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ORIGINAL ARTICLE

Ropeginterferon versus Standard Therapy for Low-Risk Patients with Polycythemia Vera

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Abstract

BACKGROUND Whether phlebotomy alone can adequately maintain target hematocrit in patients with low-risk polycythemia vera (PV) remains elusive.

METHODS In a phase 2 open-label randomized trial, we compared ropeginterferon alfa-2b (ropeg; 100 μg every 2 weeks) with phlebotomy only regarding maintenance of a median hematocrit level (≤45%) over 12 months in the absence of progressive disease (primary end point). In follow-up, crossover to the alternative treatment group was allowed if the primary end point was not met.

RESULTS In total, 127 patients were enrolled (ropeg: n=64; standard group: n=63). The primary end point was met in 81% and 51% in the ropeg and standard groups, respectively. Responders continued the assigned treatment until month 24 and maintained response in 83% and 59%, respectively (P=0.02). Ropeg responders less frequently experienced moderate/severe symptoms (33% vs. 67% in the standard group) and palpable splenomegaly (14% vs. 37%) and showed normalization of ferritin levels and blood counts. Nonresponders at 12 months crossed over to the standard (n=9) or ropeg (n=23) group; in patients switched to ropeg only, 7 of 23 met the response criteria in 12 months, and phlebotomy need was high (4.7 per patient per year). Discontinuation because of adverse events occurred in seven patients treated with ropeg.

CONCLUSIONS In this 24-month trial, ropeg was superior to phlebotomy alone in maintaining hematocrit on target. No dose-limiting side effects or toxicities were noted; 9.2%

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of patients on ropeg and no patients on standard treatment developed neutropenia. (Funded by AOP Health and others; ClinicalTrials.gov number, NCT03003325.)

Introduction

Polycythemia vera (PV) is a myeloproliferative neoplasm characterized by uncontrolled clonal proliferation of multipotent bone marrow progenitors, largely sustained by mutations in the Janus tyrosine kinase 2 (*JAK2*) gene. The clinical course is complicated by arterial and venous events, disease-related symptoms, and transformation into myelofibrosis and acute leukemia.[1]

Therapy is titrated to keep the hematocrit at or below a target of 45%, a "cut point" to lower the thrombotic cardiovascular complications.[2] Patients younger than 60 years of age without prior thrombosis are considered "low risk." For such people, guidelines recommend only phlebotomy and low-dose aspirin. Patients older than 60 years of age with prior thrombosis are considered "high risk." In such patients, cytoreductive drugs are indicated in addition to phlebotomy and aspirin.[3,4]

Over the past 20 years, the incidence of thrombosis in patients at high risk has declined from 10.9[5] to 3.4% per patient year,[6,7] whereas in patients at low risk, it has remained substantially unchanged at 2.5% per patient year,[8,9] an incidence two to three times higher than in the general population.[10,11]

Thus, one may argue whether a conservative approach is appropriate in patients with low-risk PV. There is evidence that only 20 to 30% of patients with PV can reach and maintain the recommended target of hematocrit less than or equal to 45%,[12,13] which in the Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) randomized trial, was associated with a fourfold reduced rate of thrombosis compared with a level of 45 to 50%.[2] Moreover, phlebotomy alone might also be poorly effective in controlling disease-associated symptoms. Hydroxyurea is the standard cytoreductive drug in patients at high risk, but it is discouraged in younger patients and patients at low risk[3,4,14] because of a concern for secondary leukemia. Interferon-alfa is a potential alternative,[15-18] and among several long-acting formulations of this agent, ropeginterferon alfa-2b (ropeg; BESREMi) has demonstrated a favorable risk–benefit profile.[19] On the basis of phase 2 and 3 studies,[19,20] ropeg was recently approved by the European Medical Agency and the U.S. Food and Drug Administration as a long-acting interferon for the treatment of PV.

We report herein the final results of the phase 2 randomized clinical trial, the Low-PV trial, testing the safety and efficacy profile of ropeg versus a stringent phlebotomy-only program for the treatment of patients with low-risk PV. A preplanned interim analysis was published after enrollment of the first 100 patients,[21] corresponding to two thirds of the expected sample size, and on the basis of these results, the data safety monitoring board decided to stop patient accrual because of overwhelming efficacy and to continue follow-up of enrolled patients for 2 years per protocol. Here, we report the final results of the trial.

Methods

STUDY DESIGN

Low-PV was a multicenter, phase 2, open-label, two-group, randomized trial with a group sequential adaptive design involving adult patients with low-risk PV according to European LeukemiaNet (ELN)[3] and National Comprehensive Cancer Network[4] criteria (i.e., <60 years of age and no history of thrombosis) from 21 Italian tertiary hematologic centers (Table S1 in the Supplementary Appendix). Patients were stratified according to age (≤50 or >50 years) and time elapsed between PV diagnosis and enrollment (naïve or nonnaïve patients), and they were randomly assigned in a 1:1 ratio to receive ropeg on top of the standard phlebotomy regimen or phlebotomy alone. Unless contraindicated, all patients received low-dose (100 mg) aspirin.

