

Myeloproliferative Disorders-Research Consortium (MPD-RC)

MPD-RC 112

Randomized Trial of Pegylated Interferon Alfa-2a versus Hydroxyurea Therapy in the Treatment of High Risk Polycythemia Vera and High Risk Essential Thrombocythemia

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MPD-RC 112 PEGHU-Phase 3
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**Randomized Trial of Pegylated Interferon Alfa-2a versus Hydroxyurea Therapy in the
Treatment of High Risk Polycythemia Vera and High Risk Essential Thrombocythemia**
Mandatory Companion Protocol MPD-RC 107
EudraCT #2010-019501-41

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MPD-RC 112 PEGHU-Phase 3

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Patient Registration:

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List of Abbreviations

ACD	Acid Citrate Dextrose
ALT	Alanine transaminase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area Under the Curve
BD	Becton, Dickinson and Company
BFI	Brief Fatigue Inventory
BM	Bone marrow
BPI	Brief Pain Inventory
BSP	Bromsulphalein
BUN	Blood urea nitrogen
C	Celcius
CALR	Calreticulin
CBC	Complete blood count
CML	Chronic myelogenous leukemia
CMV	Cytomegalovirus
COSMYD	Collaborative Study of Myeloproliferative Disorders
CR	Complete response
CRA	Clinical research associate
CRF	Case report form
CRP	C-reactive protein
CTSU	Clinical Trials Service Unit
CVA	Cerebrovascular accident
DARF	Drug Accountability Record Form
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
DVT	Deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
EKG	Electrocardiogram
ESRD	End stage renal disease
ET	Essential thrombocythemia
EU	European Union
F	Fahrenheit
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCT	Hematocrit
HIV	Human immunodeficiency virus

List of Abbreviations

HU	Hydroxyurea
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
JAK2	Janus kinase, type 2 gene
LASA	Linear analog scale assessment
LFTs	Liver function tests
MDS	Myelodysplastic syndrome
MI	Myocardial infarction
MPD-RC	Myeloproliferative Disorders Research Consortium
MPN	Myeloproliferative Neoplasm
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
MW	Molecular weight
NCI	National Cancer Institute
NDC	National Drug Code
PE	Pulmonary embolism
PEGASYS	Peginterferon alfa-2a
PIN	Patient identification number
pK _a	Acid dissociation constant
PNH	Paroxysmal nocturnal hemoglobinuria
PR	Partial response
PT-1	Primary Thrombocythemia-1 trial
PV	Polycythemia Vera
QOL	Quality of life
RCM	Red cell mass
SAE	Serious adverse event
SC	Subcutaneous
SCE	Sister chromatid exchange
SUSAR	Suspected unexpected serious adverse drug reaction
TB ID	Tissue bank ID number
TIA	Transient ischemic attack
TIA	Transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
USP	United States Pharmacopeia
WBC	White blood cell count
WHO	World Health Organization

Protocol Summary

Title of clinical trial	PEGHU-Phase3
Sponsor name	Myeloproliferative Disorders Research Consortium Icahn School of Medicine at Mount Sinai One Gustave L. Levy Place Box 1079 New York, New York 10029 United States
EudraCT number for trial	2010-019501-41
IND number for trial	106,511 (Exempt)
Medical condition or disease under investigation	High Risk Polycythemia Vera and High Risk Essential Thrombocythemia
Primary objectives:	<ul style="list-style-type: none"> To compare the complete hematologic response rates (by LeukemiaNet Criteria) in patients randomized to treatment with the Pegylated Interferon Alfa-2a (PEGASYS) vs. Hydroxyurea in two strata of patients with (1) high risk polycythemia vera or (2) high risk essential thrombocythemia.
Secondary objectives:	<ul style="list-style-type: none"> To compare the toxicity, safety and tolerability of therapy (Pegylated Interferon Alfa-2a vs. Hydroxyurea) in the study populations. To compare the hematologic partial response rates on therapy (Pegylated Interferon Alfa-2a vs. Hydroxyurea) by LeukemiaNet criteria. To compare specific pre-defined toxicity and tolerance of therapy (Pegylated Interferon Alfa-2a vs. Hydroxyurea) and validate the utility of sequential structured symptom assessment package of patient reported outcome instruments. To compare the impact of therapy (Pegylated Interferon Alfa-2a vs. Hydroxyurea) on key biomarkers of the disease(s) – JAK2V617F, CALR, hematopoietic cell clonality in platelets and granulocytes in females, bone marrow histopathology, and cytogenetic abnormalities. To estimate survival and incidence of development of myelodysplastic disorders, myelofibrosis, or leukemic transformation while on active treatment or observation following end of treatment (Pegylated Interferon Alfa-2a vs. Hydroxyurea). To estimate incidence of major cardiovascular events (defined as cardiovascular death, myocardial infarction, stroke, transient ischemic attack, pulmonary embolism, Budd Chiari syndrome, deep vein thrombosis, and any other clinically relevant thrombotic event) while on active treatment or observation following end of treatment (Pegylated Interferon Alfa-2a vs. HU).

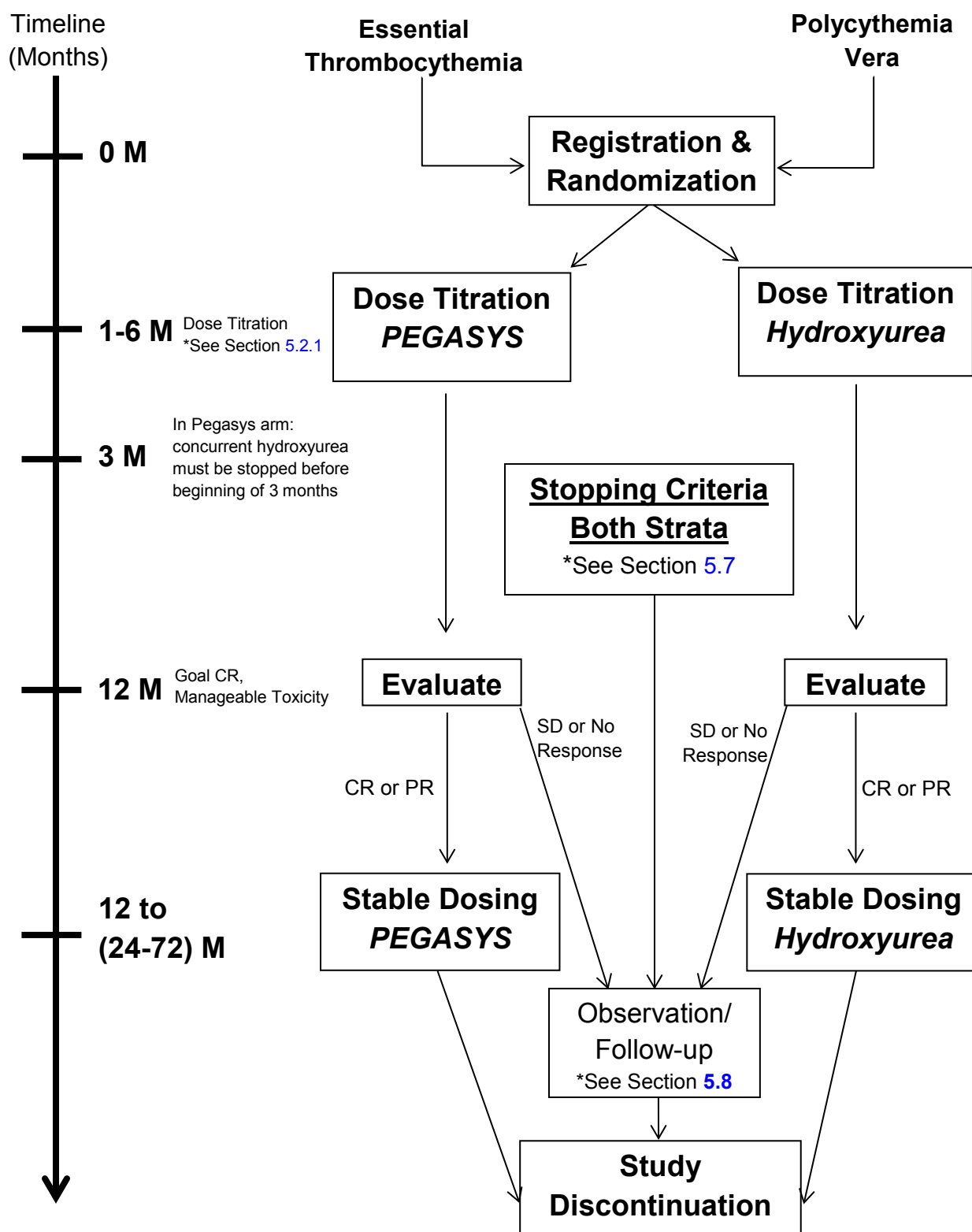
Study Design	A randomized open label clinical trial between hydroxyurea and Pegylated Interferon Alfa-2a in: (1) high risk polycythemia vera and (2) high risk essential thrombocythemia.
Sample Size	300 subjects
Summary of eligibility criteria	<p>Inclusion Criteria:</p> <p>High risk PV ANY ONE of the following:</p> <ul style="list-style-type: none"> • Age ≥ 60 years • Previous documented thrombosis, erythromelalgia or migraine either after diagnosis or within 10 years before diagnosis and considered to be disease related • Significant splenomegaly (i.e. $> 5\text{cm}$ below costal margin on palpation) or symptomatic (pain, early satiety) splenomegaly • Platelets $> 1000 \times 10^9/\text{L}$ • Diabetes or hypertension requiring pharmacological therapy <p>High risk ET ANY ONE of the following factors:</p> <ul style="list-style-type: none"> • Age ≥ 60 years • Platelet count $> 1500 \times 10^9/\text{L}$ • Previous thrombosis • Previous hemorrhage related to ET • Diabetes or hypertension requiring pharmacological therapy <p>Other Inclusion criteria</p> <ul style="list-style-type: none"> • Diagnosed less than 5 years prior to entry on trial • Never treated with cytoreductive drugs except hydroxyurea for up to 3 months maximum (phlebotomy, aspirin allowed, anagrelide allowed) • Age: ≥ 18 years (no upper limit) • Ability and willingness to comply with all study requirements • Signed informed consent to participate in this study. • Willing to participate in associated correlative science biomarker study • Serum creatinine $\leq 1.5 \times$ upper limit of normal • AST and ALT $\leq 2 \times$ upper limit of normal • No known PNH (paroxysmal nocturnal hemoglobinuria) clone • No concurrent hormonal oral contraceptive use <p>Exclusion criteria: (ANY of)</p> <ul style="list-style-type: none"> • Known to meet the criteria for primary myelofibrosis (as opposed to ET) by WHO 2008 • Patients with a prior malignancy within the last 5 years (except for basal or squamous cell carcinoma, or in situ cancer of the cervix)

	<ul style="list-style-type: none"> • Any contraindications to pegylated interferon or hydroxyurea • Presence of any life-threatening co-morbidity • History of active substance or alcohol abuse within the last year • Subjects who are pregnant, lactating or of reproductive potential and not practicing an effective means of contraception • History of psychiatric disorder (e.g. depression): Subjects with a history of mild depression may be considered for entry into this study, provided that a pretreatment assessment of the subject's affective status supports that the subject is clinically stable based on the investigator's normal practice for such subject. • History of active or uncontrolled autoimmune disorder (e.g. hepatitis) • Hypersensitivity to interferon alfa • Hepatitis B or C infection (HBV), or untreated systemic infection • Known HIV disease • Evidence of severe retinopathy (e.g. CMV retinitis, macular degeneration) or clinically relevant ophthalmological disorder (e.g. due to diabetes mellitus or hypertension) • History or other evidence of decompensated liver disease • History or other evidence of chronic pulmonary disease associated with functional limitation • Thyroid dysfunction not adequately controlled • Neutrophil count $<1.5 \times 10^9/L$ • JAK2 exon 12 mutation: PV that lacks the JAK2V617F mutation but is characterized by the exon 12 mutation. • Meets criteria for post PV or post ET-MF (see Appendix A) • Subjects with any other medical condition, which in the opinion of the investigator would compromise the results of the study by deleterious effects of treatment. • Previous exposure to any formulation of pegylated interferon • History of major organ transplantation • History of uncontrolled severe seizure disorder • Inability to give informed written consent • Total bilirubin $>1.5 \times ULN$ (patients that have an isolated indirect bilirubin that causes total bilirubin to be elevated beyond $1.5 \times ULN$ due to documented Gilbert's syndrome or hemolysis may be included).
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MPD-RC 112 PEGHU-Phase 3

Investigational medicinal product and dosage	Hydroxyurea (also known as Hydroxycarbamide). Dosage of this is dependent on each individual's hematocrit and platelet count. Aspirin in low doses is to be administered to all patients (unless patient is intolerant to this in which case substitution of alternative is permitted)
Active comparator product(s)	Pegylated Interferon Alfa-2a. Dosage is dependent upon achievement of therapeutic target and assessment of toxicity.
Treatment Duration	Patients will be treated for up to 12 months (with 3 months for confirmation - therefore up to 15 months) to achieve CR or PR. Patients who achieve a CR or PR will be followed and remain on drug for up to a maximum of 6 years from randomization. Minimum follow up is 2 years from the time the last patient is randomized.
Route(s) of administration	Subcutaneous – (pegylated interferon alpha 2a) or oral – (hydroxyurea)
Maximum duration of treatment of a subject	6.0 years

PROTOCOL SCHEMA



*See Section 3.0 for Eligibility Criteria

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TRIAL CENTERS

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1.0 OBJECTIVES

1.1 Primary Objective:

To compare the complete hematologic response rates (By LeukemiaNet Criteria and revised ELN and IWG-MRT consensus criteria) with Pegylated Interferon Alfa-2a (*PEGASYS*) vs. Hydroxyurea in patients with (1) high risk polycythemia vera or (2) high risk essential thrombocythemia.

1.2 Secondary Objectives:

- To compare the toxicity, safety and tolerability of therapy (Pegylated Interferon Alfa-2a vs. Hydroxyurea) in the study populations.
- To compare the hematologic partial response rates on therapy (Pegylated Interferon Alfa-2a vs. Hydroxyurea) by LeukemiaNet criteria and revised ELN and IWG-MRT consensus criteria.
- To compare specific pre-defined toxicity and tolerance of therapy (Pegylated Interferon Alfa-2a vs. Hydroxyurea) and validate the utility of sequential structured symptom assessment package of patient reported outcome instruments.
- To compare the impact of therapy (Pegylated Interferon Alfa-2a vs. Hydroxyurea) on key biomarkers of the disease(s) – JAK2V617F, CALR, hematopoietic cell clonality in platelets and granulocytes in females, bone marrow histopathology, and cytogenetic abnormalities.
- To estimate survival and incidence of development of a myelodysplastic syndrome, myelofibrosis, or leukemic transformation (Pegylated Interferon Alfa-2a vs. Hydroxyurea).
- To estimate incidence of major cardiovascular events (defined as cardiovascular death, myocardial infarction, stroke, transient ischemic attack, pulmonary embolism, Budd Chiari syndrome, deep vein thrombosis, and any other clinically relevant thrombotic event) (Pegylated Interferon Alfa-2a vs. Hydroxyurea).

2.0 INTRODUCTION AND RATIONALE

2.1 Introduction

The Philadelphia chromosome negative myeloproliferative neoplasms (MPN) are a group of clonal hematological malignancies that are characterized by a chronic course which can be punctuated by a number of disease related events including thrombosis, hemorrhage, pruritis and leukemic transformation. These disorders include polycythemia Vera (PV), essential thrombocythemia (ET) and primary myelofibrosis. Recently an acquired somatic mutation in the intracellular kinase, JAK2 (JAK2V617F) has been observed in 95% of patients with PV, 50% of patients with ET and 50% of patients with primary myelofibrosis. At present the chemotherapeutic agent hydroxyurea is the standard of care for high risk patients with PV. Concern exists about prolonged use of this drug leading to leukemia and the inability of hydroxyurea to eliminate the malignant clone. Quantitation of the JAK2V617F allele burden provides for the first time the opportunity to follow the effect of potential therapeutic agents on the malignant clone in patients with PV. Great enthusiasm has been expressed for the use of small molecule inhibitors of JAK2 for the treatment of patients with MPN. Phase 1/2 trials have indicated greater than expected toxicity, non specificity of action and an inability of these compounds to dramatically alter the JAK2V617F allele burden.

Interferon ($\text{rIFN}\alpha\text{-2b}$), is a drug that appears to be non-leukemogenic (contrary to ^{32}P , alkylating agents, and possibly other cytotoxic drugs used to treat patients with PV), and may have a preferential activity on the malignant clone in PV, as suggested by cytogenetic remissions obtained in patients treated with $\text{rIFN}\alpha\text{-2b}$. Several investigators recently reported that patients with PV treated with $\text{rIFN}\alpha\text{-2b}$ had lower JAK2V617F allele burdens as compared to a control group that included patients treated with phlebotomy, hydroxyurea, or anagrelide, or who remained untreated (Liu et al., 2003). The results confirm the hypothesis that $\text{rIFN}\alpha\text{-2b}$ preferentially targets the malignant clone in PV and raises the possibility that the JAK2V617F allele burden, and a reversion of clonal hematopoiesis monitored in females by expression of X-chromosome polymorphic alleles may be useful in monitoring minimal residual disease in PV patients.

Symptom Assessment and QOL in ET/PV: Utilizing the information gathered from the internet based survey of MPN patients (Mesa, 2007) we created a new QOL instrument specifically for patients with MPNs, the MPN symptom assessment form (MPN-SAF). This 19 item instrument includes the previously validated 9 item brief fatigue inventory (BFI) (Mendoza, 1999), symptoms related to splenomegaly, inactivity, cough, night sweats, pruritus, bone pains, fevers, weight loss, and an overall quality of life assessment ([Appendix D](#)). The instrument yields an independent result for each symptom (fatigue is a composite score), as this methodology (of linear analog scale assessment (LASA)) has proven valid in the past (Locke, 2007). This instrument was validated prospectively (by comparison to a panel of instruments each containing an aspect of the MPN-SAF) for administration at a single time point (Mesa, 2009).

Symptomatic Toxicities Specific to Pegylated Interferon Alfa-2a: Pegylated interferon-2 alpha (PEGASYS) has been shown in phase II trials of patients with PV (Kiladjan, 2008, Quintas-Cardama, 2009) and ET (Quintas-Cardama, 2009) to have clinical efficacy as measured by normalization of myeloproliferation, lack of vascular events while on therapy, and a decrease in the JAK2V617F allele burden. Overall the tolerability of the therapy was acceptable, with each of these trials having a dropout rate secondary to toxicity of less than 10% of those enrolled. This represents a potential improvement in tolerability as compared to other previous trials of standard interferon regimens. However randomized data does not exist to support the latter observation and

issues of dose and schedule are important before such a conclusion can be reached. Although dropout rates due to toxicity were low therapy was not without symptomatic toxicity (Table 1), and indeed a spectrum of toxicities (graded many < grade 3) might be encountered and need to be weighed in the analysis of the net clinical benefit patients experience with a clinical trial of Pegylated Interferon Alfa-2a.

2.2 Rationale for Interventions

2.2.1 JAK2V617F Status

Data from the PT1 trial shows that JAK2V617F positive patients with ET have an MPN that resembles PV (Campbell, 2005), but crude comparisons show that JAK2V617F-positive ET has about 2/3 the rate of complications of PV patients in the ECLAP cohort (Marchioli, 2005) (although the ET patients were on average 5 years younger, and more likely to be female and receive aspirin). Preliminary data in approximately 150 patients with primary myelofibrosis showed that JAK2V617F positive patients had smaller transfusion requirements but poorer survival than JAK2V617F negative patients (Campbell, 2006a).

JAK2V617F positive patients are therefore a logical group to include in a trial of a therapy which would have the potential to reduce the JAK2V617F level and to study if this therapy would improve disease control and affect the complication rate compared to standard therapy.

2.2.2 Hydroxyurea

Hydroxyurea inhibits the enzyme ribonucleotide diphosphate reductase which has a rate-limiting role in DNA synthesis. It has been shown to be efficacious in PV in the PVSG-08 study (Donovan, 1984). In this phase II study results of those who had not received any previous treatment were compared with a historical control group, the venesection only arm of the PVSG-01 study (Kaplan, 1986). The control group had a much higher rate of thrombotic events but did not experience a significantly greater incidence of leukemia. The drug was effective in reducing blood counts. This and a number of small single center studies show that hydroxyurea controls blood counts and reduces the rate of thromboembolic events in PV. Reported side effects include fever, rash, stomatitis, gastrointestinal upset, leg ulcers, jaundice and elevated creatinine.

Hydroxyurea has also been shown to be effective in ET. In a randomized study of hydroxyurea as compared to a control group the number of thrombotic episodes was significantly reduced (Cortelazzo, 1995) in the hydroxyurea treated group. Hydroxyurea in combination with aspirin it was also shown to be superior to anagrelide (Harrison, 2005).

Potential leukemogenicity of hydroxyurea has been an ongoing concern. In the non-clonal disorder sickle cell anemia a large numbers of patients have been treated for many years and there has not been an increase in the number of patients with leukemia (Halsey, 2003). An increase in acquired DNA mutations was not observed in patients with MPN exposed to hydroxyurea *in vivo* (Hanft, 2000) and in a series of patients with ET treated with hydroxyurea alone with 17p deletions the risk of leukemia was low at 3.5% (Sterkers, 1998). Overall, the case for the leukemogenicity of hydroxyurea therapy alone remains unproven although it would appear to be leukemogenic if used in combination with other cytotoxic agents or following other cytotoxic agents.

2.2.3 Interferons

Interferon has been shown to be effective and tolerable in the treatment of PV, but is associated with a significant number of adverse events. Polyethylene glycol-conjugated pegylated derivatives

of interferon alpha-require less frequent dosing and may have a more tolerable toxicity profile. A recent phase 2 study has shown that following pegylated interferon alfa-2a therapy the malignant clone as quantitated by the percentage of the mutated allele JAK2V617F was reduced in treated patients (Kiladjian, 2006). Interferon was shown to reverse clonal to polyclonal hematopoiesis in some females (Liu, 2003). However, these studies included only limited numbers of patients treated with IFN-alpha, at various dosages (from 1 MU 3 times weekly to 3 MU daily) and for very different periods (13-132 months).

A subsequent trial was performed at the MD Anderson Cancer Center (Quintas-Cardama 2009). A total of 76 patients were enrolled and treated thus far (36 ET, 40 PV). The initial starting dose of PEG-IFN- α -2a was 450 micrograms/week, but that was modified to the current starting dose of 90 micrograms /week. Dose modifications were allowed according to response or toxicity. Patients received a variety of doses including: 450 micrograms (n=1), 270 micrograms (n=3), 180 micrograms (n=14), 135 micrograms (n=8), 90 micrograms (n=27), and 45 micrograms (n=7). After a median follow-up of 23 months (range, 2-38), 63 (85%) of 74 eligible patients responded. The median time to response was 4 weeks (range, 0.5-26). Complete response (CR) was achieved by 60 (81%) patients (for ET: platelets $<440 \times 10^9/L$ in the absence of thromboembolic events; for PV: Hb <15 g/dL no phlebotomy, with absence of splenomegaly) whereas 3 (4%) patients (1 PV, 2 ET) had a partial response ([PR]; no phlebotomy, but still had splenomegaly). Of 5 eligible patients with an abnormal karyotype at the start of the study, 2 reverted to a diploid karyotype. The mutant JAK2V617F to total JAK2 ratio was determined by quantitative pyrosequencing assay in all 76 patients prior to PEG-IFN- α -2a and was repeated at least once during therapy in 41 JAK2V617F- positive patients. Overall, 23 (56%) had $>10\%$ reduction in JAK2V617F expression, including 14 (34%) who had a $>50\%$ reduction. In 5 (11%) of the latter the mutant allele became undetectable. PEG-IFN- α -2a was well tolerated in most patients. Thirty-nine episodes of grade 3-4 toxicity were reported: neutropenia (n=15), elevated transaminases (n=5), infection (n=4), fatigue (n=3), pain (n=3), cardiac (n=2), and anemia, thrombocytopenia, depression, shortness of breath, pruritus, thrombosis, and dizziness in 1 case each (Table 1). Sixteen (21%) patients were taken off study after a median of 8 months (range, 2-26) on PEG-IFN- α -2a but only 7 (9%) of them due to therapy-related toxicities: grade 3 neutropenia, anorexia, depression, ischemic retinopathy, dyspnea, confusion, and pruritic rash.

