URN 2420: Peginterferon alfa-2 and ropeginterferon alfa-2b to treat myeloproliferative neoplasms (Polycythaemia Vera)

Narrative summary of papers presented for review

Three papers were presented for review by NHS England. Paper 1 is phase 3, open-label, non-inferiority randomised controlled trial (RCT) (PROUD-PV) (n=254) comparing ropeginterferon alfa-2b (n=127) to hydroxyurea (n=127) for 12 months in patients with polycythaemia vera (PV). Paper 1 also reports the interim results (at 36 months) from the extension study to this RCT (CONTINUATION-PV) (n=171). In the extension study, patients either continued treatment with ropeginterferon alfa-2b (n=95) or received best available treatment (n=76), which was either hydroxyurea or another standard first-line treatment. The studies were conducted in 48 centres in Europe. Paper 2 reports the six year outcomes of the PROUD-PV RCT and the CONTINUATION-PV extension study. 67/95 (71%) patients in the ropeginterferon alfa-2b group and 52/74 (70%) patients in the best available treatment group completed at least six years of follow-up. Paper 3 reports the five year outcomes of the PROUD-PV RCT and the CONTINUATION-PV extension study. 70/95 (74%) patients in the ropeginterferon alfa-2b group and 57/76 (75%) patients in the best available treatment group completed five years of follow-up.

Paper 1: Gisslinger et al 2020. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study.

This paper reports a phase 3, open-label, non-inferiority RCT (PROUD-PV) comparing ropeginterferon alfa-2b to hydroxyurea for 12 months. This paper also reports the interim results (at 36 months) from the extension study to this RCT (CONTINUATION-PV). In this extension study, patients either continued treatment with ropeginterferon alfa-2b or received best available treatment, which was either hydroxyurea or another standard first-line treatment (see below for further details). The studies were conducted in 48 centres in Europe with patients recruited between September 2013 and March 2015.

Participants in PROUD-PV were 254 adults (≥18 years old) with early stage[1] PV diagnosed by the World Health Organisation's 2008 criteria, including a *JAK2* Val617Phe mutation. Patients with previous cytoreductive treatment other than hydroxyurea were excluded, as were patients with major comorbidities that could be exacerbated by interferon alfa treatment. Patients were also required to have a stable haematocrit of less than 45% before randomisation. Median age was 60.0 years (range 30 to 85) in the ropeginterferon alfa-2b group and 59 (54%) were females. Median age was 60.0 years (range 21 to 81) in the hydroxyurea group and 60 (53%) were females. Randomisation was stratified by age, history of thromboembolic events and previous hydroxyurea treatment. The intervention group received ropeginterferon alfa-2b (n=127), administered subcutaneously every two weeks starting at 100 µg, or 50 µg if the patient was transitioning from hydroxyurea. The comparator groups received oral hydroxyurea (n=127) starting at 500 mg per day. In both

[1] No history of cytoreductive treatment or less than three years of previous hydroxyurea treatment. Patients with no history of cytoreductive therapy required a documented need of cytoreductive therapy. Patients previously treated with hydroxyurea for less than three years were eligible if they could potentially benefit from participation in the trial due to no complete response, resistance or intolerance to hydroxyurea according to modified European LeukemiaNet criteria.

groups, dosing was individualised for each patient and increased until blood counts normalised[2] (up to a maximum of 500 µg every two weeks for ropeginterferon alfa-2b and up to a maximum of 3,000 mg daily for hydroxyurea[3]). The mean efficacious dose was reached after approximately 3.7 months for ropeginterferon alfa-2b and approximately 2.6 months for hydroxyurea. All patients received concomitant treatment with low-dose aspirin unless contraindicated. Twenty-one (17%) patients from the ropeginterferon alfa-2b group and 16 (13%) patients from the hydroxyurea group discontinued the RCT prematurely after receiving treatment. Median follow-up was 52.0 weeks (IQR 51.9 to 52.1) in the ropeginterferon alfa-2b group and 52.0 weeks (IQR 51.9 to 52.1) in the hydroxyurea group.