Enrollment started in February 2017 and was stopped in May 2020 following the results of the second interim analysis. The study was closed in March 2023. Details of the adaptive trial design have been previously published,[21] and the protocol is available with the full text of this article at evidence.nejm.org.

The primary end point evaluation was planned after 12 months from randomization (end of core study), and an extension phase of a further year of follow-up was scheduled, allowing for a crossover to the alternative group if the primary end point was not met (Fig. 1). A substudy concerning biologic assessment was also conducted, mainly aiming to measure the effects of ropeg treatment on *JAK2*V617F allele

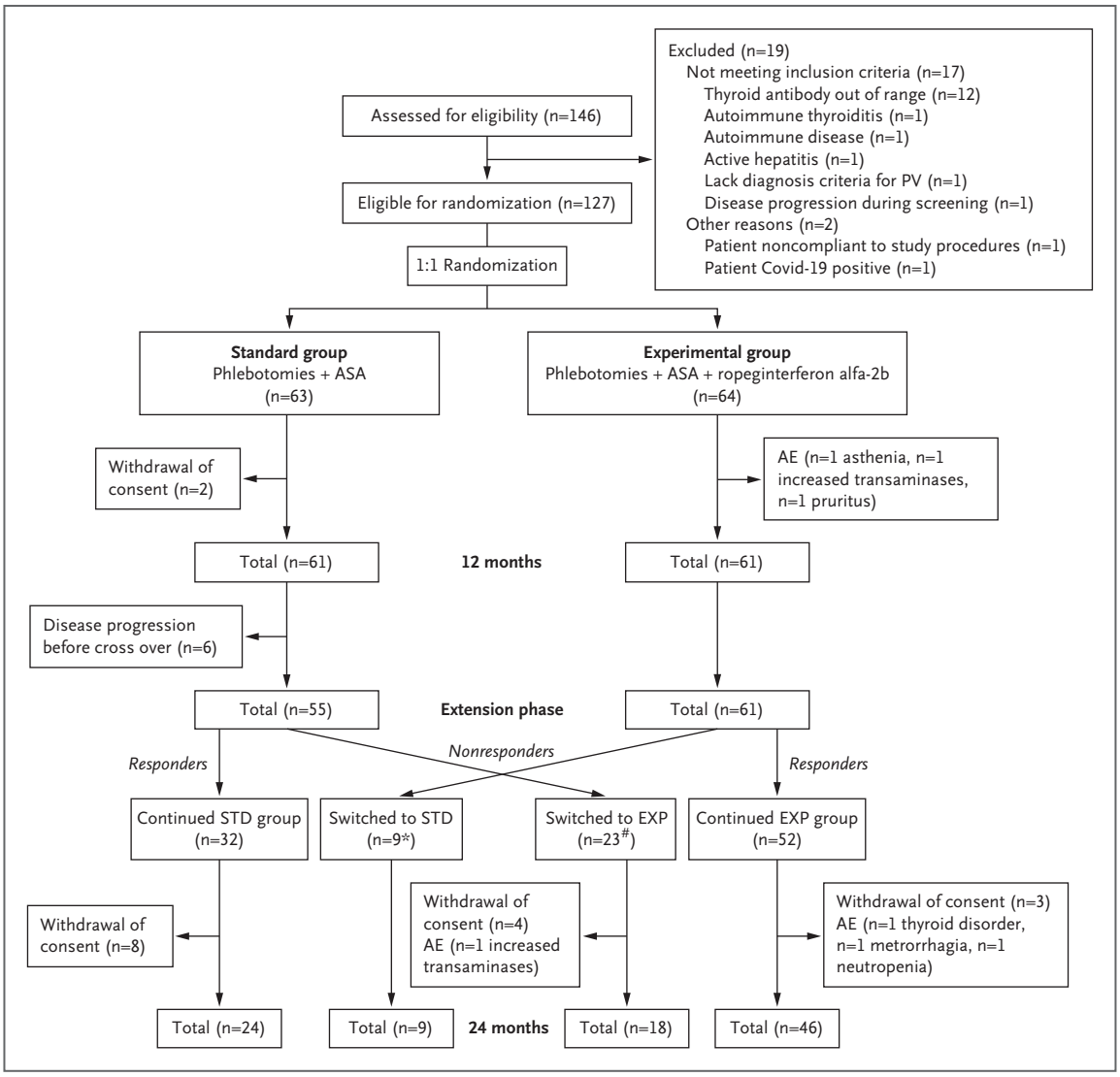

Figure 1. Trial Profile.

AE denotes adverse event; ASA, acetylsalicylic acid; EXP, experimental group; PV, polycythemia vera; and STD, standard group. *Nonresponders of EXP were crossed over to STD for lack of hematocrit (HCT) control (n=9). #Nonresponders of STD were crossed over to EXP for lack of HCT control (n=21) or thrombocytosis (n=2).

burden measured on DNA from granulocytes by real-time quantitative polymerase chain reaction assays.[22] Blood sample processing and analyses were centralized at an experienced and certified laboratory in Florence, Italy.