Table 1 Symptomatic toxicities at least possibly attributed to pegylated interferon alfa-2a therapy in patients with polycythemia vera (PV) or essential thrombocythemia (ET)

	MDACC Trial (Quintas-Cardama 2009)									PV-NORD Trial (Kiladjan 2008)			
	ET (N=39)				PV (N=40)					PV (N=40)			
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4		Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	31%	31%	3%	0%	28%	45%	5%	0%			25%	0%	0%
Flu-like	23%	15%	0%	0%	38%	5%	0%	0%					
Dizziness	13%	0%	3%	0%	10%	10%	0%	0%			0%	0%	0%
Inj site rxn	10%	0%	0%	0%	15%	3%	0%	0%					
Dyspnea	10%	13%	0%	0%	3%	10%	3%	0%					
Pain	8%	23%	7%	0%	18%	38%	3%	0%			5%	0%	0%
Depression	8%	23%	3%	0%	0%	25%	0%	0%			20%	0%	0%
Blurred Vision	8%	3%	0%	0%	8%	5%	0%	0%			0%	0%	0%
Insomnia	8%	8%	0%	0%	10%	8%	0%	0%					
Anorexia	5%	3%	0%	0%	3%	5%	0%	0%					
Weight Loss	3%	3%	0%	0%	3%	3%	0%	0%			3%	0%	0%
Weakness	3%	13%	0%	0%	5%	15%	0%	0%					
Pruritis	3%	8%	0%	0%	8%	15%	3%	0%					
Sweating	3%	3%	0%	0%	8%	5%	0%	0%					
Fever	0%	0%	0%	0%	0%	0%	0%	0%			18%	0%	0%
Decreased Libido	0%	0%	0%	0%	0%	0%	0%	0%			3%	0%	0%
Hot Flashes	0%	0%	0%	0%	0%	0%	0%	0%			3%	0%	0%
Flushing	0%	5%	0%	0%	0%	5%	0%	0%					

2.2.4 Aspirin

The ECLAP study established the therapeutic benefit of aspirin in PV (Landolfi, 2004). Patients were randomized between aspirin 100mg daily and placebo. Aspirin significantly reduced the risk of the combined end-point of nonfatal thromboembolic events, or death from cardiovascular causes. The risk of major or minor thrombosis was also significantly decreased. A significant increase in hemorrhage was not observed. Thus there is evidence justifying the use of low dose aspirin in all patients with PV in the absence of a specific contra- indication.

If the patient has a contra-indication to aspirin, an aspirin substitute may be prescribed but is not mandatory.

2.3 Investigational Agents

2.3.1 Pegylated Interferon Alfa-2a (PEGASYS)

Data in this section is presented from the U.S. Package Insert. The dose titrations and modifications outlined in section 5.1 and 6.0 are to be used to adjust dose in this trial.

2.3.1.1 DESCRIPTION

PEGASYS, pegylated interferon alfa-2a, is a covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight [MW] 20,000 daltons) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate MW 40,000 daltons). The PEG moiety is linked at a single site to the interferon alfa moiety via a stable amide bond to lysine. Pegylated interferon alfa-2a has an approximate molecular weight of 60,000 daltons. Interferon alfa-2a is produced using recombinant DNA technology in which a cloned hydroxyureaman leukocyte interferon gene is inserted into and expressed in *Escherichia coli*.

The study drug, pegylated interferon alfa-2a (PEGASYS), in North America will be provided by Mount Sinai to the individual sites participating in this study. It will be shipped in prefilled 180 microgram syringes or single-use vials. These syringes are the same as commercial supply with markings for 90, 135, and 180 microgram. The local institutional pharmacist will be responsible for packing the study supply into individual containers and providing to the study subjects.

The study drug (pegylated interferon alfa-2a; PEGASYS), in Europe, will be provided by Roche Pharmaceuticals or contracted drug distributors to the individual sites participating in this study. It will be shipped in prefilled 135 or 180 microgram syringes or single-use pen devices.

Subcutaneous (SC) administration of 1.0 mL delivers 180 micrograms of drug product (expressed as the amount of interferon alfa-2a), 8.0 mg sodium chloride, 0.05 mg polysorbate 80, 10.0 mg benzyl alcohol, 2.62 mg sodium acetate trihydrate, and 0.05 mg acetic acid. The solution is colorless to light yellow and the pH is 6.0 ± 0.01 .

Patients will self-administer a dose of Pegylated Interferon Alfa-2a as a subcutaneous injection once per week every week. Doses will be adjusted according to response and adverse events (see section 5.2 and 6.0). These doses will be administered at home. Study staff will be instructing patients in self-injection at the appropriate dose level, proper handling of utilized syringes, return of used and unused syringes and medication, instructing the patient in how to properly fill out their diary, and provide the patient with education material on the aforementioned activities. See [Appendix E](#) for patient medication diaries.

2.3.1.2 CLINICAL ACTIVITY

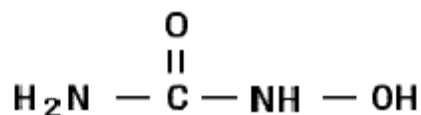
Clinical activity of PEGASYS in MPNs is presented in section 2.2.3.

2.3.2 Hydroxyurea®/Hydroxyurea/Hydroxy Carbamide

2.3.2.1 DESCRIPTION

Hydroxyurea® (hydroxyurea capsules, USP), Hydroxycarbamide, is an antineoplastic agent available for oral use as capsules providing 500 mg hydroxyurea. Inactive ingredients: citric acid, colorants (D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red 40, and D&C Red 28), gelatin, lactose, magnesium stearate, sodium phosphate, and titanium dioxide.

Hydroxyurea/Hydroxycarbamide occurs as an essentially tasteless, white crystalline powder. Its structural formula is:



2.3.2.2 CLINICAL PHARMACOLOGY

2.3.2.2.1 Mechanism of Action

The precise mechanism by which hydroxyurea produces its antineoplastic effects cannot, at present, be described. However, the reports of various studies in tissue culture in rats and humans lend support to the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or of protein. This hypothesis explains why, under certain conditions, hydroxyurea may induce teratogenic effects.

Three mechanisms of action have been postulated for the increased effectiveness of concomitant use of hydroxyurea therapy with irradiation on squamous cell (epidermoid) carcinomas of the head and neck. *In vitro* studies utilizing Chinese hamster cells suggest that hydroxyurea (1) is lethal to normally radioresistant S-stage cells, and (2) holds other cells of the cell cycle in the G1 or pre-DNA synthesis stage where they are most susceptible to the effects of irradiation. The third mechanism of action has been theorized on the basis of *in vitro* studies of HeLa cells: it appears that hydroxyurea, by inhibition of DNA synthesis, hinders the normal repair process of cells damaged but not killed by irradiation, thereby decreasing their survival rate; RNA and protein syntheses have shown no alteration.

2.3.2.2.2 Pharmacokinetics

Absorption

Hydroxyurea is readily absorbed after oral administration. Peak plasma levels are reached in 1 to 4 hours after an oral dose. With increasing doses, disproportionately greater mean peak plasma concentrations and AUCs are observed.

There are no data on the effect of food on the absorption of hydroxyurea.

Distribution

Hydroxyurea distributes rapidly and widely in the body with an estimated volume of distribution approximating total body water.

Plasma to ascites fluid ratios range from 2:1 to 7.5:1. Hydroxyurea concentrates in leukocytes and erythrocytes.

Metabolism

Up to 60% of an oral dose undergoes conversion through metabolic pathways that are not fully characterized. One pathway is probably saturable hepatic metabolism. Another minor pathway may be degradation by urease found in intestinal bacteria. Acetohydroxamic acid was found in the serum of three leukemic patients receiving hydroxyurea and may be formed from hydroxylamine resulting from action of urease on hydroxyurea.

Excretion

Excretion of hydroxyurea in humans is likely a linear first-order renal process.

2.3.2.2.3 Special Populations

Geriatric, Gender, Race

No information is available regarding pharmacokinetic differences due to age, gender, or race.

Renal Insufficiency

As renal excretion is a pathway of elimination, consideration should be given to decreasing the dosage of hydroxyurea in patients with renal impairment. In adult patients with sickle cell disease, an open-label, non-randomized, single-dose, multicenter study was conducted to assess the influence of renal function on the pharmacokinetics of hydroxyurea. Patients in the study with normal renal function (creatinine clearance [CrCl] >80 mL/min), mild (CrCl 50–80 mL/min), moderate (CrCl = 30–<50 mL/min), or severe (<30 mL/min) renal impairment received hydroxyurea as a single oral dose of 15 mg/kg, achieved by using combinations of the 200 mg, 300 mg, or 400 mg capsules. Patients with end-stage renal disease (ESRD) received two doses of 15 mg/kg separated by 7 days; the first was given following a 4-hour hemodialysis session, the second prior to hemodialysis. In this study the mean exposure (AUC) in patients whose creatinine clearance was <60 mL/min (or ESRD) was approximately 64% higher than in patients with normal renal function. The results suggest that the initial dose of hydroxyurea should be reduced when used to treat patients with renal impairment. Close monitoring of hematologic parameters is advised in these patients.

Hepatic Insufficiency

There are no data that support specific guidance for dosage adjustment in patients with hepatic impairment. Close monitoring of hematologic parameters is advised in these patients.

Drug Interactions

There are no data on concomitant use of hydroxyurea with other drugs in humans.

Animal Pharmacology and Toxicology

The oral LD50 of hydroxyurea is 7330 mg/kg in mice and 5780 mg/kg in rats, given as a single dose.

In subacute and chronic toxicity studies in the rat, the most consistent pathological findings were an apparent dose-related mild to moderate bone marrow hypoplasia as well as pulmonary congestion and mottling of the lungs. At the highest dosage levels (1260 mg/kg/day for 37 days then 2520 mg/kg/day for 40 days), testicular atrophy with absence of spermatogenesis occurred; in several animals, hepatic cell damage with fatty metamorphosis was noted. In the dog, mild to marked bone marrow depression was a consistent finding except at the lower dosage levels. Additionally, at the higher dose levels (140 to 420 mg or 140 to 1260 mg/kg/week given 3 or 7 days weekly for 12 weeks), growth retardation, slightly increased blood glucose values, and hemosiderosis of the liver or spleen were found; reversible spermatogenic arrest was noted. In the monkey, bone marrow depression, lymphoid atrophy of the spleen, and degenerative changes in the epithelium of the small and large intestines were found. At the higher, often lethal, doses (400 to 800 mg/kg/day for 7 to 15 days), hemorrhage and congestion were found in the lungs, brain, and urinary tract. Cardiovascular effects (changes in heart rate, blood pressure, orthostatic hypotension, EKG changes) and hematological changes (slight hemolysis, slight methemoglobinemia) were observed in some species of laboratory animals at doses exceeding clinical levels.

2.3.2.3 INDICATIONS AND USAGE

Hydroxyurea®/Hydroxycarbamide is currently the treatment of choice in patients with high risk polycythemia vera and essential thrombocythemia. Significant tumor response to hydroxyurea (hydroxyurea capsules, USP) has been demonstrated in melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic, or inoperable carcinoma of the ovary.

Hydroxyurea used concomitantly with irradiation therapy is intended for use in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip.

2.3.2.4 CONTRAINDICATIONS

Hydroxyurea is contraindicated in patients with marked bone marrow depression, i.e., leukopenia ($<2.5 \times 10^9/L$ WBC) or thrombocytopenia ($<100 \times 10^9/L$), or severe anemia. (This information is a general guide from the manufacturer, but treatment parameters for this protocol are outlined in section 5.2 and 6.0 and are the operative guide for this study.)

Hydroxyurea is contraindicated in patients who have demonstrated a previous hypersensitivity to hydroxyurea or any other component of its formulation.

2.3.2.5 WARNINGS

Treatment with hydroxyurea should not be initiated if bone marrow function is markedly depressed. Bone marrow suppression may occur, and leukopenia is generally its first and most common manifestation. Thrombocytopenia and anemia occur less often and are seldom seen without a preceding leukopenia. However, the recovery from myelosuppression is rapid when therapy is interrupted. It should be borne in mind that bone marrow depression is more likely in patients who have previously received radiotherapy or cytotoxic cancer chemotherapeutic agents; hydroxyurea should be used cautiously in such patients. (This information is a general guide from the manufacturer, but treatment parameters for this protocol are outlined in section 5.2 and 6.0 and are the operative guide for this study.)

Peripheral neuropathy, which was severe in some cases, has been reported in HIV infected patients receiving hydroxyurea in combination with antiretroviral agents, including didanosine, with or without stavudine.

Severe anemia must be corrected before initiating therapy with hydroxyurea. Erythrocytic abnormalities: megaloblastic erythropoiesis, which is self-limiting, is often seen early in the course of hydroxyurea therapy. The morphologic change resembles pernicious anemia, but is not related to vitamin B₁₂ or folic acid deficiency. Hydroxyurea may also delay plasma iron clearance and reduce the rate of iron utilization by erythrocytes, but it does not appear to alter the red blood cell survival time. (This information is a general guide from the manufacturer, but treatment parameters for this protocol are outlined in section 5.2 and 6.0 and are the operative guide for this study.)

Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen. (This information is a general guide from the manufacturer, but treatment parameters for this protocol are outlined in section 5.2 and 6.0 and are the operative guide for this study.)

In patients receiving long-term hydroxyurea for myeloproliferative disorders, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or associated with the patient's

underlying disease.

Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with MPN during therapy with hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with MPN, hydroxyurea should be discontinued if cutaneous vasculitic ulcerations develop and alternative cytoreductive agents should be initiated as indicated.

2.3.2.5.1 Carcinogenesis and Mutagenesis

Hydroxyurea is genotoxic in a wide range of test systems and is thus presumed to be a human carcinogen. In patients receiving long-term hydroxyurea for MPN, such as polycythemia vera and thrombocythemia, secondary leukemia has been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patient's underlying disease. Skin cancer has also been reported in patients receiving long-term hydroxyurea.

Conventional long-term studies to evaluate the carcinogenic potential of hydroxyurea have not been performed. However, intraperitoneal administration of 125–250 mg/kg hydroxyurea (about 0.6–1.2 times the maximum recommended human oral daily dose on an mg/m^2 basis) thrice weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to control. Hydroxyurea is mutagenic *in vitro* to bacteria, fungi, protozoa, and mammalian cells. Hydroxyurea is clastogenic *in vitro* (hamster cells, human lymphoblasts) and *in vivo* (SCE assay in rodents, mouse micronucleus assay). Hydroxyurea causes the transformation of rodent embryo cells to a tumorigenic phenotype.

2.3.2.5.2 Pregnancy

Drugs which affect DNA synthesis, such as hydroxyurea, may be potential mutagenic agents. The physician should carefully consider this possibility before administering this drug to male or female patients who may contemplate conception.

Hydroxyurea can cause fetal harm when administered to a pregnant woman. Hydroxyurea has been demonstrated to be a potent teratogen in a wide variety of animal models, including mice, hamsters, cats, miniature swine, dogs, and monkeys at doses within 1-fold of the human dose given on a mg/m^2 basis. Hydroxyurea is embryotoxic and causes fetal malformations (partially ossified cranial bones, absence of eye sockets, hydrocephaly, bipartite sternebrae, missing lumbar vertebrae) at 180 mg/kg/day (about 0.8 times the maximum recommended human daily dose on an mg/m^2 basis) in rats and at 30 mg/kg/day (about 0.3 times the maximum recommended human daily dose on an mg/m^2 basis) in rabbits. Embryotoxicity was characterized by decreased fetal viability, reduced live litter sizes, and developmental delays. Hydroxyurea crosses the placenta. Single doses of 375 mg/kg (about 1.7 times the maximum recommended human daily dose on an mg/m^2 basis) to rats caused growth retardation and impaired learning ability. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

2.3.2.6 PRECAUTIONS

2.3.2.6.1 General

Therapy with hydroxyurea requires close supervision. The complete status of the blood, including bone marrow examination, if indicated, as well as kidney function and liver function should be determined prior to, and repeatedly during, treatment. The determination of the hemoglobin level, total leukocyte count, and platelet count should be performed at least once a week throughout the course of hydroxyurea therapy. If the white blood cell count decreases to less than $2.5 \times 10^9/L$, or the platelet count to less than $100 \times 10^9/L$, therapy should be interrupted until the values rise significantly toward normal levels. Severe anemia, if it occurs, should be managed without interrupting hydroxyurea therapy. (This is information is a general guide from the manufacturer, but treatment parameters for this protocol are outlined in section [5.2](#) and [6.0](#) and are the operative guide for this study.)

Hydroxyurea should be used with caution in patients with marked renal dysfunction.

Hydroxyurea is not indicated for the treatment of HIV infection; however, if HIV infected patients are treated with hydroxyurea, and in particular, in combination with didanosine and/or stavudine, close monitoring for signs and symptoms of pancreatitis is recommended. Patients who develop signs and symptoms of pancreatitis should permanently discontinue therapy with hydroxyurea.

An increased risk of hepatotoxicity, which may be fatal, may occur in patients treated with hydroxyurea and in particular, in combination with didanosine and stavudine. This combination should be avoided.

2.3.2.6.2 Carcinogenesis, Mutagenesis, Impairment of Fertility

Impairment of Fertility: Hydroxyurea administered to male rats at 60 mg/kg/day (about 0.3 times the maximum recommended human daily dose on an mg/m² basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

2.3.2.6.3 Pregnancy

Pregnancy Category D. (See section [2.3.2.5.2](#))

2.3.2.6.4 Drug Interactions

Prospective studies on the potential for hydroxyurea to interact with other drugs have not been performed.

Concurrent use of hydroxyurea and other myelosuppressive agents or radiation therapy may increase the likelihood of bone marrow depression or other adverse events.

Since hydroxyurea may raise the serum uric acid level, dosage adjustment of uricosuric medication may be necessary.

2.3.2.7 ADVERSE REACTIONS

Adverse reactions have been primarily bone marrow depression (leukopenia, anemia, and occasionally thrombocytopenia), and less frequently gastrointestinal symptoms (stomatitis, anorexia, nausea, vomiting, diarrhea, and constipation), and dermatological reactions such as maculopapular rash, skin ulceration, dermatomyositis-like skin changes, peripheral and facial erythema. Hyperpigmentation, atrophy of skin and nails, scaling, and violet papules have been

observed in some patients after several years of long-term daily maintenance therapy with hydroxyurea. Skin cancer has been reported. Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with MPN during therapy with hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. Dysuria and alopecia occur very rarely. Large doses may produce moderate drowsiness. Neurological disturbances have occurred extremely rarely and were limited to headache, dizziness, disorientation, hallucinations, and convulsions. Hydroxyurea occasionally may cause temporary impairment of renal tubular function accompanied by elevations in serum uric acid, BUN, and creatinine levels. Abnormal BSP retention has been reported. Fever, chills, malaise, edema, asthenia, and elevation of hepatic enzymes have also been reported.

Adverse reactions observed with combined hydroxyurea and irradiation therapy are similar to those reported with the use of hydroxyurea or radiation treatment alone. These effects primarily include bone marrow depression (anemia and leukopenia), gastric irritation, and mucositis. Almost all patients receiving an adequate course of combined hydroxyurea and irradiation therapy will demonstrate concurrent leukopenia. Platelet depression ($<100 \times 10^9/L$) has occurred rarely and only in the presence of marked leukopenia. Hydroxyurea may potentiate some adverse reactions usually seen with irradiation alone, such as gastric distress and mucositis.

The association of hydroxyurea with the development of acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever, and dyspnea has been reported rarely. Pulmonary fibrosis also has been reported rarely.

Fatal and nonfatal pancreatitis and hepatotoxicity, and severe peripheral neuropathy have been reported in HIV-infected patients who received hydroxyurea in combination with antiretroviral agents, in particular, didanosine plus stavudine. Patients treated with hydroxyurea in combination with didanosine, stavudine, and indinavir in Study ACTG 5025 showed a median decline in CD4 cells of approximately $100/\text{mm}^3$.

2.3.2.8 OVERDOSAGE

Acute mucocutaneous toxicity has been reported in patients receiving hydroxyurea at dosages several times the therapeutic dose. Soreness, violet erythema, edema on palms and soles followed by scaling of hands and feet, severe generalized hyperpigmentation of the skin, and stomatitis have also been observed.

2.3.2.9 HOW SUPPLIED

Hydroxyurea ® (hydroxyurea capsules, USP)

500 mg capsules in bottles of 100 (NDC 0003-0830-50).

Storage

Store at 25° C (77° F); excursions permitted to 15°–30° C (59°–86° F) Controlled Room Temperature. Keep tightly closed.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

- A diagnosis of ET or PV ≤ 5 years prior to entry shall be made in accordance with the WHO (2008) criteria (Swerdlow 2008) as shown below.
 - **Polycythemia Vera** (2 major criteria required)*
 1. Hb $>18.5\text{g/dl}$ (♂) or 16.5g/dl (♀) **or**
HCT >99 percentile reference range **or**
Elevated red cell mass ($>25\%$ above mean predicted value) **or**
Hb $>17\text{g/dl}$ (♂) or 15g/dl (♀) if associated with a sustained rise from baseline with no apparent cause (e.g. treated iron deficiency).
 2. Presence of JAK2V617F.

* If source documentation of diagnostic criterion #1 cannot be obtained, then diagnosis can be made with (1) the addition of an erythropoietin level below the reference range of normal AND (2) bone marrow biopsy showing hypercellularity for age with trilineage (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation.
 - **Essential Thrombocythemia** (all 6 criteria required)
 1. Platelets count $\geq 450 \times 10^9/\text{L}$
 2. Megakaryocyte proliferation with large and mature morphology. No significant increase or left shift of neutrophil granulopoiesis or erythropoiesis. Patients may have up to and including 2+ marrow reticulin fibrosis (0, 1 or 2 on scale 0 -4).
 3. Not meeting WHO criteria for CML, PV, MDS, PMF or other myeloid neoplasms.
 4. Demonstration of clonal cytogenetic marker or no evidence of reactive thrombocytosis.
 5. Absence of a leukoerythroblastic blood picture.
 6. May participate in study without presence of JAK2V617F.
- Patients must have high risk disease as defined below:
 - **High risk PV** ANY ONE of the following:
 1. Age ≥ 60 years
 2. Previous documented thrombosis, erythromelalgia or migraine (severe, recurrent, requiring medications, and felt to be secondary to the MPN) either after diagnosis or within 10 years before diagnosis and considered to be disease related
 3. Significant splenomegaly (>5 cm below the left costal margin on palpitation) or symptomatic splenomegaly (splenic infarcts or requiring analgesia)
 4. Platelets $\geq 1000 \times 10^9/\text{L}$
 5. Diabetes or hypertension requiring pharmacological therapy for > 6 months
 - **High risk ET** ANY ONE of the following:
 1. Age ≥ 60 years
 2. Platelet count $\geq 1500 \times 10^9/\text{L}$
 3. Previous documented thrombosis, erythromelalgia or migraine headaches (severe, recurrent, requiring medications, and felt to be secondary to the MPN)

either after diagnosis or within 10 years before diagnosis and considered to be disease related

4. Previous hemorrhage related to ET
5. Diabetes or hypertension requiring pharmacological therapy for > 6 months

- **Other Inclusion criteria (Both Strata)**

- Diagnosed less than 5 years prior to entry on trial
- Never treated with cytoreductive drugs except hydroxyurea for up to 3 months maximum (phlebotomy, aspirin allowed, anagrelide allowed)
- Age: ≥ 18 years (no upper limit)
- Ability and willingness to comply with all study requirements
- Signed informed consent to participate in this study.
- Willing to participate in associated correlative science biomarker study
- Serum creatinine ≤ 1.5 x upper limit of normal
- AST and ALT ≤ 2 x upper limit of normal
- No known PNH (paroxysmal nocturnal hemoglobinuria) clone
- No concurrent hormonal oral contraceptive use

3.2 Exclusion Criteria

Exclusion criteria: (ANY of the following, both strata)

- Known to meet the criteria for primary myelofibrosis (as opposed to ET) by WHO 2008
- Patients with a prior malignancy within the last 5 years (except for basal or squamous cell carcinoma, or in situ cancer of the cervix)
- Any contraindications to pegylated interferon or hydroxyurea
- Presence of any life-threatening co-morbidity
- History of active substance or alcohol abuse within the last year
- Subjects who are pregnant, lactating or of reproductive potential and not practicing an effective means of contraception
- History of psychiatric disorder (e.g. depression): Subjects with a history of mild depression may be considered for entry into this study, provided that a pretreatment assessment of the subject's affective status supports that the subject is clinically stable based on the investigator's normal practice for such subject.
- History of active or uncontrolled autoimmune disorder (e.g. hepatitis)
- Hypersensitivity to interferon alfa
- Hepatitis B or C infection (HBV), or untreated systemic infection
- Known HIV disease
- Evidence of severe retinopathy (e.g. CMV retinitis, macular degeneration) or clinically relevant ophthalmological disorder (e.g. due to diabetes mellitus or hypertension)
- History or other evidence of decompensated liver disease
- History or other evidence of chronic pulmonary disease associated with functional limitation
- Thyroid dysfunction not adequately controlled
- Neutrophil count $< 1.5 \times 10^9/L$
- JAK2 exon 12 mutation: PV that lacks the JAK2V617F mutation but is characterized by the exon 12 mutation.

- Meets criteria for post PV or post ET-MF (see [Appendix A](#))
- Subjects with any other medical condition, which in the opinion of the investigator would compromise the results of the study by deleterious effects of treatment.
- Previous exposure to any formulation of pegylated interferon
- History of major organ transplantation
- History of uncontrolled severe seizure disorder
- Inability to give informed written consent
- Total bilirubin $>1.5 \times \text{ULN}$ (patients that have an isolated indirect bilirubin that causes total bilirubin to be elevated beyond $1.5 \times \text{ULN}$ due to documented Gilbert's syndrome or hemolysis may be included).