171 patients continued to the prospective CONTINUATION-PV extension study. Patients were eligible for the extension study if they had completed PROUD-PV and had normalisation of at least two of three main blood parameters (haematocrit, platelets and white blood cells), or a reduction of more than 35% from baseline in at least two of three main blood parameters, or normalisation of spleen size or clinically confirmed benefit from treatment with ropeginterferon alfa-2b[4]. Patients originally randomised to ropeginterferon alfa-2b continued the same treatment with individualised dosing every two, three or four weeks (n=95). At 36 months, median dose per administration of ropeginterferon alfa-2b was 425 µg (IQR 250 to 500). Patients originally randomised to hydroxyurea received best available treatment (n=76), selected by the investigator from hydroxyurea, conventional interferon alfa, pegylated interferon alfa (other than ropeginterferon alfa-2b), anagrelide, a *JAK2* inhibitor, phosphorus-32 or busulfan. The authors stated that at 36 months, 97% of the best available treatment group were receiving hydroxyurea and 3% conventional interferon alfa. At 36 months, median dose per administration of hydroxyurea was 1,000 mg (750 to 1,375). Seventeen (18%) patients from the ropeginterferon alfa-2b group and seven (9%) patients from the best available treatment group discontinued the study prematurely after receiving treatment. Median follow-up was 182.1 weeks (IQR 166.3 to 201.7) in the ropeginterferon alfa-2b group and 164.5 weeks (IQR 144.4 to 169.3) in the best available treatment group.

Paper 2: Gisslinger et al 2023. Event-free survival in patients with polycythemia vera treated with ropeginterferon alfa-2b versus best available treatment.

This paper reports on the prospective long term (six year) follow up of the RCT (n=254) and extension study (n=171) reported in Paper 1. Efficacy outcomes after six years follow-up were reported for patients who continued in the CONTINUATION-PV extension study (n=119). Safety outcomes after six years follow-up were reported for all patients who participated in the original PROUD-PV RCT (n=254) regardless of whether they continued to the extension study. A total of 67/95 (71%) patients in the ropeginterferon alfa-2b group and 52/74 (70%) patients in the best available treatment group completed at least six years of follow-up. In the sixth year of treatment, the median four-weekly dose of ropeginterferon alfa-2b was 499 µg (IQR ± 268 to 782) administered at an extended three or four week interval in most (62%) patients. The authors stated that most (88%) patients in the best available

[2] Dosing was increased until the haematocrit was less than 45% without phlebotomy and normalised platelet and leucocyte counts (platelet count <00 x 10^9/L and leucocyte count <10 x 10^9/L) were reached and maintained (defined by the investigator's discretion).
[3] Detail of the maximum doses in PROUD-PV was reported in Gisslinger et al 2023 (Paper 2).
[4] Normalisation of disease-related micro-vasculatory symptoms, substantial decrease of *JAK2* Val617Phe allelic burden.

treatment group remained on hydroxyurea with a median dose of 1,000 mg per day (IQR 750 to 1,500). The maximum treatment duration was 7.3 years.

Paper 3: Kiladjian et al 2022. Long-term outcomes of polycythemia vera patients treated with ropeginterferon alfa-2b.

This paper reports on the prospective long term (five year) follow up of the RCT (n=254) and extension study (n=171) reported in Gisslinger et al 2020 (Paper 1). Haematological and molecular outcomes after five years follow-up were reported for patients who continued in the CONTINUATION-PV extension study (n=119). Safety outcomes after five years follow-up were reported for all patients who participated in the original PROUD-PV RCT (n=254) regardless of whether they continued to the extension study. A total of 70/95 (74%) patients in the ropeginterferon alfa-2b group and 57/76 (75%) patients in the best available treatment group completed five years of follow-up. Patients in the ropeginterferon alfa-2b group continued the same treatment with individualised dosing every two, three or four weeks. At five years, the authors stated that *"most patients in the best available treatment arm received only hydroxyurea, but at 60 months, five had switched to interferon therapy (ropeginterferon alfa-2b, pegylated interferon alfa-2b or recombinant interferon alfa-2a) and two had switched to ruxolitinib".*

Effectiveness

Complete haematological response[5] with normal spleen size[6]

Gisslinger et al 2020 reported that in the PROUD-PV RCT, 26/122 (21%) patients with PV in the ropeginterferon alfa-2b group and 34/123 (28%) patients with PV in the hydroxyurea group had a complete haematological response with normal spleen size at 12 months (group difference -6.57 (95%CI -17.23 to 4.09), non-inferiority not shown[7], p=0.23).

Gisslinger et al 2020 also reported complete haematological response with normal spleen size in the CONTINUATION-PV extension study at three follow-up timepoints, with no statistical significance between the groups (Table 1).