STUDY OVERSIGHT

The trial was designed and conducted by the sponsor (Fondazione per la Ricerca Ospedale di Bergamo [FROM] - Ente del Terzo settore) and endorsed by the Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative. The sponsor collected the data, monitored the conduct of the trial, and performed statistical analyses. Drug supply (ropeg) and financial support were provided by AOP Health (Vienna, Austria) without any involvement in data analyses, interpretation, or submission of the manuscript for publication. The first author prepared the first draft of the manuscript and made the final decision to submit the manuscript for publication. All authors reviewed and amended the manuscript and vouch for the accuracy and completeness of the data. No medical writer was involved.

The protocol was approved by the institutional review board or central ethics committee at each participating institution and was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guideline of the International Conference on Harmonisation. All patients provided written informed consent.

TRIAL PROCEDURES

Patients were randomly allocated in a 1:1 ratio to the standard group (i.e., phlebotomy and low-dose aspirin) or experimental group (i.e., ropeg on top of phlebotomy and aspirin). Details concerning the randomization sequence, techniques, and procedures have been published[18] and are reported in the Supplementary Appendix (p. 3).

Each enrolled patient was treated with phlebotomy before starting any treatment by removing 250 to 400 ml every other day or twice a week until the target hematocrit of less than or equal to 45% was reached.

Patients randomly assigned to the standard group were treated with phlebotomy only (300 ml each) according to recommendations,[23] whereas patients randomly assigned to the experimental group received, in addition, ropeg (AOP Health) subcutaneously every 2 weeks at a fixed dose of 100 μg by means of a ready-to-use injection pen.

Per protocol, each patient was observed monthly by the investigator, and if blood counts revealed a hematocrit value greater than 45%, one or more phlebotomies were carried out as needed to reach a hematocrit level lower than 45%. This policy applied to both groups. Supplemental iron therapy was prohibited. Any other treatment for controlling cardiovascular risk factors was encouraged but not mandated or regulated by the study design. Details of trial visits schedule and assessments are provided in Table S3.

END POINTS

The primary end point was defined as maintenance of the median hematocrit value of less than or equal to 45% for 12 months in the absence of progressive disease at 12 months from randomization. For the purpose of this trial, the following criteria for disease progression were used: progressive splenomegaly, thrombocytosis, or leukocytosis; PV-related death (death because of cardiovascular events, myelofibrosis, myelodysplasia, or leukemia); PV-related nonfatal events (myocardial infarction, stroke, transient ischemic attack [TIA], pulmonary embolism, deep or splanchnic vein thrombosis, superficial thrombosis, or other arterial or venous relevant vascular events). Further details are reported in Table S2.

Secondary end points included changes from baseline in leukocyte and platelet counts, ferritin levels, spleen size at palpation, quality of life, and *JAK2*V617F allele burden. Quality of life was assessed through the Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (version 10 questionnaire),[24] which consists of 10 items graded from 0 (absent) to 10 (worst). Individual scores were also categorized into increasing severity classes according to Mesa et al.[25] Other secondary end points were the mean number of phlebotomies per patient year and the proportion of patients achieving a molecular response as defined by ELN criteria.[26] All secondary end points were calculated at 12 months (end of core study) and at 24 months for responding patients who met the primary end point at 12 months or after 12 months from crossover to the alternative group in nonresponders.

Safety end points were estimated at 24 months and included treatment withdrawal because of any drug-related toxicity and clinically relevant adverse events (AEs) as defined according to Common Terminology Criteria for Adverse Events (version 4.0) and Medical Dictionary for Regulatory Activities (version 19.1) coding. In the study extension, because of the crossover design, AEs were assessed by the treatment actually received and not by the group assigned at randomization.

STATISTICAL ANALYSIS

Sample size determinations as well as actual timing and frequency of interim analyses have been detailed previously.[21] The efficacy analysis for the primary end point was performed according to the intention-to-treat principle and included all randomly assigned patients. The primary end point was analyzed using a logistic regression model, and treatment effect was estimated as an odds ratio with 95% confidence interval (CI) on the basis of maximum likelihood. Assessments of change from baseline included all patients with baseline and 12- or 24-month measurements and differences tested using repeated-measures analysis of variance. The mean number of phlebotomies per patient was compared between groups with the Mann–Whitney two-sample statistic.

Safety end points concerning frequencies and types of AEs were analyzed using chi-square or Fisher's exact tests. The safety analysis set included all patients in the primary

analysis set who received at least one dose of ropeg in the experimental group or who were phlebotomized at least once in the phlebotomy-only group. Patients with missing assessments that prevented the evaluation of primary and secondary end points were considered as nonresponders.

