluation of hepatotoxicity and major cardiovascular adverse events (interim analysis after 6 months)
- Part B: observation for an additional 12 months of ropeginterferon alfa-2b treatment for the evaluation of hepatotoxicity and major cardiovascular adverse events

Participation will be offered to patients who receive ropeginterferon alfa-2b in the frame of clinical routine. Due to the non-interventional nature of this study, the decision to prescribe ropeginterferon alfa-2b is clearly separated from inclusion.

Ropeginterferon alfa-2b therapy will be in accordance with the physician´s routine clinical practice (who is experienced in the management of PV) and with the recommendations in the product information for ropeginterferon alfa-2b (Annex 1).

- **Safety endpoints:**
  - Liver enzymes (i.e. ALT, AST, GGT), and bilirubin
  - Cardiovascular events (thromboembolic adverse events and major adverse cardiac events [MACE])
  - Treatment-emergent hepatobiliary adverse drug reactions
  - All treatment-emergent adverse events

<u>Evaluation of effectiveness of risk minimization measurements for the important, identified risk “hepatotoxicity”:</u>

The effectiveness of the recommendation to monitor hepatic enzymes during long-term ropeginterferon alfa-2b treatment as described in section 4.4 of the SmPC will be evaluated by assessing the frequency of hepatic enzyme and bilirubin evaluation in routine clinical practice.

The effectiveness of the routine risk communication to address dose adjustment or treatment discontinuation in case of hepatotoxicity, as described in section 4.2 and 4.4 of the SmPC, will be evaluated by assessing rate of dose adjustments or treatment discontinuations due to hepatoxicity, the rate of hepatobiliary adverse events occurring despite dose reduction or treatment discontinuation due to elevated liver enzymes, the rate of, and time to resolution of significant elevations of ALT, AST, GGT (≥3 times ULN) and/or bilirubin (> 2 times ULN) and/or hepatobiliary adverse drug reactions as well as the number of patients experiencing

hepotobiliary adverse events after significant elevations of liver enzymes ALT, and/or AST, and/or GGT (≥3 times ULN) and/or bilirubin (>2 times ULN).

- **Endpoints for the evaluation of effectiveness of risk minimization measurements for the important, identified risk "hepatotoxicity":**
  - Evaluations of liver enzymes (i.e. ALT, AST, GGT), and bilirubin in routine clinical practice
  - Hepatobiliary adverse events after dose reduction or treatment discontinuation due to elevated liver enzymes
  - Dose reduction or treatment discontinuation due to hepatotoxicity
  - Liver enzymes (i.e. ALT, AST, GGT), and bilirubin after dose reduction or treatment discontinuation
  - Treatment-emergent hepatobiliary adverse drug reactions after dose reduction or treatment discontinuation
  - Number of patients with hepatobiliary adverse events after significant elevations of liver enzymes ALT, and/or AST, and/or GGT (≥3 times ULN) and/or bilirubin (>2 times ULN)

9.2. Setting

Due to the start of commercialization of Besremi in Austria and Germany, this post-authorization safety study will be conducted in approximately 10 sites in Austria and 15 sites in Germany.

9.2.1 Medicinal Product (MP)

The MP for this study is ropeginterferon alfa-2b (Besremi). Ropeginterferon alfa-2b is licensed as 250 micrograms or 500 micrograms solution for injection in a pre-filled pen. The Investigator will record the MP lot number(s) in the eCRF. Administration, packaging, labelling, and storage for the MP are described in the product information for ropeginterferon alfa-2b (Annex 1).

9.2.1.1 Ropeginterferon alfa-2b treatment phases

Titration phase

The ropeginterferon alfa-2b dose is titrated individually with a recommended starting dose of 100 micrograms (or 50 micrograms in patients under another cytoreductive therapy). The dose should be gradually increased by 50 micrograms every two weeks (in parallel, other cytoreductive therapy should be decreased gradually, as appropriate) until stabilisation of the haematological parameters is achieved (haematocrit <45%, platelets <400 x 10^9/L and leukocytes <10 x 10^9/L). The maximum recommended single dose is 500 micrograms injected every two weeks.

Maintenance phase

The ropeginterferon alfa-2b dose at which stabilisation of the haematological parameters is achieved should be maintained in a two-week administration interval for at least 1.5 years. After that, the dose may be adapted and/or the administration interval prolonged up to every four weeks, as appropriate for the patient.

Detailed information on the recommended posology and method of administration can be found in the product information for ropeginterferon alfa-2b (Annex 1).

9.2.1.2 MP (ropeginterferon alfa-2b) complaints

Any complaints and queries (e.g. wrong strength/labelling, malfunction of devices, faulty closure, empty vial) concerning the MP have to be reported by the Investigator to the Sponsor immediately by sending an e-mail to quality@aoporphan.com.

9.2.2 Duration of Study Period(s) and Subject Participation

The overall duration of the study is expected to be approximately 3.5 years from study initiation (i.e. first patient receiving ropeginterferon alfa-2b treatment within the study [first patient in]) to study completion (i.e. the end of the observation time of the last patient within the study [last patient out]). The recruitment period is expected to be approximately 2 years.

