Official Title: A Phase 2, Prospective Study Of PRM-151 In Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera MF (post-PV MF), OR Post-Essential Thrombocythemia MF (post-ET MF)

NCT Number: NCT01981850

Document Date: Protocol Version 6: 15-December-2016

Clinical Trial Protocol: Study PRM-151G-101

Study Title:	A Phase 2, Prospective Study Of PRM-151 In Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera MF (post-PV MF), Or Post-Essential Thrombocythemia MF (post-ET MF)
Study Number:	PRM-151G-101
Study Phase:	2
Product Name:	PRM-151
IND Number:	116,932
EudraCT Number:	2015-001718-80
Indication:	Primary Myelofibrosis (PMF), Post-Polycythemia Vera MF (post-PV MF), Or Post-Essential Thrombocythemia MF (post-ET MF)
Sponsor:	Promedior, Inc. 101 Hartwell Ave. Lexington, MA 02421 Tel: 1-781-538-4200 Fax: 1-781-538-4300
Sponsor Contact:	[redacted], RN
Medical Director:	[redacted], MD, PhD

	Date
Original Protocol:	Version 1.0 17 Jan 2013
Amendment 1:	Version 2.0 22 Feb 2013
Amendment 2:	Version 3.0 10 May 2013
Amendment 3:	Version 4.0 14 Feb 2014
Amendment 4:	Version 5.0 04 May 2015
Amendment 5:	Version 5.1 UK 09 Nov 2015
Amendment 6:	Version 5.1 France 08 Aug 2016

Amendment 7: **Version 6.0** 15 Dec 2016

SYNOPSIS: STAGE 2

Sponsor:
Promedior, Inc.

Name of Finished Product:
Recombinant human Pentraxin-2; PRM-151

Study Title:
A Phase 2, Prospective Study Of PRM-151 In Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera MF (post-PV MF), Or Post-Essential Thrombocythemia MF (post-ET MF)

Study Number:
PRM-151G-101

Study Phase: Phase 2

Investigational Product; Dose; and Mode of Administration:
PRM-151; 0.3 mg/kg; 3 mg/kg and 10 mg/kg intravenous

Comparator; Dose; and Mode of Administration:
Not applicable

Primary Objectives(s):

- To determine the effect size of three different doses of PRM-151 on reduction in bone marrow fibrosis by $\geq$ 1 grade in intermediate-1, intermediate-2, and high risk subjects with PMF, post-PV MF, or post ET-MF who are anemic or thrombocytopenic and who are ineligible for, intolerant of, or have had an inadequate response to ruxolitinib.

Secondary Objective(s):

- To determine if there is a difference in efficacy between the three doses of PRM-151 used in the study
- To evaluate the safety and tolerability of three different does of PRM-151
- To assess the duration of effect of three doses of PRM-151 on reduction in bone marrow fibrosis
- To assess the effect and duration of effect of three doses of PRM-151 on disease related anemia, thrombocytopenia, and constitutional symptoms
- To assess IWG-MRT response (Complete Response, Partial Response, Clinical Improvement), stable and progressive disease in subjects treated with three doses of PRM-151

Exploratory Objectives

- To measure changes in bone marrow fibrosis by quantitative image analysis and evaluate changes in bone marrow morphology in subjects receiving PRM-151
- To assess the effect of PRM-151 on other disease related parameters, including hematologic abnormalities and spleen size
- To assess the effect of PRM-151 on prognostic factors associated with increased mortality as measured by the DIPSS (Dynamic International Prognostic Scoring System)
- To evaluate the interaction between selected genetic mutations and cytogenetic abnormalities and response to PRM-151
- To explore potential biomarkers of PRM-151 activity in bone marrow samples
- To assess the effect of PRM-151 on bone marrow metabolism by PET imaging (at selected institutions)
- To evaluate the correlation of baseline PTX-2 levels with outcomes
- To evaluate the relationship between bone marrow fibrosis reduction and hematologic improvements in subjects treated with PRM-151
- To measure progression-free and overall survival in subjects receiving PRM-151

Study Endpoints:

Primary:

- Bone marrow response rate, defined as the percent of subjects with a reduction in bone marrow fibrosis score by at least one grade according to WHO criteria (APPENDIX D) at any time during the study as determined by a central adjudication panel of expert hematopathologists, blinded to subject, treatment, and time of biopsy

Secondary:

- Comparison of primary and secondary efficacy parameters between doses
- Incidence of adverse events (AEs), serious adverse events (SAEs), and changes in laboratory test results
- Bone marrow improvement:

- Bone marrow response rate at weeks 12, 24, and 36
- Duration of bone marrow response

- Hemoglobin improvement

Baseline Status	Categories of Hemoglobin Improvement
Subjects who are transfusion dependent (≥ 2 units PRBC every 4 weeks for 12 weeks prior to or after C1D1), regardless of baseline hemoglobin level	Percent of subjects with Red cell transfusion independence (no transfusions for ≥ 12 consecutive weeks) OR 50% reduction in RBC transfusions for ≥ 12 consecutive weeks
Subjects with baseline hemoglobin < 100 g/L AND Not transfusion dependent	Percent of subjects with ≥ 10 g/L and ≥ 20 g/L increase in hemoglobin for ≥ 12 consecutive weeks without transfusions

- Platelet improvement:

Baseline Status	Categories of Platelet Improvement
Subjects who are transfusion dependent (≥ 2 platelet transfusions in any 12 weeks prior to or after C1D1), regardless of baseline platelet level Platelet transfusion = either 1 unit apheresed (single donor) platelets or 4-8 units pooled random donor platelets	Percent of subjects with: Platelet transfusion independence (no transfusions for ≥ 12 consecutive weeks) OR 50% reduction in platelets transfusions for ≥ 12 consecutive weeks
Subjects with 25 < baseline platelets < 50 x 10^9/L AND Not platelet transfusion dependent	Percent of subjects with: Doubling of baseline platelet count for ≥ 12 consecutive weeks without platelet transfusions OR Platelet count > 50 x 10^9/L for ≥ 12 consecutive weeks without platelet transfusions
Subjects with baseline platelet count < 25 x 10^9/L AND Not platelet transfusion dependent	Percent of subjects with: Doubling of baseline platelet count for ≥ 12 consecutive weeks without platelet transfusions OR

	Platelet count > 25 x 10^9/L for ≥ 12 consecutive weeks without platelet transfusions

- Hematologic improvement:

Baseline Status	**Categories of Hematologic Improvement**
Subjects with both Hemoglobin < 100 g/L and Platelets < 50 x 10^9/L	Percent of subjects who have **EITHER** Hemoglobin improvement **OR** Platelet improvement as described above and no worsening of hemoglobin or platelets from baseline
Subjects with only Hemoglobin < 100 g/L	Percent of subjects who have Hemoglobin improvement as described above **AND** Did not develop platelets < 50 x 10^9/L
Subjects with only Platelets < 50 x 109/L	Percent of subjects who have Platelet improvement as described above AND Did not develop Hemoglobin < 100 g/L or new transfusion dependence

- Symptom improvement:
    - Percent of subjects with 25% and 50% reduction in MPN-SAF Total Symptom Score from baseline at Week 36
    - Mean change from baseline at EORTC QLQ-C30 at 36 weeks
- Duration of all improvement parameters listed above
- Percent of subjects with complete response, partial response, clinical improvement, stable disease, and progressive disease according to IWG-MRT criteria (Tefferi 2013, APPENDIX B)

Exploratory:

- Bone marrow
    - Percent of subjects with Grade 0-1 bone marrow fibrosis grade at any time during the study and at weeks 12, 24, and 36

- Duration of Grade 0-1 bone marrow fibrosis grade
- Mean change from baseline to 12, 24, and 36 weeks in bone marrow fibrosis by quantitative image analysis
- Changes from baseline to weeks 12, 24, and 36 in bone marrow metabolism by FDG or FLT PET scan (where feasible)
- Assessment of changes in bone marrow morphology at 12, 24, and 36 weeks

- Hematologic and other disease related laboratory parameters
  - Mean change from baseline to 36 weeks in: hemoglobin, # RBC units transfused in previous 12 weeks, platelet count, # platelet transfusions in previous 12 weeks, white blood cell count, absolute neutrophil count, reticulocyte count, peripheral blood blast count, and lactic dehydrogenase (LDH)
  - Percent of subjects with increase in Hgb from < 100 g/L to > 100g/L without transfusions, increase in platelets from < 50 x 10^9/L to > 100 x 10^9/L, decrease in WBC from > 25 to < 25, increase in ANC from < 1500 to $\geq$ 1500, decrease in peripheral blood blasts from > 1% to < 1%, and disappearance of leukoerythroblastosis, at 36 weeks and for $\geq$ 12 weeks at any time during the study
  - Duration of increase in Hgb from < 100 g/L to > 100 g/L without transfusions, increase in platelets from < 50 x 10^9/L to > 100 x 10^9/L, decrease in WBC from > 25 to < 25, increase in ANC from < 1500, to $\geq$ 1500, decrease in peripheral blood blasts from > 1% to < 1%, and disappearance of leukoerythroblastosis

- Spleen improvement:
  - Percent of subjects with 10% and 35% reduction in spleen size from baseline by CT at 36 weeks
  - Duration of 10% and 35% reduction in spleen size from baseline
  - Mean change from baseline in spleen size by CT or MRI at 36 weeks
  - Change in spleen and liver metabolism by FDG or FLT PET scan at 12, 24, and 36 weeks

- DIPSS
  - Percent of subjects with a reduction in DIPSS score and category at week 36
  - Mean change in DIPSS score from baseline to Week 36

- Mutational Status and Cytogenetics
    - Association of baseline mutational status of JAK2V617F, MPLW515, Calreticulin, ASXLI, EZH2, SRSF2, IDH1/2 with selected primary and secondary endpoints
    - Changes in allele burden of JAK2V617F at week 36. Changes in allele burden of MPLW515, Calreticulin, ASXLI, EZH2, SRSF2, IDH1/2 at week 36 will be measured as commercially available assays become available
    - Association of baseline cytogenetic abnormalities and selected primary and secondary endpoints
- Association of baseline PTX-2 levels with selected primary and secondary endpoints
- Evaluation of potential biomarkers of PRM-151 activity in bone marrow biopsies taken at baseline, weeks 12, 24, and 36
- Measurement of progression-free and overall survival

Stage 2 Study Design:
This is a randomized, double-blind Phase 2 study to determine the efficacy and safety of three different does of PRM-151 in subjects with PMF and post ET/PV MF. Subjects will be randomized to one of three doses: 0.3 mg/kg, 3.0 mg/kg or 10 mg/kg of PRM-151. This is the second stage of an adaptive design study as defined in FDA Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics, February 2010. Modifications to dose levels, schedule, and regimen have been made in Stage 2 based on data from Stage 1.

Approximately 84 subjects with intermediate-1, intermediate-2, or high risk MF who meet study eligibility requirements will be enrolled and randomized to treatment with single agent PRM-151 at doses of 0.3, 3, or 10 mg/kg IV on Days 1, 3, and 5 of Cycle 1 and Day 1 of each subsequent 28 day cycle for nine cycles. The randomization will be stratified according to type of subject (subjects with Hgb < 100 g/L and having received $\geq$ 2 units PRBC in the 12 weeks prior to study entry OR subjects with platelet count < 50 x 10^9/L) and will ensure that the final study population will include at least 50% of subjects from the second stratum (platelet count < 50 x 10^9/L). As outlined in APPENDIX J, all subjects completing 9 cycles of the originally assigned treatment may switch to an open label extension and receive PRM-151 10 mg/kg every 4 weeks.

The first cycle of the open label phase contains a loading dose of 10 mg/kg on days 1, 3, and 5. This will allow for subjects from all three dosing cohorts to receive a loading dose of 10 mg/kg while maintaining the blind. Additionally, subjects who have entered the open label extension study prior to the approval of this amendment may receive a loading dose (10 mg/kg on days 1, 3, and 5), to be administered on their next scheduled cycle after approval of this protocol amendment. This will allow for these subjects to receive any potential pharmacologic benefit of the loading dose.
As of 14-Nov 16, we have blinded safety data, although limited, on 21 subjects receiving a similar 10 mg/kg loading dose in the open label of the PRM-151-202 IPF study after 24 weeks of exposure to PRM-151 or placebo in 2:1 ratio. No incremental risk has been reported in these subjects.

Subjects enrolled in the open-label phase extension protocol of Stage 1 should continue to follow the study procedures outlined in APPENDIX L.
Enrolled subjects will be considered evaluable for response if they are on study drug for at least twelve weeks.

Study Duration:
Each subject will participate in the study for approximately 44 weeks. Participation will include a screening evaluation within four weeks prior to the first PRM-151 administration, nine study cycles of four weeks each, and an end of study visit four weeks after the end of the last cycle. After completion of 9 cycles, subjects may continue with PRM-151 dosing in the open label extension in the absence of disease progression or toxicity warranting discontinuation of therapy.
It is estimated that the study will be completed in approximately 18 months.

Study Inclusion and Exclusion Criteria: Inclusion Criteria:

1. Subjects must be ≥ 18 years of age at the time of signing the Informed Consent Form (ICF);
2. Subjects must voluntarily sign an ICF;
3. Subjects must have a pathologically confirmed diagnosis of PMF as per the WHO diagnostic criteria (APPENDIX C) or post ET/PV MF;
4. At least Grade 2 marrow fibrosis according to the WHO Grading of Bone Marrow Fibrosis (APPENDIX D);
5. Intermediate -1, intermediate -2, or high risk disease according to the IWG-MRT Dynamic International Prognostic Scoring System (APPENDIX E);
6. A bone marrow biopsy must be performed within four weeks prior to Cycle 1 Day 1 treatment to establish the baseline fibrosis score;
7. Subjects must not be candidates for ruxolitinib based on EITHER:
    a. Platelet count < 50 x 10^9/L, OR
    b. Hgb < 100 g/L have received ≥ 2 units PRBC in the 12 weeks prior to study entry, and be intolerant of or had inadequate response to ruxolitinib;
8. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2 (APPENDIX F);
9. Life expectancy of at least twelve months;
10. At least four weeks must have elapsed between the last dose of any MF-directed drug treatments for myelofibrosis (including investigational therapies) and study enrollment;
11. Recovery to ≤ Grade 1 or baseline of any toxicities due to prior systemic treatments, excluding alopecia;
12. Women of child bearing potential (WCBP), defined as a sexually mature woman not surgically sterilized or not post-menopausal for at least 24 consecutive months if ≤ 55 years or 12 months if > 55 years, must have a negative serum pregnancy test within four weeks prior to the first dose of study drug and must agree to use highly effective methods of birth control throughout the study. Highly effective methods of contraception include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation by oral, intravaginal, or transdermal administration; progestogen-only hormonal contraception associated with inhibition of ovulation by oral, injectable, or implantable administration; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; partner vasectomy, and total abstinence (only if total abstinence is the preferred method and usual lifestyle of the subject). Adequate contraceptive use should be continued until 28 days after the final dose of the study drug.
13. Ability to adhere to the study visit schedule and all protocol requirements;
14. Must have adequate organ function as demonstrated by the following:

    - ALT (SGPT) and/or AST (SGOT) ≤ 3 x upper limit of normal (ULN), or ≤ 4 x ULN (if upon judgment of the treating physician, it is believed to be due to extramedullary hematopoiesis [EMH] related to MF);
    - Direct bilirubin ≤ 1.5 x ULN; or ≤ 2 x ULN (if upon judgment of the treating physician, it is believed to be related to MF);

- Serum creatinine ≤ 2.5 x ULN.

Exclusion Criteria:

1. White blood cell count > 25 x 10^9/L or >10% peripheral blood blasts;
2. Other invasive malignancies within the last 3 years, except non-melanoma skin cancer and localized cured prostate and cervical cancer;
3. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months;
4. Presence of active serious infection;
5. Any serious, unstable medical or psychiatric condition that would prevent, (as judged by the Investigator) the subject from signing the informed consent form or any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study;
6. Known history of human immunodeficiency virus (HIV), or known active hepatitis A, B, or C infection;
7. Organ transplant recipients other than bone marrow transplant;
8. Women who are pregnant or lactating.

Efficacy Assessments:
Efficacy will be assessed by evaluation of WHO bone marrow fibrosis grade, changes in hemoglobin, platelets, peripheral blood blasts, disease related symptoms, and spleen size.