Two-sided P values of 0.05 or less were considered to indicate statistical significance. No multiplicity adjustments for the secondary and exploratory end points were defined. Therefore, only point estimates and 95% CIs are provided. The CIs have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects. All analyses were performed using Stata (version 16.0, StataCorp, College Station, TX) statistical software. Reporting of study results was in accordance with the Adaptive Designs Consolidated Standards of Reporting Trials (CONSORT) Extension statement.[27]

Results

PATIENT CHARACTERISTICS

As reported previously, 127 patients were randomly assigned (standard group, 63 or experimental group, 64). In a preplanned second interim analysis of the core study carried out after enrollment of two thirds (100 patients) of the entire planned sample size (150 patients), 50 patients treated with ropeg compared with 50 patients in the phlebotomy plus low-dose aspirin group maintained their hematocrit at or below the target level of 45% in the absence of disease progression defined per protocol. These findings prompted the data safety monitoring board and the steering committee to close enrollment for efficacy; new patients were not added, but the enrolled patients continued follow-up for 24 months per protocol. The updated estimate of the primary end point calculated at the end of the 24-month period confirmed the rejection of the null hypothesis according to the corresponding threshold of efficacy boundary (Fig. S1).

The two treatment groups were well balanced (Table 1 and Table S4). Overall, 70% of patients had a disease duration of less than 3 years; 53% and 83% had leukocytosis ($>10\times10^9$/l) and thrombocytosis ($>400\times10^9$/l), respectively. Mild splenomegaly at palpation (<5 cm) was ascertained in 31% of patients, and bone marrow histology was consistent with PV in all cases. At enrollment, a minority of patients (15%) were asymptomatic, and 20% presented with severe symptoms.

CORE STUDY

The composite primary end point at 12 months was met by 52 of 64 patients (81%) in the ropeg group and 32 of 63 (51%) in the phlebotomy group (P<0.001) (Table 2), corresponding to an odds ratio of 4.20 (95% CI, 1.77 to 10.23). This estimate was significantly higher than the corresponding critical value of the efficacy boundary (Fig. S1). The number of patients who met hematocrit values less than or equal to 45% during the 12-month period was 52 of 64 (81%) in the experimental group and 37 of 63 (59%) in the standard group (odds ratio, 3.05; 95% CI, 1.28 to 7.50) (Table 2). Disease progression, defined per protocol, was only detected in 8 of 63 patients (13%) assigned to the phlebotomy group. Of these, six developed progressive thrombocytosis confirmed after 30 days (platelet counts of $>1000\times10^9$/l with a baseline of $\leq600\times10^9$/l); these values were associated with microvascular symptoms (migraine-like headache, dizziness, and acroparesthesias) requiring cytoreductive treatment. Two patients were given diagnoses of cerebral TIA and splenic vein thrombosis, respectively. Over 12 months, the mean numbers of phlebotomies per patient per year were 2.91 and 4.17 in the ropeg and phlebotomy groups, respectively (mean difference, 1.27; 95% CI, 0.27 to 2.26) (Table 2).

EXTENSION PHASE

In this report of the extension phase of the trial, patients were defined as responders or nonresponders to their respective treatment on the basis of reaching or not reaching the primary composite end point (Fig. 1). Eleven patients (8.7%) did not enter the extension phase because of early disease progression (n=6), withdrawal of consent (n=2), or AEs (n=3). A total of 116 patients rolled over to the extension phase, continuing the treatment assigned at randomization (responders; n=84, 66.1%) or crossing over to the alternative group (nonresponders; n=32, 25.2%) depending on whether they responded to phlebotomy or ropeg, respectively.

Fifty-two responders (81%) in the ropeg group and 32 (51%) in the phlebotomy-only group continued the treatment assigned at randomization. We did not find relevant differences regarding the enrollment baseline characteristics of the two groups; at 12 months, hematocrit values were comparable as well as the phlebotomy need. Blood counts and *JAK2* variant allele burden for the two groups at the start of the extension are given in Table S5.

According to intention-to-treat analysis, combined treatment response from randomization to 24 months was reached in 43 of 64 (67%) patients treated with ropeg

