Supplemental Material

This supplement has been provided by the authors to give readers additional information about their work.

Supplement to: Rogeginterferon alfa-2b: efficacy and safety in different age groups

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Supplemental Methods

Trial Design

These PROUD/CONTINUATION-PV trials were multicentre, randomized, open-label, active-controlled phase 3 trials conducted in Europe (48 sites). The list of investigators is provided in supplemental appendix. In PROUD-PV, a total of 254 patients were randomly assigned at a 1:1 ratio to receive either ropeginterferon alfa-2b or hydroxyurea (HU) for 12 months. Patients were stratified according to prior HU treatment, age at screening (≤60 or >60 years) and presence or absence of thromboembolic events in the past. A cross over between the randomized treatment arms (ropeginterferon alfa-2b group or control group) was not allowed. All participants received low-dose aspirin during the trials, unless contraindicated.

PROUD-PV (12-Months)

Patients were administered subcutaneous injections of ropeginterferon alfa-2b every 2 weeks (with a starting dose of 100 µg [or 50 µg if patient was transitioning from HU]) or HU (control group) as a daily oral dose (with a starting dose of 500 mg).

In order to achieve and maintain an optimal disease response (haematocrit < 45% without phlebotomies, platelet count of < 400 x 10^9/L and leukocyte count of < 10 x 10^9/L) the dose was adjusted during the initial titration phase (first 12 weeks following randomization) in PROUD-PV. When a disease response was achieved, the respective dose was continued in the maintenance phase (from week 13 onwards) of the study. The necessity of a dose modification was evaluated at every treatment site visit.

Ropeginterferon alfa-2b administration

The dose escalation scheme during the initial titration phase is presented in Table S1. The dose level 1 was the starting dose if patients switched from HU; dose level 2 was the starting dose for cytoreductive naïve patients. Dose levels were escalated every two weeks until an optimal disease response was achieved. The highest dose administered was dose level 10, i.e. the highest dose of ropeginterferon alfa-2b administered in the study was 500 µg every two weeks.

Hydroxyurea administration

The dose escalation scheme for HU during the initial titration phase is presented in Table S2. Starting dose was at dose level 2 (500 mg). The daily dose was split into a morning and evening dose.

Switching of hydroxyurea treated patients assigned to ropeginterferon alfa-2b in PROUD-PV

The PROUD-PV study protocol allowed enrolment of cytoreductive untreated polycythaemia vera (PV) patients or pre-treated (currently treated) HU patients (with a total HU treatment duration up to 3 years). For currently treated or pre-treated HU patients, randomized to the ropeginterferon alfa-2b treatment arm, a transition phase was defined as the first part of the dose titration phase. Within a 12-week time period, the transition of patients from HU treatment at the time of screening to ropeginterferon alfa-2b treatment was done. The treatment transition plan for these patients is summarized below and is outlined in Figure S1.

Week 1 and 2: In addition to the HU dose as recorded at screening patients received 50 µg ropeginterferon alfa-2b (as a single subcutaneous application).

Week 3 to 12: The HU level was decreased to the next lower level every two weeks. According to the titration dose scheme for HU in the PROUD-PV Study, the dose levels were determined in 500 mg intervals until no lower dose level was available. In parallel, every two weeks, the ropeginterferon alfa-2b dose level was increased to the next higher level according to the titration scheme for ropeginterferon alfa-2b (Table S1; the dose level intervals were determined in 50 µg steps); until (a) the individual, (disease response) maintenance dose was achieved, or (b) if no further dose level was available, the dose remained in the highest dose level (i.e. 500 µg ropeginterferon alfa-2b).

Week 13 onwards: Latest timepoint for discontinuation of the HU weekly dose and maintenance dose of ropeginterferon alfa-2b achieved.

CONTINUATION-PV (Long-Term Extension Phase)

Patients who completed the PROUD-PV trial, continued treatment in the long-term extension phase (CONTINUATION-PV). Subjects who had received ropeginterferon alfa-2b in PROUD-PV, continued to receive ropeginterferon alfa-2b every 2, 3 or 4 weeks; and who had received HU in PROUD-PV received standard therapy/best available treatment (BAT) (control group) selected by the investigator. Standard therapy at month 24 included HU (in 98.4% of the patients), interferon alfa (in 3.1%) and acetylsalicylic acid (in 1.6%).

Changes to the trial protocol

Three amendments in PROUD-PV:

1st Amendment: According to FDA submission requirements, the endpoint "durable disease response" was added in the study protocol; however, for study submission in Europe the primary endpoint "disease response at 12 months" remained unchanged. A separate, USA specific statistical analysis plan (SAP) was written. All endpoints as per study protocol were

included in both SAPs; the statistical methods and sample size justification were consistent in both SAPs. In addition, the power calculation for "durable disease response" was presented in the separate USA specific SAP.

2nd Amendment: Clarification on patients who will have an immunogenicity sample drawn on week 4 and who have already started the study at the time this was implemented.

3rd Amendment: The primary objective was changed from "To demonstrate superiority of ropeginterferon alfa-2b vs. hydroxyurea in terms of disease response rate in both hydroxyurea naïve and currently treated patients, diagnosed with Polycythaemia Vera" to "To demonstrate noninferiority of ropeginterferon alfa-2b vs. hydroxyurea in terms of disease response rate in both hydroxyurea naïve and currently treated patients, diagnosed with Polycythaemia Vera."

Two amendments in CONTINUATION-PV:

1st Amendment: Implementation of the hydroxyurea arm to CONTINUATION-PV for collecting further data from the patients who were randomized into the hydroxyurea arm in PROUD-PV.

2nd Amendment: Study endpoints were changed, and co-primary endpoints added (all changes to the study endpoints were finalised before the data snapshot for analysis took place). Rewording of hydroxyurea arm to best available treatment arm also included patients with other first line therapy than hydroxyurea. Efficacy parameters were collected for both arms every three months.

Randomisation and masking

Randomisation was block-stratified by the following strata: previous HU treatment [yes/no], age at screening [≤60 or >60 years] and history of thromboembolic events [yes/no]). Treatment assignment was conducted using an electronic case report form system (Merge eClinical OS) at the sites. A statistician generated the randomisation list using SAS version 9.3. PROUD-PV study was not blinded; however, the sponsor had no access to cumulative data prior to database lock.

Procedures

After randomisation in PROUD-PV (baseline), patients attended efficacy assessment visits every three months and this schedule of assessments continued during CONTINUATION-PV comprising haematocrit, platelet count, leucocyte count, erythrocyte count, requirement for phlebotomy, spleen size, quality of life (determined using the EQ-5D-3L questionnaire), and disease burden (splenomegaly, microvascular disturbances, pruritus and headache). In PROUD-PV, hematologic assessments for the primary endpoint were performed at the central laboratory; local site laboratories were utilised in CONTINUATION-PV. Spleen size was

determined by blinded central magnetic resonance imaging or computed tomography at month 12 for the assessment of the primary endpoint in PROUD-PV and at the local sites using ultrasound sonography at all other timepoints. Quantitative *JAK2*V617F allelic burden using the *JAK2*V617F ipsogen® JAK2 MutaQuant® kit (QIAGEN GmbH, Hilden, Germany) was assessed centrally every six months. Bone marrow histology, reviewed at the central laboratory, was mandatory to confirm PV at baseline if used as a major diagnostic criterion. In addition, optional bone marrow samples were collected at screening, at 12 months and at the patient's final visit and assessed by an independent pathology board.

Safety was evaluated at each visit for treatment administration, based on reported adverse events, urinalysis, haematology and clinical chemistry. Additional safety assessments were performed at 3-monthly intervals, including physical examination, evaluation of coagulation parameters, immunological parameters, Eastern Cooperative Oncology Group performance status, HADS score, and if clinically indicated, ocular examination and chest radiograph. Standard 12-lead electrocardiograms and echocardiograms were performed every three months for the first year and 6-monthly thereafter.

Dose interruption was permitted for toxicity of grade ≥3 and dose reduction for grade 2. Treatment was discontinued in the case of: a) unresolved treatment-related toxicity, b) Hospital anxiety and depression scale (HADS) score ≥11 (either subscale), c) suicidal ideation, or clinically significant depression, d) increased hepatic enzyme levels, e) autoimmune disease, f) ophthalmologic disorder, or g) loss of efficacy of ropeginterferon alfa-2b.

Inclusion and exclusion criteria PROUD-PV

Inclusion Criteria

A patient who met all of the following criteria qualified for entry into the study:

- Male or female, 18 years or older.
- Diagnosis of polycythaemia vera according to the World Health Organization (WHO) 2008 criteria[1] with the mandatory presence of *JAK2*V617F mutation as the major disease criterion.
- For previously cytoreduction untreated patients – documented need for cytoreductive treatment (one or more of the following criteria):
    - Age > 60 years at the planned day of the first drug administration.

- At least one previous well documented major cardiovascular polycythaemia vera-related event, except bleeding and polycythaemia vera-related thromboembolic complications in the abdominal area, see exclusion criterion 7) in the medical history.
- Poor tolerance (defined as a phlebotomy/procedure-related adverse event [AE] causing significant adverse impact on the patient and limiting ability to apply phlebotomy with the intention to keep haematocrit < 45%) or frequent need for phlebotomy (more than one phlebotomy within last three months prior entering the study, while each of these phlebotomies was performed to reduce haematocrit level from > 45%, or if one phlebotomy was not able to reduce haematocrit level to < 45% for the next three months following phlebotomy);
- Progressive splenomegaly (*de novo* appearance of a palpable spleen, or appearance of the symptoms, related to the enlarged spleen, e.g. pain, early satiety etc., with confirmed size increase).
- Platelet count > 1000 x 10^9/L (for two measurements within one week).
- Leucocytosis (white blood cell count > 10 x 10^9/L for two measurements within one week).

- For patients currently treated or pre-treated with hydroxyurea, all of the following criteria:
  - being non-responders (as defined by the response criteria for primary endpoint in this protocol).
  - Total hydroxyurea treatment duration shorter than three years.
  - No documented resistance or intolerance as defined by modified criteria. [2]
- Hospital anxiety and depression scale (HADS) score 0-7 on both subscales.
- Patients with a HADS score of 8-10 inclusive on either or both of the subscales may have been eligible following psychiatric assessment that excluded clinical significance of the observed symptoms in the context of potential treatment with an interferon-α.
- Signed written informed consent.

Exclusion Criteria

A patient who met any of the following criteria did not qualify for entry into this trial:

- Any systemic cytoreduction for polycythaemia vera in the medical history prior to study entry with exception of hydroxyurea for shorter than 3 years (see respective inclusion criterion).
- Any contraindication to any of the investigational medicinal products (IMPs) (pegylated interferon or hydroxyurea) or their excipients.
- Any systemic exposure to a non-pegylated or pegylated interferon-α in the medical history.
- Documented autoimmune disease at screening or in the medical history.
- Clinically relevant pulmonary infiltrates, pneumonia, and pneumonitis at screening.
- Infections with systemic manifestations, e.g., hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) at screening.
- Known, polycythaemia vera-related thromboembolic complications in the abdominal area (e.g. portal vein thrombosis, Budd-Chiari syndrome) and/or splenectomy in the medical history.
- Any investigational drug less than 6 weeks prior to the first dose of study drug or not recovered from effects of prior administration of any investigational agent.
- History or presence of depression requiring treatment with antidepressant.
- HADS score equal to or above 11 on either or both of the subscales.
- Any risk of suicide at screening or previous suicide attempts.
- Any significant morbidity or abnormality which may interfere with the study participation.
- Pregnancy and breast-feeding females of reproductive potential and males not using effective means of contraception. Note: women of childbearing potential not using effective contraceptive methods were not eligible for the study. A woman of childbearing potential was defined as any female having experienced menarche and who is not postmenopausal or permanently sterilized (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy) (according to the United Kingdom Medicines and Healthcare products Regulatory Agency [MHRA] guidance[3]).
- History of active substance or alcohol abuse within the last year.

- Evidence of severe retinopathy (e.g. cytomegalovirus retinitis, macular degeneration) or clinically relevant ophthalmological disorder (due to diabetes mellitus or hypertension).
- Thyroid dysfunction (clinical symptoms of thyroid hyper- or hypofunction) not adequately controlled.
- Patients tested positively to thyroglobulin (TgAb) autoantibodies and / or thyroid peroxidase (TPOAb) autoantibodies at screening.
- History of major organ transplantation.
- History of uncontrolled severe seizure disorder.
- Leukocytopenia at the time of screening (leukocytes below the lower limit of normal).
- Thrombocytopenia at the time of screening (platelets below the lower limit of normal).
- History of malignant disease, including solid tumours and haematological malignancies (except basal cell and squamous cell carcinomas of the skin and carcinoma *in situ* of the cervix that have been completely excised and are considered cured) within the last 3 years.

With regard to aspirin (acetylsalicylic acid), the following contraindications were known for low dose acetylsalicylic acid: active peptic ulceration or history of peptic ulceration, haemophilia, hypersensitivity to acetylsalicylic acid or any other non-steroidal anti-inflammatory drugs (NSAIDs), including those in whom attacks of asthma, angioedema, urticaria, rhinitis have been precipitated by acetylsalicylic acid or any other NSAID, hypersensitivity to any of the other constituents. If any of the contraindications were observed, the patient was still allowed to participate in the study without being administered aspirin (acetylsalicylic acid).

Inclusion and Exclusion Criteria CONTINUATION-PV

Inclusion Criteria

A patient who met all of the following criteria qualified for entry into the trial:

1. Patients who completed the PROUD-PV trial:
    a. Normalization of at least two out of three main blood parameters (haematocrit, platelets and white blood cells) if these parameters were

moderately increased (haematocrit < 50%, white blood cell count < 20 x 10^9/L, platelet count < 600 x 10^9/L) at baseline of the PROUD-PV trial, OR

b. Greater than 35% decrease of at least two out of three main blood parameters (haematocrit, platelets and white blood cells) if these parameters were massively increased (haematocrit > 50%, white blood cell count > 20 x 10^9/L, platelet count > 600 x 10^9/L), at baseline of the PROUD-PV trial, OR

c. Normalization of spleen size, if spleen was enlarged at baseline of the PROUD-PV trial, OR

d. Otherwise a clear, medically verified benefit from treatment with ropeginterferon alfa-2b (e.g. normalization of disease-related micro-vasculatory symptoms, substantial decrease of *JAK2*V617F allelic burden).

2. Signed written informed consent form.

Exclusion Criteria

Patients who met any of the following criteria did not qualify for entry into this trial:

Withdrawal criteria, as specified in the predecessor trial, which mandated treatment discontinuation.

1. Non-recovery from the ropeginterferon alfa-2b related toxicities to the grade (usually, grade I) which allowed continuation of the treatment.
2. Hospital Anxiety and Depression Scale depression scale score of 11 or higher on either or both of the subscales, and /or development or worsening of the clinically significant depression or suicidal thoughts.
3. Progressive and clinically significant increase of liver enzyme levels despite dose reduction, or if such increase was accompanied by increased bilirubin level or any signs or symptoms of a clinically significant autoimmune disease.
4. Clinically significant development of a new ophthalmologic disorder, or worsening of a pre-existing one, during the study.
5. Ropeg only: Loss of efficacy of ropeginterferon alfa-2b or any comparable situation where no further benefits of treatment continuation were expected by the Investigator.

Safety Analysis

Safety assessment included:

- Incidence, causality and intensity of AEs according to Common Terminology Criteria for Adverse Events (CTCAE) 4.0

- Laboratory safety data:
- Haematology parameters: haemoglobin, platelet count, red blood cell count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and reticulocytes), mean corpuscular volume
- Blood chemistry: Blood urea nitrogen [BUN] or urea, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total bilirubin, Na+, K+, Ca++, Cl-, uric acid, blood glucose, alkaline phosphatase, amylase, lipase, creatinine, total protein, albumin, cholesterol, triglycerides, serum iron, transferrin, thyroid stimulating hormone (TSH) and fT4
- Coagulation parameters: Partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT), and fibrinogen
- Immunological parameters: antinuclear antibodies (ANA), TgAb, TPOAb
- Standard 12-lead electrocardiogram (ECG)
- Physical examination
- Vital signs: heart rate, systolic and diastolic blood pressure
- Immunogenicity
- Urine, β2 microglobulin

All treatment-emergent adverse events were listed with Medical Dictionary for Regulatory Activities coded terms. Separate listings were created for serious adverse events, death and events leading to study discontinuation. Absolute and relative frequencies of patients with treatment-emergent adverse events and incidence of events by primary System Organ Class and preferred term were calculated.

Statistical analysis

Primary analysis of efficacy in PROUD-PV were performed with the use of the Cochran-Mantel-Haenszel test with the defined stratification factors. Differences in the response rates between treatment groups and the 95% confidence intervals were calculated. Further, a logistic regression model was used to explore differences in response rates for hydroxyurea-exposed and naïve patients. In the interim analysis of the CONTINUATION-PV study, comparisons of efficacy among the treatment groups were performed using a log binomial regression model. The rate ratio (RR) of responders between treatment groups and the 95%

confidence intervals were calculated from estimates of regression coefficients. Two sensitivity analyses of the primary endpoint were performed: (a) complete haematological response (without the spleen criterion) and (b) complete haematological response with improved disease burden where splenomegaly is defined as spleen size >17 cm (replacing the investigators assessment). All analyses were conducted using Statistical Analysis System software, version 9.3 or higher (SAS Institute, Cary, NC, USA).

