IQWiG Reports – Commission No. A19-72

Ropeginterferon alfa-2b (polycythaemia vera) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse events
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D	European Quality of Life – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HU	hydroxyurea
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
JAK2	janus kinase 2
PT	Preferred Term
PV	polycythaemia vera
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	Symptom Organ Class
SPCs	Summaries of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ropeginterferon alfa-2b. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 28 August 2019.

Research question

The aim of this report was to assess the added benefit of ropeginterferon alfa-2b in comparison with the appropriate comparator therapy (ACT) in adult patients with polycythaemia vera without symptomatic enlargement of the spleen.

The research questions presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of ropeginterferon alfa-2b

Research question	Subindication	ACT[a]
1	Treatment-naive adult patients with polycythaemia vera without symptomatic enlargement of the spleen or patients pretreated with hydroxyurea who are not resistant to or intolerant of hydroxyurea[b, c]	Hydroxyurea
2	Adult patients with polycythaemia vera without symptomatic enlargement of the spleen pretreated with hydroxyurea and resistant to or intolerant of hydroxyurea[c]	Ruxolitinib

a. Presentation of the respective ACT specified by the G-BA.
b. Also comprised patients who had not adequately responded to treatment with hydroxyurea before.
c. Bloodletting therapy (phlebotomy) is recommended as primary and/or concomitant therapy of polycythaemia vera in order to lower the haematocrit stably to below 45%. Accordingly, phlebotomy should be an option in both study arms.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

For question 1 (treatment-naive patients or patients pretreated with hydroxyurea [HU] without resistance or intolerance to HU), the company specified HU as appropriate comparative therapy. For research question 2 (patients pretreated with HU, who are resistant to or intolerant of HU), it specified ruxolitinib. The company thus followed the G-BA's specifications for both research questions.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs were used for the derivation of the added benefit. This concurred with the company's inclusion criteria.

Results for research question 1: Treatment-naive patients or patients pretreated with HU without resistance or intolerance to HU

Study pool and study characteristics

The study pool included the PROUD-PV study. In its dossier, the company additionally used the results of the extension study CONTINUATION-PV of the PROUD-PV study. However, this extension study cannot be interpreted for the benefit assessment, since the proportion of patients who switched from the PROUD-PV study to the extension study is too low on the one hand, and on the other, it differs significantly between the treatment arms.

PROUD-PV is an open-label, randomized active-controlled trial on the comparison of ropeginterferon alfa-2b with HU and a study duration of 12 months. The study included adult treatment-naive patients or adult patients pretreated with HU with polycythaemia vera. A total of 257 patients were randomized in a ratio of 1:1; 127 patients to the ropeginterferon alfa-2b arm and 130 patients to the HU arm. The study treatment was performed in compliance with the recommendations of the respective Summaries of Product Characteristics (SPCs). Unless contraindicated, patients in both study arms were additionally administered daily doses of 100 mg acetylsalicylic acid. Phlebotomy should be performed when the haematocrit value exceeds 45%.

Primary outcome of the study was the haematological response (haematocrit < 45% without phlebotomy within the last 3 months and platelet count < 400 x 10^9/L and white blood cell count < 10 x 10^9/L and normal spleen size).

Results

Overall consideration of the available data results in the following picture:

- The data presented by the company were incomplete with regard to content. Informative data are only available for the outcomes of the categories “overall survival” and “side effects”. No data are available for the outcome category “morbidity” except for “health status (European Quality of Life – 5 Dimensions [EQ-5D] visual analogue scale [VAS])”. In particular, there is a lack of information on the patients' symptoms during the course of the study. The dossier also contained no data for health-related quality of life. Subgroup analyses on the PROUD-PV study are completely missing. The incomplete data situation permitted no final weighing of positive and negative effects of ropeginterferon alfa-2b.
- Based on the available data, an inferiority of ropeginterferon alfa-2b in comparison with HU cannot be excluded with regard to essential treatment goals (avoidance of late complications, reduction in symptom burden). On the one hand, this applies because data are missing (see above). On the other hand, the outcomes “haematological response” and “number of phlebotomies” presented as supplementary information imply that treatment with ropeginterferon alfa-2b might be inferior to treatment with HU, since the direction of effect for both outcomes was to the disadvantage of ropeginterferon alfa-2b, and moreover the result on phlebotomies in the maintenance phase is statistically significant. Whether