Table 1. Patient Characteristics at Randomization by Groups.*

Characteristic	Standard Group (n=63)	Experimental Group (n=64)
Male sex — n (%)	39 (61.9)	47 (73.4)
Age — years, median (IQR)	48.2 (43.7–57.4)	51.7 (45.5–55.3)
Months from diagnosis to enrollment — median (IQR)	15.0 (4.2–32.7)	12.4 (5.2–37.6)
<3 years — n (%)	48 (76.2)	48 (75.0)
3–5 years — n (%)	10 (15.9)	8 (12.5)
≥5 years — n (%)	5 (7.9)	8 (12.5)
Physical examination		
Body-mass index — median (IQR)	24.8 (21.5–27.8)	24.8 (22.4–27.1)
Palpable splenomegaly — n (%)	18 (28.6)	21 (33.3)
Spleen size — cm, median (IQR)	2.5 (2.0–5.0)	2.0 (2.0–3.0)
Hematology		
Hemoglobin — g/dl, median (IQR)	13.7 (12.6–14.3)	13.4 (12.8–14.3)
Hematocrit — %, median (IQR)	44.0 (42.3–45.8)	44.2 (42.4–45.0)
Red blood cells — $\times 10^{12}$/l, median (IQR)	6.1 (5.5–6.8)	6.3 (5.8–6.7)
Platelets — $\times 10^{9}$/l, median (IQR)	657.0 (460.0–803.0)	632.0 (489.5–738.0)
$\geq 400 \times 10^{9}$/l — n (%)	51 (81.0)	54 (84.4)
$\geq 1000 \times 10^{9}$/l — n (%)	7 (11.1)	9 (14.1)
White blood cells — $\times 10^{9}$/l, median (IQR)	10.3 (7.5–13.7)	10.4 (8.6–13.8)
$\geq 10 \times 10^{9}$/l — n (%)	34 (54.0)	33 (51.6)
Symptoms — n (%)		
Absent	10 (15.9)	9 (14.1)
Mild	24 (38.1)	29 (45.3)
Moderate	12 (19.1)	13 (20.3)
Severe	14 (22.2)	11 (17.2)
Undetermined	3 (4.8)	2 (3.1)

* Spleen size was measured below the costal margin. Symptom burden was assessed with the Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (MPN-SAF TSS) questionnaire, which consists of 10 items (fatigue, early satiety, abdominal discomfort, inactivity, problems with concentration, night sweats, itching, bone pain, fever, and unintentional weight loss) graded from 0 (absent) to 10 (worst). The MPN-SAF TSS was defined as the sum of all 10 symptoms (range, 0 to 100). Severity designations for the MPN-SAF TSS were 0, absent; 1–3, mild; 4–6, moderate; and greater than or equal to 7, severe. Complete data at randomization are presented in Table S4. The body-mass index is the weight in kilograms divided by the square of the height in meters. IQR denotes interquartile range.

Table 2. Main Efficacy Results of the Core Study.*

	Randomized Groups			
Core Study (12 Months)	**EXP (n=64)**	**STD (n=63)**	**P Value**	**Effect Estimate† (95% CI)**
Treatment response — n (%)	52 (81.3)	32 (50.8)	<0.001	4.20 (1.77–10.23)
Hematocrit control	52 (81.3)	37 (58.7)		3.05 (1.28–7.50)
Disease progression	0 (0.0)	8 (12.7)		—‡
No. of phlebotomies per patient year — mean (SD)	2.9 (2.4)	4.2 (3.2)		1.27 (0.27–2.26)
	EXP (n=55)	**STD (n=43)**		
Absolute *JAK2*V617F VAF change from baseline — %, mean (SD)	−11.9 (20.7)	1.8 (9.0)		13.73 (7.00–20.46)
Partial molecular response — n (%)	16 (29.1)	0 (0.0)		—‡

* Treatment response was obtained in the core study at 12 months by randomized groups. CI denotes confidence interval; EXP, experimental group; SD, standard deviation; STD, standard group; and VAF, variant allele frequency.

† For categorical and continuous end point estimates, odds ratios and mean differences are provided, respectively, with 95% CIs.

‡ Exact confidence levels are not possible with zero count cells.

Table 3. Main Efficacy Results of the Extension Phase.*

Extension Phase (24 Months)	Responders				Nonresponders			
	EXP (n=52)	STD (n=32)	P Value	Effect estimate† (95% CI)	STD to EXP (n=23)	EXP to STD (n=9)	P Value	Effect Estimate† (95% CI)
Treatment response — n (%)	43 (82.7)	19 (59.4)	0.02	3.27 (1.07–10.17)	7 (30.4)	1 (11.1)	0.39	3.50 (0.33–177.12)
Hematocrit control	43 (82.7)	20 (62.5)		2.87 (0.92–8.99)	7 (30.4)	1 (11.1)		3.50 (0.33–177.12)
Disease progression	0 (0.0)	1 (3.1)		—‡	0 (0.0)	0 (0.0)		—‡
No. of phlebotomies per patient year — mean (SD)	1.5 (1.6)	1.9 (2.0)		0.40 (−0.39 to 1.19)	4.7 (3.1)	5.9 (2.4)		−1.19 (−3.56 to 1.17)
	EXP (n=29)	STD (n=5)			STD to EXP (n=12)	EXP to STD (n=3)		
Absolute *JAK2*V617F VAF change from baseline — %, mean (SD)	−23.1 (28.9)	15.4 (30.5)		38.49 (9.76–67.21)	−4.9 (13.5)	14.7 (13.1)		−19.60 (−38.32 to −0.88)
Partial molecular response — n (%)	16 (55.2)	1 (20.0)		4.92 (0.40–257.25)	2 (16.7)	0 (0.0)		—‡

* Treatment response was obtained in the extension phase by groups of responders and nonresponders resulting from the crossover design. CI denotes confidence interval; EXP, experimental group; EXP to STD, switched from the experimental group to the standard group; SD, standard deviation; STD, standard group; STD to EXP, switched from the standard group to the experimental group; and VAF, variant allele frequency.

† For categorical and continuous end point estimates, odds ratios and mean differences are provided, respectively, with 95% CIs.

‡ Exact confidence levels are not possible with zero count cells.

versus 19 of 63 (30%) on phlebotomy-only therapy (odds ratio, 4.74; 95% CI, 2.11 to 10.77). At 24 months, the composite treatment response was confirmed in 43 of 52 (83%) and 19 of 32 (59%; odds ratio, 3.27; 95% CI, 1.07 to 10.17) patients who were considered as responders to ropeg and phlebotomy only, respectively, at 12 months (Table 3). One patient in the phlebotomy-only group had progressive thrombocytosis and microvascular symptoms (acroparesthesia), leading to study discontinuation.

Response in the ropeg group was associated with normal leukocyte and platelet counts (Fig. S2A and S2B). The blood ferritin levels (Fig. S2C) at 24 months were 61.7±54.6 and 8.8±4.3 ng/ml for the ropeg and control groups, respectively. The percentages of patients with splenomegaly were 14% in the ropeg treatment group versus 37% in the phlebotomy-only group (odds ratio, 0.18; 95% CI, 0.04 to 0.85) (Fig. S3).

Quality-of-life data are shown in Figure 2A. At baseline, 39% and 43% in the ropeg and standard groups, respectively, had moderate or severe symptoms; after 24 months, these values were 33% and 67%, respectively. Figure 2B shows the change from the baseline of symptoms reported by the treatment group over the 24-month study period.

Changes in *JAK2*V617F allele burden from baseline to 12 and 24 months were assessed in 98 and 49 patients, respectively (Tables 2 and 3). Ropeg-treated patients showed a change of *JAK2*V617F variant allele frequency (VAF) from baseline to 12 and 24 months (−11.9% and −23.1%, respectively); this was more marked in patients with baseline VAF levels of more than 50% (Fig. S4). *JAK2*V617F VAF remained substantially unchanged in the standard group.

Patients who had not reached the primary end point at 12 months (nonresponders) crossed over to standard (n=9) or ropeg (n=23) therapy (Fig. 1). Of the patients who crossed over to ropeg, 7 of 23 (30%) met the composite response in the subsequent 12 months. These patients received 4.7 phlebotomies per patient per year; in contrast, patients receiving ropeg over the first 12 months from randomization received 2.9 phlebotomies per patient per year. The impact on leukocytosis, thrombocytosis (Fig. S2), splenomegaly (Fig. S3), and *JAK2*V617F VAF (Table 3) in these crossover patients is given in the Supplementary Appendix as noted. In Table S5, we provide an exploratory analysis of whether these results could be attributed to clinical and laboratory differences at randomization and at the time of crossover.