The individual patient participation is a maximum of 18 months (6 months in Part A and 12 months in Part B)

9.2.3 Study population

Participation will be offered to patients who receive ropeginterferon alfa-2b in the frame of clinical routine and according to its approved labeling. Due to the non-interventional nature of this study, the prescription of ropeginterferon alfa-2b must be separated from the decision to include a patient into this study.

9.2.3.1 Inclusion and exclusion criteria

The study will include approximately 228 adult PV patients. The inclusion and exclusion criteria are listed below.

- *Inclusion criteria:*

1. Patients who receive ropeginterferon alfa-2b in the frame of clinical routine and according to its approved labelling: monotherapy in adults (≥ 18 years old) for the treatment of PV without symptomatic splenomegaly and according to the recommendations in the product information for ropeginterferon alfa-2b (Annex 1)
2. Patient's medical history[2] is available
3. Patient provides written informed consent prior to study entry

- *Exclusion criteria:*

1. Patients with any contraindication to ropeginterferon alfa-2b treatment according to the product information for ropeginterferon alfa-2b (Annex 1)
2. Patients involved in any study with another investigational product or therapy (in the prior 30 days)
3. Previous ropeginterferon alfa-2b treatment
4. Patient is a family member or employee of the Investigator

9.2.3.2 Pregnancy and lactation

Women of childbearing potential/contraception in females

Women of childbearing potential have to use effective contraception during the treatment with ropeginterferon alfa-2b, unless otherwise discussed with the Investigator.

According to product information, ropeginterferon alfa-2b is not recommended during pregnancy and during breast-feeding (Annex 1).

9.2.4 Informed consent and enrolment

Any volunteer who provides informed consent (i.e. signs and dates the informed consent form) is considered enrolled in the study (Section 10.5).

[2] PV disease history, cardiovascular risk-factors, pre-existing liver disease, pre-existing cardiac disease.

9.2.5 Patient identification code

Each patient will be pseudonymized by using a unique ID which does not contain any information enabling identification of individual patients without access to the source data. The ID consists of a country specific code (e.g. AT or DE), a two-digit site number and a three-digit subject number, starting with 001 at each site.

Sites will be asked to maintain an identification log, see also Section 10.2.

9.2.6 Screening and study visits

The study site is responsible for maintaining an enrolment/screening log that includes all patients screened and enrolled. The log will also serve to document the reason for screening failure. All screening data will be collected and reported in eCRFs, regardless of screening outcome.

Patient visits occur in the course of routine clinical practice. Due to the non-interventional nature of this study, no visit regime is prescribed. The Investigator documents a baseline visit (defined as 1st ropeginterferon alfa-2b administration within the study) and follow-up visits in Part A and Part B for each patient in the eCRF. The eCRF will allow for the documentation of visits as performed according to the management of the individual patient within routine clinical practice.

The subject participation is a maximum of 18 months from enrolment to completion (i.e. last study visit).

The study will include two parts:

Part A:

Part A will be the initial observation phase during the first 6 months of ropeginterferon alfa-2b treatment. Patients receiving ropeginterferon alfa-2b for the first time will be monitored for hepatotoxicity and cardiovascular adverse events.

An interim analysis will be performed after completion of Part A.

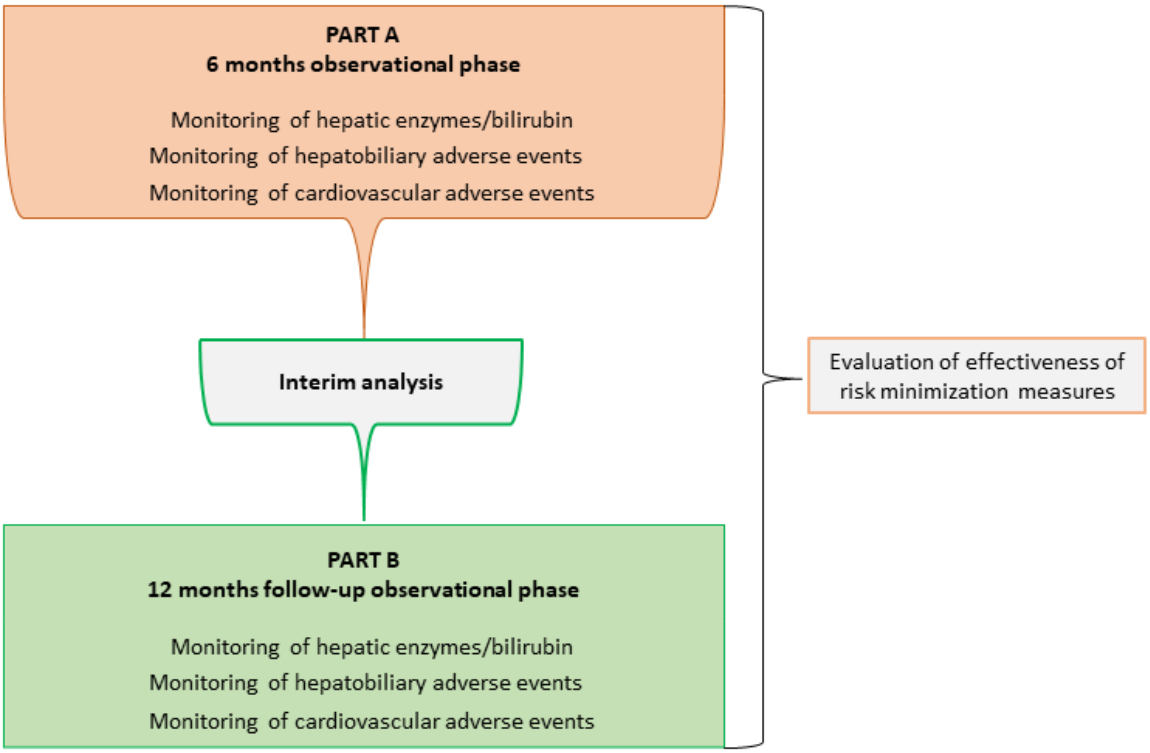
Part B:

Part B will be the follow-up phase of the initial observation phase (i.e. Part A). Patients will be monitored for hepatotoxicity and cardiovascular adverse events for an additional 12 months.

The effectiveness of risk minimization measures will be evaluated over the entire study period.

The overall study design is illustrated in Figure 1. Details on the procedures to be performed during the study can be found in Table 1 (Section 9.3).

Figure 1. Post-authorisation Safety Study of Ropeginterferon alfa-2b. Part A and Part B of the Study.



9.2.7 Patient withdrawal and patient discontinuation

Any patient may voluntarily withdraw consent for continued participation and data collection. The reason for withdrawal will be recorded on the eCRF page. The data collected on withdrawn patients will be used in the analyses and included in the study report.

Study discontinuation (i.e. complete withdrawal from study participation) may be due to:

- Dropout of the patient (i.e. active discontinuation by patient).
- Patient is lost to follow-up (i.e. discontinuation by patient without notice or action; the Investigator should contact the patient either by telephone or through a clinic visit to establish as completely as possible the reason for the withdrawal.).
- Discontinuation of the patient on Investigator´s discretion if, in his/her judgement, continued participation would pose an unacceptable risk for the patient.

In case the patient discontinues the study (i.e. discontinuation of ropeginterferon alfa-2b treatment), the Investigator should collect and document information on new PV therapy. In case of ropeginterferon alfa-2b treatment discontinuation due to hepatotoxicity, follow-up of the AE as performed in routine clinical practice (e.g. evaluation of hepatic enzymes) should be documented.

9.2.8 Patient´s dose change/ dose interruption

The recommendations in the product information for ropeginterferon alfa-2b dosing (including dose changes or temporarily treatment interruption) should be followed (Annex 1). Any ropeginterferon alfa-2b dose change/interruption has to be documented including the reason for

dose change/interruption. A temporary ropeginterferon alfa-2b treatment interruption is no reason for study discontinuation.

9.2.9 Patient completion

A patient is considered to have completed the study when he/she ceases active participation in the study because the patient has, or is presumed to have, completed all study procedures according to the protocol (see Figure 1).

Completion will be documented on the respective eCRF page, including the reason for completion (e.g. study completed, screening failure, adverse event occurrence [e.g. death], study discontinuation (section 9.2.7)). Regardless of the reason, all data available for the patient up to the time of completion should be recorded on the appropriate eCRF pages.

9.3. Variables

9.3.1 Safety Variables

9.3.1.1 Adverse events of special interest

- **Hepatotoxicity[3] during study participation:**
  - Clinically significant elevations of ALT, AST, GGT (≥3 times ULN) and/or bilirubin (> 2 times ULN)
  - Treatment-emergent hepatobiliary adverse drug reactions
- **Cardiovascular adverse events:**
  - Thromboembolic adverse events
  - MACE [i.e. nonfatal stroke, nonfatal myocardial infarction and cardiovascular death]

Diagnostic procedures will be conducted according to the needs of the patients, and parameters of standard assessments will be monitored in this study and entered in the eCRF as available (Table 1). Definition of treatment-emergent adverse events and treatment-emergent adverse drug reactions is included in Section 11.1.1.

9.3.1.2 Other safety variables

- All treatment-emergent adverse events

9.3.2 Evaluation of risk minimization measures

- Frequency of evaluation of hepatic enzymes (AST, ALT, GGT) and bilirubin in clinical routine
- Hepatobiliary adverse events after dose reduction or treatment discontinuation due to significant elevations of liver enzymes ALT, and/or AST, and/or GGT (≥3 times ULN) and/or bilirubin (>2 times ULN)
- Dose adjustments or treatment discontinuations due to hepatotoxicity
- Hepatic enzymes (AST, ALT, GGT) and bilirubin after dose reduction or treatment discontinuation due to significant elevations of ALT, AST, GGT (≥3 times ULN) and/or bilirubin (> 2 times ULN)
- Follow-up of hepatobiliary AEs after dose reduction or treatment discontinuation due to Treatment-emergent hepatobiliary adverse drug reactions

[3] Important identified risk in the ropeginterferon alfa-2b Risk Management Plan.

