Risk Management Plan
for
Besremi® (ropeginterferon alfa-2b)

RMP version to be assessed as part of this application:

RMP Version number:	3.0
Data lock point for this RMP:	24-Jun2025
Date of final sign-off:	electronic signature and date are available on the last page
Rationale for submitting an updated RMP:	Update of Besremi PASS timelines.
Summary of significant changes in this RMP:	Part III: Besremi PASS timelines were updated, Annex 2 was updated accordingly.

Other RMP versions under evaluation:

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QPPV name:	Dr. Juri Hodisch AOP Orphan Pharmaceuticals GmbH Leopold-Ungar Platz 2, 1190 Vienna, Austria

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on the last page.

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	ropeginterferon alfa-2b
Pharmacotherapeutic group(s) (ATC Code)	L03AB15
Marketing Authorisation Holder or Applicant	AOP Orphan Pharmaceuticals GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Besremi®
Marketing authorisation procedure	Centralised (EMEA/H/C/004128/0000)
Brief description of the product	Chemical class: Pegylated-Proline-Interferon alfa-2b (in this document named as ropeginterferon alfa-2b) belongs to Interferons (ATC Code L03AB)
	Summary of mode of action: Interferon alfa belongs to the class of type I interferons which exhibit their cellular effects by binding to a transmembrane receptor termed interferon alpha receptor (IFNAR). IFNAR engagement initiates a downstream signalling cascade through the activation of kinases and activator of transcription (STAT) proteins. Nuclear translocation of STAT proteins control distinct gene-expression programs and exhibit various cellular effects such as induction of antimicrobial states in pathogen infected cells, modulation of innate immune responses and activation of the adaptive immune system. Interferon alfa was shown to have an inhibitory effect on the proliferation of hematopoietic and bone marrow fibroblast progenitor cells and antagonized the action of growth factors and other cytokines that may have a role in the development of myelofibrosis. These actions may be involved in the therapeutic effects of interferon alpha in polycythaemia vera.
	Important information about its composition: Ropeginterferon alfa-2b is conjugated with a two-arm methoxypolyethylene glycol (mPEG) at a degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 60 kDa, of which the protein moiety constitutes approximately 19 kDa.
Hyperlink to the Product Information	Link to SmPC Link to PIL
Indication(s) in the EEA	Current: Besremi is indicated as monotherapy in adults for the treatment of polycythaemia vera without symptomatic splenomegaly.
	Proposed: Not applicable.
Dosage in the EEA	Current: *Titration phase* The 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 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. If adverse events develop during therapy, the administered dose should be reduced or treatment discontinued temporarily until adverse events abate; further, treatment should be re-initiated with a lower dose than the dose that caused adverse events. If an increase of haematological parameters is observed, the dose and/or dosing interval needs to be adapted individually. *Method of administration* For subcutaneous use. The medicinal product is intended for long-term treatment and can be administered by a physician, nurse, family member or patient when trained in the administration of subcutaneous injections with the pre-filled pen. The instructions for use in the package leaflet should be followed. The recommended injection site is the abdominal skin around but not within 5 cm of the navel or the thigh. Do not inject into an area where the skin is irritated, reddened, bruised, infected or scarred. The pen can be adjusted to administer doses in 50 microgram intervals in the range of 50 to 250 micrograms or 50 to 500 micrograms.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: Solution for injection in pre-filled pen (injection); 250 µg or 500 µg ropeginterferon alfa-2b
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Module SI - Epidemiology of the indication(s) and target population(s)

SI.1 Indication

Ropeginterferon alfa-2b is indicated as monotherapy for the treatment of adult patients with polycythaemia vera without symptomatic splenomegaly.

SI.1.1 Incidence and prevalence:

Polycythaemia Vera (PV) is a Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) characterised primarily by an increased red blood cell mass. Patients with PV have excessive proliferation of not only erythroid but also myeloid and megakaryocytic components in the bone marrow, resulting in high red blood cell, white blood cell and platelet counts (Griesshammer *et al.*, 2015)[10].

MPNs constitute one of nine categories of myeloid malignancies, according to the World Health Organization (WHO) classification system for haematopoietic tumours (Arber *et al.*, 2016)[2]. There is a wide variation in both prevalence and incidence estimates observed across European data sources. Among various registries, the incidence of PV ranged from 0.4 to 2.8 per 100,000 per year, while the literature estimated the range of PV incidence to be 0.68–2.6 per 100,000 per year (Moulard *et al.,* 2014)[2020]. The prevalence of PV is estimated to be 44 to 57 cases per 100,000 persons and approximately 148,000 persons are living with PV in the United States (Stein *et al.*, 2015)[26].

SI.1.2 Demographics of the population in the proposed indication and risk factors for the disease:

The incidence of PV is higher among men than among women in all races and ethnicities, with rates of approximately 2.8 per 100,000 men and approximately 1.3 per 100,000 women. PV is typically diagnosed in persons 60 to 65 years of age, and the disorder is relatively uncommon among individuals younger than 30 years. The condition is observed more often among Jews of Eastern European descent than among other European populations and Asians (Raedler *et al.,* 2014[24]; Griesshammer *et al.*, 2015[10])[24].

In a study of more than 1,500 patients with PV, risk factors for survival included advanced age, leucocytosis, venous thrombosis, and abnormal karyotype. These observations were further validated by a population-based study of 327 patients with PV where multivariate analysis identified age >70 years, leucocyte count >13 × 10^9/l and thrombosis at diagnosis, as risk factors for poor survival (Tefferi *et al.*, 2013)[30.]

The aetiology of MPN is not completely understood, but acquired somatic mutations of Janus kinase 2, i.e. JAK2V617F and JAK2 exon 12, resulting in constitutive kinase activity and cytokine independent myeloproliferation have been demonstrated to play a crucial role in the pathogenesis of many cases of Ph-neg MPN (Levine *et al.*, 2005)[18]. JAK2V617F mutations are present in approximately 95% of all PV patients and in about 50% of patients with essential thrombocythaemia (ET) (Tefferi *et al.*, 2011, 2015b[29,31], Stein *et al.*, 2015[26]).

SI.1.3 The main existing treatment options:

The management of PV is guided by its clinical features that include substantial symptom burden and impaired survival resulting from arterial and venous vascular incidents, evolution to myelofibrosis, or leukemic transformation (Stein *et al.*, 2015[26], Falchi *et al*., 2015[8]).

As a consequence, there are three treatment goals in PV:

(1) Managing disease symptoms aiming for improved quality-of-life

(2) Managing the long-term risk of thromboembolic and thrombohaemorrhagic complications

(3) Managing the long-term risk of disease progression/evolution or leukemic transformation

Therapeutic options of PV are limited, and no cure is available. Risk-stratification for cytoreductive treatment is still based on the traditional risk factors for thrombosis, i.e. older age (≥ 60 years) and previous history of thrombosis. Currently, most patients with PV regardless of risk are treated with phlebotomy and low-dose aspirin as the front-line therapy to correct abnormal blood viscosity associated with increased red cell volume, and to control the risk of vascular events, whereas high-risk patients receive cytoreductive treatment (Barbui *et al.*, 2011[3]; Vannucchi *et al.*, 2009[33], Tefferi *et al.*, 2015a[28]).

Treatment decisions for high-risk PV patients are based on European Leukemia Net (ELN) recommendations (Barbui *et al.*, 2011)[3]. The ribonucleoside reductase inhibitor hydroxyurea (HU; also named hydroxycarbamide) currently is the only first-line therapy licensed in the EU for patients of all age groups requiring cytoreductive treatment. However, HU-treated patients can eventually become resistant to treatment or experience unacceptable adverse effects, such as cutaneous carcinomas and other severe skin toxicities leading to a high proportion of treatment intolerant patients (Spivak *et al.*, 2011[25], Griesshammer *et al.*, 2015[10]). In addition, due to its mechanism of action, HU has the potential to be mutagenic and may be associated with an increased risk of leukemic transformation after long-term use in PV patients (Barbui *et al.*, 2011[3], Spivak *et al.*, 2011[25], Björkholm *et al.*, 2014[6]). The JAK2 inhibitor ruxolitinib is indicated for the treatment of PV, but is only indicated and used as second line therapy in patients who are resistant to or intolerant of HU (Kiladjian et al, 2015[16], Tefferi *et al.*, 2015a[28]).

Additional antithrombotic medications are used off-label in the therapy of PV and include non-pegylated and (poly-)pegylated interferons, anagrelide, and alkylating agents. Use of the alkylating agent busulfan may be considered in elderly patients (>70 years) (Barbui *et al.*, 2011)[3]. Interferon alpha (IFN alfa) has been shown to be effective in MPNs for more than 25 years and is recommended by ELN and by several national guidelines and investigators as alternative first-line treatment for PV (Barbui *et al.*, 2011, 2012[3,4]Andersen *et al.*[1], Hensley *et al.*, 2013[12], Falchi *et al.*, 2015[8], Griesshammer *et al.*, 2015[10]). It is often preferred to HU, since it is non-leukaemogenic and non-teratogenic, and may result in better control of thrombohaemorrhagic complications (Kiladjian *et al.*, 2011, 2015)[15,16].

SI.1.4 Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The key clinical features of PV are highly variable and may include increased red blood cell mass (haematocrit), increased white blood cell (WBC) and platelet (PLT) counts in the peripheral blood, and splenomegaly, or any combination of these. Mild clinical symptoms of PV are unspecific and related to the increased blood cell count resulting in high blood viscosity, e.g. headache, fatigue, dizziness, vision disturbances, vertigo, tinnitus, pruritus, or erythromelalgia. However, PV is a long-term debilitating and life-threatening condition as it is associated with the risk of thrombosis (including cerebrovascular, myocardial and peripheral atrial thrombosis, deep vein thrombosis, transient ischemic attack, stroke, and pulmonary embolism), haemorrhage, and a long term propensity to develop myelofibrosis (MF) and secondary acute myeloid leukaemia (sAML) (Stein *et al.*, 2015[26], Griesshammer *et al.*, 2015[10])[26]. Thrombosis is the most common complication of PV, leading to serious morbidity and is implicated in as many as 37% of deaths (Stein *et al.*, 2015)[26]. Transformation to leukaemia or progression to MF is largely related to older age, leucocytosis, and disease duration, and has been reported to occur in up to 10% of cases for sAML, and up to 21% for MF (Falchi *et al.*, 2015[8], Stein *et al.*, 2015[26]).

SI.1.5 Important co-morbidities:

As PV is predominantly a disease of the elderly, certain co-morbidities can exist which are expected in this age group: diabetes mellitus, hypertension, cardiac disorders, coronary artery disease, cerebrovascular disease and cancer (Fillenbaum *et al.*, 2000)[99].

Module SII - Non-clinical part of the safety specification

SII.1 Key Safety findings (from non- clinical studies) and relevance to human usage

SII.1.1 Toxicity

SII.1.1.1 Single and repeat-dose toxicity

Toxicological evaluation of ropeginterferon alfa-2b was initiated in rats and cynomolgus monkeys.

In the non-pivotal study in rats, the lack of biological activity of human interferon was evident, implying that studies in rodents are of limited value and toxicological assessment in single non-rodent species is justified. Nevertheless, the study supports the absence of toxicologically critical impurities.

A pivotal repeat dose toxicity study tested repeated *s.c.* administration of ropeginterferon alfa-2b to male and female cynomolgus monkeys at the doses of 0, 0.675, 2 and 6.75 mg/kg on days 1, 4, 8, 11, 15, 18, 22 and 24. The study showed no treatment-related clinical signs, ocular or ECG findings. The most prominent effects included loss of appetite and slight weight loss. No macroscopic findings or changes in organ weights were recorded and histological examination of organs was unremarkable. The no observed adverse effect level (NOAEL) for ropeginterferon alfa-2b when given to male and female cynomolgus monkeys *via s.c.* injection once daily for 8 non-consecutive days within four weeks followed by a four-week recovery period was defined at 6.75 mg/kg.

Another non-pivotal study was conducted in cynomolgus monkeys. The same dose levels 0.675, 2 and 6.75 mg/kg of ropeginterferon alfa-2b were administered as four non-consecutive doses. Using the same first four dosing time points as for the pivotal toxicity study, NOAEL was determined as 2 mg/kg.

The findings in these two studies were similar, thus the difference in the determined NOAEL levels possibly stems from the fact that the observations in the pivotal toxicity study were evaluated in the context of their reversibility following the four-week recovery period.

Two bridging studies showed that clinical lots manufactured with a new producer strain and manufacturing process were comparable in terms of induced effects.

The duration of the pivotal toxicity study does not cover the chronic use of ropeginterferon alfa-2b in patients with the treatment length exceeding six months and application every two weeks.

The peak concentrations in sera and exposure were vastly greater in cynomolgus monkeys than in patients, further pointing to a high safety margin of the NOAEL to the maximum applied dose of 540 µg/patient.

SII.1.1.2 Reproductive and developmental toxicity

In a study conducted by Enright *et al.*, IFN alfa-2b was shown to be abortifacient in rhesus monkeys. Treatment of female cynomolgus monkeys with pegylated IFN alfa-2b or IFN alfa-2b inhibited ovarian function, as evidenced by decreased peak serum oestradiol and progesterone levels (Enright *et al.*, 2009)[7]. The dose-dependent irregularities in duration of menstrual cycle were reversible following cessation of the treatment.

Ropeginterferon alfa-2b is expected to have the similar effects on female reproduction since the active moiety human IFN alfa-2b is the same as for the approved IFN alfa-2a/2b products (Roferon®A and Intron®A). Women of childbearing potential treated with ropeginterferon alfa-2b will be advised to employ appropriate contraception methods during treatment.

SII.1.1.3 Genotoxicity

Mutagenic and clastogenic potential of ropeginterferon alfa-2b was examined in two *in vitro* assays, Ames test and chromosomal aberration assay in CHO cells.

Ropeginterferon alfa-2b tested clearly negative in the Ames assay up to the highest evaluated dose of 5 mg/plate of but resulted in an increase in chromosomal aberrations in cultured CHO cells in a short-term incubation with metabolic activation. It is possible that the chromosomal aberrations observed at these high concentrations were associated with cytotoxicity as detached floating cells were noted at these concentrations. No increase in chromosomal aberrations was detected following short or long-term incubations without metabolic activation.

Interferon alfa-2b and Peg-IFN products consistently tested negative for genotoxicity or clastogenicity.

SII.1.1.4 Carcinogenicity

Carcinogenicity testing of ropeginterferon alfa-2b is inappropriate and unnecessary, a position which is considered to be in accordance with the current ICH guideline S6 and also nonclinical testing of other approved interferon products.

SII.1.1.5 Immunogenicity

Analysis of humoral immune response was performed as part of the Good Laboratory Practice toxicity studies in cynomolgus monkeys. In a pivotal toxicity study, s.c. treatment with ropeginterferon alfa-2b at doses of 0.675, 2 and 6.75 mg/kg consistently induced anti-drug and neutralising antibodies by the end of the four-week treatment period, demonstrating immunogenicity of the test item.

Even though cynomolgus monkeys are the closest animal models to humans for the evaluation of ropeginterferon alfa-2b, toxicology studies longer than 4 weeks are limited by the emergence of neutralizing antibodies.

SII.1.2 Safety pharmacology

Safety pharmacology studies comprised an in vitro hERG assay, a cardiovascular study in cynomolgus monkeys and central nervous system and respiration studies in rats

The hERG assay suggested a negligible potential to interfere with the cardiac function.

A cardiovascular study was carried out in cynomolgus monkeys treated intravenously up to the dose of 600 mcg/kg. No negative effects on the duration of the QT interval were noted.

Another study was conducted in rats to study the safety of ropeginterferon alfa-2b in the central nervous system. A single s.c. administration up to the dose of 20 mg/kg did not elicit any adverse effects on central nervous system or body temperature in rats. Similarly, single i.v. dose of ropeginterferon alfa-2b at 10 mg/kg to rats had no negative effects on respiration.

In the toxicity studies in cynomolgus monkeys treated s.c. up to the dose of 6.75 mg/kg, no clinical signs indicating influence of the test item on central nervous or respiratory system were noted.

No evidence for adverse effects on the central nervous, cardiovascular or respiratory system were observed.

SII.1.3 Other toxicity-related information or data

None available.

Module SIII - Clinical trial exposure

Ropeginterferon alfa-2b is indicated in adults for the treatment of Polycythaemia Vera without symptomatic splenomegaly. The clinical study program for Ropeginterferon alfa-2b in patients with PV included four clinical studies (one Phase I/II study ´PEGINVERA´ EudraCT No.: 2010-018768-18, two Phase III studies ´PROUD-PV´ EudraCT No.: 2012-005259-18 and ´PEN-PV´ EudraCT No.: 2014-001356-31 and one phase IIIb study ´CONTINUATION-PV´ EudraCT No.: 2014-001357-17).

In the four AOP-sponsored studies, 178 patients were exposed to Ropeginterferon alfa-2b and 127 were exposed to an active comparator.

Trial exposure is calculated based on data from the AOP-sponsored clinical studies PEGINVERA, PROUD-PV, CONTINUATION-PV and PEN-PV.

SIII Table 1: Estimated Cumulative Subject Exposure (AOP-sponsored clinical studies)

Treatment	Number of subjects
Ropeginterferon alfa-2b	178*#
Comparator	Hydroxyurea (HU): 127** (171***)
Total subjects	305

 # Patients received s.c. doses (every two weeks to up to four weeks) between 50 to 500 µg. Specifically, in the PEGINVERA-PV Study Stage I, the maximal tolerable dose (MTD) was determined with 540 µg. In the Phase III clinical studies (PROUD-PV, PEN-PV, and CONTINUATION-PV Study), the mean dose per administration was approximately 380 µg with a median dose of 450 µg. The mean dose in the PEGIVERA-PV Study (Phase I/II) was 245.1 µg (median 243.8 µg).
**Represents PEGINVERA Study and PROUD-PV Study patients. CONTINUATION-PV Study and PEN-PV Study patients have previously participated in PROUD-PV Study and therefore exposures are counted in PROUD-PV Study. Out of the 127 PROUD-PV Study patients in ropeginterferon alfa-2b arm, 47 patients were receiving HU in their treatment history.*
***Patients from HU treatment arm during PROUD-PV Study. CONTINUATION-PV Study patients receiving BAT (standard first line treatment for treatment of PV disease, as per investigator's discretion) are not separated.*
****PROUD-PV Study: Patients receiving HU at the time of screening but randomized to ropeginterferon alfa-2b arm received both study drugs: HU and ropeginterferon alfa-2b arm in the transition phase lasting up to 12 weeks.*

Out of the 178 patients who received ropeginterferon alfa-2b, 127 patients (68 females, 59 males) were enrolled in PROUD-PV Study and 51 patients (20 females, 31 males) in PEGINVERA Study. The age repartition was represented by 130 patients (73.0%) between 18-65 years, 37 patients (20.8%) between 66-75 years and 11 patients (6.2%) ≥76 years.

SIII Table 2: Estimated cumulative Subject Exposure to ropeginterferon alfa-2b by Age and Sex*

Age range	Number of subjects				
	Male		Female		Total
	PEGINVERA study	PROUD-PV study	PEGINVERA study	PROUD-PV study	
<18	0	0	0	0	0
18-65	21	46	14	49	130
66-75	8	11	3	15	37
≥76	2	2	3	4	11
Total	**31**	**59**	**20**	**68**	**178**

* Data from completed and ongoing AOP sponsored studies as of 14-Feb-2022

SIII Table 3: Estimated cumulative Subject Exposure to ropeginterferon alfa-2b by Racial Group*

Racial group	Number of subjects		Total
	PEGINVERA study	PROUD-PV study	
Caucasian	50	127	177
Black	0	0	0
Asian	1	0	1
Other	0	0	0
Unknown	0	0	0
Total	**51**	**127**	**178**

* Data from completed and ongoing AOP sponsored studies as of 14-Feb-2022

Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

SVI.1 Table 4 Assessment of Exclusion criteria as Missing Information

Criterion	Reason for exclusion	Considered to be included as missing information?	Rationale
Patients with hypersensitivity to ropeginterferon alfa-2b or to any of the excipients of the medicinal product.	Serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been rarely observed with other interferon alfa preparations.	No	The use of ropeginterferon alfa-2b is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients of the medicinal product.
Thyroid dysfunction (clinical symptoms of thyroid hyper- or hypofunction) not adequately controlled.	Thyroid function abnormalities or worsening of pre-existing thyroid disorders have been reported with the use of alfa interferons.	No	The use of ropeginterferon alfa-2b is contraindicated in patients with pre-existing thyroid disease unless it can be controlled with conventional treatment.
Clinically significant history or known presence of psychiatric disorders, including but not limited to depression, anxiety and sleep disorders.	Severe neuropsychiatric effects have been observed in some patients with the use of alfa interferons.	No	Ropeginterferon alfa-2b is contraindicated in patients with the existence of or history of severe psychiatric disorders, particularly severe depression, suicidal ideation or suicide attempt.
Uncontrolled hypertension (systolic >150 mmHg and diastolic >100 mmHg, or clinically significant (i.e., active) cardiovascular disease: cardiovascular attack/stroke (≤3 months prior to enrolment), myocardial infarction (≤3 months prior to enrolment), significant coronary artery stenosis, unstable angina, New York	Hypertension, supraventricular arrhythmias, congestive heart failure, chest pain and myocardial infarction have been associated with alfa interferon therapies.	No	Ropeginterferon alfa-2b is contraindicated in patients with severe pre-existing cardiovascular disease, i.e., uncontrolled hypertension, congestive heart failure (≥ NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina or recent stroke or myocardial infarction.

Criterion	Reason for exclusion	Considered to be included as missing information?	Rationale
Heart Association Class 2 or greater Congestive heart failure or serious cardiac arrhythmia requiring medication. Clinically significant ECG findings.			
Organ transplant, past or planned.	The safety and efficacy of interferon alfa have not been established in patients with liver and other organ transplantations. Liver and renal graft rejections have been reported with interferon alfa, alone or in combination with ribavirin.	No	The use of ropeginterferon alfa-2b is contraindicated in immunosuppressed transplant recipients.
Acute or chronic infections or autoimmune diseases (collagen diseases, polyarthritis, immune thrombocythemia, thyroiditis, psoriasis, lupus nephritis or any other autoimmune disorder).	The development of auto-antibodies and autoimmune disorders has been reported during treatment with alfa interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk.	No	Ropeginterferon alfa-2b is contraindicated in patients with history or presence of autoimmune diseases.
Pregnant females	An abortion-inducing effect was reported in primates receiving other interferon alfa preparations.	No	As ropeginterferon alfa-2b may have the same effect as shown in primates with other interferon alfa preparations, the medicinal product is not recommended during pregnancy.
Lactating females	It is unknown whether the components of the medicinal product are excreted in human milk.	No	The medicinal product is not recommended in lactating females, since a risk to the suckling child cannot be excluded. In case a lactating woman requires treatment with ropeginterferon alfa-2b, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Besremi therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Inadequate liver function	Liver disorders and abnormal hepatic laboratory parameters have been	No	Ropeginterferon alfa-2b is contraindicated in patients with decompensated

Criterion	Reason for exclusion	Considered to be included as missing information?	Rationale
	reported in patients after long-term ropeginterferon alfa-2b therapy.		cirrhosis of the liver (Child-Pugh B or C).
Renal disease	The renal clearance of Ropeginterferon alfa-2b may be reduced in patients with impaired renal function.	No	Ropeginterferon alfa-2b is contraindicated in patients with end stage renal disease.
Previous treatment with cytoreductive drugs	Avoidance of potential confounding of the results.	No	Caution must be exercised when administering ropeginterferon alfa-2b in combination with other potentially myelosuppressive/ chemotherapeutic agents.
Diagnosis of any malignant disease, including solid tumours and haematological malignancies (except basal cell and squamous cell carcinomas of the skin and carcinoma in situ of the cervix that have been completely excised and are considered cured) within the last 3 years.	Avoidance of potential confounding of the results.	No	Caution must be exercised when administering ropeginterferon alfa-2b in combination with other potentially myelosuppressive/ chemotherapeutic agents.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

SIV.3 Table 5: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	not included in the clinical development program
Breastfeeding women	
Paediatric patients	
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment	not included in the clinical development program

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

No defined daily dose (DDD) has been published for ropeginterferon alfa-2b by the WHO Collaborating Centre for Drug Statistics Methodology.

Therefore, to estimate the patient's exposure, the DDD was calculated based on the median maintenance dose of 400 µg from the CONTI-PV clinical trial (derived from the 72 months CSR). Considering that the patients were treated with 400 µg of ropeginterferon alfa-2b every 2 weeks, the DDD was 0,029 mg:

$$\frac{400\mu g \div 14\ days}{1000} = 0{,}029\ mg\ \text{(DDD)}$$

An estimate of the number of Daily Doses of ropeginterferon alfa-2b during the reporting period was calculated from the sales volumes according to the following formula:

$$Number\ of\ Daily\ Doses\ = \frac{\text{Total quantity of ropeginterferon alfa} - \text{2b sold (mg)}}{DDD\ (mg)}$$

The total quantity of ropeginterferon alfa-2b sold (in mg) was determined by multiplying the number of units (pens) by the strength of the formulation (0,25mg) and summing the totals. Note that no data was available regarding age and/or sex of the exposed patients, or exposure in at risk populations (e.g., patients with renal or hepatic impairment).

To determine patient-years the number of Daily Doses has to be divided by 365:

$$Patient\ years\ = \frac{Number\ of\ Daily\ Doses}{365\ days}$$

Note: DDD was previously calculated based on median maintenance dose of 450 µg from the CONTI-PV clinical trial (derived from the 24 months CSR). Considering that the patients were treated with 450 µg of ropeginterferon alfa-2b every 2 weeks, the DDD was 0,032 mg.

SV.1.2 Exposure

SV.1.2 Table 6: Total exposure (cumulative until 14 February 2022)

Besremi®	**Cumulative – 14 February 2022**
Total patient years	1,047 patient-years

Note: DLP for patient's exposure based on the DLP from the last PSUR.

Cumulatively, until the DLP of 14 February 2022, the number of Daily Doses sold was estimated to be 381,983. From the estimated number of daily doses, the exposure in patient-years was 1,047.

Note: The above-mentioned calculation assumes that not a single box has been lost, or damaged, or thrown away, or simply has not been used in the specified period of time by a pharmacist, physician, nurse or patient.

Module SVI - Additional requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Considering the nature of the product and the nature of the disease for which it is indicated, the potential for illegal use is very low.

Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

The following safety concerns (refer to Table 7), were identified in the first RMP submission after 30-Mar-2017, the date for the second version of GVP Module V coming into effect. The identified and potential risks were selected according to section 4.3 Contraindications and section 4.4 Special warnings and precautions for use in the SmPC. Additionally, "Thrombotic microangiopathy", "Neoplasms, benign and malignant", "Demyelinating disorders" were suggested as important potential risks by the Regulatory Agency (Committee for Medicinal Products for Human Use, Procedure No. EMEA/H/C/4128, 22-Jun-2017).

SVII.1 Table 7: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hepatotoxicity • Thyroid dysfunction • Neuropsychiatric adverse effects • Ocular disorders, including decreased visual acuity, loss of vision, blindness, and retinal detachment • Cardiac events including cardiomyopathy, myocardial infarction, myocardial ischaemia • Pulmonary disorders including pulmonary fibrosis, lung infiltration, pneumonitis and pneumonia • Diabetes mellitus
Important potential risks	• Pulmonary arterial hypertension • Thrombotic microangiopathy • Neoplasms, benign and malignant • Reproductive toxicity/ spontaneous abortions • Demyelinating disorders
Missing information	• None

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the initial RMP:

The adverse events noted below are included in the prescribing information but are not considered important for inclusion in the list of safety concerns for the purpose of risk management planning.

The reasons for excluding these are outlined below:

Reason for excluding adverse events from the list of safety concerns	**Adverse Events**	
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	Abdominal distension Abdominal pain Abdominal wall disorder Arthralgia Aura Blood uric acid increased Bone pain	Headache Hypoesthesia Injection site erythema Injection site pain Injection site pruritus Injection site reaction Micturition urgency

Reason for excluding adverse events from the list of safety concerns	Adverse Events	
	Constipation Coombs test positive Decreased appetite Dental and Periodontal disorders Diarrhoea Dizziness Dry eye Dysuria Eczema eyelid Erectile dysfunction Flatulence Flushing Frequent bowel movements Gastritis General physical health deterioration Gingival bleeding Groin pain	Migraine Muscle spasms Muscular weakness Musculoskeletal pain Myalgia Nail dystrophy Nausea Neck pain Odynophagia Pain in extremity Paraesthesia Photosensitivity reaction Raynaud's phenomenon Hypertension Sensitivity to weather change Somnolence Tremor Umbilical haematoma Weight decreased
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated	Acute Hypersensitivity Reactions Cystitis haemorrhagic Hearing loss Hypertriglyceridemia	Increased Risk of Infections and Sarcoidosis Mental impairment Urinary retention
Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting	Anaemia Dermatitis acneiform Dry skin Erythema Hyperhidrosis Hyperkeratosis Influenza like illness and associated symptoms: Fatigue, Pyrexia, Asthenia, Chills Leukopenia	Alopecia Nail dystrophy Neutropenia Pancytopenia Pruritus, Rash Skin exfoliation Thrombocytopenia Xeroderma

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the initial RMP

Important Identified Risk 1: Hepatotoxicity

Risk-benefit impact: Hepatotoxicity has been identified as an important risk due to its clinically significant impact on patient's daily life activities and quality of life.

Important Identified Risk 2: Thyroid dysfunction

Risk-benefit impact:

Thyroid dysfunction has been identified as an important risk due to its clinically significant impact on patient's daily life activities and quality of life. While thyroid dysfunction is reversible after cessation of IFN therapy in the majority of cases (Baudin *et al.*, 1993)[5], permanent thyroid hormone replacement therapy will be required in certain proportion of affected patients (Nadeem *et al.*, 2010)[21].

Important Identified Risk 3: Neuropsychiatric adverse effects

Risk-benefit impact:

Neuropsychiatric adverse effects have been identified as an important risk due to its clinically significant impact on patient's daily life activities and quality of life. Severe depression can be life-threatening or fatal in case of a suicide attempt.

Important Identified Risk 4: Ocular disorders, including decreased visual acuity, loss of vision, blindness, and retinal detachment

Risk-benefit impact:

Ocular disorders have been identified as an important risk due to its clinically significant impact on patient's daily life activities and quality of life. Although visual loss was rarely observed in patients treated with IFN alfa, the potential risk for irreversible damage and blindness cannot not be excluded.

Important identified Risk 5: Cardiac events including cardiomyopathy, myocardial infarction, myocardial ischaemia

Risk-benefit impact:

Cardiac events have been identified as an important risk due to its potentially clinically significant consequences requiring medical intervention in patients at risk.

Important identified Risk 6: Pulmonary disorders including pulmonary fibrosis, lung infiltration, pneumonitis and pneumonia

Risk-benefit impact:

Pulmonary disorders have been identified as an important risk due to its potentially clinically significant consequences for patients at risk (i.e. those with pre-existing respiratory disorders). The clinical implication of not recognizing IFN associated pulmonary toxicity is the continued occurrence of pulmonary damage that may lead to pulmonary fibrosis.

Important identified Risk 7: Diabetes mellitus

Risk-benefit impact:

Diabetes mellitus has been identified as an important risk due to its clinically significant impact on patient's daily life activities and quality of life, including need for continuous therapy to manage blood sugar levels with insulin and diet to prevent complications.

Important Potential Risk 1: Pulmonary arterial hypertension (PAH)

Risk-benefit impact:

PAH has been identified as a potential risk due to its clinically significant consequences to the patient. Early diagnosis and corresponding treatment are critical in increasing the life expectancy in patients with PAH.

Important Potential Risk 2: Thrombotic microangiopathy (TMA)

Risk-benefit impact:

TMA has been identified as a potential risk due to its potentially life-threatening complications in the context of serious organ damage. Because of the rarity of this disorder and the non-specific clinical and laboratory features, the diagnosis (and its underlying causes) can be easily overlooked or missed, leading to morbidity and/or mortality.

Important Potential Risk 3: Neoplasms, benign and malignant

Risk-benefit impact:

Neoplasms, benign and malignant have been identified as a potential risk due to its clinically significant consequences to the patient as well as life expectancy in case of malignant neoplasms with disease progression.

Important Potential Risk 4: Reproductive toxicity/spontaneous abortions

Risk-benefit impact:

Reproductive toxicity/ spontaneous abortions have been identified as a potential risk as it could lead to clinically significant consequences requiring medical intervention.

Important Potential Risk 5: Demyelinating disorders

Risk-benefit impact:

Demyelinating disorders have been identified as a potential risk due to its clinically significant consequences to the patient. Depending on the type of demyelinating disorder and affected areas of the central or peripheral nervous system, patients may be significantly restricted in their daily life activities (temporal or permanent disability/incapacity of the patient). Moreover, life-threatening consequences might evolve in the most dramatic cases.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns.

The risks below, which were included in the previous editions of RMP, are considered to be adequately described in the SmPC; no additional risk minimisation measures are warranted and surveillance within routine pharmacovigilance activities is considered sufficient.

These risks (below) have, therefore, been removed from the list of safety concerns:

Thyroid disorders (previously classified as important identified risk)

Reasons for removal from the list of safety concerns

Mentioned in the SmPC Section 4.8, Undesirable effects:
“hypothyroidism, hyperthyroidism, thyroiditis” (frequency common)

in SmPC Section 4.4, Special warnings and precautions for use:
“Before ropeginterferon alfa-2b therapy, any pre-existing thyroid disease needs to be treated and controlled with conventional therapy (see section 4.3). Patients who develop symptoms indicative of a thyroid dysfunction during ropeginterferon alfa-2b therapy, should evaluate their thyroid stimulating hormone (TSH) levels. If TSH levels can be controlled within the normal range, the therapy can be continued”.

Moreover, ropeginterferon alfa-2b is contraindicated in patients with pre-existing thyroid disease, unless it can be controlled with conventional treatment (SmPC section 4.3).

Neuropsychiatric adverse effects (previously classified as important identified risk)

Reasons for removal from the list of safety concerns

Mentioned in the SmPC Section 4.8, Undesirable effects:
"depression, aggression, insomnia, anxiety, mood altered, mood swings, listless" (frequency common)
"suicide attempt, suicidal ideation, confusional state, acute stress disorder, hallucination, emotional distress, nervousness, apathy, nightmare, irritability" (frequency uncommon)
"bipolar disorder, mania" (frequency rare)

Description of selected adverse reactions:
"In the clinical development program of ropeginterferon alfa-2b, two cases of serious depression (1.1%; incidence rate: 0.4 events/100 patients per year) occurred. The patients recovered completely after permanent medicinal product discontinuation. One patient who experienced serious acute stress disorder (0.6%; incidence rate: 0.2 events/100 patients per year) with moderate intensity recovered completely after the dose of ropeginterferon alfa-2b was reduced. CNS effects including suicide attempt, suicidal ideation, aggression, bipolar disorder, mania and confusion have been reported with interferon alfa (see section 4.4)".

And in SmPC Section 4.4, Special warnings and precautions for use:
"CNS effects, particularly depression, have been observed in some patients treated with ropeginterferon alfa-2b during the clinical development program (see section 4.8). Other CNS effects, including suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion have been observed with other interferon alfa medicinal products. Patients should be closely monitored for any symptoms of psychiatric disorders and therapeutic management should be considered by the treating physician if such symptoms emerge. If psychiatric symptoms worsen, it is recommended to discontinue ropeginterferon alfa-2b therapy. Ropeginterferon alfa-2b must not be administered in patients with existence of or history of severe psychiatric disorders, particularly severe depression, suicidal ideation or suicide attempt (see section 4.3)".

Recommendations that patients who experience dizziness, somnolence or hallucinations during therapy with Besremi must not drive or use machines is included in SmPC section 4.7.

Moreover, ropeginterferon alfa-2b is contra-indicated in patients with existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation or suicide attempt (SmPC section 4.3).

Ocular disorders, including decreased visual acuity, blindness, and retinal detachment (previously classified as important identified risk)

Reasons for removal from the list of safety concerns

Mentioned in the SmPC Section 4.8, Undesirable effects:
"dry eye" (frequency common)
"retinal haemorrhage, retinal exudates, visual impairment, visual acuity reduced, vision blurred, ocular discomfort, eczema eyelids" (frequency uncommon)
"retinopathy, optic neuropathy, retinal artery occlusion#, retinal vein occlusion" (frequency rare)
"blindness" (frequency very rare)
"retinal detachment" (frequency not known)

Description of selected adverse reactions:
"Visual system: Serious eye disorders have been reported with interferon alfa such as retinopathy, retinal haemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion (see section 4.4)"

And in SmPC Section 4.4, Special warnings and precautions for use:
"Severe eye disorders such as retinopathy, retinal haemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion which may result in blindness have been observed rarely in patients treated with interferon alfa (see section 4.8). Patients should have eye examinations before and during ropeginterferon alfa-2b therapy, specifically in those patients with retinopathy associated disease such as

diabetes mellitus or hypertension. Any patient reporting a decrease or loss of vision or reporting other eye symptoms should have an immediate eye examination. Discontinuation of ropeginterferon alfa-2b should be considered in patients who develop new or worsening eye disorders".

Cardiac events including cardiomyopathy, myocardial infarction, myocardial ischaemia (previously classified as important identified risk)

Reasons for removal from the list of safety concerns

Mentioned in the SmPC Section 4.8, Undesirable effects:
"atrial fibrillation" (frequency common)
"myocardial infarction, atrioventricular block, intracardiac thrombus, aortic valve incompetence, cardiovascular disorder" (frequency uncommon)
"cardiomyopathy, angina pectoris" (frequency rare)
"myocardial ischemia" (frequency very rare)

Description of selected adverse reactions:
"Cardiovascular system: During ropeginterferon alfa-2b therapy, three cases of atrial fibrillation (1.1%; incidence rate: 0.5 events/100 patients per year) with intensity grade 1 to 3 occurred in two patients. Ropeginterferon alfa-2b treatment was continued and the patients received appropriate medicinal products to treat these events. Patients recovered from the two events; one event was ongoing at the time of assessment"

And in SmPC Section 4.4, Special warnings and precautions for use:
"Cardiac events including cardiomyopathy, myocardial infarction, atrial fibrillation and ischaemic coronary artery disorders have been associated with interferon alfa treatment (see section 4.8). Patients with pre-existing or a history of cardiovascular disorders should be closely monitored during ropeginterferon alfa-2b therapy. This medicinal product is contraindicated in patients with severe pre-existing cardiovascular disease or patients who had recently suffered from a stroke or myocardial infarction (see section 4.3)".

Moreover, ropeginterferon alfa-2b is contra-indicated in patients severe pre-existing cardiovascular disease, (i.e. uncontrolled hypertension, congestive heart failure (≥ NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction (SmPC section 4.3)

Pulmonary disorders including pulmonary fibrosis, lung infiltration, pneumonitis, pneumonia (previously classified as important identified risk) and pulmonary arterial hypertension (previously classified as important potential risk)

Reasons for removal from the list of safety concerns

Mentioned in the SmPC Section 4.8, Undesirable effects:
"dyspnoea" (frequency common)
"pneumonitis, cough, epistaxis, throat irritation" (frequency uncommon)
"lung infiltration" (frequency very rare)
"pulmonary fibrosis, pneumonia, pulmonary arterial hypertension" (frequency not known)

Description of selected adverse reactions:
"Respiratory system: Cases of pulmonary arterial hypertension (PAH) have been reported with interferon alfa, notably in patients with risk factors for PAH (such as portal hypertension, HIV infection, cirrhosis). Events were reported at various time points typically several months after starting treatment with interferon alfa".

And in SmPC Section 4.4, Special warnings and precautions for use: "Respiratory disorders such as lung infiltration, pneumonitis, pneumonia or pulmonary arterial hypertension have been observed rarely in

patients treated with interferon alfa (see section 4.8). Patients who develop respiratory symptoms should be monitored closely and if necessary, ropeginterferon alfa-2b therapy should be discontinued".

Diabetes mellitus (previously classified as important identified risk)

Reasons for removal from the list of safety concerns

Mentioned in the SmPC Section 4.8, Undesirable effects:
"diabetes mellitus" (frequency uncommon)

and in SmPC Section 4.4, Special warnings and precautions for use:
"Diabetes mellitus have been observed with other interferon alfa medicinal products (see section 4.8). Patients with this condition who cannot be effectively controlled by medicinal products should not begin ropeginterferon alfa-2b therapy. Patients who develop this condition during treatment and cannot be controlled by medicinal products should discontinue ropeginterferon alfa-2b therapy".

Reproductive toxicity / spontaneous abortions (previously classified as important potential risk)

Reasons for removal from the list of safety concerns

Section 4.6 of the SmPC states:
"Women of childbearing potential must use effective contraception during the treatment with ropeginterferon alfa-2b, unless otherwise discussed with the physician";
"there are no or limited amount of data from the use of interferon alfa in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). As ropeginterferon alfa-2b may have the same effect, Besremi is not recommended during pregnancy and in women of childbearing potential not using contraception".

Section 5.3 of the SmPC states:
"Reproductive and developmental studies were not performed with ropeginterferon alfa-2b. Interferon alfa was shown to be abortifacient in primates and ropeginterferon alfa-2b is expected to have a similar effect. Effects on fertility was not assessed"

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified risk 1: Hepatotoxicity

Potential mechanisms:

The mechanisms underlying these effects observed during treatment with IFNα remain unclear (Tovey *et al.*, 2010)[32].

Evidence source(s) and strength of evidence:

Hepatotoxicity has been identified as a risk associated with IFN alfa use. Hepatotoxicity such as increase in gamma-glutamyl transferase, alanine aminotransferase and aspartate aminotransferase or hepatic failure was reported with IFNα treatment.

Characterisation of the risk:

1) *Clinical studies*

Continuation-PV Study

(source: Clinical Study Report on the Longitudinal Evaluation of AOP2014 in Comparison to a Control Group (Standard First Line Treatment) through 72 Months of Treatment, dated 22 December 2021, Version 1.0):

AEs (by PT) that were related to AOP2014 (investigational product AOP2014, now marketed as BESREMi®), with a frequency > 10% in the AOP2014 treatment arm (involving 127 patients):

- Increased gamma-glutamyl transferase (57 events in 16/127 [12.6%] patients);
- increased alanine aminotransferase (30 events in 14/127 [11.0%] patients);

Severe ADRs were: 13 events of increased gamma glutamyl transferase [in 7/127 patients], 8 events of increased alanine aminotransferase [in 5/95 patients], 3 events of increased aspartate aminotransferase [in 2/127 patients] and one event of increased hepatic enzyme. Additionally, 1 AE assessed as related to AOP2014 was classified as life threatening (PT: increased gamma-glutamyl transferase). No AOP2014-related hepatic AEs had a fatal outcome.

Dose reduction in the AOP2014 treatment arm due to increased gamma-glutamyl transferase was required in 8 patients (14 events in 8/127 [6.3%] patients).

Dose interruption in the AOP2014 arm due to increased gamma-glutamyl transferase was required in 5 patients (10 events in 5/127 [3.9%] patients).

One (0.8%) patient in the AOP2014 arm discontinued the study due to events alanine amino transferase increased and aspartate aminotransferase increased; both were considered as related to study drug.

Phase I/II: PEGINVERA Study (n=51)

Seventeen (17) ADRs associated with hepatic dysfunction/hepatotoxicity were observed: 1 ADR of *Hepatotoxicity,* 8 ADRs of *Transaminases increased* (n=4)*,* 2 ADRs of *ALT increased* (n=2)*,* 2 ADRs of *AST increased* (n=2)*,* 4 ADRs of *GGT increased (n=4).* The majority of ADRs were of Grade 1 and Grade 2 intensity with recovery as outcome. One patient experienced *Transaminases increased* as Grade 2. The event was assessed as SAE due to hospitalization. The study drug dose was reduced but the patient did not recover from the event.

BosuPeg clinical trial (EudraCT number: 2018-001044-54 NCT03831776): A Study of Efficacy and Safety of Long-acting Low Dose ropeginterferon alfa-2b in Patients With Chronic Myeloid Leukemia Treated With Bosutinib From Diagnosis: a Randomized Prospective Trial

(source: safety report BosuPeg for Safety Committee and ANSM, interim analysis, dated Feb2022)

The combination patients (Bosutinib +PegIFN therapy) had mild and reversible transaminitis. Attributability was difficult to distinctly assign as several of the patients also experienced mild transaminitis during Bosutinib treatment before randomization. In some cases of transaminitis on combination therapy, mild ALAT elevations attributable to ropeginterferon alfa-2b were observed, sometimes subsiding, sometimes causing discontinuation. The addition of ropeginterferon alfa-2b appeared safe and manageable. Liver toxicity did not significantly hamper the Bosutinib + ropeginterferon alfa-2b therapy in the patients eligible for randomization.

2) Post-marketing

Hepatotoxicity has been reported with marketed interferon alfa preparations such as PegIFN alfa-2a.

Post-marketing data up to 14-Feb-2022:

Two (2) serious cases and 30 non serious cases were associated with hepatic dysfunction/hepatotoxicity, a total of 38 ADRs were reported: Alanine aminotransferase increased (8), Aspartate aminotransferase increased (7), Bilirubin conjugated increased (1); Gamma-glutamyltransferase increased (11); Hepatic enzyme increased (6); Hepatic steatosis (1); Hepatomegaly (1); Hepatotoxicity (2); Transaminases increased (1)

3) *Literature data*

In a pooled analysis of 1,300 patients with several oncologic diseases treated with IFN alfa, elevations in ALT were observed in 77%, AP in 48% and bilirubin in 31% of cases. These conditions were rarely severe or dose limiting, generally did not require dose attenuation and no cases of hepatitis were observed (Jones *et al.*, 1986)[13]. Mild elevations in hepatic enzymes without clinical symptoms were common in patients who are treated with IFN alfa-2b (Hauschild *et al.*, 2008)[11].

IFN has been demonstrated to trigger and exacerbate autoimmune hepatitis (AIH) when used to treat chronic HCV infection in a non-transplant setting. HCV itself has a strong association with autoimmune disease independent of exposure to IFN. The prevalence of antinuclear antibodies in patients with chronic HCV was 14% prior to IFN treatment and then increased to 35% following treatment in one study. This evidence suggests a synergistic effect of HCV and IFN in triggering autoimmunity (Kontorinis *et al.*, 2006)[17].

Experience with PegIFN (or IFN) plus ribavirin in the treatment of patients with compensated cirrhosis has shown a higher rate of treatment-related adverse effects than with patients who do not have cirrhosis. With the use of IFN-based therapies, treatment of decompensated cirrhosis has been problematic due to potential severe treatment-related adverse effects, such as development of anaemia, neutropenia, thrombocytopenia, severe infections, bleeding, renal insufficiency, and hepatic decompensation. Among these potential serious adverse effects, the development of hepatic decompensation is the most important and is associated with a high mortality (Jones *et al.*, 1986)[13].

Risk factors and risk groups:

Determination of drug induced liver injury includes an individual susceptibility. This susceptibility is governed by genetic, pre-existing and environmental factors. Predisposing factors are generally thought to be important to somehow explain the unpredictability of the phenomena through which substances turn into hepatotoxins, and consist of ethnic and racial factors, CYP polymorphisms, concomitant liver diseases, age, nutritional status and diet, gender and pregnancy (Tarantino *et al.*, 2009)[27].

Preventability:

Liver enzymes and hepatic function should be regularly controlled in patients with long-term ropeginterferon alfa-2b therapy. In patients who develop evidence of hepatic decompensation during treatment, ropeginterferon alfa-2b should be discontinued. Ropeginterferon alfa-2b is contraindicated in patients with severe hepatic impairment or in patients with decompensated cirrhosis.

Impact on the risk-benefit balance of the product:

Hepatotoxicity has been identified as an important risk due to its clinically significant impact on patient's daily life activities and quality of life.

Public health impact:

The potential impact in public health is expected to be low, providing that precautions and risk factors are taken into account.

SVII.3.2 Presentation of the important potential risks

Important potential risk 1: Thrombotic microangiopathy

Potential mechanisms:

IFNα has been shown to increase leukocyte adhesion to endothelial cells. This triggers endothelial damage and release of large multimers of von Willebrand factor causing endothelial swelling, platelet aggregation and intraluminal microthrombi formation. Activated leukocytes and/or their products such as TNF, IFN, IL-1 and free radicals are implicated in causing tissue injury (Kundra et al., 2017).

Evidence source(s) and strength of evidence:

TMA has been identified as a potential risk due to its potentially life-threatening complications in the context of serious organ damage. Because of the rarity of this disorder and the non-specific clinical and laboratory features, the diagnosis (and its underlying causes) can be easily overlooked or missed, leading to morbidity and/or mortality.

Characterisation of the risk:

Clinical studies

No ADRs of TMA were reported in the phase III study program (Proud-PV + Pen-PV + Continuation-PV Study).

Four (4) ADRs of *Microangiopathy* occurred in 2 patients in the Peginvera Study. The ADRs were of Grade 1 to Grade 2 intensity with recovery as outcome.

Post-marketing

TMA has been reported with marketed IFNα preparations.

Literature data

Case reports have linked TMA to both IFNα and IFNß therapies. Type I IFN therapies caused a direct dose-dependent TMA and the IFN protein itself could directly damage small blood vessels (Kavanagh et al., 2016).

A systematic review of the literature showed that TMA has been reported as a complication of every subtype of recombinant type I IFN in clinical use; IFNα-2a, IFNα-2b, IFNß-1a and IFNß-1b. These subtypes exert an almost identical effect on endothelial cells. TMA with IFNα and IFNß therapy display a similar clinical phenotype. In particular, both are associated with prolonged exposure to high doses of IFN, with chronic changes observed i.e. panendothelial disease with prominent renal, cerebral and cardiac involvement which may evolve over months. Some patients on IFNα therapy, TMA can occasionally present with a broader phenotype more suggestive of thrombotic thrombocytopenic purpura (TTP), in particular patients with underlying haematological malignancies (Kavanagh et al., 2016).

Risk factors and risk groups:

Patients with deficiency of ADAMTS13 are at risk of developing TMA. Secondary TMAs develop in the setting of various clinical conditions, such as infection, medication, malignancy (especially adenocarcinomas) and various underlying diseases. For instance, acquired TMAs are often associated with connective tissue diseases, and also treatment using several specific drugs. A significant number of drugs have been associated with TMAs, including anti-platelet thienopyridine derivative drugs, antineoplastic drugs such as mitomycin C, and quinine (Fujimura et al., 2010).

Preventability:

Patients on IFN therapy should be closely monitored for signs and symptoms of TMA. If necessary, ropeginterferon alfa-2b therapy should be discontinued.

Impact on the risk-benefit balance of the product:

TMA has been considered as potential risk due to its potentially life-threatening complications in the context of serious organ damage. Because of the rarity of these disorders and the nonspecific clinical and laboratory features, this diagnosis (and its underlying causes) can be easily overlooked or missed leading to morbidity and/or mortality.

Public health impact:

The potential impact in public health is expected to be low with appropriate awareness of the possibility of TMA during treatment with IFN and corresponding clinical management.

Important potential risk 2: Neoplasms, benign and malignant

Potential mechanisms:

Potential mechanism is unknown.

Evidence source(s) and strength of evidence:

Neoplasms, benign and malignant, is a potential risk associated with IFNα use. Cases of neoplasms such as glioblastoma and basal cell carcinoma were reported with IFNα treatment. However, a causal relationship could not be determined between these events and the IFNα treatment.

Characterisation of the risk:

Clinical studies

No ADRs of *Neoplasms, benign and malignant* were reported in the phase III study program (Proud-PV + Pen-PV + Continuation-PV Study) and in the phase I/II PEGINVERA Study.

Post-marketing

Neoplasms, benign and malignant, has been reported with marketed IFNα preparations such as pegIFN alfa-2a.

Literature data

-

Risk factors and risk groups:

Many reviews and textbooks describe the risk factors for cancer including family history and genetic predisposition, chronic inflammation, radiation, sunlight, tobacco use, exposure to cancer-causing substances, immunosuppression, etc.

Preventability:

Patients should be monitored for the occurrence of neoplasm during treatment with IFN to ensure early diagnosis and corresponding clinical management.

Impact on the risk-benefit balance of the product:

Neoplasms, benign and malignant have been identified as a potential risk due to its clinically significant consequences to the patient as well as life expectancy in case of malignant neoplasms with disease progression.

Public health impact:

The potential impact in public health is expected to be low with close surveillance for the occurrence of neoplasm during and after treatment with IFN, early diagnosis and adequate clinical management.

Important potential risk 3: Demyelinating disorders

Potential mechanisms:

It remains unknown whether IFNα itself can trigger the development of demyelinating disorders. The possible mechanisms suggest autoimmune phenomenona such as T cell mediated tissue damage which might be initiated or aggravated by IFN therapy (Fazil et al., 2015).

Evidence source(s) and strength of evidence:

Demyelinating disorders is a potential risk associated with IFNα use. Cases of demyelinating disorders in patients with hepatitis C or hepatitis B infection and chronic myelogenous leukemia were reported during INFα treatment.

Characterisation of the risk:

Clinical studies

No ADRs of demyelinating disorders were reported in the phase III study program (Proud-PV + Pen-PV + Continuation-PV Study).

One (1) ADR of *Peripheral motor neuropathy* with moderate intensity was reported in a patient in the Peginvera Study. The study drug dose was not changed and the outcome was recovery.

Post-marketing

Demyelinating disorders have been reported with marketed IFNα preparations.

Literature data

Demyelinating disorders associated with IFN therapy have been reported in literature and include chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), acute demyelinating polyneuropathy (AIDP) with atypical features for Guillain-Barre syndrome (GBS), typical GBS, multiple sclerosis like condition.

Kataoka et al., 2002 reported a chronic myelogenous leukemia (CML) patient in chronic phase who developed multiple sclerosis (MS) in association with IFNα-2b administration. The IFNα-2b therapy induced hematologically complete and cytogenetically major partial response for CML first, however sequential CNS dysfunction evolved, which subsided shortly after the cessation of administration. Myeloablative therapy led to lasting stable state of MS and finally to complete cytogenetic remission of CML. This patient's presenting clinical course and laboratory data suggested that both exertion of anti-leukemic activity and autoimmune process of MS might have been mediated by mutual mechanisms, such as enhancement of specific cellular immunity induced by IFNα.

Boz et al., 2004 described a patient who developed AIDP on the sixth week of IFNα therapy for HBV infection. Clinical findings, electrodiagnostic studies and elevated cerebrospinal fluid protein levels without cells supported the diagnosis of GBS. Other potential causes of GBS were ruled out.

Höftberger et al., 2007 described a patient with chronic HCV infection who developed acute MS-like demyelinating disease after IFNα administration. The patient died after a disease duration of 6 months.

Authors suggested that development of fulminant demyelinating disease after administration of IFNα had been associated with an autoimmune response via T cell mediated tissue damage initiated or aggravated by IFNα therapy. Additionally, the presence of HCV RNA within the demyelinated lesion indicated a possible role in triggering or propagating disease.

Niazi et al., 2010 reported a case of GBS associated with PegIFNα-2a and ribavirin used for treatment of CHC infection.

Fazil et al., 2015 described a MS like condition in a HCV infected patient associated with IFNα treatment.

Naito et al., 2016 reported a case of CIDP resulting after treatment with PegIFNα-2a. Neurological symptoms were prolonged despite suspension of the treatment. Subsequent treatment with intravenous immunoglobulin improved both clinical symptoms and temporal dispersion.

Risk factors and risk groups:

Infection and (auto)immune mechanisms are likely to contribute to the pathogenesis of demyelinating disorders (Reeves et al., 2008).

Preventability:

Patients with IFN therapy should be closely monitored for any signs or symptoms of demyelinating disease.

Impact on the risk-benefit balance of the product:

Demyelinating disorders have been identified as a potential risk due to its clinically significant consequences to the patient. Depending on the type of demyelinating disorder and affected areas of the central or peripheral nervous system, patients may be significantly restricted in their daily life activities (temporal or permanent disability/incapacity of the patient). Moreover, life-threatening consequences might evolve in the most dramatic cases.

Public health impact:

The potential impact in public health is expected to be low, taking into consideration that only isolated cases were observed.

SVII.3.3 Presentation of the missing information

No missing information is included into the list of safety concerns.

Module SVIII - Summary of the safety concerns

SVIII Table 8: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hepatotoxicity
Important potential risks	• Thrombotic microangiopathy • Neoplasms, benign and malignant • Demyelinating disorders
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

The Marketing Authorisation Holder (MAH) has a pharmacovigilance system at its disposal, which is based on the current European legislation. Routine pharmacovigilance activities are considered sufficient to monitor the safety profile of the product. Detailed information on the pharmacovigilance system is available in the current Pharmacovigilance Master File (PSMF).

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities are proposed.

III.2 Additional pharmacovigilance activities

Non-interventional Post-authorisation Safety Study (Category 3): Besremi-PASS

Study short name and title: Besremi-PASS. A Prospective, Multicentre, Non-interventional, Observational, Post-authorisation Safety Study of ropeginterferon alfa-2b in Polycythaemia Vera Patients.

Rationale and study 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.

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.

Study population: 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.

Milestones:

Milestone	Planned date
Study protocol	25 April 2019 (actual)
Start of data collection (first patient in)	17 December 2019 (actual)
Recruitment completed (last patient in)	06 June 2023 (actual)
Interim report	Q3 2025
End of data collection (last patient out)	Q1 2025
Final report of study results	Q1 2026

The final agreed protocol (link) is provided in Annex 3 – part C.

III.3 Summary Table of additional Pharmacovigilance activities

III.3 Table 9: On-going and planned additional pharmacovigilance activities

Study Status	Objective	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Besremi-PASS Ongoing	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	Hepatotoxicity	Study protocol Patient enrolment: First patient in Last patient in Last patient out Study report: Interim report Final report	25 April 2019 17 Dec 2019 06 Jun 2023 Q1 2025 Q3 2025 Q1 2026

Study Status	Objective	Safety concerns addressed	Milestones	Due dates
	cardiovascular risk factors, with/without pre-existing cardiovascular disease).			

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

Routine pharmacovigilance activities are considered sufficient to monitor the safety profile of the product.

V.1. Routine Risk Minimisation Measures

V.1 Table 10: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk: Hepatotoxicity	Routine risk communication: • SmPC section 4.2, 4.3, 4.4, 4.8, 5.2 • PL section 2, 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning that ropeginterferon alfa-2b is contra-indicated in patients with decompensated cirrhosis (i.e. Child Pugh B or C) and that the pharmacokinetics was not evaluated in patients with increased severity of hepatic impairment is included in SmPC sections 4.2, 4.3, 4.4, 5.2 and in PL section 2. • Recommendations to monitor regularly the liver enzymes and hepatic function in patients on long-term therapy with ropeginterferon alfa-2b SmPC section are included in SmPC section 4.4 and in PL section 2. Recommendations to reduce the dose of ropeginterferon alfa-2b in case the increase in liver enzyme levels is progressive and persistent or to discontinue treatment with ropeginterferon alfa-2b if the increase in liver enzymes is progressive and clinically significant despite dose reduction, or if there is evidence of hepatic decompensation are included in SmPC sections 4.2, 4.4. Other routine risk minimisation measures beyond the Product Information: • Legal status: Prescription only medicine (POM)
Important potential risk: Thrombotic microangiopathy	Routine risk communication: • SmPC section 4.8 • PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine (POM)
Important potential risk: Neoplasms, benign and malignant	Routine risk communication: • SmPC section 4.5 PL section 2Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine (POM)
Important potential risk: Demyelinating disorders	Routine risk communication: • SmPC section 4.8

	• PL section 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine (POM)

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

V.3 Table 11: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Hepatotoxicity	Routine risk minimisation measures: • SmPC sections 4.2, 4.3, 4.4, 4.8, 5.2 • PL sections 2, 4 • Legal status: Prescription only medicine (POM) Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Besremi-PASS
Important potential risk: Thrombotic microangiopathy	Routine risk minimisation measures: • SmPC section 4.8 • PL sections 4 • Legal status: Prescription only medicine (POM) Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important potential risk: Neoplasms, benign and malignant	Routine risk minimisation measures: • SmPC section 4.5 • PL section 2Legal status: Prescription only medicine (POM) Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important potential risk: Demyelinating disorders	Routine risk minimisation measures: • SmPC section 4.8 • PL sections 4 • Legal status: Prescription only medicine (POM) Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Part VI: Summary of the risk management plan

Summary of risk management plan for Besremi® (ropeginterferon alfa-2b)

This is a summary of the risk management plan (RMP) for Besremi®. The RMP details important risks of Besremi®, how these risks can be minimised, and how more information will be obtained about Besremi®'s risks and uncertainties (missing information).

Besremi®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Besremi® should be used.

This summary of the RMP for Besremi® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Besremi®'s RMP.

I. The medicine and what it is used for

Besremi® is authorised for treatment of Polycythaemia Vera without symptomatic splenomegaly (see SmPC for the full indication). It contains Pegylated-Proline-Interferon alfa-2b as the active substance and it is given subcutaneously by pre-filled pen with 250 µg or 500 µg ropeginterferon alfa-2b.

Further information about the evaluation of Besremi®'s benefits can be found in Besremi®'s EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/Besremi®.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Besremi®, together with measures to minimise such risks for learning more about Besremi®'s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Besremi® is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Besremi® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Besremi®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Hepatotoxicity
Important potential risks	• Thrombotic microangiopathy • Neoplasms, benign and malignant • Demyelinating disorders
Missing information	• None

II.B Summary of important risks

Important identified risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Hepatotoxicity has been identified as a risk associated with IFN alfa use. Hepatotoxicity such as increase in gamma-glutamyl transferase, alanine aminotransferase and aspartate aminotransferase or hepatic failure was reported with IFN alfa treatment.
Risk factors and risk groups	Determination of drug induced liver injury includes an individual susceptibility. This susceptibility is governed by genetic, pre-existing and environmental factors. Predisposing factors consist of ethnicity, CYP polymorphisms, concomitant liver diseases, age, nutritional status and diet, gender and pregnancy (Tarantino *et al.*, 2009)[27].
Risk minimisation measures	Routine risk minimisation measures: • SmPC sections 4.2, 4.3, 4.4, 4.8, 5.2 • PL sections 2, 4 • Legal status: Prescription only medicine (POM) Additional risk minimisation measures: • None
Important potential risk: Thrombotic microangiopathy	
Evidence for linking the risk to the medicine	Thrombotic microangiopathy (TMA) is a potential risk associated with IFNα use. Case reports have linked TMA to IFNα treatment. Type I IFN therapies caused direct dose-dependent TMA and the IFN protein itself could directly damage small blood vessels.
Risk factors and risk groups	Patients with deficiency of ADAMTS13 are at risk of developing TMA. Secondary TMAs develop in the setting of various clinical conditions, such as infection, medication, malignancy (especially adenocarcinomas) and various underlying diseases. For instance, acquired TMAs are often associated with connective tissue diseases, and also treatment using several specific drugs. A significant number of drugs have been associated with TMAs, including anti-platelet thienopyridine derivative drugs, antineoplastic drugs such as mitomycin C, and quinine (Fujimura et al., 2010).
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.8 • PL sections 4 • Legal status: Prescription only medicine (POM)

	Additional risk minimisation measures: • None
Important potential risk: Neoplasms, benign and malignant	
Evidence for linking the risk to the medicine	Neoplasms, benign and malignant, is a potential risk associated with IFNα use. Cases of neoplasms such as glioblastoma and basal cell carcinoma were reported with IFNα treatment. However, a causal relationship could not be determined between these events and the IFNα treatment.
Risk factors and risk groups	Cancer in the family history, genetic predisposition, chronic inflammation, radiation, sunlight, tobacco use, exposure to cancer-causing substances, immunosuppression are risk factors.
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.5 • PL section 2 • Legal status: Prescription only medicine (POM) Additional risk minimisation measures: • None
Important potential risk: Demyelinating disorders	
Evidence for linking the risk to the medicine	Demyelinating disorders is a potential risk associated with IFNα use. Cases of demyelinating disorders in patients with hepatitis C or hepatitis B infection and chronic myelogenous leukemia were reported during INFα treatment.
Risk factors and risk groups	Infection and (auto) immune mechanisms are likely to contribute to the pathogenesis of demyelinating disorders (Reeves et al., 2008).
Risk minimisation measures	Routine risk minimisation measures: • SmPC section 4.8 • PL sections 4 • Legal status: Prescription only medicine (POM) Additional risk minimisation measures: • None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Besremi®.

II.C.2 Other studies in post-authorisation development plan

Non-interventional Post-authorisation Safety Study: Besremi-PASS

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.

Part VII : Annexes

Annex 1– EudraVigilance Interface

Annex 2– Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex II Table 12: Planned and on-going studies

Study	Summary of objectives	Safety concerns addressed	Milestones
Besremi-PASS Category 3 Ongoing	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).	Hepatotoxicity	Study protocol 25 April 2019 Patient enrolment First patient in 17 Dec 2019 Last patient in 06 Jun 2023 Study end Last patient out Q1 2025 Study report Interim report: Q3 2025 Final report: Q1 2026

Annex 3 – Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

Part A: Requested protocols of studies in the pharmacovigilance plan, submitted for regulatory review with this updated version of the RMP

Not applicable.

Part B: Requested amendments of previously approved protocols of studies in the pharmacovigilance plan, submitted for regulatory review with this updated version of the RMP

Not applicable.

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

Procedure: EMEA/H/C/004128/MEA/001.3

Date of outcome: 17 September 2020 (date of CHMP adoption)

Protocol link: *https://www.encepp.eu/encepp/openAttachment/fullProtocolLatest/37462*

Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable.

Annex 5 – Protocols for proposed and on-going studies in RMP part IV

Not applicable.

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 – Other supporting data (including referenced material)

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Annex 8 – Summary of changes to the risk management plan over time

Version	Approval date Procedure	Change
1.0	12-Dec-2018 EMEA/H/C/004128/0000	New document.
1.1	Not approved CP EMEA/H/C/004128/0000	- Update of Besremi PASS timelines (as requested by PRAC) - Addition of the final results of CONTINUATION-PV trial - The proposal to remove six important identified risks (thyroid dysfunction; neuropsychiatric adverse effects; ocular disorders, including decreased visual acuity, loss of vision, blindness, and retinal detachment; cardiac events including cardiomyopathy, myocardial, infarction, myocardial ischaemia; pulmonary disorders including pulmonary fibrosis, lung infiltration, pneumonitis and pneumonia; diabetes mellitus) and five important potential risks (pulmonary arterial hypertension; reproductive toxicity/spontaneous abortions; thrombotic microangiopathy; neoplasms, benign and malignant; demyelinating disorders) in line with GVP V rev. 2
1.2	Not approved CP EMEA/H/C/004128/0000	Address the comments from the Procedure No. EMEA/H/C/004128/II/0025): - The ATC Code was updated to "L03AB15" in line with the information available for ropeginterferon alfa-2b in https://www.whocc.no/atc_ddd_index/?code=L03AB15 (Last updated: 2021-12-14) and in line with Besremi's SmPC section 5.1 - The "Pharmaceutical form" was updated to "Solution for injection in pre-filled pen (injection)" in line with section 3 of the SmPC - The references to the national procedures of Switzerland and Israel were deleted from the EU-RMP. - Correction the typos in AEs calculation for important identified risk "Hepatotoxicity" Revision of the texts as recommended by the assessor (criterion "Pregnant females", "Lactating females") Provision of additional information about the risks of thrombotic microangiopathy; neoplasms, benign and malignant; demyelinating disorders with the proposal to keep these safety concerns as important potential risks; update of the corresponding sections across the RMP - Updating the PASS study objectives with more detailed information - For the important identified risk "Hepatotoxicity", reintroduce all relevant sections of SmPC and PL under "Routine risk communication" in V.1 Table 10: Description of routine risk minimisation measures by safety concern, as made in table of section V.3 of the RMP
2.0	01-Dec-2022 CP EMEA/H/C/004128/0000	Comments from procedure EMEA/H/C/004128/II/0025 were addressed: - in Table Part I.1 – Product Overview: the updated "Pharmaceutical form" should be moved from the field "proposed" to "current", as it is only a correction of the current pharmaceutical form's description, keeping "Not applicable" in the "proposed" field. - all information regarding the 3 important potential risks, as included in the last approved RMP, should be kept (without any update), namely in section SVII.3.2 of the RMP.
2.0 corr	01-Dec-2022 CP EMEA/H/C/004128/0000	Information regarding the 3 important potential risks, as included in the last approved RMP, corrected in Part VI – section IIB.
3.0	Pending	Update of Besremi PASS timelines: Part III, Annex 2 was updated.

[redacted]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signatures.

Signatory Table

Action Name	User Name	Title	Signature Date
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

* Dates are displayed according to the system time zone: (GMT+02:00) Central European Summer Time (Europe/Vienna)