Table 1: Complete haematological response with normal spleen size in CONTINUATION-PV reported by Gisslinger et al 2020

	Ropeginterferon alfa-2b	Best available treatment	Difference between groups
12 months	27/91 (30%)	33/76 (43%)	p=0.066
24 months	34/91 (37%)	23/67 (34%)	p=0.68
36 months	38/90 (42%)	21/69 (30%)	p=0.16

One included paper reported no statistically significant difference in complete haematological response with normal spleen size at 12 months between patients with PV who received ropeginterferon alfa-2b (n=127) or hydroxyurea (n=127) (non-inferiority not shown). The same paper also reported no statistically significant

[5] Complete haematological response was defined as haematocrit <45% without phlebotomy (at least three months since the last phlebotomy), platelet count <400 x 10^9/L and leucocyte count <10 x 10^9/L.
[6] Longitudinal diameter of ≤12cm for women and ≤13cm for men.
[7] The null hypothesis was inferiority of the response for ropeginterferon alfa-2b by at least 10.5% of the response for hydroxyurea after 12 months.

difference in complete haematological response with normal spleen size at 12 months (n=167), 24 months (n=158) or 36 months (n=159) between patients with PV who received ropeginterferon alfa-2b or best available treatment.

Complete haematological response[5] and improved disease burden[8]

Gisslinger et al 2020 reported complete haematological response and improved disease burden for patients with PV in the CONTINUATION-PV extension study at three follow-up timepoints, with the difference between groups reaching statistical significance at 36 months (Table 2).

Table 2: Complete haematological response and improved disease burden in CONTINUATION-PV reported by Gisslinger et al 2020

	Ropeginterferon alfa-2b	Best available treatment	Rate ratio (95% CI)
12 months	44/95 (46%)	36/76 (51%)	0.91 (0.67 to 1.23), p=0.52
24 months	47/95 (50%)	27/71 (38%)	1.27 (0.89 to 1.81), p=0.18
36 months	50/95 (53%)	28/74 (38%)	1.42 (1.01 to 2.00), p=0.044

CI: confidence intervals

Gisslinger et al 2020 also stated that the proportion of patients who maintained their complete haematological response with improved disease burden over the 36-month follow-up was statistically significantly higher with ropeginterferon alfa-2b than best available treatment (28/95 (30%) vs 11/76 (15%), p=0.025).

One included paper reported no statistically significant difference in complete haematological response and improved disease burden at 12 months (n=171) or 24 months (n=166) between patients with PV who received ropeginterferon alfa-2b or best available treatment. At 36 months (n=169), the response was statistically significantly better with ropeginterferon alfa-2b (53%) compared to best available treatment (38%). The same paper also reported that a statistically significantly higher proportion of patients who received ropeginterferon alfa-2b maintained their response over the 36-month follow-up (30% vs 15%).

Complete haematological response[5]

Gisslinger et al 2020 reported that in the PROUD-PV RCT, 53 of 123 (43%) patients with PV in the ropeginterferon alfa-2b group and 57 of 125 (46%) patients with PV in the hydroxyurea group had a complete haematological response at 12 months (group difference -3.02 (95%CI -15.55 to 9.52), p=0.63). The authors stated that previous hydroxyurea treatment had no significant effect on complete haematological response at 12 months.

[8] Disease burden was defined as disease-related signs (clinically significant splenomegaly) and symptoms (microvascular disturbances and headache) as assessed by the investigator.

Gisslinger et al 2020 also reported complete haematological response in the CONTINUATION-PV extension study at three follow-up timepoints, with the difference between groups reaching statistical significance at 24 months (Table 3).

Table 3: Complete haematological response in CONTINUATION-PV reported by Gisslinger et al 2020

	Ropeginterferon alfa-2b	Best available treatment	Rate ratio (95% CI)
12 months	59/95 (62%)	57/76 (75%)	0.85 (0.70 to 1.04), p=0.12
24 months	67/95 (71%)	33/67 (49%)	1.42 (1.08 to 1.86), p=0.011
36 months	67/95 (71%)	38/74 (51%)	1.38 (1.07 to 1.79), p=0.012

CI: confidence intervals

Gisslinger et al 2020 stated that the proportion of patients with PV who maintained their complete haematological response over the 36-month follow-up was statistically significantly higher with ropeginterferon alfa-2b than best available treatment (37/95 (39%) vs 11/76 (15%), p=0.0011).

Kiladjian et al 2022 reported that after five years follow-up of the CONTINUATION-PV population, there was no statistically significant difference in the proportion of patients with PV who had a complete haematological response between the ropeginterferon alfa-2b group (53/95, 55.8%) and the best available treatment group (33/75, 44.0%) (rate ratio 1.30 (95%CI 0.95 to 1.77), p=0.0974).

Gisslinger et al 2023 reported that after six years follow-up of the CONTINUATION-PV population, a statistically significantly higher proportion of patients with PV in the ropeginterferon alfa-2b group had a complete haematological response (48/88, 54.5%) compared to patients with PV in the best available treatment group (2/63, 34.9%) (risk ratio 1.55 (95%CI 1.07 to 2.26), p=0.02). Gisslinger et al 2023 also stated that patients receiving ropeginterferon alfa-2b spent a statistically significantly higher proportion of time in complete haematological response (mean 60.9%) than patients receiving best available treatment (mean 41.2%) (p=0.04).

One included paper reported no statistically significant difference in complete haematological response at 12 months between patients with PV who received ropeginterferon alfa-2b (n=127) or hydroxyurea (n=127). The same paper also reported no statistically significant difference in complete haematological response at 12 months (n=171) between patients with PV who received ropeginterferon alfa-2b or best available treatment. At 24 months (n=162) and 36 months (n=169), the response was statistically significantly better with ropeginterferon alfa-2b (71% at both timepoints) compared to best available treatment (49% and 51% respectively). The same paper also reported that a statistically significantly higher proportion of patients who received ropeginterferon alfa-2b maintained their response over the 36-month follow-up (39% vs 15%). The second and third included papers reported longer term follow-up (five and six years respectively) of the patients reported in the first paper. There was no statistically significant difference in complete haematological response

at five years (n=170) between patients with PV who received ropeginterferon alfa-2b or best available treatment. At six years (n=151) a statistically significantly higher proportion of patients had a complete haematological response with ropeginterferon alfa-2b (55%) compared to best available treatment (35%). The same paper also reported that a statistically significantly higher proportion of patients who received ropeginterferon alfa-2b spent a higher mean proportion of time in complete haematological response over the six-year follow-up (61% vs 41%).

Molecular response[9]

Gisslinger et al 2020 reported that in the PROUD-PV RCT, 42 of 123 (34%) patients with PV in the ropeginterferon alfa-2b group and 52 of 123 (42%) patients with PV in the hydroxyurea group had a molecular response at 12 months (group difference -8.07 (95%CI -19.99 to 3.84), p=0.19). The authors stated that a reduction in mean *JAK2* Val617Phe allele burden compared with baseline was evident in both groups at 12 months (from 42% (standard deviation (SD) 23.5) to 31% (SD 22.7) in the ropeginterferon alfa-2b group and from 43% (SD 24.1) to 26% (SD 21.5) in the hydroxyurea group).

Gisslinger et al 2020 also reported molecular response in the CONTINUATION-PV extension study at three follow-up timepoints, with the difference between groups reaching statistical significance at 24 months (Table 4).

Table 4: Molecular response in CONTINUATION-PV reported by Gisslinger et al 2020

	Ropeginterferon alfa-2b	Best available treatment	Rate ratio (95% CI)
12 months	41/94 (44%)	38/75 (51%)	0.84 (0.62 to 1.15), p=0.29
24 months	64/94 (68%)	25/75 (33%)	1.94 (1.38 to 2.72), p=0.0001
36 months	62/94 (66%)	20/74 (27%)	2.31 (1.56 to 3.42), p<0.0001

CI: confidence intervals

The authors stated that the ropeginterferon alfa-2b group showed a steady decrease in mean *JAK2* Val617Phe allele burden from baseline to 36 months (43% (SD 23.4) vs 20% (SD 21.3)). The best available treatment group showed a transient reduction from baseline which was lost by 36 months (43% (SD 23.0) vs 39% (SD 25.9)). The difference in *JAK2* Val617Phe allele burden between groups was statistically significant (p<0.0001)[10].

Kiladjian et al 2022 reported that after five years follow-up of the CONTINUATION-PV population, the proportion of patients with PV in the ropeginterferon alfa-2b group with a molecular response (65/94, 69.1%) was statistically significantly higher than for patients with PV in the best available treatment group (16/74, 21.6%) (rate ratio 3.04 (95%CI 1.96 to 4.71), p<0.0001).

[9] Molecular response was defined as reduction of any molecular abnormality to undetectable levels (complete molecular response) or a reduction from baseline value of ≥50% in patients with <50% *JAK2* Val617Phe allele burden at baseline; a reduction from baseline value of ≥25% in patients with ≥50% *JAK2* Val617Phe allele burden (partial molecular response). A partial molecular response applied only to patients with a baseline value of *JAK2* Val617Phe allele burden >10%.

[10] The difference between groups was also statistically significant at 24 months (data not extracted)

Kiladjian et al 2022 also reported that the median *JAK2* Val617Phe allele burden decreased from baseline (37.3%) to five years (8.5%) in the ropeginterferon alfa-2b group compared to an increase from baseline (38.1%) to five years (44.4%) in the best available treatment group, with a statistically significant difference between the groups (p<0.0001). Allele burden <1% at five years was also statistically significantly lower with ropeginterferon alfa-2b than best available treatment (19.6% vs 1.4%, p=0.0002).