- Number of patients with hepatobiliary adverse events after significant elevations of liver enzymes ALT, and/or AST, and/or GGT (≥3 times ULN) and/or bilirubin (>2 times ULN)

9.3.3 Demographics

At baseline, the patient´s demographics will be collected for the following according to routine clinical practice:

- Age
- Gender
- Weight [kg]
- Height [cm]
- Body mass index [kg/m^2], calculated
- Blood pressure
- Heart rate

9.3.4 Medical History

At baseline, the patient's clinically relevant medical history will be collected for the following:

- PV disease history (date of diagnosis, criteria of diagnosis)
- Assessment of cardiovascular risk-factors[4]
- Assessment of pre-existing liver disease (yes/no, details)
- Assessment of pre-existing cardiac disease (yes/no, details)
- Assessment of previous thromboembolic events (yes/no, details)
- Assessment of alcohol intake (yes/no, details)

During study participation, the following information on medical history will be collected:

- Any medical history relevant for the characterization of treatment emergent adverse events

9.3.5 Concomitant Medication

At baseline, the following information will be collected:

- Previous treatment for PV

During study participation, the following information on concomitant medication will be collected:

- Non-steroidal anti-inflammatory drugs
- Medication assessed by the investigator to impact hepatic parameters
- Cardio-vascular medication

[4] Unhealthy lifestyle (cigarette smoking, physical inactivity, diet high in fat); high risk diseases (hypertension, obesity, dyslipidaemia, diabetes)

- Any medication relevant for the characterization of treatment emergent adverse events

9.3.6 Other PV-related treatments and procedures

- Dosing ropeginterferon alfa-2b
- Concomitant PV-treatment (other than ropeginterferon alfa-2b)
- Phlebotomy

Table 1. Parameter assessment during ropeginterferon alfa-2b PASS Part A and Part B.

Activity / Assessment	Eligibility#	Baseline*,#	Part A#	Part B#
Inclusion/Exclusion criteria	X			
Medical history		X		
Demographics		X		
Ropeginterferon alfa-2b administration		X	X	X
Clinical laboratory: Hematology[1] Chemistry[2]		 X X	 X X**	 X X**
Concomitant medication		X	X	X
Phlebotomy performed		X	X	X
Adverse events of special interest: - Treatment-emergent hepatobiliary adverse drug reactions - Thromboembolic adverse events - Major adverse cardiac events (MACE)			 X X X	 X X X
All treatment-emergent adverse events			X	X

*defined as 1st ropeginterferon alfa-2b administration within study.
** for hepatotoxicity assessment in Part A and Part B; see Section 9.2.6.
#assessed during routine clinical practice.

[1] Laboratory parameters: Haemoglobin (Hb), haematocrit, platelets, red blood cells, white blood cells.

[2] Laboratory parameters: Hepatic parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], total bilirubin).

9.4. *Data sources*

Source data are defined as all the information related to clinical findings, observations, or other activities in the study, written down in original records or certified copies of original records allowing reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies), which may be in paper and/or electronic format, can comprise the following (but not limited): hospital records, medical records, clinical and office charts, laboratory notes, and memoranda.

The Investigator will ensure that the eCRF is correctly completed. The eCRF will be

electronically signed by the Investigator signifying agreement with and responsibility for the recorded data.

9.5. *Study size*

The primary endpoint of the Besremi-PASS study is the incidence of clinically significant increases of liver enzymes or bilirubin during part A of the study, i.e., within 6 months. Results of the PROUD-PV study suggest an incidence of 23.6% for clinically significant increases of liver enzymes or bilirubin within one year. Thus, an incidence of 12.6% for clinically significant increases of liver enzymes or bilirubin can be expected during Part A. Therefore, in a sample of 169 patients, an observed incidence rate of 7.5 – 17.4% can be expected with a probability of 95%, resulting in 95% confidence interval ≤10%, if the confidence intervals are estimated according to Wald. If the more conservative exact estimation is used, a sample of 186 patients is expected to result in an incidence rate of 8.0 – 18.0% (95% confidence interval ≤10%). Thus, the inclusion of 178 evaluable patients, i.e., the median of 169 and 186, is envisaged.

In the Besremi-PASS study patients shall be observed for 18 months. During the Proud-PV study a drop-out rate of 20% was observed over one year. Thus, a dropout rate of 28.5% is assumed for 18 months. Therefore, a total of 228 patients is required in order to observe 178 evaluable patients for the entire study period of 18 months.

9.6. *Data management*

All responsible parties shall adhere to good documentation practice (GDocP) for all maintained records and any applicable changes to these.

9.6.1 Data Collection Methods

- The Investigator will maintain complete and accurate paper format study documentation in a separate file. Study documentation may include medical records, records detailing the progress of the study for each patient, signed informed consent forms, correspondence with the Ethics Committee (EC) and the Monitor, and data clarifications requested by Data Management (DM)/responsible party.
- Case report forms (CRFs) will be provided in electronic form (i.e. eCRF).
- The Investigator will comply with the procedures for data recording and reporting.
- The handling of data by the responsible party, including data quality assurance, will comply with regulatory guidelines and the standard operating procedures of the responsible party. DM and control processes specific to the study will be described in the DM plan.

9.6.2 Electronic Case Report Forms (eCRFs)

- The eCRF will be provided by the Sponsor and will be used to collect all data. Data will be obtained from the patient´s medical record.
- All information entered in the eCRF is considered to accurately display original data. The Investigator is responsible for patient data procuration and for the quality of data recorded in the patient´s eCRF. Access to the eCRF is restricted by username and password.
- For each patient in the study, an eCRF will be completed and signed electronically by the Investigator. The eCRFs may also be completed by trained and authorized personnel at the investigational site. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to 3rd parties without written permission of the Sponsor, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

- During data entry and after completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Sponsor personnel (or designees) and will be answered by authorized personnel at the site.
- Errors occurring in eCRFs will be modified by the Investigator and all changes will be tracked in the audit trail that captures respective changes.
- In no case the eCRF is to be considered as source data for this study.