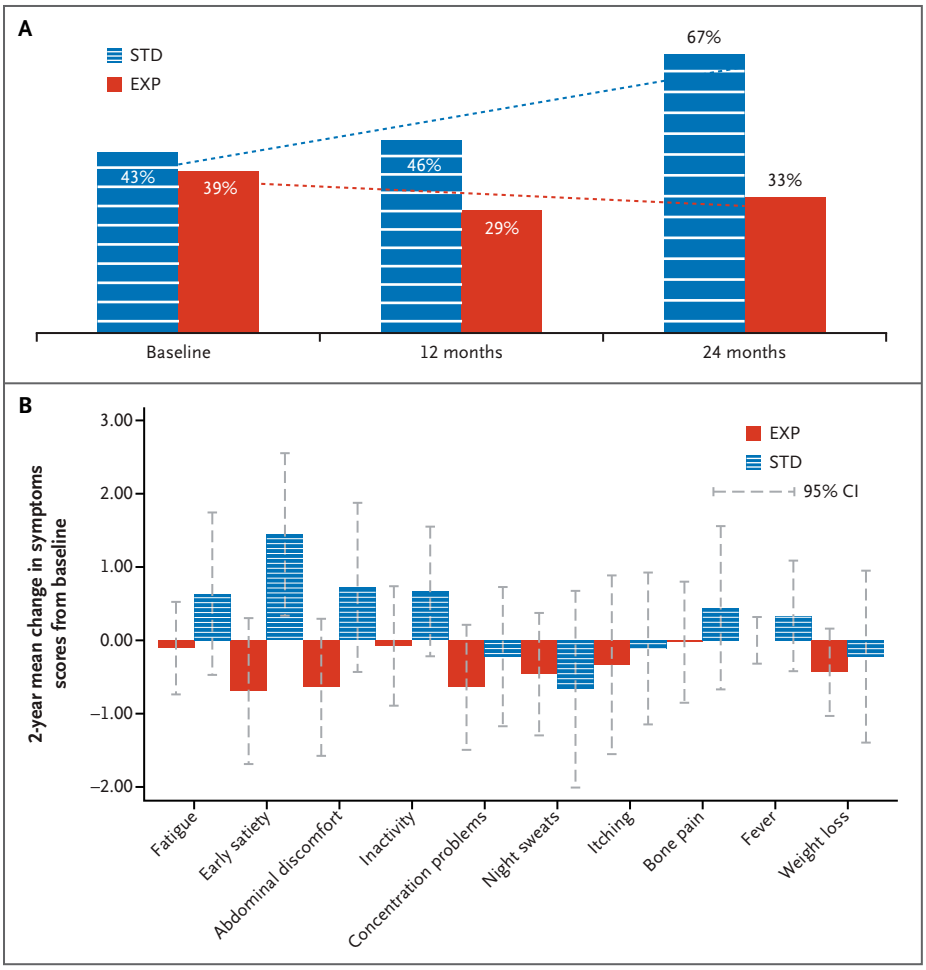

Figure 2. Change in Quality of Life over Time by Study Group.

Quality of life was measured with the Myeloproliferative Neoplasm Symptom Assessment Form total symptom score questionnaire. (Panel A) Percentage of patients with moderate or severe symptoms according to the classification proposed by Mesa et al.[25] (i.e., scores 3 to 6 = moderate; scores ≥7 = severe). (Panel B) Two-year score mean change from baseline (and corresponding 95% confidence interval [CI]) of each quality-of-life item in responders to the experimental group (EXP) and the standard group (STD).

SAFETY

During the 24-month study period, 48 AEs (55%) were attributed to treatment in a total of 87 patients exposed to ropeg (64 since randomization and 23 after crossover); only 4 AEs in 72 patients (6%) were assigned to phlebotomy-only therapy (63 treated since randomization and 9 after crossover, respectively) (Table S6). Grades 3 and 4 AEs occurred in 8 of 87 (9%) and 6 of 72 (8%) receiving ropeg and phlebotomy only, respectively (odds ratio, 1.11; 95% CI, 0.32 to 4.10). AEs leading to therapy discontinuation under ropeg occurred in 7 of 87 patients (8%) because of hypertransaminasemia (n=2), neutropenia, persistent itching, nausea/asthenia, metrorrhagia, and hyperthyroidism. Of note, grades 3 and 4 neutropenia was reported in 9.2% of patients on ropeg and in no patients on the control treatment. Hypertransaminasemia and hypertriglyceridemia of any grade occurred in eight and six patients on ropeg, respectively, and in no patients on the control treatment. AEs reported in more than 10% of patients on ropeg, regardless of inferred causality, were leukopenia/neutropenia and flu-like symptoms (Table 4).

Discussion

In this final report of the Low-PV phase 2 trial, we provide definite evidence that ropeg at a fixed dose of 100 μg is superior to a stringent phlebotomy program alone in

Table 4. Adverse Events by Treatment Received and Severity Regardless of Causality.*

	Experimental (n=87)		Standard (n=72)	
Adverse Event	**Grade 1 and 2**	**Grade 3 and 4**	**Grade 1 and 2**	**Grade 3 and 4**
Neutropenia	13 (14.9)	8 (9.2)	0 (0.0)	0 (0.0)
Hypertransaminasemia	6 (6.9)	2 (2.3)	0 (0.0)	0 (0.0)
Hypertriglyceridemia	4 (4.6)	2 (2.3)	0 (0.0)	0 (0.0)
Pruritus	3 (3.4)	1 (1.1)	1 (1.4)	0 (0.0)
Fatigue	1 (1.1)	1 (1.1)	1 (1.4)	0 (0.0)
Carditis pericardium myocardium	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Skin symptoms	0 (0.0)	0 (0.0)	2 (2.8)	3 (4.2)
Thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Acute appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Knee impingement syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Pain not otherwise specified	0 (0.0)	0 (0.0)	2 (2.8)	1 (1.4)
Flu-like symptoms	11 (12.6)	0 (0.0)	1 (1.4)	0 (0.0)
Leucopenia	10 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	8 (9.2)	0 (0.0)	1 (1.4)	0 (0.0)
Nausea	8 (9.2)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	7 (8.0)	0 (0.0)	3 (4.2)	0 (0.0)
Fever	6 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperpyrexia	6 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	6 (6.9)	0 (0.0)	1 (1.4)	0 (0.0)
Amylase increased	5 (5.7)	0 (0.0)	1 (1.4)	0 (0.0)
Back pain	5 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperthermia	4 (4.6)	0 (0.0)	2 (2.8)	0 (0.0)
Vertigo	4 (4.6)	0 (0.0)	1 (1.4)	0 (0.0)
Anemia	0 (0.0)	0 (0.0)	4 (5.6)	0 (0.0)

* Values are presented as n (%). Adverse events are reported under the treatment actually received (i.e., 87 patients received ropeginterferon alfa-2b: 64 since randomization and 23 after crossover; 72 patients received phlebotomy only: 63 since randomization and 9 after crossover). All grade 3 or 4 adverse events are reported. Grade 1 or 2 adverse events that occurred in at least 5% of patients are reported.

consistently maintaining patients with low-risk PV on a hematocrit target of less than or equal to 45% in the absence of thrombotic events, progression of leukocytosis, thrombocytosis, and worsening of splenomegaly.

Interestingly, 2 of 63 patients (3.2%) in the standard group developed splenic vein thrombosis and cerebral TIA, highlighting the persistent risk of major events even in conventionally defined patients at low risk treated with a monthly intensive phlebotomy regimen; we did not observe similar thrombotic events in the ropeg group. In line with a recent observational study of 453 patients with low-risk PV,[13] 6 (9.5%) of our patients in the phlebotomy-only group developed progressive thrombocytosis associated with symptomatic microvascular events, despite aspirin prophylaxis. In addition to the primary outcome, the trends in the number of phlebotomies, disease-related symptoms, frequency of iron deficiency, normalization of leukocyte and platelet blood counts, and progressive reduction of *JAK2*V617F allele burden all provide support for the superiority of ropeg versus control treatment. Therefore, even though these results cannot prove a direct antithrombotic effect, ropeg showed efficacy with respect to these potential surrogate end points of thrombosis, as demonstrated in the CYTO-PV trial.[2]

After a further 12 months of observation, 83% of ropeg responders (n=52) and 59% of phlebotomy-only responders (n=32) maintained their responses (P=0.02). In addition, patients who continued ropeg had persistently normal blood counts, normal blood ferritin, and reduction of disease-related symptoms.

The effect of ropeg on *JAK2*V617F allele burden was evaluated in responders after 24 months of drug exposure. Partial responses according to ELN[26] were reached in 16 of 29 (55%) patients, corresponding to a reduction of VAF

from a mean baseline value of 38 to 15% after 2 years of treatment (mean absolute difference, −23%). This value is roughly the same as that obtained after 24 months in the PROUD-PV/CONTINUATION-PV studies,[19] which used a much higher ropeg dose (average of 425 μg). Of note, the quantitative decline of *JAK2* VAF at 24 months was double the values attained after 12 months in the core study (−11.9% vs. −23.1%), and this was particularly evident in patients with baseline VAF greater than 50%. As expected, *JAK2* VAF remained substantially unchanged in patients in the phlebotomy-only group.

Patients who at 12 months had not reached the primary end point (nonresponders) crossed over to the standard (n=9) or ropeg (n=23) group. In contrast to responders, among patients switched to ropeg, only 7 of 23 (30%) met the composite treatment efficacy end point at 24 months, and more frequent phlebotomies (4.7 per patient per year) were required to maintain a hematocrit of less than or equal to 45%. Moreover, modest effects were seen regarding secondary end points, likely because of the clinical and laboratory characteristics of nonresponders at baseline: high body-mass index values, higher phlebotomy demand, elevated blood counts, and high *JAK2*V617F allele burden. On the basis of these observations, we speculate that the subgroup of patients who switched to ropeg from phlebotomy might require higher doses of ropeg to be effective, as in the Pegylated Interferon Alpha-2b Versus Hydroxyurea in Polycythemia Vera (PROUD-PV) study and its extension, the CONTINUATION-PV study.[19]

Treatment safety was assessed in all patients treated over 24 months in both the core and extension phases of the study. In the 87 individuals exposed to ropeg, grades 3 and 4 AEs were similar in type and severity as those observed in the 72 treated with phlebotomy only. Moreover, type and severity were not substantially different from those reported in the PROUD-PV/CONTINUATION-PV studies,[19] suggesting that AEs are not dose dependent. Conversely, the discontinuation rate because of AEs was lower (n=7 of 87, 8%) than in the PROUD-PV/CONTINUATION-PV (13%), and this is probably because of the different clinical characteristics, such as older age and prior exposure to hydroxyurea. However, our study groups are small, and 24 months is a short treatment period for a condition that may require a lifetime of therapy. Longer study periods and larger treatment cohorts are needed before the full safety profile can be known.

Regarding the generalizability of the results, we note that the patients were White, that they were from the same geographic area, and that there was a slight excess of males over females (Table S7) as recently reported in low-risk PV.[28] Limitations of this study include the short follow-up period and the lower-than-planned number of patients because of the adaptive study design. In this regard, the sample size modification did not affect the estimate of the primary research question, which was also confirmed in the extension phase. However, we cannot exclude that it might have influenced the detection power for late-occurring secondary outcomes.

In conclusion, we provide evidence that in patients with low-risk PV, exposure to low-dose ropeg for 2 years was more efficacious than the standard treatment of therapeutic phlebotomy and aspirin. Treatment with ropeg consistently maintained hematocrit at the target level with a reduction of phlebotomy need without thrombotic complications.

Disclosures

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