ROPEGINTERFERON ALFA-2B ACHIEVES PATIENT-SPECIFIC TREATMENT GOALS IN POLYCYTHEMIA VERA: A DISCUSSION OF THE FINAL RESULTS FROM THE PROUD-PV/CONTINUATION-PV STUDIES

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INTRODUCTION

- In the United States, PV has an estimated incidence rate of 1.57/100,000 person-years.[1]
- PV is a long-term, debilitating, potentially life-threatening disease that is associated with the risk of thrombosis, bleeding, and progression to sMF and sAML.[2-5]
- There are limited treatment options for PV; most patients receive therapeutic phlebotomy and low-dose aspirin to normalize blood counts and to reduce blood viscosity and the risk of cardiovascular events.[6-8]
- Slowing disease progression and preventing cardiovascular events are considered important treatment goals for PV.[9]
- Patients with PV also experience a wide array of symptoms that affect their QoL, including fatigue, abdominal discomfort, night sweats, and itching.[10,11]
  - To improve the QoL, therapy should address symptoms of PV while reducing phlebotomies to avoid adverse effects associated with iron deficiency.[12]
- Ropeginterferon alfa-2b is a monopegylated recombinant interferon alfa-2b with improved pharmacokinetic characteristics enabling administration every 2-4 weeks[13] and is approved for all lines of treatment in patients with PV by the EMA (in patients without symptomatic splenomegaly)[14] and the FDA (without restriction regarding splenomegaly).[15]
- The randomized, open-label, phase 3 trial PROUD-PV (NCT01949805) and its extension CONTINUATION-PV (NCT02218047) were conducted to compare the safety and efficacy of ropeginterferon alfa-2b with standard therapy (HU/BAT) in patients with PV and were completed in July 2021.
- Here we present the 6-year results from the CONTINUATION-PV Study.

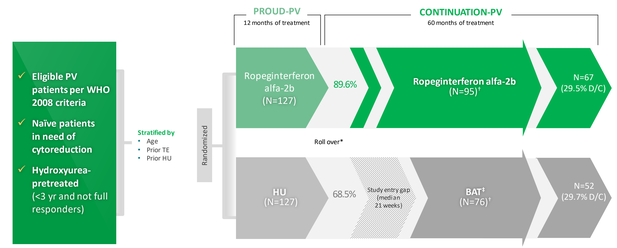
BAT, best available treatment; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HU, hydroxyurea; PV, polycythemia vera; QoL, quality of life; sAML, secondary acute myeloid leukemia; sMF, secondary myelofibrosis.

METHODS

- Patients enrolled in the PROUD-PV Study were randomized to receive either ropeginterferon alfa-2b or HU for up to 12 months. Patient visits were scheduled every 2 weeks (**Figure 1**).
  - Ropeginterferon alfa-2b was administered subcutaneously at a starting dose of 100 µg every 2 weeks.
  - HU was administrated orally at a starting dose of 500 mg daily.
- Patients who completed treatment in the PROUD-PV Study were eligible to enroll in the CONTINUATION-PV Study, a phase 3b, open-label continuation study of the PROUD-PV Study.
- The primary endpoints for the CONTINUATION-PV Study were CHR and normal spleen size, CHR*, and CHR and resolution and/or clinical improvement of disease-related signs and disease-related symptoms.*
- Secondary safety endpoints were analyzed using CTCAE 4.0.
- In a post-hoc analysis, the patient-reported PV symptom burden was assessed using the abbreviated version of the MPN-10.[11]
  - Patient assessments of adverse events were documented in the patient diary and recorded at each visit.
  - MPN-10 symptoms were evaluated based on the adverse events and their respective medical synonyms.

*Additional endpoints analyzed in biologics license application based on FDA input.
BAT, best available treatment; CHR, complete hematologic response (hematocrit <45% without phlebotomies; platelet count ≤400 × 10^9/L, WBC count ≤10 × 10^9/L); CTCAE, common terminology criteria for adverse events; FDA, US Food and Drug Administration; D/C, discontinued; HU, hydroxyurea; IFN-α, interferon alfa; MPN-10, Myeloproliferative Neoplasm Symptom Assessment Form; PV, polycythemia vera; TE, thrombotic events; WHO, World Health Organization.

Figure 1. PROUD-PV/CONTINUATION-PV Study Design



*There were no significant differences between patients who entered the CONTINUATION-PV study and those who did not roll over; †Full analysis set; ‡Control group received BAT; 88% of patients received HU as of month 72.

MAJOR INCLUSION CRITERIA

- Diagnosed with PV according to WHO 2008 criteria.
- For cytoreductive treatment-naïve patients: documented need for cytoreductive treatment.
- For patients currently treated or pretreated with HU:
  - Non-response to HU.
  - Total HU treatment duration <3 years.
  - No documented resistance/intolerance.

MAJOR EXCLUSION CRITERIA

- Any systemic cytoreduction for PV with the exception of HU.
- Any contraindications to IFN-α.
- Previous therapy with nonpegylated or pegylated IFN-α.

RESULTS

- A total of 257 patients were initially enrolled in the PROUD-PV Study; 171 patients (Ropeg IFN: N=95; Control: N=76) continued in the CONTINUATION-PV Study.
- Demographic and baseline characteristics were generally balanced between treatment groups (**Table 1**).

Table 1. Demographics and Patient Characteristics at Baseline

Patients analyzed in CONTINUATION-PV		
Characteristics at screening in PROUD-PV	**Ropeginterferon alfa-2b (N=95)**	**Control (N=74)**
Caucasian, n (%)	100%	100%
Female, n (%)	48 (50.5%)	39 (52.7%)
Age, median (range)	58 (30-85)	60 (32-79)
Disease duration, median (range), years*	1.8 months (0-146)	1.6 months (0-92)
HU pretreated, n (%)	31 (32.6%)	23 (31.1%)
Duration of prior HU treatment, n, median (range)	30, 9.5 months (2.8-25.1)	20, 8.2 months (2.6-23.0)
Hematocrit, mean (SD)	48.3 (±5.30)	50.1 (±5.47)
Spleen length, length (range)	13.5 cm (8.5-25.0)	12.8 cm (7.5-22.0)
Spleen normal,† n (%)	39 (41.1%)	36 (48.6%)
Clinically significant splenomegaly at baseline,‡ n (%)	7 (7.4%)	8 (10.8%)
Disease-related symptoms at baseline,‡ n (%)	15 (15.8%)	17 (23.0%)
Median *JAK2V617F* allele burden, % (range)	37.3% (2.6-94.9)	39.4% (2.5-86.6)

*All patients, both HU-naïve and pretreatment; †≤12cm for females, ≤13cm for males; ‡Investigator assessment.

- As of Year 6, 88% of patients in the control arm remained on HU as the BAT.
- The remaining 12% of patients in the control arm switched to interferon therapy as the BAT. At Year 6, patients were analyzed according to the assigned treatment group.
- The median 4-week cumulative dose of ropeginterferon alfa-2b was 499 µg (IQR: ±268-782 µg) in the 6th year of treatment; the median dose of HU was 1000 mg/day (IQR: ±750-1500 mg).

PRIMARY EFFICACY ENDPOINT

- Results from CONTINUATION-PV at 6 years agreed with the previously published interim analysis,[16,17] demonstrating higher rates of CHR and MR (partial/complete) using ELN criteria among ropeginterferon alfa-2b–treated patients compared with the control group (**Table 2**).

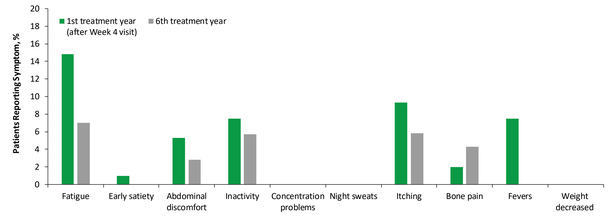
Table 2. Response Rates at 6 Years

	Ropeginterferon alfa-2b N=95		Control N=74		RR (95% CI)	p value
CHR*	48/88	54.6%	22/63	34.9%	1.55 (1.07 to 2.26)	p=0.02
MR*	62/94	66.0%	14/72	19.4%	3.23 (2.01 to 5.19)	p<0.0001

*CHR based on blood counts; MR according to ELN criteria[18] with the last observation carried forward.

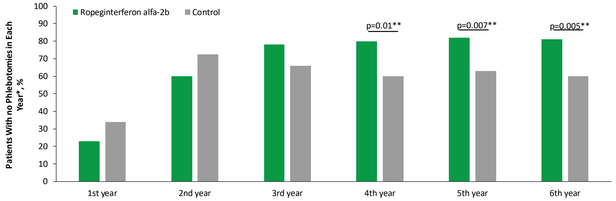
- Occurrence of disease-related symptoms remained low over long-term treatment. Symptoms were reported in 15.7% of patients in the ropeginterferon alfa-2b arm and 20.7% in the control arm during the 6th year of treatment.
  - Occurrence of symptoms defined in the MPN-SAF-TSS (MPN-10) was lower in the 6th year of treatment with ropeginterferon alfa-2b than during the 1st year (from Week 4) for 6 of the 10 symptoms (**Figure 2**).

Figure 2. Change in Occurrence of Symptoms During Ropeginterferon alfa-2b Treatment



- In the 6th year of treatment, no phlebotomies were required to maintain hematocrit <45% in 81.4% of patients receiving ropeginterferon alfa-2b compared with 60.0% of patients in the control arm (p=0.005; **Figure 3**).

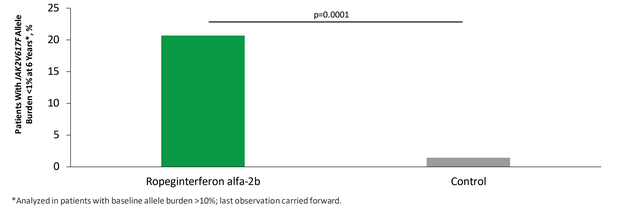
Figure 3. Freedom From Phlebotomy



*Among patients with available data for each treatment year; **Likelihood of ratio test (incidence ratio for no phlebotomy vs at least 1 phlebotomy).

- After 6 years of treatment, the *JAK2V617F* allele burden decreased to <1% in 20.7% of patients in the ropeginterferon alfa-2b arm (**Figure 4**).
  - In comparison, only 1.4% of patients in the control arm achieved an allele burden <1% at 6 years of treatment (p=0.0001).

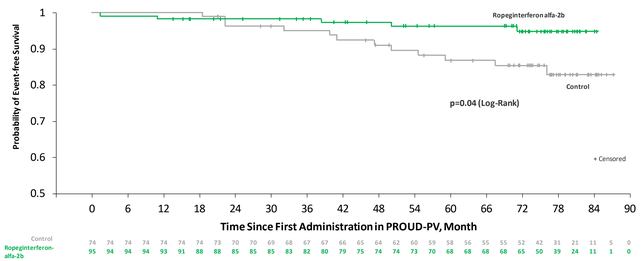
Figure 4. *JAK2V617F* Allele Burden <1% at 6 Years



*Analyzed in patients with baseline allele burden >10%; last observation carried forward.

- The probability of event-free survival was significantly higher among patients treated with ropeginterferon alfa-2b compared with the control arm (maximum treatment period 7.3 years; **Figure 5**).

Figure 5. Event-Free Survival



BAT, best available treatment; CHR, complete hematologic response (hematocrit <45% without phlebotomies; platelet count ≤400 × 10^9/L, WBC count ≤10 × 10^9/L); ELN, European LeukemiaNet; HU, hydroxyurea; IFN, interferon; IQR, interquartile range; MPN-SAF-TSS (MPN-10), Myeloproliferative Neoplasm Symptom Assessment Form; MR, molecular response; RR, rate ratio.

SUMMARY

- Fewer patients receiving long-term ropeginterferon alfa-2b reported disease-related symptoms compared with those receiving control therapy (15.7% vs 20.7%).
- A majority of patients receiving ropeginterferon alfa-2b did not require phlebotomies (81.4%) compared with those receiving control therapy (60%) at Year 6.
- More patients receiving ropeginterferon alfa-2b demonstrated a decrease to <1% *JAK2V617F* allele burden compared with those receiving control therapy (20.7% vs 1.4%).
- The probability of event-free survival at Year 6 was higher in patients receiving ropeginterferon alfa-2b compared with those receiving control therapy (~93% vs ~82%).

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