9.6.3 Database management

- After the data have been entered and verified, various edit checks will be performed for the purpose of ensuring the accuracy, integrity, and validity of the database. After last patient out, when the database is complete and accurate, it will be locked. Any changes to the database after that time can only be made by joint written agreement between the Sponsor, the study statistician and the data manager. An interim database lock is planned after completion of Part A.
- It is the responsibility of the Investigator to resolve all data queries forwarded by DM in a timely manner.
- Adverse events, prior and concomitant illnesses/medications will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system. Coding will start after completion of Part A, by using the last version of the dictionaries available at that timepoint.

9.6.4 Handling of protocol deviations

- Except for a situation in which proper care for protection, safety and well-being of the study patients requires medical treatment, the study will be conducted as described in the approved protocol.
- Any deviation from the study protocol (i.e. any deviation from the routine clinical practice that follows the recommendations in the product information of ropeginterferon alfa-2b) in the conduct or documentation of the study will be notified to the Sponsor (by the Investigator and/or Monitor) on ongoing basis and explained by the Investigator. Protocol deviations will be documented in the monitoring visit report and/or in a cumulative listing.
- All protocol deviations will be recorded in the eCRF.

9.7. *Data analysis*

9.7.1 Datasets and analysis cohorts

- Safety dataset:

The safety dataset will contain all patients who were enrolled in this study, received ropeginterferon alfa-2b treatment at least once during routine medical setting and from whom data is available.

- Full analysis dataset:

The full analysis dataset 1 (FAS1) will contain all patients who completed Part A of the study. The full analysis dataset 2 (FAS2) will contain all patients who completed Part B of the study.

- Per protocol dataset:

The per protocol set (PPS) will consist of patients included in the FAS who complete a certain pre-specified minimal exposure to the treatment regimen, have all measurements needed for assessment of the primary endpoint available and do not violate the study protocol in major concerns.

9.7.2 Methods of analysis

9.7.2.1 Primary safety endpoint

Incidence of (1) significant elevations of liver enzymes ALT, and/or AST, and/or GGT (≥3 times ULN) and/or bilirubin (>2 times ULN), and (2) treatment-emergent hepatobiliary adverse drug reactions in Part A (i.e. first 6 months of treatment).

9.7.2.2 Secondary safety endpoints

- Incidence of (1) significant elevations of liver enzymes ALT, and/or AST, and/or GGT (≥3 times ULN) and/or bilirubin (>2 times ULN), and (2) treatment-emergent hepatobiliary adverse drug reactions over the entire study period.
- Incidence of cardiovascular adverse events (i.e. thromboembolic adverse events and MACE) during PART A and over the entire study period.

9.7.2.3 Additional endpoints

- Incidence of all treatment-emergent adverse events
- Incidence of adverse events of special interest
- Duration of significant elevation of liver parameters

9.7.2.4 Effectiveness of risk minimization measure endpoints:

- Frequency of evaluation of liver enzymes (AST, ALT, GGT) and bilirubin
- Frequency of dose adjustments or treatment discontinuation in case of hepatotoxicity
- Rate of hepatobiliary adverse events after dose reduction or treatment discontinuation due to significant elevations of liver enzymes ALT, and/or AST, and/or GGT (≥3 times ULN) and/or bilirubin (>2 times ULN)
- Rate of liver enzyme/bilirubin normalization after dose reduction or discontinuation due to significant elevations of liver enzymes ALT, and/or AST, and/or GGT (≥3 times ULN) and/or bilirubin (>2 times ULN)
- Time to liver enzyme/bilirubin normalization after dose reduction or discontinuation due to significant elevations of liver enzymes ALT, and/or AST, and/or GGT (≥3 times ULN) and/or bilirubin (>2 times ULN)
- Rate of hepatobiliary adverse event resolution after dose reduction or discontinuation due to treatment-emergent hepatobiliary adverse drug reaction
- Time to hepatobiliary adverse event resolution after dose reduction or discontinuation due to treatment-emergent hepatobiliary adverse drug
- Number of patients with hepatobiliary adverse events after significant elevations of liver enzymes ALT, and/or AST, and/or GGT (≥3 times ULN) and/or bilirubin (>2 times ULN)

9.7.2.5 Additional subgroup analyses

- Subgroup analysis of incidence of significant elevations of liver enzymes and bilirubin for patients with and without co-medication with nonsteroidal anti-inflammatory drugs
- Subgroup analysis of incidence of significant elevations of liver enzymes and bilirubin for patients with and without pre-existing liver disease/or patients with baseline liver parameter elevation
- Subgroup analysis of incidence of treatment-emergent hepatobiliary adverse drug reactions for patients with and without co-medication with nonsteroidal anti-

inflammatory drugs

- Subgroup analysis of incidence of treatment-emergent hepatobiliary adverse drug reactions for patients with and without pre-existing liver disease/or patients with baseline liver parameter elevation
- Subgroup analysis of incidence of cardiovascular events (i.e. thrombo-embolic adverse events and MACE) for patients with and without cardiovascular risk factors
- Subgroup analysis of incidence of cardiovascular events (i.e. thrombo-embolic adverse events and MACE) for patients with and without pre-existing cardiovascular disease

Absolute and relative frequencies of patients with treatment emergent adverse events, count and incidence rate (including two-sided 95% CIs) of events overall and by MedDRA primary System Organ Class and Preferred Term will be calculated.