Gisslinger et al 2023 reported that after six years follow-up of the CONTINUATION-PV population, a statistically significantly higher proportion of patients with PV in the ropeginterferon alfa-2b group achieved a molecular response (62/94, 66.0%) compared to patients with PV in the best available treatment group (14/72, 19.4%) (risk ratio 3.23 (95%CI 2.01 to 5.19), p<0.0001).

Gisslinger et al 2023 also reported that median *JAK2* Val617Phe allele burden at six years was 8.5% for the ropeginterferon alfa-2b group compared to 50.4% for the best available treatment group (p<0.0001). Allele burden >50% at six years was also statistically significantly lower with ropeginterferon alfa-2b than best available treatment (11.6% vs 50.0%, p<0.0001).

One included paper reported no statistically significant difference in molecular response at 12 months between patients with PV who received ropeginterferon alfa-2b (n=127) or hydroxyurea (n=127), with both groups reporting a reduction in mean *JAK2* Val617Phe allele burden compared with baseline. The same paper also reported no statistically significant difference in molecular response at 12 months (n=169) between patients with PV who received ropeginterferon alfa-2b or best available treatment. At 24 months (n=169) and 36 months (n=168), the response was statistically significantly better with ropeginterferon alfa-2b (68% and 66% respectively) compared to best available treatment (33% and 27% respectively). The same paper also reported that the ropeginterferon alfa-2b group showed a steady decrease in mean *JAK2* Val617Phe allele burden from baseline to 36 months (43% vs 20%) whereas the best available treatment group showed a transient reduction from baseline which was lost by 36 months (43% vs 39%). The second and third included papers reported longer term follow-up (five and six years respectively) of the patients reported in the first paper. After five (n=168) and six years (n=166) follow-up, a statistically significantly higher proportion of patients had a molecular response with ropeginterferon alfa-2b (69% and 66% respectively) compared to best available treatment (22% and 19% respectively). The same two papers also reported that the median *JAK2* Val617Phe allele burden in patients who received ropeginterferon alfa-2b decreased from baseline (37%) to 8.5% after both five and six years follow-up. In contrast, median *JAK2* Val617Phe allele burden in patients who received best available treatment increased from baseline (38%) to 44% after five years and 50% after six years respectively.

Leukocytosis

Gisslinger et al 2023 reported that after six years follow up of the CONTINUATION-PV population, patients with PV who received ropeginterferon alfa-2b (n=67) achieved a greater reduction in leukocyte count from baseline values compared to patients with PV who received best available treatment (n=52) (mean absolute change -6.67 x 10^9/L vs -3.59 x 10^9/L, p<0.0001). Gisslinger et al 2023 also reported that patients who received ropeginterferon alfa-2b spent statistically significantly more time with normal leukocyte

counts compared to patients who received best available treatment (mean proportion of time in response 93.7% vs 80.9%, p=0.02).

One included paper reported that at six years follow-up (n=119), patients with PV who received ropeginterferon alfa-2b had a statistically significantly greater reduction from baseline in leukocyte count than patients who received best available treatment. Patients who received ropeginterferon alfa-2b also spent statistically significantly more time with normal leukocyte counts (94% vs 81%).

Event-free survival

Gisslinger et al 2023 reported that risk events occurred in 5/95 (5.3%) patients with PV receiving ropeginterferon alfa-2b and 12/74 (16.2%) patients with PV receiving best available treatment after six years follow-up of the CONTINUATION-PV population. The probability of event-free survival was statistically significantly higher in the ropeginterferon alfa-2b group compared to best available treatment (0.94 vs 0.82, p=0.04; hazard ratio 0.34 (95%CI 0.12 to 0.97)). First risk events in the ropeginterferon alfa-2b group were death (n=2), thromboembolic events (n=2) and myelofibrosis (n=1). First risk events in the best available treatment group were thrombotic events (n=5), death (n=3), myelofibrosis (n=2) and acute leukaemia (n=2).

One included paper reported that at six years follow-up (n=169), patients with PV who received ropeginterferon alfa-2b had a statistically significantly higher event-free survival than patients who received best available treatment (0.94 vs 0.82).

Number and causes of deaths

Gisslinger et al 2020 reported two deaths among the 127 patients with PV who received ropeginterferon alfa-2b and two deaths among the 127 patients with PV who received best available treatment after 36 months follow-up. One death in the best available treatment group was considered to be related to treatment (acute leukaemia considered as hydroxyurea related together with concurrent pneumonia and sepsis unrelated to treatment). Other causes of death were considered unrelated to treatment and were PV, glioblastoma and unspecified illness other than PV.

One included paper (n=254) reported two deaths in patients with PV who received ropeginterferon alfa-2b and two deaths in patients who received best available treatment after 36 months follow-up. One death (in the best available treatment group) was considered to be related to treatment.

Quality of life[11]

Gisslinger et al 2020 reported a similar mean change in total quality of life score from baseline to 36 months follow-up between patients with PV receiving ropeginterferon alfa-2b (n=95) or best available treatment (n=76) in CONTINUATION-PV (-0.0 (SD 1.1) vs -0.1 (SD 1.5)). No statistical analysis reported.

One included paper (n=171) reported a similar mean change in quality of life from baseline to 36 months follow-up between patients with PV who received ropeginterferon alfa-2b or best available treatment. No statistical analysis reported.

[11] Assessed using the EQ-5D-3L questionnaire. The total score is derived from the five dimensions of mobility, self-care, usual activities, pain or discomfort and anxiety or depression.

Safety

Any adverse event

Gisslinger et al 2020 reported the proportion of patients with PV experiencing any adverse event after 36 months follow-up of the PROUD-PV and CONTINUATION-PV populations. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. No statistical comparison between groups was reported.

- Grade 4 adverse events were observed in 3/127 (2%) patients who received ropeginterferon alfa-2b and 1/127 (1%) patients who received best available treatment.
- Grade 3 adverse events were observed in 40/127 (32%) patients who received ropeginterferon alfa-2b and 33/127 (26%) patients who received best available treatment.
- Grade 1-2 adverse events were observed in 113/127 (89%) patients who received ropeginterferon alfa-2b and 114/127 (90%) patients who received best available treatment.
- Serious adverse events considered to be treatment related were observed in 3/127 (2%) patients who received ropeginterferon alfa-2b and 5/127 (4%) patients who received best available treatment. One treatment-related serious adverse event in the best available treatment group was fatal (acute leukaemia considered as hydroxyurea related together with concurrent pneumonia and sepsis unrelated to treatment).
- Any adverse events considered to be treatment related were observed in 95/127 (75%) patients who received ropeginterferon alfa-2b and 100/127 (79%) patients who received best available treatment.

The most frequently reported grade 3 and 4 treatment-related adverse events in the ropeginterferon alfa-2b group were increased y-glutamyltransferase (7/127, 6%) and increased alanine aminotransferase (4/127, 3%). In the best available treatment group these were leukopaenia (6/127, 4%) and thrombocytopaenia (5/127, 4%).

The most common adverse events (>10% patients) in the ropeginterferon alfa-2b group (n=127) were thrombocytopaenia (22%), leukopaenia (20%), increased y-glutamyltransferase (19%), fatigue (13%), increased alanine aminotransferase (13%), anaemia (13%), increased aspartate aminotransferase (13%), headache (12%), arthralgia (12%) and dizziness (11%).

The most common adverse events (>10% patients) in the best available treatment group (n=127) were thrombocytopaenia (29%), anaemia (25%), leukopaenia (23%), fatigue (14%), headache (13%), nausea (12%) and diarrhoea (11%).

Kiladjian et al 2022 reported the proportion of patients with PV experiencing any adverse event after five years follow up of the PROUD-PV and CONTINUATION-PV populations. The authors stated that these are the *"number of patients in whom the event was reported throughout the entire study period"*[12]. Adverse events were graded according to the National

[12] It is not clear what this means, but this definition may relate to the differences in the numbers of adverse events reported at the different follow-up points. Numbers extracted are as reported in the papers.

Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. No statistical comparison between groups was reported.

- Grade 5 adverse events were observed in 0/127 (0%) patients who received ropeginterferon alfa-2b and 1/127 (1%) patients who received best available treatment.
- Grade 4 adverse events were observed in 1/127 (1%) patients who received ropeginterferon alfa-2b and 0/127 (0%) patients who received best available treatment.
- Grade 3 adverse events were observed in 21/127 (16.5%) patients who received ropeginterferon alfa-2b and 20/127 (15.7%) patients who received best available treatment.
- Grade 2 adverse events were observed in 75/127 (59.1%) patients who received ropeginterferon alfa-2b and 62/127 (48.8%) patients who received best available treatment.
- Grade 1 adverse events were observed in 73/127 (57.5%) patients who received ropeginterferon alfa-2b and 79/127 (62.2%) patients who received best available treatment.
- Serious adverse events were observed in 30/127 (23.6%) patients who received ropeginterferon alfa-2b and 32/127 (25.2%) patients who received best available treatment.
- Serious adverse events considered to be treatment related were observed in 4/127 (3.1%) patients who received ropeginterferon alfa-2b and 5/127 (3.9%) patients who received best available treatment.
- Any adverse events were observed in 116/127 (91.3%) patients who received ropeginterferon alfa-2b and 117/127 (92.1%) patients who received best available treatment.
- Any adverse events considered to be treatment related were observed in 100/127 (78.7%) patients who received ropeginterferon alfa-2b and 100/127 (78.7%) patients who received best available treatment.

Gisslinger et al 2023 reported that after at least six years follow up of the PROUD-PV and CONTINUATION-PV populations, the rates of adverse events ≥ grade 3 were 15.7% amongst patients with PV who received ropeginterferon alfa-2b (n=127) and 16.5% amongst patients with PV who received best available treatment (n=127). No statistical comparison between groups was reported.

One included paper (n=254) reported the proportion of patients with PV experiencing adverse events of different severity after 36 months follow-up and also specified where adverse events were considered to be treatment-related. A second included paper reported longer term (five year) follow-up of the same 254 patients reported in the first paper. Serious adverse events considered to be treatment-related after 36 months and five years were observed in 2% and 3% of patients who received ropeginterferon alfa-2b respectively. For patients who received best available treatment this was 4% at both timepoints. Adverse events considered to be treatment-related after 36 months and five years were observed in 75% and 79% of patients who received ropeginterferon alfa-2b respectively. For patients who received best available treatment this was 79% at both timepoints. A third included paper reported six year follow-up of the same 254 patients. This reported that after six years, the rate of adverse events of grade 3 or more was 16% for patients who received

ropeginterferon alfa-2b and 17% for patients who received best available treatment. No statistical analysis reported.

Adverse events of special interest

Gisslinger et al 2020 reported the proportion of patients with PV experiencing specific types of adverse events of "*special interest*" after 36 months follow-up (Table 5). No statistical comparison between groups was reported.

Table 5: Adverse events of special interest reported by Gisslinger et al 2020

		Ropeginterferon alfa-2b (n=127)	Best available treatment (n=127)
Endocrine disorders	Any adverse event	8 (6%)	2 (2%)
	Related to treatment	6 (5%)	0 (0%)
Psychiatric disorders	Any adverse event	5 (4%)	6 (5%)
	Related to treatment	2 (2%)	1 (1%)
Musculoskeletal and connective tissue disorders	Any adverse event	2 (2%)	0 (0%)
	Related to treatment	2 (2%)	0 (0%)
Major cardiovascular adverse event		13 (10%); 16 events	8 (6%); 25 events
Major thromboembolic adverse event		4 (3%); 6 events	4 (3%); 4 events
Any neoplasm		9 (7%); 11 events	10 (8%); 12 events
Leukaemic transformation (acute leukaemia)		0 (0%)	2 (2%); 2 events
Skin cancers related to treatment (basal cell carcinoma and melanoma)		0 (0%)	3 (2%); 3 events

Kiladjian et al 2022 reported disease progression[13] and major thromboembolic adverse events for patients with PV after five years follow-up of the CONTINUATION-PV population. The cumulative exposure period was 499 patient years in the ropeginterferon alfa-2b group and 401 patient years in the best available treatment group. The incidence of disease progression in the ropeginterferon alfa-2b group was 0.2%-patient years (1 myelofibrosis case in 1/127 patients (1%)) and 1.0%-patient years in the best available treatment group (2 myelofibrosis cases and 2 acute leukaemia cases in 4/127 patients (3%)). There were five major thromboembolic adverse events in 4/127 patients (3.1%) in the ropeginterferon alfa-2b group (incidence rate 1.0%-patient years) and five events in 5/127 patients (3.9%) in the best available treatment group (incidence rate 1.2%-patient years).

Kiladjian et al 2022 also reported cases of any neoplasm after five years follow-up in 12/127 patients (9.4%) who received ropeginterferon alfa-2b and 15/127 patients (11.8%) who received best available treatment. There were no cases (0%) of skin cancers related to treatment after five years follow-up amongst 127 patients who received ropeginterferon alfa-2b and 3/127 cases (2.4%) amongst patients who received best available treatment.

One included paper (n=254) reported the proportion of patients with PV experiencing specific types of adverse events of "*special interest*" after 36 months follow-up. The most common types of adverse event in the ropeginterferon alfa-2b group were major

[13] Secondary myelofibrosis or leukemic transformation

cardiovascular events, any neoplasm and endocrine disorders. The most common type of adverse events in the best available treatment group were any neoplasm, major cardiovascular events and psychiatric disorders. A second included paper reported longer term (five year) follow-up of the same 254 patients reported in the first paper. This paper reported disease progression (secondary myelofibrosis or leukemic transformation) after five years follow-up in 1% patients who received ropeginterferon alfa-2b and 3% patients who received best available treatment. Major thromboembolic events after five years follow-up were reported for 3% patients who received ropeginterferon alfa-2b and 4% patients who received best available treatment. Any neoplasms after five years follow-up were reported for 9% patients who received ropeginterferon alfa-2b and 12% patients who received best available treatment.

Adverse events requiring dose adjustment[14]

Gisslinger et al 2020 reported adverse events requiring dose reduction after 36 months follow-up for 51/127 (40%) patients with PV in the ropeginterferon alfa-2b group and 74/127 (58%) patients with PV in the best available treatment group. No statistical analysis reported.

Gisslinger et al 2020 also reported adverse events requiring dose interruption after 36 months follow-up for 29/127 (23%) patients in the ropeginterferon alfa-2b group and 23/127 (18%) patients in the best available treatment group. No statistical analysis reported.

One included paper (n=254) reported adverse events requiring dose reduction in 40% patients with PV who received ropeginterferon alfa-2b and 58% patients who received best available treatment after 36 months follow-up. The same paper reported adverse events requiring dose interruption in 23% patients with PV who received ropeginterferon alfa-2b and 18% patients who received best available treatment after 36 months follow-up. No statistical analysis reported.

Discontinuation due to adverse events

Gisslinger et al 2020 reported discontinuation due to drug-related toxicity after 36 months follow-up for 11/127 (8%) patients with PV in the ropeginterferon alfa-2b group and 5/127 (4%) patients with PV in the best available treatment group. No statistical analysis reported. Adverse events leading to discontinuation in the ropeginterferon alfa-2b group included hypothyroidism (n=2), thrombocytopaenia (n=1), dyspnoea and pneumonitis (n=1), increased aspartate aminotransferase and alanine aminotransferase (n=1), microcytic anaemia and anaemia (n=1), anxiety (n=1), psoriasis (n=1), depression (n=1), Sjögren's syndrome (n=1) and rheumatoid arthritis (n=1). Adverse events leading to discontinuation in the best available treatment group included thrombocytopaenia and anaemia (n=1), basal cell carcinoma (n=1), pyrexia (n=1), skin ulcer (n=1) and intolerance to hydroxyurea (n=1).

Kiladjian et al 2022 reported that after five years follow up of the PROUD-PV and CONTINUATION-PV populations, 13/127 (10.2%) of patients with PV who received ropeginterferon alfa-2b and 4/127 (3.1%) patients with PV who received best available

[14] Dose reduction was permitted for grade 2 toxicity. Dose interruption was permitted for grade 3 or higher toxicity.

treatment discontinued treatment due to drug-related adverse events[15]. No statistical analysis reported.

Gisslinger et al 2023 reported that after at least six years follow up of the PROUD-PV and CONTINUATION-PV populations, 14/127 (11.0%) patients with PV who received ropeginterferon alfa-2b and 3/127 (2.4%) patients with PV who received best available treatment discontinued treatment due to drug-related toxicity. No statistical analysis reported.

One included paper (n=254) reported discontinuation due to drug-related toxicity in 8% patients with PV who received ropeginterferon alfa-2b and 4% patients who received best available treatment after 36 months follow-up. A second included paper reported longer term (six year) follow-up of the same 254 patients reported in the first paper. After six years, discontinuation due to drug-related toxicity was 11% in patients who received ropeginterferon alfa-2b and 3%[16] in patients who received best available treatment. A third included paper reported the proportion of patients who discontinued treatment due to drug-related adverse events after five years follow-up (n=254) for the same population of patients reported in the first two papers. This was 10% for patients who received ropeginterferon alfa-2b and 3% in patients who received best available treatment. No statistical analysis reported.

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[15] This outcome was reported as discontinuation due to adverse events in Kiladjian et al 2022 and discontinuation due to drug-related toxicity in Gisslinger et al 2020 and Gisslinger et al 2023. In Gisslinger et al 2020 it was stated that treatment was discontinued in the case of unresolved treatment-related toxicity, a score of at least 11 on the Hospital Anxiety and Depression Scale (either subscale), suicidal ideation, clinically significant depression, increased hepatic enzyme levels, autoimmune disease, ophthalmological disorder or less of efficacy of ropeginterferon alfa-2b.

[16] Numbers as reported in the papers. It is not clear why the number of patients who discontinued treatment is lower at six years

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