Safety Assessments:
Safety will be evaluated from reported adverse events, scheduled physical examinations, vital signs, and clinical laboratory test results.

A blinded DMC will be established to review safety data from this study, thereby better ensuring the safety of study participants. Consistent with US Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry, Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006), the DMC will be constituted of independent clinicians expert in the field of MF and clinical research. A formal charter will be established for the conduct of the DMC.

- The committee is planned to review the safety data in a blinded manner, but a procedure will be in place to allow the committee an immediate unblinding of either specific cases or of the whole study in case of detection of a potential safety signal necessitating an unblinded review of some (or all) subjects.

Statistical Methods:

General considerations:
Continuous variables will be summarized by dose group with descriptive statistics (e.g., number of observations, number of missing observations, mean, standard deviation [SD], median, interquartile range, maximum, and minimum). Categorical variables will be tabulated by frequency of subjects per dose group, and percentages will be calculated using the number of available observations as the denominator (i.e. excluding missing values).

Determination of Sample Size
The chosen sample size of 72 subjects (i.e. 24 subjects per dose arm) is deemed sufficient to provide adequate precision to the estimation of the response rate in each treatment arm. The trial will enroll 84 subjects to allow for a discontinuation rate of 15%.

Considerations on the precision of estimate and the power for comparisons planned as secondary analyses are provided in the body of the protocol.

Randomization and Stratification

This study is randomized with a 1:1:1 randomization ratio. A central randomization system will be used. The randomization will be stratified according to the subjects' baseline haematologic status: baseline anemia alone or baseline thrombocytopenia or baseline anemia associated with baseline thrombocytopenia. The randomization system will also ensure that at least 50% of the subjects in the final study population will have baseline thrombocytopenia.

Missing values:

All available efficacy and safety data will be included in data listings and tabulations.

For the primary efficacy criterion, subjects with a reduction in bone marrow fibrosis score by at least one grade according to WHO criteria (central adjudication) at any post baseline visit will be considered as responders. Subjects without any central assessment of bone marrow fibrosis will be considered as non-responders. In addition, subjects who discontinue due to toxicity prior to completion of one cycle of study drug will be also considered non-responders for the efficacy analyses.

All other analyses will be based on observed data only; no missing data will be imputed.

Efficacy analysis populations:
The primary efficacy analysis will be conducted on the Full Analysis Set (FAS; all randomized subjects having received at least one administration of the study medication with at least one post-baseline assessment of BMRR (primary efficacy criterion) available. Subjects who discontinue due to toxicity prior to completion of one cycle of study drug will also be kept in the FAS and considered non-responders for the efficacy analysis). A per-protocol analysis will also be carried out on the Per Protocol (PP) set, a subset of the FAS composed of all subjects treated with the investigational medicinal product (IMP), having received at least the planned IMP infusions on days 1, 3, 5, and weeks 4 ,8, and 12 and who did not present any major protocol deviations.

The per-protocol set will be used for secondary analyses of the primary efficacy criterion and for the analysis of some selected secondary efficacy criteria.

Primary analysis of efficacy
The primary efficacy analysis will consist in computing the bone marrow response rate (percent of subjects with a reduction in bone marrow fibrosis score by at least one grade) and its 97.5% two-sided confidence interval within each treatment arm. This analysis will be conducted on the FAS analysis set.

Inferential interpretation: for the 3 mg/kg and 10 mg/kg arms, the lower limit of the 97.5% two-sided confidence interval will be compared to 10%, a threshold assumed to define the minimal clinically relevant effect. If the lower limit of the confidence interval is above 10%, the corresponding dose will be claimed to have demonstrated clinically relevant efficacy.

The confidence intervals computation will use a method consistent with the stratified design.

Comparison of PRR between treatment arms at week 36
Pairwise comparisons between the three dose groups will be performed using the Cochran-Mantel-Haenszel (general association) statistic in the SAS Freq procedure, to take into account the stratified design.

Two pairwise comparisons (3 mg/kg versus 0.3 mg/day and 10 mg/kg versus 0.3 mg/day) will be computed with the aim to demonstrating superiority and, consequently, will use an adjusted a two-sided 0.025 level of significance.

The third comparison (10 mg/kg versus 3 mg/kg) is not expected to have enough power to demonstrate any difference with the planned sample size. This comparison is considered exploratory and will be conducted using an unadjusted 0.05 level of significance.

Other efficacy analyses: Sensitivity efficacy analysis, secondary efficacy analyses and exploratory efficacy analyses: see body of the protocol.

Safety analyses: see body of the protocol.

Date of Original Protocol: Version 1.0 – 17 Jan 2013

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AUC ($AUC_{0-\infty}$)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC (AUC_{0-24})	area under the concentration-time curve from time zero extrapolated to 24 hours
AST	aspartate aminotransferase
ASXLI	additional sex combs like transcriptional regulator 1
BUN	blood urea nitrogen
C	Centigrade
CBC	complete blood count
CFR	Code of Federal Regulations
CI	clinical improvement
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
C_{max}	maximum observed concentration
CPK	creatine phosphokinase
CR	complete remission
CRA	Clinical Research Associate
CRF	case report form
CRO	Contract Research Organization
CRP	C reactive protein
CSA	Clinical Study Agreement
CTC	common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
DIPPS	Dynamic International Prognostic Scoring System
dL	Deciliter
EC	ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
eCRF	electronic case report form
e.g.	exempli gratia (for example)
EMH	extramedullary hematopoiesis
ET	essential thrombocytopenia
EZH2	enhancer of zeste 2 polycomb repressive complex 2 subunit
FDA	Food and Drug Administration
G-CSF	granulocyte colony stimulating factor

GCP	Good Clinical Practice
GM-CSF	granulocyte microphage colony stimulating factor
Hct	Hematocrit
Hgb	Hemoglobin
Hr	Hour
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council on Harmonisation
IDH ½	isocitrate dehydrogenase ½ genes
IEC	independent ethics committee
IND	Investigational New Drug
INR	international normalized ratio
IPF	idiopathic primary fibrosis
IRB	institutional review board
IU	international unit
IV	intravenous, intravenously
IRS	interactive response system
IWG	International Working Group
JAK	Janus kinase
Kg	Kilograms
LCM	Lower costal margin
LDH	lactate dehydrogenase
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
Mg	Milligrams
mL	Milliliter
MPN-SAF	myeloproliferative neoplasm symptom assessment form
Mreg	Macrophage in a protective regulatory state
MSCs	mesenchymal stromal cells
n	Number
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
OLE	open label extension
ORR	overall response rate
PD	progressive disease
PK	pharmacokinetic(s)
PMF	primary myelofibrosis
PR	partial remission
PRBC	packed red blood cells
PT	prothrombin time
PTT	partial thromboplastin time
PTX-2	pentraxin-2

PV	polycythemia vera
QOL	quality of life
QTc	corrected QT interval
RBC	red blood cell
REB	Research Ethics Board
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan; Serum Amyloid Protein
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SRSF2	Serine/Arginine-Rich Splicing Factor 2
TGF β1	transforming growth factor beta 1
TKI	tyrosine kinase inhibitor
t_{max}	time of maximum observed concentration
ULN	Upper limit of normal
UUO	unilateral ureteral obstruction
V_d	volume of distribution
WBC	white blood cell
WCBP	women of child-bearing potential
WHO-DD	World Health Organization Drug Dictionary
w/v	weight/volume

1. INTRODUCTION AND STUDY RATIONALE

1.1. Overview

Pentraxin-2 (PTX-2), also called Serum Amyloid Protein (SAP) is an endogenous protein that circulates in the bloodstream. Recent discoveries about the biology of tissue repair and fibrosis have elucidated the important role that PTX-2 plays biologically in regulating processes that relate to scar prevention and healing. PTX-2 is an agonist that binds to Fc gamma receptors on monocytes and promotes their differentiation into regulatory macrophages (Mreg), which function to promote epithelial healing and resolution of inflammation and scarring. PTX-2 also prevents the differentiation of monocytes into M2 pro-fibrotic macrophages and fibrocytes, preventing the formation of fibrosis. PRM-151 is a recombinant human PTX-2. Pre-clinical and clinical data exist to support the investigation of PRM-151 in the treatment of fibrotic diseases.

Myelofibrosis [including Primary Myelofibrosis (MF), Post-Polycythemia Vera (PV) MF and Post-Essential Thrombocythemia (ET) MF] is a clonal myeloprolilferative neoplasm, characterized by progressive bone marrow fibrosis and subsequent ineffective erythropoiesis, dysplastic megakaryocyte hyperplasia, and extramedullary hematopoiesis. The typical clinical presentation includes marked splenomegaly, progressive anemia, and constitutional symptoms. Bone marrow transplant is the only treatment that can cure subjects with MF, but is associated with high morbidity and mortality (Stewart, Pearce et al. 2010); (Ballen 2012). Bone marrow fibrosis resolves in subjects after successful transplant as early as one month (Przepiorka, Giralt et al. 1998).

Until recently, there was no approved medical therapy for MF and most subjects were managed with various combinations of growth factors, immunomodulatory agents, cytotoxic chemotherapy, and steroids. None of these therapies produced significant responses in the majority of subjects. For this reason, no medication has been approved for MF until recently.

Ruxolitinib is a Janus kinase inhibitor, recently approved in the US and EU for the treatment of subjects with intermediate or high-risk myelofibrosis, including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF) and post-essential thrombocythemia (post-ET MF) (JAKAFI® Full Prescribing Information 2011). Treatment with ruxolitinib results in reduction in spleen volume and improvement in constitutional symptoms, but does not appear to have an effect on bone marrow fibrosis, and symptoms return within one week of discontinuing the drug. (Verstovsek 2012). Other Janus kinase inhibitors are in clinical development. There is a clear unmet medical need for new therapies that could improve bone marrow fibrosis in subjects with myelofibrosis with a resultant improvement in blood counts and other disease-related factors.

1.2. Preclinical Experience

1.2.1. Pharmacology

Following the initial *in vitro* discovery by Gomer and Pilling suggesting that PTX-2 may regulate monocyte differentiation into spindle shaped fibrocytes (Pilling, Buckley et al. 2003), they, with others, published several studies on the activity of species-specific serum-derived PTX-2 in preventing fibrosis in models of bleomycin-induced lung fibrosis in rats and mice and also in a model of ischemia reperfusion injury to mouse heart (Pilling, Roife et al. 2007), (Haudek, Xia et al. 2006). Promedior and its collaborators have expanded the animal fibrosis model data using human serum-derived PTX-2 and PRM-151 to demonstrate potent anti-fibrotic activity in models of lung injury, skin injury, kidney injury, liver injury, radiation-induced injury, and a rabbit trabeculectomy model of eye injury.

1.2.2 Nonclinical Metabolism and Pharmacokinetics

Promedior, Inc. has used species-specific analytical methods to study the pharmacokinetics of human serum-derived PTX-2 and PRM-151 in mice, rats, rabbits, and cynomolgus monkeys by different routes of administration. Dose-proportional increases in systemic exposure of human PTX-2 have been observed in rats following IV dosing. Additionally, the pharmacokinetics of PTX-2 and PRM-151 in rats were compared and found to be equivalent. In multiple—dose studies, no differences in pharmacokinetic parameters were observed between the first and last dose following two doses of PTX-2 in rats and five doses of PRM-151 in rabbits. Further, the pharmacokinetics of IV-dosed PRM-151 in monkeys was shown to be comparable to other mammalian species.

The $t_{1/2}$ of IV-dosed PTX-2/PRM-151 (2-7 mg/kg) has been calculated for multiple species, with the following results: mouse (4-8 hr) < rabbit (7.3 hr) < monkey (6-15 hr) < rat (13-23 hr) < human (30 hr, [human $t_{1/2}$ from Promedior single, ascending dose study, PRM151A-11EU; 10 mg/kg dose in healthy volunteers]) (Hawkins and Pepys 1990).

1.2.3. Toxicology

PRM-151 has been tested in an *in vitro* blood compatibility study and found to be non-hemolytic. No dose-limiting toxicity was observed following single – or 5-day repeated-dosing of PRM-151 in rats or mice up to the limit dose of 200 mg/kg. Intravenous dosing of PRM-151 to CD-1 mice produced a strong immunogenic response following the third weekly dose. As a result of this immunogenicity, rats were used as the rodent species for subsequent repeated-dosing toxicity studies. In a cynomolgus monkey dose range-finding study, renal toxicity was identified in one out of four animals at the end of the single, escalating dose portion of the study. Due to the design of the study, a definitive no observed adverse effect level (NOAEL) could not be determined. Based on findings from the dose range-finding study, the top dose for the definitive repeat-dose study in monkeys was reduced to 120 mg/kg.

A definitive 14-day intravenous dose study in Sprague Dawley rats demonstrated no adverse toxicological effects at doses ranging from 10 to 200 mg/kg/day. Neurobehavioral evaluations (functional observational battery) conducted during this study identified no treatment-related

findings. No adverse toxicological effects were identified in a definitive 14-day intravenous dose study in cynomolgus monkeys at doses ranging from 12 to 120 mg/kg/day. Histological examination of the kidneys identified no renal toxicity in any of the 28 study animals dosed for 14 days with PRM-151. Electrocardiography measurements collected during this study were qualitatively and quantitatively normal with no abnormalities in rhythm.

In chronic toxicology studies in Sprague Dawley rats (1368-010) and cynomolgus monkeys (1368-011), PRM-151 was initially dosed at 50, 100, and 200 mg/kg IV bolus on Days 1, 3, 5, 8 and weekly thereafter for 26 weeks. Findings from the rat study (1368-010) and the monkey study (1368-011) included signs and symptoms in both rats and monkeys consistent with acute infusion reactions at 50 mg/kg, 100 mg/kg and 200 mg/kg dose levels. These reactions were observed at all time points in the rat, with deaths occurring on days 15 and 22. Following a modification of the protocol to reduce the highest dose to 150 mg/kg and to lengthen the infusion time from 5 minutes to 30 minutes, infusion reactions were significantly decreased and no further deaths occurred.

Acute reactions in the monkey chronic toxicology study (1368-011) were first observed at the 200 mg/kg dose level on day 15, with continued occurrence on Days 15, 22, and 29. Most reactions resolved within ten minutes with therapeutic diphenhydramine, but deaths of two monkeys, one at 50 and one at 100 mg/kg, resulted in termination of the study.

These findings were unexpected because no acute infusion reactions, dose limiting toxicities, or deaths occurred in two prior GLP studies of 14 consecutive daily doses of PRM-151 in rats and monkeys, and because PRM-151 has already been administered safely to humans (as a single dose to 18 healthy volunteers and 3 subjects with idiopathic pulmonary fibrosis (IPF) and for multiple doses on days 1, 3, 5, 8 and 15 to 15 subjects with idiopathic pulmonary fibrosis). In studies 1368-010 and 1368-011, PRM-151 manufactured at CMC Biologics at the 2500 L scale and formulated at the testing site was administered to rats and monkeys on days 1, 3, 5, 8 and weekly thereafter. In prior GLP toxicology studies, PRM-151 DS manufactured at Catalent Biosciences at the 200 L scale with no additional formulation was administered to rats and monkeys on days 1-14. Both prior clinical studies utilized GMP drug product manufactured at Catalent Biosciences at the 200 L scale. To determine if the unexpected findings in studies 1368-010 and 1368-011 were due to differences in drug product or to differences in dosing schedule, and to explore mitigation of acute reactions by slower infusion rates, study 1368-012 was conducted.

Study 1368-012 in rats, assessed the frequency and severity of acute infusion reactions to both formulations of PRM-151 on both daily and weekly dosing schedules, and investigated the benefit of slower infusion rates in mitigation of acute toxicity. Animals in all arms received 200 mg/kg of PRM-151. Severe acute infusion reactions and deaths identical to the events in study 1368-010 occurred only on the intermittent bolus schedules and with all forms of PRM-151, indicating that the unexpected acute infusion reactions and deaths observed in studies 1368-010 and 1368-011 were due to intermittent dosing rather than product differences. Prolonging the rate of infusion to 60 minutes significantly reduced the frequency and severity of infusion

reactions and no deaths occurred in animals receiving PRM-151 at the 60 minute infusion rate. The increased toxicity with intermittent dosing is most likely due to enhanced immunogenicity in the context of cross-species reactivity to a foreign protein. Immunogenicity of human proteins in animals is generally not predictive of reactions in humans.