In addition, tables will be prepared to list each serious and non-serious adverse event, the number of patients who experience an event at least once, and the proportion of patients with adverse events/serious adverse events/adverse events of special interest.

Adverse events will be grouped by system organ class (SOC). Each event will be then divided into defined intensity grades (mild, moderate, and severe) by the Investigator. The tables will also divide the adverse events into those considered related to treatment (ropeginterferon alfa-2b) and those not related, as well as adverse events considered related to underlying disease PV.

The statistical analysis will be done in agreement with the ICH Topic E9, Statistical Principles for Clinical Trials and Statistical Analysis Plan (SAP) finalized and approved by the Sponsor and the study statistician before database lock. Analyses will be conducted using Statistical Analysis System (STATA®) software,
by using the last version of the dictionaries available at that timepoint.

9.7.3 Planned interim analysis of the study

An interim analysis is planned after finalization of Part A of the study.

9.8. *Quality control*

The sites in each country will be selected based on the availability of patient

population targeted for this study.

The selected Investigators and study sites will have the ability to appropriately conduct this study in accordance with applicable legal and regulatory requirements.

9.8.1 Investigator´s responsibility

- The Investigator will comply with the study protocol, applicable local regulatory requirements and with the ethical principles that have their origin in the Declaration of Helsinki.
- The Investigator is responsible for the conduct of the study at the study site.
- If any responsibilities are delegated, the Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated significant study-related duties.

9.8.2 Direct access to source data/records

- The Investigator guarantees that the Monitors, Auditors, members of the EC, authorized

personnel of the Sponsor or regulatory authorities will have direct access to all relevant source data/documents and patients' medical records providing that the confidentiality of patients is preserved.

9.8.3 Study monitoring and source data verification

- The Sponsor will nominate a qualified Monitor to maintain a close contact with the Investigator and study staff to ensure the study is being conducted in accordance with the protocol, regulatory requirements and local law and that GCP guidelines will be followed whenever possible to reach high standard of quality. This liaison will consist of regular documented personal visits, and/or telephone or e-mail communication prior to study initiation and at regular intervals during the study.
- The Monitor will arrange regular visits to the study centre(s) to check and confirm the completeness of patient records, the accuracy of entries in the eCRFs, consistency of source data with the eCRF entries, the adherence to the protocol and that GCP guidelines will be followed whenever possible to reach high standard of quality.
- The Monitor will ensure that the Investigator/study team personnel understand the protocol requirements and the regulatory responsibilities as an Investigator.
- Key study team personnel should be available to assist the responsible Monitor during these visits and correct the errors found by the Monitor in eCRFs and/or other documents pertinent to the project.
- The Monitor will also check the completeness of the Investigator site file (ISF) and related documentation (e.g. team delegation log).
- The Sponsor monitoring standards require full verification for the presence of Informed Consent, adherence to the inclusion/exclusion criteria, and the recording of the study objective. Details will be described in the study-specific monitoring plan.

9.8.4 Auditing

- The study may be audited by the Sponsor or inspected by regulatory authorities during the study and/or after study completion. The Investigator will permit and fully cooperate with the Sponsor during audits, EC review(s) and/or regulatory inspection(s), and provide direct access to all study relevant documents and data.

9.9. *Limitations of the research methods*

Data are captured in real-world setting. Patients may be exposed to a multitude of other medical procedures, are aware of their treatment and are not compared to a control group. Due the observational nature of the study, it should be taken into consideration that there might be incomplete datasets among the participating centres.

The Sponsor has selected approximately 10 Sites in Austria and 15 sites in Germany, covering a large proportion of the pool of suitable patients in both countries, to participate in this study. In the unlikely case of slow recruitment, the Sponsor will evaluate the inclusion of additional sites and assess the possibility of adding sites in additional countries, depending on the status of commercialization of Besremi.

The primary endpoint of the Besremi-PASS study is the incidence of significant elevations of liver enzymes ALT, and/or AST, and/or GGT (≥3 times ULN) and/or bilirubin (>2 times ULN), and (2) treatment-emergent hepatobiliary adverse drug reactions in the first 6 months of treatment. A dropout rate of 20% over one year was observed in the PROUD-PV study, from which a dropout rate of 10% can be assumed after 6 months of treatment. The extrapolated dropout rate of 28.5% over 18 months used for sample size calculations is therefore highly conservative and will allow for evaluation of the primary endpoint even if dropout rates over 6 months of treatment are higher than expected.

9.10 Other aspects

Not applicable; all aspects of the study are described in the other protocol sections.

10. Protection of human subjects

Due to the non-interventional nature of this study, patients are not exposed to any study-specific medical procedures, and therefore to no study-specific medical risk.

10.1 Compliance statement

This study will be conducted in accordance with this protocol and applicable national and local requirements for good pharmacovigilance practices.

10.2 Patient privacy

- All study information and documentation collected by the Investigator will be kept confidential. The Investigator must ensure that patient confidentiality is maintained. In eCRFs or other documents submitted to the Sponsor, the patient should not be identified by their names, but by a PIC (see section 9.2.6).
- The Investigator will keep a separate log of patient codes, names and addresses. This log and other documents not for submission to the Sponsor (e.g. ICF) should be maintained by the Investigator in strict confidentiality in the ISF.
- The medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare, if the patient/patient's legal representative agrees.
- Site staff will be provided with a unique eCRF login information (username and password), giving access limited only to data of the site.

10.3 Approval of study protocol

- A notification of the planned study to the Competent Authority (CA) will be performed and a favourable opinion from the relevant EC will be obtained prior to the start of the study.
- The CA and EC will be notified about the end of the study and a report summarizing the study results will be sent to the CA and EC according to local legislation.
- If the study is terminated early or study enrolment must be suspended, the CA and EC will be notified according to local legislation.
- If mandated by local legislation enrolment can only be resumed after authorization by the CA and EC.

10.4 Protocol amendments

- Amendments to the study protocol may be made following the procedures specified by local laws and regulations.
- Substantial amendments to the study protocol (i.e. due to changes to the protocol or from new information relating to the scientific documents in support of the study) may be implemented only if the notification to the CA was performed and a favourable opinion of the EC have been obtained.

10.5 Informed consent

- Written informed consent will be obtained from each patient or (if the patient is unable to provide informed consent) the patient´s legally authorized representative prior to the patient´s study participation.
- In obtaining and documenting informed consent, the Investigator will comply with applicable legal requirements and with the ethical principles that have their origin in the Declaration of Helsinki; the consent process includes providing the patient with an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study which may influence the patient's decision to participate. The Investigator will explain that the patients are completely free to refuse participation in the study and may withdraw at any time, without any consequences for their further care and without the need to justify their decision.

11. Management and reporting of adverse events / adverse reactions

11.1 Definitions

11.1.1 Adverse Events / Adverse Drug Reactions

- An **adverse event (AE)** is any untoward medical occurrence in a patient or study subject administered a MP and which does not necessarily have a causal relationship with this treatment.
  An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a MP, whether or not considered related to the MP.
- An **adverse drug reaction (ADR)** is a response to a medicinal product which is noxious and unintended.
  The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a MP and an occurrence is suspected.
  For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse reaction. Therefore, all spontaneous reports notified by healthcare professionals or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the reporters specifically state that they believe the events to be unrelated or that a causal relationship can be excluded.
- A **treatment-emergent** AE/ADR is any AE/ADR that occurred only since time of the first MP (ropeginterferon alfa-2b) administration.

11.1.2 Solicited / Unsolicited Reports

- **Solicited reports** of suspected adverse reactions are those derived from organised data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare professionals, compassionate use or name patient use, or information gathering on efficacy or patient compliance. Reports of suspected adverse reactions obtained from any of these data collection systems should not be considered spontaneous.
- A **spontaneous report** is an **unsolicited** communication by a healthcare professional,

or consumer to a competent authority, marketing authorisation holder or other organisation (e.g. regional pharmacovigilance centre, poison control centre) that describes one or more suspected adverse reactions in a patient who was given one or more medicinal products.

11.1.3 Causality

- Medical judgement should be used to determine the causal relationship between AEs and administered MP (ropeginterferon alfa-2b), considering relevant factors, such as pattern of reaction, temporal relationship, concomitant medication, concomitant diseases and relevant history. The following categories are used:
  - **Related** to MP (reasonable possibility): The temporal relationship of the clinical event to MP administration makes a causal relationship possible; and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event. Reports including good reasons and sufficient information to assume a causal relationship in the sense that it is plausible, conceivable, or likely or reports containing sufficient information to indicate the possibility of a causal relationship in the sense of it not being impossible and not unlikely, although the connection may be uncertain or doubtful (e.g. due to missing data, insufficient evidence etc.).
  - **Not related** to MP (no reasonable possibility): The temporal relationship of the clinical event to MP administration makes a causal relationship unlikely; or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the event.
- Note that if causality is unknown, it should be attributed to the MP (ropeginterferon alfa-2b) until documented otherwise by the Investigator.

11.1.4 Seriousness

- A Serious Adverse Event (SAE) / Serious Adverse Drug Reaction (SADR) is any untoward medical occurrence that at any dose:
  - Results in **death**;
  - Is **life-threatening**;
  - Requires in-patient **hospitalization** or **prolongation of existing hospitalization**;
  - Results in a **persistent or significant disability/incapacity**;
  - Is a **congenital anomaly/birth defect**
- The term “life-threatening” refers to an event or reaction in which the patient was at risk of death at the time of the event or reaction. It does not refer to an event or reaction which hypothetically might have caused death if it were more severe.
- **Medically important events**:
  Medical judgement should be exercised in deciding whether other situations should be considered serious. Some medical events may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events (IME) should be considered serious. The EudraVigilance Expert Working Group IME list should be consulted for assessment of medical importance.

11.1.5 Intensity

- AE intensity according to Common Terminology Criteria for Adverse Events (CTCAE) criteria, version 5.0, will be assessed as follows:
  - Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- Note: Laboratory values that are out of range i.e. CTCAE Grade 3 or higher, must be reported as AE irrespective of clinical significance assessed by the Investigator (except for the laboratory values ALT, AST, GGT and bilirubin for which an AESI documentation threshold is pre-specified [see section 9.3.1.1]).

11.1.6 Expectedness

An adverse reaction, the nature or severity of which is not consistent with the applicable product information, is considered **unexpected**. The safety profile of ropeginterferon alfa-2b is described in the current product information (Annex 1), which is defined as Reference Safety Information (RSI) for the study.

11.2 Documentation of AEs

All AEs will be collected and recorded in the eCRF over the course of the study from first ropeginterferon alfa-2b exposure to study completion (see section 9.2.2). In case of ropeginterferon alfa-2b treatment discontinuation due to hepatotoxicity, follow-up of the AE as performed in routine clinical practice (e.g. evaluation of hepatic enzymes) should be documented.

- AEs of special interest (as specified in the study protocol section 9.3.1.1), will be documented as solicited AEs.

- For each AE, the Investigator will provide the onset date and time, end date and time, treatment required, outcome, and action taken with the MP (ropeginterferon alfa-2b) and document in the eCRF AE page. It is preferred to use the medical diagnosis, or, if no diagnosis could be established at the time of AE reporting, a symptom or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions.
- Each AE will be evaluated by the Investigator for:
  - seriousness
  - intensity
  - causal relationship to medicinal product exposure and
  - relationship to underlying disease PV
- The Investigator must pursue and obtain information adequate to both determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor or its designated representative.
- The Investigator must ensure that the follow-up of the patient is appropriate to the nature of the event. Follow up of the patient should continue until resolution of the event or at least stabilization of the patient's clinical status and reported in the eCRF as performed in routine clinical practice.
- If the follow-up of the patient could not be conducted by the Investigator (e.g. patient was transferred to another hospital, etc.), the Investigator will do everything possible to

collect additional information by establishing and maintaining the contact with the person in charge of the patient.

11.3 Management and reporting of AEs/ADRs

The management and reporting of AEs/ADRs will follow the Guideline on Good Pharmacovigilance Practice (GVP), Module VI.C.1.2.1.1 for non-interventional post-authorization studies with a design based on primary data collection.

11.3.1 Investigators' Reporting responsibility to Sponsor

- Adverse events are reported via the eCRF to the Sponsor. In case of eCRF failure, there are paper reporting forms available, which should be faxed or emailed to the contact details specified on those forms. If reporting by telephone, the immediate report should be followed by detailed written reports.
- All SAEs regardless of suspected relationship to ropeginterferon alfa-2b must be reported by the Investigator immediately, or within no more than 24 hours after notice. If reporting by telephone, the immediate report should be followed by detailed written reports.
- The minimum information required from the Investigator when reporting an SAE is as follows:
  1. Investigator's identification (name and centre number).
  2. Protocol identification number.
  3. Patient identification number.
  4. SAE description including criteria for seriousness and the immediate outcome.
- The Investigator is obligated to pursue and provide information as requested by the Sponsor or designated representative. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality.
- Information on other possible causes of the event, including concomitant medications and illnesses must be provided.
- The Investigator's assessment of causality must also be provided. If causality is unknown, it should be attributed to ropeginterferon alfa-2b until documented otherwise by the Investigator.
- In the case of a patient death, a summary of available autopsy findings (if available) should be submitted as soon as possible.

11.3.2 Reporting procedures to Health Authorities

- **Expedited reporting** of individual safety reports to Health Authorities is performed via EudraVigilance following post marketing reporting procedures according to Directive 2001/83/EC and Regulation (EC) No 726/2004. This is the responsibility of the Marketing Authorization Holder (MAH) and Sponsor of this study.
  All solicited and unsolicited ADRs are reported within the following timelines:
  - **serious** ADRs: within **15 calendar days**
  - **non-serious** ADRs: within **90 calendar days**

  These timelines apply for initial information as well as follow-up reports.
  Details on the management of individual safety reports are laid down in the MAHs Pharmacovigilance System Master File (PSMF).
- **Periodic reporting** to Health Authorities for ropeginterferon alfa-2b is performed according to the timelines agreed in the marketing authorization and published in the

EURD List following legal requirements according to Regulation (EC) No 726/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC.
Details on the management of Periodic Safety Update Reports (PSURs) are laid down in the MAHs Pharmacovigilance System Master File (PSMF).

- Any new safety information that might influence the evaluation of the benefit-risk balance of the product is processed through the MAHs **signal management** system, following legal requirements according to Regulation (EC) No 726/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012.
  Details on the Signal management processes are laid down in the MAHs Pharmacovigilance System Master File (PSMF).

12. Plans for disseminating and communicating study results

After completion of the study, the results will be tabulated, evaluated and issued as a complete final study report according to the EMA Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies. The Sponsor will send a summary of this study report to the EC and CA within time periods required, as mandated by local legislation. Results of this study are expected to be published in a scientific journal.

13. References

None.

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	-	15FEB2019	Ropeginterferon alfa-2b Product Information

Annex 2. ENCePP checklist for study protocols

Annex 3. Additional information

None.