this applies equally to treatment-naive and pretreated patients is unclear due to the lack of corresponding subgroup analyses. The differences in the area of side effects in favour of ropeginterferon alfa-2b (gastrointestinal disorders [Symptom Organ Class (SOC)] and influenza [Preferred Term (PT)]) did not lead to the derivation of an added benefit of ropeginterferon alfa-2b in this data situation.

Overall, this resulted in no hint of an added benefit of ropeginterferon alfa-2b in comparison with hydroxyurea. An added benefit is therefore not proven.

Results for research question 2: patients pretreated with HU, who are resistant to or intolerant of HU

No data are available for the assessment of ropeginterferon alfa-2b for the treatment of adult patients with polycythaemia vera pretreated with HU without symptomatic enlargement of the spleen and with resistance or intolerance to HU. This resulted in no hint of an added benefit of ropeginterferon alfa-2b in comparison with ruxolitinib. An added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug ropeginterferon alfa-2b in comparison with the ACT was assessed as follows:

Research question 1: Treatment-naive patients or patients pretreated with HU without resistance or intolerance to HU

Based on the incomplete data presented by the company, an added benefit of ropeginterferon alfa-2b versus the ACT HU has not been proven in treatment-naive patients or in patients with polycythaemia vera pretreated with HU without symptomatic enlargement of the spleen and without resistance or intolerance to HU.

Research question 2: patients pretreated with HU, who are resistant to or intolerant of HU

Since the company presented no data for the assessment of the added benefit of ropeginterferon alfa-2b in comparison with the ACT ruxolitinib in adult patients pretreated with HU without symptomatic enlargement of the spleen and with resistance or intolerance to HU, an added benefit of ropeginterferon alfa-2b is not proven.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3 presents a summary of the probability and extent of the added benefit of ropeginterferon alfa-2b.

Table 3: Ropeginterferon alfa-2b – probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit**
1	Treatment-naive adult patients with polycythaemia vera without symptomatic enlargement of the spleen or patients pretreated with hydroxyurea who are not resistant to or intolerant of hydroxyurea[b, c]	Hydroxyurea	Added benefit not proven
2	Adult patients with polycythaemia vera without symptomatic enlargement of the spleen pretreated with hydroxyurea and resistant to or intolerant of hydroxyurea[c]	Ruxolitinib	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Also comprised patients who had not adequately responded to treatment with hydroxyurea before.
c. Bloodletting therapy (phlebotomy) is recommended as primary and/or concomitant therapy of polycythaemia vera in order to lower the haematocrit stably to below 45%. Accordingly, phlebotomy should be an option in both study arms.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of ropeginterferon alfa-2b in comparison with the appropriate comparator therapy (ACT) in adult patients with polycythaemia vera without symptomatic enlargement of the spleen.

The research questions presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of ropeginterferon alfa-2b

Research question	Subindication	ACT[a]
1	Treatment-naive adult patients with polycythaemia vera without symptomatic enlargement of the spleen or patients pretreated with hydroxyurea who are not resistant to or intolerant of hydroxyurea[b, c]	Hydroxyurea
2	Adult patients with polycythaemia vera without symptomatic enlargement of the spleen pretreated with hydroxyurea and resistant to or intolerant of hydroxyurea[c]	Ruxolitinib

a. Presentation of the respective ACT specified by the G-BA.
b. Also comprised patients who had not adequately responded to treatment with hydroxyurea before.
c. Bloodletting therapy (phlebotomy) is recommended as primary and/or concomitant therapy of polycythaemia vera in order to lower the haematocrit stably to below 45%. Accordingly, phlebotomy should be an option in both study arms.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

For question 1 (treatment-naive patients or patients pretreated with HU without resistance or intolerance to HU), the company specified HU as ACT. For research question 2 (patients pretreated with HU, who are resistant to or intolerant of HU), it specified ruxolitinib. The company thus followed the G-BA's specifications for both research questions.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs were used for the derivation of the added benefit. This concurred with the company’s inclusion criteria.