In the Phase 1 ascending, single IV-dose study in humans (described in 1.3.1), a 10 mg/kg dose produced a mean AUC $_{0-\infty}$ 3,005 µg*/hr/mL. Following the first IV dose in the 14-day toxicology studies, AUC $_{0-24}$ was 16,237 µg*/hr/mL in rats and 8,081 µg*hr/mL in monkeys, establishing safety margins of 5.4-fold and 2.7-fold, respectively. Due to the design of the 14-day toxicology studies (daily dosing), AUC $_{0-\infty}$ could not be calculated, and the AUC $_{0-24}$ is an underestimation of total systemic exposure. Therefore, these calculated safety margins are expected to be conservative estimates.

1.3. Clinical Experience

PRM-151 has been evaluated in humans by intravenous administration in a Phase 1, single-ascending dose study in healthy subjects and subjects with idiopathic pulmonary fibrosis (IPF; PRM151A-11EU) and in a Phase 1, Multiple Ascending Dose Study in subjects with IPF (PRM151F-12GL) and in Stage 1 of PRM-151G-101, PRM-151 has also been evaluated in humans as a sub-conjunctival injection in a randomized, double-masked, placebo-controlled study of PRM-151 in the Prevention of Postoperative Scarring in Glaucoma Subjects Following Primary Trabeculectomy (PRM151B-21GL). The relevance to humans of acute infusion reactions observed in ongoing non-clinical toxicology studies is unknown; the reactions occurred at doses significantly higher than the dose intended in this study, and in vivo studies of recombinant human proteins in conventional animals are not particularly useful to access the immunogenicity and risk of hypersensitivity reactions in humans since they are foreign to the animals. In Stage 1 of PRM-151G-101, two subjects each experienced a single, non-serious, Grade 2 hypersensitivity event, related to PRM-151. Both events were managed with medication. One subject developed the infusion reaction on Day 58 and continued to be treated with PRM-151. The other subject developed the infusion reaction on day 225 during the extension study. The hypersensitivity reactions to date have occurred as isolated events and have been manageable (refer to Investigator's Brochure for details).

1.3.1 Single Ascending Dose Study

The results of the single-ascending dose study indicate that single doses of PRM-151 administered intravenously at doses of 0.1 mg/kg to 20 mg/kg are safe and well tolerated. In this study, the plasma concentrations of PRM-151 were measurable only above 0.5 mg/kg dose. The exposure to PRM-151 increased with dose and its half-life was 30 hours in healthy subjects. PRM-151 showed limited volume of distribution in healthy subjects. Pharmacokinetics of PRM-151 were similar in healthy subjects and IPF subjects following the 10 mg/kg dose.

1.3.2 Multiple Ascending Dose Study

The results of multiple-ascending dose study indicate that doses of PRM-151 administered by intravenous infusion over 30 minutes at doses of 1.0 mg/kg, 5 mg/kg, and 10 mg/kg on days 1, 3, 5, 8 and 15 are safe and well-tolerated. The most common AEs in the PRM-151 treated subjects

were cough (n=7; 47%), productive cough (n=4; 27%) and dizziness (n=4; 27%), followed by fatigue (n=3; 20%) and headache (n=3; 20%). The incidences of these events were similar in the placebo group (cough, 33%, productive cough, 33%; dizziness, 17%, fatigue, 17% and headache, 17%). Treatment emergent events of cough, dysphonia and hypotension were numerically more frequent in test article-treated subjects than in placebo-treated subjects. They occurred in PRM-151 treated subjects with the following frequencies: cough 40% (n=6), dysphonia 13% (n=2), hypotension 13% (n=2). No placebo treated subjects reported a treatment emergent adverse event of dysphonia or hypotension, and the frequency of cough was 17% (n=1). Frequency of treatment emergent productive cough was 33% (n=2) in the placebo treated subjects and 27% (n=4) in PRM-151 treated subjects.

1.3.3. Phase 2 Glaucoma Study

The results of the randomized study of PRM-151 in glaucoma following trabeculectomy indicate that PRM-151 administered as a subconjunctival injection post-operatively on Days 1, 2, 3, 5 and 9 is safe and well-tolerated. The majority of adverse events that occurred were ocular events that were reported at similar rates for placebo and PRM-151 treated subjects. The most common AE reported was intraocular pressure increased occurring in 15 subjects (24.2%) in the PRM-151 group and 13 subjects (21.0%) in the placebo group. The majority of adverse events were mild to moderate in severity, and most were not considered related to study drug. A total of 20 serious adverse events have been reported in 14 subjects; none of the SAEs were considered related to study drug.

Complete summaries of the toxicology and safety of PRM-151 are provided in the Investigator's Brochure for PRM-151.

1.4. Study Rationale

PTX-2 and PRM-151 have demonstrated the ability to reduce pre-existing fibrosis in multiple pre-clinical models in different fibrotic diseases, including TGF-β1 and bleomycin-induced lung fibrosis, unilateral ureteral obstruction (UUO) and ischemia reperfusion injury (IRI) induced renal fibrosis, and radiation induced oral mucositis. The pathogenesis of fibrosis in myelofibrosis is not well understood, but preliminary data suggests that, similar to other fibrotic diseases, insufficient production of PTX-2 may play a role. In idiopathic pulmonary fibrosis (IPF), for example, studies have shown that subjects with IPF have lower levels of PTX-2 than healthy volunteers, and lower levels of PTX-2 are associated with poorer lung function in IPF subjects (Murray, Chen et al.2011).

Until recently, the fibrosis in myelofibrosis was thought to be "reactive;" with overproduction of cytokines by malignant cells stimulating fibroblast-like cells derived from non-malignant mesenchymal stromal cells. This hypothesis has been weakened by the fact that ruxolitinib, which causes significant reduction of PMF-associated cytokine levels, does not appear to affect bone marrow fibrosis (Verstovsek, Kantarjian et al. 2010). Verstovsek *et al* (Verstovsek 2013, manuscript in preparation) have recently reported findings that suggest that bone marrow derived fibrocytes from subjects with myelofibrosis come from the malignant clone rather than from mesenchymal stromal cells (MSCs). Clonal neoplastic fibrocytes were identified in bone

marrows of subjects with PMF, and Jak2 mutations and chromosomal abnormalities present in the malignant clones in several subjects were present in the bone marrow derived fibrocytes but not in the MSCs. Furthermore, serum PTX-2 levels were significantly lower in subjects with PMF than healthy volunteers, and PTX-2 inhibited differentiation of monocytes from PMF bone marrows into fibrocytes in vitro. Data with PRM-151 in other fibrotic disease models combined with these findings in PMF subject bone marrows support investigation of PRM-151 in subjects with PMF.

PRM-151 differs from traditional mAb-based antagonist drugs. Preclinical pharmacology and *in vitro* cell biology indicate that PTX-2 acts as a partial agonist of Fc*γ*R signaling in monocytes/macrophages, stimulating their differentiation into a protective regulatory state (Mreg); these cells then secrete IL-10 locally in the tissues. For this reason, it is likely that the optimal dose scheduling of PRM-151 will not follow a direct PK/PD relationship that is typical of mAb-based antagonists. Instead, our data indicate that a threshold dosing interval must be achieved for PRM-151 in order to effectively modulate the monocyte/macrophage populations in tissues, but once modulated, the biologic activity is long lasting. This suggests that intermittent dosing of PRM-151 will be effective to produce the desired pharmacologic effect. In preclinical models of lung fibrosis, efficacy was seen at 1.6 mg/kg of mouse PTX-2 in mice, at 1.6 mg/kg of rat PTX-2 in rats and at 6-10 mg/kg of human PTX-2 in mice. Efficacy was also observed following abbreviated therapeutic dose schedules of PTX-2 in both the mouse TGF-β1 lung fibrosis model and in the mouse bleomycin-induced lung fibrosis model, further supporting the hypothesis that intermittent dosing of PRM-151 may be feasible. Importantly, the beneficial effects of PTX-2 appear to last well beyond the period of treatment. In a study of PRM-151 in TGFβ1 continuous lung injury model of pulmonary fibrosis, mice were treated with vehicle or PRM-151 10 mg/kg on days 10, 11, and 12 and sacrificed on either Day 21 or Day 42; vehicle treated mice had progressive increase in lung collagen from Day 10 through Day 42, whereas PRM-151 treated mice had only a modest increase in lung collagen on Day 21, which remained stable through Day 42, resulting in a statistically significant difference in lung collagen between vehicle and PRM-151 treated mice at Day 42 (Study 11-014, 2012).

Nonclinical studies have been conducted to gain an understanding of the relationship between a minimal effective dose, dose schedule and PRM-151's pharmacodynamics effects. Study 06-002, "Effect of hSAP on TGF-β1 Induced Lung Fibrosis in Mice," dosed h PTX-2 every 2 days from day -1 to day 13. The TGF-β1 induced increase in total lung collagen was reduced by greater than 50% at the 6 mg/kg and 20 mg/kg dose groups. The 2 mg/kg dose group had no effect in this model, suggesting that the minimal efficacious h PTX-2 dose level in this model was 2-6 mg/kg. Study 08-042, "Effects of delayed dosing of hSAP on TGF-β1-induced pulmonary fibrosis in mice" dosed h PTX-2 at 6 mg/kg every 2 days from day 4 to day 10. The TGF-β1-induced increase in total lung collagen was again reduced by greater than 50%, and the durability of effect lasted through the end of study at Day 21, 11 days after dosing was stopped. Similarly, PRM-151 was dosed for 3 consecutive days starting on Day 11 in Study 08-034, "Local Delivery and Altered PRM-151 Dose Schedules in a Bleomycin Model". In this model of established lung disease, lung collagen levels were reduced in all dose groups; however, the group dosed with PRM-151 daily on days 11-13 showed the most pronounced reduction in

collagen deposition. The durability of the effect of human PTX-2 following dosing in this model was also demonstrated to last through end of study at day 21. These data support PRM-151 dosing frequencies of every two weeks at a dose level of 2-6 mg/kg.

Dose ranging studies in the bleomycin lung model in rats and mice have recently been completed, and indicate that doses of PRM-151 higher than 10 mg/kg are less effective than doses in the 2-10 mg/kg range, and that doses $\leq$ 0.5 mg/kg are ineffective in these species. In an *in vitro* assessment of PRM-151 in mouse and human fibrocyte assays, the IC_{50} of PRM-151 is 2.0 µg/ml for mouse fibrocytes and 0.2 µg/ml for human fibrocytes, indicating that PRM-151 is more potent in humans than in mice. PRM-151 is also more potent in human fibrocytes than endogenous human PTX-2. Preclinical and clinical data suggest a potentially effective dose range of PRM-151 in humans of 0.2 to 10 mg/kg.

In a recently completed Phase 1, randomized, blinded, placebo-controlled, multiple ascending dose study of PRM-151 in subjects with IPF (PRM151F-12GL), PRM-151 was well tolerated at all doses tested. Subjects in all three PRM-151 dose groups demonstrated improvement in Percent Predicted Forced Vital Capacity (FVC) at Day 57 after receiving PRM-151 on Days 1, 3, 5, 8 and 15. Mean change from baseline in Percent Predicted FVC at Day 57 was + 2.4 (SD 3.8) for all PRM-151 treated subjects and -1.5 (SD 3) for placebo treated subjects (p=0.0524) (PRM151F-12GL Draft Clinical Study Report, 2012).

The PRM-151 dose and administration schedule for Stage 1 was chosen based upon the Phase 1 multiple ascending dose study in IPF, in which subjects received up to 10 mg/kg PRM-151 on days 1, 3, 5, 8 and 15. Preclinical data supports dosing at two week intervals after an initial "loading" period. In the multiple-ascending dose study, PRM-151 was safe and well-tolerated, with no increase in toxicity with increasing dose levels and no acute infusion reactions. Vertsovsek et al (manuscript in preparation) have demonstrated that bone marrow derived fibrocytes from PMF subjects are less sensitive to PTX-2 than fibrocytes from normal bone marrow, suggesting that more intense dosing may be required for a disease modifying effect. This study will evaluate an every four week dosing schedule, following a loading period.

Additional information can be found in the Investigator's Brochure.

1.5 Rationale for Stage 2 Changes

All treatment arms in Stage 1 of PRM-151G-101 met the pre-specified efficacy criteria of $\geq$ 1 response to be considered for continued evaluation in Stage 2. Key findings from Stage 1 that led to the changes for Stage 2 are listed below.

- Overall response rate was 43% at 24 weeks and 50% at 36 weeks
    - At 36 weeks of treatment
        - 10 Bone Marrow responses
        - 4 IWG Symptom responses

  - 10/17 subjects with baseline Hgb < 10 g/L and/or PLT < 50 x 10^9/L showed improvement in Hgb and/or PLT
- There was no apparent difference in efficacy or safety between PRM-151 administered once a week or every four weeks
- Hematologic improvements were more common with PRM-151 alone
- Most subjects had improvements in symptoms and modest reductions in splenomegaly, although not meeting IWG response criteria
- PRM-151 was very well tolerated both as a single agent and added to ruxolitinib, although adverse events were more common in the subjects also receiving ruxolitinib

Based on these results, the following changes have been made for Stage 2:

Design element	Stage 1	Stage 2	Rationale
Primary Objective	Evaluate the efficacy of two different dose schedules of PRM-151 in intermediate-1, intermediate-2, or high risk subjects with PMF, post-PV MF, or post ET-MF who are not receiving therapy for MF, and in subjects with PMF, post-PV MF, or post ET-MF on a stable dose of ruxolitinib for at least three months.	To determine the effect size of three different doses of PRM-151 on reduction in bone marrow fibrosis by $\geq$ 1 grade in intermediate-1, intermediate-2, and high risk subjects with PMF, post-PV MF, or post ET-MF who are anemic or thrombocytopenic and who are ineligible for, intolerant of, or have had an inadequate response to ruxolitinib.	Single agent efficacy at 10 mg/kg every 4 weeks supports continued evaluation Identification of minimal effective dose is important for further development Translational data suggests equal to greater efficacy at lower doses
Primary Endpoint	Percent of subjects with IWG-MRT response or reduction in bone marrow fibrosis by $\geq$ 1 grade	Percent of subjects with reduction in bone marrow fibrosis by $\geq$ 1 grade	Reduction in bone marrow fibrosis is most closely linked to the mechanism of action of PRM-151; assessment of clinical benefit related to decreased fibrosis, including IWG-MRT responses, will be done via secondary endpoints

Secondary Endpoints	Safety Change in bone marrow fibrosis Change in symptoms Duration of response PK	Safety Change in bone marrow fibrosis Improvement in hemoglobin Improvement in platelets Improvement in symptoms IWG-MRT response rate Duration of improvements	Individual assessment of disease related abnormalities will help to define the clinical benefit of PRM-151 and guide future clinical trials
Eligibility	Intermediate-1, 2, or high risk Myelofibrosis Grade 2 or 3	Intermediate-1, Intermediate-2 or High risk Myelofibrosis Grade 2 or 3 Not candidates for ruxolitinib based on EITHER Hgb < 100 g/L and requiring at least 2 units PRBC in the 12 weeks prior to study entry and intolerant of or had in adequate response to ruxolitinib OR PLT <50 x 10^9/L	Subjects with clinically significant anemia or thrombocytopenia had the greatest benefit in Stage 1, and will provide the best opportunity to define the clinical benefit of PRM-151 Limiting eligibility to subjects who are not candidates for ruxolitinib ensures that we are enrolling subjects with the highest unmet need
Duration	24 weeks	36 weeks	Improvements in bone marrow fibrosis, hemoglobin, and platelets were all greater at 36 weeks than at 24 weeks, suggesting that PRM-151 effects improve over time and that clinical benefit may be underestimated at

			24 weeks. There is insufficient data at present to indicate that a longer study duration is required, but longer term data obtained from study extensions will be informative for future trials
Single agent or combination with ruxolitinib	Single agent AND added to a stable dose of ruxolitinib	Single agent	Hematologic improvements were more apparent in subjects on single agent PRM-151; dosing ranging can be done best with single agent. Future studies will assess PRM-151 in combination with ruxolitinib
Dose	10 mg/kg	0.3, 3, and 10 mg/kg	Efficacy has been observed in clinical studies at 1, 5, and 10 mg/kg, but recent dose ranging studies in rats and mice and IC50 data from in vitro studies suggest an effective dose range in humans of 0.2-10 mg/kg.
Schedule	Every week AND every 4 weeks	Every 4 weeks	No apparent difference in efficacy or safety between schedules in Stage 1
Randomization	No	Yes, randomized, blinded and stratified	Eliminating weekly dosing makes randomization and blinding possible, reducing bias and

			increasing the rigor of the study. Stratification allows for independent assessment of anemic and thrombocytopenic subjects.
Control Arm	None	None	All three doses will be evaluated independently. Secondary analyses will compare doses; indication of a dose response will provide evidence of efficacy.