3.3 Subject Recruitment and Screening

Subjects will be recruited and screened for the study from the clinical services of the participating study centers.

The sponsor may advertise in academic publications in order to raise awareness about the study.

3.4 Early Withdrawal of Subjects

Withdrawal of the subject is defined as no longer participating in the study. This includes all remaining study visits and follow-up procedures. Subjects who discontinue treatment will continue on study for observational follow-up (see section [5.8](#)).

3.4.1 When and How to Withdraw Subjects

In accordance with the Declaration of Helsinki and the guidelines of the country of the participating institution, each subject is free to withdraw from the study at any time. An investigator also has the right to withdraw a subject from the study in the event of the patient suffering an intercurrent illness, adverse events, or other reasons concerning the health or well-being of the patient, or in the case of lack of cooperation by the patient. All serious adverse reactions need to be followed up until resolution and information returned to study coordinators.

Should a subject decide to withdraw after administration of study drug, or should the investigator decide to withdraw the subject, all efforts should be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A final evaluation at the time of the subject's withdrawal should be made on the last day the subject takes the study drug, or as soon as possible thereafter. If a subject withdraws from the study beyond the time of the last clinical evaluation, then every effort should be made to evaluate the subject during the next scheduled visit. The reason for and the date of withdrawal must be recorded on the CRF. The study discontinuation/end-of-study visit will occur at 30 days after the patient withdraws from the study (± 7 days).

Subjects with clinically significant abnormal laboratory values as determined by the investigator or who have ongoing clinically significant treatment related adverse events during their last scheduled clinical evaluation will be monitored and treated until resolution or stabilization is achieved. Or, in the event that the subject's condition is not likely to improve because of disease progression, the subject will be monitored until the cause of the abnormal test result or adverse event can be determined.

3.4.2 Data Collection and Follow-up for Withdrawn Subjects

The reason for and date of withdrawal from study drug treatment and the reason for and date of withdrawal from the study will be recorded on the case report form (CRF). If a subject withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event or a clinically significant abnormal laboratory test result, monitoring will continue until the event has resolved or stabilized, until the subject is referred to the care of a local health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made. The specific event or test result(s) must be recorded on the CRF. All evaluations will be performed, according to the protocol, 30 days after the patient withdraws from the study (± 7 days). A subject will be considered to be lost to follow-up if all of the following criteria have been met:

1. More than 3 phone calls to the subject are unanswered.
2. A next of kin is contacted and no information is available.
3. The referring physician is contacted and no information is available.
4. A telegram or certified letter is unanswered.

4.0 REGISTRATION, MANDATORY SAMPLE SUBMISSION, AND DATA MANAGEMENT

4.1 Registration Requirements

4.1.1 Site Registration with MPD-RC

Before an MPD-RC Institution can enroll patients, protocol specific regulatory documents must be submitted to the MPD-RC 112 Regulatory Coordinator via E-mail (PDF file preferred) or fax:

MPD-RC 112 Regulatory Coordinator

Jane Lew

Phone: (212) 241-0481

Fax: (212) 876-5276

E-mail: jane.lew@mssm.edu

Required Protocol Specific Regulatory Documents (E-mailed by PDF format preferred):

- Copy of IRB approval letter
- Copy of IRB approved consent
- US Centers ONLY: Completed Pharmacy Drug Order Sheet*
- Copy of the CV of the Research Pharmacist
- CV of the ordering physician
- Completed Form FDA 1572

* E-mail the completed drug order sheet directly to the regulatory coordinator. The total amount of drug ordered with each order form will be determined based on the amount of study drug available at the time, onsite at the Icahn School of Medicine at Mount Sinai.

4.1.2 Study Drug Shipment

Before Study Drug can be shipped to begin accruing patients the above regulatory documents will be required to be sent to the MPD-RC Central Office to the attention of the Regulatory Coordinator, as noted above.

4.1.3 Correlative Biomarker Study (MPD-RC 107)

There is a correlative science biomarker study for which participation is mandatory (MPD-RC protocol 107). The patient must be enrolled in the mandatory companion biomarker study in order to participate in this treatment study (MPD-RC 112).

4.1.4 Informed Consent

The patient must willingly consent after being informed of the experimental nature of the therapy, alternatives therapies, potential benefits, side effects, risks, and discomforts. Human Protection Committee approval of this protocol and of its consent form is required.

4.2 Patient Registration

This study uses the MPD-RC on-line Patient Registration system (<http://www.mpd-rc.org>). Registration will be accepted only through members of the MPD-RC institutions using the on-line Patient Registration system. Registration must occur **prior** to the initiation of therapy.

Confirm eligibility criteria (section 3.0). Complete the Registration Worksheet. Access the on-line Patient Registration system via the patient registration icon on the MPD-RC Information Systems IS Application main menu. If the registering clinical research associate (CRA) requires assistance he/she may consult the on-line help file located under the Help menu of the MPD-RC application. Enter the required information to submit the form.

When the patient is registered, a patient identification number will be generated. Registration will not be completed if eligibility requirements are not met for the selected trial.

The registering institution will receive a Confirmation of Registration that requires review by the registering institution and then either submission of acceptance or corrections to the MPD-RC Data Management Center.

E-Mail MPD112@negrisud.it

At the completion of the registration process, the assignment of the patient to the protocol treatment arm will be made on-line.

Method for Assigning Subjects to Treatment Groups

Patients in the high risk group of PV or ET will be randomized within disease strata to treatment with either pegylated interferon alfa-2a or hydroxyurea. Patients will be further stratified by prior treatment with hydroxyurea (in past 3 months, Stratum A) or no prior treatment with hydroxyurea (Stratum B).

A confirmatory e-mail with the treatment assignment will be sent to the investigator.

5.0 TREATMENT PLAN

A treatment cycle is defined as a one calendar month period of treatment (i.e. January 15th, February 15th, March 15th, etc.)

5.1 Dose Titration and Study Duration

Goal: The goal is to titrate up the dose of the therapeutic agent to the maximal tolerated dose (MTD), or that dose which achieves a complete response by LeukemiaNet criteria (see section 10.0), unless the anticipated toxicity outweighs further clinical benefit.

Treatment Duration: Patients will be treated for 12 months (with a 3 month confirmation period for a total of up to 15 months) to achieve CR or PR. Those not achieving at least a confirmed PR will stop therapy at the end of 15 months of treatment with pegylated interferon alfa-2a or hydroxyurea and continue on the observational follow-up. Length of therapy for responders will be determined by subject's entrance onto the study. The last subject to enter the study receive therapy for at most 24 months and the first subjects entered onto the study could receive therapy for up to 72 months (assuming toxicity or loss of response does not intervene) (see section 9.2 for study calendar).

Specific Goals for Efficacy:

- Hematocrit ≤ 0.45 without phlebotomy (PV Only) and
- Platelet count $\leq 400 \times 10^9/L$ and
- WBC $\leq 10 \times 10^9/L$ and
- Normal spleen size by imaging

Limitation to further increases in dose of each agent, either pegylated interferon alfa-2a or hydroxyurea:

- Hematologic:
 - Platelets $< 100 \times 10^9/L$
 - Neutrophil Count $< 1.0 \times 10^9/L$
 - Development of new drug associated anemia (hemoglobin $< 10.0g/dL$)
- Non-Hematologic (See section 6.0)

5.2 Specific Dosing for Each Agent

5.2.1 Dose Titration of Hydroxyurea

Specific Titration of hydroxyurea Dosing (1 cycle is 1 month for the purposes of titration)

1. Stratum A: Patients randomized to hydroxyurea who enter the trial with ≤ 3 months hydroxyurea will begin at 500mg twice daily* assuming:
 - a. criteria for CR does not already exist and
 - b. dose limiting toxicity (DLT) does not already exist

* If at current dose the patient meets criteria for CR and DLT does not exist, patient can remain on that dose at trial entry.
2. Stratum B: Patients randomized to Hydroxyurea who enter the trial naïve to hydroxyurea will begin at 500mg twice daily (or 500mg daily if clinically indicated).

3. Dose titration for both groups 1 and 2 will occur at each monthly visit (or dose reduction in between interval visits (but not dose increases) according to [Table 2](#). Further fine tuning between dose levels is allowed at site investigators discretion. Levels above +4, or below -3 (if associated with toxicity) likely represent a failure of hydroxyurea in this trial.

Table 2 Dose Levels of Hydroxyurea

Dose Level	Dose of Hydroxyurea
-3	500 mg every other day
-2	500 mg every day
-1	500 mg day 1, 1000 mg day 2 - alternating
0	1000 mg daily (500 mg twice daily)
+1	1000mg day 1, 1500 mg day 2 - alternating
+2	1500mg daily (500 mg three times/ day)
+3	1500mg day 1, 2000 mg day 2 - alternating
+4	2000 mg/ day (1000 mg twice daily)

5.2.2 Dose Titration of Pegylated Interferon Alfa-2a

1. Stratum A: Patients randomized to Pegylated Interferon Alfa-2a and entering with ≤ 3 months hydroxyurea will begin at 45 micrograms per week. If patient is currently on hydroxyurea when entering therapy, patient will begin at 45 micrograms per week, and increases of pegylated interferon alfa-2a during the first 2 months will be made at a rate that will allow cessation of hydroxyurea prior to initiating treatment at the beginning of month 3.
2. Stratum B: Patients randomized to Pegylated Interferon Alfa-2a who enter the trial naïve to hydroxyurea will begin at 45 micrograms/week. Dose can be increased after at least one month of therapy (as tolerated) if one of the following has not occurred.
 - a. criteria for CR does not already exist
 - b. dose limiting toxicity (DLT) does not already exist
3. Dose titration for both strata A and B will occur at each monthly visit (or dose reduction in between interval visits according to [Table 3](#)). Dose escalations can only be done on the scheduled study visits until after 6 months, in which dose escalations can occur between study visits not less than a month apart. Interval Dose Levels (0.5, 1.5, and 2.5) are meant to allow for titration and can be used even if patient is not having side effects. Dose escalation to levels > 135 micrograms/ week will occur only after 3 months of therapy (unless part of Stratum A and needed for cessation of hydroxyurea). Levels below -3 (if associated with limiting toxicity) or above +3 likely represent a failure of Pegylated Interferon Alfa-2a in this trial.

Table 3 Dose Levels of Pegylated Interferon Alfa-2a

Dose Level	Dose of Pegylated Interferon Alfa-2a
-3	45 micrograms every fourth week (\pm 2 days)
-2	45 micrograms every third week (\pm 2 days)
-1	45 micrograms every other week (\pm 2 days)
0	45 micrograms/ week (\pm 2 days)
0.5	45 micrograms one week, 90 micrograms week 2 alternating (\pm 2 days)
1	90 micrograms weekly (\pm 2 days)
1.5	90 micrograms one week, 135 micrograms week 2 alternating (\pm 2 days)
2	135 micrograms weekly (\pm 2 days)
2.5	135 micrograms one week, 180 micrograms week 2 alternating (\pm 2 days)
3	180 micrograms weekly (\pm 2 days)

5.3 Phlebotomy Guidelines

All patients will continue to receive venesection where required, the target hematocrit (HCT or packed cell volume) will be 0.45 for men and women.

5.4 Aspirin Therapy

A standard dose of 81mg or 100mg of aspirin (depending on standard practice in each country) (to be taken with food) will be used in all patients. At this dosage side-effects are very uncommon. However, aspirin may be contraindicated in a few patients because they have a history of intolerance to aspirin, MPN-associated hemorrhage, recent peptic ulceration or aspirin sensitive asthma.

5.5 Pregnancy

Neither agent used in this trial is indicated, not proven safe in pregnancy. Patients will be advised to use effective contraception and to avoid pregnancy while on the trial. In the event of pregnancy the patient will be removed from the study and alternative therapy (at the discretion of the treating physician) will be used. The patient and offspring will be followed monthly until 6 months after delivery.

5.6 Intolerance or resistance to Hydroxyurea

Either Intolerant or resistant to HU according to established criteria as follows:
Any ONE of the following:

- Platelet count $> 600 \times 10^9/L$ after 3 months of at least 2g/day or maximally tolerated dose (MTD) of hydroxyurea (2.5 g/day in patients with a body weight > 80 kg)
- Platelet count $> 400 \times 10^9/L$ and WBC less than $2.5 \times 10^9/L$ at any dose of HU
- Platelet count $> 400 \times 10^9/L$ and Hb less than 10 g/dl at any dose of HU
- Progressive splenomegaly or hepatomegaly (> 5 cm from initiation of hydroxyurea) or the

appearance of new splenomegaly or hepatomegaly while on MTD of hydroxyurea.

- Not achieving a Hct < 45% in order to eliminate the need for supplemental phlebotomies after 3 months of at least 2g/day or MTD of hydroxyurea
- Not achieving a WBC of < $10 \times 10^9/L$ after 3 months of at least 2g/day or MTD of hydroxyurea
- Presence of leg ulcers or other unacceptable HU-related non-hematological toxicities, such as unacceptable mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis or fever at any dose of HU.

5.7 Discontinuation of Treatment

The following conditions are reasons to interrupt and discontinue the trial treatment:

- The patient fails to achieve adequate response as defined by a platelet count > $600 \times 10^9/L$ at the end of 12 months from trial entry.
- If after the initial 12 months of therapy the patient cannot maintain a platelet count < $600 \times 10^9/L$ for a period of more than 3 months. (i.e. months 12 thru 15)
- Major thrombosis (CVA, myocardial infarction, pulmonary embolism, DVT); Transient ischemic attack (TIA) is not for this purpose considered a major event.
- Major hemorrhagic event (non-epistaxis, requiring medical intervention)
- Progression to myelofibrosis ([Appendix A](#))
- Progression to Acute Leukemia ([Appendix A](#))
- The patient is progressing on the assigned treatment, i.e. blood counts (white blood cells or platelets) not controllable as dosage of drug is increased to the maximal tolerated or the maximum of 180 micrograms and patient is refractory
- The patient decides it is in his/her best interest (patient unwilling to continue therapy)
- Serious adverse experience(s) i.e. bleeding, irreversible cytopenias, lower extremity ulceration, neuropsychiatric disturbances; pulmonary infiltrates, congestive heart failure, renal or hepatic insufficiency, colitis, pancreatitis and specific ophthalmological complications suspected to be treatment induced. Discretion is granted to the treating physician to determine, dependent on the severity, relationship to therapy of the adverse events in conjunction with the potential response to either reduce the dose of the study agent or stop treatment or withdraw the patient from the study.
- Pregnancy
- The patient is found to be intolerant or resistant to hydroxyurea as defined in section 5.2.4.
- Non-Compliance

Trial treatment should not be attempted where the patient meets criteria for failing to achieve and adequate response or in the event of serious adverse reactions which are related to pegylated interferon alfa-2a for example irreversible cytopenias, neuropsychiatric disturbances; pulmonary infiltrates, congestive heart failure, renal or hepatic insufficiency, colitis, pancreatitis and specific ophthalmological complications

Patients with a treatment interruption should continue the protocol visit schedule and comply with all study procedures, except treatment. Patients with the above endpoints or the inability to continue on therapy will be considered off treatment at the time of the event and would be followed for the next 30 days only or until any drug related adverse events have resolved (even if more than 30 days after the last dose of pegylated interferon alpha 2a).

5.8 Treatment Failure/Observational Follow-up

Patients who meet the criteria for treatment failure as defined in section 5.7 or by unwilling to continue therapy, will continue on study with observational follow-up. The observational follow-up will be conducted every 6 months from the time the patient goes off treatment until 6 years from the start of their treatment or 2 years after the last patient enters the study (whichever comes first).

The following information will be collected during these observational follow-up time points:

- Survival
- Incidence of development of myelodysplastic disorders, myelofibrosis, or leukemic transformation
- Incidence of cardiovascular events (defined as cardiovascular death, myocardial infarction, stroke, transient ischemic attack, pulmonary embolism, Budd Chiari syndrome, deep vein thrombosis, and any other clinically relevant thrombotic event)
- Changes in treatment: treatments received after end of study drug while on observation

6.0 DOSE DELAYS/DOSE MODIFICATIONS

The following grades and definitions of toxicity are used. Further details are available at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

Grades (General Definitions)

- 0 = No adverse event or within normal limits
- 1 = Mild adverse event
- 2 = Moderate adverse event
- 3 = Severe and undesirable adverse event
- 4 = Life-threatening or disabling adverse event
- 5 = Death related to adverse event

Dose adjustments should be made as follows:

- **Grade 1 or 2 toxicity:** should be maintained on the same dose where possible. For grade 2 ALT or hematologic toxicities, follow instruction in the next bullet points
- **Grade 2 ALT:** stop pegylated interferon alfa-2a then restart at one dose level lower per [Table 2](#) or [Table 3](#) when toxicity improves to grade 1 or better
- **Grade 2 hematologic toxicity:** reduce one dose level lower per [Table 2](#) or [Table 3](#)
- **Grade 3 or 4 toxicity:** (for fevers, flu-like symptoms and chills consider restricting this to grade 4); stop pegylated interferon alfa-2a then restart at one dose level lower per [Table 3](#) when toxicity improved to grade 1 or better (caveat to this is a grade 3 or 4 AE that is unrelated to study drug and in the opinion of the investigator restarting or continuing therapy does not pose a safety risk), or discontinue at the discretion of the treating physician in the case of grade 4 toxicity; stop Hydroxyurea then restart at one dose level lower when toxicity improved to grade 1 or better, or discontinue at the discretion of the treating physician in the case of grade 4 toxicity. In both instances reduce dose by at least 1 dose level (see [Table 2](#) and [Table 3](#) above in section 5.2).

If toxicity improves to grade 1 or better and the subject restarts at one dose level lower, the treating investigator may re-escalate following the guidelines in section 5.2. However, if the subject experiences the same toxicity a second time, the subject should be withdrawn from study.

For non-hematological toxicities, the study drug can be held up to 3 months before it is considered a treatment failure (see section 5.8). For hematological toxicity, the study drug can be held indefinitely. When restarting study drug after the treatment interruption, the treating physician can re-escalate the dose as outlined in section 5.1. If the subject experiences the same toxicity that causes treatment interruption a second time, it should be considered a treatment failure (see section 5.8).

Thyroid diseasePrior to pegylated interferon alfa-2a:

If patient has abnormal TSH and/or presence of thyroid antibodies, treat underlying thyroid condition before introducing pegylated interferon alfa-2a.

During therapy with pegylated interferon alfa-2a:

Hyperthyroidism – test Thyroid antibodies and Thyroid scan

- if Graves, treat with standard therapy and consider withdrawal of pegylated interferon alfa-2a
- if destructive thyroiditis, use beta blocker and consider withdrawal of pegylated interferon alfa-2a

Hypothyroidism – thyroid replacement, continue pegylated interferon alfa-2a and monitor thyroid therapy

Psychiatric: Depression

Guidelines for modification or discontinuation of pegylated interferon alfa-2a (PEGASYS) and the scheduling of visits for patients with depression are provided in [Table 4](#).

Table 4 Depression Guidelines

Depression Severity (as defined by CTCAE v. 4.0)	Initial Management (1-2 months)		Depression		
	Dose modification	Visit schedule	Remains stable	Improves	Worsens
Mild	No change	Evaluate once weekly by visit and/or phone	Continue weekly visit schedule	Resume normal visit schedule	(See moderate or severe depression)
Moderate	Decrease PEGASYS dose by one dose level per Table 3	Evaluate once weekly (visit at least every other week)	Consider psychiatric consultation. Continue reduced dosing	Resume normal visit schedule	(See severe depression)
Severe	Discontinue PEGASYS permanently	Obtain immediate psychiatric consultation	Psychiatric therapy necessary		

Renal Function and Liver

Patients who qualify by eligibility criteria will be monitored for renal toxicity or hepatic toxicity. Guidelines for dose modifications will be made as described previously for Grade 3 or 4 non-hematological toxicity.

7.0 PHARMACEUTICAL INFORMATION

7.1 Pegylated Interferon Alfa-2a (IND #106,511)

7.1.1 Description

PEGASYS, pegylated interferon alfa-2a, is a covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight [MW] 20,000 daltons) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate MW 40,000 daltons). The PEG moiety is linked at a single site to the interferon alfa moiety via a stable amide bond to lysine. Pegylated interferon alfa-2a has an approximate molecular weight of 60,000 daltons. Interferon alfa-2a is produced using recombinant DNA technology in which a cloned hydroxyureaman leukocyte interferon gene is inserted into and expressed in *Escherichia coli*.

7.1.2 Packaging of Study Drug Pegylated Interferon Alfa-2a

The study drug pegylated interferon alfa-2a (PEGASYS), in North America will be provided by the Icahn School of Medicine at Mount Sinai to the individual sites participating in this study. It will be shipped in prefilled 180 microgram/0.5mL syringes or 180 microgram/1.0mL single-use vials. The local institutional pharmacist will be responsible for packing the study supply into individual containers and providing to the study subjects.

The study drug (pegylated interferon alfa-2a; PEGASYS), in Europe, will be provided by Roche Pharmaceuticals by Roche affiliates or contracted drug distributors located in each individual country in Europe participating in the trial to the individual sites participating in this study. The delivery of study drug may vary in European countries, but could be made available as prefilled 135 or 180 microgram syringes or single-use pen devices.

7.1.3 Method for Assigning Subjects to Treatment Groups

Patients in the high risk group of PV or ET will be randomized to treatment with either pegylated interferon alfa-2a or hydroxyurea within strata defined by their disease and use of hydroxyurea (less than 3 months or never). Registration and randomization is done through the MPD-RC Data Management website.

7.1.4 Prior and Concomitant Therapy

Patients must have had PV or ET for not more than 3 years and not received more than 3 months of hydroxyurea therapy prior to study entry. Patients cannot have any other form of chemotherapy, hydroxyurea, interferon, or JAK2 inhibitors.

If a patient who is randomized to pegylated interferon alfa-2a is currently on hydroxyurea when entering the study, they should be tapered off hydroxyurea over a period of up to 2 months when pegylated interferon alfa-2a is started.

7.1.5 Receiving, Storage, Dispensing and Return of Study Drug pegylated interferon alfa-2a

7.1.5.1 Receipt of Drug Supplies

Drug supply for the USA sites will be shipped from Genentech to the Mount Sinai Medical Center (New York), from which it will then be distributed to the sub-sites of the trial. It will be shipped in

180 microgram pre-filled syringes or single-use vials.

European drug distribution will be provided by Roche Pharmaceuticals or contracted drug distributors to the individual sites participating in this study. It will be shipped in prefilled 135 or 180 microgram syringes or single-use pen devices, depending on the availability of Pegasys in the European regions.

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment should be documented in the study files. The investigator must notify the MPD-RC of any damaged or unusable study treatments supplied to the investigator's site. The site is required to maintain adequate accountability records that are equivalent to the NCI DARF. See Appendix F: NCI DARF.

7.1.5.2 Storage

The study drug should be stored, under adequate security, in the pharmacy at the study center at a refrigerator at a temperature of 2°C to 8°C (36°F to 46°F) until taken by the study patients or until returned to Roche Pharmaceuticals.

7.1.5.3 Dispensing of Study Drug

The study drug in North America may be requested from the Mount Sinai Medical Center (New York) by the Principal Investigator (or their authorized designee) at each participating site (See section 4.1.1 for required regulatory documentation). In Europe, Roche Pharmaceuticals will ship the drug directly to the institution where the patient is to be treated. Transfer of drugs between MPD-RC member institutions is not permitted.

7.1.5.4 Return or Destruction of Study Drug

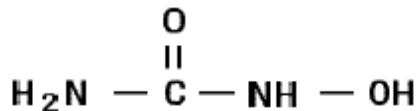
At the completion of the study, there will be a final account of drug shipped, drug consumed, and drug remaining. This accounting process will be logged on the drug accounting form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

7.2 Hydroxyurea

7.2.1 Description

Hydroxyurea® (hydroxyurea capsules, USP), Hydroxy Carbamide, is an antineoplastic agent available for oral use as capsules providing 500 mg hydroxyurea. Inactive ingredients: citric acid, colorants (D&C Yellow No. 10, FD&C Blue No. 1, FD&C Red 40, and D&C Red 28), gelatin, lactose, magnesium stearate, sodium phosphate, and titanium dioxide.

Hydroxyurea/Hydroxycarbamide occurs as an essentially tasteless, white crystalline powder. Its structural formula is:



A complete description is located in section [2.3.2](#).

7.2.2 Packaging

Hydroxyurea is an FDA approved drug. Patients or their insurance providers will be responsible for the cost of this drug. Hydroxyurea ® (hydroxyurea capsules, USP) **500 mg capsules** in bottles of 100 (NDC 0003-0830-50).

7.2.3 Storage

Store at 25° C (77° F); excursions permitted to 15°–30° C (59°–86° F) Controlled Room Temperature. Keep tightly closed.

Hydroxyurea will be dispensed by physician prescription and is not provided specifically for use in this study.