2.3 Research question 1: Treatment-naive patients or patients pretreated with HU without resistance or intolerance to HU

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on ropeginterferon alfa-2b (status: 8 July 2019)
- bibliographical literature search on ropeginterferon alfa-2b (last search on 8 July 2019)
- search in trial registries for studies on ropeginterferon alfa-2b (last search on 8 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ropeginterferon alfa-2b (last search on 18 September 2019)

The check identified no additional relevant study.

2.3.1.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: study pool - RCT, direct comparison: ropeginterferon alfa-2b vs. hydroxyurea

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
PROUD-PV	Yes	Yes	No
a. Study for which the company was sponsor.			
RCT: randomized controlled trial; vs.: versus			

The study pool included the PROUD-PV study. In its dossier, the company additionally used the results of the extension study CONTINUATION-PV of the PROUD-PV study. However, this extension study cannot be interpreted for the benefit assessment, since the proportion of patients who switched from the PROUD-PV study to the extension study is too low on the one hand, and on the other, it differs significantly between the treatment arms. Thus, the structural equality between the patient populations of the treatment arms is not guaranteed in the extension study (see Section 2.6.3.2).

Section 2.3.4 contains a reference list for the studies included.

2.3.1.2 Study characteristics

Table 6 and Table 7 describe the PROUD-PV study for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: ropeginterferon alfa-2b vs. hydroxyurea

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PROUD-PV	RCT, open-label, parallel	Treatment-naive[b] patients or patients pretreated with HU[c] (≥ 18 years) with polycythaemia vera, with and without splenomegaly	Ropeginterferon alfa-2b (N = 127) HU (N = 130)	Screening: up to 28 days Treatment: 12 months Follow-up: 28 days	48 centres in Austria, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Poland, Romania, Russia, Slovakia, Spain, Ukraine 10/2013–04/2016	Primary: Haematological response[d] Secondary: Mortality, health status, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.

b. Treatment-naive patients had to meet at least one of the following criteria: > 60 years of age, at least 1 prior cardiovascular PV-related event (stroke, acute cerebrovascular event such as transient ischaemic attack (TIA), myocardial infarction, unstable angina pectoris, acute peripheral arterial occlusive disease, other significant arterial event, pulmonary infarction [pulmonary embolism], splanchnic vein thrombosis [mesenteric ischemia], portal vein thrombosis, Budd-Chiari syndrome, iliofemoral vein thrombosis [deep vein thrombosis], other significant venous events) or poor tolerance of phlebotomies, progressive splenomegaly, thrombocytes > 1000 x 10^9/L or leukocytes > 10 x 10^9/Ll.

c. Patients pretreated with HU had to be non-responders with regard to the primary outcome, had to have been pretreated with HU for no longer than 3 years and had to be free of resistance or intolerance to HU (need for phlebotomy to reduce haematocrit < 45% or uncontrolled myeloprofliferation [platelet count > 400 x 10^9/L and white blood cell count 10 x 10^9/L], after 3 months of treatment with 2 g/day or the individual maximum tolerated HU dose, lower leg ulcers).

d. Primary outcome consisting of the components: haematocrit < 45% without phlebotomy within the last 3 months and platelet count < 400 x 10^9/L and white blood cell count < 10 x 10^9/L and normal spleen size (≤ 12 cm for women, ≤ 13 cm for men).

AE: adverse event; HU: hydroxyurea; N: number of randomized patients; PV: polycythaemia vera; RCT: randomized controlled trial; TIA: transient ischaemic attack

Table 7: Characteristics of the intervention – RCT, direct comparison: ropeginterferon alfa-2b vs. hydroxyurea (multipage table)

<table>
<tr><th>Study</th><th>Intervention</th><th>Comparison</th></tr>
<tr><td rowspan="3">PROUD-PV</td><td>Treatment-naive patients:
Ropeginterferon alfa-2b every 2 weeks, starting dose 100 µg SC:
▪ response-guided[a] dose adjustment by 50 µg every 2 weeks up to a maximum of 500 µg in week 12
▪ maintenance phase[b] after week 12</td><td>Treatment-naive patients:
HU starting dose, 500 mg, orally, as capsules, daily
▪ gradual response-guided[a] dose adjustment every 2 weeks:
HU[d] dosing steps
<table>
<tr><th>Grade</th><th>HU dosage</th></tr>
<tr><td>1</td><td>500 mg per day (starting dose)</td></tr>
<tr><td>2</td><td>500 mg per day and 1000 mg per day, alternating</td></tr>
<tr><td>3</td><td>1000 mg per day</td></tr>
<tr><td>4</td><td>1000 mg per day and 1500 mg per day, alternating</td></tr>
<tr><td>5</td><td>1500 mg per day</td></tr>
<tr><td>6</td><td>1500 mg per day and 2000 mg per day, alternating</td></tr>
<tr><td>7</td><td>2000 mg per day</td></tr>
<tr><td>8</td><td>2500 mg per day</td></tr>
<tr><td>9</td><td>3000 mg per day</td></tr>
</table>
▪ Maintenance phase[b] after week 12</td></tr>
<tr><td>Patients[c] pretreated with HU
ropeginterferon alfa-2b, starting dose 50 µg SC:
▪ response-guided[a] dose adjustment by 50 µg every 2 weeks up to a maximum of 500 µg until week 12 at simultaneous gradual reduction of the HU dose[c]
▪ maintenance phase[b] after week 12</td><td>Patients pretreated with HU:
▪ at the start of the study, maintenance of the previous HU dose followed by a response-guided dose adjustment every 2 weeks following the same scheme as in the therapy-naïve patients
▪ maintenance phase[b] after week 12</td></tr>
<tr><td colspan="2">Pretreatment
Allowed:
▪ HU < 3 years
Not allowed:
▪ systemic cytoreductive treatment
▪ systemic treatment with pegylated or non-pegylated interferon alfa
Concomitant treatment
Allowed:
▪ acetylsalicylic acid 100 mg/day unless acetylsalicylic acid is contraindicated
▪ phlebotomy at haematocrit > 45%
▪ nonsteroidal anti-inflammatory drugs (e.g. paracetamol) and antihistamines as monotherapy or in combination for the treatment of injection site reactions
administration of paracetamol or NSAID 8–10 hours, 24 hours and 48 hours after administration of the study medication was recommended to avoid flu-like symptoms
▪ anticoagulants for the avoidance of thromboembolic adverse events
Not allowed:
▪ cytoreductive drugs (e.g. pipobroman, busulfan, radioactive P32)</td></tr>
</table>

Table 7: Characteristics of the intervention – RCT, direct comparison: ropeginterferon alfa-2b vs. hydroxyurea (multipage table)

Study	Intervention	Comparison
a. Response criteria: haematocrit < 45%, platelet count < 400 x 10^9/L and white blood cell count < 10 x 10^9/L b. In the maintenance phase, dose adjustments were possible in this arm. c. In weeks 1–2, the previous HU dose was administered in addition to ropeginterferon alfa-2b. From week 3 to week 12, HU was gradually reduced at 2-week intervals. From week 13, HU was no longer administered. d. From 1000 mg, the daily dose was divided into 2 portions to be taken in the morning and evening, without dividing tablets. 1500 mg were divided into 1000 mg and 500 mg and 2500 mg in 1500 mg and 1000 mg. AE: adverse event; HU: hydroxyurea; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SC: subcutaneous		

Study PROUD-PV

PROUD-PV is an open-label, randomized active-controlled trial on the comparison of ropeginterferon alfa-2b with HU and a study duration of 12 months. The study included adult treatment-naive patients or adult patients pretreated with HU with polycythaemia vera. Treatment-naive patients had to meet at least one of the following criteria: more than 60 years of age, at least 1 prior (PV-related) cardiovascular event or poor tolerance of phlebotomies. Patients pretreated with HU had to be non-responders with regard to the primary outcome (haematocrit < 45% without phlebotomy within the last 3 months and platelet count < 400 x 10^9/L and white blood cell count < 10 x 10^9/L and normal spleen size). Moreover, they had to have been pretreated with HU for no longer than 3 years and had to be free of resistance or intolerance to HU. Resistance to HU has been operationalized in the study according to the criteria of Barosi 2009 [3] (including the continued need for phlebotomies after patients have been treated with at least 2 g HU per day for at least 3 months).

A total of 257 patients were randomized in a ratio of 1:1; 127 patients to the ropeginterferon alfa-2b arm and 130 patients to the HU arm. Randomization was stratified by prior HU treatment (yes/no), age (≤ 60/> 60 years) and history of a thromboembolic event (yes/no). 3 patients in the control group were randomized, but not treated, because they had withdrawn their informed consent to participation in the study.

The study treatment corresponded to the recommendations of the respective Summary of Product Characteristics (SPCs) for ropeginterferon alfa-2b [4] and HU [5]. Unless contra-indicated, patients in both study arms were additionally administered daily doses of 100 mg acetylsalicylic acid. Phlebotomy should be performed when the haematocrit value exceeds 45%. At the start of the study, pretreated patients in the HU arm initially underwent continued treatment with unchanged individual HU doses. Since these patients were non-responders to the previous treatment with HU, optimization of the HU dosage was necessary and was to be performed according to the scheme described in Table 7. However, the study documents contain no information on the actual dose adjustments made in the patients pretreated with HU.

Primary outcome of the study was the haematological response (haematocrit < 45% without phlebotomy within the last 3 months and platelet count < 400 x 10^9/L and white blood cell count < 10 x 10^9/L and normal spleen size). Patient-relevant secondary outcomes were "mortality", "health status" and "AEs". The treatment was carried out over 12 months, after which further treatment was possible in the extension study CONTINUATION-PV.

Table 8 presents the characteristics of the patients included in the PROUD-PV study.

Table 8: Characteristics of the study population – RCT, direct comparison: ropeginterferon alfa-2b vs. hydroxyurea

Study Characteristics Category	**Ropeginterferon alfa-2b**	**Hydroxyurea**
PROUD-PV	N[a] = 127	N[a] = 130
Age [years], mean (SD)	59 (11)	58 (13)
Sex [F/M], %	54/46	53/47
Duration of the PV disease [months]		
Mean (SD)	12.6 (24.7)	15.7 (25.7)
Median [Q1; Q3]	1.9 [0.7; 11.2]	3.6 [0.7; 20.0]
Pretreatment with HU, n (%)		
Yes	45 (35.4[b])	37 (29.1[b])
No	82 (65.6)[b]	90 (70.1)[b]
Duration of the pretreatment with HU[c] [months], mean (SD)	12.6 (11.1)	12.2 (10.6)
JAK2 mutation, n (%)		
Yes	127 (100)	126 (99.2)
Missing	0 (0)	1 (0.8)
Haematocrit [%], mean (SD)	49.5 (5.4)	49.8 (5.5)
Leucocytes [10^9/L], mean (SD)	12.2 (5.3)	12.6 (5.2)
Platelets [10^9/L], mean (SD)	556.7 (257.0)	528.3 (236.4)
Spleen size [cm], mean (SD)	13.4 (3.2)	13.6 (3.3)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	21 (16.5)	19 (14.6)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant (> 10 percent).
b. Institute's calculation.
c. Based on patients pretreated with HU.

F: female; HU: hydroxyurea; JAK2: janus kinase 2; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; PV: polycythaemia vera; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Patient characteristics were largely balanced between the treatment arms. The mean age of the patients was approx. 59 years; slightly more than half of them were women. With 3.6 months, patients in the HU arm had a slightly longer median disease duration than those in the

ropeginterferon alfa-2b arm with approx. 2 months. Almost all patients had janus kinase 2 (JAK2) mutation. There are no data on the number of performed phlebotomies and on treatment discontinuations.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: ropeginterferon alfa-2b vs. hydroxyurea

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
PROUD-PV	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes of the PROUD-PV study was rated as low. This concurs with the company's assessment.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

The following patient-relevant outcomes should be considered in the assessment (for reasons see Section 2.6.4.3):

- Mortality
  - overall survival
- Morbidity
  - symptoms of the disease (e.g. fatigue, pruritus)
  - health status (EQ-5D VAS)
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs
  - severe AEs (CTCAE grade 3)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.6.4.3.2 of the full dossier assessment).

Table 10 shows for which outcomes data were available in the study included.

Table 10: Matrix of the outcomes – RCT, direct comparison: popeginterferon alfa-2b vs. hydroxyurea

Study	Outcomes									
	All-cause mortality	Symptoms of the disease	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3)	Gastrointestinal disorders (SOC, AE)	Nausea (PT, AE)	Influenza (PT, AE)
PROUD-PV	Yes	No[a]	Yes	No[a]	Yes	Yes	Yes	Yes	Yes	Yes

a. No data available

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life – 5 Dimensions; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The outcomes “haematological response (haematocrit < 45% and without phlebotomy within the last 3 months) and number of phlebotomies are presented as supplementary information.

2.3.2.2 Results

Overall consideration of the available data results in the following picture:

- The data presented by the company were incomplete with regard to content. Informative data are only available for the outcomes of the categories “overall survival” and “side effects”. No data are available for the outcome category “morbidity” except for “health status (EQ-5D VAS)”. In particular, there is a lack of information on the prevention of thromboembolic events and on the patients' symptoms during the course of the study. However, the prevention of thromboembolic events as well as an improvement of the disease-related symptoms – such as fatigue or pruritus – are the main goals of treatment in the present therapeutic indication [6-8]. Data for health-related quality of life are also lacking. Moreover, subgroup analyses on the PROUD-PV study are completely missing, also for the stratification factors “pretreatment”, “age” and “history of thromboembolic

events". The incomplete data situation permitted no final weighing of positive and negative effects of ropeginterferon alfa-2b.

Appendix A.1 presents the results on those outcomes for which data are available as supplementary information; Appendix A.2 shows the tables on common AEs.

- Based on the available data, an inferiority of ropeginterferon alfa-2b in comparison with HU cannot be excluded with regard to essential treatment goals (avoidance of late complications, reduction in symptom burden). On the one hand, this applies because relevant data are missing (see above). On the other hand, the outcomes "haematological response" and "number of phlebotomies" presented as supplementary information imply that treatment with ropeginterferon alfa-2b might be inferior to treatment with HU, since the direction of effect for both outcomes was to the disadvantage of ropeginterferon alfa-2b, and moreover the result on phlebotomies in the maintenance phase is statistically significant. Whether this applies equally to treatment-naive and pretreated patients is unclear due to the lack of corresponding subgroup analyses. The differences in the area of side effects in favour of ropeginterferon alfa-2b (gastrointestinal disorders [System Organ Class (SOC)] and influenza [Preferred Term (PT)]) did not lead to the derivation of an added benefit of ropeginterferon alfa-2b in this data situation.

Overall, this resulted in no hint of an added benefit of ropeginterferon alfa-2b in comparison with hydroxyurea. An added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

Based on the incomplete data presented by the company, an added benefit of ropeginterferon alfa-2b versus the ACT "HU" has not been proven in treatment-naive patients or in patients pretreated with HU with polycythaemia vera without symptomatic enlargement of the spleen and without resistance or intolerance to HU.

2.3.4 List of included studies

PROUD-PV

AOP Orphan Pharmaceuticals. Pegylated interferon alpha-2b versus hydroxyurea in polycythemia vera (PROUD-PV): study details [online]. In: ClinicalTrials.gov. 28.11.2016 [Accessed: 02.10.2019]. URL: https://ClinicalTrials.gov/show/NCT01949805.

AOP Orphan Pharmaceuticals. A randomized, open-label, multicenter, controlled, parallel arm, phase III study assessing the efficacy and safety of AOP2014 vs. hydroxyurea in patients with polycythemia vera [online]. In: EU Clinical Trials Register. [Accessed: 02.10.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-005259-18

AOP Orphan Pharmaceuticals. A randomized, open-label, multicenter, controlled, parallel arm, phase III study assessing the efficacy and safety of AOP2014 vs. hydroxyurea in patients with polycythemia vera: clinical trial results [online]. In: EU Clinical Trials Register. 11.03.2018 [Accessed: 02.10.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-005259-18/results.

AOP Orphan Pharmaceuticals. A randomized, open-label, multicenter, controlled, parallel arm, phase III study assessing the efficacy and safety of AOP2014 vs. hydroxyurea in patients with polycythemia vera: study PROUD-PV; clinical study report [unpublished]. 2017.

2.4 Research question 2: patients pretreated with HU, who are resistant to or intolerant of HU

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on ropeginterferon alfa-2b (status: 8 July 2019)
- bibliographical literature search on ropeginterferon alfa-2b (last search on 8 July 2019)
- search in trial registries for studies on ropeginterferon alfa-2b (last search on 8 July 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ropeginterferon alfa-2b (last search on 18 September 2019)

No relevant study was identified from the check.

2.4.2 Results on added benefit

No data are available for the assessment of ropeginterferon alfa-2b for the treatment of adult patients with polycythaemia vera pretreated with hydroxyurea without symptomatic enlargement of the spleen and with resistance or intolerance to hydroxyurea. This resulted in no hint of an added benefit of ropeginterferon alfa-2b in comparison with ruxolitinib. An added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of ropeginterferon alfa-2b in comparison with the ACT ruxolitinib in adult patients pretreated with HU with polycythaemia vera without symptomatic enlargement of the spleen and with resistance or intolerance to HU, an added benefit of ropeginterferon alfa-2b is not proven.

2.4.4 List of included studies

Not applicable as the company did not present any relevant data for the benefit assessment.

2.5 Probability and extent of added benefit – summary

Table 11 presents a summary of the probability and extent of the added benefit of ropeginterferon alfa-2b.

Table 11: Ropeginterferon alfa-2b – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Treatment-naive adult patients with polycythaemia vera without symptomatic enlargement of the spleen or patients pretreated with hydroxyurea who are not resistant to or intolerant of hydroxyurea[b, c]	Hydroxyurea	Added benefit not proven
2	Adult patients with polycythaemia vera without symptomatic enlargement of the spleen pretreated with hydroxyurea and resistant to or intolerant of hydroxyurea[c]	Ruxolitinib	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Also comprised patients who had not adequately responded to treatment with hydroxyurea before.
c. Bloodletting therapy (phlebotomy) is recommended as primary and/or concomitant therapy of polycythaemia vera in order to lower the haematocrit stably to below 45%. Accordingly, phlebotomy should be an option in both study arms.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived an indication of major added benefit for research question 1 (treatment-naive patients or patients pretreated with HU without resistance or intolerance to HU), based on the results of the extension study CONTINUATION-PV. For research question 2 (patients pretreated with HU with resistance or intolerance to HU), the company also assessed the added benefit as not proven.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-72-ropeginterferon-alfa-2b-polycythaemia-vera-benefit-assessment-according-to-35a-social-code-book-v.12597.html.