The remainder of this protocol amendment applies only to Stage 2. Please refer to APPENDIX K for more information on Stage 1and APPENDIX L for Stage 1 Open Label Extension.

In the stage 2 study, all subjects completing 9 cycles of the originally assigned treatment may switch to an open label extension and receive PRM-151 10 mg/kg every 4 weeks. The first cycle of the open label phase contains a loading dose of 10 mg/kg on days 1, 3 and 5. This will allow for subjects from all three dosing cohorts to receive a loading dose of 10 mg/kg while maintaining the blind. Additionally, subjects who have entered the open label extension study prior to the approval of this amendment may receive a loading dose (10 mg/kg on days 1, 3, and 5), to be administered on their next scheduled cycle after approval of this protocol amendment. This will allow for these subjects to receive any potential pharmacologic benefit of the loading dose. As of 14-Nov 16, we have blinded safety data, although limited, on 21 patients receiving a similar 10 mg/kg loading dose in the open label of the PRM-151-202 IPF study after 24 weeks of exposure to PRM-151 or placebo in 2:1 ratio. No incremental risk has been reported in these subjects.

2. STAGE 2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To determine the effect size of three different does of PRM-151 on reduction in bone marrow fibrosis by ≥ 1 grade in intermediate-1, intermediate-2, and high risk subjects with PMF, post-PV MF, or post ET-MF who are anemic or thrombocytopenic and who are ineligible for, intolerant of, or have had an inadequate response to ruxolitinib.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To determine if there is a difference in efficacy between the three doses of PRM-151 used in the study
- To evaluate the safety and tolerability of three different doses of PRM-151
- To assess the duration of effect of three doses of PRM-151 on reduction in bone marrow fibrosis
- To assess the effect and duration of effect of three doses of PRM-151 on disease related anemia, thrombocytopenia, and constitutional symptoms
- To assess IWG-MRT response (Complete Response, Partial Response, Clinical Improvement), stable and progressive disease in subjects treated with three doses of PRM-151

2.3. Exploratory Objectives

The exploratory objectives of this study are:

- To measure changes in bone marrow fibrosis by quantitative image analysis and evaluate changes in bone marrow morphology in subjects receiving PRM-151
- To assess the effect of PRM-151 on other disease related parameters, including hematologic abnormalities and spleen size
- To assess the effect of PRM-151 on prognostic factors associated with increased mortality as measured by the DIPSS (Dynamic International Prognostic Scoring System)
- To evaluate the interaction between selected genetic mutations and cytogenetic abnormalities and response to PRM-151
- To explore potential biomarkers of PRM-151 activity in bone marrow samples
- To assess the effect of PRM-151 on bone marrow metabolism by PET imaging (at selected institutions)
- To evaluate the correlation of baseline PTX-2 levels with outcomes
- To evaluate the relationship between bone marrow fibrosis reduction and hematologic improvements in subjects treated with PRM-151
- To measure progression-free and overall survival in subjects receiving PRM-151

3. STAGE 2 STUDY ENDPOINTS

3.1 Primary Endpoint

The Primary endpoint for the study is:

- Bone marrow response rate, defined as the percent of subjects with a reduction in bone marrow fibrosis score by at least one grade according to WHO criteria (APPENDIX D) at any time during the study as determined by a central adjudication panel of expert hematopathologists, blinded to subject, treatment, and time of biopsy

3.2. Secondary Endpoints

The secondary endpoints for the study are:

- Comparison of primary and secondary efficacy parameters between doses
- Incidence of adverse events (AEs), serious adverse events (SAEs), and changes in laboratory test results
- Bone marrow improvement:
  - Bone marrow response rate at weeks 12, 24, and 36
  - Duration of bone marrow response
- Hemoglobin improvement

Baseline Status	**Categories of Hemoglobin Improvement**
Subjects who are transfusion dependent (≥ 2 units PRBC every 4 weeks for 12 weeks prior to or after C1D1), regardless of baseline hemoglobin level	Percent of subjects with Red cell transfusion independence (no transfusions for ≥ 12 consecutive weeks) OR 50% reduction in RBC transfusions for ≥ 12 consecutive weeks
Subjects with baseline hemoglobin < 100 g/L AND Not transfusion dependent	Percent of subjects with ≥ 10 g/L and ≥ 20 g/L increase in hemoglobin for ≥ 12 consecutive weeks without transfusions

- Platelet improvement

Baseline Status	**Categories of Platelet Improvement**
Subjects who are transfusion dependent (≥ 2 platelet transfusions in any 12 weeks prior to or after C1D1), regardless of baseline platelet level	Percent of subjects with: Platelet transfusion independence (no transfusions for ≥ 12 consecutive weeks) OR

Platelet transfusion = either 1 unit apheresed (single donor) platelets or 4-8 units pooled random donor platelets	50% reduction in platelets transfusions for ≥ 12 consecutive weeks
Subjects with 25 < baseline platelets < 50 X 10^9/L AND Not platelet transfusion dependent	Percent of subjects with: Doubling of baseline platelet count for ≥ 12 consecutive weeks without platelet transfusions OR Platelet count > 50 X 10^9/L for ≥ 12 consecutive weeks without platelet transfusions,
Subjects with baseline platelet count < 25 x $10^{9/L}$ AND Not platelet transfusion dependent	Percent of subjects with: Doubling of baseline platelet count for ≥ 12 consecutive weeks without platelet transfusions OR Platelet count > 25 x 10^9/L for ≥ 12 consecutive weeks without platelet transfusions

- Hematologic improvement

Baseline Status	**Categories of Hematologic Improvement**
Subjects with both Hemoglobin < 100 g/L and Platelets < 50 x 10^9/L	Percent of subjects who have **EITHER** Hemoglobin improvement **OR** Platelet improvement as described above and no worsening of hemoglobin or platelets from baseline
Subjects with only Hemoglobin <100 g/L	Percent of subjects who have Hemoglobin improvement as described above **AND** Did not develop platelets < 50 x 10^9/L
Subjects with only Platelets <50 x 10^9/L	Percent of subjects who have Platelet improvement as described above **AND** Did not develop Hemoglobin <100 g/L or new transfusion dependence

- Symptom improvement:

- Percent of subjects with 25% and 50% reduction in MPN-SAF Total Symptom Score from baseline at Week 36
- Mean change from baseline in EORTC QLQ-C30 at 36 weeks

- Duration of all improvement parameters listed above
- Percent of subjects with complete response, partial response, clinical improvement, stable disease, and progressive disease according to IWG-MRT criteria (Tefferi 2013, APPENDIX B)

3.3 Exploratory Endpoints

The exploratory endpoints for the study include:

- Bone marrow:
  - Percent of subjects with Grade 0-1 bone marrow fibrosis grade at any time during the study and at weeks 12, 24, and 36
  - Duration of Grade 0-1 bone marrow fibrosis grade
  - Mean change from baseline to 12, 24, and 36 weeks in bone marrow fibrosis by quantitative image analysis
  - Changes from baseline to weeks 12, 24, and 36 in bone marrow metabolism by FDG or FLT PET scan (where feasible)
  - Assessment of changes in bone marrow morphology at 12, 24, and 36 weeks
- Hematologic and other disease related laboratory parameters:
  - Mean change from baseline to 36 weeks in: hemoglobin, # RBC units transfused in previous 12 weeks, platelet count, # platelet transfusions in previous 12 weeks, white blood cell count, absolute neutrophil count, reticulocyte count, peripheral blood blast count, and -lactic dehydrogenase (LDH)
  - Percent of subjects with increase in Hgb from < 100 g/L to > 100 g/L without transfusions, increase in platelets from $< 50 \times 10^9$/L to $> 100 \times 10^9$/L, decrease in WBC from > 25 to < 25, increase in ANC from < 1500 to ≥ 1500, decrease in peripheral blood blasts from $> 1\%$ to $< 1\%$, and disappearance of leukoerythroblastosis, at 36 weeks and for ≥ 12 weeks at any time during the study

- Duration of increase in Hgb from < 100g/L to > 100 g/L without transfusions, increase in platelets from < 50 x 10^9/L to > 100 x 10^9/L, decrease in WBC from > 25 to < 25, increase in ANC from < 1500 to $\geq$ 1500, decrease in peripheral blood blasts from > 1% to < 1%, and disappearance of leukoerythroblastosis

- Spleen improvement:
  - Percent of subjects with 10% and 35% reduction in spleen size from baseline by CT at 36 weeks
  - Duration of 10% and 35% reduction in spleen size from baseline
  - Mean change from baseline in spleen size by CT or MRI and palpation (in subjects with palpable spleen at baseline) at 36 weeks
  - Change in spleen and liver metabolism by FDG or FLT PET scan at 12, 24, and 36 weeks
- DIPSS:
  - Percent of subjects with a reduction in DIPSS score and category at week 36
  - Mean change in DIPSS score from baseline to Week 36
- Mutational Status and Cytogenetics:
  - Association of baseline mutational status of JAK2V617F, MPLW515, Calreticulin, ASXL1, EZH2, SRSF2, IDH1/2 with selected primary and secondary endpoints
  - Changes in allele burden of JAK2V617F at week 36. Changes in allele burden of MPLW515, Calreticulin, ASXL1, EZH2, SRSF2, IDH1/2 at week 36 will be measured as commercially available assays become available.
  - Association of baseline cytogenetic abnormalities and selected primary and secondary endpoints
- Association of baseline PTX-2 levels with selected primary and secondary endpoints
- Evaluation of potential biomarkers of PRM-151 activity in bone marrow biopsies taken at baseline, weeks 12, 24, and 36

- Measurement of progression-free and overall survival

4. OVERALL STAGE 2 STUDY DESIGN AND PLAN

4.1.1. Study Design:

Stage 2: This is a randomized, double-blind Phase 2 study to determine the efficacy and safety of three different does of PRM-151 in subjects with PMF and post ET/PV MF. Subjects will be randomized to one of three doses: 0.3 mg/kg, 3.0 mg/kg or 10 mg/kg of PRM-151. This is the second stage of an adaptive design study as defined in FDA Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics, February 2010. Modifications to dose levels, schedule, and regimen have been made in Stage 2 based on data from Stage 1.

Approximately 84 subjects with intermediate-1, and intermediate -2, or high risk MF who meet study eligibility requirements will be enrolled and randomized to treatment with single agent PRM-151 at doses of 0.3, 3, or 10 mg/kg IV on Days 1, 3, 5 of Cycle 1 and Day 1 of each subsequent 28 day cycle for nine cycles.

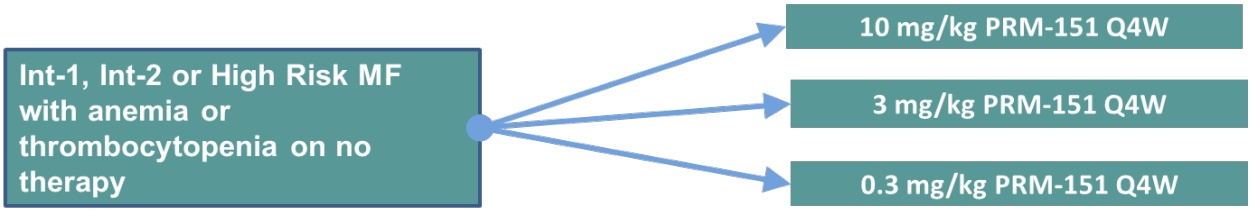
All subjects completing 9 cycles of the originally assigned treatment may switch to an open label extension and receive PRM-151 10 mg/kg every 4 weeks. The first cycle of the open label phase contains a loading dose of 10 mg/kg on days 1, 3 and 5. This will allow for subjects from all three dosing cohorts to receive a loading dose of 10 mg/kg while maintaining the blind. Additionally, subjects who have entered the open label extension study prior to the approval of this amendment may receive a loading dose (10 mg/kg on days 1, 3, and 5), to be administered on their next scheduled cycle after approval of this protocol amendment. This will allow for these subjects to receive any potential pharmacologic benefit of the loading dose.

Enrolled subjects will be considered evaluable for response if they are on study drug for at least twelve weeks.

The Schedule of Events can be found in APPENDIX A.

4.1.2. Subject Assignment to Treatment Groups

Subjects will be randomized to one of three doses of PRM-151. The randomization will be stratified according to type of baseline hematologic abnormality (subjects with Hgb < 100g/L and having received $\geq$ 2 units PRBC in the 12 weeks prior to study entry OR subjects with platelet count < 50 X 10^9/L) and will ensure that the final study population will include at least 50% of subjects from the second stratum (platelet count < 50 X 10^9/L).



4.1.3. Study Duration

Each subject will participate in the study for approximately 44 weeks. Participation will include a screening evaluation within four weeks prior to the first PRM-151 administration, nine study cycles of four weeks each, and an end of study visit four weeks after the end of the last cycle.

All subjects may switch to an open label extension utilizing the 10 mg/kg dose after completing 9 cycles of the originally assigned treatment. Subjects may continue with PRM-151 dosing in the absence of disease progression or toxicity warranting discontinuation of therapy. Please see APPENDIX J for details.

It is estimated that the study will be completed in approximately 18 months.

5. STAGE 2 SELECTION OF STUDY POPULATION

5.1 Study Population

5.1.1. Inclusion Criteria

This Phase 2 study will enroll up to 111 subjects with MF, 27 in Stage 1, and up to an additional 84 subjects in Stage 2

Each subject must meet all of the following inclusion criteria to be enrolled in the study:

1. Subjects must be ≥ 18 years of age at the time of signing the Informed Consent Form (ICF);
2. Subjects must voluntarily sign an ICF;
3. Subjects must have a pathologically confirmed diagnosis of PMF as per the WHO diagnostic criteria (see APPENDIX C) or post ET/PV MF;
4. At least Grade 2 marrow fibrosis according to the WHO Grading of Bone Marrow Fibrosis (APPENDIX D);
5. Intermediate -1, intermediate -2, or high risk disease according to the IWG-MRT Dynamic International Prognostic Scoring System (see APPENDIX E);
6. A bone marrow biopsy must be performed within four weeks prior to Cycle 1 Day 1 treatment to establish the baseline fibrosis score;
7. Subjects must not be candidates for ruxolitinib based on EITHER:
    a. Platelet count < 50 x 10^9/L, OR
    b. Hgb < 100 g/L have received ≥ 2 units PRBC in the 12 weeks prior to study entry, and be intolerant of or had inadequate response to ruxolitinib;
8. Subjects must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2. (APPENDIX F);
9. Life expectancy of at least twelve months;
10. At least four weeks must have elapsed between the last dose of any MF-directed drug treatments for myelofibrosis (including investigational therapies) and study enrollment;
11. Recovery to ≤ Grade 1 or baseline of any toxicities due to prior systemic treatments, excluding alopecia;
12. Women of child bearing potential (WCBP), defined as a sexually mature woman not surgically sterilized or not post-menopausal for at least 24 consecutive months if < 55 years or 12 months if > 55 years, must have a negative serum pregnancy test within four weeks prior to the first dose of study drug and must agree to use highly effective methods of birth control throughout the study. Highly effective methods of contraception include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation by oral, intravaginal, or transdermal administration; progestogen-only hormonal contraception associated with inhibition of ovulation by oral, injectable, or implantable administration; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; partner vasectomy, and total abstinence (only if

total abstinence is the preferred method and usual lifestyle of the subject). Adequate contraceptive use should be continued until 28 days after the final dose of the study drug.

13. Ability to adhere to the study visit schedule and all protocol requirements;
14. Must have an adequate organ function as demonstrated by the following:
    - ALT (SGPT) and/or AST (SGOT) $\leq$ 3 x upper limit of normal (ULN), or $\leq$ 4 x ULN (if upon judgment of the treating physician, it is believed to be due to extramedullary hematopoiesis [EMH] related to MF);
    - Direct bilirubin $\leq$ 1.5 x ULN; or $\leq$ 2 x ULN (if upon judgment of the treating physician, it is believed to be due to EMH related to MF);
    - Serum creatinine $\leq$ 2.5x ULN.