The sample size in PROUD-PV was estimated according to the anticipated size of treatment effect in an overall rate of responders at 12 months (25% at least). The assumed rate of responders was 15% (control group) and 40% (ropeginterferon alfa-2b group). Supposed drop-out rate was 20%. The dropped-out patients were considered as non-responders according the definition of the primary endpoint which would decrease assumed rate of responders to 12% (control group) and 32% (ropeginterferon alfa-2b group). Based on these assumptions, 126 patients per group (252 in total) would be needed to be analysed in order to detect the difference in response rate between treatment groups at 1% (two-sided) significance level with 90% power using standard chi-square test. Considering divisibility by 8 (in order to enable equal proportion of all strata subgroups) 128 patients per treatment group (256 in total) were planned to be enrolled. An interim analysis was planned with the possibility to re-assess sample size but was deemed unnecessary by the independent DMC. Following the change in the PROUD-PV study objective from superiority to non-inferiority of ropeginterferon alfa-2b versus HU, and before sponsor unblinding, a blinded power simulation was performed using the pooled sample sizes in each stratum and the defined non-inferiority margin of 10.5%. This calculation showed that a difference of 0.04 in responder rates between the treatment arms (in favour of the test drug) would provide statistical power of 81%, which was considered to be sufficient and did not require an increase in sample size. No formal hypothesis was planned to be tested in the CONTINUATION-PV Study; therefore, no power calculation or sample size calculation was performed. Of the 217 patients who completed the PROUD-PV Study, 171 patients continued in CONTINUATION-PV.

An analysis of efficacy and safety in the age categories <60 years and ≥60 years was conducted and included all 171 patients who entered the CONTINUATION-PV extension study.

Supplemental Results and Discussion

In PROUD-PV, age-eligible participants were recruited from October 2013 to March 2015; patients attended assessment visits at the time of randomization (baseline) and at 3-month intervals. From 257 patients who underwent randomization, 217 (84%) completed the trial; from these, 171 (67%) continued treatment in CONTINUATION-PV. The patient flow charts for both trials (PROUD-PV and CONTINUATION-PV) are provided in Figure S2. In PROUD-PV, 127 patients received ropeginterferon alfa-2b and HU, respectively; 95 (75%) patients continued to receive ropeginterferon alfa-2b in CONTINUATION-PV; from the patients who received HU in PROUD-PV, 76 (60%) continued with standard therapy. Standard therapy at month 24 included HU (in 98.4% of the patients), interferon alfa (in 3.1%) and acetylsalicylic acid (in 1.6%). The mean dose of ropeginterferon alfa-2b and HU remained constant over time.

Dosing During the Initial (Titration) Treatment Phase

In HU treated patients, the most effective dose was accomplished faster, however due to adverse events suspected to be related to the study drug (i.e. study drug indicated toxicities) the number of dose reductions was increased (65/127 [51.2%]) when compared to ropeginterferon alfa-2b treated patients (32/127 [25.2%]). A comparable number of dose interruptions due to adverse events suspected to be related to study drug was observed between the treatment arms (15/127 [11.8%]).

Molecular parameter outcomes

Mean *JAK2*V617F value at 24 months of treatment was 18.2% for ropeginterferon alfa-2b arm and 34.3% for control arm (p=0.0002). The change in mean *JAK2*V617F value from baseline up to 24 months of treatment was -24.4% and -10.4%, respectively in the ropeginterferon alfa-2b and control (HU/BAT) arm.

At 24 months of treatment, no complete response was observed in both treatment arms. The molecular response (i.e. partial molecular response) was 69.2% (54/78) for ropeginterferon alfa-2b and 28.6% (10/35) for the control. The response RR was 2.13 (95% CI: 1.26 to 3.59), indicating statistically significant higher response rates for the ropeginterferon alfa-2b treatment arm (p=0.0046).

Maintenance rate

The maintenance rates for complete haematological response were 43.2% (41/95) vs. 18.4% (14/76); RR 2.33, 95% CI 1.38 to 3.93; p=0.0015) in patients treated with ropeginterferon alfa-2b compared to control arm at 24 months of treatment. The median duration of complete

haematological response maintenance was 15.3 months and 6 months, respectively for ropeginterferon alfa-2b and control arm; the probability to lose response was significantly decreased (HR [95% CI]: 0.26 [0.14 to 0.47], p<0.0001).
Haematological response and improvement in disease burden was achieved and maintained in 30.5% of ropeginterferon alfa-2b and 17.1% of HU/BAT treated patients at 24 months of treatment (RR 1.78, 95% CI 1.00 to 3.18; p=0.0510).

Interpretation and applicability of the phase III trial findings

In patients with early PV, without splenomegaly, ropeginterferon alfa-2b was effective in inducing haematologic responses. Response rates to ropeginterferon alfa-2b continued to increase over time with higher rates compared to HU at 24 months.
The randomised controlled PROUD/CONTINUATION-PV trials provide the first and largest comparison of an IFNa vs. HU in PV and was the basis of European approval of ropeginterferon alfa-2b as a first-line treatment of PV. Ropeginterferon alfa-2b offers a new treatment option for patients with PV that has greater benefits than standard therapy after the second year of exposure, suggesting that ropeginterferon alfa-2b treatment should be considered as early as possible in the course of disease.

Limitations of the phase III trial

A limitation of the PROUD/CONTINUATION-PV studies was the low number of patients who presented with splenomegaly at baseline, which precluded a clinically meaningful assessment of the spleen response to treatment. The cohort studied represents an early PV population with a median duration since diagnosis of a few months (1.9 months for ropeginterferon alfa-2b arm, 3.6 months for control). Both cytoreduction-naïve and HU pre-treated patients were included (ropeginterferon alfa-2b group: 35.4% were HU pre-treated, control group: 29.1% HU pre-treated). Consequently, almost half of the patients (46.5%) had normal spleen size at baseline; most of the remaining patients had modestly enlarged spleens and only very few patients presented with splenomegaly (ropeginterferon alfa-2b group: 9.4%; control group: 11.8%). A further limitation of the presented studies is the lack of pathologic response data in support of hematologic and clinical efficacy outcomes, since very few patients consented to the optional bone marrow assessment. Further limitations posed by the design of the extension study are statistical power was not recalculated after the initial 12 months, and although the results indicate that the treatments groups were balanced after roll-over, selection bias cannot be ruled out.

References

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Supplemental Tables

Table S1 Dose Levels of Ropeginterferon alfa-2b in PROUD-PV and CONTINUATION-PV

	PROUD-PV	CONTINUATION-PV
Dose level	ropeginterferon alfa-2b dose, s.c. every two weeks	ropeginterferon alfa-2b, s.c. every 2, 3 or 4 weeks
1	50 µg*	-
2	100 µg†	100 µg
3	150 µg	150 µg
4	200 µg	200 µg
5	250 µg	250 µg
6	300 µg	300 µg
7	350 µg	350 µg
8	400 µg	400 µg
9	450 µg	450 µg
10	500 µg	500 µg

s.c. indicates subcutaneous.
*Starting dose if patients switched from hydroxyurea treatment.
†Starting dose for ropeginterferon alfa-2b in cytoreductive naïve patients.

Table S2 Dose Levels of Hydroxyurea in PROUD-PV

Dose level	Dose of hydroxyurea
1	500 mg every other day
2	500 mg daily - starting dose
3	500 mg day 1, 1000 mg day 2 - alternating
4	1000 mg daily
5	1000 mg day 1, 1500 mg day 2 - alternating
6	1500 mg daily
7	1500 mg day 1, 2000 mg day 2 - alternating
8	2000 mg daily
9	2500 mg daily
10	3000 mg daily

Table S3 Primary Endpoints and Main Secondary Endpoints of PROUD-PV and CONTINUATION-PV

PROUD-PV	CONTINUATION-PV
Primary endpoint Disease response rate at month 12: • Complete haematological response - Haematocrit < 45% without phlebotomy (at least 3 months since last phlebotomy), - Platelet count < 400 x 10^9/L, - Leukocyte count < 10 x 10^9/L, and Normal spleen size (≤ 12 cm females, ≤ 13 cm males)	*Co-primary endpoint* Disease response rate at assessment visits: • Complete haematological response - Haematocrit < 45% without phlebotomy (at least 3 months since last phlebotomy), - Platelet count < 400 x 10^9/L, - Leukocyte count < 10 x 10^9/L, and Normal spleen size (≤ 12 cm females, ≤ 13 cm males)

PROUD-PV	CONTINUATION-PV
	and • Complete haematological response and resolution and/or clinically improvement of disease-related signs and disease-related symptoms* *Primary endpoint sensitivity analysis* • Complete haematological response • Complete haematological response and splenomegaly defined as spleen size > 17 cm
Main secondary endpoints • Complete haematological response • Change in haematological parameters from baseline • Change in spleen size from baseline • Time to disease response • Disease response duration • Phlebotomy need • Change of disease-related symptoms *Other* • Change in QoL (EQ-5D-3L) from baseline • Change in *JAK2*V617F allelic burden[§] from baseline	*Main secondary endpoints* • Change in haematological parameters from baseline • Change in spleen size from baseline • Time to disease response • Maintenance rate of disease response • Duration of response maintenance • Progression free time • Phlebotomy need • Change of disease related signs and disease-related symptoms† • Change in QoL (EQ-5D-3L) from baseline • Change in *JAK2*V617F allelic burden[§] from baseline
Safety endpoints • Incidence, causality and intensity of AEs according to CTCAE 4.0. • Events leading to dose reduction or permanent treatment discontinuation • Adverse events of special interest	*Safety endpoints* • Incidence, causality and intensity of AEs according to CTCAE 4.0. • Events leading to dose reduction or permanent treatment discontinuation • Adverse events of special interest[‡]

*Disease-related signs as assessed by the investigators was clinically significant splenomegaly. Disease-related symptoms as assessed by investigators included microvascular disturbances such as erythromelalgia, coronary artery disease, atypical TIAs, peripheral gangrene, amaurosis fugax, hemorrhages including bruises, ecchymoses, epistaxis bleeding after tooth extraction and gastrointestinal bleeding etc. as defined according to Michiels et al. (2004)[4], and pruritus and headache. Disease-related signs and symptoms were identified in medical history records and adverse events records. The occurrence of disease related signs and symptoms were analysed descriptively by the same way as adverse events. Resolution and/or clinical improvement of disease-related signs and symptoms were binary variables (achieved, not achieved) and the same statistical methods of analysis as for the primary endpoint was used.

† Massive splenomegaly according to Kercher (2002)[5].

‡ Adverse events of special interest included psychiatric events (particularly depression associated with suicidal thoughts), ocular events (particularly events suspected to be due to thrombosis of ocular vessels), immunologic reactions including development of anti-thyroid antibodies with clinical symptoms as well as interferon-induced hypersensitivity and major disease-related cardiovascular events.

§ Measured using the *JAK2*V617F ipsogen® JAK2 MutaQuant® kit, QIAGEN GmbH, Hilden, Germany. Limit of detection: 0.061% (upper bound of 90% confidence interval: 0.091%). Values ≥ 0.091% were interpreted to indicate the presence of a *JAK2*V617F mutation.

Table S4 Clinical Characteristics of Patients at Month 12 (PROUD-PV) and at CONTINUATION-PV (Baseline)*

	PROUD-PV¶		CONTINUATION-PV‖	
Characteristic	**Ropeginterferon alfa-2b (N=106)**	**Control (N=111)**	**Ropeginterferon alfa-2b (N=95)**	**Control (N=76)**
Complete haematological response and normal spleen size – no. (%) †				
Non-responder	71 (67.0)	63 (56.8)	64 (67.4)	43 (56.6)
Responder	31 (29.2)	48 (43.2)	27 (28.4)	33 (43.4)
Age at baseline, years	58.0 (±10.88)	58.0 (±12.38)	57.4 (±10.62)	57.5 (±11.46)
Positive status for *JAK2*V617F mutation				
No. (%)	103 (97.2)	108 (97.3)	92 (96.8)	74 (97.4)
Allele burden (%) ‡	30.7 (±22.66)	25.9 (±21.49)	30.1 (±23.03)	24.4 (±20.56)
Haematocrit, %				
Mean	41.5 (±3.57)	40.2 (±4.32)	41.8 (±3.54)	40.1 (±3.99)
Median (IQR)	42.0 (39.1-43.8)	40.9 (38.3-42.9)	42.1 (39.3-44.0)	40.5 (38.0-42.8)
Range	30.8-50.0	23.0-49.0	30.8-50.0	28.0-48.0
Platelet count – x 10^9/L				
Mean	230.1 (±110.07)	265.5 (±119.78)	223.5 (±106.09)	261.2 (±104.93)
Median (IQR)	215.5 (158-276)	240.0 (194-307)	204.0 (147-266)	244.0 (194.5-302.5)
Range	73.0-665.0	69.0-988.0	73.0-665.0	69.0-653.0
Leukocyte count – x 10^9/L				
Mean	6.1 (±2.95)	6.1 (±2.34)	6.0 (±2.84)	6.0 (±1.95)
Median (IQR)	5.2 (4.2- 6.8)	5.7 (4.7-7.2)	5.1 (4.2-6.6)	5.7 (4.7-7.2)
Range	2.7-19.8	1.5-18.5	2.7-19.8	2.6-13.3
Spleen size, cm§				
Mean	13.4 (±3.13)	12.4 (±2.73)	13.4 (±3.17)	12.2 (±2.67)
Median (IQR)	13.3 (11.0-14.5)	12.0 (10.5-14.0)	13.5 (11.0-15.0)	12.0 (10.5-14.0)
Range	7.5-27.5	6.5-22.0	7.5-27.5	6.5-18.5
Presence of clinically significant splenomegaly, no. (%)	10 (9.4)	15 (13.5)	7 (7.4)	10 (13.2)

*Plus-minus values are means ±SD.

†Complete haematological response was defined as haematocrit < 45% without phlebotomy (at least 3 months since last phlebotomy), platelet count < 400 x 10^9/L, leukocyte count < 10 x 10^9/L, and normal spleen size was defined as ≤ 12 cm females and ≤ 13 cm males. Data were not available for 4 patients in the ropeginterferon alfa-2b treatment group in PROUD-PV.

‡Data were not available for 3 patients in the ropeginterferon alfa-2b treatment group, and for 3 patients in the control group in PROUD-PV.

§Data were not available for 5 patients in the ropeginterferon alfa-2b treatment group, and for 4 patients in the control group in PROUD-PV.

¶Clinical characteristics of all patients in PROUD-PV who completed the trial (month 12).

‖ Clinical characteristics of patients at baseline of CONTINUATION-PV (month 12 of PROUD-PV)

Table S5 Dosing at 24 Months by Age Subgroups

	Ropeginterferon alfa-2b [µg]		Control [mg]	
Statistics	**< 60 years**	**≥ 60 years**	**< 60 years**	**≥ 60 years**
	N = 49	N = 39	N = 33	N = 31
N/Nmiss	48/1	37/2	31/2	30/1
Mean (±SD)	361 (±142)	397 (±141)	1032 (±391)	1024 (±485)
Q1 / Median / Q3	250 / 350 / 500	300 / 500 / 500	750 / 1000 / 1500	750 / 1000 / 1250
Min / Max	50 / 500	100 / 500	500 / 1500	250 / 2750

Table S6 Efficacy Results at 24 Months

	Ropeginterferon alfa-2b (Ropeg)	Control (HU/BAT)	RR [95% CI] (Ropeg/Control)	P-value
Complete Hematologic Response	70.5% (67/95)	49.3% (33/67)	1.42 [1.09 to 1.87]	0.0101
Complete Hematologic Response and Improvement in Disease Burden	49.5% (47/95)	36.6% (26/71)	1.34 [0.93 to 1.92]	0.1183
Molecular Response	69.2% (64/94)	28.6% (26/75)	2.13 [1.26 to 3.59]	0.0046

Table S7 Efficacy Results at 24 Months in Age Subgroups

	Ropeginterferon alfa-2b (Ropeg)	Control (HU/BAT)	RR [95% CI] (Ropeg/Control)	P-value
Complete Hematologic Response (CHR)				
Age < 60 years	77.6% (38/49)	55.9% (19/34)	1.39 [1.00 to 1.94]	0.0525
Age ≥ 60 years	63.0% (29/46)	42.4% (14/33)	1.48 [0.94 to 2.34]	0.0906
CHR and Improvement in Disease Burden				
Age < 60 years	55.1% (27/49)	37.1% (13/35)	1.49 (0.91 to 2.43)	0.1092
Age ≥ 60 years	43.5 (20/46)	36.1% (13/36)	1.22 (0.70 to 2.11)	0.4774
Maintenance of CHR				
Age < 60 years	49.0% (24/49)	17.9% (7/39)	2.82 (1.37 to 5.79)	0.0048
Age ≥ 60 years	37.0% (17/46)	18.9 (7/37)	1.96 (0.91 to 4.22)	0.0845
Maintenance of CHR and Improvement in Disease Burden				
Age < 60 years	32.7% (16/49)	15.4% (6/39)	2.21 (0.96 to 5.06)	0.0618
Age ≥ 60 years	28.3% (13/46)	18.9% (7/37)	1.52 (0.68 to 3.43)	0.3113
Molecular Response - Last observation carried forward imputation (LOCF)				
Age < 60 years	77.1% (37/48)	33.3% (13/39)	2.17 (1.38 to 3.42)	0.0008
Age ≥ 60 years	58.7% (27/46)	36.1% (13/36)	1.53 (0.95 to 2.48)	0.0822
***JAK2*V617[%] LOCF relative change from baseline (Mean [± SD])**				

	Ropeginterferon alfa-2b (Ropeg)	Control (HU/BAT)	RR [95% CI] (Ropeg/Control)	P-value
Age < 60 years	-54.8 (± 59.86)	- 4.5 (±147.32)	-51.15 [-78.92 to -23.37]	0.0003
Age ≥ 60 years	-35.1 (± 50.23)	-18.4 (±48.05)	-15.85 [-32.16 to 0.46]	0.0568

Table S8 Long-term safety comparison in two age cohorts – 24 Months Population

	Ropeginterferon alfa-2b		Control	
	<60 years N=49	**≥60 years N=46**	**<60 years N=39**	**≥60 years N=37**
Patients with adverse event(s), regardless of causality	44 (89.8%)	43 (93.5%)	36 (92.3%)	34 (91.9%)
Patients with serious adverse events(s), regardless of causality	3 (6.1%)	10 (21.7%)	4 (10.3%)	9 (24.3%)
Patients with adverse events related to study treatment	38 (77.6%)	29 (63.0%)	29 (74.4%)	33 (89.2%)
Patients with serious adverse events related to study treatment	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.4%) *
Patients with ≥ grade 3 adverse event(s), regardless of causality	10 (20.4%)	16 (34.8%)	10 (25.6%)	14 (37.8%)
Patients who had adverse event(s) with a fatal outcome	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Patients who recovered from adverse event(s)	43 (87.8%)	40 (87.0%)	35 (89.7%)	34 (91.9%)
Adverse events of special interest (investigator's definition)	3 (6.1%)	6 (13.0%)	1 (2.6%)	4 (10.8%)
Endocrine disorders	Hyper-, hypothyreosis	-	-	Autoimmune thyroiditis
Psychiatric disorders	-	Irritability†, Anxiety/Depression	Depression	-
Ocular events	-	Retinal injury †	-	-
Tissue disorders	Psoriasis	Dermatitis acneiform, Sjogren's S.	-	-

	Ropeginterferon alfa-2b		Control	
	<60 years N=49	≥60 years N=46	<60 years N=39	≥60 years N=37
Cardiac/Vascular disorders	-	Thrombotic event, stroke	-	Thrombotic event, pericardial effusion, haematoma

*Four cases of serious treatment-related adverse events in two patients: acute leukemia, anemia, leukopenia, granulocytopenia

†Adverse events of special interest (irritability, retinal injury) occurred in the same patient

Supplemental Figures

Figure S1 Switching of hydroxyurea treated patients assigned to ropeginterferon alfa-2b in PROUD-PV

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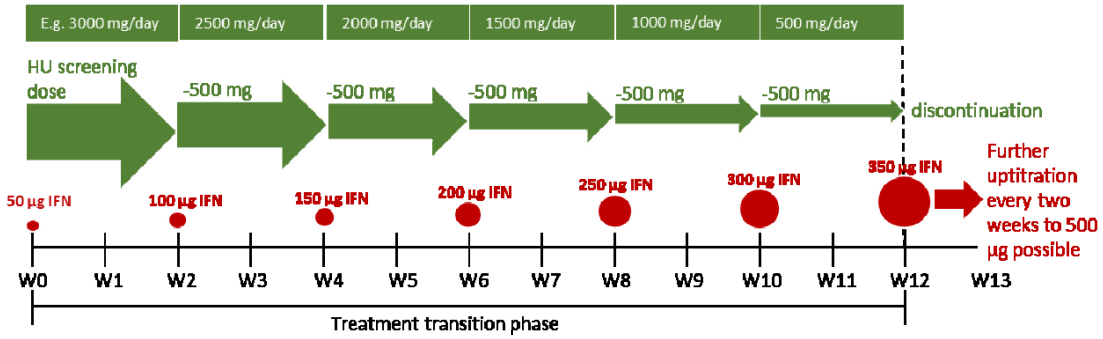
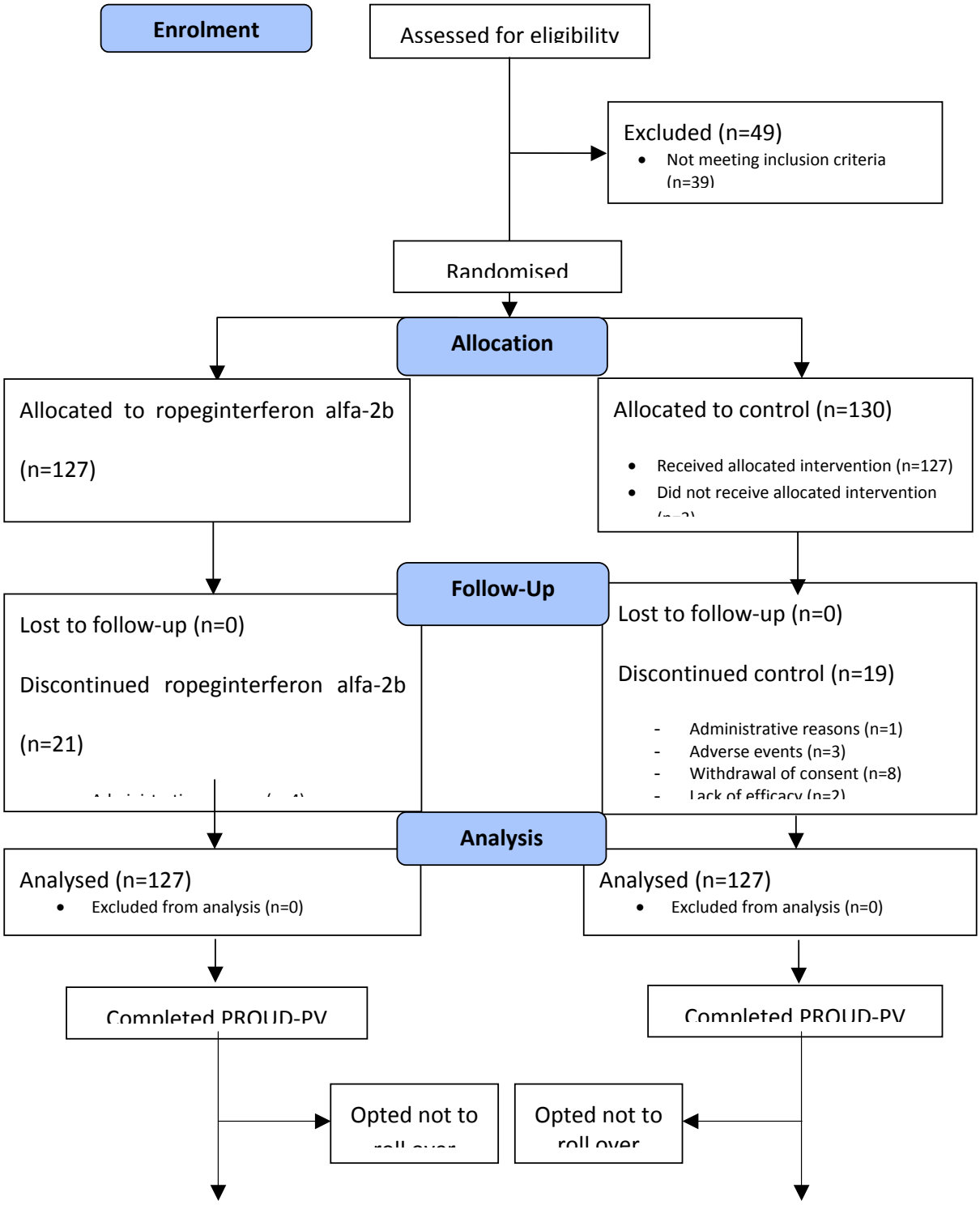
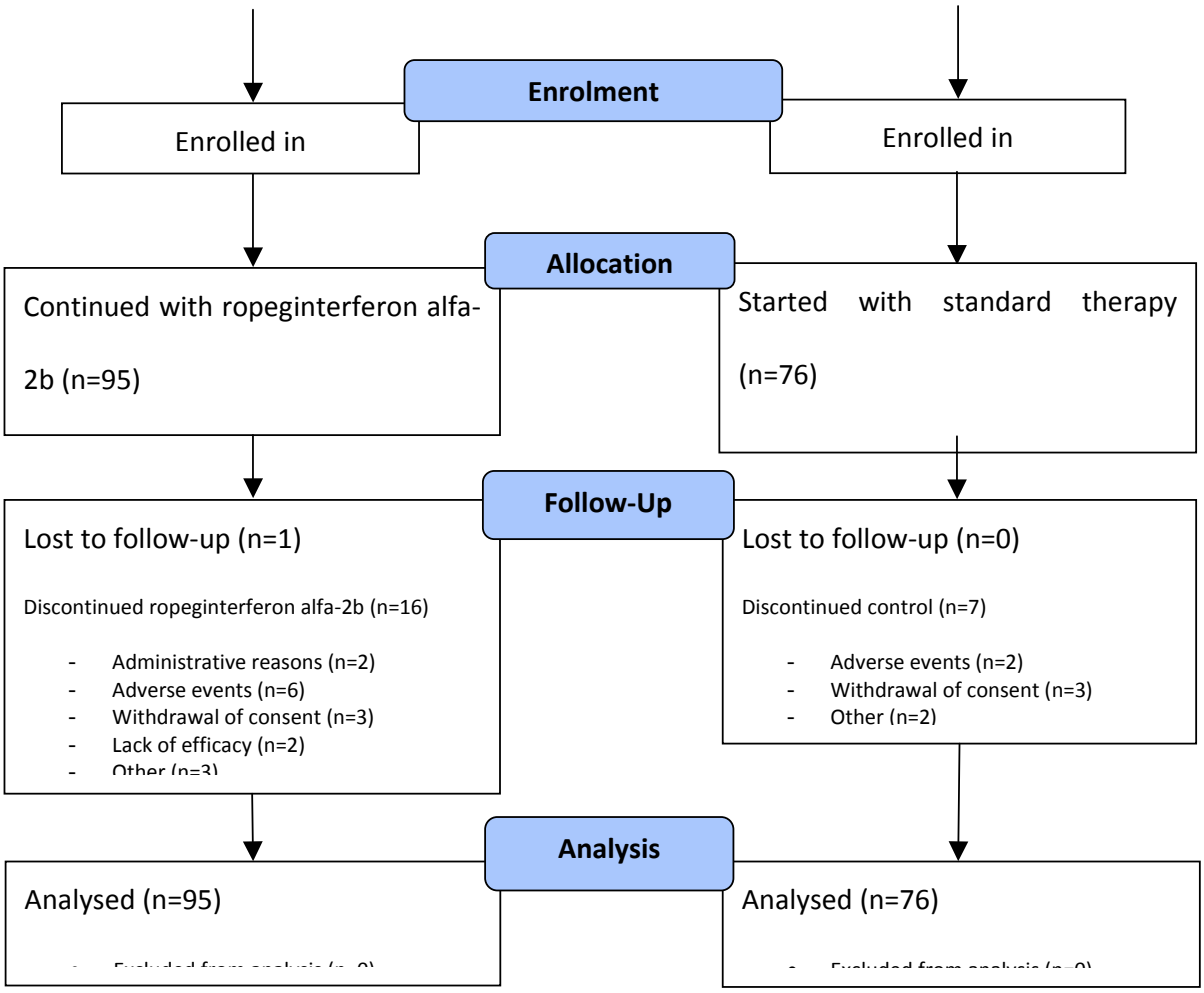


HU indicates hydroxyurea; W, week; IFN, ropeginterferon alfa-2b.

Figure S2 Trial flow diagram of PROUD/CONTINUATION-PV




Enrolment
Enrolled in
Enrolled in
Allocation
Continued with ropeginterferon alfa-2b (n=95)
Started with standard therapy (n=76)
Follow-Up
Lost to follow-up (n=1)
Discontinued ropeginterferon alfa-2b (n=16)
- Administrative reasons (n=2)
- Adverse events (n=6)
- Withdrawal of consent (n=3)
- Lack of efficacy (n=2)
Lost to follow-up (n=0)
Discontinued control (n=7)
- Adverse events (n=2)
- Withdrawal of consent (n=3)
- Other (n=2)
Analysis
Analysed (n=95)
Analysed (n=76)

Supplemental Appendix

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