7.2.4 Method for Assigning Subjects to Treatment Groups

Patients in the high risk group of PV or ET will be randomized to treatment with either pegylated interferon alfa-2a or hydroxyurea within strata defined by their disease. Within each disease stratum, patients will also be stratified by exposure to hydroxyurea (Stratum A (current hydroxyurea for 3 months or less) and Stratum B (no prior hydroxyurea)). Registration and randomization is done through the MPD-RC Data Management website.

7.2.5 Prior and Concomitant Therapy

Patients must have had PV or ET for not more than 3 years and not received more than 3 months of hydroxyurea therapy prior to study entry. Patients cannot have any other form of chemotherapy, interferon, or JAK2 inhibitors.

7.3 Aspirin

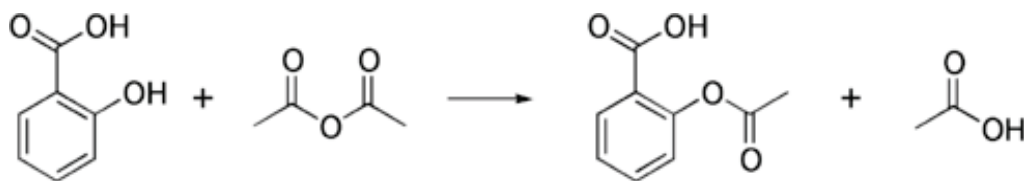
All subjects on this study, regardless of randomized medication, will receive aspirin as part of their therapy.

Aspirin is an acetyl derivative of salicylic acid that is a white, crystalline, weakly acidic substance, with melting point 135°C. Acetylsalicylic acid decomposes rapidly in solutions of ammonium acetate or of the acetates, carbonates, citrates or hydroxides of the alkali metals. Acetylsalicylic acid is stable in dry air, but gradually hydrolyses in contact with moisture to acetic and salicylic acids. In solution with alkalis, the hydrolysis proceeds rapidly and the clear solutions formed may consist entirely of acetate and salicylate.

Synthesis

The synthesis of aspirin is classified as an esterification reaction. Salicylic acid is treated with acetic anhydride, an acid derivative, causing a chemical reaction that turns salicylic acid's alcohol group into an acetyl group, (R-OH > R-OCOCH₃). This process yields aspirin and acetic acid, which is considered to be a byproduct of this reaction. Small amounts of sulfuric acid (and

occasionally phosphoric acid) are almost always used as a catalyst.



Formulations containing high concentrations of aspirin often smell like vinegar. This is because aspirin can decompose in moist conditions, yielding salicylic acid and acetic acid.

The acid dissociation constant (pK_a) for acetylsalicylic acid is 3.5 at 25°C.

8.0 BIOMARKERS

The correlative biomarker study (MPD-RC 107-Appendix 10.2) will evaluate a series of biomarkers at baseline, after month 12, 24 and either at the time of relapse/progression or at termination of study, that is off study drug permanently for any reason (i.e. intolerance or completing required course of study drug).

8.1 Samples to be Collected

The following samples noted in Table 5 are to be collected at baseline, the end of month 12, 24 and at the time of a bone marrow aspirate and biopsy to evaluate for relapse/progression or at off-treatment, that is off study drug permanently for any reason (i.e. intolerance or completing required course of study drug).

Table 5 Samples to be collected

Sample:		Baseline	After 12 Months	After 24 Months	Off-Treatment ⁴
<u>Bone marrow aspirate</u>	<u>Copy of Local Institutional Histopathology Report</u>	X	X	X	X
Histopathology ¹	Three (3) air dried unstained slides	X	X	X	X
Cytogenetics ²	At local institution, upload data and karyotypes to website. If no aspirate, provide peripheral blood karyotypes ² .	X	X	X	X
Biomarkers ³	2 to 5 mL of bone marrow aspirate in a green top, heparinized tube (BD catalog #366480)	X	X	X	X
<u>Bone marrow biopsy</u>	<u>Copy of Local Institutional Histopathology Report</u>	X	X	X	X
Histopathology ¹	One (1) H & E stain	X	X	X	X
	One (1) Iron stain	X	X	X	X
	One (1) Silver impregnated reticulin stain	X	X	X	X
	Three (3) Unstained paraffin-fixed slides each with at least 2 sections	X	X	X	X
	three (3) air-dried, unstained bone marrow aspirate slides (if available)	X	X	X	X
	If no aspirate, two (2) air dried unstained touch preps, 8 touches/slide, 2 horizontal rows of 4 touches.	X	X	X	X

Sample:		Baseline	After 12 Months	After 24 Months	Off-Treatment ⁴
<u>Blood</u>					
Histopathology ¹	Four (4) Unstained peripheral blood films, thin smears	X	X	X	X
Cytogenetics ²	If no BM aspirate karyotypic analysis ²	X	X	X	X
Biomarkers ³	<u>Hematocrit < 32, 37 mL</u> Three (3) ACD: yellow (BD #364606; 8.5 mL)	X	X	X	X
	One (1) EDTA: lavender (BD #366450; 8.5 mL)	X	X	X	X
	One (1) sodium citrate: light blue (BD #366415; 4.5 mL)	X	X	X	X
	<u>Hematocrit >= 32, 76 mL</u> Five (5) ACD: yellow (BD #364606; 8.5 mL)	X	X	X	X
	One (1) EDTA: lavender (BD #366450; 8.5 mL)	X	X	X	X
	Four (4) sodium citrate: light blue (BD #366415; 4.5 mL)	X	X	X	X
<u>Nails</u> ³	2 clippings (pre-treatment, at enrollment only)	X			

- All slides must be registered via the MPC-RC website the day they are collected and prior to shipment.** All slides MUST BE LABELED properly. Labels are to include the patient's tissue bank ID number (TB ID), protocol number (e.g., Protocol 112), time of study (e.g., baseline, 6 months), type of specimen (e.g., BM biopsy, BM aspirate, blood), type of stain (e.g., Iron, H&E). For unstained slides, use a pencil to label the slides. All slides are to be shipped to the tissue bank laboratory in a labeled slide box. The label on the box is to include the patient's TB ID, protocol number, and time of study. Slides may be shipped in batches together with the local institution's histopathology report. All slides are shipped to Dr. Rona Singer Weinberg. See Protocol 107, section 5.0 Procurement for additional labeling and shipping information.
- Cytogenetic analyses are performed as a standard of care at the institution where the patient is being treated. Karyotypic analysis of unstimulated bone marrow after direct 24 and 48 hours, if available, or peripheral blood shall be performed. Karyotypic analysis using G-banding technology is required. Data and karyotypes are uploaded to the website. See Protocol 107, section 5.0 Procurement for additional reporting information.
- All tissue samples must be registered via the MPC-RC website the day they are collected and prior to shipment.** All tubes, and envelopes (nails) must be labeled with patient's tissue bank ID number (TB ID), protocol number (e.g., Protocol 112), sample ID number (provided by the data bank at the time of registration), time of study (e.g., baseline, 6 months), type of specimen (e.g., BM biopsy, BM aspirate, blood) and date of collection.
- Off-Treatment is defined as 30 (\pm 7) days after patient permanently stops treatment for **any reason** at **any time** during the study (i.e. study drug intolerance, relapse/progression, study completion, etc.)

Fresh blood and bone marrow are to be shipped at ambient temperature and must be shipped the day that they are collected.

Nails are to be shipped at ambient temperature and may be shipped together with blood and bone marrow samples or subsequently.

All slides are to be shipped to the tissue bank laboratory in a labeled slide box. The label on the box is to include the patient's TB ID, protocol number, and time of study. Slides may be shipped in batches together with the local institution's histopathology report. All slides are shipped to Dr. Rona Singer Weinberg. See Protocol 107 section 5.0 Procurement for additional labeling and shipping information.

All shipments must be sent by overnight courier for delivery before 10 AM or morning delivery the next day. For Friday shipments (to arrive on Saturday), notify the laboratory prior to collection of tissue and shipment. For shipments sent on Friday for Saturday delivery be certain to request Saturday AM delivery directly to the lab. It is not possible for lab personnel to go to the courier's office for pick-up.

Shipping:

In North America ship to:

Dr. Rona Weinberg
New York Blood Center
310 East 67th Street
Second Floor
New York, New York 10065
Phone: (212) 570-3488
Fax: (212) 570-3495
rweinberg@nybloodcenter.org
Laboratory Phone: (212) 570-3412
Laboratory Fax: (212) 570-3495
MPDLab@nybloodcenter.org

Office hours: Monday through Friday 9AM to 5PM ET. **For shipments to be received at other times, contact Dr. Weinberg in advance of collection of samples and shipment**

Or

In Europe ship to:

Dr. Silvia Salmoiraghi
MPD-RC Tissue Bank
Azienda Ospedaliera Papa Giovanni XXIII
Laboratorio Paolo Belli USC Ematologia
Torre 7, Ingresso 55, piano 1
Piazza OMS- Organizzazione Mondiale della Sanità, 1
24127 Bergamo
Phone: +39 035-2673769
lab.paolobelli@hpg23.it

Office hours: Monday through Friday 9AM to 5PM. **For shipments to be received at other times, contact Dr. Silvia Salmoiraghi in advance of collection of samples and shipment.**

8.2 Collection of Biomarker Samples:

The samples obtained as noted in [Table 5](#) will be separated as follows. (also see Protocol 107, Appendix 10.2 for the time points to obtain samples)

8.2.1 Bone Marrow

Bone marrow samples will be collected for histopathology, biomarkers, and cytogenetics/FISH. For biomarkers (2-5 ml) and cytogenetics (1-2 ml) (performed at the local institution), obtain a total of 3-7 mL of aspirated bone marrow. Samples are to be divided as follows:

For Biomarkers: 2-5 mL of bone marrow in a green top, heparinized tube (BD catalog number 366480). Cytogenetics 1-2 ml.

8.2.2 Peripheral Blood

Up to 67 mL of blood (use sterile technique):

- For hematocrit < 32, 37 mL of blood: three ACD (yellow top) tubes (BD catalogue number 364606; 8.5 mL tubes), one EDTA (lavender top) tube (BD catalog number 366450), and one sodium citrate (light blue top) tube (BD catalogue number 366415, 4.5 mL).
- For hematocrit \geq 32, 67 mL of blood: Five ACD (yellow top) tubes (BD catalogue number 364606; 8.5 mL tubes), one EDTA (lavender top) tube (BD catalog number 366450), and four sodium citrate (light blue top) tubes (BD catalogue number 366415, 4.5 mL).

8.2.3 Nail Clippings

Two nail clippings are to be obtained from each patient during the initial entry onto the protocol. Clippings are to be placed in a paper envelope and the envelope is to be sealed. The sealed envelope may be stored and shipped at room temperature.

8.3 Central Morphological Review of Bone Marrow Aspirate Smears and Biopsies for Patients Entering MPD-RC Treatment Studies

8.3.1 Bone Marrow and Peripheral Blood Histopathology

(See protocol 107, Appendix 10.2, for more detailed information)

At entry into the trial, after 12 months, after 24 months, and at off-treatment for any reason (completion of study, relapse, progression, intolerance to drug, etc.) the following bone marrow aspiration and biopsy specimens must be obtained and submitted for central review:

Bone marrow biopsy slides:

- One (1) biopsy slide stained with H & E
- One (1) biopsy slide stained for iron
- One (1) biopsy slide stained with the silver for reticulin fibrosis stain should be submitted for confirmatory cytologic and cytochemical studies.
- Three (3) unstained paraffin-fixed bone marrow biopsy slides each containing at least 2 sections.
- Two (2) air dried unstained bone marrow biopsy touch preps for patients with no aspirate sample (these are made with 8 touches per slide – 4 horizontal touches in 2 rows on the slide)

Bone marrow aspirate slides:

- Three (3) air-dried, unstained bone marrow aspirate slides (if available)

Peripheral blood slides:

- Four (4) unstained peripheral blood films (thin smears)

Slides should be submitted together with the final institutional pathology, cytochemistry, and immunophenotyping reports (if possible). Bone marrow studies should be repeated at 12 and 24 months following treatment and aspirate and biopsy specimens as described above again submitted for central review. They should also be repeated if transformation to MDS, myelofibrosis or acute leukemia is suspected and if a patient goes off-treatment permanently for any reason (i.e. intolerance of drug, completion of study) after at least 6 months treatment.

The histopathology slides may be batch shipped every 3 Months to Dr. Weinberg in North America or Dr. Salmoiraghi in Europe.

There must be an adequate amount of marrow biopsy specimen in each smear. The above requirements are considered minimal. Contact the MPD-RC Study Chair with any questions.

Identify each slide with the patient's MPD-RC tissue bank ID number, protocol number, type of specimen (example: BM biopsy, BM touch prep, BM aspirate), type of stain (example: H&E, iron, reticulin), and time of study (example: baseline, 12 month, 24 month) pack carefully in protective slide boxes (not cardboard folders), and mail to:

(North America)

Dr. Rona Weinberg
New York Blood Center
310 East 67th Street
Second Floor
New York, New York 10065
Phone: (212) 570-3488
Fax: (212) 570-3495
rweinberg@nybloodcenter.org
Laboratory Phone: (212) 570-3412
Laboratory Fax: (212) 570-3495
MPDLab@nybloodcenter.org
Monday through Friday Noon EST

Or

(Europe)

Dr. Silvia Salmoiraghi
 MPD-RC Tissue Bank
 Azienda Ospedaliera Papa Giovanni XXIII
 Laboratorio Paolo Belli USC Ematologia
 Torre 7, Ingresso 55, piano 1
 Piazza OMS- Organizzazione Mondiale della Sanità,1
 24127 Bergamo
 Phone: +39 035-2673769
lab.paolobelli@hpg23.it
 Monday through Friday Noon

Send a copy of the institutional bone marrow aspiration and biopsy report generated at your institution as soon as it is complete to the MPD-RC central laboratory in New York or Bergamo, Italy. This report must include differential cell counts on the marrow aspirate, if performed.

8.3.2 Cytogenetics and FISH Cytogenetic and FISH Requirements

Diagnostic and follow up cytogenetics and or FISH will be performed by local institutional laboratories. All karyotypes will be centrally reviewed (see below). To ensure uniformity of cytogenetic preparations all participating local laboratories must adhere to the following requirements established by the central karyotype review committee.

General Inclusion Criteria for Conventional Cytogenetics

- 1) Banding level 300 or more and structural aberrations are accepted at 400 or higher banding level or confirmed by FISH.
- 2) Minimum requirements for baseline assessments: From each patient, bone marrow (PV, ET) and or unstimulated PB (PMF) specimen must be set up into two, preferably three, different cultures (direct, 24 hrs with and without marrow max media). Every effort should be made to obtain the growth of cells that are cytogenetically abnormal.
- 3) 20 metaphase evaluated from two or more cell cultures or from marrow max culture only.
- 4) Only G-banding of chromosomes is acceptable. Other banding methods are not acceptable.
- 5) Analysis of cell at 300 band resolution, or low quality banding, irrespective of the findings, to be complemented with FISH screening for subtle aberrations, including del(20)(q11q13) with D20S108 probe.
- 6) SCN 2009 must be used to describe the karyotype.
- 7) Aberrations classified as clonal should be present in at least 2 cells by G-banding or confirmed by FISH.
- 8) Unusual or novel findings should be fully characterized by FISH using appropriate probes.
- 9) Three karyotypes (and metaphase cells) from each patient must be uploaded electronically into the MPD-RC data base to document the stated cytogenetic diagnosis. The karyotypes are uploaded either as TIFF or JPEG files.

FISH studies, IF POSSIBLE and recommended

- 10) Case normal by G banding, if possible, ought to be screened for cryptic changes by interphase FISH using a MPN panel of 12 probes: CEP1(or 1q12)/1q21, 5p15.2/5q31(*EGR1*), CEP7/7q31, CEP8, CEP9/9p21, *RBI* at 13q14, P53/CEP17, 20q12/*D20S108*.

- 11) FISH studies are performed on BM or PB on interphase cells processed directly (no culture) using Abbott Molecular FISH probes. A minimum of 200 cells at baseline should be scored by two individuals. Image of FISH results should be uploaded as JPEG or TIFF file into the MPD-RC data base.

Central karyotype review committee consists of Vesna Najfeld, Ph.D., Director, Tumor Cytogenetics, The Mount Sinai Medical Center, NY (chair) Elisabeth Nacheva, MD, Ph.D, FRC Path, Director of Cytogenetics, UCL Medical School, Royal Free Campus, London, UK, Cristina Mecucci, MD, PhD, Director of Cytogenetic laboratory, University of Perugia, Perugia, Italy and Ursula Giussani, Ph.D., Director of Laboratorio di Genetica Medica, Bergamo, Italy. Central karyotype review committee will have biannual teleconferences and central karyotype review and will meet annually to resolve difficult karyotypes, perform QC, and discuss correlative studies with hematological response and other biomarkers. Karyotypes that were not uploaded or faxed pictures of karyotypes cannot be reviewed.

One of the Quality Control indicators is a proper entry and submission of cytogenetic forms and karyotypes by the institutional cytogenetic laboratories. If the local laboratory fails two consecutive specimens (poor quality of chromosome banding, missed abnormality, wrong ISCN nomenclature) or lack of entering cytogenetic results into MPD- RC, the laboratory will be informed, and the third failure will result in placing the local laboratory on probation and the institutional PI will be informed. If required, either the central lab in NY or other

MPD-RC approved cytogenetic lab will perform the studies from the institution whose cytogenetic lab is placed on probation. Each institution in the MPD-RC will receive quarterly information regarding the cytogenetic entry results on the MPD-RC data base.

For any questions please call Joe Tripodi MS, Cytogenetic Research Coordinator, Mount Sinai Medical Center: 212 241-8801 or Dr. Vesna Najfeld at 212-241-8801.

8.4 Clonality

Applicable to informative females = probable 50 – 60% of patients. Sample amount for this test is already included in the samples being collected. No further sample collection needs to be done for this test (already included in the sample collection).

8.5 Symptom Assessment Package

The Symptom Assessment Package (*MPN-SAF*, EORTC-QLQ C30, Exploratory Questions, Pegylated Interferon Alfa-2a /PEGASYS Specific Questions) (see section 9.6) will be given to the patient to answer and complete. At baseline these questionnaires will be given to the patient and completed by the patient and returned to the local investigator prior to being provided with information regarding the treatment assignment. The time points for collection are at baseline (pre-randomization), month 4 day 1, after months 6, 9, 12, and then every 6 months while on study, and at off-treatment. The data on the forms are to be electronically entered into the MPD-RC CRFs online in data web site.

8.6 Registration Procedure

Register patients via the MPD-RC website: <http://www.mpd-rc.org>. A summary and a schedule of the collection and distribution of tissue samples are provided in Table 5 above.

8.7 Biomarker Evaluations

The biomarkers that will be monitored in this trial at baseline, after 12 and 24 months, and at time of a bone marrow to assess for relapse/progression or at the termination of the patients receiving study medication and are listed in [Table 5](#). In each disease stratum the proportions of patients on each treatment arm who are abnormal at baseline will be estimated and changes over time will be examined. The JAK2V617F allele burden will be monitored at baseline, 12, 24 months and at time of a bone marrow to assess for relapse/progression or at the termination of the patients receiving study medication. The presence of somatic mutations in CALR will be assessed at baseline, 12, 24 months and at relapse/progression or at the termination of the patients receiving study medication. The cytogenetics and bone marrow histopathology will be performed at 12, 24 months and at time of a bone marrow to assess for relapse/progression or at the termination of the patients receiving study medication. The hematopoietic cell clonality will be performed in select female patients who are informative at baseline and at remission, progression/relapse, 12 and 24 months and termination of the patients receiving study medication. The anticipated effects of the treatments provided on the various biomarkers are summarized in [Table 6](#):

Table 6 Biomarker Evaluations

<u>Test</u>	<u>Result</u>	<u>Modulation</u>
Clonality	Clonal	Polyclonal JAK2V617F
CALR	Abnormal	Normal
Allele Burden	High	Low or absent
Cytogenetics	Abnormal	Normal
Bone Marrow Histopathology	Abnormal morphology	Normalization

9.0 STUDY EVENTS

9.1 Screening and Enrollment

Each subject must sign and complete an informed consent form prior to the performance of study-specific procedures. Any procedures or tests during the screening period that are obtained as part of routine medical care can be used in lieu of the study specific evaluations.

9.1.1 Baseline Data

Prior to randomization, all patients should be assessed for their eligibility of the study. At this time the following procedures should be performed and appropriately recorded into the source notes.

- Patient Informed Consent
- History and physical examination
- Fundoscopic Eye exam
- Vital signs
- Body Surface area
- ECOG performance status
- ECG
- Splenic size by clinical examination and by ultrasound examination.
- Complete blood count with differential and blood smear
- Biochemistry screen (LFT, renal function and uric acid)
- Thyroid function tests
- Symptom Assessment Package ([Appendix D](#))
- Negative pregnancy test
- Bone marrow aspirate and biopsy
- Cytogenetics
- Biomarker blood samples for MPD-RC 107
- JAK2V617F (if not previously done)
- Concomitant medication
- Nail Clippings

STUDY REQUIREMENTS MUST BE PERFORMED WITHIN 14 DAYS PRIOR TO REGISTRATION EXCEPT BONE MARROW AND CYTOGENETICS WHICH MUST BE DONE WITHIN 90 DAYS PRIOR TO REGISTRATION AS LONG AS THERE IS NO CHANGE IN CLINICAL STATUS OR CHANGE IN THERAPY.

9.2 Study Calendar

Every “Month” in the study calendar is defined as a calendar month. Subjects should come in on the same date of every study visit month (i.e. January 15th, February 15th, March 15th, etc.).

	Baseline	PEGASYS ¹ or Hydroxyurea							
Parameter	Within 2 weeks prior to registration	Month 1 Days 1 ² , 15 ³	Month 2-5 Day 1 ³	End of Month 6 ^{3,4}	End of Month 9 ^{3,4}	End of Month 12 ^{3,4}	Every 3 Months While on Active Treatment ^{3,4}	Off-Treatment ⁹	Observational Follow-up
Informed consent	X								
Medical History	X								
Prior Diagnosis / Prior Treatment	X								
Height	X								
Weight	X	X ⁵	X	X	X	X	X	X	
Vital Signs	X	X ⁵	X	X	X	X	X	X	
Physical Examination	X	X ⁵	X	X	X	X	X	X	
Spleen Size by physical examination (cm)	X	X	X	X	X	X	X	X	
Spleen Size by Abdominal Ultrasound	X	12 months ⁶ , (and 15 months if necessary to confirm a CR) at relapse/progression or off treatment for any reason							
ECOG Performance status	X	X ⁵	X	X	X	X	X	X	
Serum or Urine HCG ⁷	X	X ⁵							
CBC with Differential	X	X	X	X	X	X	X	X	
Chemistries (sodium, potassium, creatinine, chloride, AST, Alk. Phosphatase, LDH, and uric acid)	X	X	X	X	X	X	X	X	
Thyroid Function T4, TSH	X	X ⁵	X	X	X	X	X	X	
Thyroid Antibodies	X							X	
JAK2V617F mutation analysis	X ¹⁰								
EKG	X								
Fundoscopy Eye Exam ⁸	X								
Nail clippings	X								
Symptom Assessment Packet	X (pre-randomization)		Month 4 Day 1, After Months 6, 9, 12, every 6 months thereafter, and at off-treatment.						

Parameter	Baseline	PEGASYS ¹ or Hydroxyurea							
	Within 2 weeks prior to registration	Month 1 Days 1 ² , 15 ³	Month 2-5 Day 1 ³	End of Month 6 ^{3,4}	End of Month 9 ^{3,4}	End of Month 12 ^{3,4}	Every 3 Months While on Active Treatment ^{3,4}	Off-Treatment ⁹	Observational Follow-up
Bone Marrow biopsy and aspirate for -Cellularity -Morphology on H & E -Blast Percentage -Reticulin Fibrosis Grade	X	Months 12 ⁶ and 24 and at time of relapse/progression or off treatment for any reason							
Cytogenetics	X	Months 12 ⁶ and 24 and at time of relapse/progression or off treatment for any reason							
Biomarkers	X								
Concomitant Medications	X	Ongoing							
Adverse Events NCI CTCAE v4.0	X	Ongoing							
Assessment of survival; development of myelodysplastic disorders, myelofibrosis, or leukemic transformation; cardiovascular events; and treatment changes		Ongoing							See section 5.8

- 1 The subject will be taught how to administer the study drug injection to themselves by the research staff. The subject will inject the dosage amount needed and recap the syringe with the unused portion of the study drug, placing the capped syringe in a container and brought back to the clinic to be checked and recorded by the study staff. See [Appendix E](#).
- 2 If Day 1 procedures were completed within 3 days of “Day 1”, they do not need to be repeated.
- 3 The month 1 day 15 visit may occur +/- 1 day. All other subsequent visits can occur +/- 7 days.
- 4 All subsequent study visits should occur at the end of the month (i.e. end of month 9, end of month 12, end of month 15, etc.). Note that there is a 2 month gap between “Month 5 Day 1” and “End of Month 6”
- 5 Day 1 Only
- 6 The Month 12 visit should be done at the end of month 12 +/- 7 days.
- 7 If the patient is a woman capable of having children.
- 8 Any patient complaining of decreased vision or loss of vision while receiving study drug must have a prompt and complete eye examination.
- 9 Off-Treatment is defined as 30 (±7) days after patient permanently stops treatment for any reason at any time during the study (i.e. study drug intolerance, relapse/progression, study completion, etc.)
- 10 JAK 2V617F test does not need to be repeated if previously performed.

9.3 Procedures for the follow-up visit

Refer to the study calendar (Section 9.2) for visit schedule and procedures to be completed.

9.4 Interruption of Treatment

See Section 6.0.

9.5 Drug Compliance

Patients will be given a diary to record drug usage and clinicians will be asked to confirm drug usage with patient. See Appendix E for patient medication diaries.

9.6 Symptom Assessment Package

Given there is no currently validated instrument for QOL for serial administration in patients with ET or PV to be used in a clinical trial setting we have adopted a standard validation approach used for new QOL instruments. The MPN-SAF and EORTC-QLQ C30 will be given to patients at baseline, at month 4 day 1, after months 6, 9, 12, and then every 6 months (either previously or widely validated instruments to be used for cross-validation – see below). If the subject is randomized to pegylated interferon alfa-2a, the Pegylated Interferon Alfa-2a /PEGASYS Specific Questions will also be given and the same time points mentioned above. The symptom assessment package of instruments will be completed by enrolled patients on-site at the time of their study visits.

MPN-SAF: The MPN-SAF (Appendix D) was created to address the constellation of symptoms most frequent in MPN patients based on the results of our internet based survey of 1179 MPN patients ((PV (N=405); ET (N=304); MF (N=456))(Mesa, *et al* 2007). Our survey demonstrated that the vast majority of the MPN patients have very significant fatigue compared to age matched published data. Given the central importance of this symptom, and need for accurate measurement on a trial, the previously validated Brief Fatigue Inventory is included as item 1-9 (Mendoza, *et al* 1999), and a composite score is generated for the BFI (the score is the mean result of all 9 items). Items 10-13 address spleen related symptoms (early satiety, abdominal pain), inactivity, and cough. Items 14-18 address the central MPN symptoms of night sweats, pruritus, bone pain, fever, and weight loss. Although some of these symptoms are more frequent in PMF, they are still present in significant numbers of ET and PV patients and are of relevance in this trial given the high risk patients included on study will also include those who already have mild features of post ET/PV MF respectively. Item 19 includes a single item overall quality of life measure. Items 10-16 and 19 are measured on a linear analog scale assessment (LASA). The LASA methodology has proven very valid in the past (Locke, *et al*, 2007). Additionally, the lack of a composite score overall for the MPN-SAF is a positive attribute for this instrument for serial assessment in a clinical trial for MPN patients as individual symptoms may respond (or worsen) independently with therapy.

The MPN-SAF has previously been validated for use at a single time point (Mesa, *et al*, 2009) by co-administration with previously validated instruments (the Memorial Symptom Assessment Scale), the Brief Pain Inventory (BPI). Measurement of individual symptoms which existed on other validated instruments was highly correlated with single item results on the MPN-SAF. Additionally, patient anonymous feedback demonstrated the MPN-SAF was easy to understand. Additionally patients were questioned to respond to any major symptoms which were not included

in the MPN-SAF, and no symptom was mentioned by more than one patient demonstrating the relatively comprehensive nature of the instrument for MPN patients.

EORTC-QLQ C30 (Appendix D2): The EORTC-QLQ-C30 version 3.0 (Aaronson, *et al* 1993) is included as our main instrument for co-validation on these trials, and redundant capture of impact of information for impact of protocol therapy on patient's symptoms, mood, and quality of life. The initial EORTC QLQ-C36 questionnaire, later shortened and validated with 30 questions, has the following advantages namely being a) cancer specific b) multidimensional in structure c) appropriate for self- administration d) applicable across a range of cultural settings. This instrument has been thoroughly validated for serial use in cancer clinical trial setting, and is available in standard and validated translations for Italian, French, Swedish, and German (all languages required for the enrolling centers on these trials). This instrument although highly valid for a portion of the symptom changes we wish to capture with this trial, nevertheless is not as comprehensive for MPN specific symptoms and hence the need for both instruments to be administered.

Pegylated Interferon Alfa-2a /PEGASYS Specific Questions (Appendix D3): Analysis of the drug related toxicities from the 2 prior pegylated interferon trials in ET/PV, four toxicities possibly related to the drug were identified. These will be specifically addressed in the questionnaire, but only for this trial and not for the MPN- SAF as these toxicities are not core symptoms identified in patients with MPNs. The symptoms include flu like symptoms, injection site reaction, blurred vision or vision changes and flushing.

10.0 DEFINITION OF RESPONSE CRITERIA

10.1 Primary Endpoints

The following criteria for clinicohematologic will be used for ET and PV as designed by the European LeukemiaNet (Barosi 2008) (Table 7 and Table 8). The primary endpoint is CR or PR achieved by these criteria by the end of the first 12 months on treatment with duration confirmed of at least 3 months. Alternative criteria will be used for patients with Splanchnic Vein Thrombosis (see Table 9)

Table 7 Criteria for Response in ET

CRITERIA FOR RESPONSE IN ET
Complete response <ul style="list-style-type: none"> ○ Platelet count $\leq 400 \times 10^9/L$ AND ○ No disease-related symptoms* AND ○ Normal spleen size on imaging AND ○ WBC $\leq 10 \times 10^9/L$
Partial response In patients who do not meet criteria for complete response Platelet count $\leq 600 \times 10^9/L$ OR $>50\%$ reduction from baseline
No response Any response that does not satisfy partial criteria

* Disease-related symptoms: microvascular disturbances, pruritis, headache

Table 8 Criteria for Response in PV

CRITERIA FOR RESPONSE IN PV
Complete response defined as <ul style="list-style-type: none"> ○ Hematocrit ≤ 0.45 without phlebotomy AND ○ Platelet count $\leq 400 \times 10^9/L$ AND ○ WBC $\leq 10 \times 10^9/L$ AND ○ Normal spleen size on imaging AND ○ No disease related symptoms*
Partial response In patients who do not meet criteria for complete response, Hematocrit $< 45\%$ without phlebotomy OR response in any 3 of the remaining 4 criteria
No response Any response that does not satisfy partial response

* Disease-related symptoms: microvascular disturbances, pruritis, headache

Table 9 Criteria for Response in Patients with Splanchnic Vein Thrombosis

CRITERIA FOR RESPONSE IN PATIENTS WITH SPLANCHNIC VEIN THROMBOSIS:	
Complete response defined as:	
○ Hematocrit ≤ 0.42 without phlebotomy AND	
○ Platelet count $100-200 \times 10^9/L$ AND	
○ WBC $2-8 \times 10^9/L$ AND	
○ No spleen enlargement from enrollment baseline AND	
○ No disease related symptoms*	
Partial response	
In patients who do not meet criteria for complete response, Hematocrit $< 45\%$ without phlebotomy OR response in any 3 of the remaining 4 criteria	
No response	
Any response that does not satisfy partial response	

* Disease-related symptoms: microvascular disturbances, pruritis, headache

In addition, the revised ELN and IWG-MRT consensus response criteria for PV and ET will be utilized (3).

10.2 Secondary Outcomes

- To evaluate the toxicity and tolerability of therapy (Pegylated Interferon Alfa-2a vs. hydroxyurea) in the study populations
- The ability of therapy (Pegylated Interferon Alfa-2a vs. hydroxyurea) to achieve a complete (CR) or partial response (PR) by LeukemiaNet criteria.
- To evaluate specific pre-defined toxicity and tolerance of therapy (Pegylated Interferon Alfa-2a vs. hydroxyurea) through a sequential structured symptom assessment package of patient reported outcome instruments.
- Observed survival and incidence of development of a myelodysplastic disorder, myelofibrosis, or leukemic transformation (Pegylated Interferon Alfa-2a vs. hydroxyurea).
- Observed incidence of major cardiovascular events (defined as cardiovascular death, myocardial infarction, stroke, transient ischemic attack, pulmonary embolism, Budd Chiari syndrome, deep vein thrombosis, and any other clinically relevant thrombotic event) (Pegylated Interferon Alfa-2a vs. hydroxyurea).
- To measure the impact of therapy (Pegylated Interferon Alfa-2a vs. hydroxyurea) on key biomarkers of the disease(s) – JAK2V617F, CALR, hematopoietic cell clonality in platelets and granulocytes in females, bone marrow histopathology, and cytogenetic abnormalities. A definition of a molecular response is provided in [Table 10](#) and of a histologic response in [Table 11](#).

Table 10 Definition of molecular response in ET and PV

Response Grade	Definition
Complete response	Reduction of any specific abnormality to undetectable levels
Partial response*	(1) A reduction of $\geq 50\%$ from baseline value in patients with $< 50\%$ mutant allele burden at baseline OR
	(2) reduction of $\geq 25\%$ from baseline value patients with $> 50\%$ mutant allele burden at baseline
No response	Any response that does not satisfy partial response

* Applies only to patients with a baseline value of mutant allele burden greater than 10%

Table 11 Criteria for histologic response in ET and PV

Essential Thrombocythemia	Polycythemia Vera
Bone marrow histologic remission Absence of megakaryocyte hyperplasia	Bone marrow histologic remission Presence of age-adjusted normocellularity and no reticulin fibrosis

11.0 STATISTICAL CONSIDERATIONS

With 300 patients randomized to two treatment groups in two strata, we can detect a difference in complete clinical hematologic response rates of 15% from 15% to 30% with an overall two sided alpha of 0.05 and power of 85% for the two disease strata combined.

Randomization will be carried out centrally within strata defined by disease (ET/PV). Within each of these disease strata, patients will be randomized within strata defined by current use of hydroxyurea or no current use within each center.

Table 12 below provides the stopping boundaries for the difference in complete response rates between the two treatment arms at each of the two interim analyses and at the final analysis. The first interim analysis will be performed when 75 patients (25% of total planned accrual) would have had sufficient time on study to be evaluable for response. At that time, a blinded sample size re-estimation will be carried out to evaluate the underlying assumptions with respect to the anticipated overall CR+PR rate at 12 months and sample size will be adjusted, if necessary, should the study not be stopped for futility. The second interim analysis will be conducted when 50% of randomized patients are evaluable for response.

Table 12 O-Brien Fleming Stopping Boundaries to Reject Null (H0) or Alternative (H1 Futility) Hypotheses for Interim Analyses of Clinical Hematologic Response Rates (2-sided alpha =0.05, power =85%). Complete Response Rate on Hydroxyurea Assumed =15%; on Pegylated Interferon Alfa-2a Assumed =30%

		Critical Value of Z Statistic (p-value)		Observed Difference in Proportions of Patients with Complete Response	
<i>Analysis</i>	Number of Patients	Reject Null Hypothesis	Reject Alt. Hypothesis	Reject Null Hypothesis	Reject Alt. Hypothesis
Interim 1	75	+/-4.333 (0)	+/-0.0029 (≥0.998))	≥ 0.430	≤ 0.0003
Interim 2	150	+/-2.963 (≤0.003)	+/-0.269 ≥0.788	≥ 0.208	≤ 0.0189
Final	300	+/-1.957 (≤0.0504)	+/-1.957 (<0.0504)	≥ 0.0971	< 0.0971

[Computations from EAST 6.2, Cytel, Inc., 2013.]

11.1 Safety Monitoring/ Stopping Rules

The study is designed to allow for early stopping if the efficacy on either arm is much better or worse than the comparator or if the possibility of achieving the expected outcome is futile. In order to ensure that patients are not at excess risk of overall disease complications, we will also monitor the overall complication free survival rate in the total population under study. We can detect a hazard ratio of 0.50 (Pegylated Interferon Alfa-2a /hydroxyurea) in overall complication free survival (free of major thrombotic event (definition 13.3.1), major hemorrhagic complications (definition 13.3.3), progression to myelofibrosis (definition 13.3.4), progression to acute leukemia (definition 13.3.4) or death) with 300 patients randomized into the trial with an unadjusted log rank

test with an overall power of 80.3% and 2-sided alpha of 0.05. If we enroll an average of 75 patients/year over approximately 4 years, the expected maximum study duration would be 6 years. [Table 13](#) below provides the stopping boundaries for this plan:

Table 13 O'Brien Fleming Stopping Boundaries for Complication Free Survival: 300 Patients Randomized to Pegylated Interferon Alfa-2a vs. Hydroxyurea (2-sided overall alpha =0.05, power =80%)

Analysis	Number of Events	Approximate Expected Timing (months)	Critical Value of Z-Statistic	Hazard Ratio: Pegylated Interferon Alfa-2a /Hydroxyurea	p-value (cumulative alpha spent)
Interim 1	26	30	+/-2.279	$\leq 0.405; \geq 2.47$	$\leq 0.011 $ (0.023)
Interim 2	52	48	+/-2.295	$\leq 0.526; \geq 1.902$	$\leq 0.011 $ (0.038)
Final Analysis	77	67	+/-2.296	$\leq 0.592; \geq 1.691$	$\leq 0.011 $ (0.050)

[Computations from EAST 6.2, Cytel, Inc., 2013.]

Overall complication free survival will be monitored to ensure that the trial can be considered for early stopping if the hazard ratio for Pegylated Interferon Alfa-2a /Hydroxyurea is very favorable or very unfavorable. The timing of these analyses (shown in section 9.2) is expected to occur at 30 months when accrual has completed for the first analysis, and at 48 months when the study is scheduled to complete for the second analysis. These analyses will have no impact on study accrual, but will impact continuation on study should a major difference in complication free survival be observed.

11.2 Statistical Analysis

Within each disease stratum, descriptive statistics will be used to compare the distributions of baseline patient and disease characteristics at randomization for patients treated with Pegylated Interferon Alfa-2a or hydroxyurea. Frequency distributions and chi-square tests will be used to screen for major imbalances in the two randomization groups for qualitative variables; graphical displays including and box plots and summary statistics (e.g., mean, median, standard deviation, ranges, etc.) will be used for quantitative variables with t-tests (after appropriate transformations if necessary to meet the assumptions of the methods).

The primary analysis will be based on the comparison of the proportions of patients with complete clinical hematologic responses based on a 2-sided z-test for proportions. All patients randomized to the study will be included in this intent to treat analysis. The distribution of responses will also be summarized for each of the two treatment groups for each disease. Cochran-Mantel log rank tests as well as logistic regression methods will be used to provide additional analyses that take into account any covariates that might potentially impact response to treatment within each disease stratum.

Safety and toxicity will be summarized to compare the distributions of incidence and severity of adverse events and laboratory toxicities on the two treatment groups within each disease stratum. Frequency distributions and time to event analyses will be used to summarize the results.

11.3 Additional Analyses

The characteristics of patients at entry will be summarized within strata defined by disease. These characteristics include disease characteristics, biomarker levels, prior treatment, disease duration, demographic characteristics, comorbidity, and other covariates using summary statistics and graphical methods. Logistic regression models will be used to examine the associations of best response as defined above with these characteristics and biomarker levels within each of the disease classes. The distributions of each of the biomarker measurements will be displayed graphically within strata defined by platelet level at entry as well as by other important features of disease history (disease duration, age, sex, and other potential covariates). Similarly, for each biomarker, the proportions of patients who are normal at baseline (of each biomarker as defined by each of the laboratories) will be estimated. Changes from baseline and summary statistics will be provided over time, along with t-tests (and analysis of variance F-tests) or chi square tests and odds ratios where appropriate to identify potential differences among subgroups of patients defined by clinical features at the time of registration.

Additional analyses include comparisons of thrombotic complication free survival and survival using 2-sided log-rank tests of the hazard ratio of Pegylated Interferon Alfa-2a compared to hydroxyurea treated patients. Cox proportional hazards models will be used to examine the effects of covariates on outcomes.

A major focus of this study is to examine biomarker normalization over time within a disease stratum. Rates of normalization for each individual marker and for one or more of these markers will be estimated at each time point. Each of the biomarkers will be examined over time using methods for longitudinal data analysis. In particular, each of the markers shown in section 8.0 will be examined using Linear Mixed Effects Models with time as a fixed effect and a random effect to account for patient variability in the individual marker (Diggle, P.J., et al, 2002; Venables, W.N. and Ripley, B.D., 2002; Fitzmaurice, G., Laird, N., and Ware, J., 2004). General estimating equations (GEE) will also be used to address these issues. The effects of baseline characteristics as covariates will be incorporated into the models. Transformations of variables will be carried out if necessary to meet the assumptions of the proposed analyses.

Correlations will also be examined within and across the strata to identify potential interactions and redundancies among variables. Data are expected to be missing in relation to treatment failure and/or disease complications. That is, missingness may be informative and related to treatment and/or outcome. Approaches to incorporate informative missing data into the longitudinal models such as those proposed by Verbeke, G. and Molenberghs, G. (2000) and Little and Rubin (2002) will be used.

11.4 Quality of life analysis

Descriptive statistics will be used to summarize the individual items in the MPN-SAF as well overall scores on each of the quality of life instruments in each disease stratum at baseline and subsequent time points for each of the instruments described in [Appendix D](#). The changes in the specific components of the MPD-RC will be evaluated over time and the associations with changes in standard instruments will be summarized. These analyses will also include comparisons between the two treatment groups within each disease stratum. The MPN-SAF components and overall results at baseline and over time will also be compared with the presence/absence of toxicities and side effects of disease and treatment with Pegylated Interferon Alfa-2a or hydroxyurea. Results will also be evaluated by best response outcome.

Longitudinal data analysis methods will be used to evaluate patients' quality of life over time for

the components of the MPN-SAF and other standard instruments. The objectives of these exploratory analyses will be to identify components of quality of life that are influenced by treatment with Pegylated Interferon Alfa-2a. The limitations of these analyses will be evaluated. These issues include the potential effects of informative missing and data and patient perception/knowledge of response status.

11.5 Statement of Design

The trial is a randomized Phase III study conducted in patients with high risk PV or ET.

12.0 DURATION OF PATIENT PARTICIPATION

Patients will be recruited for 4.0 years and will be followed-up for an additional 2.0 years following the last patient enrolled.

12.1 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without compromising their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Serious adverse event
- Patient request
- Non-compliance
- Administrative reasons
- Failure to return for follow-up
- General or specific changes in the patient's condition unacceptable to further treatment in the judgment of the investigator

The primary reason for a patient's withdrawal from the study is to be recorded in the source documents and on the "Off Treatment Notice" form available on the MPD-RC website.

12.2 Required Data

Laboratory and clinical parameters during the treatment courses are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that participants will be cared for by physicians experienced in the treatment and supportive care of patients with MPN.

13.0 ADVERSE EVENTS: ASSESSMENT OF SAFETY

13.1 Definitions

Adverse event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product. Such adverse events should be followed until resolution or until stabilization.

Pre-existing conditions

In this study, a pre-existing condition (i.e. a disorder present before randomization and noted on the medical history) should not be reported as an adverse event unless the condition worsens. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Study Disease

Deterioration in the study disease should be reported as an adverse event.

Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. A medical condition for which an unscheduled procedure was performed, should however be reported if it meets the definition of an AE. For example the acute appendicitis should be reported as an adverse event rather than the appendectomy.

Laboratory values

A laboratory abnormality should be documented as a clinical adverse event if *any one of the following* conditions is met:

- The laboratory abnormality is not otherwise corrected by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Adverse reaction of an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship or no other reasonable etiology.

Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SPC) for an authorized product). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be

considered as unexpected. The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.

Serious adverse event or serious adverse reaction

Any untoward medical occurrence or affect that:

- results in death
- is life-threatening
- requires hospitalization or prolongation of existing inpatient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- other serious (important medical events)

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Suspected unexpected serious adverse reactions (SUSARs) should be notified to MPD-RC office within 24 hours of the site becoming aware of the event occurring.

13.2 Expected Adverse Drug Reactions

The medications used within the trial have been marketed for some time and consequently the following adverse drug reactions have been observed and reported. Consequently the following adverse reactions need not be reported as Suspected Unexpected Serious Adverse Reaction (SUSAR).

13.2.1 Hydroxyurea

Bone marrow depression is the dose limiting toxicity. Gastrointestinal side effects are common but require rarely dose reduction or cessation of treatment.

Common $\geq 1/100$ to $< 1/10$

Blood: Bone marrow depression, leucopenia, megaloblastosis.

Gastrointestinal: Diarrhea, constipation.

Uncommon ($> 1/1,000$, $< 1/100$)

Blood: Thrombocytopenia, anemia

Body as a whole: Nausea, vomiting, anorexia, stomatitis. Drug fever, chills, malaise.

Skin: Maculopapular rash, facial erythema, aural erythema.

Liver: Elevation of liver enzymes, bilirubin.

Urogenital: Transient impairment of the renal tubular function accompanied by elevation in serum uric acid, urea and creatinine.

Rare $\geq 1/10,000$ to $< 1/1000$

Body as a whole: Hypersensitive reactions

Skin: Alopecia.

Respiratory: Acute pulmonary reactions consisting of diffuse pulmonary infiltrates, fever and dyspnea, allergic alveolitis.

Urogenital: Dysuria.

Neurological: Rare neurological disturbances including headache, dizziness, disorientation, hallucinations.

Very rare: (< 1/10,000)

Skin: Dermatomyositis-like skin changes, Hyperpigmentation or atrophy of skin and nails, cutaneous ulcers (especially leg ulcers), Pruritus, actinic keratosis, skin cancer (squamous cell cancer, basal cell carcinoma), violet papules, desquamation.

Urogenital: renal impairment. In rare cases dysuria or renal impairment, hypersensitive reactions.

Blood: In the therapy with hydroxyurea megaloblastosis may occur which does not respond to treatment with folic acid or vitamin B12. The bone- marrow suppression subsides, however, when therapy is discontinued. In patients receiving long-term treatment with hydroxyurea for MPN, such as PV and thrombocythemia, secondary leukemia may develop. To what extent this relates to the underlying disease or to treatment with hydroxyurea is presently unknown. Hydroxyurea can reduce plasma iron clearance and iron utilization by erythrocytes. However, it does not appear to alter the red blood cell survival time.

Gastrointestinal: Severe gastric distress (nausea, emesis, anorexia) resulting from combined hydroxyurea and irradiation therapy may usually be controlled by temporarily discontinuing hydroxyurea administration. Hydroxyurea may aggravate the inflammation of mucous membranes secondary to irradiation. It can cause a recall of erythema and hyperpigmentation in previously irradiated tissues.

Skin: Erythema, atrophy of skin and nails, desquamation, violet papules, alopecia, dermatomyositis-like skin changes, actinic keratosis, skin cancer (squamous cell cancer, basal cell carcinoma), cutaneous ulcers (especially leg ulcers), pruritus and hyperpigmentation of skin and nails have been observed in isolated cases partly after years of long-term daily maintenance therapy with hydroxyurea.

Neurological: High doses may cause moderate drowsiness. Rare neurological disturbances including headache, dizziness, disorientation, hallucinations, and convulsions have been reported.

Respiratory: In individual cases allergic alveolitis.

13.2.2 Pegylated Interferon Alfa-2a/PEGASYS

Very Common $\geq 1/10$

Metabolism and Nutrition Disorders: Anorexia

Psychiatric disorders: Depression*, anxiety, insomnia*

Nervous system disorders: Headache, dizziness*, concentration impaired

Respiratory, thoracic and mediastinal disorders: Dyspnea, Cough

Gastrointestinal disorders: Diarrhea*, nausea*, abdominal pain*

Skin and Subcutaneous tissue disorders: Alopecia, dermatitis, pruritis, dry skin

Musculoskeletal connective tissue and bone disorders: Myalgia, arthralgia

General disorders and administration site conditions: Pyrexia, rigors*, pain*, asthenia, fatigue, injection site reaction*, irritability*

*These adverse reactions were common ($\geq 1/100$ to $< 1/10$) in Chronic Hepatitis B patients treated with Pegylated Interferon Alfa-2a /PEGASYS monotherapy

Common $\geq 1/100$ to $< 1/10$

Infections and infestations: Upper respiratory infection, bronchitis, oral candidiasis, herpes simplex, fungal, viral and bacterial infections

Blood and lymphatic system disorders: Thrombocytopenia, anemia, lymphadenopathy

Endocrine disorders: Hypothyroidism, hyperthyroidism

Psychiatric disorders: Emotional disorders, mood alteration Aggression, nervousness, libido decreased

Nervous system disorders: Memory impairment, syncope, weakness, migraine, hypoesthesia, hyperesthesia, paraesthesia, tremor, taste disturbance, nightmares, somnolence

Eye disorders: Vision blurred, eye pain, eye inflammation, xerophthalmia

Ear and labyrinth disorders: Vertigo, earache

Cardiac disorders: Tachycardia, palpitations, edema peripheral

Vascular disorders: Flushing

Respiratory, thoracic and mediastinal disorders: Dyspnea exertional, epistaxis, nasopharyngitis, sinus congestion, nasal congestion, rhinitis, sore throat

Gastrointestinal disorders: Vomiting, dyspepsia, dysphagia, mouth ulceration, gingival bleeding, glossitis, stomatitis, flatulence, dry mouth

Skin and Subcutaneous tissue disorders: Rash, sweating increased, psoriasis, urticaria, eczema, skin disorder, photosensitivity reaction, night sweats

Reproductive system and breast disorders: Impotence

Musculoskeletal connective tissue and bone disorders: Back pain, arthritis, muscle weakness, bone pain, neck pain, musculoskeletal pain, muscle cramps

General disorders and administration site conditions: Chest pain, influenza like illness, malaise, lethargy, hot flushes, thirst

Investigations: Weight decreased

Uncommon $\geq 1/1000$ to $< 1/100$

Infections and infestations: Pneumonia, skin infection

Neoplasms benign and malignant: Hepatic neoplasm

Immune system disorders: Sarcoidosis, thyroiditis

Endocrine disorders: Diabetes

Metabolism and Nutrition Disorders: Dehydration

Psychiatric disorders: Suicidal ideation, hallucinations

Nervous system disorders: Peripheral neuropathy

Eye disorders: Retinal hemorrhage

Ear and labyrinth disorders: Hearing loss

Vascular disorders: Hypertension

Respiratory, thoracic and mediastinal disorders: Wheezing

Gastrointestinal disorders: Gastrointestinal Bleeding

Hepato-biliary Disorders: Hepatic Dysfunction

Rare $\geq 1/10,000$ to $< 1/1000$

Infections and infestations: Endocarditis, otitis externa

Blood and lymphatic system disorders: Pancytopenia

Immune system disorders: Anaphylaxis, systemic lupus erythematosus, rheumatoid arthritis

Endocrine disorders: Diabetic ketoacidosis

Psychiatric disorders: Suicide, psychotic disorder

Nervous system disorders: Coma, convulsions, facial palsy

Eye disorders: Optic neuropathy, papilledema, retinal vascular disorder, retinopathy, corneal ulcer

Cardiac disorders: Myocardial infarction, congestive heart failure, angina, supraventricular tachycardia, arrhythmia, atrial fibrillation, pericarditis, cardiomyopathy

Vascular disorders: Cerebral hemorrhage, vasculitis

Respiratory, thoracic and mediastinal disorders: Interstitial Pneumonitis including fatal outcome, pulmonary embolism

Gastrointestinal disorders: Peptic ulcer, pancreatitis

Hepato-biliary Disorders: Hepatic failure, cholangitis, fatty liver

Musculoskeletal connective tissue and bone disorders: Myositis

Renal and urinary disorders: Renal insufficiency

Injury and poisoning: Substance overdose

Very rare $< 1/10,000$

Blood and lymphatic system disorders: Aplastic anemia

Immune system disorders: Idiopathic or thrombotic Thrombocytopenic purpura

Eye disorders: Vision loss

Skin and Subcutaneous tissue disorders: Toxic epidermal necrolysis, Stevens- Johnson syndrome, angioedema, erythema multiform

13.2.3 Aspirin

- Dyspepsia, nausea and vomiting.
- Less commonly irritation of the gastrointestinal mucosa may lead to erosion, ulceration and gastrointestinal bleeding.
- Hepatotoxicity, which occurs rarely.
- Hypersensitivity reactions including urticaria, rhinitis, angioneurotic edema and severe bronchospasm.
- Aspirin may enhance the effects of anticoagulants and may inhibit the action of uricosurics.
- Aspirin may precipitate bronchospasm and may induce attacks of asthma in susceptible subjects.

- Aspirin may cause salt and water retention as well as deterioration in renal function

13.3 Expected Serious Adverse Events

Within these patient populations the following serious adverse events are expected and need not be reported as a SUSAR.

13.3.1 THROMBOTIC EVENTS

New infarction or recurrent myocardial infarction

Myocardial infarction is defined as the presence of **two or more** of the following criteria:

- a) Symptoms of cardiac ischemia
 - Characteristic ischemic chest pain in the pericardium or associated referral areas, lasting for at least 20 minutes
- b) Significant cardiac enzyme elevations
 - Elevation of CPK, LDH, or AST to at least twice the upper limit of normal for the given laboratory in the absence of other explanation.
- c) EKG changes
 - Occurrence of new 40 msec Q waves in at least two adjacent ECG leads, **or** development of a new dominant R wave in V1 **or** of new ST elevation or depression or persistent (>48 hours) new T wave inversion.

Stroke and stroke type

A stroke is a new focal neurologic deficit of presumed vascular origin which persists for > 24 hours or results in death within 24 hours.

Stroke type:

- Hemorrhagic: A stroke caused by primary intracranial hemorrhage diagnosed by CT, MRI, or other objective means, or by autopsy.
- Ischemic: A stroke of atherothrombotic or embolic origin as diagnosed by CT, MRI or other objective means, or by autopsy.
- Uncertain: A stroke not otherwise classified by the above criteria.

Transient cerebral ischemic attack (TIA)

A Transient Ischemic Attack is defined as the abrupt onset of unilateral motor or sensory disturbance, speech defect, homonymous hemianopia, constructional apraxia, or transient monocular blindness (defined as the abrupt onset of unilateral decreased visual acuity involving a portion or the entirety of the visual field) that resolved completely in less than 24 hours.

Deep vein thrombosis (DVT)

A deep vein thrombosis (DVT) is defined as a typical clinical picture with positive investigation: i.e. phlebography, ultrasonography, CT in unusual sites. In case of suspected recurrence in a site of previous DVT (e.g. ipsilateral limb) diagnosis is accepted only if the investigation shows extension or recurrence of thrombosis as compared to a previous test.

Pulmonary embolism

A pulmonary embolism is defined as a typical clinical picture with positive angiography or high-probability V/Q scanning.

Thrombotic digital ischemia

Characteristic purplish discoloration of toes/fingers, which may progress to infarction if untreated.

Digital ischemia may occasionally be associated with erythromelalgia.

Unstable angina

Defined in accordance with TIMI criteria as presence of prolonged angina or recurrent angina at rest, together with one of the following: new ST segment depression, requirement for revascularization procedure, cardiac enzyme rise to less than twice the upper limit of normal or past history of documented coronary artery disease.

OR

Ischemic discomfort at rest lasting 5 minutes or greater and associated with at least one of the following new/presumably new ST segment elevation > 0.5mm; T-wave inversion > 3mm in 3 leads or left bundle branch block; cardiac enzyme rise to less than twice the upper limit of normal.

Other thrombotic event

Thrombosis in sites not covered above. In particular, characteristic symptoms of peripheral limb ischemia with evidence of thrombosis. In addition characteristic syndromes of abdominal thrombosis for example Budd Chiari syndrome.

13.3.2 OTHER VASCULAR OCCLUSIVE EVENTS

Other transient neurological events

This is defined as the abrupt onset of poorly or non-localizing neurological symptoms such as unsteadiness, blurred vision, hearing disturbance or unstable gait.

Erythromelalgia

Erythromelalgia is defined as the onset of pain at the extremities associated with temperature increase and redness of the skin. Erythromelalgia usually manifests in the lower extremities and/or rarely in the hands with frequent recurrences in the same areas.

Other occlusive event

Occlusion in sites not covered above. In particular, characteristic symptoms of cardiac, abdominal or peripheral limb ischemia supported by objective evidence of vessel disease and/or ischemia

13.3.3 HAEMORRHAGIC EVENTS

Major hemorrhage

Overt hemorrhage associated with either:

- a decrease in hemoglobin level of at least 2g/dl or
- a need for blood transfusion of 2 or more units of blood, or
- if hemorrhage is retroperitoneal or intracranial.

Minor hemorrhage

Overt hemorrhage not meeting the criteria of major hemorrhage.

13.3.4 TRANSFORMATION

Transformation to ET or PV myelofibrosis

(Barosi 2008) The criteria for Post PV/myelofibrosis are provided below.

Required criteria:

1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria
2. Bone marrow fibrosis grade 2–3 (on 0–3 scale) 3 or grade 3–4 (on 0–4 scale) 4

Additional criteria (two are required):

1. Anemia or sustained loss of requirement of either phlebotomy (in the absence of

- cytoreductive therapy) or cytoreductive treatment for erythrocytosis
- 2. A leukoerythroblastic peripheral blood picture
- 3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
- 4. Development of 1 of three constitutional symptoms: 10% weight loss in 6 months, night sweats, unexplained fever ($> 37.5^{\circ}\text{C}$)

Criteria for post-ET myelofibrosis (Barosi 2008)

Required criteria:

- 1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria
- 2. Bone marrow fibrosis grade 2–3 (on 0–3 scale) 3 or grade 3–4 (on 0–4 scale) 4

Additional criteria (two are required):

- 1. Anemia and a ≥ 2 g/L decrease from baseline hemoglobin level
- 2. A leukoerythroblastic peripheral blood picture
- 3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
- 4. Increased LDH (above the baseline level and exceeding the normal reference range without other obvious cause)
- 5. Development of 1 of three constitutional symptoms: 10% weight loss in 6 months, night sweats, unexplained fever (37.5°C)

Transformation to leukemic phase is defined by:

The threshold for a diagnosis of achieving blast phase is 20% blood or marrow blasts (persisting for 4 weeks) or the presence of an acute leukemia–defining karyotypic lesions despite blast percentage (t[8;21][q22;q22], inv[16][p13;q22], t[16;16][p13;q22], or t[15;17][q22;q12]).

13.3.5 DEATH

The cause of death should be given, including post mortem findings where possible. Information about the death should be recorded immediately in the source document, and also in the appropriate adverse event module of the CRF. All deaths must be reported to the MPD-RC Central Coordinating Office if it occurs within 30 days of receiving the study drugs.

13.4 Recording and evaluation of adverse events

Individual adverse events should be evaluated by the investigator and, where indicated, they should be reported to the sponsor for evaluation on the annual follow up form. This includes the evaluation of its seriousness and the causality between the investigational medicinal product(s) and/or concomitant therapy and the adverse event. The sponsor has to keep detailed records of all AEs reported to them by the investigator(s) and to perform an evaluation with respect to seriousness, causality and expectedness. After each contact with the subject, the investigator must seek information on adverse events by specific questioning and, when appropriate, by examination. Information about all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document and should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed to determine their final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

13.4.1 Assessment of severity

Assessment of severity should be assessed according to The NCI Common Terminology Criteria for Adverse Events v 4.0. This is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term. It can be found on the following website:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

All other adverse events should continue to be collected on the CRF pages.

13.4.2 Assessment of causality

Definitely: A causal relationship that can only be the result of the investigational medicinal product and there is no other plausible cause of the AE.

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product.

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible.

13.4.3 Outcome

The outcome of the event should be recorded. Typically these will include the following: Resolved; Resolved with sequela; Death; or ongoing if not resolved at the end of the study.

13.5 Reporting of Serious Adverse Events

13.5.1 Study Sponsor Notification by Investigator

A serious adverse event must be reported to the MPD-RC Data Monitor within 24 hours of the event following the appropriate MPD-RC Standard Operating Procedures (SOP):

- SOP 2-1: Serious Adverse Event (SAE) reporting – USA sites
- SOP 2-2: Serious Adverse Event (SAE) reporting – EU sites
- SOP 2-3: Serious Adverse Event (SAE) reporting – Canada site

To ensure subject safety, every SAE, regardless of suspected causality must be reported per protocol to the MPD-RC Central Office within 24 working hours of learning of its occurrence. The SAE should be reported in the Web-based data entry system (WBDES) on the “Immediate AE Reporting” (Part A) e-form and also on a Medwatch form 3500A. A signed and dated Medwatch 3500A should be emailed to the MPD-RC Data Monitor, Study Chair, Safety Officer, and PI of Project 6. At the time of the initial report the following information at minimum should be provided

- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment
- Study treatment dose

Significant new information on ongoing serious adverse events should be provided promptly to the study sponsor by entering the information into the database on the “Intermediate (Part B) AE Reporting” e-form. Update on all SAEs must be provided every two weeks (15 days) by the investigators to the coordinating center using the “Intermediate (Part B) AE Reporting” e-form.

The clinical course of the SAE is “concluded” when either the AE has reached a resolution or it becomes a chronic disorder not prone to further evolution. When the AE is “concluded”, the investigator is required to inform the coordinating center using the “Final (Part C) AE Reporting” e-form.

13.5.2 EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the local institutional EC/IRB within 10 working days. Copies of each report and documentation of EC/IRB notification and receipt will be kept in the Clinical Investigator’s binder.

13.5.3 Notifications by Sponsor

FDA

The study sponsor shall notify the FDA by telephone or by facsimile transmission (1-800-332-0178) of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days from the sponsor’s original receipt of the information. All other unexpected, serious adverse events that are considered related to study treatment will be reported on a MedWatch form by the Study Sponsor to the FDA within 15

calendar days. If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

Europe

The sponsor is responsible for the prompt notification to all concerned investigator(s), the Research Ethics Committees and competent authorities (e.g. MHRA) of each concerned Member State / Country of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the competent authority's authorization to continue the trial in accordance with Directive 2001/20/EC and other regulations as appropriate. In each country a PI designate will be utilized to facilitate this process.

Roche

The MPD-RC will report SUSAR and other serious adverse events to the safety office at Roche in parallel with submission to the FDA or equivalent European regulatory bodies.

13.6 MPD-RC Reporting of Suspected Unexpected Serious Adverse Reactions

(SUSARs) Regulatory Bodies and Ethics Committees

All suspected adverse reactions related to an investigational medicinal product (the tested IMP) which occurs in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. These events should be reported by the individual investigators to the MPD-RC with details as described in section 13.5.1.

13.6.1 MPD-RC Reporting of SUSARs.

MPD-RC, or designee, should report all the relevant safety information previously described to the concerned competent authorities and to the Ethics Committee concerned. MPD-RC or designee shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects. All SUSAR reports will also be reported to the FDA, European Research Ethics Committees and competent authorities (e.g. MHRA) of each concerned Member State / Country and Roche.

13.6.2 When to report

Fatal or life-threatening SUSARs

The MPD-RC should notify the Competent Authorities (CA) and the Research Ethics Committees/IRBs as soon as possible but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to the Competent Authorities and the Ethics Committee within an additional eight calendar days.

Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to the competent authority and the Ethics Committee in the concerned countries as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

13.6.3 How to report

Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited

reports should be submitted by the Sponsor within the time limits as soon as the minimum following criteria are met:

- a) a suspected investigational medicinal product,
- b) an identifiable subject (e.g. study subject code number),
- c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
- d) an identifiable reporting source, and, when available and applicable:
 - a unique clinical trial identification (EudraCT number or in case of non-European Community trials the sponsor's trial protocol code number)
 - a unique case identification (i.e. sponsor's case identification number).

Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. The sponsor should report further relevant information after receipt of follow-up reports. In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

Format of the SUSARs reports

Electronic reporting should be the expected method of the Sponsor for expedited reporting of SUSARs to the competent authority. In that case, the format and content as defined by the Guidance of the Competent Authorities should be adhered to. The CIOMS-I form is a widely accepted standard for expedited adverse reactions reporting. However, no matter what the form or format used, it is important that the basic information/data elements described in annex 3 of the EU directive or as per country requirement, when available, be included in any expedited report (some items may not be relevant, depending on the circumstances).

13.7 Stopping Rules

A patient may discontinue participation in the study at any time for any reason (e.g., lack of efficacy, consent withdrawn, adverse event). The investigator and/or sponsor can withdraw a patient from the study at any time for a protocol violation or for noncompliance, adverse event or any other reason. The reason for early withdrawal will be recorded on the treatment withdrawal page of the CRF.

13.8 Medical Monitoring

It is the responsibility of the local institutional Responsible Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

13.9 Monitoring Plan and Period of Observation

The monitoring plan for this study is maintained by the MPD-RC and contains the following elements:

- This study will be conducted according to the policies and procedures of the MPD-RC;
- All MPD-RC provided drug supplies will be returned to the MPD-RC or are to be disposed in accordance with procedure agreed to by investigator and the MPD-RC;

13.10 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must inform her treating physician immediately and permanently discontinue study drug. The pregnancy must be followed through delivery for SAEs (See Section [13.5](#)).

14.0 ADMINISTRATIVE REQUIREMENTS

14.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator should be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents should be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

14.2 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments should be submitted to a properly constituted independent EC or IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study should be made in writing to the investigator and a copy of this decision should be provided to the MPD-RC Central Office before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the MPD-RC Central Office.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See section 15.0 for a copy of the Subject Informed Consent Form. This consent form should be submitted with the protocol for review and approval by the EC/IRB for the study. The consent of a subject, using the EC/IRB-approved consent form, must be obtained before a subject is allowed to participate. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator obtaining the consent.

14.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent should be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent should comply with ICH-GCP and all applicable regulatory requirement(s).

14.4 Patient Confidentiality

Information about study subjects should be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

The patient has the right to revoke their authorization for use of their PHI. In the event that a

subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

14.5 Protocol Compliance

The investigator should conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Changes to the protocol will require approval of the MPD-RC and written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The MPD-RC will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

14.6 Management of Information

The MPD-RC at the Icahn School of Medicine at Mount Sinai will maintain sponsorship authority at the Icahn School of Medicine at Mount Sinai and all other participating sites.

Eligibility criteria will be confirmed using the electronic CRF. All inclusion and exclusion criteria are listed; the investigator is obliged to fill in all items. Subjects are enrolled in the study only if he/she fulfills all inclusion and no exclusion criteria.

Before the site can enroll a subject, the site must be activated as described in section 4.1.1.

Data Submission: Forms should be submitted to the MPD-RC Data Management Center. Data must be entered electronically by logging onto the MPD-RC web site and locating the specific web-ready form.

MPD-RC Form#	MPD-RC FORM NAME	SUBMISSION SCHEDULE
00	Parameter List	@ Registration
01	Recruitment	@ Registration
02	Baseline	Within 1 week after registration
03	Follow-up visit	Monthly X3, then every 3 months
04	Additional follow-up visit not planned in study protocol	As needed
05	Follow-up visit after drug interruption	Within 2 weeks of drug interruption
06	Adverse Event Form	Immediately report all SAE's and complete all non-reportable A/E's Monthly

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MPD-RC Form#	MPD-RC FORM NAME	SUBMISSION SCHEDULE
07	Outcome event Myocardial Infarction	Monthly and when/if it occurs
08	Outcome event Stroke	Monthly and when/if it occurs
09	Outcome event TIA	Monthly and when/if it occurs
10	Outcome event DVT	Monthly and when/if it occurs
11	Outcome event PAT	Monthly and when/if it occurs
12	Outcome event PE	Monthly and when/if it occurs
13	Outcome event Hemorrhage	Monthly and when/if it occurs
14	Outcome event STP	Monthly and when/if it occurs
15	Outcome event Pregnancy/Abortion	Monthly and when/if it occurs
16	Outcome event Malignancy	Monthly and when/if it occurs
17	Off treatment notice	Within 2 weeks going off treatment
18	Death notification form	Immediately
19	End of study	Within 2 weeks of completing study
20	MPN-SAF	Pre-registration, month 3, 6, 9, 12, then every 6 months
21	EORTC QLQ-C30	Pre-registration, month 3, 6, 9, 12, then every 6 months
22	Exploratory questions and patient feedback	Pre-registration, month 3, 6, 9, 12, then every 6 months
23	Bone marrow	Baseline, month 12,24, @ time of relapse/progression and study termination for any reason
24	Cytogenetic	Baseline, month 12,24, @ time of relapse/progression and study termination for any reason
25	Drug Administration	Monthly

In addition, all protocol amendments will be generated through and distributed by the MPD-RC Central Coordinating Office, which will also maintain records of IRB approval, amendments, SAEs, and annual reviews.

Serious adverse event reporting is detailed in section [13.5](#).

The MPD-RC will monitor study progress on an on-going basis; this will include electronic and telephone correspondence between the central coordinating office and with individual investigators at other sites.

14.7 Drug Accountability

Accountability for the study drug at all study sites is the responsibility of the MPD-RC. The responsible investigator at each participating center will ensure that the study drug is used only in accordance with this protocol, drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and return. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers. See NCI Drug Accountability Record Form (DARF) in [Appendix F](#).

14.8 Source Documents

Source data includes all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

14.9 Case Report Forms

The study CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded. CRFs may be found online at the MPD-RC website under the address MPD112@negrisud.it.

14.10 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the Trial Steering Committee there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the study drug

14.11 Record Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents must be retained at least 2 years following completion of the last follow-up on patients on active study. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

14.12 Endpoint Verification

The endpoint validation committee will centrally review and validate all end points following pre-defined criteria ([Appendix A](#)). All the clinical events included in the primary and secondary endpoints will be validated by an *ad hoc* committee of expert clinicians blinded to the treatment assigned. Copies of physicians' and hospital records and death certificates will be reviewed by a Primary Endpoint Committee for event validation. Each event will be independently evaluated by two evaluators. Disagreement between the two evaluators will be addressed by the chairman of the committee.

14.13 Data Safety Monitoring Board

An External Data and Safety Monitoring Board has been established. All members have experience and expertise in clinical trials. DSMB members are not directly involved in any phase of MPD-RC clinical trials and they have no major financial or intellectual conflict of interest that would prevent them from objectively reviewing the interim data and providing advice to the Trials Steering Committees and the Clinical Advisory Group. They function independently of all other individuals, processes, and progress to ensure study integrity, monitor patient safety (providing quarterly safety reports), evaluate the results of interim analysis to assess efficacy, and make recommendations about protocol amendments and early termination to the Trials Steering Committees. The External Data Safety and Monitoring Board must meet at least two times a year.

The interim efficacy and safety analyses will be performed blinded to treatment assignment.

The DSMB statistician will possess a copy of the treatment codes for unblinding purposes if required by the members of the board.

15.0 MODEL CONSENT FORM

(This consent template is meant as an aide in preparing your institution's informed consent document. You may alter the language to fit your IRB's requirements. You may add information to the various informative sections (e.g. "What is involved", "Risks", etc.) but not remove information because the minimum amount of disclosure has been provided to inform the subject adequately.)

TITLE OF RESEARCH STUDY:

Title: MPD-RC 112: Randomized Trial of Pegylated Interferon Alfa-2a versus Hydroxyurea Therapy in the Treatment of High Risk Polycythemia Vera and High Risk Essential Thrombocythemia

PRINCIPAL INVESTIGATOR (HEAD RESEARCHER) NAME AND CONTACT INFORMATION:

Name: *(Fill in this section with information for your institution)*

Physical Address:

Mailing Address:

Phone:

WHAT IS A RESEARCH STUDY?

A research study is when scientists try to answer a question about something that we don't know enough about. Participating may not help you or others.

People volunteer to be in a research study. The decision about whether or not to take part is totally up to you. You can also agree to take part now and later change your mind. Whatever you decide is okay. It will not affect your ability to get medical care at *(Name of Institution)*.

Someone will explain this research study to you. Feel free to ask all the questions you want before you decide. Any new information that develops during this research study that might make you change your mind about participating will be given to you promptly.

Basic information about this study will appear on the website <http://www.ClinicalTrials.gov>. There are a few reasons for this: the National Institutes of Health (NIH) encourages all researchers to post their research; some medical journals only accept articles if the research was posted on the website; and, for research studies the U.S. Food and Drug Administration (FDA) calls "applicable clinical trials" a description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

PURPOSE OF THIS RESEARCH STUDY:

This research looks at two conditions, Essential Thrombocythemia (ET) and Polycythemia Vera

(PV). ET causes people to produce too many blood cells called platelets and PV causes too many platelets and red blood cells to be made. Platelets are particles which circulate in the blood stream and normally prevent bleeding and bruising. Having too many platelets in the blood increases the risk of developing blood clots, which can result in life threatening events like heart attacks and strokes. When the number of red blood cells is increased in PV this will slow the speed of blood flow in the body and increases the risk of developing blood clots.

The purpose of this study is to look at the effectiveness of giving participants who have been diagnosed with ET or PV one of two different study regimens over time. Your study doctor would want to follow your condition for about 6 years. The study regimens are either “PEGASYS” (or Pegylated Interferon Alfa-2a) or “Aspirin and Hydroxyurea” (also called Hydroxycarbamide). All subjects participating in this study will also receive Aspirin as part of their study regimen regardless of which study drug they will receive. More information on these study regimens will be described later in this information sheet. To enter this study you may be a newly diagnosed subject or a subject already receiving treatment for either ET or PV. Each of the study drugs used in this study is already being used to treat subjects with ET or PV currently but we are unsure which study drug is better.

You may qualify for this study because you have been diagnosed by your study doctor as having the condition ET or PV and are over 18 years of age.

Funds for conducting this research are provided by the Myeloproliferative Disorders Research Consortium and the study drug (PEGASYS) is being supplied by Roche Pharmaceuticals.

LENGTH OF TIME AND NUMBER OF PEOPLE EXPECTED TO PARTICIPATE

Participation in this study is expected to last from 2 to 6 years depending upon your entry into the study. Optimally you will receive study drug for 2 years (if you achieve a complete or partial response) and then you will be in follow-up, where you will come in every 3 months for a study visit, for an additional 4 years.

The number of people at *(Name of Institution)* expected to participate in this study is approximately *(number at institution)* subjects, but because this is a cooperative group study approximately 300 subjects will be enrolled to the MPD-RC study throughout Europe and the United States.