5.1.2. Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study:

1. White blood cell count > 25 x 10^9/L or > 10% peripheral blood blasts;
2. Other invasive malignancies within the last 3 years, except non-melanoma skin cancer and localized cured prostate and cervical cancer;
3. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months;
4. Presence of active serious infection;
5. Any serious, unstable medical or psychiatric condition that would prevent, (as judged by the Investigator) the subject from signing the informed consent form or any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study;
6. Known history of human immunodeficiency virus (HIV), or known active hepatitis A, B, or C infection;
7. Organ transplant recipients other than bone marrow transplant;
8. Women who are pregnant or lactating.

6. STAGE 2 STUDY TREATMENT(S)

6.1. Investigational Product

PRM-151 will be supplied by Promedior as a solution for Injection.

6.2. Treatment(s) Administered

All subjects will receive intravenous (IV) infusions of 0.3 mg/kg, 3.0 mg/kg or 10 mg/kg PRM-151, with dose based on the subject's weight on Day 1 for Days 1, 3 and 5 of Cycle 1, and all subsequent doses based on the subjects' weight on the first day of each cycle. Subjects will be observed for one hour after each dose. Refer to the Pharmacy Manual and the Investigator's Brochure for detailed instructions on special precautions and handling.

PRM-151 will be held for any treatment emergent Grade 3 non-hematologic or any Grade 4 adverse event and resumed when adverse event has resolved to Grade 1 or baseline.

6.3. Dose for Each Subject

Subjects will be randomized to treatment with single agent PRM-151 at doses 0.3, 3, or 10 mg/kg IV administered as a 60 minute intravenous infusion on Days 1, 3, and 5 of Cycle 1 and Day 1 of each subsequent 28 day cycle for nine cycles.

For OLE dosing refer to Appendix J.

6.4. Method of Assigning Subjects to Treatment Groups

Subjects will be randomized to treatment cohorts in a double-blind fashion. Randomization will be accomplished using an interactive response system (IRS). The IRS will contain the randomization schedule. At the screening visit, the investigative site will contact IRS. The site will enroll the subject into the IRS by indicating minimal information to sufficiently distinguish one subject from another and will receive the subject ID number. At the Cycle 1, Day 1 visit, the unblinded pharmacist (or designee) will access IRS to randomize the subject. The system will associate that subject with the next available treatment on the randomization schedule. IRS will inform the unblinded pharmacist (or designee) to which PRM-151 dose the subject has been assigned.

The unblinded pharmacist will contact IRS at each dosing visit. The randomization schedule allows for overage, such as enrollment, which will be controlled by IRS and when a sufficient number of subjects have been enrolled, the randomization part of the system will be stopped. The portion of the system that manages re-supply will remain active until the last subject completes the study.

6.5. Blinding

This study will be Subject, Investigator, Assessor (central adjudication panel of expert hematopathologists) and Sponsor-blinded. The site Pharmacist will be unblinded to the dose assignment. Additional details regarding procedures for maintaining the blind can be found in the Pharmacy Manual.

6.5.1. Breaking the Blind

Blinding should only be broken in emergency situations for reasons of subject safety. Whenever possible, the Investigator should attempt to contact the Promedior Medical Monitor before breaking the blind. When the blind is broken, the reason must be fully documented in the source documents and entered into the eCRF as applicable. At all other times treatment and randomization information will be kept confidential and will not be release to the Investigator/blinded study staff until conclusion of the study.

6.6. Concomitant Medications, Therapies and Medical/Surgical Interventions

Concomitant medications, therapies, and medical/surgical interventions must be documented on the electronic case report form (eCRF) beginning at the signing of informed consent. Subjects are not permitted to receive any treatment for myelofibrosis.

The following concomitant medications are excluded during the study:

- Hematopoietic growth factors, including erythropoietin, G-CSF, GM-CSF, thrombopoietin. Exception: G-CSF may be used as part of the management of febrile neutropenia, and must be documented in the CRF.
- Any therapy that is or may be active against myelofibrosis including JAK kinase inhibitors, chemotherapy, biologics (including antibodies), androgens, radiation therapy, any tyrosine kinase inhibitors (TKIs), any immunomodulatory agents, or investigational agents other than the treatment regimen in this protocol.
- Hydroxyurea is not permitted
- Anagrelide is not permitted
- Steroids, with the exception of prednisone $\leq$ 10 mg po qd at a stable dose for at least three months for a condition unrelated to MF, or as intra-articular injection for an acute problem. If steroids are required for management of an infusion reaction, it will be documented in the CRF.

6.7. Treatment Compliance

PRM-151 is administered under controlled conditions by the Investigator or designee; therefore, full subject compliance with study treatment is anticipated in this study.

6.8. Packaging and Labeling

PRM-151 is supplied in 10 ml single use vials as a clear to opalescent, sterile 20.0 mg/mL solution 10 mM sodium phosphate, 5% (w/v) sorbitol, and 0.01% (w/v) polysorbate 20 with a pH of 7.5. Each vial contains 8 ml PRM-151 (160 mg of PRM-151).

6.9. Storage and Accountability

PRM-151 will be provided to the clinical site in a temperature controlled, monitored container. Investigational product should be stored under refrigerated conditions (2 C-8 C [35.6 ºF-46.4ºF] and protected from light. Vigorous mixing or vortexing should be avoided.

Investigational product will be dispensed at the study site and stored in a locked storage area. The disposition of all investigational product delivered to a Principal Investigator must be recorded on a subject-by-subject basis by completing the Clinical Trial Material Accountability Log. The date and time of administration of the investigational product must be documented on the appropriate eCRF.

The Principal Investigator, Clinical Research Coordinator, or designee (e.g., Pharmacist) must ensure that all documentation regarding investigational product receipt, storage, dispensing, loss/damaged and return of used/unused product is complete, accurate, and ready for review at each monitoring visit and/or audit. The sites must ensure that the investigational product is available for the monitor to inventory and prepare for return shipment to the Sponsor or designee, if required.

All packing slips and other shipment documentation must be retained as well as any investigational product return forms.

See the Pharmacy Manual for additional details.

7. STUDY PROCEDURES

Detailed descriptions of subject evaluations required for this protocol are described in this section. These evaluations will be performed during the indicated days and weeks of the study as described in Stage 2 Study Activities and in the Schedule of Events table in APPENDIX A.

Subjects enrolled in the open-label extension protocol of Stage 1 will continue to follow the study procedures outlined in Appendix L.

Subjects following Stage 2 extension protocol should continue to follow the study procedures outlined in Appendix J.

All data collected are to be recorded on the appropriate eCRF page.

The Investigator at the clinical trial site is responsible for maintaining a record of all subjects pre-screened, screened, and enrolled into the study.

7.1. Informed Consent

Prior to conducting any study-related procedures, written informed consent must be obtained from the subject or the subject's legally authorized representative.

The nature, scope, and possible consequences, including risks and benefits, of the study will be explained to the subject by the Investigator or designee in accordance with the guidelines described in Section 11.4. Documentation and filing of informed consent documents should be completed according to Section 11.4.

7.2. Study Entrance Criteria

At Screening, each subject will be reviewed for eligibility against the study entrance criteria. Subjects who do not meet the study entrance criteria will not be allowed to participate in the study. The reason(s) for the subject's ineligibility for the study will be documented. All subjects must undergo a bone marrow biopsy for grading of bone marrow fibrosis. Subjects with a myelofibrosis Grade < 2, according to the WHO criteria (APPENDIX D), as determined by the local pathologist, will not be allowed to participate in the study.

7.3. Confirmation of Study Eligibility

Subject eligibility according to the study inclusion and exclusion criteria will be confirmed at study entry on the basis of review of the study entrance criteria.

7.4. Demographics

Subject demographic information including gender, age, date of birth, race, ethnicity and number of years since diagnosis of MF will be collected prior to the subject receiving the first dose of PRM-151.

7.5. Medical History

Medical history will be recorded in the eCRF. Any relevant and/or significant previous or existing medical condition(s) that occurred within 5 years prior to time of informed consent should be reported as medical history. Prior therapies for myelofibrosis will be recorded in the eCRF. Transfusion history and complete blood counts for three months prior to screening, and between screening and first dose, will be recorded in the eCRF. Results of prior bone marrow biopsies will be collected and recorded in the eCRF.

7.6. Height and Weight

Height and weight will be recorded for all subjects.

7.7. Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed following the Eastern Cooperative Oncology Group (ECOG) scoring system (APPENDIX F).

7.8. Investigational Product Administration

Medical personnel authorized by the Investigator will be responsible for the administration of study drug and for observation of each subject throughout the study.

Subjects will receive PRM-151 administered as a 60 minute intravenous infusion at a dose of 0.3 mg/kg, 3.0 mg/kg, or 10 mg/kg on Days 1, 3 and 5 of Cycle 1 and Day 1 of each subsequent 28 day cycle for nine cycles.

Subjects responding to treatment with PRM-151 may continue to receive it as long as there is benefit. Please see APPENDIX J for details.

In the case of Grade 2 occurrence of signs and symptoms consistent with infusion related reaction, follow institutional protocol and reduce the rate of infusion of PRM-151 to half the initial rate; consider discontinuing infusion of PRM-151 if symptoms do not respond to medical intervention. If signs and symptoms resolve with intervention including discontinuation of PRM-151, PRM-151 infusion may be restarted at half the initial rate.

In the case of Grade 3 or greater occurrence of signs and symptoms consistent with infusion related reaction, discontinue infusion of PRM-151.

If PRM-151 resulted in signs consistent with Grade 2 or 3 infusion related reaction, during a prior administration, infuse PRM-151 over 1 hour and use the following premedication for all subsequent PRM-151 administration:

a. Diphenhydramine 50 mg IV or clemastine 2 mg IV or an equivalent dose of an antihistaminic drug
b. Dexamethasone 10 mg IV or equivalent corticosteroid

7.9. Pharmacokinetic Assessments

In Stage 2, samples for pharmacokinetic analysis will not be collected. Pentraxin-2 levels will be drawn prior to each dose for pharmacodynamic assessment and correlation with potential anti-pentraxin 2 antibodies.

7.10. Exploratory Laboratory Assessments

At time points throughout the study, as indicated in the Schedule of Events (APPENDIX A), blood samples will be collected and DNA will be isolated from peripheral whole blood for the purpose of associating baseline mutational status with select primary and secondary endpoints. DNA sampling is not mandatory for subjects. Subjects can still enroll in the trial if they opt out of DNA sampling. Samples will be analyzed for cytogentic abnormalities and for mutations JAK2V617F, MPLW515, Calreticulin, ASXL1, EZH2, SRSF2, IDH1/2. Samples will also be analyzed to assess changes in the allele burden of JAK2V617F at week 36 (Cycle 1 Day 1 to Cycle 9 Day 29). These samples will also be analyzed to assess changes in the allele burden of MPLW515, Calreticulin, ASXL1, EZH2, SRSF2, IDH1/2 at week 36 (Cycle 9, Day 29) as quantitative assays become commercially available.

Additional assays may be performed that contribute to the objectives of the trial. Additional bone marrow biopsy slides will be collected for immunohistochemical analysis for disease and mechanism related proteins and cellular markers.

Sample handling details will be provided.

7.11. Efficacy Assessments

The following efficacy assessments, in addition to some of the safety assessments described in 7.12 will be performed.

7.11.1 Bone Marrow Biopsy

Bone marrow biopsy will be performed at screening, Cycle 4, Day 1, Cycle 7, Day 1, and Cycle 9, Day 29. Analysis will include confirmation of diagnosis and assessments of reticulin stain and trichrome stain. Slides will be sent to a central committee of hematopathologists who will be

blinded to subject, treatment, and collection time for centralized grading of fibrosis. A charter will be established for the central committee. Quantification of marrow fibrosis will be performed in a blinded fashion by computer assisted image analysis. Unstained slides will be collected for analysis of disease and mechanism related changes.

7.11.2 Assessment of transfusions

Subjects will be required to enter all RBC and platelet transfusion in a transfusion diary, which will be reviewed at each visit. Data will be entered in the eCRF.

7.11.3 Assessment of spleen size

7.11.3.1. Palpation

During the physical examination, the spleen will be measured in centimeters below the left costal margin and recorded in the eCRF.

7.11.3.2. Imaging

On Cycle 1 Day 1, Cycle 4 Day 1, Cycle 7 Day 1, and Cycle 9 Day 29, CT or MRI will be used to measure spleen volume in all subjects. For subjects who receive PET-CT imaging as described in 7.11.5, the PET-CT will be used to assess spleen volume and subjects will not require additional imaging.

7.11.4 Assessment of Symptoms

7.11.4.1 Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)

The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) will be administered to evaluate the effects of PRM-151 treatment on subject quality of life (QOL) (APPENDIX G).

7.11.4.2. EORTC QLQ-C30

The EORTC QLQ-C30 will be administered to evaluate the effects of PRM-151 treatment on subject quality of life (QOL) (APPENDIX H).

7.11.5. FDG or FLT PET-CT Imaging

At sites where it is feasible, FDG or FLT PET-CT scans will be done to assess changes in metabolism of bone marrow, spleen, and liver at Cycle 1 Day 1, Cycle 4 Day 1, Cycle 7 Day 1 and Cycle 9 Day 29. Subjects receiving PET-CT imaging will not require additional CT or MRI scans as described in 7.11.3.2.

7.11.6. Response Assessments

Subjects will be assessed for response at Cycle 2 through Cycle 9. Response Assessments are based on International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria, to measure the overall response rate (ORR), defined as a clinical improvement (CI), partial remission (PR), and complete remission (CR) according to the International Working Group (IWG) Criteria (APPENDIX B).

7.12. Safety Assessments

7.12.1. Physical Examination

Abbreviated physical examinations will be performed by the Investigator and will include a review of the subject's general appearance as well as evaluation of the following body systems (Table 1). Any abnormal change in findings after exposure to the study drug will be recorded as an adverse event (AE) on the appropriate eCRF.

Table 1: Assessments for Physical Examinations

Assessment	Assessment
General appearance	Throat
Head and neck	Cardiovascular
Eyes	Abdomen
	Chest and lungs

7.12.2 Vital Signs

Vital signs, including pulse, temperature (oral, temporal, or tympanic), respiration rate, and systolic and diastolic blood pressure will be measured and recorded on the eCRF.

7.12.3. Clinical Laboratory Tests

Blood samples will be collected for clinical laboratory testing and sent to a central laboratory as listed below. In the event the central lab cannot be used to get a reliable result for a laboratory test, local laboratory tests may be used after this has been agreed upon by the Medical Monitor.

Table 2: Clinical Laboratory Tests

Clinical Chemistry:

- Sodium
- Bicarbonate
- Glucose
- Asparate transaminase (AST)
- Alkaline phosphatase
- Uric acid
- Potassium
- Calcium
- Albumin
- Alanine aminotransferase (ALT)
- Creatine phosphokinase (CPK)
- Chloride
- Creatinine
- Phosphorus
- Bilirubin, direct and indirect
- Lactate dehydrogenase (LDH)
- Blood urea nitrogen (BUN)
- Serum pregnancy test

- Urine pregnancy test (local lab)

Hematology:

- Hemoglobin
- Hematocrit
- Platelets
- White Blood Cell (WBC) with differential
- Red Blood Cell (RBC)
- Reticulocyte count
- Blast count
- Absolute Neutrophil (ANC)
- Partial thromboplastin time (PTT)
- Prothrombin time (PT)
- International normalized ratio (INR)
- Nucleated red blood cells, immature cells, and other leukoerythroblasitc changes

For subjects receiving warfarin, the PT, PTT and international normalized ratio (INR) must be obtained. Abnormal INRs will be tested twice weekly until the INR is stable for one month, followed by monthly monitoring of the INRs.

7.12.4. Pregnancy Test

A serum β-hCG pregnancy test will be performed for women of childbearing potential within 4 weeks prior to dosing on Cycle 1 Day 1. The serum pregnancy test will be sent to a central laboratory for testing and the results must be available and negative before dosing. Pregnancy testing is not required for postmenopausal or surgically sterilized women. Urine pregnancy test will be performed at the local lab thereafter, as indicated in Schedule of Events table in APPENDIX A.

7.12.5. Electrocardiograms (ECG) Assessments

Electrocardiograms (ECG) Assessments will be performed at screening and in the event of an infusion reaction.

7.12.6. Immune Response Assessments

Blood samples (4 mL) will be collected prior to each dose of PRM-151 to measure antibodies to PTX-2. In addition, if a subject experiences an acute infusion related reaction, a blood sample will be collected for cytokines and antibodies against PRM-151. A blood sample for cytokines and antibodies against PRM-151 may be obtained in the event of a suspected adverse reaction. All samples collected may not be analyzed.

7.12.7. Sample Collection, Storage, and Shipping

Detailed instructions for laboratory sample collection, processing, and shipping instructions will be provided. All samples for exploratory assessments from the study will be stored at – 80C.

7.13. Adverse Events Assessments

7.13.1 Definitions of Adverse Events and Serious Adverse Events

7.13.1.1 Adverse Event

An AE is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of a clinical study, whether or not considered investigational product-related. This includes an exacerbation of a pre-existing condition.

Adverse events include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study;
- Intercurrent illnesses;
- Drug interactions;
- Events related to or possibly related to concomitant medications;
- Abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the Investigator considers to be clinically important);
- Clinically significant abnormalities in physical examination, vital signs, and weight.

Throughout the study, the Investigator must record all AEs on the AE eCRF, regardless of the severity or relationship to investigational product. The Investigator should treat subjects with AEs appropriately and observe them at suitable intervals until the events stabilize or resolve. Adverse events may be discovered through observation or examination of the subject, questioning of the subject, complaint by the subject, or by abnormal clinical laboratory values.

In addition, AEs may also include laboratory values that become significantly out of range. In the event of an out-of-range value, the laboratory test should be repeated until it returns to normal or can be explained and the subject's safety is not at risk.

Additional illnesses present at the time when informed consent is obtained are regarded as concomitant illnesses and will be documented on the appropriate pages of the eCRF. Illnesses first occurring or detected during the study, and worsening of a concomitant illness during the study, are to be regarded as AEs and must be documented as such in the CRF.

Infusion reactions were reported in two subjects in Stage 1 of this study. In the event of acute hypersensitivity or other infusion reaction, institutional protocol should be initiated and a blood sample drawn for anti-PTX-2 antibodies and cytokines. Signs and symptoms of an infusion reaction may include the following: headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, hypotension, lightheadedness, palpitations, urticaria and somnolence. Although unlikely, serious allergic reactions (e.g., anaphylaxis) may occur at any time during the infusion.

In the case of Grade 2 occurrence of signs and symptoms consistent with infusion related reaction, follow institutional protocol and reduce the rate of infusion of PRM-151 to half the initial rate; consider discontinue infusion of PRM-151 if symptoms do not respond to medical intervention. If

signs and symptoms resolve with intervention including discontinuation of PRM-151, PRM-151 infusion may be restarted at half the initial rate.

In the case of Grade 3 or greater occurrence of signs and symptoms consistent with infusion related reaction, discontinue infusion of PRM-151.

If PRM-151 resulted in signs and symptoms consistent with Grade 2 or 3 Infusion related reaction, infuse PRM-151 over 1 hour and use the following premedication for all subsequent PRM-151 administration:

a. Diphenhydramine 50 mg IV or clemastine 2 mg IV or an equivalent dose of an antihistaminic drug
b. Dexamethasone 10 mg IV or an equivalent corticosteroid

Infusion related reactions must be reported to Promedior as described in section 7.13.2.1.1, Reporting of Adverse Events of Special Interest.

7.13.1.2. Serious Adverse Event

A serious AE (SAE) is any AE occurring at any dose that results in any of the following outcomes:

- Death;
- Is life-threatening;
- Requires hospitalization;
- Requires prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly or birth defect;

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A life-threatening AE is defined as an AE that placed the subject, in the view of the initial reporter, at immediate risk of death from the AE as it occurred (i.e., it does not include an AE that, had it occurred in a more severe form, might have caused death).

7.13.1.3. Classification of Adverse Events and Serious Adverse Events

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 grading scale (APPENDIX I) should be referenced when assessing the intensity of an AE. If an AE is not described in the NCI CTCAE v 4.0, the severity should be recorded based on the scale below. The severity of all AEs/SAEs should be recorded on the appropriate eCRF page as Grade 1, 2, 3, or 4 corresponding, respectively, to a severity of mild, moderate, severe, or life threatening as outlined in Table 3.

http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Table 3: Adverse Event Grading

Severity	Definition
Grade 1	Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Clarification between Serious and Severe: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) and causality serve as a guide for defining regulatory reporting obligations.

7.13.1.4. Data Monitoring Committee

A DMC will be established to review safety data from this study, thereby better ensuring the safety of study participants. Consistent with US Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry, Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006), the DMC will be constituted of independent clinicians expert in the field of MF and clinical research. A formal charter will be established for the conduct of the DMC.

The committee is planned to review unblinded safety data at periodic intervals. The DMC may ask to schedule ad-hoc meetings as needed. No interim efficacy data are planned to be reviewed by the DMC. Details of safety review are provided in the DMC Charter.

7.13.1.5. Relatedness of Adverse Events and Serious Adverse Events

Relationship of an AE or SAE to investigational product is to be determined by the Investigator based on the definitions in Table 4.

Table 4: Adverse Event Relatedness

Relationship to Product(s)	Definition
Not Related	Unrelated to investigational product.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of investigational product, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biologic plausibility, at least on theoretical grounds.

7.13.2. Procedures for Recording and Reporting Adverse Events

7.13.2.1. Adverse Event Monitoring and Period of Observation

Adverse events (AEs) will be monitored continuously throughout the study.

For the purposes of this study, the period of observation extends from the time at which the subject or the subject's legally authorized representative gives informed consent until the subject's final evaluation of the study. If the Investigator considers it necessary to report an AE in a study subject after the end of the safety observation period, he or she should contact the Sponsor to determine how the AE should be documented and reported.

7.13.2.1.1. Reporting of Adverse Events of Special Interest

The Investigator must report suspected Infusion Related Reaction, regardless of severity, on an Adverse Event of Special Interest (AESI) form. This form must be completed and submitted, either by e-mail or fax, immediately but no later than 24 hours of the Investigator's learning of the event to Pivotal's Safety Unit:

- e-mail: drugsafety@pivotal.es

- Fax (US SAEs): +1 877 853 3275
- Fax (non-US SAEs): +34 91 307 60 47

7.13.2.2. Reporting Serious Adverse Events

The Investigator must report all SAEs to the Safety Unit of Pivotal S.L. within 24 hours of discovery either by e-mail or fax to:

- e-mail: drugsafety@pivotal.es
- Fax (US SAEs): +1 877 853 3275
- Fax (non-US SAEs): +34 91 307 60 47

A completed SAE report is to be sent to Pivotal's Safety Unit within 24 hours of discovering the event. The initial report should include at least the following information:

- Subject's Study Number;
- Description and date of the event;
- Criterion for serious; and
- Preliminary assignment of causality to study drug.

The Safety unit will contact the Investigator either by email or telephone for follow-up information regarding the SAE, as appropriate.

The Investigator must promptly report all required information to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Research Ethics Boards (REB). It is the responsibility of the Sponsor to ensure that each Investigator receives a copy of any CIOMS I/MedWatch report that has been submitted to the appropriate regulatory agencies notifying them of an unexpected related SAE. The Investigator or Sponsor must ensure that the IRB/IEC/REB receives a copy of the report and that a copy is also filed within their study files.

7.13.3 Reporting Pregnancies

Pregnancy itself is not considered an AE. If a subject becomes pregnant or the partner of a subject participating in the study becomes pregnant during the study or within 3 months of discontinuing any study drug, the Investigator should report the pregnancy on a separate pregnancy report form provided to the sites. Only pregnancies occurring from the time of first study treatment dose administered to the subject will be reported and documented. The study treatment will be immediately discontinued for any female subject who becomes pregnant during study participation, if study treatment is ongoing at that time. The subject/partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. This pregnancy report form must be completed and submitted, either by e-mail or fax, immediately but no later than 24 hours of the Investigator's learning of the event to Pivotal's Safety Unit:

- e-mail: drugsafety@pivotal.es

- Fax (US SAEs): + 1 877 853 3275
- Fax (non-US SAEs): +34 91 307 60 47

Any pregnancy complication, spontaneous or elective abortion, still birth, neonatal death, or congenital anomaly will be recorded as an AE or SAE, and reported, as applicable.

7.13.4. Medication Error

A medication error is defined as a mistake made in prescribing, dispensing, administration and/or use of the investigational medicinal product. All medication errors must be recorded in the eCRF.

7.14. Removal of Subjects from the Trial or Investigational Product

A subject's participation in the study may be discontinued at any time at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to remove a subject from the study:

- Non-compliance, including failure to appear at one or more study visits;
- The subject withdraws consent;
- The subject was erroneously included in the study;
- The subject develops an exclusion criterion;
- The subject suffers an intolerable adverse event;
- The subject becomes pregnant;
- The study is terminated by the Sponsor.

The subject is free to withdraw consent and discontinue participation in the study at any time without prejudice to further treatment. If a subject discontinues participation in the study, or the subject is discontinued by the Investigator, the Investigator will notify the Sponsor and, when possible, will perform the procedures indicated for the final visit. Follow-up information will be obtained during the final telephone contact, if possible, for subjects who discontinue their participation in or are withdrawn from the study.

Any adverse events (AEs) experienced up to the point of discontinuation must be documented on the AE eCRF. If AE's are present when the subject withdraws from the study, the subject will be re-evaluated within 30 days of withdrawal. All ongoing SAEs at the time of withdrawal will be followed until resolution.

Subjects withdrawn from the study will be replaced at the discretion of the medical monitor and the Investigator. A replacement subject will be randomized to treatment with single agent PRM-151 at doses of 0.3, 3, or 10 mg/kg IV.

7.15. Other Study Procedures

Not applicable

7.16. Appropriateness of Measurements

Subjects will be assessed for safety at all visits based on history, physical examination, and laboratory values. Subjects will be assessed for efficacy every four weeks by hematologic parameters (Hgb, WBC with differential, ANC, and platelet count), measurement of splenomegaly, and symptom assessment, and at Weeks 12, 24, and 36 by bone marrow biopsy to assess change in fibrosis. Global assessment of fibrosis will be assessed at Baseline, Weeks 12, 24, and 36 by FDG or FLT PET-CT.

8.0 STAGE 2 STUDY ACTIVITIES

The Schedules of Events can be found in APPENDIX A. Quality of Life assessments (MPN-SAF and EORTC QLQ-C30) should be done as early in the visit as possible and prior to phlebotomy, bone marrow biopsy or any other procedure that may affect subject responses. In the event the central lab cannot be used to get a reliable result for a laboratory test, local laboratory tests may be used after this has been agreed upon by the Medical Monitor.

8.1. Screening Visit (≤ 28 Days Prior to First Dose)

- Provide written informed consent
- Recording of demographics and medical history
- Assessment of inclusion/exclusion criteria
- MPN-SAF
- EORTC QLQ-C30
- IWG-MRT DIPPS (risk assessment)
- Bone marrow biopsy (< 4 weeks prior to first dose)
- Abbreviated physical examination with spleen measurement (as defined in Table 1).
- Recording of prior and concomitant medications
- Assessment of Adverse Events
- Vital signs
- Height and weight
- ECOG Performance Status
- Serum pregnancy test for women of child-bearing potential (central lab (< 4 weeks prior to first dose)
- Complete blood count (CBC) (central lab)
- Chemistry evaluations (central lab)
- Coagulation parameters (central lab)
- 12 lead Electrocardiogram (ECG)
- Review of transfusions
- Review of excluded medications
- Access IRS to register subject

8.2. Cycle 1, Day 1 (+/- 1 day)

- FDG or FLT PET-CT (where feasible) or CT or MRI (within 2 weeks prior to C1D1)
- Update medical history
- Re-assess inclusion/exclusion criteria
- MPN-SAF
- EORTC QLQ-C30
- IWG-MRT DIPSS (risk assessment)
- Abbreviated physical exam with spleen measurement
- Recording of concomitant medications
- Monitoring of adverse events
- Vital signs (before, immediately after study drug infusion and 1 hour post infusion)
- Weight
- ECOG Performance Status
- Urine pregnancy test for women of child-bearing potential (local lab)
- Complete blood count (CBC) (central lab)
- Chemistry evaluations (central lab)
- Coagulation parameters (central lab)
- Blood sample for Infusion Related Reaction Cytokines and anti-pentraxin 2 antibodies (pre-dose)
- Blood samples for genetic analysis
- Review of transfusions
- Review of excluded medications
- Blood sample for pentraxin-2 levels (pre-dose)
- Blood sample for anti-pentraxin 2 antibodies (pre-dose)
- Unblinded Pharmacist (or designee) to access IRS to randomize subject to dosing cohort
- PRM-151 administration

8.3. Cycle 1, Days 3 and 5 (+/- 1 day)

- Recording of concomitant medications
- Monitoring of adverse events
- Vital signs
- ECOG Performance Status
- Unblinded Pharmacist (or designee) to access IRS to confirm dosing
- PRM-151 administration

8.4. Cycles 2 through 9, Day 1 (+/- 3 days)

- MPN-SAF
- EORTC QLQ-C30
- IWG-MRT Response Assessment (PMF, post-EV MF and post PV MF patients)
- Bone marrow biopsy (Cycle 4 and Cycle 7, Day 1 +/- 3 days)
- FDG or FLT PET-CT (where feasible) or CT or MRI (Cycle 4 and Cycle 7, Day 1 +/- 3 days)
- Abbreviated physical exam with spleen measurements
- Response Assessment
- Recording of concomitant medications
- Monitoring of adverse events
- Vital signs
- Weight
- ECOG Performance Status
- Urine pregnancy test for women of child-bearing potential (local lab)
- Complete blood count (CBC) (central lab)
- Chemistry evaluations (central lab)
- Coagulation parameters (central lab)
- Review of transfusions
- Review of excluded medications
- Blood sample for pentraxin -2 levels (pre-dose)
- Blood sample for anti pentraxin 2 antibodies (pre-dose)
- Unblinded Pharmacist (or designee) to access IRS to confirm dosing
- PRM-151 administration

8.5 Cycle 9, Day 29 (Week 36) (+/- 3 days)

- MPN-SAF
- EORTC QLQ-C30
- IWG-MRT DIPSS (risk assessment)
- IWG-MRT Response Assessment (PMF, post-EV MF and post PV MF patients)
- PET-CT or CT or MRI (+/- 3 days)
- Bone marrow biopsy (+/- 3 days)
- Abbreviated physical exam with spleen measurements
- Recording of concomitant medications
- Monitoring of adverse events
- Vital signs
- ECOG Performance Status
- Complete blood count (CBC) (central lab)

- Chemistry evaluations (central lab)
- Coagulation parameters (central lab)
- Review of transfusions
- Review of excluded medications
- Blood sample for pentraxin-2 levels (pre-dose if continuing treatment in extension)
- Blood sample for anti-pentraxin 2 antibody (pre-dose)
- Blood samples for genetic analysis

8.6. End of Study Visit (approximately 28 days [+/- 3 days] after Cycle 9 Day 29 or withdrawal from study)

- MPN-SAF
- EORTC QLQ-C30
- Abbreviated physical exam and spleen measurement
- Recording of concomitant medications
- Monitoring of adverse events
- Vital signs
- ECOG Performance Status
- Complete blood count (CBC) (central lab)
- Chemistry evaluations (central lab)
- Review of transfusions
- Review of excluded medications

9. QUALITY ASSURANCE AND CONTROL

Training will occur at the site initiation visit; instruction manuals will be provided to aid consistency in data collection and reporting across sites.

Clinical sites will be monitored by the Sponsor or its designee to ensure the accuracy of data against source documents.

The required data will be captured in a validated clinical data management system that is compliant with the FDA 21 Code of Federal Regulations (CFR) Part 11 Guidance. The clinical trial database will include an audit trail to document any evidence of data processing or activity on each data field by each user. Users will be trained and given restricted access, based on their role(s) in the study, through a password-protected environment.

Data entered in the system will be reviewed manually for validity and completeness against the source documents by a clinical monitor from the Sponsor or its designee. If necessary, the study site will be contacted for corrections or clarifications; all missing data will be accounted for.

10. STAGE 2 PLANNED STATISTICAL METHODS

10.1 Determination of Sample Size

The chosen sample size of 72 subjects (i.e. 24 subjects per dose arm) is deemed sufficient to provide adequate precision to the estimation of the response rate in each treatment arm. The trial will enroll 84 subjects to allow for a discontinuation rate of 15%.

On the basis of the available data, it is assumed that the response rate on the primary endpoint will be 5% in the 0.3 mg/kg arm, 46% in the 10 mg/kg arm and at least 46% in the 3 mg/kg arm. A sample size of 24 subjects will ensure an absolute precision of +/- 8% to the evaluation of the response rate in the 0.3 mg/kg arm (assuming the response rate is 5%) and an absolute precision of +/- 20% of the response rate in the 3 mg/kg and 10 mg/kg arms (assuming the response rate is 46%).

In addition, with 24 subjects in each arm, the probability to demonstrate that the observed response rate in the 3 mg/kg and 10 mg/kg arms is larger than 10% by comparing the lower limit of the exact 97.5% two-sided confidence interval of the observed rate to 10% is larger than 0.999 (assuming the response rate is 46%)

In addition, it is planned to perform pairwise comparisons between dose arms as part of the secondary efficacy analysis. A sample size of 24 subjects per arm will ensure a power of 82% to detect a difference of 39% between two treatment arms (assuming the best response rate is 46%) with a two-sided type one error of 0.025. Consequently if the assumption of response rates of 5% in the 0.3 mg/kg arm and 46% in the 3 and 10 mg/kg arm is true, the study will be sufficiently powered (power = 82%) to demonstrate a significant superiority of any of the higher doses over the smallest dose, using an adjusted two-sided 0.025 type-one error rate.

10.2. Randomization and Stratification

This study is randomized with a 1:1:1 randomization ratio. A central randomization system will be used. The randomization will be stratified according to the subject's baseline hematologic status: baseline anemia (Hgb < 100 g/L and having received $\geq$ 2 units PRBC in 12 weeks prior to study entry) alone or baseline thrombocytopenia (platelet count < 50 x 10^9/L) alone; or baseline anemia associated with baseline thrombocytopenia. The randomization system will also ensure that at least 50% of the subjects in the final study population will have baseline thrombocytopenia.

10.3. General considerations for statistical analysis

10.3.1 Statistical Analysis Plan

The statistical section of the protocol presents the main features of the planned statistical analysis. A detailed statistical analysis plan (SAP) will be prepared by the Venn Life Sciences

statistician, validated by the sponsor and signed before the database lock prior to any unblinded statistical analysis.

Any change to the planned statistical methods will be documented in the clinical study report.

10.3.2 Descriptive statistics

Quantitative variables will be described by treatment group using the following statistics: number of available data, number of missing values, mean, standard deviation, median, Q1, Q3, minimum and maximum values. When relevant, confidence intervals will also be computed.

Qualitative variables will be described by treatment group using number of available data, number of missing values, frequency counts for each category and corresponding percentage. Percentages will be calculated using the number of available data as the denominator (i.e. not including missing values). When relevant, confidence intervals will also be computed.

10.3.3. Inferential statistics

The primary efficacy analysis is both descriptive and inferential. The exact confidence interval for the response rate in each arm will be computed and its lower bound will be compared to 10%.

In addition, one secondary objective of the study is to determine if there is a difference in efficacy between the three doses of PRM-151 used in the study. These comparisons will be done only if at least one dose arm is demonstrated to have a response rate superior to 10% in the primary analysis. The comparison between the 3 mg/kg arm and 10 mg/kg arm is not expected to be sufficiently powered to detect any statistically significant difference. The two main comparisons (3 mg/kg arm versus 0.3 mg/kg arm and 10 mg/kg arm versus 0.3 mg/kg) will use an adjusted type-one error rate of 0.025 to control the overall type-one error rate. The 3 mg/kg versus 10 mg/kg comparison will only be provided with an exploratory purpose and will be done without correction of the type-one error.

For all the other secondary efficacy analyses involving formal statistical comparisons, no adjustment of the type-one error rate will be conducted. As a consequence, the results of these tests will have to be interpreted bearing in mind the issue of multiplicity and the increased risk of erroneously obtaining statistically significant results.

10.3.4. Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. For the primary efficacy criterion analysis, subjects with a reduction in bone marrow fibrosis score by at least one grade according to WHO criteria (central adjudication) at any post baseline visit will be considered as responders. Subjects without any central assessment of bone marrow fibrosis will be considered as non-responders. In addition, subjects who discontinue due to toxicity prior to completion of one cycle of study drug will also be considered non-responders for the efficacy analyses.

Except for the imputation of missing values for the analysis of the primary criterion as described above, all other analyses will be based on observed data only; no missing data will be imputed.

10.3.5. Interim Analyses

There is no interim analysis planned.

10.3.6. Software used for statistical analyses

The < SAS software, version 9.2 or higher >, will be used for the statistical analysis.

10.4 Protocol deviations

Major protocol deviations are defined as deviations liable to prevent or change the interpretation of the results of the primary efficacy analysis of the study. The following deviations will be considered as major (this list is not exhaustive and will be reviewed at the time of the blind review meeting):

- non compliance with the inclusion or non inclusion criteria
- non compliance with study treatment
- no post-baseline data for the primary efficacy endpoint
- intake of forbidden medication

All other deviations will, a priori, be considered as minor deviations. However, all deviations will be reviewed and adjudicated as either major or minor during the blind review meeting before database lock and code break.

10.5. Analysis datasets

The statistical analysis will be conducted on the following subject data sets:

10.5.1. Efficacy Analysis Sets:

The Full Analysis Set (FAS) will consist in all randomized subjects having received at least one administration of the study medication with at least one post-baseline assessment of BMRR (primary efficacy criterion) available. Subjects who discontinue due to toxicity prior to completion of one cycle of study drug will also be kept in the FAS and considered non-responders for the efficacy analysis.

The full analysis set will be the primary population for the efficacy analyses in this trial.

The Per Protocol (PP) set: a subset of the FAS consisting of all subjects who are randomized, and who did not present any major protocol deviations, who are evaluable based on having received at least 3 cycles of study drug, and who have an ORR measurement. The per-protocol set will be used for secondary analyses of the primary efficacy criterion and for the analysis of some selected secondary efficacy criteria.

10.5.2. Safety Analysis Sets:

The Safety (SAF) dataset: composed of all randomized subjects having received at least one dose of study drug and having a post-baseline safety observation. This data set will be used to perform the analysis of safety.

10.6. Planned Statistical Analyses and Methods

10.6.1 Efficacy Analyses

10.6.1.1. Primary analysis of efficacy

The primary efficacy analysis will consist in computing the bone marrow response rate (percent of subjects with a reduction in bone marrow fibrosis score by at least one grade, see Section 3.1) and its 95% (unadjusted) and 97.5% (adjusted) two-sided confidence intervals within each treatment arm. This analysis will be conducted on the FAS analysis set.

Inferential interpretation: for the 3 mg/kg and 10 mg/kg arms, the lower limit of the 97.5% two-sided confidence interval will be compared to 10%, a threshold assumed to define the minimal clinically relevant effect. If the lower limit of the confidence interval is above 10%, the corresponding dose will be claimed to have demonstrated clinically relevant efficacy.

The confidence intervals computation will use a method consistent with the stratified design.

10.6.1.2. Sensitivity analyses on the primary endpoint:

Sensitivity analyses on the FAS:

To further examine a potential stratum effect, the BMRR and its confidence interval will be computed for each dose arm within each stratum, at least for the dose by stratum combination cells with sufficiently large sample sizes (i.e. greater than 10).

Sensitivity analyses on the PP set:

The analysis described above in Section 10.6.1.1. for the primary analysis on the FAS will be repeated on the PP analysis.

10.6.1.3. Secondary and exploratory efficacy analyses:

10.6.1.3.1. Comparison of PRR between treatment arms

Pairwise comparisons between the three dose groups will be performed using the Cochran-Mantel-Haenszel (general association) statistic in the SAS Freq procedure, to take into account the stratified design, using the following statement:

*tables Stratum*Treatment*Response / cmh;*

The Breslow-Day Test for Homogeneity of the Odds Ratios will be examined to detect a potential significant stratum difference in the odds ratios.

Two pairwise comparisons (3 mg/kg versus 0.3 mg/day and 10 mg/kg versus 0.3 mg/day) will be computed with the aim to demonstrating superiority and, consequently, will use an adjusted a two-sided 0.025 level of significance.

The third comparison (10 mg/kg versus 3 mg/kg) is not expected to have enough power to demonstrate any difference with the planned sample size. This comparison is considered exploratory and will be conducted using an unadjusted 0.05 level of significance.

These analyses will be computed on both the FAS (primary analysis set) and PP analysis sets.

10.6.1.3.2. Analyses of categorical secondary and exploratory efficacy endpoints:

Percentages and or rates will be computed, together with their 95% confidence intervals, within each treatment arm.

10.6.1.3.3. Analyses of quantitative secondary and exploratory efficacy endpoints:

Descriptive statistics for quantitative variables (see Section 10.3.2) will be computed, together with the 95% CI of the mean (or median depending on the variable)

10.6.1.3.4. Inferential analyses for secondary and exploratory efficacy endpoints:

For all categorical or quantitative secondary efficacy endpoints, formal pairwise between arms comparisons will be computed. These comparisons will use a two-sided 0.05 level of significance, hence without any correction for multiplicity (See section 10.3.3). The results of these tests will have to be interpreted cautiously bearing in mind the issue of multiplicity and the increased risk of erroneously obtaining statistically significant results.

No between arms comparisons will be computed for the exploratory efficacy endpoints, only descriptive analyses will be computed.

10.6.2. Safety Analysis

Safety evaluations will be based on the incidence, intensity, and type of adverse events, and clinically significant changes in the subject's physical examination, vital signs and clinical laboratory results. Safety variables will be tabulated and presented for all subjects who receive any amount of study medication. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) adverse event coding system for purposes of summarization. All adverse events occurring on study will be listed in by-subject data listings. Treatment-emergent events (TEAEs) will be tabulated, where treatment-emergent is defined as any adverse event that occurs after administration of any amount of study drug, or any event that is present at baseline but worsens in intensity or is subsequently considered drug-related by the Investigator. By treatment tabulations will be performed by MedDRA system organ class (SOC) and preferred term (PT) for deaths if any, serious adverse events; all treatment-emergent adverse events; TEAEs leading to discontinuation of study therapy due to adverse event or toxicity and TEAEs resulting in study discontinuation. Events that are considered related to treatment (possibly or probably drug-related) will also be tabulated. Tabulation will also be provided that enumerates adverse events by maximum severity.

Laboratory evaluations will be summarized by time of collection and by treatment group. In addition, change from baseline to any post-dose values will be summarized for vital signs and clinical laboratory results.

The frequency of subjects with abnormal safety laboratory results will be tabulated by treatment. Shift tables for each cycle will be produced for selected laboratory parameters, to include at least hemoglobin, WBC count, neutrophils, lymphocytes, platelets, AST, ALT, bilirubin, LDH, creatinine, alkaline phosphatase and electrolytes. These tables will summarize by cycle and dose level the number of subjects with each baseline CTC grade and changes to the maximum CTC grade in the cycle.

Clinically significant laboratory abnormalities will be tabulated or presented in individual data listings, depending on their number.

Vital signs assessments will be summarized over time in a similar fashion to laboratory parameters, and any abnormal values will be tabulated.

10.6.3. Other Analyses

10.6.3.1. Subject Disposition

A listing and table of proportions of subjects discontinuing the study for each reason will be provided by treatment / dose group. Details will be included in the Statistical Analysis Plan.

10.6.3.2. Demographic and Baseline Characteristics

Summary statistics will be provided for the demographic and baseline characteristics; details will be in the Statistical Analysis Plan.

10.6.3.3. Subject Adherence and Extent of Exposure

Compliance with study drug will be computed for each subject as proportion of prescribed study drug actually taken. Details will be included in the Statistical Analysis Plan.

Extend of exposure: Summary statistics will be provided for overall duration of study treatment, number of injections received and cumulative dose of IP received.

10.6.3.4. Concomitant Medications

A listing of table of proportions of subjects taking each concomitant medication will be provided. Details will be included in the Statistical Analysis Plan.

11. ADMINISTRATIVE REQUIREMENTS

11.1. Investigators and Study Administrative Structure

Before initiation of the study, the investigators must provide the sponsor with a completed Form FDA 1572. Investigational product may be administered only under the supervision of the investigators listed on this form. Curriculum vitae must be provided for the investigators and sub-investigators listed on Form FDA 1572.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study treatments, and their study related duties and functions. The Investigator must maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study related duties.

11.2 Institutional Review Board (IRB), Independent Ethics Committee (IEC) Approval, or Research Ethics Board Attestation (REB)

Before initiation of the study, the Investigator must provide the Sponsor with a copy of the written IRB/IEC/REB approval of the protocol and the informed consent form. This approval must refer to the informed consent form and to the study title, study number, and version and date of issue of the study protocol, as given by the Sponsor on the cover page of the protocol.

Status reports must be submitted to the IRB/IEC/REB at least once per year. The IRB/IEC/REB must be notified of completion of the study. Within three months of study completion or termination, a final report must be provided to the IRB/IEC/REB. A copy of these reports will be sent to the study clinical monitor. The Investigators must maintain an accurate and complete record of all submissions made to the IRB/IEC/REB, including a list of all reports and documents submitted. AEs which are reported to FDA or other Regulatory agencies (IND Safety Reports) must be submitted promptly to the IRB/IEC/REB.

11.3. Ethical Conduct of the Study

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigators abide by Good Clinical Practice (GCP) as described in the 21 CFR Parts 50, 54, 56, and 312 and the International Conference on Harmonisation (ICH) GCP Guidelines. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the Declaration of Helsinki.

11.4. Subject Information and Consent

Before enrolling in the clinical study, the subject must consent to participate after the nature, scope, and possible consequences of the clinical study and have been explained in a form understandable to him or her.

An informed consent form (assent form if applicable) that includes information about the study will be prepared and given to the subject. This document will contain all GCP and ICH-required elements. The informed consent (or assent) form must be in a language understandable to the subject and must specify who informed the subject.

After reading the informed consent form, the subject must give consent in writing. Consent must be confirmed at the time of consent by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions.

If the subject is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (e.g., the subject's thumbprint or mark). The witness and the person conducting the informed consent discussions must also sign and personally date the informed consent document. It should also be recorded and dated in the source document that consent was given.

A copy of the signed and dated consent document(s) must be given to the subject. The original signed and dated consent document will be retained by the Investigator.

The investigator will not undertake any measures specifically required solely for the clinical study until valid consent has been obtained.

A model of the informed consent form to be used in this study will be provided to the sites separately from this protocol.

11.5. Subject Confidentiality

Subject names will not be supplied to the Sponsor. Only the subject number and subject initials will be recorded in the eCRF, and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be told that representatives of the Sponsor, a designated CRO, the IRB/IEC/REB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws. The Investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

11.6. Study Monitoring

Monitoring procedures that comply with current Good Clinical Practice (GCP) guidelines will be followed. Review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be performed by a representative of the Sponsor (Clinical Study Monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and GCP guidelines by frequent site visits and communications (e.g., email, letter, telephone, and facsimile).

11.7. Case Report Forms and Study Records

Case report forms are provided for each subject in electronic format. Electronic Data Capture (EDC) will be used for this study. The study data will be recorded from the source documents into the eCRF. The electronic files will be considered as the eCRFs.

All forms must be filled out by authorized study personnel. All corrections to the original eCRF entry must indicate the reason for the change. The Investigator is required to sign the eCRF after all data have been captured for each subject/subject. If corrections are made after review and signature by the Investigator, he or she must be made aware of the changes, and his or her awareness documented by re-signing the eCRF.

11.8. Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established for purposes of independent assessment of safety during study conduct, as described in Section 7.13.1.4.

11.9. Central Bone Marrow Review Committee

All bone marrow assessments will be performed by a committee of expert hematopathologists, who will be blinded to subject, dose, and time of biopsy. The rules for assessment and adjudication will be defined in the Central Bone Marrow Review Committee charter.

11.10 Protocol Violations/Deviations

The Investigator will conduct the study in compliance with the protocol. The protocol will not be initiated until the IRB/IEC/REB and the appropriate regulatory authorities have given approval/favorable opinion. Modifications to the protocol will not be made without agreement of the Sponsor. Changes to the protocol will require written IRB/IEC/REB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC/REB may provide, if applicable regulatory authorities permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC/REB. The sponsor will submit all protocol modifications to the regulatory authorities in accordance with the governing regulations.

A record of subjects screened, but not entered into the study, is also to be maintained. For any subject who does not meet the inclusion or exclusion criteria, a protocol exception may be requested by the Investigator. This exception may be approved by the Sponsor's Medical Monitor prior to enrollment and the protocol exception must be fully documented in the source documents and on the appropriate page of the eCRF.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor or its designee, if circumstances permit, to discuss the planned course of action. Any departures form the protocol must be fully documented as a protocol deviation. Protocol deviations may be required to be submitted to the IRB/IEC/REB in accordance with local requirements.

Protocol modifications will only be initiated by the Sponsor and must be approved by the IRB/IEC/REB and submitted to FDA or other applicable international regulatory authority before initiation.

11.11. Premature Closure of the Study

If the Sponsor, Investigator, or regulatory authorities discover conditions arising during the study which indicate that the clinical investigation should be halted due to an unacceptable subject risk, the study may be terminated after appropriate consultation between the Sponsor and the Investigator(s). In addition, a decision on the part of the Sponsor to suspend or discontinue development of the investigational product may be made at any time. Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study;
- Failure of the Investigator to comply with pertinent global regulations;
- Submission of knowingly false information from the study site to the Sponsor or other pertinent regulatory authorities;
- Insufficient adherence by the Investigator to protocol requirements;
- Administrative reasons as determined by the Sponsor.

11.12. Access to Source Documentation

Regulatory authorities, the IRB/IEC/REB, or the Sponsor or its designee may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities. Monitoring and auditing procedures that comply with current GCP guidelines will be followed. On-site review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters may be performed.

11.13. Data Generation and Analysis

The clinical database will be developed and maintained by the Sponsor or designee (CRO) or an electronic data capture technology provider as designated by the Sponsor.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 12.0 or later. Concomitant medication will be coded using WHO-Drug Dictionary (WHO-DD). Centralized laboratories may be employed as described in the study manual to aid in consistent measurement of efficacy and safety parameters.

11.14. Retention of Data

Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will notify the Investigator if these documents must be retained for a longer period of time. It is the responsibility of the Sponsor to inform the Investigator or institution as to when these documents no longer need to be retained.

Records will be maintained by the Sponsor for a period of 25 years and will be accessible for onsite inspection by regulatory agency inspectors.

11.15. Financial Disclosure

The Investigator should disclose any financial interests in the Sponsor as described in 21 CFR Part 54 prior to beginning this study. The appropriate form will be provided to the Investigator by the Sponsor, which will be signed and dated by the Investigator, prior to the start of the study and one year after the conclusion of the study.

11.16. Liability and Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating subjects and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

11.17. Publication Policy

Publication of any data from this trial by the investigators must be carried out in accordance with the Clinical Study Agreement.

12. USE OF INFORMATION

This document contains information that is confidential and/or proprietary to the Sponsor. This information is being provided to you solely for the purpose of evaluating and/or conducting a clinical study for the Sponsor. You may disclose the contents of this document only to study personnel under your supervision, IRBs, ECs, or duly authorized representatives of regulatory agencies for this purpose under the condition that they maintain confidentiality. The contents of this document may not be used in any other clinical study, disclosed to any other person or entity, or published without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any applicable governmental regulations or laws; however, you will give prompt notice to the Sponsor prior to any such disclosure. All other nonpublic information provided by the Sponsor, as well as any information that may be added to this document, also is confidential and/or proprietary to the Sponsor and must be kept in confidence in the same manner as the contents of this document.

13. INVESTIGATOR AGREEMENT

I have read and approve this protocol. My signature, in conjunction with the signature of the Sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

_____
Principal Investigator printed name

_____ _____
Principal Investigator signature Date

_____

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_____
Investigational site or name of institution and location (printed)

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APPENDIX A **Schedule of Events**

	Screening < 28 days	**Cycle 1 28 Day Cycle Length**			**Cycle 2, 3, 4, 5, 6, 7, 8, 9, 28 Day Cycle Length**	**Cycle 9, Day 29**	**End of Study[14]**
		Day (+/- 1 day)			**Day (+/- 3 days)**	**(+/- 3 days)**	**(+/- 3 days)**
		1	**3**	**5**	**1**		
Informed Consent	x						
Demographics	x						
Past Medical History	x	x					
Inclusion/Exclusion	x	x					
Bone Marrow Biopsy[1]	x				x	x	
Physical Exam [2]	x	x			x	x	x
IWG-MRT Response Assessment					x	x	
Prior/Concomitant Medications	x	x	x	x	x	x	x
Transfusion history (previous 12 weeks and between screening visit)	x	x			x	x	x
Review of transfusion diaries	x	x			x	x	x
AE/SAE Assessment[3]	x	x	x	x	x	x	x
Vital Signs [4]	x	x	x	x	x	x	x
Height (cm)	x						
Weight (kg)	x	x			x		
ECOG Performance Score	x	x	x	x	x	x	x
Pregnancy test [5]	x	x			x		
Complete Blood Count [6]	x	x			x	x	x
Chemistry, BUN/creatinine [7]	x	x			x	x	x
Coagulation [8]	x	x			x	x	
12 lead ECG [9]	x						
PET-CT Scan or CT or MRI[10]		x			x	x	
Exploratory laboratory assessments[11]		x				x	
Special list of excluded medications	x	x			x	x	x
Anti-pentraxin 2 antibodies, pre-dose		x			x	x	
Pentraxin-2 , pre-dose		x			x	x	
MPN-SAF [12]	x	x			x	x	x
EORTC-QLQC30 [13]	x	x			x	x	x
Access IRS [14]	x	x	x	x	x		
IWG-MRT DIPPS (risk assessment)	x	x				x	

PRM-151 Administration [16]		x	x	x	x		
Infusion Related Reaction Cytokines and anti-pentraxin 2 antibodies [15]		x					

1 Bone marrow biopsy at Screening must have been performed within 4 weeks prior to first infusion of PRM-151; subsequent bone marrow biopsies on Cycle 4, Day 1, Cycle 7, Day 1 and on Cycle 9, Day 29 performed +/- 3 days of scheduled visit

2 Abbreviated physical exam including spleen measurement by palpation at all time points

3 Pre-treatment adverse events, including serious adverse events will be collected from the time of informed consent and after the medical history has been obtained

4 Vital signs (including temperature, blood pressure, pulse rate, and respiratory rate) will be performed before and immediately after PRM-151 infusion ,and at the conclusion of the one hour observation period

5 Serum pregnancy test within 4 weeks prior to the first dose of the study drug (central lab) Urine pregnancy test at all subsequent time points (local lab)

6 Complete blood count (CBC) includes red blood cell count (RBC), hemoglobin, hematocrit, white blood cell count with differential, absolute neutrophil count (ANC), reticulocyte count, blast count, platelets, and review for blood nucleated red blood cells and immature myeloid cells

7 Blood chemistry lab parameters include lactic dehydrogenase (LDH), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), direct and indirect bilirubin, alkaline phosphatase, creatinine phosphokinase (CPK), uric acid, calcium, phosphorus, sodium, potassium, chloride, albumin, bicarbonate, BUN, creatinine, and glucose

8 Coagulation testing at screening for all subjects to include prothrombin time (PT), and partial thromboplastin time (PTT) For subjects receiving warfarin, the PT, PTT and international normalized ratio (INR) must be obtained Abnormal INRs will be tested twice weekly until the INR is stable for one month, followed by monthly monitoring of INRs

9 ECGs will be obtained at screening and in the event of an infusion related reaction

10 FDG or FLT PET-CT scans (depending on feasibility) or CT or MRI at Cycle 1 Day 1 (or within 2 weeks prior), Cycle 4 Day 1, Cycle 7 Day 1 and Cycle 9 Day 29

11 Whole blood samples for cytogentics and mutational status to be obtained on Cycle 1 Day 1 and whole blood samples for changes in allele burden will be obtained on Cycle 9 Day 29

12 If possible, the questionnaire should be completed prior to performing laboratory and radiology procedures, particularly bone marrow biopsy

13 At the Screening visit IRS can be assessed to register a subject by any member of the site staff Beginning at Cycle 1 Day 1, only the unblinded Pharmacist (or designee) may access IRS

14 End of Study Visit is 28 days after Cycle 9, Day 29 or withdrawal from study

15 Infusion Related Reaction Cytokines (TNF-α, IFN-γ, IL-2, IL-4, IL-6, IL-8, IL-10) and anti-pentraxin 2 antibodies will be drawn pre-dose on Cycle 1 Day 1 and repeated only in the event of an infusion related reaction or a suspected adverse reaction

16 Subjects will be observed one hour after each dose

APPENDIX B: International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia*

Response categories	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)
CR	Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF† and Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥ 1 × 10^9/L and <UNL; Platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
PR	Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF†, and peripheral blood: Hemoglobin ≥85 but <100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥50, but <100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement (CI)	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia§
Anemia response	Transfusion-independent patients: a ≥20 g/L increase in hemoglobin level‖ Transfusion-dependent patients: becoming transfusion-independent¶
Spleen response#	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable** or A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50%** A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response A spleen response requires confirmation by MRI or computed tomography showing ≥35% spleen volume reduction
Symptoms response	A ≥50% reduction in the MPN-SAF TSS††
Progressive disease‡‡	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or Leukemic transformation confirmed by a bone marrow blast count of ≥20% or A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 × 10(9)/L that lasts for at least 2 weeks
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or Loss of anemia response persisting for at least 1 month or Loss of spleen response persisting for at least 1 month
	Recommendations for assessing treatment-induced cytogenetic and molecular changes
Cytogenetic remission	At least 10 metaphases must be analyzed for cytogenetic response evaluation and requires confirmation by repeat testing within 6 months window CR: eradication of a preexisting abnormality PR: ≥50% reduction in abnormal metaphases (partial response applies only to patients with at least ten abnormal metaphases at baseline)
Molecular remission	Molecular response evaluation must be analyzed in peripheral blood granulocytes and requires confirmation by repeat testing within 6 months window CR: Eradication of a pre-existing abnormality PR: ≥50% decrease in allele burden (partial response applies only to patients with at least 20% mutant allele burden at baseline)
Cytogenetic/molecular relapse	Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing

EMH, extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhepatosplenic EMH); LCM, left costal margin; UNL, upper normal limit.

*Baseline and posttreatment bone marrow slides are to be interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

†Grading of MF is according to the European classification

Thiele et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. *Haematologica.* 2005;90:1128.

It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.

‡Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, <5% immature myeloid cells is allowed.

§See above for definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥25 000 × 10(9)/L and absolute neutrophil count of ≥0.5 × 10(9)/L.

‖Applicable only to patients with baseline hemoglobin of <100 g/L. In patients not meeting the strict criteria for transfusion dependency at the time of study enrollment (see as follows), but have received transfusions within the previous month, the pretransfusion hemoglobin level should be used as the baseline.

¶Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBC), in the 12 weeks prior to study enrollment, for a hemoglobin level of <85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥85 g/L.

#In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy.

**Spleen or liver responses must be confirmed by imaging studies where a ≥35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

††Symptoms are evaluated by the MPN-SAF TSS.[17] The MPN-SAF TSS is assessed by the patients themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). Symptoms response requires ≥50% reduction in the MPN-SAF TSS.

‡‡Progressive disease assignment for splenomegaly requires confirmation my MRI or computed tomography showing a ≥25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to posttreatment measurements.

***Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: International Working Group -Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. Blood. 2013; 122:1395-1398.**

APPENDIX C: Proposed Revised World Health Organization Criteria for Primary Myelofibrosis

Major criteria

1. Presence of megakaryocyte proliferation and atypia[1], usually accompanied by either reticulin and/or collagen fibrosis, or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)
2. Not meeting WHO criteria for PV[2], CML[3], MDS[4], or other myeloid neoplasm
3. Demonstration of *JAK2*617V_F or other clonal marker (eg, *MPL*515W_L/K), or in the absence of a clonal marker, no evidence of bone marrow fibrosis due to underlying inflammatory or other neoplastic diseases

Minor criteria

1. Leukoerythroblastosis
2. Increase in serum lactate dehydrogenase level[5]
3. Anemia
4. Palpable splenomegaly

Diagnosis requires meeting all 3 major criteria and 2 minor criteria.

[1]Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.

[2]Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels. Red cell mass measurement is not required.

[3]Requires the absence of *BCR-ABL*.

[4]Requires the absence of dyserythropoiesis and dysgranulopoiesis.

[5]Degree of abnormality could be borderline or marked.¶

Secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies. It should be noted that subjects with conditions associated with reactive myelofibrosis are not immune to primary myelofibrosis and the diagnosis should be considered in such cases if other criteria are met,

Tefferi A, Thiele J, et al. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. Blood. 2007; 110:1092-1097.

APPENDIX D: WHO Grading of Bone Marrow Fibrosis (EU Consensus Criteria)

Grading	Description*
MF - 0	Scattered linear reticulin with no intersections (cross overs) corresponding to normal bone marrow
MF – 1	Loose network of reticulin with many intersections, especially in perivascular areas
MF – 2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
MF – 3	Diffuse and dense increase in reticulin with extensive intersections with course bundles of collagen, often associated with significant osteosclerosis

*Fiber density should be assessed in hematopoietic (cellular) areas.

Thiele J, Kvasnicka HM, Facchetti F, et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. *Haematologica* 2005; 90:1128-1132

APPENDIX E: International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Dynamic International Prognostic Scoring System (DIPSS) for primary myelofibrosis*

The IWG-MRT Dynamic Prognostic Scoring System is based on 5 prognostic variables at presentation:

		Value	
Prognostic Variable	**0**	**1**	**2**
Age, y	≤ 65	> 65	
White blood cell count, x 10^9/L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional Symptoms, Y?N	N	Y	

The values for the prognostic variables are added together to produce a total score, and subjects are assigned to risk groups based on their score.

Risk Group	Number of Risk Factors
Low	0
Intermediate-1	1-2
Intermediate-2	3-4
High	5-6

(Passamonti, Cervantes et al. 2010) A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood. 2010;115:1703-1708.

APPENDIX F: Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status*	Grade
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

*As published in Am. J. Clin. Oncol.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5:649-655. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

APPENDIX G: Myeloproliferative Neoplasm Symptom Assessment Form(MPN-SAF)

Myeloproliferative Neoplasm Symptom
Assessment Form (MPN-SAF)
and
Myelolproliferative Neoplasms Symptom
Assessment Form Total Symptom Score (MPN-SAF TSS)

Symptoms among the Myeloroliferative Neoplasms (MPNs) are severe and are correlated with poor prognosis. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) and Myelolproliferative Neoplasms Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) are currently the only two validated measures symptom burden specific to the Myeloproliferative Neoplasms. The MPN-SAF is a 27-item measure that utilizes the 10-item Brief Fatigue Inventory in conjunction with a 17-item assessment of disease symptoms specific to the Myeloproliferative Neoplasms.

In order to ease survey administration, the 10- MPN-SAF total symptom score (MPN-SAF TSS), was created which includes a one-item assessment of worst fatigue from the BFI and 9 items from the original MPN-SAF. This abbreviated measure only includes the most pertinent and representative of the MPN symptoms and is intended to be used either as a one-time assessment or as a 7-day diary. Both surveys have been validated in clinical setting to be administered during a routine office visit (see references and articles below).

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Scherber R, Dueck AC, Johansson P, Barbui T, Barosi G, Vannucchi AM, et. al. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. *Blood.* 2011 Jul 14;118(2):401-8.

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Emanuel R, Dueck, A, Geyer, H, Kiladjian JJ, Slot S, Zweegman Z, et. al. The Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS): Prospective International Assessment of an Abbreviated Symptom Burden Scoring System among 1408 MPN Patients. *Journal of Clinical Oncology*, in press.

SUBJECT #_____

Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)

Instructions: Please circle the number corresponding with how each symptom as affected you.

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)
• 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 (Worst Imaginable)
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 H: EORTC QLQ-C30

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 long walk?	1	2	3	4
3. Do you have any trouble taking a short 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 family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social 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 you

29. 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 I: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

The United States of America (USA) National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE, v.4.0) can be found on the following website.

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40
[Accessed: 13 February 2013]

This version of CTCAE is compatible at the AE (Adverse Event) term level where each CTCAE term is a Medical Dictionary for Regulatory Activities Terminology (MedDRA) LLT (Lowest Level Term). CTCAE v4.0 includes 764 AE terms and 26 'Other, specify' options for reporting text terms not listed in CTCAE. