27 June 2024
EMA/326584/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pegasys

International non-proprietary name: Peginterferon alfa-2a

Procedure No. EMEA/H/C/000395/II/0119/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
AI	Autoimmune
ALT	Alanine aminotransferase
ANSM	Agence nationale de sécurité du médicament et des produits de santé
ASAT	Aspartate aminotransferase
BM	Bone marrow
BMR	Bone marrow response
CALR	Calreticulin
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
CHR	Complete haematologic response
CI	Confidence interval
CML	Chronic myeloid leukemia
CR(s)	Complete response(s)
CMR	Complete molecular response
DCs	Dendritic cells
DLP	Data lock point
DNA	Deoxyribonucleic acid
ELN	European LeukaemiaNet
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
ET	Essential thrombocythaemia
EU	European Union
FBC	Full blood count
GHS	Global health status
HCT	Haematocrit
HR	Haematological response
HU	Hydroxyurea
IBD	International birth date
ICC	International Consensus Classification
IFN(s)	Interferon(s)
IPSET	International prognostic score of thrombosis for ET
ITT	Intent-to-treat
IU	International unit(s)
JAK	Janus kinase
JAK2V617F	Single Mutation in the myeloproliferative group of disorders
MAH	Marketing authorization holder
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MPD-RC	Myeloproliferative Disorders Research Consortium
MPL	Myeloproliferative leukaemia protein
MPN(s)	Myeloproliferative neoplasm(s)
MPN-SAF	Myeloproliferative neoplasm symptom assessment form
MR(s)	Molecular response(s)
NCCN	National Comprehensive Cancer Network
NK	Natural killer

NR	No response
OHR	Overall haematological response
OMR	Overall molecular response
ORR	Overall response rate
PBRER	Periodic benefit-risk evaluation report
PEG	Pegylated, polyethylene glycol
Ph	Philadelphia chromosome
PHR	Partial haematological response
PMF	Primary myelofibrosis
PMR	Partial molecular response
PR	Partial response
PV	Polycythaemia vera
QoL	Quality of life
R/I	Refractory or intolerant
RMP	Risk management plan
SAE(s)	Serious adverse event(s)
SB	Symptom burden
S.c.	Subcutaneous(ly)
SMQ	Standardised MedDRA queries
STAT	Signal transducer and activator of transcription
TN	Treatment-naïve
TSS	Total symptom score
US	United States
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, pharmaand GmbH submitted to the European Medicines Agency on 31 October 2023 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Grouped application consisting of:
Extensions of indication to include treatment of Polycythaemia Vera (PV) and Essential thrombocytopenia (ET) for PEGASYS for the pre-filled syringes, based on published data of clinical studies conducted in support of the efficacy and safety of Pegasys for the treatment of ET and PV. As a consequence, sections 4.1, 4.2, 4.8 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.2 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.3.

The group of variations requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No. 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	31 October 2023
Start of procedure:	25 November 2023
CHMP Rapporteur Assessment Report	19 January 2024
PRAC Rapporteur Assessment Report	19 January 2024
PRAC Outcome	8 February 2024
CHMP members comments	12 February 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 February 2024
Request for supplementary information (RSI)	22 February 2024
MAH's responses submitted to the CHMP on:	22 March 2024
CHMP Rapporteur Assessment Report	26 April 2024
PRAC Rapporteur Assessment Report	26 April 2024
PRAC members comments	07 May 2024
Updated PRAC Rapporteur Assessment Report	08 May 2024
CHMP members comments	17 May 2024
Updated CHMP Rapporteur Assessment Report	23 May 2024
2nd request for supplementary information	30 May 2024
MAH's responses submitted to the CHMP on:	04 June 2024
Rapporteur's preliminary assessment report circulated on:	12 June 2024
Joint Rapporteur's updated assessment report circulated on:	20 June 2024
CHMP opinion:	27 June 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Diseases or conditions

Polycythaemia vera (PV) and Essential thrombocythaemia (ET) belong to a group of heterogeneous disorders of the haematopoietic system - so called myeloproliferative neoplasms (MPNs) - characterised by an overproduction of blood cells. A variety of abnormalities in cell counts is observed

depending on the type of MPN, including erythrocytosis, thrombocytosis, and leukocytosis. (Gerds et al., JNCCN 2022)

Central to the pathology of MPNs is a constitutively activated JAK/STAT signalling pathway, caused by various, mostly mutually exclusive driver mutations, such as JAK2-V617F, myeloproliferative leukaemia protein (MPL)-W515L/K, CALR exon 9 indels, or other less known mutations within the JAK/STAT signalling pathway.

Polycythaemia vera (PV)

PV characteristically displays trilineage (erythroid, megakaryocytic and granulocytic) proliferation in the bone marrow (BM) with predominantly erythrocytosis in the peripheral blood and commonly suppressed endogenous erythropoietin production. (Amerikanou et al., Best. Pract. Res. Cl. Ha. 2022)

Clinical features in PV include mild-to-moderate degree of splenomegaly, and of constitutional symptoms, including fatigue and pruritus, weight loss, night sweats, early satiety, bone pain, symptoms of hyperviscosity, leukocytosis, thrombocytosis, microvascular symptoms (e.g., headaches, lightheadedness, visual disturbances, atypical chest pain, erythromelalgia, paresthesia), thrombotic and bleeding complications, and risk of leukaemic transformation or fibrotic progression. (Gerds et al., JNCCN 2022, Tefferi et al., Blood Cancer Journal 2018b)

About one-third (36 %) of PV patients present with palpable splenomegaly, 14 % with significant constitutional symptoms, and 25 % with a history of thrombosis (15-16 % arterial and 8-13 % venous) or major haemorrhage (4 %). Pruritus is common in PV (48 %) and may be provoked by warm water ("aquagenic"). (Tefferi and Barbui, Am. J. Hematol. 2023)

In a retrospective study of 1545 adult patients (median age 61 years) with World Health Organization (WHO)-defined PV, conducted by the International Working Group for MPN Research and Treatment, thrombosis history at diagnosis was documented in 23 % of the patients (16 % arterial and 7.4 % venous events). The rate of post-diagnosis vascular events, after a median follow-up of 6.9 years, was 21 % (12 % arterial and 9 % venous events). Leukaemic transformation incidence ranges from 5.5-18.7 % over the course of 15 years. (Tefferi et al., Blood Cancer Journal 2018b)

Overall survival in PV exceeds 13 years and maybe as high as 37 years in younger patients (age <40 years). Variables associated with reduced survival in PV include advanced age, leukocytosis, abnormal karyotype, SRSF2 mutation, and treatment with pipobroman, chlorambucil or radioactive phosphorous. (Thiele et al., Am J Hematol. 2022) The major life-threatening complications in PV are leukaemic transformation, fibrotic progression and thrombosis. (Tefferi et al., Blood Cancer Journal 2018b)

Essential thrombocythaemia (ET)

ET belongs to the chronic MPNs characterised by the increase of mature haematopoietic cells. Although this disease has an increased risk of transformation to acute leukaemia and progression to myelofibrosis (MF), the major causes of morbidity and mortality in ET are cardiovascular complications. (How, Hobbs, 2022)

The hallmarks of ET are megakaryocyte hyperplasia with resultant thrombocytosis and abnormally high platelet production (Amerikanou et al., Best. Pract. Res. Cl. Ha. 2022, Bose and Verstovsek, Ther Adv Hematol 2019).

Clinical symptoms in ET include mild splenomegaly, leukocytosis, microvascular symptoms, thrombotic and bleeding complications, increased occurrence of first trimester miscarriage, and time-dependent risk of leukaemic transformation or fibrotic progression (Tefferi et al., Blood Cancer Journal 2018a).

Thrombotic complications occur in 10-20 % of ET patients with a predominance of arterial thrombotic events. For example, 109 (12 %) of 891 adult ET patients experienced arterial (n=79) or venous (n=37) thrombosis after a median follow-up of 6.2 years. (Tefferi et al., Blood Cancer Journal. 2018a, Tefferi, Barbui, Am. J. Hematol. 2020)

Leukaemic transformation incidence ranges from ~2.1-5.3 % over the course of 15 years for adult ET patients. (Tefferi et al., Blood Cancer Journal 2018a)

Median survival in ET has been reported to range from approximately 15-22 years. Age is by far the most important risk factor for survival in ET, with median survival of 35 years for patients age ≤40 years, 22 years for ages 41-60 years, and 11 years for ages >60 years. Besides age, the absolute neutrophil count, and the absolute lymphocyte count, abnormal karyotype and mutations in SF3B1, SRSF2, and TP53 might also be relevant risk factors. (Thiele et al., Am J Hematol. 2022)

Claimed therapeutic indications

The MAH proposed initially the following additional indications for the pre-filled syringes:

Polycythaemia vera (PV)

Pegasys is indicated as monotherapy in adult patients with PV who are resistant and/or intolerant to hydroxyurea.

Essential thrombocythaemia (ET)

Pegasys is indicated as monotherapy in adult patients with ET who are resistant and/or intolerant to hydroxyurea.

The MAH finally proposed the following indications:

Polycythaemia vera (PV)

Pegasys is indicated as monotherapy in adults for the treatment of polycythaemia vera.

Essential thrombocythaemia (ET)

Pegasys is indicated as monotherapy in adults for the treatment of essential thrombocythaemia.

The indications for the solution for injection are unchanged.

Epidemiology

PV

The overall incidence of PV in the EU is estimated to be 0.4-2.8 per 100,000 patients per year (Nurgat, Lawrence, J. Onc. Pharm. Pract 2022, Vannucchi et al., Annals of Oncology 2015). The incidence of PV increases with increasing age. Among patients diagnosed with PV, only 1 % present before the age of 25, and only 0.1 % are less than 20 years old (Cario et al., Ann Hematol. 2009, El-Sharkawy, Margolskee, Clin Lab Med 2021). The median age at PV diagnosis ranges from 61 to 65 years. (Shallis et al., Hematol Oncol Clin N Am 2021).

In 2021, the overall prevalence of PV in the EU was approximately 3 in 10,000 people. (EMADOC-628903358-3059).

ET

As mentioned before, for the discussion of the epidemiology of MPNs, one must consider the evolution of its classification and the piecemeal identification of related molecular drivers in 2005 that now serve as diagnostic criteria. These circumstances influence the accuracy of epidemiologic data regarding disease incidence, prevalence, and survival based on evaluations that have been conducted before 2005. (Shallis et al., Hematol Oncol Clin N Am 2021)

ET is a rare disease in adults with an annual incidence rate of 0.38-1.7 per 100,000 in the EU, while ET is exceptionally rare in childhood with a worldwide annual incidence ranging between 0.004 and 0.11 per 100,000 in children aged 0-16 years (Stockklausner et al., Annals of Hematology 2021, Titmarsh et al., Am J Hematol. 2014) or 0.6 per 100,000 in children and young people under the age of 20 (Putti et al., Cancers 2021).

The median age at ET diagnosis ranges from 54 to 73 years (Shallis et al., Hematol Oncol Clin N Am 2021).

In 2022, the overall prevalence of ET in the EU was approximately 3.4 in 10,000 people (EMA/COMP/772376/2022).

Clinical presentation, diagnosis

PV

According to the International Consensus Classification (ICC) (Arber et al., Blood 2022), PV diagnosis requires 3 major criteria or the first 2 major criteria plus the minor criterion (Figure 1).

Figure 1: 2022 ICC diagnostic criteria for PV.

Major criteria

1. hemoglobin >16.5 g/dL in men and >16 g/dL in women, or hematocrit >49% in men and >48% in women, or red cell mass >25% above mean normal predicted value
2. bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. presence of *JAK2*V617F or *JAK2* exon 12 mutation

Minor criterion

- serum erythropoietin level below the reference range for normal

*Diagnostic thresholds: hemoglobin: >16.5 g/dL in men and >16.0 g/dL in women; hematocrit: >49% in men and >48% in women; red blood cell mass: >25% above mean normal predicted value. †It is recommended to use highly sensitive assays for JAK2 V617F (sensitivity level <1%); in negative cases, consider searching for noncanonical or atypical JAK2 mutations in exons 12 to 15. ‡A bone marrow biopsy may not be required in patients with sustained absolute erythrocytosis (hemoglobin concentrations of >18.5 g/dL in men or >16.5 g/dL in women and hematocrit values of >55.5% in men or >49.5% in women) and the presence of a JAK2 V617F or JAK2 exon 12 mutation. (Arber et al., Blood 2022)

ET

ET diagnosis requires meeting all 4 major criteria according to the ICC classification (Arber et al., Blood 2022) or the first 3 major criteria plus the minor criteria. (Figure 2).

Figure 2: 2022 ICC diagnostic criteria for ET.

Major criteria

1. Platelet count $\geq 450 \times 10^9$/L
2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters*; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant BM fibrosis†
3. Diagnostic criteria for BCR::ABL1-positive CML, PV, PMF, or other myeloid neoplasms are not met
4. JAK2, CALR, or MPL mutation‡

Minor criteria

- Presence of a clonal marker§ or absence of evidence of reactive thrombocytosis‖

*Three or more megakaryocytes lying adjacent without other BM cells in between; in most of these rare clusters ≤6 megakaryocytes may be observed, increase in huge clusters (>6 cells) accompanied by granulocytic proliferation is a morphological hallmark of pre-PMF. †Very rarely a minor increase in reticulin fibers may occur at initial diagnosis (grade 1). ‡It is recommended to use highly sensitive assays for JAK2 V617F (sensitivity level <1%) and CALR and MPL (sensitivity level 1% to 3%); in negative cases, consider a search for noncanonical JAK2 and MPL mutations. §Assessed by cytogenetics or sensitive NGS techniques. ‖Reactive causes of thrombocytosis include a variety of underlying conditions like iron deficiency, chronic infection, chronic inflammatory disease, medication, neoplasia, or history of splenectomy. (Arber et al., Blood 2022)

If a somatic mutation indicative of myeloid malignancies or myeloproliferative disease is detected, BM examination including reticulin staining and cytogenetics will allow to confirm the diagnosis of MPN. As underlined by Tefferi et al., BM morphology is required to distinguish between ET and prefibotic-PMF. (Tefferi and Barbui, Am J Hematol 2019)

The International Prognostic Score of Thrombosis for ET (IPSET) identified 4 categories of risk on the basis of 3 adverse variables (history of thrombosis, age >60 and JAK2-V617F): very low (no adverse signs), low (presence of the JAK2-V617F mutation), intermediate (age >60) and high (history of thrombosis or presence of both advanced age and the JAK2-V617F mutation). (ANSM, PEGASYS Compassionate Prescribing Framework 2022, Haider et al., Am J Hematol 2016).

Management

PV

Current treatments in PV aim at reducing the risk of thrombosis and haemorrhage, and transformation to acute myeloid leukaemia and MF, and at the alleviation of symptoms. (How and Hobbs, JNCCN. 2022, Thiele et al., Am J Hematol. 2022)

To prevent thrombo-haemorrhagic complications, all patients require phlebotomies. Phlebotomy can be initiated as an emergency treatment at diagnosis in patients with very high HCT levels and clinical signs of hyperviscosity, and also as a longer-term maintenance treatment to keep HCT levels below 45 % to effectively reduce the risk of thrombotic events (Tefferi and Barbui, Am. J. Hematol 2023, Thiele et al., Am J Hematol. 2022, Tremblay, Mascarenhas, Curr Hematol Malig Rep 2020).

In addition, daily low dose aspirin (81-100 mg) is recommended for all PV patients, in the absence of contraindications. (Gerds et al., JNCCN 2021, Tefferi, Barbui, 2023, Thiele et al., Am J Hematol. 2022, Vannucchi et al., Annals of Oncology 2015)

Cytoreductive therapy is dictated by the individual risk for thrombosis, which considers 2 major risk factors: age >60 years and history of thrombosis. The presence of either one of these 2 risk factors defines high-risk for thrombosis and their absence low-risk. (Thiele et al., Am J Hematol. 2022)

First-line cytoreductive treatment in PV is HU-based therapy. The exact mechanism of action of HU is unknown, its most important effect appears to be in blocking the ribonucleotide reductase system resulting in the inhibition of deoxyribonucleic acid (DNA) synthesis.

Dosing depends on the clinical response and the effect on the full blood count (FBC); the recommended dose of HU is initially 15-20 mg/kg, adjusted according to response on HCT and platelet count; a usual daily dose being 500-1000 mg given orally.

PV patients treated with HU may develop resistance to the drug or intolerance. Symptoms of intolerance may also include gastrointestinal symptoms, pneumonitis, and fever at any dose of HU. (Nurgat, Lawrence, J. Onc. Pharm. Pract 2022) Additionally, skin ulcers, a reduction in blood cells, gastrointestinal problems, oral ulcers, stomatitis, hyperkeratosis, or actinic keratosis have been reported as symptoms of HU intolerance (Griesshammer et al., 2015).

HU presents a potential genotoxic risk that contraindicates conception during treatment for both, men and women. In addition, patients who have received or are receiving HU for long periods have developed secondary leukaemia, with no established link to HU treatment or the primary disease itself, or skin cancer. (SmPC Hydrea, 2021 and 2023) Consequently, younger patients, who may have had longer exposure to HU, potentially have an increased carcinogenic risk (Tremblay, Mascarenhas, 2020). Of note, although assumed in multiple publications, neither prospective nor well-designed retrospective studies in PV patients implicate HU as amplifying the intrinsic vulnerability of PV patients for leukaemic transformation (Tefferi, Barbui, Am. J. Hematol. 2023).

Another product, PEG-formulation of IFN-α (ropegIFN-α-2b, Besremi) is authorised as first-line monotherapy in adults for the treatment of PV without symptomatic splenomegaly since 2019. (EMA, 2022a)

In second-line treatment, ruxolitinib is indicated in cases of resistance or intolerance to HU at a dose of 10 mg given orally twice daily. Animal studies have shown that ruxolitinib is embryotoxic and foetotoxic. (EMA, 2023). In a large international nested case-control study including 1881 patients with MPNs, a significantly higher risk of non-melanoma-skin cancer was documented for ruxolitinib (OR = 3.87, 95% CI 1.18-12.75) (Barbui et al., Am. J. Hematol. 2019).

ET

The main goal of current treatments in ET, similar to PV, is to reduce the risk of thrombosis and haemorrhage, and transformation to acute myeloid leukaemia and MF, as well as at the alleviation of symptoms (How, Hobbs, 2022).

A risk-adapted therapy in ET patients is based on the likelihood of patients developing thrombotic complications. These complications are the leading cause of morbidity and mortality in ET patients. (Vannucchi et al., Annals of Oncology 2015)

Very low risk ET (age ≤60 years, no thrombosis history) might not require treatment while low-dose aspirin (81-100 mg) therapy is advised for low-risk disease, in the absence of contraindications. (Gerds et al., 2021, Thiele et al., Am J Hematol. 2022)

Cytoreductive therapy is dictated by individual risk for thrombosis, which considers 2 major risk factors: age >60 years and history of thrombosis. The presence of either one of these 2 risk factors defines high-risk for thrombosis and their absence low-risk. (Thiele et al., Am J Hematol. 2022)

First-line drug of choice for cytoreductive therapy is HU (Thiele et al., Am J Hematol. 2022). As described before, the exact mechanism of action is unknown for HU, while its most important effect appears to be in blocking the ribonucleotide reductase system resulting in the inhibition of DNA synthesis.

Dosing depends on the clinical response and the effect on the FBC, the recommended dose of HU is initially 15–20 mg/kg, adjusted according to response on HCT and platelet count; a usual daily dose is 500–1000 mg given orally.

ET patients treated with HU may develop resistance or intolerance. Symptoms of intolerance may include gastrointestinal symptoms, pneumonitis, and fever at any dose of HU. (Nurgat, Lawrence, J. Onc. Pharm. Pract 2022) Additionally, skin ulcers, a reduction in blood cells, gastrointestinal problems, oral ulcers, stomatitis, hyperkeratosis, or actinic keratosis have been reported as symptoms of HU intolerance (Griesshammer et al., Ann Hematol 2015).

HU treatment has a potential genotoxic risk that contraindicates conception during treatment for both men and women. In addition, patients who have received or are receiving HU for long periods have developed secondary leukaemia, with no established link to HU treatment or the primary disease itself, or skin cancer. (SmPC Hydrea, 2021 and 2023). Consequently, younger patients, who may have had longer exposure to HU, potentially have an increased carcinogenic risk (Tremblay, Mascarenhas, 2020). Of note, although supposed in multiple publications, neither prospective nor well-designed retrospective studies in ET patients implicate HU as amplifying the intrinsic vulnerability of ET patients for leukaemic transformation (Tefferi and Barbui, Am. J. Hematol. 2023).

Alternatively, anagrelide is authorised in the EU for the reduction of elevated platelet counts in at risk ET patients (60 years of age or older or a platelet count $>1000\times10^9$/L or a history of thrombo-haemorrhagic events) who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. The recommended starting dose of anagrelide is initially 0.5 mg given orally twice daily with dose adjustments at weekly intervals (max 0.5 mg/day in any one week) according to the response; the usual dose is 1-3 mg daily in divided doses, the recommended maximum single dose should not exceed 2.5 mg. (Nurgat and Lawrence, J. Onc. Pharm. Pract. 2022)

2.1.2. About the product

Pegylated (PEG) interferon (IFN)-α-2a is the active pharmaceutic ingredient of Pegasys, which was approved in the European Union (EU) through the centralised procedure on 20th of June 2002 (MA No. EU/1/02/221/003-010, 017). The authorised indications of Pegasys are treatment of chronic hepatitis B (CHB) in adults and children aged 3 years and older or chronic hepatitis C (CHC) in adults and children aged 5 years and older.

Mechanism of action

PEG-IFN-α-2a belongs to the Type I IFNs. They exert their effects through human IFN-α receptor chains, which activate signalling via the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway.

The anti-viral properties of IFN have led to its successful use in diseases such as CHB and CHC and Kaposi sarcoma. IFN's mechanism of action in MPNs is less clear. Numerous studies have demonstrated an apoptotic effect on haematopoietic progenitors, with a preference for the mutated clone. Colony unit megakaryocyte proliferation is also directly targeted, which likely accounts for IFN's

effects on thrombocytosis. In addition, there is evidence that IFN inhibits thrombopoietin activation via suppression of JAK2 substrate phosphorylation.

Although a comprehensive elucidation of its mechanism of action is still lacking, IFN-α efficacy is likely the consequence of a broad range of biological properties, including enhancement of immune response, direct effects on malignant cells and ability to cycle dormant malignant stem cells. Moreover, sustained clinical, molecular and morphological responses after IFN-α discontinuation, substantiate the suspicion, that IFN-α is the only drug that has the potential to eliminate and modify malignant clones harbouring JAK2-V617F or CALR mutations. (Kiladjian et al., Leukemia 2016)

In contrast, molecular relapses have also been described in patients treated with IFN-α, but the reason for these specific cases are unknown (Saleiro et al., Nature Communications 2022). Kiladjian et al. suggested that the molecular complexity of MPNs could hamper IFN-α efficacy, as the presence of additional non-driver mutations could be associated with resistance to IFN-α. (Kiladjian et al., Leukemia 2016).

An off-label use of PEG-IFN-α-2a for the treatment of MPNs, like polycythaemia vera (PV) and essential thrombocythaemia (ET) has been documented over the last decades and its benefit/risk profile is well described in publicly available literature (>140 publications) in these indications.

The French authority (Agence nationale de sécurité du médicament et des produits de santé, ANSM) published a positive opinion regarding the compassionate use of Pegasys for MPNs (PV, ET and primary myelofibrosis (PMF)) on 2nd of December 2022. (ANSM, 2022a, 2022b)

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The application is based on literature data mainly from three key studies which were prospective clinical trials including PV and ET patients.

- **MPD-RC 111 Yacoub et al., Blood 2019** (efficacy and safety). This study reports a single arm trial including HU intolerant or resistant subjects.
- **MPD-RC 112 Mascarenhas et al., Blood 2022** (efficacy and safety). This was an open-label RCT comparing hydroxyurea and peginterferon alfa in treatment-naïve subjects.
- **NCT00452023 Masarova et al. Lancet 2017** (efficacy). This is a single centre case series with either newly diagnosed or previously treated subjects.

In addition, in terms of safety data the following key trial was reviewed: NCT00241241: Multicenter Phase 2 Study of Efficacy and Safety of Pegylated Interferon-alfa 2a in Polycythemia Vera Patients (Kiladjian et al., Blood 2008). In the above-mentioned trials, Pegylated Interferon-alfa 2a (the active substance of Pegasys) was used as intervention.

Further, for the safety evaluation, the MAH briefly discussed the latest post-marketing information from the original MAH Roche (PBRER 2020) and from the current MAH in the EU (pharmaand GmbH), together with other relevant safety information from published articles or conference abstracts describing clinical trials or retrospective analyses of PEG-IFN-α-2a use in patients with PV and ET.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. In support for the non-clinical section the MAH submitted 8 literature references and an ERA (further discussed below).

2.2.1. Ecotoxicity/environmental risk assessment

The MAH submitted a Phase I ERA including LogKow and PEC calculations. The MAH presents a LogKow value below -1 based on a safety data sheet for PEG 4000 and $PEC_{Surfacewater}$ calculations based on maximum daily doses resulting in PEC under the limit concentration of 0.01 µg/l. The MAH concludes that no further testing of possible environmental effects is necessary based on this calculation.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data has been submitted in this application, which is considered acceptable. In support for the non-clinical section the MAH submitted 8 literature references covering aspects of *in vitro* pharmacology effects on cells from patients with polycythaemia vera, secondary pharmacology, formation of anti-polyethylene glycol (PEG) antibodies after administration of PEG-IFN-α-2a to mice, pharmacokinetics and toxicology. The safety profile of Pegasys is considered covered by the existing clinical data.

The MAH submitted a Phase I ERA including LogKow and PEC calculations. The CHMP does not require an ERA for the PEG component, in line with other Pegylated proteins. As such the CHMP considers that a phase I ERA is not necessary and that PEG conjugates in this context are unlikely to pose an environmental hazard.

2.2.3. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. The pharmacology and toxicology profile of Pegasys is considered covered by the existing non-clinical data.

Considering the above, Peginterferon alfa-2a is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

Not applicable, this application is primarily based on bibliographical clinical data.

2.4. Clinical efficacy

Recombinant IFN-α was first described for the treatment of PV and ET in 1988 (Giles et al., The Lancet 1988, Gisslinger et al., The Lancet 1989, Silver, The Lancet 1988). Since then, IFN has been used "off-label" in PV and ET (first- or second-line) (Masarova et al., Curr Hematol Malig Rep 2019). The efficacy of PEG-IFN-α-2a in the cytoreductive treatment of PV and ET is described in several publications during the last 15 years.

The results of various analyses and sub-analyses of the 3 most relevant studies (NCT01259856 (MPD-RC 112)/ NCT01259817 (MPD-RC 111)/ NCT00452023) have been presented in different publications. Some of these analyses have not been stratified by diagnosis and those results are presented for PV/ET patients as one population. Therefore, the MAH presents these results ahead of more specific analyses, where efficacy results relevant for each individual indication (PV or ET) will be presented.

Moreover, international guidelines (e.g. from the European Society for Medical Oncology (ESMO), European LeukaemiaNet (ELN), National Comprehensive Cancer Network (NCCN) recommend the use of IFN-α for high-risk PV and ET patients (Barbui et al., Leukemia. 2018a, Gerds et al., JNCCN 2021, Vannucchi et al., Annals of Oncology 2015).

2.4.1. Main studies

Study MPD-RC 111 (NCT01259817) Yacoub A et al Blood 2019. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea.

Study MPD-RC 111 was a single-arm, open-label, multicenter phase II trial evaluating the hematologic response to PEG-IFN-α-2a in 50 PV and 65 ET patients who were resistant or intolerant to HU.

Methods

Study participants

From the published paper: The diagnosis of ET or PV was established using criteria outlined by the WHO 2008. High-risk features included a history of thrombosis; age > 60 years; a history of bleeding (ET only); platelet counts >1500 x 10^9/L in ET and >1000 x 10^9/L in PV; vasomotor symptoms (erythromelalgia, severe migraine headaches); significant or symptomatic splenomegaly; and the presence of diabetes or uncontrolled hypertension.

The patients enrolled were resistant to and/or intolerant of HU, according to previously published criteria. These criteria include failure to achieve adequate cytoreduction (platelet count >600 x 10^9/L; hematocrit [HCT], >45% or continued need for therapeutic phlebotomy; or white blood cell [WBC] count >10 x 10^9/L), the development of or progression of splenomegaly, development of major thrombotic episodes, despite the maximum tolerated dose (MTD) of HU, or development of hematologic or nonhematologic toxicities at any dose of HU.

Patients were excluded if they had received previous therapy for ET and PV with an agent other than HU, had had prior therapy with IFN, or had contraindications to IFN therapy, such as an uncontrolled autoimmune disorder, uncontrolled depression, or severe retinal disease.

Treatments

From the published paper: The drug was administered subcutaneously at a starting dose of 45 µg weekly and titrated monthly in 45-µg increments for response up to a maximum of 180 µg weekly. Dose escalation occurred when the criteria for CR and dose-limiting toxicity were not met.

Subjects with a CR or PR at month 12 were eligible to continue treatment at the same dose until loss of response, unacceptable toxicity, patient/physician decision, or completion of the study period at 4 years. Subjects with no response or stable disease at month 12 did not continue receiving treatment.

Objectives

To evaluate the hematologic response to PEG-IFN-α-2a in PV and ET patients who were resistant or intolerant to HU.

Outcomes/endpoints

From the published paper: The primary end point consisted of complete response (CR) and PR (overall response rate, ORR) at 12 months, as determined by European LeukemiaNet (ELN) criteria.

An ITT response evaluation was performed every 12 months. Patients who achieved at least a PR remained on treatment and were observed for a maximum of 4 years. All enrolled patients were included in response assessments.

Secondary endpoints included the evaluation of toxicity, safety, and tolerability of PEG; the impact of PEG on key disease biomarkers; the incidence of disease transformation; the evaluation of changes in bone marrow (BM) histopathology, quality of life (QoL), and patient-reported symptoms; and the assessment of major cardiovascular events.

Figure 3: Definition of clinicohematologic response in ET and PV (ELN criteria) (Barosi et al. Blood 2009)

Response grade	Definition	
	Essential thrombocythemia	**Polycythemia vera**
Complete response	(1) Platelet count ≤ 400 × 10^9/L, AND (2) no disease-related symptoms,* AND (3) normal spleen size on imaging, AND (4) white blood cell count ≤ 10 × 10^9/L	(1) Hematocrit < 45% without phlebotomy AND (2) platelet count ≤ 400 × 10^9/L AND (3) white blood cell count ≤ 10 × 10^9/L, AND (4) normal spleen size on imaging AND (5) no disease-related symptoms*
Partial response	In patients who do not fulfill the criteria for complete response, platelet count ≤ 600 × 10^9/L OR decrease > 50% from baseline	In patients who do not fulfill the criteria for complete response, hematocrit < 45% without phlebotomy ORresponse in 3 or more of the other criteria
No response	Any response that does not satisfy partial response	Any response that does not satisfy partial response

* Disease-related symptoms: microvascular disturbances, pruritus, headache.

Sample size

From the published paper: The study was designed to accrue 84 patients each with ET or PV for a total of 168 patients, but because of lack of study drug availability, the study was closed to accrual in December 2016.

Randomisation and Blinding (masking)

The study was open label single arm.

Statistical methods

From the published paper: For each disease cohort, a 50% ORR achieved during the first 12 months was considered acceptable. With the original sample size of 84 patients in each cohort, a difference in ORR from 35% to 50% provided 80% power (a = 0.05). Patients who dropped out prior to 12 months for lack of response, tolerability, or complications were considered non responders (NRs).

Responses at 12 months were reported and ORR (CR+PR) along with exact 95% confidence intervals (CIs) were reported. For each cohort, an independent z test was conducted to test the null hypothesis that the ORR was equal to 35%. Clinical variables were examined according to clinical response using the independent-samples Student t test or the x2 test for frequency data. Logistic regression was used to examine the association of CR at 12 months with patient demographic and clinical characteristics.

Results

Participant flow

A total of 115 patients (ET, 65; PV, 50) participated in the study.

Recruitment

The study was conducted in North America and Europe. 115 patients were enrolled from February 2012 through December 2015.

Conduct of the study

Not described.

Baseline data

Table 1: Patient demographics and clinical characteristics

Characteristic	ET (n = 65)	PV (n = 50)	Total (N = 115)
Sex			
Female	33 (50.8)	24 (48.0)	57 (49.6)
Male	32 (49.2)	26 (52.0)	58 (50.4)
Age >60 y*	38 (58.5)	33 (66.0)	71 (61.7)
Race			
White	54 (83.1)	47 (94.0)	101 (87.8)
Black or African American	6 (9.2)	2 (4.0)	8 (7.0)
Asian	2 (3.1)	0	2 (1.7)
Not reported	3 (4.6)	1 (2.0)	4 (3.5)
ECOG performance status (grade)			
0	44 (67.7)	33 (66.0)	77 (67.0)
1	21 (32.3)	16 (32.0)	37 (32.2)
2	0 (0.0)	1 (2.0)	1 (0.9)
Previous thrombosis	21 (32.3)	11 (22.0)	32 (27.8)
Previous hemorrhage	7 (10.8)	6 (12)	13 (11.2)
Splenomegaly	12 (18.5)	28 (56.0)	40 (34.8)
Disease duration in months since diagnosis, median (range)	37.3 (0.4-291)	54.8 (0.5-394)	42.3 (0.5-394)
HU resistant	20 (31.3)	17 (34.0)	37 (32.5)
Not achieving platelet count <600 × 10⁹/L†	15 (75)	4 (23.5)	19 (51.4)
Progressive splenomegaly or hepatomegaly or new splenomegaly or hepatomegaly†	2 (10)	7 (44.2)	9 (24.3)
Not achieving a HCT <45 without phlebotomy†	2 (10)	5 (29.4)	7 (18.9)
Not achieving a WBC <10 × 10⁹/L†	5 (29.4)	2 (10)	7 (18.9)
Development of a major thrombotic episode†	7 (35.0)	2 (11.8)	9 (24.3)
HU intolerant	44 (68.8)	33 (66.0)	77 (67.5)
WBC < 2.5 × 10⁹/L or hemoglobin <11 g/dL at any dose of HU	11 (25.0)	6 (18.2)	17 (22.1)
Having a platelet count <100 × 10⁹/L	1 (2.3)	3 (9.1)	4 (5.2)
Presence of leg ulcers or other unacceptable HU-related nonhematological toxicities	37 (84.1)	25 (75.8	62 (80.5)
HU therapy discontinued	26 (40.0)	16 (32.0)	42 (36.5)
HU therapy ongoing	39 (60.0)	34 (68.0)	73 (63.5)‡
WBC (×10⁹/L), median (range)	7.4 (2.4-55.7)	11.1 (2.3-45.3)	8.5 (2.3-55.7)
Platelets (×10⁹/L), median (range)	609 (124-1899)	378 (15.2-1698)	485 (15.2-1899)
HCT %, median (range)	39.4 (40-53.7)	44 (27.5-55.8)	41 (40-55.8)
Driver mutations, n			
JAK2V617F	31	48	—
CALR	23	—	—
MPL	4	1	—
Triple negative or unavailable	8	2	—

Data are n (%), unless otherwise noted.

*Median: 64.0 y (range, 20-85).

†After 3 months of at least 2 g/d of HU or MTD of HU.

‡Median: 22.5 months (range, 1.0-153).

Numbers analysed

From the published paper: All 115 patients were included in ITT response assessment at 12 months.

Outcomes and estimation

Primary endpoint

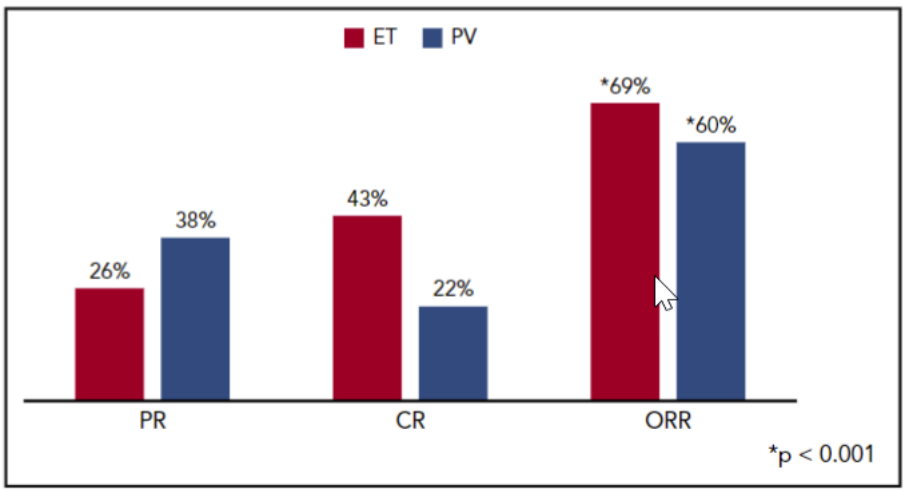
From the published paper: Median follow-up time was 19.6 months (range, 0.6-56.6).

In ET patients, CR and PR at 12 months were observed in 28 (43.1%) and 17 (26.2%) patients, for an ORR of 69.2% (95% CI, 56.6%-80.0%), which differed significantly from the null hypothesis of 35% (z = 5.79; P < .001).

In PV patients, 11 (22%) attained a CR and 19 (38%) a PR, for an ORR of 60% (95% CI, 45.2%-73.6%), which also differed significantly from 35% (z = 3.71; P < .001; Figure 2).

The best response (ORR) at any time point was 70.8% (95% CI, 58.2%-81.4%) for ET patients and 64.0% (95% CI, 49.2%-77.1%) for PV patients; 96.2% of all clinical responses were achieved within 12 months of treatment.

Figure 4: Response assessment. Overall response rate at 12 months



At 12 months, 23 of 50 (46%) PV patients had achieved <45% HCT. In PV patients, 27 of 50 (54%) were receiving phlebotomy at enrollment with a median of 2.0 (range, 1-12) phlebotomies in the prior 6 months before enrollment. In these patients, the median number of phlebotomies was 1.0 (range, 0-6) during the first 6 months of study; 10 of 27 were phlebotomy independent during these 6 months. At 12 months, 45 of 65 (69.2%) ET patients had achieved a platelet count <400 x 10^9/L.

Response at 12 months was examined in relation to clinical factors. Age, HU resistance vs intolerance, maximum dose of PEG, and disease duration were not predictors of attaining CR. Patients with ET had higher CR rates than those with PV (43% vs 22%; odds ratio [OR], 2.68; 95% CI, 1.17-6.15).

BM response

Seventy-four patients were evaluated for BM response. Histopathologic remission was observed in 9 patients (12.2%; ET, 5; PV, 4). Histopathologic remissions were associated with a hematologic PR/CR in 8 of the 9 patients. In 7 patients, BM fibrosis progressed to grade 2+ (scale, 0-3+) while they were receiving PEG therapy, but only 1 patient met clinical criteria for transformation to MF. The remaining patients had stable degrees of BM fibrosis.

Cytogenetic and molecular response

Seventeen patients had abnormal baseline karyotype, and 4 were noted to have changes in their chromosomal abnormalities with PEG treatment. One patient with PV and a normal karyotype at

baseline developed +8 and +9. Three PV patients, all harboring JAK2V617F, lost part, or all, of their clonal karyotypic abnormalities on treatment, and all 3 achieved a CR at 12 months.

Analysis of JAK2V617F allele burden revealed that patients with CR had a significantly lower VAF at baseline compared with those who achieved NR. Decreases in the JAK2V617F VAF appeared to be greater among patients achieving a clinical response. The median absolute change in JAK2V617F VAF was -6% (range, -84% to 47%) in patients achieving a CR vs +4% (range, -18% to 56%) in those with PR and NR. A similar pattern of enrichment for CR among patients with a decreased CALR VAF was noted, but because of the small number of patients with CALR mutations (n = 21), this finding was not statistically significant.

Spleen responses

Of 52 patients with a baseline spleen size .13 cm by imaging, 17 (32.7%) had normalization (decrease to <13 cm on imaging) with treatment. The median absolute change in spleen size was only 2%.

Number of vascular events

No major bleeding events occurred during the study period. Cumulative incidence of major vascular events at 1 year was 2% (95% CI, 1%-8%) and at 2 years was 5% (95% CI, 2%-15%) and consisted of a grade 3 venous thromboembolic event, grade 3 cardiovascular disease, and 2 coronary artery occlusions: 1 grade 2 and 1 grade 3 myocardial infarction.

Evolution of disease

One patient with ET transformed to AML within 8 weeks of therapy, but the baseline BM biopsy favored a diagnosis of prefibrotic MF rather than ET. Transformation to MF occurred in 1 PV patient.

Table 2: Summary of Efficacy for trial MPD-RC 111

Title: Yacoub et al., Blood 2019			
Study identifier	MPD-RC 111		
Design	Study MPD-RC 111 was a single-arm, open-label, multicenter phase II trial evaluating the hematologic response to PEG-IFN-α-2a in 50 PV and 65 ET patients who were resistant or intolerant to HU.		
	Duration of main phase:	N/A	
Hypothesis	null hypothesis: ORR of 35%		
Treatments groups	PEG-IFN-α-2a		
	n=115 (PV 50, ET 65)		
Endpoints and definitions	Primary endpoint	ORR	ORR (%) at 12 months
	Secondary endpoint	CR	CR (%) at 12 months
Database lock	N/A		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		

Effect estimate per comparison	Treatment group	PEG-IFN-α-2a	
	Number of subjects	PV n=50	ET n=65
	ORR (95% CI)	60% (45.2%-73.6%)	69% (56.6%-80.0%)
	ORR differed from 35%	P < .001	P < .001
	CR	22%	43%

Study MPD-RC 112 (NCT01259856), Mascarenhas, J; et al. Blood 2022 A randomized phase 3 trial of interferon-α vs hydroxyurea in polycythemia vera and essential thrombocythemia.

MPD-RC 112 was a randomised, investigator-initiated, open-label, multicenter phase III trial to compare HU to PEG-IFN-α-2a in treatment-naïve (TN), high-risk patients with ET (n=81) or PV (n=87).

Methods

Study participants

From the published paper: Eligibility required a diagnosis of ET or PV according to WHO 2008 diagnostic criteria and high-risk disease. High-risk disease was defined by 1 of the following factors: history of thrombosis, age > 60 years, history of bleeding (ET only), platelet count >1500 x 10^9/L in ET and > 1000 x 10^9/L in PV, vasomotor symptoms (erythromelalgia, severe migraine headaches), significant or symptomatic splenomegaly, and the presence of diabetes or hypertension requiring pharmacologic intervention (full inclusion/exclusion criteria are available on the Blood Web site). Therefore, in addition to classic risk factors for thrombohemorrhagic complications, patients were also included in this study if cytoreductive therapy was merited to address significant symptom and spleen burden.

Eligibility required: "Never treated with cytoreductive drugs except hydroxyurea for up to 3 months maximum (phlebotomy, aspirin allowed, anagrelide allowed)".

Treatments

From the published paper: PEG was self-administered by subcutaneous injection at 45 µg weekly and titrated in 45-µg increments monthly to a maximum of 180 µg weekly. HU was initiated at 500 mg twice daily. Dose modification occurred when criteria for hematologic complete response (CR) were not met or dose-limiting toxicity occurred.

Guidance and direction for dosing and escalations for both agents were provided in the protocol; the dosing protocol guidelines are included in the supplemental Appendix to the published paper.

Objectives

To compare HU to pegylated IFN-a (PEG) in treatment-naïve, high-risk patients with ET/PV.

Outcomes/endpoints

From the published paper: An intention-to-treat (ITT) evaluation was performed at 12, 24, and 36 months. Patients achieving at least a hematologic partial response (PR) remained on treatment, and length of therapy was determined by time of entrance into the study. The last subject to enter the study could receive therapy for at most 12 months, and the first subjects could receive therapy for up to 64 months. All patients were included in response assessments.

The primary endpoint was the comparison of CR rates (as defined by European LeukemiaNet [ELN] criteria to after 12 months of therapy). CR was defined as a platelet count < 400 x 10^9/L, hematocrit <45% without phlebotomy for patients with PV only, white blood cell count < 10 x 10^9/L, resolution of splenomegaly, and resolution of disease-related symptoms (microvascular disturbances, headache, and pruritus).

Responses were assessed by a central review committee blinded to treatment. Splenomegaly was assessed by ultrasound measurement of the craniocaudal axis (splenomegaly defined as > 13 cm).

Sample size

From the published paper: The study was designed to include 300 patients to detect a difference in complete clinical hematologic response rate of 15% from 15% (assumed HU rate) to 30% (assumed PEG rate, a = 0.05, two-sided, power = 0.85).

In 2013, the study was amended from an original sample size of 612 total patients (306 per ET/PV strata) to allow increased disease duration from 3 to 5 years. Under the amended protocol, planned interim analysis was conducted in July 2016 after the first 75 patients were enrolled in the study (HU: 39; PEG: 36).

The CR rate for HU was 33% (13/39) and 28% (10/36) for PEG (P = .60), which did not cross stopping boundaries for either efficacy or futility. The overall response rate (ORR; CR 1 PR) was 69% for HU (27/39) and 81% (29/36) for PEG. The study was continued until enrolment reached 168 patients, when a decision was made by the manufacturer to halt PEG access. With 170 patients randomized to 2 treatment groups in 2 strata, a difference of 19% in CR rates (from 15% to 34%) could be detected for the 2 disease strata combined, with a power of 82%.

Randomisation

From the published paper: Patients were randomly assigned 1:1 to HU or PEG within strata defined by disease type (ET/PV) using block randomization.

Blinding (masking)

The study was open label.

Statistical methods

From the published paper: Patients who dropped out due to lack of response, tolerability, or complications before the 12-month evaluation were considered nonresponders per ITT analysis.

For response assessment at 24 months, only patients enrolled before June 2015 were included (n = 106 due to study closure) and analyzed in an ITT fashion. Similarly, for response assessment at 36 months, only patients enrolled before June 2014 were evaluated.

The primary analysis consisted of a comparison of proportions for CR and ORR by arm based on a 2-sided z-test for proportions. The Cochran-Mantel-Haenszel test for heterogeneity for disease strata (ET/PV) was also conducted. ET and PV rates are reported separately, but all comparisons were conducted for patients with combined ET/PV by arm only.

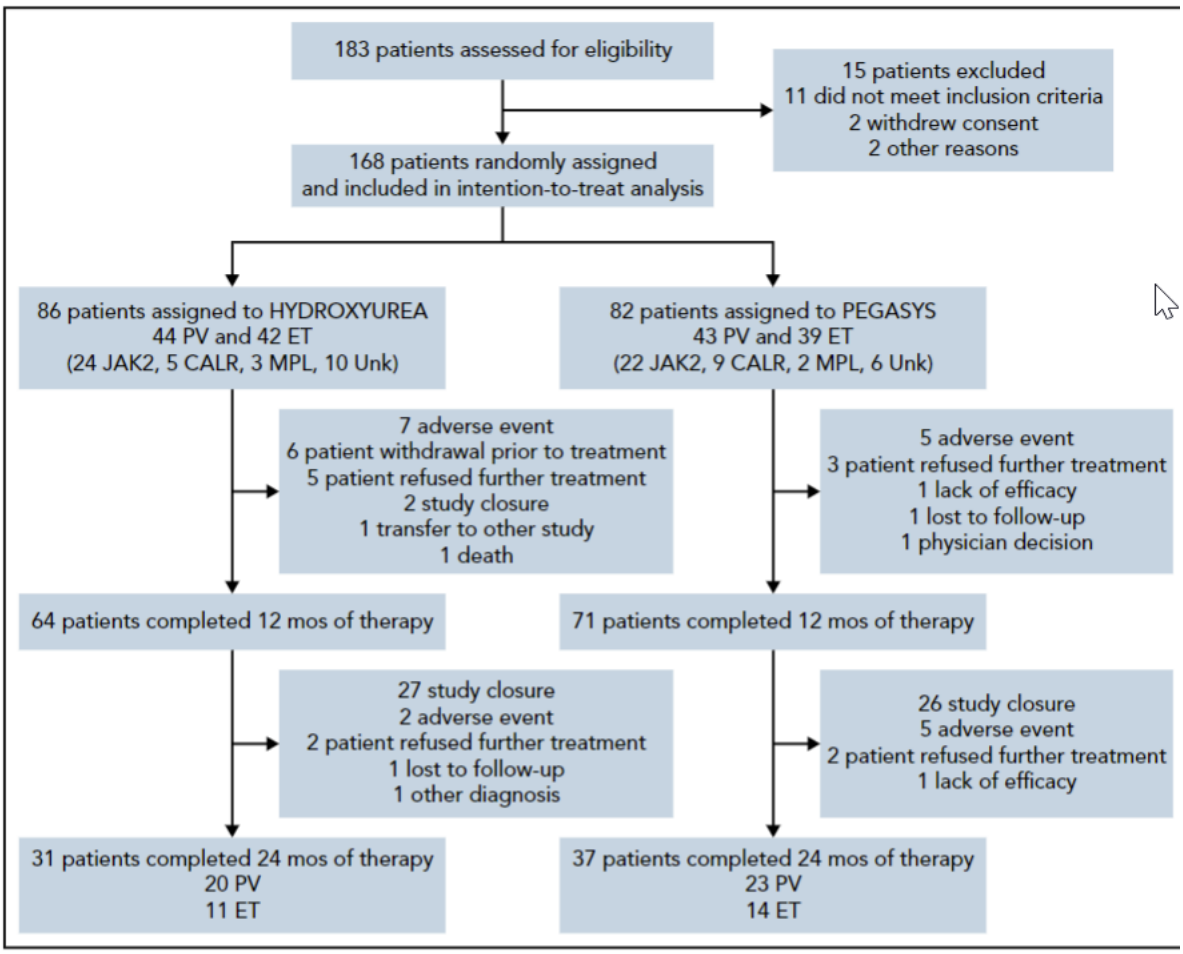
Safety and toxicity were summarized to compare the distributions of incidence and severity of adverse events (AEs) by treatment.

Results

Participant flow

From the published paper: 86 were randomized to HU and 82 to PEG. Eighty-one patients had ET and 87 had PV.

Figure 5: Consort diagram for participant flow by treatment arm



Recruitment

MPD-RC 112 was conducted at 24 North American and European sites. A total of 168 patients were enrolled from September 2011 to June 2016.

Conduct of the study

Not described.

Baseline data

From the published paper:

Table 3: Patient demographics and clinical characteristics by treatment arm

	Arm A: HU (n = 86)	Arm B: PEG (n = 82)	Total (N = 168)
Age, y	63 (18-87)	60 (19-79)	61 (18-87)
Gender, %			
Female	37 (44)	33 (40)	70 (42)
Male	49 (56)	49 (60)	98 (58)
MPN subtype, %			
ET	42 (49)	39 (48)	81 (48)
PV	44 (51)	43 (52)	87 (52)
ECOG, %			
0	72 (84)	65 (79)	137 (82)
1	13 (15)	15 (18)	28 (17)
2+	1 (1)	2 (2)	3 (2)
Disease duration, mo	3.1 (1-84.2)	2.6 (0.4-41.7)	2.8 (0.4-84.2)
Age >60 y, %	56 (65)	42 (51)	98 (58)
History of thrombosis, %	20 (23)	26 (32)	46 (27)
ET, %	8 (19)	13 (33)	21 (26)
PV, %	12 (27)	13 (30)	25 (29)
Aspirin use, %	72 (84)	64 (78)	136 (81)
Anticoagulant use, %	5 (6)	6 (7)	11 (7)
Spleen length by ultrasound, cm*	12.5 (2.1-20)	12.5 (6.5-22)	12.5 (2.1-22)
Leukocytes, $\times 10^9$L	9.2 (3.0-34.4)	8.6 (4.0-24.8)	8.8 (3.0-34.4)
Hemoglobin, g/dL	14.3 (11.3-16.4)	14.6 (8.4-16.6)	14.5 (8.4-16.6)
Hematocrit, %	43.1 (40-70.2)	43.8 (40-61.9)	43.5 (40-70.2)
Platelets $\times 10^9$/L	612 (112-1444)	602 (112-1662)	606 (112-1662)
*JAK2*V617F, %†	68 (92)	65 (89)	133 (91)
CALR exon 9, %†	4 (5)	7 (10)	11 (8)
*MPL*W515L/K, %†	3 (4)	2 (3)	5 (3)
Driver mutation present, %†	71 (96)	69 (95)	140 (95)

n (%) presented for categorical variables and median (range) for continuous variables.
ECOG, Eastern Cooperative Oncology Group.
*Baseline spleen imaging available in 158 patients.
†Baseline mutational status available in 147 patients.

Numbers analysed

From the published paper: All 168 patients were included in response assessment per ITT analysis at 12 months. Six patients in the HU treatment arm withdrew before starting treatment; all patients in the PEG arm received treatment.

Outcomes and estimation

Clinico-hematologic response

The median (range) duration of treatment was 81.0 weeks (0-268) and 94.6 weeks (2.9-287.3) in the HU and PEG arms, respectively. Seventy-four percent of patients receiving HU and 87% of patients receiving PEG were treated for 12 months or longer.

CR at 12 months was 37% for HU and 35% for PEG (P = .80).

ORR at 12 months was 70% for HU and 78% for PEG (P = .22).

In patients with ET, CR at 12 months was observed in 45% of those receiving HU and 44% for those receiving PEG. ORR at 12 months was 71% for HU and 69% for PEG.

In patients with PV, CR at 12 months was observed in 30% for those receiving HU and 28% for those receiving PEG. ORR at 12 months was 68% for HU and 86% for PEG.

Sensitivity analysis (accounting for 6 patients on HU who withdrew before treatment) for CR at 12 months for HU arm was 40% (difference of 5%; 95% CI, -11% to 20% vs PEG) and ORR was 75%.

Table 4: Response by treatment arm

	HU (n = 86), %	PEG (n = 82), %	Difference in proportions for combined ET/PV, 95% CI (PEG – HU)	Rate ratio (95% CI)
12 mo				
Complete response	32 (37)	29 (35)	−2%	0.95
ET	19 (45)	17 (44)	(−16 to 13)	(0.64, 1.42)
PV	13 (30)	12 (28)		
Overall response	60 (70)	64 (78)	8%	1.12
ET	30 (71)	27 (69)	(−5 to 21)	(0.93, 1.34)
PV	30 (68)	37 (86)		

Bone marrow response

In 109 evaluable patients (pre- and posttreatment biopsy), HU had a histopathologic response (HPR) of 12/52 (23%) vs 3/57 (5%) for PEG (P = .01).

Best HPR response was seen in 18/54 (33%) of patients receiving HU and 10/59 (17%) patients receiving PEG (P = .05).

HPR was more frequent in the ET cohort at 12 months 13/46 (24%) as well as best response 20/48 (42%) compared with the PV cohort at 4/63 (6%) and 8/66 (12%), respectively.

Cytogenetic response

One hundred forty-four of 168 (86%) patients had baseline cytogenetics. Abnormalities were seen in 22/144 (15%) patients: 14/71 (20%) patients treated with HU and 8/73 (11%) patients treated with PEG.

Three of 14 (21%) patients treated with HU and 3/8 (38%) patients treated with PEG had a chromosomal abnormality [trisomy 9, del(20q), t(14;21)(q24;q22); trisomy 8, and loss of Y chromosome] (P = .62).

After 24 to 36 months of follow-up, 3/71 (4%) patients receiving HU and 1/73 (1%) patients receiving PEG had gain of del(20q), loss of Y and del(16q). There was no association between cytogenetic response and CR/PR.

Molecular response

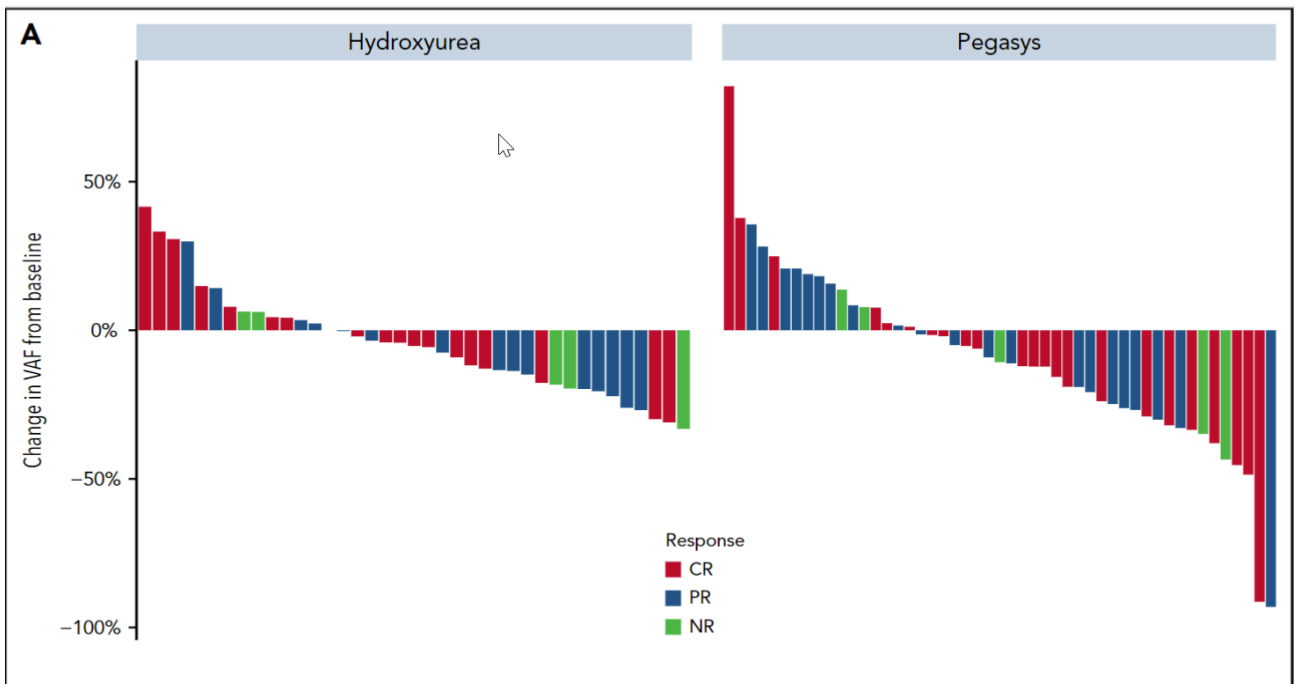
Reductions in JAK2V617F VAF were observed in most patients treated with HU or PEG (Figure x) and no differences were seen by clinical response.

Results were similar for ET and PV groups. Similarly, decreases in CALR and TET2 VAFs were observed in both treatment arms.

The median greatest change from baseline in JAK2V617F VAF was -5.3% and -10.7% in patients treated with HU and PEG, respectively. Notably, the median JAK2V617F VAF decreased consistently from baseline through month 24 in the PEG arm but increased in the HU arm after month 12. Mixed-model estimates for JAK2 VAF reduction at 24 months were -0.004 (95% CI, 20.08, 0.08) for HU and -0.16 (95% CI, 20.23, 20.10) for PEG (P = .002 for interaction effect; Figure 3B).

No significant differences were observed between baseline JAK2V617F VAF in responders and non-responders treated with either drug. The driver mutation type was not associated with achieving response. By contrast, an ASXL1 mutation was associated with decreased odds of achieving hematologic CR status on multivariable analysis (P = .055).

Figure 6: Kinetics of JAK2V617F allele burden of patients treated in the MPD-RC 112 trial. (A) Maximum change in JAK2V617F allele burden from baseline by response status.



Complication-free survival

Five events (HU: 3; PEG: 2) occurred during the trial with an hazard ratio = 0.60 (95% CI, 0.10-3.62).

One patient treated with PEG had a bleeding event consisting of macroscopic hematuria that required red cell transfusions.

A second patient treated with PEG had a cerebral vascular accident.

One patient treated with HU developed bilateral vertebral artery blockage noted on imaging but without clinical consequences.

One patient treated with HU progressed to MF after 46 months. One patient treated with HU died of lung cancer at 9 months.

Cumulative incidence of thrombosis was 2% (95% CI, 0.3-13) for HU and 2% (95% CI, 0.3-15) for PEG at 24 months.

Table 5: Summary of Efficacy for trial MPD-RC 112

Title: Mascarenhas et al., Blood 2022				
Study identifier	MPD-RC 112			
Design	A randomised, investigator-initiated, open-label, multicenter phase III trial to compare HU to PEG-IFN-α-2a in treatment-naïve (TN), high-risk patients with ET (n=81) or PV (n=87).			
	Duration of main phase:		N/A	
Hypothesis	Superiority			
Treatments groups	PEG-IFN-α-2a		n=82	
	HU		n=86	
Endpoints and definitions	Primary endpoint	CR	CR (%) at 12 months	
	Sec endpoint	ORR	ORR (%) at 12 months	
Database lock	N/A			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Effect estimate per comparison	Treatment group	PEG-IFN-α-2a	HU	
	Number of subjects	n=82	n=86	
	CR	35% (PV 28%, ET 44%)	37% (PV 30%, ET 45%)	
	Difference in CR (95% CI)	-2% (-16 to 13%) P=0.8		
	ORR	78% (PV 86%, ET 69%)	70% (PV 68%, ET 71%)	
	Difference in ORR (95% CI)	8% (-5-21%) P=0.22		

Study NCT00452023 Masarova et al. Lancet Haematol. 2017 Efficacy and safety of pegylated interferon alpha-2a in patients with essential thrombocythemia (ET) and polycythemia vera (PV): results of a phase 2 study after a 7-year median follow-up

Study NCT00452023 was a prospective, open-label, single-center, phase II trial of PEG-IFN-α-2a for patients with ET or PV.

Methods

Study participants

From the published paper: This is an ad hoc analysis of data from a prospective, open-label, single-center, phase 2 trial of PEG-IFN-α-2a in patients with essential thrombocythemia and polycythemia vera. Patients older than 18 years with either newly diagnosed or previously treated essential thrombocythemia or polycythemia vera according to the 2005 Polycythemia Vera Study Group criteria were eligble to enroll. Additional inclusion criteria included Eastern Cooperative Group Oncology status ≤ 2; adequate liver (total bilirubin ≤ 2.0 mg/dl) and renal function (serum creatinine ≤ 2.0 mg/dl); and normal cardiac function. Patients must have been off chemotherapy for at least one week prior to enrollment, but could be receiving hydroxyurea or anagrelide for up to 1 month after study entry. A washout period of one month was required for patients treated with continuous or chronic high doses of steroid.

Exclusion criteria included pregnant or lactating women; history of another malignancy unless disease free for > 3 years); ischemic retinopathy; severe cardiac disease; history of medically significant psychiatric disease if not controlled, especially endogenous depression; a seizure disorder requiring anticonvulsant therapy; known infection with hepatitis B or C or HIV or other active systemic infection; renal disease requiring hemodialysis; or known autoimmune disease (except rheumatoid arthritis).

Treatments

From the published paper: The first three patients in the study received PEG-IFN-α-2a subcutaneously at 450 μg weekly. As a result of poor tolerance, the starting dose was decreased in a stepwise manner by 90-μg decrements based on tolerance (360μg weekly, n = 3; 270μg weekly, n = 19; 180μg weekly, n =26) to 90μg weekly, which was subsequently used as a starting dose in the remainder of patients (n =28) accrued to the study. PEG-IFN-α-2a was administered for as long as the patient obtained a clinical benefit. The dose was reduced based on toxicity or escalated in the absence of response and significant toxicity for 3 months. Therapy was maintained, if possible, in the event of grade 1 or 2 toxicity. In the event of persistent significant grade 2 toxicity or grade 3 or 4 toxicity, therapy was interrupted until resolution of the toxicity to grade 0 or 1 and resumed at the immediate lower dose level. Exceptionally, alternative dose schedules were allowed to achieve optimal benefit (eg. 90 μg every 2 weeks).

Objectives

The main objectives were to establish the efficacy and tolerability of PEG-IFN-α-2a in patients with PV or ET and the impact of this therapy on the dynamics of JAK2V617F mutation.

Outcomes/endpoints

From the published paper: The primary endpoint was hematologic response rate, as defined by European LeukemiaNet criteria. Complete hematologic response (CHR) was defined as normalization of bloodcounts (essential thrombocythemia: platelets ≤ 440 x 109/L; PV: hemoglobin < 15.0 g/L without phlebotomy) with complete resolution of palpable splenomegaly/symptoms in the absence of a thrombotic event. A partial hematologic response (PR) required at least a 50% reduction in the platelet count for essential thrombocythemia or a 50% reduction in the rate of phlebotomies or 50% reduction in spleen size by palpation for polycythemia vera.

Secondary endpoints were to evaluate the toxicities in these patients as well as the bone marrow morphologic and molecular disease characteristics before and during therapy. Physical exam and blood counts were assessed every 3 months. Bone marrow aspiration and biopsy with quantitation of JAK2V617F and cytogenetics were performed at the start of therapy and every 3 to 6 months thereafter. 11,12 All patients who tested positive for the JAK2V617F mutation were evaluable for a MR if they had 2 or more adequate bone marrow samples while on therapy taken 3 months apart within the first year. Complete molecular remission (CMR; based solely on the assessment of a JAK2V617F allele burden) required undetectable JAK2V617F, while partial and minor molecular remissions (PMR, mMR) required reductions in baseline allele burden of >50% and 20–49%, respectively.

Randomisation

The study was open label.

Blinding (masking)

The study was single arm.

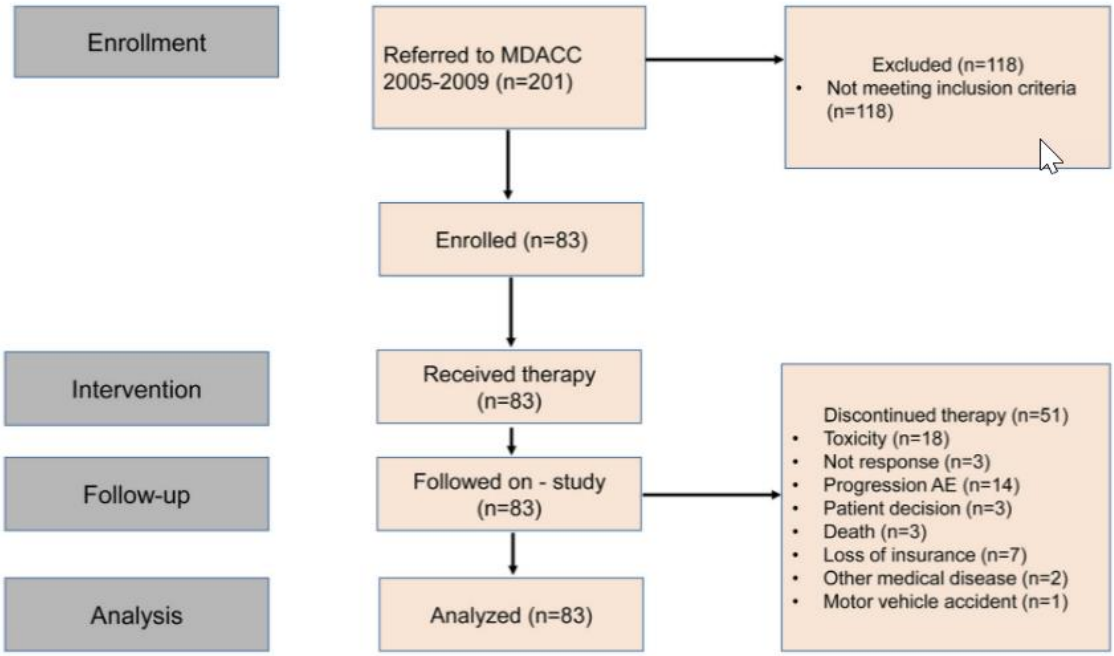
Statistical methods

From the published paper: Responses and clinical data were analyzed using descriptive statistics.

Results

Participant flow

Figure 7: Yearly discontinuation rates and reasons for treatment discontinuation. MF/AML=transformation to myelofibrosis/acute leukemia; Resp.=response, NR=no response; others [see explanation in the main text]



Recruitment

Forty-three patients with polycythemia vera and 40 with essential thrombocythemia were enrolled between May 31, 2005 and October 13, 2009. All patients were recruited from the M. D. Anderson Cancer Center.

Conduct of the study

Not described.

Baseline data

From the published paper:

Sixty-three percent of patients had received some form of therapy (in addition to aspirin) prior to enrollment, including standard IFN-α (n=14) and PEG-IFN-α-2a (n=1).

Table 6: Patient demographics and clinical characteristics

Characteristic	PV (n=43)	ET (n=40)	total (n=83)	p-value
Median age, (IQR)	54 (44–63)	52 (39–62)	53.4 (43–62)	p = 0.41
Males, n (%)	17 (40)	12 (30)	29 (35)	p = 0.49
Females, n (%)	26 (60)	28 (70)	54 (65)	p = 0.49
High risk disease, n (%)	14(33)	16(40)	30 (36)	p < 0.0001
Time from diagnosis to study entry, months (IQR)	50 (13–89)	37 (14–115)	42 (14–98)	p = 0.67
History of major thrombosis, n (%)	2 (4.6)	2 (5)	4 (5)	p = 1.00
No. JAK2 V617F-positive patients (%)	41 (95%)	19 (48%)	60 (72)*	p < 0.0001
JAK2 V617F allele burden, median (IQR)	65 (34–78)	23 (12–45)	46 (23–76)*	p < 0.0001
Abnormal karyotype, n (%)	2 (5)	4 (10)	6 (7)	p = 0.42
Median white blood cell count, 10^9/L (IQR)	11.2 (8–16)	7.2 (6–9)	9 (6–13)	p < 0.0001
Median hemoglobin, g/dL (IQR)	14.2 (13–15)	13.1 (12–14)	13.8 (12–15)	p = 0.06
Median platelet count, 10^9/L (IQR)	496 (338–786)	752 (473–1020)	592 (389–938)	p < 0.0025
¶Significant splenomegaly, n (% of known)	7/42 (16)	0/39 (0)	7/81 (8.6)	NA
Median spleen size BCM in cm (IQR)	11 (4–14)	NA	11 (4–14)	NA
Disease-related symptoms, n (%)	19 (44)	24 (60)	43 (52)	p = 0.19
Phlebotomy, n (%)	32 (74%)	NA	32	NA

High risk disease = patients ≥ 60 or previous thrombosis;

¶Significant splenomegaly defined as a palpable spleen > 5 cm below costal margin (BCM); NA = not applicable

Numbers analysed

All 83 patients were evaluated for response.

Outcomes and estimation

From the published paper:

Hematologic response

The median follow-up time was 83 months (IQR, 69–94 months). The overall response rate was 80% (n=66). The median duration of HR was 66 months (IQR, 35–83), and 26 (39%) were in HR at the time of last follow-up (all but 1 was a CHR). Neither achievement of a HR nor time to response was associated with age, gender, baseline clinical characteristics, splenomegaly, molecular status or JAK2V617F allele burden.

Overall, 40 patients lost their response. Nineteen after dose reductions or drug holds due to intolerance or toxicity; one when he developed concurrent diffuse large B-cell lymphoma; and 20 due to progressive disease, despite being treated with the highest tolerable dose of PEG-IFN-α-2a. The median response duration among patients who lost their response was 46 months (IQR, 17–68). Among patients who were treated for at least 46 months, the median dose of PEG-IFN-α-2a was

similar regardless of whether or not they lost their response (135 mcg/week vs 90 mcg/week, respectively, p=0.44). Remarkably, 7 patients

(28%, 4 essential thrombocythemia, 3 polycythemia vera) have sustained their HR after discontinuation of PEG-IFN-α-2a (median time on therapy, 77 months [IWR, 56–98 months]; median response duration off study, 6 months [IQR, 4–34 months].

Table 7: Summary of clinical efficacy in all enrolled patients

Characteristics		Total, N= 83	PV, N= 43	ET, N= 40	P-value
Median total follow-up time, months (IQR)		82.5 (69–94)	83 (65–92)	83 (74–95)	0.43
Median treatment duration, months (IQR)		68.8 (15–85)	59 (12–91)	76 (25–83)	0.49
INITIAL RESPONSE					
Hematologic Resp. (HR), n, (%)	Overall HR	66 (80)	34 (79)	32 (80)	1.00
	CHR	62 (75)	33 (77)	29 (73)	0.35
	PHR	4 (5)	3 (7)	1 (3)	0.61
Median HR duration, months (IQR)	Overall	65.7 (35–83)	65 (43–87)	58 (36–84)	0.38
	CHR	67 (36–86)	65 (33–82)	58 (33–83)	0.21
	PHR	30 (6–52)	35 (2–58)	25	NA
Median time to response, months (IQR)		4 (1.3–7.3)	1.7 (1–4.7)	4.8 (2.1–12.5)	0.11
Molecular Resp. (MR), n (%)	Overall MR	35 (63)	22 (63)	13 (37)	0.40
	CMR	10 (18)	7 (20)	3 (9)	0.71
	PMR	20 (36)	14 (40)	6 (17)	0.48
	mMR	5 (9)	1 (3)	4 (11)	0.06
Median MR duration, months (IQR)	Total	53.4 (24–70)	58 (38–77)	57 (14–60)	0.12
	CMR	69 (54–77)	70 (59–77)	54 (11–76)	0.13
	PMR	49 (24–65)	50 (22–68)	47 (32–60)	0.67
	mMR	18 (4–46.4)	17.7	18 (6–51)	NA
Median time to MR, months (range)		24 (12–35)	24 (12–30)	23 (12–42)	0.99
RESPONSE AT LAST FOLLOW-UP					
Hematologic response, n (%)	Overall HR	26/66 (39)	13/34	13/32	

Molecular response

Of the 63 (76%) JAK2V617F-positive patients, 55 (87%) were evaluable for a molecular response (MR). Eight patients who discontinued therapy in the first year and did not have 2 or more representative samples were not evaluable for a MR. The JAK2V617F allele burden was reduced in 63% (n=35) of these patients, and 10 of them had a CMR as their best response. Among all JAK2-positive patients, the median JAK2V617F allele burden was 43% at baseline and 12% at the time of best response. Among those with CMR, the JAK2V617F allele burden decreased by 35% and remained at that level.

Long-term responders

Thirty-two (38%; essential thrombocythemia 18, polycythemia vera 14) patients are still enrolled in the study, with 24 on active treatment. Nineteen are in HR. Eighteen of 24 (75%) patients are on a dose ≤ 90 µg per week. Eight patients are having therapy held (7 essential thrombocythemia, 1

polycythemia vera) due to toxicity (n=5) or for financial reasons (n=3). Two patients have been holding the drug for 6 and 6.5 years. While on hold, 3 of 8 patients have lost their response (2 HR, 1 MR). Despite losing their
responses, all 3 patients are symptom-free and prefer to stay on the study with active observation.

Table 8: Summary of Efficacy for trial NCT00452023

Title: Masarova et al. Lancet 2017			
Study identifier	Study NCT00452023		
Design	Study NCT00452023 was a prospective, open-label, single center, phase II study of PEG-IFN-α-2a in 83 (43 PV/40 ET) patients.		
	Duration of main phase:	N/A	
Hypothesis	Exploratory		
Treatments groups	PEG-IFN-α-2a		
	n=83 (PV 43, ET 40)		
Endpoints and definitions	Exploratory endpoint	Best overall hematologic response rate	OHR (%)
	Exploratory endpoint	Best complete hematologic response rate	CHR (%)
Database lock	N/A		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT. Best response rate. Median follow up: 83 months		
Effect estimate per comparison	Treatment group	PEG-IFN-α-2a	
	Number of subjects	83 (43 PV + 40 ET)	
	OHR (%)	79	80
	CHR (%)	77	73

Supportive studies

Polycythaemia vera

Results across NCT01259856 (MPD-RC 112)/ NCT01259817 (MPD-RC 111)

Yacoub et al. (Yacoub et al., Blood 2019b) presented the results of an analysis across both studies to evaluate the efficacy of PEG-IFN-α-2a in TN and refractory or intolerant (R/I) to HU PV patients. In total, 43 TN and 50 R/I PV patients were included. Median disease duration was 2.5 months in TN and

54.8 months in R/I patients. At 12 months CR/PR/ORR were 22 %/38 %/60 % observed in 50 R/I PV patients, and 27.9 %/58.1 %/86 % in 43 TN PV patients (p=0.005 for ORR).

NCT00241241 (PVN1)

The results of an open-label, multicenter phase II study of PEG-IFN-α-2a in 37 PV patients was published by Kiladjian et al. (Kiladjian et al., Neoplasia 2006, Kiladjian et al., Blood 2008). The primary endpoint was the HR rate at 12 months (CR defined as platelet count <400x10^9/L, HCT <45 % in men and <42 % in women without phlebotomy, white blood cell count <10x10^9/L and absence of splenomegaly. PEG-IFN-α-2a treatment was started at 90 µg s.c./week for 2 weeks, with a dose escalation (every 2 weeks, and in the absence of toxicity) to 135 µg s.c./week and to 180 µg s.c./week in the absence of HR. All 37 patients responded to PEG-IFN-α-2a at the 12-month evaluation (primary study end point), including 35 CHRs (94.6 %), and 2 PRs (5.4 %).

Other clinical studies.

Gill et al. (Gill et al., Hematology 2020) prospectively compared the efficacy of PEG-IFN-α-2a, HU and ruxolitinib in PV patients. PEG-IFN-α-2a resulted in significantly higher CHR than HU or ruxolitinib (89 % versus 77 % versus 43 %, P=0.045) and significantly lower median platelet counts, than the other groups from 9 months onwards (P<0.05). At a median treatment duration of 6 months, the ORR was 82 % (CHR: 52 %; PR: 30 %), which was comparable for various treatment groups. The haemoglobin fell in all groups, with the ruxolitinib group showing the lowest median haemoglobin, which at 15 months was significantly lower than the 2 other groups (P=0.03). The leucocyte and platelet counts also fell, except in the ruxolitinib group where the platelet count increased progressively during follow-up.

Crisa et al. (Crisà et al., J. Hem. & Onc. 2017) presented the results of an observational study on 65 PV patients, Thirty patients received PEG-IFN-α-2a and 35 received HU. Median follow-up was 75 months. PEG-IFN-α-2a dose started at 90 µg s.c./week and increased to 135 µg/week and HU daily dose ranged from 500 up to 2000 mg given orally. Median time to CR was 6 months and median PEG-IFN-α-2a dose at CR was 90 µg s.c./week. Median JAK2 allele burden at diagnosis was 40.5 %, and it decreased to 17 % and 15.8 % at 12 and 24 months after treatment start, respectively. Significantly better survival for PEG-IFN-α-2a patients (p=0.027) was reported with no death observed compared to 3 in the HU group.

A prospective monocenter cohort study was conducted by Betti et al. 2014, Betti et al., 46° Congress of the Italian Society of Hematology 2017) in 24 PV patients treated with PEG-IFN-α-2a. The median dosage was initially 90 µg s.c./week, and after adjustment for adverse effects and response 67 µg s.c./week. The median duration of treatment was 182 weeks. HR was complete in 6 and partial in 4 patients, resulting in an ORR of 42 %. The baseline median JAK2-V617F allele burden of the evaluable patients was 80 %; PEG-IFN-α-2a reduced the allele burden in PV patients by a median of 49 % (p=0.048).

A retrospective analysis with cohort of 55 PV patients treated with a median dose of 90 µg PEG-IFN-α-2a s.c./week was published by Gowin et al.(Gowin et al., Blood 2011, Gowin et al., haematologica 2012). The median treatment duration was 17 months. ORR, CR, PR and NR was 87 %, 54 %, 33 %, 7 %, respectively.

Dhanapal et al. (Dhanapal et al., British Journal of Haematology 2021) recently presented the results of a retrospective analysis of 16 PV patients treated with PEG-IFN-α-2a for a treatment duration of 3-60 months. CR was observed in 9 (56 %) and PR in 5 (31 %) PV patients. The average time for CR attainment was 12-18 months. One patient lost CR at 5 years and required venesection, this was a JAK2-mutated PV patient. The average maintenance dose to maintain CR/PR was 45-135 µg/week.

Mesa et al. (Mesa et al., 2011) retrospectively analysed the records of 46 PV patients treated with PEG-IFN-α-2a. Median starting dose of PEG-IFN-α-2a was 90 µg/week with peak doses ranging from 45 to 270 µg. The median duration of treatment was 17 months. Twenty PV patients achieved CR (43 %), 21 achieved PR (46 %) and NR in 5 (11 %).

Essential thrombocythaemia

Results across NCT01259856 (MPD-RC 112)/ NCT01259817 (MPD-RC 111)

Yacoub et al. (Yacoub et al., Blood 2019b) presented the results of an analysis across both studies to evaluate the efficacy of PEG-IFN-α-2a in TN and R/I to HU ET patients. In total, 39 TN and 65 R/I ET patients were available for this analysis. Median disease duration was 2.9 months in TN and 37.3 months in R/I ET patients. At 12 months CR/PR/ORR were 43.1 %/26.2 %/69.2 % observed in R/I ET patients and in 43.6 %/25.6 %/69.2 % in TN ET patients (p=0.99 for ORR).

Other clinical studies.

Gill et al. (Gill et al., Hematology 2020) compared the efficacy of PEG-IFN-α-2a, HU and ruxolitinib in ET patients. At a median treatment duration of 6 months, the ORR was 99 % (CHR: 79 %; PR: 20 %). PEG-IFN-α-2a resulted in significantly higher CHR than HU or ruxolitinib (89 % versus 77 % versus 43 %, P=0.045). Ruxolitinib treatment resulted in significantly lower haemoglobin and HCT as compared with HU and PEG-IFN-α-2a (P<0.05 from 12 months onwards for both haemoglobin and HCT). PEG-IFN-α-2a resulted in the lowest median platelet count, which was significantly lower than the other groups from 9 months onwards (P<0.05).

A prospective monocenter cohort study was conducted by Betti et al. (Betti et al., 19th EHA Congress 2014, Betti et al., 46° Congress of the Italian Society of Hematology 2017) in 32 ET patients treated with PEG-IFN-α-2a. The median dosage was initially 90 µg s.c./week, and after adjustment for adverse effects and response 67 µg s.c./week. The median duration of treatment was 34.5 weeks. HR was complete in 9 and partial in 13 patients, resulting in an ORR of 69 %. The baseline median JAK2-V617F allele burden of the evaluable patients was 80 %; no significant reduction of JAK2-V617F allele burden was observed in ET patients after PEG-IFN-α-2a treatment.

A retrospective analysis with cohort of 46 ET patients treated with a median dose of 90 µg PEG-IFN-α-2a s.c./week was published by Gowin et al. (Gowin et al., Blood 2011, Gowin et al., haematologica 2012). The median treatment duration was 17 months. ORR, CR, PR and NR was 78 %, 63 %, 15 %, 9 %, respectively.

Dhanapal et al. (Dhanapal et al., British Journal of Haematology 2021) recently presented the results of a retrospective analysis of 23 ET patients treated with PEG-IFN-α-2a for a treatment duration of 3-60 months. CR was observed in 17 (74 %) and PR in 4 (17 %) ET patients. The average time for CR attainment was 12-18 months. The average maintenance dose to maintain CR/PR was 45-135 µg/week.

In another retrospective evaluation by Ekinci and Merter (Ekinci, Merter, 25th EHA Congress 2020) 24 ET patients received 90 µg PEG-IFN-α-2a/week in the first 2 weeks and then continued with 180 µg/week. Median treatment duration for PEG-IFN-α-2a was 16 months. A statistically significant decrease in platelet counts from third month of PEG-IFN-α-2a treatment compared to initial levels was reported (p=0.013).

Mesa et al. (Mesa et al., 2011) retrospectively analysed 30 ET patients. Median starting dose of PEG-IFN-α-2a was 90 µg/week with peak doses ranging from 45 to 270 µg. The median duration of

treatment was 17 months. In ET, the CR was achieved in 15 (50 %), PR in 10 (30 %) and NR in 5 (15 %).

The results of a retrospective analysis on 58 high-risk ET patients, who received PEG-IFN-α-2a treatment with a median dose of 88 µg/week and median duration of 16 months was reported by Roy et al. (Roy et al., Blood 2010). Overall, NR was observed in 4/58 (7 %), PHR in 9/58 (16 %) and CHR in 45/58 (76 %) of patients according to the ELN criteria. Cumulative incidence of CHR at 1, 3, and 6 months was 29 %, 52 % and 65 %, respectively. At the last follow up 47/58 (81 %) of the patients were still treated with PEG-IFN-α-2a and overall 36 patients were in CHR. Median time to achieve CHR was 3 months.

Yassin et al. (Yassin et al., 2012) reported about HR after 12 months of PEG-IFN-α-2a therapy (50 µg s.c./week for 4 weeks, 135 µg s.c./week from week 5) in 40 ET patients. All of the patients responded with 35 CHRs (94.6 %), and 5 PHRs (5.4 %) within 2 months and responses were sustained beyond the first year. Median %V617F was 58 % at 12 months (P<0.001).

The same group compared a once weekly to once monthly dosing of PEG-IFN-α-2a in 40 ET patients. Patients were randomised into 2 arms, 135 µg s.c./week (arm (A), n=20) and 135 µg s.c./week (arm(B), n=20). The primary end point was HR to PEG-IFN-α-2a at 12 months of treatment. All of the patients were in CHR at the 12-month evaluation. Median relative decrease of %V617F during the first year was 52 % decreased in arm A versus 50 % in arm B. (Yassin et al., 2013)

2.4.2. Discussion on clinical efficacy

Study MPD-RC 111 (Yacoub A et al., 2019)

Study MPD-RC 111 (Yacoub A et al., 2019) was a single-arm, open-label, multicenter phase II trial evaluating the hematologic response to PEG-IFN-α-2a in 50 PV and 65 ET patients who were resistant or intolerant to HU.

Eligibility for study MPD-RC 111 required high-risk ET or PV. The definition of high-risk disease in study MPD-RC 111 corresponds to the definition of high-risk in clinical practice (recommendations from the ELN consortium, Barbui 2018). In clinical practice, high-risk disease is treated with cytoreductive therapy. The patients enrolled were resistant to and/or intolerant of HU. Thus, they correspond with both the initially sought indication and the modified indication as proposed in the second assessment round.

The posology in study MPD-RC 111 corresponds to the suggested posology in SmPC section 4.2. The primary endpoint consisted of ORR at 12 months, as determined by ELN criteria.

The study was conducted in North America and Europe. 115 patients were enrolled.

The median age was 64.0 years (range 20-85). 67.5% of patients were HU intolerant with 80.5% of them having leg ulcers or other HU-related nonhematological toxicities. 32.5% of patients were HU resistant. All 115 patients were included in the ITT response assessment at 12 months.

In PV patients ORR was 60% (95% CI, 45.2%-73.6%), which differed significantly from the null hypothesis of 35% (P < .001).

In ET patients, ORR at 12 months was 69% (95% CI, 56.6%-80.0%), which also differed significantly from 35% (P < .001).

Study MPD-RC 112 (Mascarenhas et al., Blood 2022)

Study MPD-RC 112 (Mascarenhas et al., Blood 2022) was a randomised, investigator-initiated, open-label, multicenter phase III trial to compare HU to PEG-IFN-α-2a in treatment-naïve (TN), high-risk patients with ET (n=81) or PV (n=87). Thus, the study population corresponds with the modified indication proposed in the second assessment round.

The primary endpoint was CR rate according to ELN criteria (Barosi et al., Blood 2009) at 12 months of treatment.

The posology in study MPD-RC 112 corresponds to the suggested posology in SmPC section 4.2.

The study was conducted in North America and Europe.

168 patients were enrolled and randomised to treatment arms (86 HU, 82 PEG-IFN-α-2a).

The median age was 61.0 years (range 18-87). All 168 patients were included in the ITT response assessment.

At 12 months, a CR was reached by 29 (35%) of 82 patients treated with PEG-IFN-α-2a; and 32 (38%) of 84 ET/PV patients treated with HU. Superiority of PEG was thus not shown.

In patients with PV, CR at 12 months was observed in 30% for those receiving HU and 28% for those receiving PEG.

In patients with ET, CR at 12 months was observed in 45% of those receiving HU and 44% for those receiving PEG.

Study NCT00452023 (Masarova et al. 2017)

Study NCT00452023 (Masarova et al. 2017) was a prospective, open-label, single center, phase II study of PEG-IFN-α-2a in 83 (43 PV/40 ET) patients.

It is not clear if eligibility for study NCT00452023 required high-risk ET/PV. Treatment naïve or previously treated patients were eligible.

All patients started at a dose of 90µg weekly or higher. The starting dose of PEG-IFN-α-2a was higher in study NCT00452023 compared to the dose recommended in the SmPC section 4.2.

The primary endpoint was not clearly defined. The time point for response assessment was not prespecified. Criteria for CHR was similar to CR according to ELN criteria (Barosi et al., Blood 2009). It is not clear if the primary endpoint was CHR or ORR.

Eighty-three patients (43 with PV and 40 with ET) were enrolled. All patients were recruited from the M.D. Anderson Cancer Center.

The median age of included patients was 53 years. The included patients were younger than what would be anticipated in a trial including high-risk PV/ET patients.

Sixty-three percent of patients with ET and PV had received some form of medical therapy (aspirin not accounted for) before enrolment. Phlebotomy was accounted for as a prior therapy.

Response evaluation was carried out in the ITT population.

At 83 months median follow-up, the best overall hematologic response was 79% for patients with PV and 80% for patients with ET, including a CHR rate of 77% and 73% for PV and ET, respectively.

PV

Many clinical trials in the past have characterized the efficacy of interferon-alfa in PV and clinical experience of the use of interferons in PV is considerable.

In Yacoub et al. Blood 2019) 50 patients with HU resistant or intolerant PV were treated with PEG-IFN-α-2a with an ORR of 60% (CR rate 22%).

In Mascarenhas et al. (Blood 2022) 43 patients with TN PV were treated with PEG-IFN-α-2a, the ORR was 86% and the CR rate was 28%.

In Masarova et al. (Lancet 2017) 43 patients with TN or R/I PV were included and the best ORR was 79% (CHR rate 77%).

In the PVN1 study (Kiladjian et al., Neoplasia 2006, Kiladjian et al., Blood 2008a) all patients (n=37) were treated with PEG-IFN-α-2a and all patients responded to treatment.

Gill et al. (Gill et al., Hematology 2020) prospectively compared the efficacy of PEG-IFN-α-2a, HU and ruxolitinib in PV patients. PEG-IFN-α-2a resulted in significantly higher CHR than HU or ruxolitinib (89 % versus 77 % versus 43 %, P=0.045).

In three retrospective studies of PEG-IFN-α-2a in patients with PV (Gowin et al., Blood 2011, Dhanapal et al., British Journal of Haematology 2021, Mesa et al., 2011) the CR rate was 54%, 56% and 43%.

PV is a disease without spontaneous remission. Thus, considering the absolute benefit of a treatment with PEG-IFN-α-2a based on a comparison to baseline a clear cytoreductive effect was shown for TN as well as R/I patients.

The indication initially sought was for patients R/I to HU. In all relevant treatment guidelines interferons are recommended, only the ranking of interferon in the treatment of PV, whether in first or second line, is currently still under discussion.

ESMO clinical practice guideline as well as ELN guideline recommend HU and IFN-α as first-line cytoreductive treatments for PV patients (Vannucchi et al., Annals of Oncology 2015, Barbui et al., Leukemia 2018a). National Comprehensive Cancer Network (NCCN) recommends consideration of interferon as first-line in young patients or patients considering pregnancy (Gerds, 2021).

It might be appropriate letting the treating physician making the choice of first line treatment on an individual patient basis. The MAH was therefore asked to consider an indication text not specifying the treatment line. The MAH accepted this proposal.

ET

Many clinical trials in the past have characterized the efficacy of interferon-alfa in ET and clinical experience of the use of interferons in ET is considerable.

In Yacoub A et al. (2019) 65 patients with HU resistant or intolerant ET were treated with PEG-IFN-α-2a with an ORR of 69% (CR rate 43%).

In Mascarenhas et al. (2022) 81 patients with TN ET were treated with PEG-IFN-α-2a, the ORR was 69% and the CR rate was 44%.

In Masarova et al. (2017) 40 patients with TN or R/I ET were included and the ORR was 81% (CHR rate 73%).

Gill et al. (Gill et al., Hematology 2020) compared the efficacy of PEG-IFN-α-2a, HU and ruxolitinib in ET patients. At a median treatment duration of 6 months, the ORR was 99 % (CHR: 79 %; PR: 20 %).

PEG-IFN-α-2a resulted in significantly higher CHR than HU or ruxolitinib (89 % versus 77 % versus 43 %, P=0.045).

A prospective monocenter cohort study was conducted by Betti et al. (Betti et al., 19th EHA Congress 2014, Betti et al., 46° Congress of the Italian Society of Hematology 2017) in 32 ET patients treated with PEG-IFN-α-2a. HR was complete in 9 and partial in 13 patients, resulting in an ORR of 69%.

Five retrospective studies of PEG-IFN-α-2a (Gowin et al., Blood 2011, Dhanapal et al., British Journal of Haematology 2021, Ekinci, Merter, 25th EHA Congress 2020, Mesa et al., 2011, Roy et al., Blood 2010) demonstrated efficacy in patients with ET.

ET is a disease without spontaneous remission. Thus, considering the absolute benefit of a treatment with PEG-IFN-α-2a based on a comparison to baseline a clear cytoreductive effect was shown for TN as well as R/I patients.

The indication initially sought was for patients R/I to HU. In all relevant treatment guidelines interferons are recommended, only the ranking of interferon in the treatment of ET, whether in first or second line, is currently still under discussion.

ESMO clinical practice guideline as well as ELN guideline recommend HU and IFN-α as first-line cytoreductive treatments for ET patients (Vannucchi et al., Annals of Oncology 2015, Barbui et al., Leukemia 2018a). National Comprehensive Cancer Network (NCCN) recommends consideration of interferon as first-line in young patients or patients considering pregnancy (Gerds, JNCCN 2021).

It might be appropriate letting the treating physician making the choice of first line treatment on an individual patient basis. The MAH was therefore asked to consider an indication text not specifying the treatment line. The MAH accepted this proposal.

Approved indications:

Polycythaemia vera

Pegasys is indicated as monotherapy in adults for the treatment of polycythaemia vera.

Essential thrombocythaemia

Pegasys is indicated as monotherapy in adults for the treatment of essential thrombocythaemia.

2.4.3. Conclusions on the clinical efficacy

The use of peginterferon alfa for the treatment of PV and ET is well established in the EU and recommended by consensus guidelines. The MAH has submitted published data from a number of investigator-initiated studies demonstrating clinically relevant complete response rates. Most of these data are from treatment-naïve settings. However efficacy-wise, prior exposure to hydroxyurea, regardless of whether this is associated with resistance or intolerance, is not expected to impact the activity of peginterferon alfa, provided that it is tolerated.

2.5. Clinical safety

Introduction

Pegasys (PEG-IFN-α-2a; hereafter referred to as PEG-IFN) is marketed in the EU and several other countries worldwide for over 20 years in the indications CHC and CHB in adults and children. Therefore, PEG-IFN-α-2a has a well-known safety profile.

Known risks with PEG-IFN-α-2a in adult patients with CHC or CHB include blood disorders, serious and severe infections, autoimmune disorders, endocrine system disorders, neuropsychiatric disorders, ocular disorders, cardiovascular events, hypersensitivity reactions, pulmonary disorders, and hepatic disorders.

Commonly reported adverse drug reactions from CHC and CHB studies include infections, thrombocytopenia, anaemia, lymphadenopathy, hypothyroidism, hyperthyroidism, anorexia, depression, anxiety, insomnia, aggression, headache, paraesthesia, syncope, memory impairment, vision disturbances, xerophthalmia, vertigo, tachycardia, peripheral oedema, palpitations, flushing, gastrointestinal disorders such as diarrhoea, nausea and stomatitis, alopecia, dermatitis, rash, increased sweating, photosensitivity, muscle pains, impotence, fatigue, and injection site reactions.

For the currently proposed new indications, PV and ET, the PEG-IFN-α-2a dose should be individually titrated from a starting dose of 45 µg once weekly up to a maximum of 180 µg once weekly (subcutaneous administration). The maintenance dose, 180 µg once weekly, is the same dose as that recommended for treatment of CHC and CHB. Treatment of CHC and CHB, however, has a recommended duration of up to 48 weeks, while treatment of PV or ET may continue as long as the patient benefits from and tolerates the treatment.

In support of the current variation application, in terms of safety data the MAH briefly discussed the latest post-marketing information from the original MAH Roche (PBRER 2020) and from the current MAH in the EU (pharmaand GmbH), together with relevant safety information from published articles or conference abstracts describing clinical trials or retrospective analyses of PEG-IFN-α-2a use in patients with PV and ET.

Among the literature data, three 'key studies' on safety have been identified by the MAH. These are prospective studies, using the currently proposed dosage of 180 µg/week, and are described in some detail in one or several full articles.

The key safety studies are:

- the Phase III study NCT01259856 / MPD-RC 112
- the Phase II study NCT01259817/ MPD-RC 111
- the Phase II study NCT00241241 / PVN1

One additional, prospective Phase II study, Study NCT00452023, has been described in several full articles. However, this study used a higher starting dose than that currently proposed, and was not suggested as 'key' to the safety assessment by the MAH. The MAH, however, included this study as one of the pivotal studies for the efficacy assessment (see above).

The remaining publications discussed in the MAH's safety overview describe prospective or retrospective analyses of patients treated with PEG-IFN-α-2a outside the clinical trial setting, and/or are only presented as conference abstracts or short communications.

Patient exposure

2.5.1.1. Post-marketing experience (PSUR)

No company-sponsored clinical trials addressing the indications ET or PV were completed or ongoing during the reporting interval.

The same PSUR presented a search in the company safety database for case reports of off-label indication use.

2.5.1.2. Literature data in ET and PV

Exposure in the three key studies identified by the MAH is described in Table 9 below:

Table 9: Summary of key clinical safety studies of PEG-IFN-α-2a in ET and PV

Study no	Description	Subjects	Dose	Number treated with PEG		Study Duration /Duration of exposure	References
				ET	PV		
MPD-RC 112 NCT01259856	Phase III, Open label Control: HU	Patients with high-risk ET/PV who were treatment-naïve (HU <3 months)	45 - 180 µg/wk s.c	39	43	Up to 64 months per protocol 37 patients completed 24 months of therapy (23 PV, 14 ET)	Mascarenhas et al. (Blood 2018, 2022) Mesa et al. (Blood, 2016)
MPD-RC 111 (NCT01259817)	Phase II	Patients with high-risk PV and high-risk ET who were either refractory or intolerant (R/I) to HU	45 - 180 µg/wk s.c	65	50	Duration of exposure median (range): ET: 78.5 (1-245) weeks PV: 82 (4-209) weeks.	Yacoub et al., (Blood 2017, 2019) Dueck et al., (Blood 2017) Mascarenhas et al. (Leukemia 2019)
PVN1 (NCT00241241)	Phase II	Patients with PV, no previous treatment or only phlebotomies or cytoreductive treatment (incl. HU) for less than 2 years.	90 - 180 µg/wk s.c	-	37	Study duration: 30 months Median follow-up: 31.4 months (Q1-Q3, 26.4-35.1 months).	Kiladjian et al., (Neoplasia 2006, Blood 2008)

PEG= PEG-IFN-α-2a, ET= essential thrombocytaemia, PV= polycytaemia vera, HU=hydroxyurea

Other publications mentioned in the MAH's Clinical Overview of safety are briefly described in Table 10.

Table 10: Supportive safety data

Publications	Description	Subjects	Dose/exposure
Masarova et al. (Blood 2015, Exp Hematol On 2017) Quintás-Cardama et al (J. Clin. Onc.2009, Blood 2010)	Study NCT0045202 Phase II	Untreated and prev. treated patients with ET or PV ET: n=40 PV: n=43	Initial starting dose: 450 µg/week, decreased in a stepwise manner due to toxicity to a final starting dose of 90 mcg/week. Median exposure time: 87 months (IQR, 17–85 months)
Mesa et al. (haematologica 2011)	Abstract/short communication Retrospective analysis, RWD	ET: n=30 PV: n=43 MF: n=15 80% of patients had received at least one prior cytoreductive therapy	Median starting dose 90 µg/week (range: 45-180) peak doses ranging from 45 to 270 µg/week. median duration of treatment of 17 months (range: 2.0-58)
Dhanapal et al., British Journal of Haematology 2021	Abstract/short communication Retrospective analysis, RWD United Kingdom	Patients with MPN ET n=23 PV n=16 myelofibrosis n=2 In 15 patients PEG was first-line treatment	Most patients started on a dose of 45 µg weekly. Average maintenance dose 45 to 135 µg. Treatment duration was between 3 to 60 months
Gill et al., Hematology 2020	HKUCTR-2030 Prospective cohort study. RWD	Patients with PV, ET, PMF, post-PV MF and post-ET MF who received hydroxyurea, PEG-IFNα-2A or ruxolitinib Number treated with PEG: ET, N = 27 PV, N = 9 MF, N = 19	135 µg/wk s.c. median duration of treatment 16 months (range: 1.5–24) for PEG
Loughran et al., British Journal of Haematology 2020	Abstract/short communication Single-centre, retrospective analysis	Patients with a diagnosis of MPN. ET, N=18 PV, N=12 Other, N=3	45 or 90 - 180 µg/wk s.c, or less frequent
Desterro et al., British Journal of Haematology 2019	Single-centre, retrospective study RWD	Patients with a diagnosis of ET N=53 IFN-based therapy was the first choice in 25 patients	160 µg/ month s.c. Median duration of IFN treatment (standard or pegylated) was 4.2 years (range, 0.5–16 years)
(Betti et al., 19th EHA Congress 2014, Betti et al., 46° Congress of the Italian Society of Hematology 2017)	Abstract/short communication RWD	PV, n=22 ET, n=31 MF, n=1 PEG as a first line treatment n=22 PEG after discontinuation of previous treatment n=32 (no response n=3, HU-related mucocutaneous toxicity n=12, or fever n=1)	67 - 90 µg/wk s.c. The median duration of treatment was 182 (range 4-320) weeks in PV, and 34.5 weeks (range 5-304) in ET

Gowin et al. Blood 2011, Haematologica 2012	Retrospective analysis RWD	118 patients (55 PV, 46 ET, 17 MF) The majority of patients (81%) had received at least one prior cytoreductive therapy for their disease (73 hydroxyurea, 39 anagrelide, 37 aspirin, 21 prior interferon (non pegylated), 3 phlebotomy alone)	Median starting dose 80 µg/wk Median maximum dose 90 µg/week median duration of treatment of 17 months (range: 1.0–92)
Raza et al, 19th EHA Congress 2014	Abstract/short communication Retrospective review RWD	15 patients ET n=11 PV n=3 chronic neutrophilic leukaemia n=1	No information
Mesa et al., haematologica 2011	Abstract/short communication Retrospective review RWD	90 patients 46 PV, 30 ET 14 MF 80% of patients had received at least one prior cytoreductive therapy for their disease [58 hydroxyurea, 28 anagrelide, 21 prior interferon (non-pegylated)	45 – 270 µg/wk s.c median duration of treatment 17 months (range: 2.0-58).
Roy et al., Blood 2010	Abstract/short communication Retrospective review RWD	59 patients with ET IFN-α was generally administered as second line after Hydroxyurea. No prior therapy had been used for 6 patients.	88 µg/wk s.c. Median duration 16 months (range 1 day to 45 months)
Kjær et al., PLOS ONE 2016	Retrospective review RWD Genetic analysis	21 patients	11 - 180 µg/wk s.c
Mascarenhas et al., 2019	Study 111 (see above)	Cohort with prior splenic vein thrombosis N=20	45 - 180 µg/wk s.c
Crisà et al., J. Hem. & Onc. 2017	Letter Observational study	PV patients who received either peg-IFN 30 or HU 35 according to the physician choice N=30 treated with PEG	90 - 135 µg/wk s.c.
Ekinci, Merter, 25th EHA Congress 2020	Abstract/short communication Retrospective review RWD	ET n=24 PV n=17	Median treatment duration for PEG-IFN-2a was 16 months (1-17)
Garg et al., British Journal of Haematology 2016	Abstract/short communication Retrospective review RWD	ET n=27 PV n=11	No dose information

Yassin et al, 2012, 2013	Abstract Prospective study	Patients with ET, either no previous treatment or Hydroxyurea or anagralide for less than 1 years N=40	50 µg/week – 135 µg/week or 135 µg/month

IQR = interquartile range
MF = myelofibrosis
MPN = myeloproliferative neoplasms
RWD = Real world data (i.e. patients not treated within a clinical trial)

Adverse events

2.5.1.3. PSUR data

Use in ET or PV

No clinical studies of PEG-IFN-α-2a in ET or PV were closed or ongoing during the latest PSUR period (5 July 2020 to 4 July 2023) for PEG-IFN.

Based upon review, the profile of the clinical AEs in unapproved indications is broadly consistent with the known safety profile of PEG-IFN-α-2a alfa-2a or can be explained by underlying disease.

New safety signals

2.5.1.4. Literature data

In Table 11 below, the MAH summarised the most common adverse events reported in publications included in the current application. Less common AEs in these studies are presented in Table 12. Note that some studies have been described in several different publications, e.g. at different data cutoffs.

The studies identified as 'key' are further described below.

Table 11: Most Common AEs (frequency ≥10 %) – results from clinical studies

Reference	Study	PEG-IFN-α-2a dose	AE type
Mascarenhas et al., 2019	MPD-RC 111 HU resistant/intolerant subjects ET: n=65 PV: n=50	45 - 180 µg/wk s.c	Flushing, injection site irritation, blurry vision, visual changes, bleeding
Yacoub et al., 2017, Yacoub et al., 2019a	MPD-RC 111 HU resistant/intolerant subjects ET: n=65 PV: n=50	45 - 180 µg/wk s.c	Anaemia, leukopenia, lymphocytopenia, neutropenia and thrombocytopenia.
Masarova et al., 2017d	NCT0045202 Untreated and prev. treated patients ET: n=40 PV: n=43	90 - 450 µg/wk s.c	Vascular complications: thrombotic/ bleeding events

Reference	Study	PEG-IFN-α-2a dose	AE type
Masarova et al., 2015, Masarova et al., 2017b, 2017c	NCT0045202 Untreated and prev. treated patients ET: n=40 PV: n=43	90 - 450 µg/wk s.c	Musculoskeletal, neurological, psychological, git, dermatologic, infection/fever, respiratory, cardiovascular, hypothyroidism, leukopenia/neutropenia, thrombocytopenia, anaemia, LFT elevation
Mesa et al., haematologica 2011	RWD	45 – 270 µg/wk s.c	Thrombocytopenia, leukopenia, fatigue Hematological toxicity was Grade 3 or lower
Gill et al., Hematology 2020	RWD	135 µg/wk s.c.	Neutropenia, anaemia, fatigue, liver dysfunction/transaminitis, rash
Betti et al., 19th EHA Congress 2014, Betti et al., 46° Congress of the Italian Society of Hematology 2017	RWD	67 - 90 µg/wk s.c.	Flu-like symptoms, thyroiditis, itching
Gowin et al., Blood 2015	RWD	45 - 90 µg/wk s.c.	Leukopenia, anaemia, thrombocytopenia, fatigue, transaminitis
Gowin et al. Blood 2011, Haematologica 2012	RWD	45 - 180 µg/wk s.c	Fatigue
Yassin et al., 2012, Yassin et al., 2013	Prospective study	50 - 135 µg/wk s.c	Musculoskeletal pain, skin toxicity
Crisà et al., J. Hem. & Onc. 2017	RWD	90 - 135 µg/wk s.c	Haematologic toxicity, flu-like symptoms, liver test elevation
Kiladjian et al., 2006, Kiladjian et al., 2008a	PVN1	90 - 180 µg/wk s.c.	Musculoskeletal pain, skin toxicity, asthenia, and GI symptoms

Table 12: Any AEs (≤10 % or unknown frequency) – results from clinical studies

Reference	Study	PEG-IFN-α-2a dose	AE type
Mascarenhas et al., 2016, Mascarenhas et al., 2018, Mascarenhas et al., 2022	MPD-RC 112	45 - 180 µg/wk s.c	Flu-like symptoms, injection site reaction, peripheral sensory, neuropathy, blurred vision, depression
Quintás-Cardama et al., 2009, Quintás-Cardama et al., 2010, Quintás-Cardama et al., 2013	NCT0045202	90 - 450 µg/wk s.c	Depression, stroke, infection, fatigue, shortness of breath/dyspnoea, retinal toxicity, neuropathy, neutropenia, lupus nephritis
Dhanapal et al., British Journal of Haematology 2021	Retrospective analysis, RWD	45 - 135 µg/wk s.c.	Neutropenia, anaemia, hepatotoxicity, fatigue, arthralgia/myalgia, rash
Ekinci, Merter, 25th EHA Congress 2020		90 - 180 µg/wk s.c	Fever, weight loss
Gill et al., Hematology 2020		135 µg/wk s.c.	Pericarditis, myasthenia gravis

Reference	Study	PEG-IFN-α-2a dose	AE type
Desterro et al., British Journal of Haematology 2019		160 µg/ month s.c.	Fatigue, depression, thyroiditis, second upper limb thrombosis, digital ischaemia, long saphenous vein thrombosis
Betti et al., 19th EHA Congress 2014, Betti et al., 46° Congress of the Italian Society of Hematology 2017		67 - 90 µg/wk s.c.	Atrial fibrillation, elevated liver enzymes, diarrhoea, depressive state, and pulmonary fibrosis
Garg et al., British Journal of Haematology 2016		No dose info	Elevated liver enzymes, anxiety neurosis, thrombotic cerebrovascular accidents, myocardial infarction, sepsis
Gowin et al., Blood 2015		45 - 90 µg/wk s.c.	Myalgia
Gowin et al. Blood 2011, Haematologica 2012		45 - 180 µg/wk s.c	Anaemia, Thrombocytopenia, Leukopenia, Liver function test elevation, Skin/allergic reaction
Yassin et al., 2012, Yassin et al., 2013		50 - 135 µg/wk s.c	GI symptoms
Mesa et al., haematologica 2011	Retrospective analysis, RWD	45 – 270 µg/wk s.c	Anaemia, LFT elevation, Mood disorder
Kjær et al., PLOS ONE 2016		11 - 180 µg/wk s.c	Thyroid dysfunction, abnormal liver function tests, leucopenia or mood changes/depression

2.5.1.4.1. Summary of MAH's key safety data

Study NCT01259856 / MPD-RC 112 *(ANSM, 2022a, Mascarenhas et al., 2022)*

Methods

Study NCT01259856 was a Phase III, open-label, randomised 1:1 study comparing the efficacy of peginterferon alfa-2a treatment with hydroxyurea in 81 patients with essential thrombocythemia and 87 patients with high-risk polycythemia vera. The study was conducted at 24 North American and European sites.

PEG-IFN-α-2a was self-administered by subcutaneous injection at 45 mg weekly and titrated in 45-mg increments monthly to a maximum of 180 mg weekly. HU was initiated at 500 mg twice daily.

Length of therapy was determined by time of entrance into the study. The last subject to enter the study could receive therapy for at most 12 months, and the first subjects could receive therapy for up to 64 months.

An intention-to-treat (ITT) evaluation was performed at 12, 24, and 36 months.

Results

37 patients completed 24 months of therapy (23 PV, 14 ET).

In total, 96% of PV and ET patients in study NCT01259856 had a safety evaluation (HU n=80; PEG-IFN-α-2a n=82).

Grade 3 or higher AEs were reported by 22 (28 %) treated with HU and 38 patients (46 %) treated with PEG-IFN-α-2a (z=2.48, p=0.01).

AEs related to PEG-IFN-α-2a were common (flu-like symptoms, injection site reactions, peripheral sensory neuropathies, visual disturbances). Grade 1/2 depression was reported by 15 % of patients receiving PEG-IFN-α-2a versus 3 % of patients receiving HU. Mucositis and anorexia were significantly

more frequent in the HU arm, while leukopenia, flu-like symptoms, injection site reactions, increases in hepatic aspartate aminotransferase (ASAT) transaminases and depression were more frequent in the PEG-IFN-α-2a arm. In addition, hypertension, fatigue and lymphopenia were more frequently reported in the PEG-IFN-α-2a arm.

During this study, 13 % of patients (21/168) discontinued their treatment due to AEs. Among these were 9/86 (11%) and 12/82 (15%) patients treated with HU and PEG-IFN, respectively.

Study NCT01259817 / MPD-RC 111 *(ANSM, 2022a, Yacoub et al., 2019a)*

The MPD-RC 111 (NCT01259817) study was an international, multicenter, phase 2 open-label clinical trial that evaluated PEG therapy in patients with high-risk PV and high-risk ET who were either refractory or intolerant (R/I) to HU by modified ELN criteria.

A total of 115 patients (ET, 65; PV, 50) participated in the study. One ET patient withdrew from the study before receiving treatment. The safety population therefore consists of 114 patients. Seventy-seven (67.5%) patients were classified as HU-intolerant, and 37 (32.5%) were HU-resistant.

Of the patients treated with PEG-IFN, 72 % received treatment for at least 12 months, with a median (range) duration of 78.5 (1-245) weeks for ET and 82 (4-209) weeks for PV.

At least one AE of any grade was reported by 90.4% of patients. Grade ≥3 AEs, regardless of attribution, occurred in 50 patients (43.8%). The most common AEs (occurring in >10% of patients) are described in Table 13.

The most common haematological adverse reactions of any grade were anaemia and lymphocytopenia. The most frequently reported non-haematological adverse reactions included fatigue, diarrhoea, nausea, headache and injection site reactions.

No deaths occurred in patients during treatment.

Cumulative incidence of a second cancer (excluding nonmelanoma skin cancers) at 2 years was 4% (95% CI, 1%-10%). These consisted of lung adenocarcinoma (PV, 2; ET, 0), spindle cell sarcoma (ET, 1) and melanoma (PV, 1). Four patients discontinued treatment because of secondary cancer (1 each with lung adenocarcinoma, melanoma, spindle cell sarcoma, and pre-existing renal cell cancer).

The discontinuation rate due to AEs was 13.9 %.

Table 13: AEs occurring in >10% in either disease strata, regardless of attribution

	ET (n = 64)		PV (n = 50)	
	All grades	Grade 3+	All grades	Grade 3+
Hematologic				
Anemia	16 (25.0)	4 (6.3)	8 (16.0)	—
Leukopenia	13 (20.3)	1 (1.6)	11 (22.0)	2 (4.0)
Lymphocytopenia	9 (14.1)	1 (1.6)	9 (18.0)	3 (6.0)
Neutropenia	9 (14.1)	5 (7.8)	4 (8.0)	2 (4.0)
Thrombocytopenia	6 (9.4)	—	9 (18.0)	—
Nonhematologic				
Abdominal pain	7 (10.9)	—	2 (4.0)	—
Alanine aminotransferase	6 (9.4)	2 (3.1)	5 (10.0)	—
Arthralgia	9 (14.1)	—	5 (10.0)	2 (4.0)
Bone pain	7 (10.9)	—	4 (8.0)	—
Constipation	9 (14.1)	—	7 (14.0)	—
Cough	11 (17.2)	—	4 (8.0)	—
Cramp	10 (15.6)	—	3 (6.0)	—
Creatinine increased	1 (1.6)	—	6 (12)	—
Depression	8 (12.5)	—	4 (8.0)	1 (2.0)
Diarrhea	9 (14.1)	1 (1.6)	20 (40.0)	—
Dizziness	12 (18.8)	—	7 (14.0)	—
Dyspnea	10 (15.6)	1 (1.6)	5 (10.0)	1 (2.0)
Edema	9 (14.1)	—	9 (18.0)	—
Fatigue	28 (43.8)	1 (1.6)	20 (40.0)	—
Flulike symptoms	11 (17.2)	1 (1.6)	9 (18.0)	—
Headache	20 (31.3)	2 (3.1)	13 (26.0)	1 (2.0)
Hyperuricemia	4 (6.3)	—	9 (18.0)	—
Injection site reaction	13 (20.3)	—	17 (34.0)	—
Insomnia	4 (6.3)	—	8 (16)	—
Lightheadedness	8 (12.5)	—	1 (2.0)	—
Myalgia	10 (15.6)	—	7 (14.0)	—
Nausea	15 (23.4)	—	12 (24.0)	—
Pain	12 (18.8)	1 (1.6)	15 (30.0)	1 (2.0)
Pruritus	15 (23.4)	—	11 (22.0)	—
Rash	7 (10.9)	1 (1.6)	5 (10.0)	1 (2.0)
Upper respiratory infection	8 (12.5)	—	4 (8.0)	—
Urinary tract infection	7 (10.9)	1 (1.6)	5 (10.0)	—
Vomiting	2 (3.1)	—	8 (16.0)	—

Study NCT00241241 / PVN1 *(ANSM, 2022a, Kiladjian et al., 2008a)*

This was a phase 2 multicenter study of pegylated IFN--2a in 40 PV patients. Inclusion criteria were as follows: PV diagnosis according to Polycythemia Vera Study Group (PVSG) criteria, age 18 to 65 years, and no previous treatment or only phlebotomies or cytoreductive treatment for less than 2 years.

AEs of any grade were reported by 89% of patients during the first 12 months of treatment (Table 14). A total of 239 AEs were reported. All reported AEs were of grade 1 or 2, except one grade 3 skin toxicity. The incidence of AEs decreased slightly over time from 64.9 % at the first month of treatment to 50.0 % at 12 months. Most common toxicities during the first month included musculoskeletal pain in 13 patients, skin toxicity in 6, asthenia in 6, and gastrointestinal symptoms in 4. At 12 months, those symptoms were still present in 7, 5, 7, and 2 patients, respectively.

Over the total study duration of 30 months, 9 patients (24.3 %) discontinued treatment due to AEs. In this context, causes of treatment discontinuation for toxicity during the first year (n=3) were: recurring grade 2 neutropenia (n=1), grade 3 skin toxicity after 6 months (n=1), and grade 2 fatigue and headaches after 9 months (n=1). After the first year, toxicity led to treatment discontinuation in 6

additional patients, including liver toxicity (n=1), occurrence of biologic markers of autoimmunity (n=1), muscular pain (n=2), peripheral neurologic toxicity (n=1), and fatigue (n=1).

Table 14: Study PVN1: Adverse events during the first 12 months of treatment

	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12
No. of patients treated	37	37	37	35	34	34
No. of patients with at least one adverse event (%)	24 (64.9)	18 (48.6)	21 (56.5)	19 (54.3)	16 (47.0)	17 (50.0)
No. of adverse events of grade ≥ 3	0	0	0	1 (grade 3)	0	0
Neuropsychiatric	4	6	8	8	6	3
Musculoskeletal	13	7	8	7	4	7
Gastrointestinal	4	4	1	2	2	2
Skin	6	4	5	8 (1*)†	5	5
Endocrinal	2	2	3	3	3	3
Respiratory	—	—	1	1	—	—
Asthenia	6	6	9	10	8 (1*)	7
Hematologic	1	1	2	2 (1*)	—	—
Libido	1	1	1	1	—	—
Fever	7	2	1	2	1	1
Cardiovascular	1	1	—	1	—	—
Others‡	—	—	—	2	1	—

— indicates 0 events.
*Led to treatment discontinuation.
†Including the only grade 3 toxicity recorded in the study.
‡Weight loss (6 months), hot flashes (6 and 9 months).

Study NCT0045202 *(Masarova et al, 2015, 2017)*

This study was not identified as a key safety study by the MAH, however, is suggested as one of the pivotal studies for the efficacy assessment.

Study NCT0045202 was an ad hoc analysis of data from a prospective, open-label, single-center, phase 2 trial of PEG-IFN-α-2a in patients with essential thrombocythemia and polycythemia vera. Patients could be either newly diagnosed or previously treated.

Forty-three patients with polycythemia vera and 40 with essential thrombocythemia were enrolled.

PEG-IFN-α-2a was administered subcutaneously once weekly. The initial starting dose was 450 µg/week but was decreased in a stepwise manner due to toxicity to a final starting dose of 90 µg/week: 3 patients were started at a dose of 450 µg/week, 3 at 360 µg/week, 19 at 270 µg/week, 26 at 180 µg/week, and 32 at 90 µg/week. During the study, the dose was modified based on toxicity or lack of efficacy.

Yearly discontinuation rates varied from 5% to 19%, with a median discontinuation rate of 5 patients/year (range, 3–16 patients/year). The median PEG-IFN-α-2a exposure time was 87 months (interquartile range 17–85 months).

Among all patients, fatigue (75%), muscle pain (52%), nausea/vomiting and diarrhoea (44%), and depression (32%) were the most common AEs.

Severe hematologic AEs (Grade 3/4 or recurrent events despite dose reductions) occurred in 89% (n=22/25) of patients with polycythemia vera and 83% (n=20/24) of those with essential thrombocythemia. The AE rate decreased with time on therapy, yet did not completely disappear.

New Grade 3/4 toxicities unrelated to dose occurred ≥24 months from start of therapy in 10–17% of patients annually. The most common late AEs were fatigue (prevalent in all years), anaemia and neutropenia (highest in the 3rd & 6th year), and depression (highest in 4th–6th year). Three patients with essential thrombocythemia experienced 4 episodes of Grade 4 neutropenia, 3 of which occurred on a dose < 90 mcg/week.

Autoimmune thyroiditis, the most frequently reported autoimmune side effect of IFN-α 17, was observed in 15 patients (18%), but only 2 were severe (grade 3) enough to warrant treatment discontinuation. Four other patients (3 essential thrombocythemia, 1 polycythemia vera) developed autoimmune toxicities after a median time on therapy of 47.5 months (range, 26 – 78 months). All cases were biopsy proven and included hepatitis, central nervous system vasculitis, lupus nephritis and other presentations (Sjogren syndrome, dermatitis and vasculitis).

Eighteen patients (22%) discontinued therapy due to drug-related toxicities, G1–2 in 8 (10%) or Grade 3–4 in 10 (12%). Discontinuation rates were not correlated with PEG-IFN-α-2a dosage. The median time on therapy for these patients was 11 months (range, 2–60), although 4 patients requested discontinuation after < 6 months. Half of these patients had more than 1 type of toxicity, with the most common being neuropsychiatric (n=5 patients), gastrointestinal (n=4), and hematologic (n=3).

An additional 12 patients had therapy held for >6 months due to toxicity, with a median time on hold of 29 months (range, 7–79). The most common toxicities leading to significant treatment interruptions were Grade 3 neutropenia and multiple Grade 2 toxicities, such as anaemia, fatigue, musculoskeletal pain, diarrhoea, neuropathy, and depression. Ten of 12 patients were rechallenged at a lower dose of PEG-IFN, but because of persistent and recurrent toxicities (mostly Grade 3 hematologic) they remained off therapy.

Three patients died while on study, but none were thought to be related to the study drug. One patient died of central pontine myelinolysis due to rapid correction of Grade 3 hyponatremia, one due to complications from severe aortic stenosis and pulmonary hypertension, and one as a consequence of a motor vehicle accident.

The long-term safety data from this study shows that the type and severity of late adverse events are similar to those observed earlier in the course of therapy; however, new late adverse events did occur even after 60 months on treatment, were often unrelated to dose or response status, and were therapy-limiting.

2.5.2. Discontinuation due to adverse events

The MAH summarised discontinuation rates due to adverse events in the different published studies included in the current application in Table 15.

Table 15: Discontinuation rate due to AEs

Reference	**PEG-IFN-α-2a dose**	**Discontinuation rate (% of PEG-IFN-α-2a treated patients)**
Yacoub et al., Blood 2017, 2019a (Study MPD-RC 111)	45 - 180 µg/wk s.c	13.9%
Dueck et al., Blood 2017 (Study MPD-RC 111)	45 - 180 µg/wk s.c	14%
Kiladjian et al., Neoplasia 2006, Kiladjian et al., Blood 2008a (Study PVN1)	90 - 180 µg/wk s.c.	24%
Masarova et al., Blood 2017b, Lancet Haematol 2017c (Study NCT0045202)	90 - 450 µg/wk s.c	22%

Reference	PEG-IFN-α-2a dose	Discontinuation rate (% of PEG-IFN-α-2a treated patients)
Quintás-Cardama et al., J Clin Oncol 2009, Quintás-Cardama et al.,Blood 2010, Quintás-Cardama et al., Blood 2013 (Study NCT0045202)	90 - 450 µg/wk s.c	20%
Dhanapal et al., British Journal of Haematology 2021	45 - 135 µg/wk s.c.	2%
Gill et al., Hematology 2020	135 µg/wk s.c.	9%
Loughran et al., British Journal of Haematology 2020	45 - 180 µg/wk s.c	36%
Desterro et al., British Journal of Haematology 2019	160 µg/ month s.c.	11%
Betti et al., 19th EHA Congress 2014, Betti et al., 46° Congress of the Italian Society of Hematology 2017	67 - 90 µg/wk s.c.	63%
Gowin et al., Blood 2011, Gowin et al., haematologica 2012	45 - 180 µg/wk s.c	17%
Raza et al., 19th EHA Congress 2014	No dose information	7%
Mesa et al., haematologica 2011	45 – 270 µg/wk s.c	12%
Roy et al., Blood 2010	88 µg/wk s.c.	19%
Kjær et al., PLOS ONE 2016	11 - 180 µg/wk s.c	24%
Mascarenhas et al., 2019	45 - 180 µg/wk s.c	20%
Crisà et al., J. Hem. & Onc. 2017	90 - 135 µg/wk s.c.	13%
Ekinci, Merter, 25th EHA Congress 2020	90 - 180 µg/wk s.c.	5%
Garg et al., British Journal of Haematology 2016	No dose information	8%

2.5.3. Post marketing experience

Exposure data from the latest PSUR for PEG-IFN-α-2a, covering the period 5 July 2020 to 4 July 2023, is presented in the section above.

During the reporting period, no actions were taken due to safety reasons in clinical trials with PEG IFN- α-2a.

During the reporting period, the following actions were taken due to safety reasons in the post-marketing setting with PEG-IFN-α-2a:

- Closed system transfer devices (CSTDs) appear to be used with non-antibody drug conjugate therapeutic protein products such as an additional protective measure for health care practitioners, without such devices being referenced in the drug label. The MAH has concerns about this practice because there is insufficient evidence that these CSTDs are compatible with

Pegasys and has therefore updated the Core Data Sheet (CDS) with a statement specifying the need for using a sterile needle and syringe to prepare Pegasys.

- Following a signal assessment on Neuromyelitis Optica Spectrum Disorder (NMOSD) with interferon alfa (European Pharmacovigilance Issue Tracking Tool No. 19532), the Pharmacovigilance Risk Assessment Committee (PRAC) recommended that the European Union Summary of Product Characteristics (EU SmPC) of Pegasys should be updated (adaption 03 Sep 2020, published 28 Sep 2020). The wording was provided by PRAC; the Undesirable Effect "Optic Neuritis" with frequency "not known" was included in Section 4.8 of the SmPC.

2.5.4. Discussion on clinical safety

Pegasys (PEG-IFN-α-2a) is marketed in the EU and several other countries worldwide for over 20 years in the indications CHC and CHB in adults and children. Therefore, PEG-IFN-α-2a has a well-known safety profile.

As the maximum dose proposed for PV and ET is the same as the recommended dose for CHC and CHB, safety data from the long-term experience of PEG-IFN-α-2a use in CHC and CHB may be considered largely relevant also for assessment of safety in the PV and ET indications.

Also the published data submitted with the current variation indicate a well-established use of PEG-IFN-α-2a in myeloproliferative neoplasms in clinical practice (i.e. outside clinical trials) for more than 10 years, although the dosage has varied.

The MAH primarily referred to three 'key' safety studies, which were prospective clinical trials in which the currently proposed dosage of PEG-IFN-α-2a was used. These studies included a total of 104 ET patients and 130 PV patients. Only one of these studies was controlled, with hydroxyurea (HU) as the comparator.

Altogether, the submitted published clinical studies and retrospective analyses report an overall similar safety profile in patients with myeloproliferative neoplasms as that observed in CHC and CHB patients. No new safety concerns have been raised.

In the HU-controlled study, a considerably higher rate of Grade ≥3 AEs was reported in the PEG-IFN-α-2a arm (46%) than in the HU arm (28%). The nature of the Grade ≥3 AEs was, however, not further described in the publications on this study. The discontinuation rate due to AEs was only slightly higher in the PEG arm than in the HU arm (15% vs 11%), indicating that tolerability of the two treatments was relatively similar.

Treatment durations of several years have been reported in PV and ET. CHC and CHB treatment has a recommended duration of up to 48 weeks. However, there is some experience of longer-term treatment also of CHC and CHB, and the available data do not give raise to any new safety concerns regarding treatment of longer duration. In one study in PV/ET, 18% of patients developed autoimmune thyroiditis, which is a higher rate ('Very common') than previously reported in CHC/CHB ('Common'). Further, 5% of patients in this study developed other autoimmune disorders after >2 years of treatment. A higher risk for any ADR, including autoimmune ADRs, may likely be expected with longer exposure time.

SmPC

From a safety perspective, the SmPC has been adequately updated to reflect the use of PEG in PV and ET.

In section 4.2 of the SmPC, a recommendation is given to reduce the dose or temporarily discontinue treatment if adverse reactions develop during therapy. This recommendation is somewhat vague. However, section 4.4 provides more specific information on which AEs that should lead to treatment interruption or discontinuation, which is considered sufficient.

Pegasys is contraindicated for paediatric patients with pre-existing psychiatric disorders. A contraindication for Pegasys to adult patients with pre-existing psychiatric disorders is not appropriate, as such a contraindication would exclude a large fraction of chronic hepatitis patients from treatment, given that psychiatric disorders are common in adult such patients. There is a boxed warning regarding psychiatric adverse events in the beginning of section 4.4, which is considered appropriate also for the ET/PV patient populations and allows treating physicians and patients to take an informed decision.

2.5.5. Conclusions on clinical safety

PSUR data on use in unauthorised indications as well as data from the literature indicate a well-established use of PEG-IFN-α-2a in myeloproliferative neoplasms in clinical practice for more than 10 years. The literature data submitted with the current variation do not give raise to any new safety concerns for the ET/PV populations, compared with the previously known safety profile in CHC/CHB patients. From a safety point of view, the variation can be recommended for approval.

2.5.6. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 10.2 with the following content:

Safety concerns

No important identified or potential risks have been included in the RMP. No missing information have been identified.

Pharmacovigilance plan

No Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

Risk minimisation measures

Not applicable as there are no safety concerns for Pegasys.

2.7. Update of the Product information

As a consequence of this group of new indications, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indications are:

PV

Pegasys is indicated as monotherapy in adults for the treatment of polycythaemia vera

ET

Pegasys is indicated as monotherapy in adults for the treatment of essential thrombocythaemia

PV and ET belong to a group of heterogeneous disorders of the haematopoietic system – so called myeloproliferative neoplasms (MPNs) – characterised by an overproduction of blood cells. A variety of abnormalities in cell counts are observed depending on the type of MPN, including erythrocytosis, thrombocytosis, and leukocytosis. (Gerds et al., JNCCN 2022)

Central to the pathology of MPNs is a constitutively activated JAK/STAT signalling pathway, caused by various, mostly mutually exclusive driver mutations, such as JAK2-V617F, myeloproliferative leukaemia protein (MPL), CALR, or other less known mutations within the JAK/STAT signalling pathway.

PV

PV characteristically displays trilineage (erythroid, megakaryocytic and granulocytic) proliferation in the BM with predominantly erythrocytosis in the peripheral blood. (Amerikanou et al., Best. Pract. Res. Cl. Ha. 2022)

Clinical features in PV include mild-to-moderate degree of splenomegaly, and of constitutional symptoms, including fatigue and pruritus, weight loss, night sweats, early satiety, bone pain, symptoms of hyperviscosity, leukocytosis, thrombocytosis, microvascular symptoms (e.g., headaches, lightheadedness, visual disturbances, atypical chest pain, erythromelalgia, paresthesia), thrombotic and bleeding complications, and risk of leukaemic transformation or fibrotic progression. (Gerds et al., JNCCN 2022, Tefferi et al., Blood Cancer Journal 2018b b)

In a retrospective study of 1545 adult patients (median age 61 years) with PV, conducted by the International Working Group for MPN Research and Treatment, thrombosis history at diagnosis was documented in 23 % of the patients (16 % arterial and 7.4 % venous events). The rate of post-diagnosis vascular events, after a median follow-up of 6.9 years, was 21 % (12 % arterial and 9 % venous events). Leukaemic transformation incidence ranges from 5.5-18.7 % over the course of 15 years. (Tefferi et al., Blood Cancer Journal 2018b)

The median survival of untreated symptomatic patients with PV is 6 to 18 months, whereas survival of treated patients is 10 years or more.

ET

The hallmarks of ET are megakaryocyte hyperplasia with resultant thrombocytosis and abnormally high platelet production (Amerikanou et al., Best. Pract. Res. Cl. Ha. 2022, Bose and Verstovsek, Ther Adv Hematol 2019).

Clinical symptoms in ET include mild splenomegaly, leukocytosis, microvascular symptoms, thrombotic and bleeding complications, increased occurrence of first trimester miscarriage, and time-dependent risk of leukaemic transformation or fibrotic progression (Tefferi et al., Blood Cancer Journal 2018a).

Thrombotic complications occur in 10-20 % of ET patients with a predominance of arterial thrombotic events. For example, 109 (12 %) of 891 adult ET patients experienced arterial (n=79) or venous (n=37) thrombosis after a median follow-up of 6.2 years. (Tefferi et al., Blood Cancer Journal 2018a, Tefferi, Barbui, Am. J. Hematol. 2020) Leukaemic transformation incidence ranges from ~2.1-5.3 % over the course of 15 years for adult ET patients. (Tefferi et al., Blood Cancer Journal 2018a)

Median survival in ET has been reported to range from approximately 15-22 years. Age is by far the most important risk factor for survival in ET, with median survival of 35 years for patients age ≤40 years. (Thiele et al., Am J Hematol. 2022)

3.1.2. Available therapies and unmet medical need

PV

In the initial phase of the disease, phlebotomy is the cornerstone of treatment with the objective of maintaining haematocrit below 45%, a cut-off that has been shown to be associated with a lower risk of cardiovascular death and major thrombosis. As PV patients are at a high risk of thrombosis, phlebotomy is often accompanied by low dose aspirin. Cytoreductive therapy is recommended in patients with persistent haematological abnormalities, clinical symptoms, poor compliance with or intolerance of phlebotomy, and those at a high risk of thrombosis ("high-risk PV-patients").

First-line cytoreductive treatment in PV is hydroxyurea (HU)-based therapy. The exact mechanism of action of HU is unknown, its most important effect appears to be in blocking the ribonucleotide reductase system resulting in the inhibition of deoxyribonucleic acid (DNA) synthesis.

PV patients treated with HU may develop resistance to the drug or intolerance. Symptoms of intolerance may include gastrointestinal symptoms, pneumonitis, and fever at any dose of HU. (Nurgat, Lawrence, J. Onc. Pharm. Pract 2022)

HU presents a potential genotoxic risk that contraindicates conception during treatment for both men and women. In addition, patients who have received or are receiving HU for long periods have developed secondary leukaemia, with no established link to HU treatment or the primary disease itself, or skin cancer. (SmPC Hydrea, 2021 and 2023) Consequently, younger patients, who may have had longer exposure to HU, potentially have an increased carcinogenic risk (Tremblay, Mascarenhas,

2020). Of note, although assumed in multiple publications, neither prospective nor well-designed retrospective studies in PV patients implicate HU as amplifying the intrinsic vulnerability of PV patients for leukaemic transformation (Tefferi, Barbui, Am. J. Hematol. 2023).

Another product, a PEG-formulation of IFN-α (ropegIFN-α-2b, Besremi) is authorised as first-line monotherapy in adults for the treatment of PV without symptomatic splenomegaly since 2019. (EMA, 2022a). In second-line treatment, ruxolitinib is indicated in cases of resistance or intolerance to HU.

ET

The main goal of current treatments in ET, similar to PV, is to reduce the risk of thrombosis and haemorrhage as well as at the alleviation of symptoms (How, Hobbs, 2022).

A risk-adapted therapy in ET patients is based on the likelihood of patients developing thrombotic complications. These complications are the leading cause of morbidity and mortality in ET patients. (Vannucchi et al., Annals of Oncology 2015) Very low risk ET (age ≤60 years, no thrombosis history) might not require treatment while low-dose aspirin (81-100 mg) therapy is advised for low-risk disease, in the absence of contraindications. (Gerds et al., JNCCN 2021, Thiele et al., Am J Hematol. 2022)

Cytoreductive therapy is dictated by individual risk for thrombosis, which considers 2 major risk factors: age >60 years and history of thrombosis. The presence of either one of these 2 risk factors defines high-risk for thrombosis and their absence low-risk. (Thiele et al., Am J Hematol. 2022)

First-line drug of choice for cytoreductive therapy is HU (Thiele et al., Am J Hematol. 2022). As described before, the exact mechanism of action is unknown for HU, while its most important effect appears to be in blocking the ribonucleotide reductase system resulting in the inhibition of DNA synthesis. ET patients treated with HU may develop resistance or intolerance.

HU treatment has a potential genotoxic risk that contraindicates conception during treatment for both men and women. In addition, patients who have received or are receiving HU for long periods have developed secondary leukaemia, with no established link to HU treatment or the primary disease itself, or skin cancer. (SmPC Hydrea, 2021 and 2023) Of note, although supposed in multiple publications, neither prospective nor well-designed retrospective studies in ET patients implicate HU as amplifying the intrinsic vulnerability of ET patients for leukaemic transformation (Tefferi, Barbui, Am. J. Hematol. 2023).

Alternatively, anagrelide is authorised in the EU for the reduction of elevated platelet counts in at risk ET patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. (Nurgat, Lawrence, J. Onc. Pharm. Pract 2022)

3.1.3. Main clinical studies

This application is primarily based on bibliographical data from four prospective, open-label studies performed with Pegasys (Pegylated Interferon Alfa-2a):

- Pegylated Interferon Alfa-2a Salvage Therapy in High Risk Polycythemia Vera (PV) or Essential Thrombocythemia (ET) MPD-RC 111 (NCT01259817) Yacoub et al., Blood 2019 (efficacy and safety). This study reports a single arm trial including HU intolerant or resistant subjects. The primary endpoint was ORR at 12 months. Peginterferon alfa dosing was started at 45ug. The study included 50 patients with PV and 65 patients with ET.
- Randomized Trial of Pegylated Interferon Alfa-2a Versus Hydroxyurea in Polycythemia Vera (PV) and Essential Thrombocythemia (ET) MPD-RC 112 (NCT01259856) Mascarenhas et al., Blood 2022

(efficacy and safety). This was an open-label RCT comparing hydroxyurea and peginterferon alfa in treatment-naïve subjects. The starting dose was 45ug. The primary endpoint was complete responses (CR) at 12 months. The study included 44 (HU) and 43 (PEG) patients with PV, and 42 (HU) + 39 (PEG) patients with ET.

- Pegasys in Patients With Myeloproliferative Diseases (NCT00452023) Masarova et al. Lancet 2017 (efficacy). This is a single centre case series of 43 patients with PV and 40 patients with ET. The starting dose was 450 ug/week. The primary endpoint was complete responses.
- Efficacy and Safety of Pegylated Interferon Alfa in Polycythemia Vera (NCT00241241) Kiladjian et al., Blood 2008 (safety), reports 37 patients with PV treated with 90-180 ug of peginterferon alfa.

3.2. Favourable effects

For efficacy the MAH primarily referred to three 'key' studies, which were prospective clinical trials including PV and ET patients.

- Study MPD-RC 111 had intolerance and/or resistance to HU as an inclusion criterion. The primary endpoint was ORR at 12 months.
    - In PV patients from this study, ORR was 60% (95% CI, 45.2%-73.6%), which differed significantly from the null hypothesis of 35% (P < .001).
    - In ET patients from this same study, ORR was 69% (95% CI, 56.6%-80.0%), which also differed significantly from 35% (P < .001).
    - In PV patients, 22% attained a CR and in ET 43% attained a CR.
- In study MPD-RC 112 which only enrolled treatment-naïve patients, a complete response at 12 months was reached by 30% of PV patients treated with hydroxyurea, and 28% of those treated with peginterferon alfa. ORR was 68% and 86% respectively. In patients with ET, CR at 12 months was observed in 45% of those receiving HU and 44% for those receiving PEG. ORR was 71% and 69% respectively.
- In the experience reported by Masarova, 77% of patients with PV reached a complete response, as did 73% of those with ET. Median durations of response was 65 and 58 months, respectively.

3.3. Uncertainties and limitations about favourable effects

Only one of these studies Study MPD-RC 111 reported by Yacoub et al. had resistance/intolerance to hydroxyurea (HU) as inclusion criterion. This was a single arm trial. Therefore, there is uncertainty about the precise efficacy estimate. Moreover, duration of responses does not appear to have been reported.

The supportive study MPD-RC 112 reported by Mascarenhas et al, is a small, open label investigator-initiated study, whereas study NCT00452023 reported by Masarova et al is a case series. Both support the efficacy of peginterferon alfa, but do not provide precise estimates of absolute or relative benefit. Moreover, in the Masarova case, the starting dose was substantially higher than the currently proposed posology.

Notably, objective responses are not anticipated to occur without therapy. Therefore, this endpoint isolates the effects of peginterferon alfa in ET and PV, also in the absence of a comparator.

3.4. Unfavourable effects

For safety, the MAH primarily referred to three 'key' studies, which were prospective clinical trials in which current posology of PEG-IFN-α-2a was used. These studies included a total of 104 ET patients and 130 PV patients. Only one of these studies was controlled, with hydroxyurea (HU) as the comparator. Broadly, based on the three 'key' studies, the other studies and retrospective analyses referred to, and recent PSUR data, no new safety concerns were identified in the ET/PV populations, as compared with the known safety profile in CHC or CHB patients. Thus, the previously known risks of blood disorders, infections, autoimmune disorders, endocrine system disorders, neuropsychiatric disorders, ocular disorders, cardiovascular events, hypersensitivity reactions, pulmonary disorders, and hepatic disorders were also seen in the ET/PV populations. In the controlled study, a considerably higher rate of Grade ≥3 AEs was reported in the PEG-IFN-α-2a arm (46%) than in the HU arm (28%). The nature of the Grade ≥3 AEs was not further described in the publications on this study. However, the discontinuation rate due to AEs was only slightly higher in the PEG arm than in the HU arm (15% vs 11%).

3.5. Uncertainties and limitations about unfavourable effects

Due to the nature of the data provided, i.e. published studies with limited information and including uncontrolled and/or retrospective analyses, the precise frequency of ADRs cannot be readily estimated.

3.6. Effects Table

Table 16: Effects Table for Pegasys for the treatment of patients with PV or ET who are resistant and/or intolerant to hydroxyurea

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ORR	ORR at 12 months	%	In PV patients ORR was 60% (95% CI, 45.2%-73.6%) In ET patients, ORR was 69% (95% CI, 56.6%-80.0%)	N/A (single-arm)	SoE: ORR significantly different from the null hypothesis of 35% (P < .001) SoE: same as above. P < .001	Study MPD-RC 111 (Yacoub *et al* Blood 2019) Literature data
CR (primary endpoint)	CR at 12 months	%	In PEG treated PV patients, CR was 28% In PEG treated ET patients, CR was 44%	In HU treated PV patients, CR was 30% In HU treated ET patients, CR was 45%	SoE: Rate ratio (95% CI) for combined ET/PV, 95% CI (PEG – HU) 0.95 (0.64, 1.42)	Study MPD-RC 112 (Mascarenhas *et al* *Blood* 2022) Literature data

Unfavourable Effects

Effect	Frequency (%)				Uncertainties / Strength of evidence
	ET (n=64)		PV (n=50)		
	All grades	Grade 3+	All grades	Grade 3+	Study MPD-RC 111 Literature data Uncontrolled study
Anemia	25	6.3	16	-	
Leukopenia	20	1.6	22	4	
Lymphocytopenia	14	1.6	18	6	
Neutropenia	14	7.8	8	4	
Thrombocytopenia	9.4	-	18	-	
ALT increase	9.4	3.1	10	-	
Depression	12.5	-	8	-	
Diarrhoea	14	1.6	40	-	
Edema	14	-	18	-	
Fatigue	44	1.6	40	-	
Flu-like symptoms	17	1.6	18	-	
Nausea	23	-	24	-	
Pain	19	1.6	30	2	
Pruritus	23	-	22	-	
Rash	11	1.6	8	-	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

This is a literature-based application for extensions of the indication to encompass patients with PV or ET. The use of peginterferon alfa for the treatment of these diseases is well established in the EU and recommended by consensus guidelines.

The MAH has submitted a number of investigator-initiated studies performed with Pegasys, demonstrating clinically relevant complete response rates in both disease settings. Notably, such responses do not generally occur in the natural course of ET or PV. Therefore, notwithstanding methodological limitations, efficacy estimates are identified as drug effects without a control arm.

The submitted studies are from patients that are either treatment-naïve or resistant/intolerant to hydroxyurea.

The literature data submitted with the current variation do not give raise to any new safety concerns for the ET/PV populations, compared with the previously known safety profile in CHC/CHB patients.

In the context of recommended use per relevant clinical treatment guidelines and of the submitted data, the benefit/risk balance of peginterferon alfa 2a in PV or ET is considered positive.

3.7.2. Balance of benefits and risks

The benefits outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Pegasys in ET and PV is considered positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Grouped application consisting of:
Extensions of indication to include treatment of Polycythaemia Vera (PV) and Essential thrombocytopenia (ET) for PEGASYS for the pre-filled syringes, based on published data of clinical studies conducted in support of the efficacy and safety of Pegasys for the treatment of ET and PV. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.2 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.3.

The group of variations leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I, IIIA and IIIB and to the Risk Management Plan are recommended.