DESCRIPTION OF WHAT'S INVOLVED:

If you agree to participate in this research study, the following information describes what may be involved.

In order to participate in this study, you must also be participating in the mandatory Biomarker Study (107). Once you have signed the consent forms for both this study and the mandatory Biomarker Study to say you are willing to take part in these studies you will have a screening visit to make sure that you meet all of the requirements to participate in this study. The following tests and procedures will be done during the screening visit:

The following tests and procedures will be done during the screening visit:

- **Complete history and physical**, including vital signs such as blood pressure, heart rate, body temperature, weight, body surface area, and a list of past and current medications.
- **ECOG performance status**: rating scale to rate your ability to perform daily functions.

- **Spleen measurement:** through palpation (feeling with the hands) or through ultrasound. Ultrasound technology uses sound waves to reflect off of soft tissues to create an image based upon the computer's interpretation of the wave's reflections. The sonographer will use a gel to help transmit the sound waves through the wand. It is cool and rather gooey – but not uncomfortable and the procedure does not last long.
- **Fundoscopy Eye Exam:** examination that checks the retina of the eye.
- **Blood Tests:** (Approximately a total of 7 ½ tablespoons of blood will be collected from a vein in your arm with a needle):
 - **Complete blood count** (approx. 1 ½ tsp. blood): complete blood count monitors the blood levels; red blood cells, white blood cells, platelets and other components of the blood.
 - **Blood chemistries** (approx. 1 ½ tsp. blood): tests the creatinine, glucose, bilirubin, and other chemicals in the blood that indicate how well the liver and kidneys are functioning and to check for side effects.
 - **Thyroid Function** (approx. 1 ½ tsp. blood): the thyroid is one of the largest endocrine glands in the body. This gland is found in the neck and controls how quickly the body uses energy, makes proteins, and controls how sensitive the body should be to other hormones. This blood test checks how well the thyroid gland is functioning.
 - **Plasma Viscosity** (approx. 1 ½ tsp. blood): tests for how much water is present in the blood. The less water, the thicker the blood and the more difficult it is for the blood to flow through the veins. An increase in the viscosity level can reduce the amount of oxygen that is delivered to the body.
 - **JAK2V617F:** blood test to check for the JAK2V617F mutation in your blood (1 ½ tsp. blood) If you have PV and do not have the JAK2V617F mutation in your blood you may not participate in this study. If you have ET and do not have the JAK2V617F mutation in your blood you may participate in this study.
 - **Pregnancy test:** for women of childbearing potential. (Approx. 1 tsp. blood)
 - **Extra Blood and nail clippings:** Up to 4 2/3 Tbsp. of blood will collected for research purposes for the biomarker study. Nail clippings: 2 clippings will only be gathered once (at pre-study visit). Your nail clippings will provide normal material, like DNA, for comparison with the abnormal material from your blood and/or bone marrow.
- **Bone marrow aspiration/biopsy/cytogenetics/clonality:** Bone marrow aspiration, also called bone marrow sampling, is the removal by suction (through a needle placed into the bone) of fluid from the soft, spongy material that lines the inside of most bones (marrow). (Approx. 1½ tsp) During a bone marrow aspiration/biopsy an area of the hip is numbed and a needle is placed through the skin and into the hip bone. A small sample of bone marrow and bone is withdrawn. The bone marrow will be examined to see if it is abnormal. Three teaspoons of additional bone marrow for the biomarker study will be collected prior to beginning the study drugs, again at the month 12 visit, then again at the month 24 visit, if the disease returns after a response to the medication, or if the study medications are discontinued for any reason.
- **EKG (electrocardiogram):** for this test, you will be asked to lie down while 12 sticky pads are affixed to each of your arms and legs and to your chest. The EKG will last about 10 minutes. An EKG records the electrical activity of the heart and is used to measure how fast and how regular the heart beats, as well as the size and position of the chambers, the presence of any damage to the heart, and the effects of study drugs or devices used to regulate the heart

(such as a pacemaker). An EKG is painless but sometimes the sticky pads can irritate your skin.

- **Quality of Life questionnaires:** You will be asked to fill out three quality of life questionnaires. Using a pencil you will be asked to circle answers on the questionnaires relating to how you feel. Filling out all three questionnaires should take less than 15 minutes.

Sometimes we don't know which way of treating subjects is best. To find out, we need to compare different study regimens. We put people into groups and give each group a different study regimen. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each subject is put into a group by chance (randomly-like flipping a coin) this is done because we currently think that the two study regimens under testing work equally well. We are aiming for 150 subjects to receive study drug PEGASYS and 150 to receive study drug Hydroxyurea for a total of 300 subjects.

This means that you would have a 50% (1 in 2) chance of being treated with PEGASYS and a 50% (1 in 2) chance of being treated with hydroxyurea.

If you are already on Hydroxyurea when you start this study, and by chance you are assigned to Pegasys, your Hydroxyurea dose will be slowly lowered and stopped before the third month of the study.

How often you need to visit your study doctor will depend on your blood results, which are used to measure how well you respond to the study drug. At first you might need to visit weekly but once your study regimen is stable this should be less often. Your study doctor will need to see you at appropriate intervals for your care, on average every 3 months. During these visits your study doctor will take blood samples and ask you how you have been feeling. Some of these blood samples will be sent off to measure the amounts of different proteins in your blood as part of this study to compare your response to PEGASYS with hydroxyurea. Please use this time to report any problems you have had since your last visit. During the study the following tests will be performed:

- **Complete physical**, including vital signs such as blood pressure, heart rate, body temperature, weight, and a list of past and current medications. This will be done at study visits on weeks 1 and 3, monthly for months 2, 3, 4, 5, 6, every 3 months while on active study drug, and at study discontinuation.
- **Spleen measurement:** through palpation (feeling with the hands) or through ultrasound prior to starting the study drugs, at 12 or 15 months and when the study drugs are being discontinued. Spleen measurements through palpation will be done at study visits on weeks 1 and 3, monthly for months 2, 3, 4, 5, 6, every 3 months while on active study drug, and at study discontinuation.
- **ECOG performance status:** rating scale to rate your ability to perform daily functions. This will be done at study visits on weeks 1 and 3, monthly for months 2, 3, 4, 5, 6, every 3 months while on active study drug, and at study discontinuation.
- **Blood Tests:** (Approximately a total of 2 tablespoons of blood will be drawn through a needle from a vein in the arm) (Months 12, 24 and at time of termination of study for any reason an additional 4 2/3 tablespoons will be drawn for the Biomarker Study) Blood Tests:
 - **Complete blood count** (approx. 1 ½ tsp. blood). This will be done at study visits on weeks 1 and 3, monthly for months 2, 3, 4, 5, 6, every 3 months while on active study

drug, and at study discontinuation.

- **Blood chemistries** (approx., 1 ½ tsp. blood). This will be done at study visits on weeks 1 and 3, monthly for months 2, 3, 4, 5, 6, every 3 months while on active study drug, and at study discontinuation.
- **Thyroid Function** (approx. 1 ½ tsp. blood) This will be done at study visits on weeks 1 and 3, monthly for months 2, 3, 4, 5, 6, every 3 months while on active study drug, and at study discontinuation.
- **Extra Blood:** Up to 4 2/3 Tbsp. of blood will collected for research purposes for the biomarker study. This will be done at 12 and 24 months or at time of termination of study for any reason.
- **Bone marrow aspiration/biopsy:** (Approx. 1 ½ tsp.) An additional 3 teaspoons of bone marrow will be drawn for the biomarker study (#107) (research related). This will be done after 12 and 24 months or at the time of a bone marrow for relapse or progression of disease or at termination of study treatment for any reason.
- **Quality of Life questionnaire:** You will be asked to fill in a questionnaire called, “Quality of Life”. This will be done prior to receiving any study medication then after months 3, 6, 9, 12 and then every 6 months. The information from these will be compared with the one you did at the start of the study to see if how you have been feeling has changed over time. Filling out the questionnaire should take less than 15 minutes.

Reproductive Information

If you (or your partner) become pregnant or are thinking of having a baby you should speak to your study doctor so your medication can be carefully managed. If you are given Hydroxyurea as your medication you should make sure you use adequate contraception. Both men and women must not attempt pregnancy and women must not be pregnant or breast-feeding while participating in this study. If sexually active, both men and women must use an effective method of birth control while taking the study drug. Barrier contraceptives (condoms or diaphragm) with a spermicide, intrauterine devices, hormonal contraceptives (Depo-Provera, Norplant), oral contraceptive pills, and complete abstinence are examples of effective methods. Only methods that also use condoms provide adequate protection against sexually transmitted diseases. If you or your partner become pregnant while taking the study drug, it is important that you notify your study nurse/physician immediately. If you are pregnant you may be required to stop the study drugs at which time other treatment options will be discussed with you.

Women who can still become pregnant must have a pregnancy test before taking part in this study. This pregnancy screening is standard practice at the *(Name of Institution)* in chemotherapy research studies and the results will be used to determine eligibility for the study. If you are a woman who can become pregnant, blood will be taken from a vein in your arm with a needle within 7 days before you enter the study. You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to take part in the study.

Do not forget to tell your study doctor if you start taking any new medicines, feel unwell or want to take part in a new study run by another doctor.

What is the drug being tested?

Hydroxyurea is a form of chemotherapy. This means it stops the growth of abnormal tissue. It is a drug that has been shown to reduce the chance of blood clots in subjects with ET and PV who have high risk factors for forming clots. It is a tablet and must be taken on a continuous basis usually every day.

PEGASYS is a type of interferon, which is a form of a hormone produced naturally in the body which reduces the production of blood cells. It is a drug that has been shown to reduce the amount of a protein thought to be involved in causing ET and PV in some subjects. This protein is called JAK2V617F. PEGASYS will be given by a subcutaneous injection (injected just under the skin) every week. This is an injection similar to giving insulin to diabetics. You will begin receiving the medication at a dose level of 45 micrograms weekly and gradually get increased to the maximum dose of 180 micrograms per week. You will be taught by the study staff how to give yourself the injection so that you can do the injections at home and reduce the number of visits needing to be made to the clinic. You will receive a prefilled syringe or single-use vial containing 180 micrograms of the study drug. You will be instructed by the study staff how to insert the needle under the skin to give yourself a subcutaneous injection (like diabetics receive their insulin). You will be instructed on how much of the medication to give yourself and then you will recap the syringe with the unused portion of the study medication and place the syringe in a container to bring back to the clinic with you. The study staff will check and record the syringes that were used as well as any unused syringes.

All subjects participating in this study will also receive aspirin as part of their study regimen regardless of which study drug they will receive. Aspirin (acetylsalicylic acid) works by stopping platelets from forming clots and is extensively used worldwide in patients at high risk of strokes and heart attacks. It has been shown to reduce risks of these events in PV but not directly in ET.

A standard dose of 81mg or 100mg of aspirin (to be taken with food) will be used in all patients. At this dosage side-effects are very uncommon. However, a few patients may not be able to take aspirin because they have a history of intolerance to aspirin, MPN-associated hemorrhage, recent peptic ulceration or aspirin sensitive asthma. You may be prescribed an aspirin substitute or nothing at all, an aspirin substitute not being mandatory for participation in the study.

In your third year of the study your study doctor may ask to perform another bone marrow sample. This would help the study, but it is your choice if you want this taken or not. This bone marrow procedure will be discussed with you when it comes time for the procedure and at that time you can either agree to have it done or refuse. If you decide to not have the procedure done this will in no way effect your medical care.

YOUR RESPONSIBILITIES IF YOU TAKE PART IN THIS RESEARCH:

If you decide to take part in this research study you will be responsible for the following things: taking your medication as directed by your study doctor and attending the routine clinic appointments made for you.

COSTS OR PAYMENTS THAT MAY RESULT FROM PARTICIPATION:

There is no additional cost to you for participating in this research study other than those costs associated with the treatment of your disease. Please speak your study team and with the financial/billing representative to see if your insurance will cover the expenses associated with this study, before proceeding with this research study. The study drug, PEGASYS, will be provided at no cost to you by ROCHE Pharmaceuticals. You or your insurance company will be

responsible for the costs of your clinic visits and all of the standard study treatments and procedures, including standard of care blood tests, medication (hydroxyurea and aspirin), ECG, and bone marrow aspiration/biopsy. This is because this standard care testing would be done even if you were not participating in this study.

The sponsors of this study will pay for the biomarker sub-study blood tests and for the study medication, PEGASYS. All other study expenses are your responsibility or that of your insurance carrier.

Your insurance company must be contacted to pre-authorize all the study treatments in this study. If your insurance company does not authorize these study treatments, you may choose not to participate in this research study. The study doctor will discuss these options with you. If your insurance company does not authorize the study treatment, and no alternative payment arrangement is made, and you choose to go ahead with the study, you would be responsible for the bill. Please speak to the study doctor and with the financial/billing representative before proceeding with this research study.

POSSIBLE BENEFITS:

The information gained from this study will help to give doctors a better idea of which medications minimize the risk of “life threatening events”, such as heart attacks and strokes in patients with ET and PV. We will also be using information from the additional blood samples taken in this study to see if either PEGASYS or Hydroxyurea reduce the amount of proteins in your blood that might be important in causing ET or PV, such as JAK2V617F. Additionally, there may or may not be any direct medical benefit to you from participating in this study, but the knowledge gained through this research may help other patients with ET or PV in the future.

REASONABLY FORESEEABLE RISKS AND DISCOMFORTS:

While on the study, you are at risk for the side effects listed below. You should discuss these with the study doctor and/or your regular doctor. There also may be other side effects that we cannot predict. Many side effects go away shortly after study drug is stopped, but in some cases side effects can be serious, long lasting, or permanent. It may be necessary for you to be admitted to the hospital for the treatment of these side effects.

Each of the medicines in this study is licensed for treatment of medical conditions, but not necessarily ET or PV even though they are widely used for these conditions, and for each (PEGASYS and Hydroxyurea) further information can be found in the patient information sheet with the medication you would be given. Alternatively, information about these medicines is available at <http://www.netdoctor.co.uk/medicines>.

Risks of Aspirin:

The most common unwanted affect for **aspirin** is indigestion and heartburn, and so it **should not** be used (except on medical advice) in someone who has a peptic ulcer or has had one in the past. It is important that patients with Asthma should tell their doctor as aspirin can cause shortness of breath and may start an asthma attack.

Where patients have increased levels of platelet counts, aspirin can also cause an increase in

bruising and bleeding.

Although rare, kidney problems can develop in some patients.

Risk of Hydroxyurea:

Hydroxyurea is approved for treatment of medical conditions, but not ET or PV. However, it is a well-established treatment for these conditions and has been used for some time. A serious side effect of this medication may be to decrease your white and red blood cells as well as your platelet count. The decrease in white cells can lead to an increased risk of infection and possibly to a fever developing. If this happens it is important that you contact a doctor for medical advice.

Some common side effects include tiredness, mouth ulcers, headaches and gastrointestinal upsets such as nausea, diarrhea or constipation. Rarely there might be skin rashes, leg ulcers or kidney problems.

If Hydroxyurea is taken for a long time there can be redness, scaling or increased pigmentation of skin, or thinning of skin or nails in some people.

There has been some controversy about whether Hydroxyurea increases the risk of ET or PV turning into acute leukemia in the long term (if taken for more than 10 years). This question has not yet been answered but if there is any increase in risk it is likely to be small, less than 3 in 100 after 10 years.

Risks of PEGASYS:

PEGASYS can cause serious side effects including:

- blood problems. PEGASYS can affect your bone marrow and cause low red blood cell, low white blood cell, and platelet counts
- thyroid problems
- blood sugar problems. Some people may develop high blood sugar or diabetes.
- serious eye problems. PEGASYS may cause eye problems that may lead to vision loss or blindness
- serious liver problems, worsening of liver problems, including liver failure and death
- lung problems, including:
 - trouble breathing
 - pneumonia
 - inflammation of lung tissue
 - new or worse high blood pressure of the lungs (pulmonary hypertension). This can be severe and may lead to death
- inflammation of your pancreas (pancreatitis)
- inflammation of your intestines (colitis)
- serious allergic reactions and skin reactions
- nerve problems. People who take PEGASYS can develop nerve problems such as continuing numbness, tingling, or burning sensation in the arms or legs (peripheral neuropathy)
- heart problems. Some people who take PEGASYS may get heart problems, including:
 - high blood pressure
 - fast heart rate or abnormal heart beat

- chest pain
- heart attacks
- Mental health problems and suicide. PEGASYS therapy may cause you to develop mood or behavioral problems, including:
 - irritability (getting upset easily)
 - depression (feeling low, feeling bad about yourself or feeling hopeless), and anxiety
 - aggressive behavior
 - former drug addicts may fall back into drug addiction or overdose
 - thoughts of hurting yourself or others, or suicide
- Stroke or symptoms of a stroke. Symptoms may include weakness, loss of coordination, and numbness.
- New or worsening autoimmune problems. Some people taking PEGASYS develop autoimmune problems (a condition where the body's immune cells attack other cells or organs in the body), such as rheumatoid arthritis, lupus, and psoriasis.
- Infections. Some people who take PEGASYS may get an infection. Symptoms may include:
 - fever
 - chills
 - burning and painful urination
 - urinating often
 - coughing up yellow or pink mucus (phlegm)

The most common, but less serious, side effects of PEGASYS include:

- flu-like symptoms (i.e. aches and pains, fever, chills, sweating, headache, fatigue and nausea. These tend to be worse at the start of study drug usage and improve with continued usage. You may want to take a medicine to reduce these symptoms - for example, paracetamol or ibuprofen - before the injection and for 24 hours after the injection)
- tiredness and weakness
- stomach problems
- loss of appetite
- skin reactions
- hair thinning
- trouble sleeping

Risks of EKG:

An EKG is painless. The electrodes placed on the skin detect only the electrical signals from the heart. No electricity is sent through the body, and there is no possibility of receiving an electric shock. When first applied, the disks may be cold and in rare circumstances, you may develop a localized rash or irritation where the patches are placed.

Risks of Bone marrow aspirate/biopsy:

A bone marrow aspiration/biopsy is a procedure in which an area of the hip is numbed and a needle is placed through the skin and into the hip bone. A small sample of bone marrow and bone is withdrawn. There may be some temporary pain or discomfort associated with these routine procedures. The risks therefore include bleeding which rarely requires blood transfusions,

pain at the site of the biopsy, and a small possibility of a local infection which may lead to antibiotic therapy. In extremely rare cases, an allergic reaction to the local anesthetic used to numb the hip can occur. In addition, tissue swelling around the aspiration/biopsy site may occur.

Risks of clipping nails:

There are no risks to clipping nails.

Side Effects of Blood Being Drawn:

Blood withdrawal may cause pain and bruising at the site of vein puncture, inflammation of the vein and infection; lightheadedness and/or fainting; care will be taken to minimize these risks.

Reproductive Health/Sexual Activity:

Both men and women must not attempt pregnancy and women must not be pregnant or breast-feeding while participating in this study. If sexually active, both men and women must use an effective method of birth control while taking the study drug. Barrier contraceptives (condoms or diaphragm) with a spermicide, intrauterine devices, and complete abstinence are examples of effective methods. Only methods that also use condoms provide adequate protection against sexually transmitted diseases. If you or your partner become pregnant while taking the study drug, it is important that you notify your study nurse/physician immediately. If you are pregnant you may be required to stop the study drugs at which time other treatment options will be discussed with you.

Women who can still become pregnant must have a pregnancy test before taking part in this study. This pregnancy screening is standard practice at *(Name of Institution)* in chemotherapy research studies and the results will be used to determine eligibility for the study. If you are a woman who can become pregnant, blood will be taken from a vein in your arm with a needle within 7 days before you enter the study. You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to take part in the study.

Risk of loss of confidentiality:

There is the risk for the potential loss of confidentiality. This means that the risk of release of private information from your health records can occur. Release of this private information might affect you in the future.

In addition to these risks, this research may hurt you in ways that are not known. The unknown risks might be minor or might be major (death).

OTHER POSSIBLE OPTIONS TO CONSIDER:

An option is not to participate and if you choose not to take part in the study this will not affect your level of care. Your study doctor will discuss with you what will be the best treatment and you will be seen at routine clinic appointments.

IN CASE OF INJURY DURING THIS RESEARCH STUDY:

If you are injured or made sick from taking part in this research study, medical care will be provided. Generally, this medical care will be billed to you and/or your health care insurance. In some cases, the costs of this care may be paid by someone else. In the event of injury, contact the

Principal Investigator.

ENDING PARTICIPATION IN THE RESEARCH STUDY:

You may stop taking part in this research study at any time without any penalty. This will not affect your ability to receive medical care at *(Name of Institution)* or to receive any benefits to which you are otherwise entitled.

If you decide to stop being in the research study, please contact the Principal Investigator or the research staff

If you stop being in the research study, already collected information may not be removed from the research study database and will continue to be used to complete the research analysis. You may be asked whether the investigator can collect information from your routine medical care. If you agree, this data will be handled the same as research data.

You may also withdraw your permission for the use and disclosure of any of your protected information for research, but you must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, the Principal Investigator for the research study may still use the information that was already collected if that information is necessary to complete the research study. Your health information may still be used or shared after you withdraw your authorization if you should have an adverse event (a bad effect) from participating in the research study.

Withdrawal without your consent: The study doctor, the sponsor (MPD-RC) or the institution may stop your involvement in this research study at any time without your consent. This may be because the research study is being stopped, the instructions of the study team have not been followed, the investigator believes it is in your best interest, or for any other reason. If specimens or data have been stored as part of the research study, they too can be destroyed without your consent.

CONTACT PERSON(S):

If you have any questions, concerns, or complaints at any time about this research, or you think the research has hurt you, please contact the office of the research team and/or the Principal Investigator at phone number *(XXX-XXX-XXXX)*.

This research has been reviewed and approved by an Institutional Review Board. You may reach a representative of the Program for Protection of Human Subjects at *(Name of Institution)* at telephone number *(XXX-XXX-XXXX)* during standard work hours for any of the following reasons:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You are not comfortable talking to the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

DISCLOSURE OF FINANCIAL INTERESTS:

None.

MAINTAINING CONFIDENTIALITY – HIPAA AUTHORIZATION:

As you take part in this research project it will be necessary for the research team and others to use and share some of your private protected health information. Consistent with the federal Health Insurance Portability and Accountability Act (HIPAA), we are asking your permission to receive, use and share that information.

What protected health information is collected and used in this study, and might also be disclosed (shared) with others?

As part of this research project the researchers will collect your **name**, address including zip code, telephone number, date of birth, sex, race, and ethnicity.

The researchers will also get information from your medical record (includes hospital record from *(Name of Institution)* and referring physician's records)

During the study the researchers will gather information by:

- taking a medical history (includes current and past medications or therapies, illnesses, conditions or symptoms, family medical history, allergies, etc.)
- doing a physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature
- completing the blood tests, procedures such as ECG, bone marrow aspiration/biopsy, biomarker testing as explained in the description section of this consent.

Why is your protected health information being used?

Your personal contact information is important to be able to contact you during the study. Your health information and the results of any tests and procedures being collected as part of this research study will be used for the purpose of this study as explained earlier in this consent form. The results of this study could be published or presented at scientific meetings, lectures, or other events, but would not include any information that would let others know who you are, unless you give separate permission to do so. The Principal Investigator may also use and share the results of these tests and procedures to treat you.

The research team and other authorized members of *(Name of Institution)* workforce may use and share your information to ensure that the research meets legal, institutional or accreditation requirements. For example, the *(Name of Institution)* Program for the Protection of Human Subjects is responsible for overseeing research on human subjects, and may need to see your information. If you receive any payments for taking part in this study, the *(Name of Institution)* Finance Department may need your name, address, social security number, payment amount, and related information for tax reporting purposes. If the research team uncovers abuse, neglect, or reportable diseases, this information may be disclosed to appropriate authorities.

Who, outside *(Name of Institution)*, might receive your protected health information?

As part of the study, the Principal Investigator, study team and others in the *(Name of Institution)* workforce may disclose your protected health information, including the results of the research study tests and procedures, to the following people or organizations: (It is possible that there may be changes to the list during this research study; you may request an up-to-date list at any time by contacting the Principal Investigator.)

- Research data coordinating office and/or their representative(s) who will be responsible for collecting results and findings from all the centers: Myeloproliferative Disorders Research Consortium Data Management Center
- Outside laboratory who will be performing laboratory analysis for all the research centers involved in this project: Myeloproliferative Disorders Central Laboratory located at the New York Blood Center in North America and at MPD-RC Tissue Bank, Laboratorio Paolo Belli in Europe.
- The manufacturer of the drug PEGASYS, Roche Pharmaceuticals.
- The sponsoring government agency and/or their representative who need to confirm the accuracy of the results submitted to the government or the use of government funds: In the USA this is the National Cancer Institute (NCI), in Europe this will be the individual regulatory authorities for examples the MHRA.
- A Data Safety Monitoring Board or other committee that will monitor the study on an ongoing basis for safety. This will include the *(Institution's Name)* Institutional Review Board (IRB) and the Myeloproliferative Disorders Research Consortium Data and Safety Monitoring Board.
- The United States Food and Drug Administration.
- United States Department of Health and Human Services and the Office of Human Research Protection.

In all disclosures outside of *(Name of Institution)*, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law. Some records and information disclosed may be identified with a unique code number. The Principal Investigator will ensure that the key to the code will be kept in a locked file, or will be securely stored electronically. The code will not be used to link the information back to you without your permission, unless the law requires it, or rarely if the Institutional Review Board allows it after determining that there would be minimal risk to your privacy. It is possible that a sponsor or their representatives, a data coordinating office, a contract research organization, will come to inspect your records. Even if those records are identifiable when inspected, the information leaving the institution will be stripped of direct identifiers. Additionally, the monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to your medical records for verification of the research procedures and data. By signing this document you are authorizing this access. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

For how long will *(Name of Institution)* be able to use or disclose your protected health information?

Your authorization for use of your protected health information for this specific study does not expire.

Will you be able to access your records?

During your participation in this study, you will have access to your medical record and any study information that is part of that record. The investigator is not required to release to you research information that is not part of your medical record.

Do you need to give us permission to obtain, use or share your health information?

NO! If you decide not to let us obtain, use or share your health information you should not sign this form, and you will not be allowed to volunteer in the research study. If you do not sign, it will not affect your treatment, payment or enrollment in any health plans or affect your

eligibility for benefits.

Can you change your mind?

You may withdraw your permission for the use and disclosure of any of your protected information for research, but you must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, the Principal Investigator for the research study may still use your protected information that was already collected if that information is necessary to complete the study. Your health information may still be used or shared after you withdraw your authorization if you should have an adverse event (a bad effect) from being in the study. If you withdraw your permission to use your protected health information for research that means you will also be withdrawn from the research study, but standard medical care and any other benefits to which you are entitled will not be affected. You can also tell us you want to withdraw from the research study at any time without canceling the Authorization to use your data.

If you have not already received it, you will also be given the Notice of Privacy Practices that contains more information about how *(Name of Institution)* uses and discloses your protected health information.

It is important for you to understand that once information is disclosed to others outside *(Name of Institution)*, the information may be re-disclosed and will no longer be covered by the federal privacy protection regulations. However, even if your information will no longer be protected by federal regulations, where possible, *(Name of Institution)* has entered into agreements with those who will receive your information to continue to protect your confidentiality.

If as part of this research project your medical records are being reviewed, or a medical history is being taken, it is possible that HIV-related information may be revealed to the researchers. If that is the case, the information in the following box concerns you. If this research does not involve any review of medical records or questions about your medical history or conditions, then the following section may be ignored.

Signature Block for Capable Adult

Your signature below documents your permission to take part in this research and to the use and disclosure of your protected health information. A signed and dated copy will be given to you.

DO NOT SIGN THIS FORM AFTER THIS DATE→

Signature of subject

Date and Time

Printed name of subject

Person Explaining Study and Obtaining Consent

Signature of person obtaining consent

Date and Time

Printed name of person obtaining consent

Witness Section: For use when a witness is required to observe the consent process document below (for example, subject is illiterate or visually impaired, or this accompanies a short form consent):

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

Signature of witness to consent process

Date and Time

Printed name of person witnessing consent process

16.0 REFERENCES

1. Aaronson, N.K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N.J., Filiberti, A., Flechtner, H., Fleishman, S.B., de Haes, J.C. & et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*, 85, 365-376.
2. G. Barosi, R. A. Mesa, J. Thiele, F. Cervantes, P. J. Campbell, S. Verstovsek, B. Dupriez, R. L. Levine, F. Passamonti, J. Gotlib, J. T. Reilly, A. M. Vannucchi, C. A. Hanson, L. A. Solberg, A. Orazi, and A. Tefferi. Proposed criteria for the diagnosis of post- polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment *Leukemia* 22 (2):437-438, 2008
3. G. Barosi, R. Mesa, G. Finazzi, C. Harrison, J. Kiladjian, E. Lengfelder, M. McMullin, F. Passamonti, A. Vannucchi, C. Besses, H. Gisslinger, J. Samuelsson, S. Verstovsek, R. Hoffman, A. Pardanani, F. Cervantes, A. Tefferi, and T. Barbui. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. *Blood* 2013, 121: 4778-4781
4. Barosi G, Birgegard G, Finazzi G *et al*. Response criteria for essential thrombocythemia and Polycythemia vera. Result of a European LeukemiaNet (ELN) consensus conference. *Blood* 2009; 113, 4829-4833.
5. Bretscher M, Rummans T, Sloan J, Kaur J, Bartlett A, Borkenhagen L, *et al*. Quality of life in hospice patients. A pilot study. *Psychosomatics*. 1999; 40, 309-13.
6. Campbell PJ, Scott LM, Buck G, *et al*. Definition of subtypes of essential thrombocythaemia and relation to polycythemia vera based on JAK2V617F mutation status: a prospective study. *Lancet* 2005;366,1945-53.
7. Campbell PJ, Griesshammer M. The V617F mutation in JAK2 is associated with poorer survival in idiopathic myelofibrosis. *Blood* 2006; 107:2098-2100.
8. Cannon CP, McCabe CH, Wilcox RG *et al* Oral glycoprotein IIb/IIIa inhibition with orbofian in patients with unstable coronary syndromes (OPUS-TMI 16) trial. *Circulation* 2000; 102: 149-156
9. Cortelazzo S, Finazzi G, Ruggeri M, *et al*. Hydroxyurea *for* patients with essential thrombocythemia and a high risk of *thrombosis*. *N Engl J Med* 1995;332,1132-6
10. Curran S, Andrykowski M, Studts J. Short form of the profile of mood states (POMS-SF):Psychometric Information. *Psychological Assessment*.1995;7(1):80-3
11. Diggle PJ, Heagerty P, Liang K-Y and Zeger SL (2002) *Analysis of Longitudinal Data* (2nd Ed) Oxford University Press
12. Donovan PB, Kaplan ME, Goldberg JD, *et al*. Treatment of polycythemia vera with hydroxyurea. *Am J Hematol* 1984;17, 329-34.
13. Fitzmaurice, G., Laird, N., and Ware, J. (2004) *Applied Longitudinal Data Analysis*, John Wiley and Sons

14. Halsey C, Roberts IA. The role of hydroxyurea in sickle cell disease. *Br J Haematol* 2003;120, 177-86.
15. Hanft VN, Fruchtman SR, Pickens CV, Rosse WF, Howard TA, Ware RE. Acquired DNA mutations associated with in vivo hydroxyurea exposure. *Blood* 2000;95, 3589-93.
16. Harrison CN, Campbell PJ, Buck G, *et al.* Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med* 2005;353,33-45.
17. Ishii T, Bruno E, Hoffman R, Xu M. Involvement of various hematopoietic-cell lineages by the JAK2V617F mutation in polycythemia vera. *Blood* 2006;108, 3128-24.
18. Jabbour E, Kantarjian H, Cortes J *et al.* PEG-IFN-alfa-2b therapy in BCR-ABL-negative myeloproliferative disorders. *Cancer* 2007;110, 2013-2018.
19. Jenkinson C, Layte R, Jenkinson D, Lawrence K, Petersen S, Paice C, *et al.* A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *Journal of public health medicine*. 1997: 19:179-86.
20. Jenkinson C, Layte R. Development and testing of the UK SF-12 (short form health survey). *Journal of health services research & policy*. 1997;2:14-8
21. Kaplan ME, Mack K, Goldberg JD, Donovan P, Jenkinson C, Layte R, Jenkinson D, Lawrence K, Petersen S, Paice C, *et al.* A shorter form health survey: can the SF-12 replicate results from the SF-36 in longitudinal studies? *Journal of public health medicine*. 1997;19, 179-86.
22. Kiladjian JJ, Cassinat B, Turlure P, *et al.* High molecular response rate of polycythemia vera patients treated with pegylated interferon alfa-2a. *Blood* 2006; 108, 2037-40.
23. Kiladjian J-J, Cassinat B, Chevret S *et al.* Pegylated interferon alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. *Blood* 2008;112, 3065-3072.
24. Kopec JA, Willison KD. A comparative review of four preference-weighted measures of health-related quality of life. *J Clin Epidemiol*. 2003;56, 317-25.
25. Locke, D.E., Decker, P.A., Sloan, J.A., Brown, P.D., Malec, J.F., Clark, M.M., Rummans, T.A., Ballman, K.V., Schaefer, P.L. & Buckner, J.C. (2007) Validation of single-item linear analog scale assessment of quality of life in neuro-oncology patients. *J Pain Symptom Manage*, 34, 628-638.
26. Landolfi R, Marchioli R, Kutti J, *et al.* Efficacy and safety of low-dose aspirin in polycythemia vera. *N Engl J Med* 2004;350, 114-24.
27. R. Kralovics, S. S. Teo, S. Li, A. Theocharides, A. S. Buser, A. Tichelli, and R. C. Skoda. Acquisition of the V617F mutation of JAK2 is a late genetic event in a subset of patients with myeloproliferative disorders *Blood* 108 (4):1377-1380, 200621.
28. Langer C, Lengfelder E, Thiele, J *et al.* Pegylated interferon for the treatment of high risk essential thrombocythemia: results of a phase II study. *Haematologica* 2005; 90, 1333-38.
29. Locke DE, Decker PA, Sloan JA, Brown PD, Malec JF, Clark MM, *et al.* Validation of single-item linear analog scale assessment of quality of life in neuro-oncology patients. *J Pain Symptom Manage*. 2007 ;34, 628-38.

30. Little R and Rubin D (2002) Statistical Analysis of Missing Data (2nd Ed). Wiley, New York
31. Liu, E, Jelinek J, Pastore, YD *et al.* Discrimination of polycythemias and thrombocytoses by novel, simple, accurate clonality assays and comparison with PRV-1-expression and BFU-E response to erythropoietin. *Blood* 2003, 101:3294-3301.
32. Marchioli R, Finazzi G, Landolfi R, *et al.* Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol* 2005;23, 2224-32.
33. Mathew A, Peiffer LP, Rhoades K, McGarrity TJ. Improvement in quality of life measures in patients with refractory hepatitis C, responding to re-treatment with Pegylated interferon alpha -2b and ribavirin. *Health and quality of life outcomes.* 2006;4, 30.
34. McNair D, Lorr M, Droppelman L. Profile of Mood States: Manual. San Diego, CA: Educational and Testing Services 1971.
35. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, *et al.* The rapid assessment of fatigue severity in cancer patients: use of the *Brief Fatigue Inventory*. *Cancer.* 1999 ;85:1186-96.
36. Mesa RA, Niblack J, Wadleigh M, Verstovsek S, Camoriano J, Barnes S, *et al.* The burden of fatigue and quality of life in *myeloproliferative disorders (MPDs)*: an international internet-based survey of 1179 *MPD* patients. *Cancer.* 2007 1;109, 68-76.
37. Mesa RA, Schwager S, Radia D, Cheville A, Hussein K, Niblack J, *et al.* The Myelofibrosis Symptom Assessment Form (MFSAF): An evidence-based brief inventory to measure quality of life and symptomatic response to treatment in myelofibrosis. *Leuk Res.* 2009 Feb 26 .
38. Nussenzveig RH, Swierczek SI, Jelinek, J *et al.* Polycythemia vera is not initiated by JAK2V617F mutation *Exp.Hematol* 2007; 35:32-38.
39. Perrillo R, Rothstein KD, Rubin R, Alam I, Imperial J, Harb G, *et al.* Comparison of quality of life, work productivity and medical resource utilization of peginterferon alpha 2a vs the combination of interferon alpha 2b plus ribavirin as initial treatment in patients with chronic hepatitis C. *Journal of viral hepatitis.* 2004;11, 157-65.
40. Quintas-Cardama A, Kantarjian HM, Garcia-Manero G, Cortes J, Richie MA, Borthakur G, *et al.* Pegylated Interferon Alfa-2a (PEG-IFN- α -2A; PEGASYS) Therapy Renders High Clinical and Molecular Response Rates in Patients with Essential Thrombocythemia (ET) and Polycythemia VERA (PV). *J. Clin Oncol* 2009 27(32): 5418-24.
41. Rabin R, de Charro F. EQ-5D: a measure of health status from the *EuroQol* Group. *Ann Med.* 2001;33, 337-43.
42. Rummans TA, Clark MM, Sloan JA, Frost MH, Bostwick JM, Atherton PJ, *et al.* Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: a randomized controlled trial. *J Clin Oncol.* 2006;24, 635-42.
43. R. T. Silver. Recombinant interferon-*alpha* for treatment of polycythaemia vera *Lancet* 2 (8607):403, 1988.

44. Sterkers Y, Preudhomme C, Lai JL, *et al.* Acute myeloid leukemia and myelodysplastic syndromes following essential thrombocythemia treated with hydroxyurea: high proportion of cases with 17p deletion. *Blood* 1998;91, 616-22.
45. Sugar CA, Sturm R, Lee TT, Sherbourne CD, Olshen RA, Wells KB, *et al.* Empirically defined health states for depression from the SF-12. *Health services research*. 1998;33,911-28.
46. Swerdlow SH. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues - IARC WHO Classification of Tumours v. 2, *World Health Organization*, 2008.
47. Venables WN and Ripley BD (2002) *Modern Applied Statistics with S* (4th Ed), Springer, New York.
48. Verbeke G and Molenberghs G (2000) *Linear Mixed Models for Longitudinal Data*. Springer, New York.
49. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res*. 2005;14, 1523-32.
50. Wee CC, Davis RB, Hamel MB. Comparing the SF-12 and SF-36 health status questionnaires in patients with and without obesity. *Health and quality of life outcomes*. 2008;6, 11.
51. Xiong Z, Yan Y, Liu E, *et al.* Novel tumor antigens elicit anti-tumor humoral immune reactions in a subset of patients with polycythemia vera *Clin.Immunol* 2007; 122:279- 287.
52. Xiong Z, Yan Y, Liu E, *et al.* An unconventional antigen translated by a novel internal ribosome entry site elicits antitumor humoral immune reactions *J Immunol*. 2006; 177:4907-4916.

Appendix A: Definitions of Events

A. THROMBOTIC EVENTS

1. New infarction or recurrent myocardial infarction

Myocardial infarction is defined as the presence of two or more of the following criteria:

- a. Symptoms of cardiac ischemia
 - Characteristic ischemic chest pain in the pericardium or associated referral areas, lasting for at least 20 minutes
- b. Significant cardiac enzyme elevations
 - Elevation of CK, LDH, or AST to at least twice the upper limit of normal for the given laboratory in the absence of other explanation.
- c. EKG changes
 - Occurrence of new 40 msec Q waves in at least two adjacent EKG leads, **or** development of a new dominant R wave in V1 ($R \geq 1\text{mm} > S$ in V1) **or** of new ST elevation or depression or persistent (>48 hours) new T wave inversion.

2. Stroke and stroke type

A stroke is a new focal neurologic deficit of presumed vascular origin which persists for >24 hours or results in death within 24 hours.

Stroke type

- Hemorrhagic: A stroke caused by primary intracranial hemorrhage diagnosed by CT, MRI, or other objective means, or by autopsy.
- Ischemic: A stroke of atherothrombotic or embolic origin as diagnosed by CT, MRI or other objective means, or by autopsy
- Uncertain: A stroke not otherwise classified by the above criteria.

3. Deep vein thrombosis

A deep vein thrombosis (DVT) is defined as a typical clinical picture with positive investigation: i.e. phlebography, ultrasonography, CT in unusual sites. In case of suspected recurrence in a site of previous DVT (e.g. ipsilateral limb) diagnosis is accepted only if the investigation shows extension or recurrence of thrombosis as compared to a previous test.

4. Pulmonary embolism

A pulmonary embolism is defined as a typical clinical picture with positive angiography or high- probability V/Q scanning.

5. Thrombotic digital ischemia

Characteristic purplish discoloration of toes/fingers, which may progress to infarction if untreated. Digital ischemia may occasionally be associated with erythromelalgia.

6. Unstable angina

Defined in accordance with TIMI criteria as presence of prolonged angina or recurrent angina at rest, together with one of the following: new ST segment depression, requirement for revascularization procedure, cardiac enzyme rise to less than twice the upper limit of normal, or past history of documented coronary artery disease.

OR

Ischemic discomfort at rest lasting 5 minutes or greater and associated with at least one of the following new/presumably new ST segment elevation >0.5mm; T-wave inversion >3mm in 3 leads or left bundle branch block; cardiac enzyme rise to less than twice the upper limit of normal. (40)

7. Other thrombotic event

Thrombosis in sites not covered above. In particular, characteristic symptoms of peripheral limb ischemia with evidence of thrombosis. In addition characteristic syndromes of abdominal thrombosis for example Budd Chiari syndrome.

B. OTHER VASCULAR OCCLUSIVE EVENTS (Not major)**1. Other transient neurological event**

This is defined as the abrupt onset of poorly or non-localizing neurological symptoms such as unsteadiness, blurred vision, hearing disturbance or unstable gait.

2. Erythromelalgia

Erythromelalgia is defined as the onset of pain at the extremities associated with temperature increase and redness of the skin. Erythromelalgia usually manifests in the lower extremities and/or rarely in the hands with frequent recurrences in the same areas.

C. HEMORRHAGIC EVENTS**1. Major hemorrhage**

Overt hemorrhage associated with either:

- a decrease in hemoglobin level of at least 2g/dl, or
- a need for blood transfusion of 2 or more units of blood, or
- if hemorrhage is retroperitoneal or intracranial.

2. Minor hemorrhage

Overt hemorrhage not meeting the criteria of major hemorrhage

D. TRANSFORMATION**1. Transformation to Post ET or Post PV myelofibrosis is defined by:****Criteria for post-polycythemia vera myelofibrosis (Barosi 2008)**

Required criteria:

1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria
2. Bone marrow fibrosis grade 2–3 (on 0–3 scale) 3 or grade 3–4 (on 0–4 scale) 4

Additional criteria (two are required):

1. Anemia or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Development of 1 of three constitutional symptoms: 10% weight loss in 6 months, night sweats, unexplained fever ($> 37.5^{\circ}\text{C}$)

Criteria for post-essential thrombocythemia myelofibrosis

Required criteria:

1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria
2. Bone marrow fibrosis grade 2–3 (on 0–3 scale) 3 or grade 3–4 (on 0–4 scale) 4

Additional criteria (two are required):

1. Anemia and a ≥ 2 g/L decrease from baseline hemoglobin level
2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Increased LDH (above the baseline level and exceeding the normal reference range without other obvious cause)
5. Development of 1 of three constitutional symptoms: 10% weight loss in 6 months, night sweats, unexplained fever (37.5°C)

2. Transformation to leukemic phase is defined by:

The threshold for a diagnosis of achieving blast phase was 20% blood or marrow blasts (persisting for 4 weeks) or the presence of a acute leukemia–defining karyotypic lesions despite blast percentage (t[8;21][q22;q22], inv[16][p13;q22], t[16;16][p13;q22], or t[15;17][q22;q12])

E. DEATH

The cause of death should be given, including post mortem findings where possible.

Appendix B: ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Score Ratings

At each clinic visit after the screening visit, the investigator will assess each subject's ECOG performance status according to the following scale:

- 0 Fully active, able to carry on all pre-disease performance without restriction
- 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house-work, office work
- 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 Dead

Appendix C: NCI toxicity criteria

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix D: Symptom Assessment Package

Appendix D1: MPN Symptom Assessment Form (MPN-SAF)

Instructions: Please fill out all questions, as best able, reflecting how these symptoms affected you over the **LAST WEEK** unless directed otherwise. Complete forms until the STOP instruction toward the end of the packet.

Symptom	1 to 10 (0 if absent) ranking* 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL Level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your	
• General Activity	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Mood	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Walking ability	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Normal Work (includes work both outside the home and daily chores)	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)

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• Relations with other people	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Enjoyment of life	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)

Circle the one number that describes how, during the past Week how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early Satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal pain	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with Headaches	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with Concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Dizziness/ Vertigo/ Lightheadedness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/ Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Difficulty sleeping	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Depression or sad mood	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with Sexual Desire or Function	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Cough	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night Sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone Pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
What is your Overall Quality of Life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As bad as it can be)

Appendix D2: EORTC

ENGLISH

**EORTC QLQ-C30 (version 3)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31									
----	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

Appendix D3: Symptomatic Questions Specific for Toxicities of Pegylated interferon alfa-2a

Answer these questions in reference to how these issues affected you during the Last Week

I feel like I have the flu	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Irritation at the site I receive my injections	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
I have developed blurring in my vision	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
I have developed a change in my vision	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
I have developed flushing	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Appendix E: Medication Diaries

MEDICATION DIARY

PATIENT NAME: _____

STUDY DRUG: PEGASYS

PATIENT INSTRUCTIONS: Use this calendar to record your dose of PEGASYS and Aspirin weekly. All additional medications must be approved by your treating physician.

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
EXAMPLE ONLY	Day: Monday Date: 5/2/2011 Amount of PEGASYS: 45mcg Aspirin: 80mg <input checked="" type="checkbox"/> Mon <input checked="" type="checkbox"/> Tues <input checked="" type="checkbox"/> Wed <input checked="" type="checkbox"/> Thurs <input checked="" type="checkbox"/> Fri <input checked="" type="checkbox"/> Sat <input checked="" type="checkbox"/> Sun	EXAMPLE ONLY	EXAMPLE ONLY	EXAMPLE ONLY	EXAMPLE ONLY
Day: _____ Date: _____ Amount of PEGASYS: _____ mcg Aspirin: _____ mg <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun	Day: _____ Date: _____ Amount of PEGASYS: _____ mcg Aspirin: _____ mg <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun	Day: _____ Date: _____ Amount of PEGASYS: _____ mcg Aspirin: _____ mg <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun	Day: _____ Date: _____ Amount of PEGASYS: _____ mcg Aspirin: _____ mg <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun	Day: _____ Date: _____ Amount of PEGASYS: _____ mcg Aspirin: _____ mg <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun	Day: _____ Date: _____ Amount of PEGASYS: _____ mcg Aspirin: _____ mg <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun
Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Day: _____ Date: _____ Amount of PEGASYS: _____ mcg Aspirin: _____ mg <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun	Day: _____ Date: _____ Amount of PEGASYS: _____ mcg Aspirin: _____ mg <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun	Day: _____ Date: _____ Amount of PEGASYS: _____ mcg Aspirin: _____ mg <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun	Day: _____ Date: _____ Amount of PEGASYS: _____ mcg Aspirin: _____ mg <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun	Day: _____ Date: _____ Amount of PEGASYS: _____ mcg Aspirin: _____ mg <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun	Day: _____ Date: _____ Amount of PEGASYS: _____ mcg Aspirin: _____ mg <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun

PATIENT SIGNATURE: _____

MEDICATION DIARY

PATIENT NAME: _____

STUDY DRUG: Hydroxyurea

Start Date: ____/____/____ End Date: ____/____/____ (MM/DD/YYYY)

PATIENT INSTRUCTIONS: Use this calendar to record your dose of Hydroxyurea and Aspirin daily. All additional medications must be approved by your treating physician.

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
EXAMPLE ONLY	Hydroxyurea: 500mg ____ 3 ____ (capsules) Aspirin: ____ 80 ____ mg	Hydroxyurea: 500mg ____ 3 ____ (capsules) Aspirin: ____ 80 ____ mg	Hydroxyurea: 500mg ____ 3 ____ (capsules) Aspirin: ____ 80 ____ mg	EXAMPLE ONLY	EXAMPLE ONLY	EXAMPLE ONLY
Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg
Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg
Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg
Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg	Hydroxyurea: 500mg ____ (capsules) Aspirin: ____ mg

PATIENT SIGNATURE: _____

Appendix F: NCI DARE

Collection of this information is authorized under 21 CFR 312.57. The information is collected to ensure compliance with Food and Drug Administration (FDA) requirements for NCI as an IND sponsor and that investigational agents are under the control and accounted for by competent authority. The information may be disclosed to researchers for investigational purposes, sponsors of clinical trials and their company collaborators, the applicable Institutional Review Board, NCI, FDA, and the Department of Health and Human Services. Submission of this information is voluntary however, in order for you to conduct a study in accordance with relevant, current protocols, you must complete all fields.

OMB No. 0925-0613
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Public reporting burden for this collection of information is estimated to average 4 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. **An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.** Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: NIH, Project Clearance Branch, 6705 Rockledge Drive, MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0613). Do not return the completed form to this address.

National Institutes of Health National Cancer Institute	Division of Cancer Treatment and Diagnosis Cancer Therapy Evaluation Program	PAGE NO. CONTROL RECORD <input type="checkbox"/> SATELLITE RECORD <input type="checkbox"/>
Investigational Agent Accountability Record		
Name of Institution:	NCI Protocol No.:	
Agent Name:	Dose Form and Strength:	
Protocol Title:	Dispensing Area:	
Investigator Name:	CTEP Investigator ID:	

Line No.	Date	Patient's Initials	Patient's ID No.	Dose	Quantity Dispensed or Received	Balance Forward	Manufacturer and Lot No.	Recorder's Initials
						Balance		
1.								
2.								
3.								
4.								
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6.								
7.								
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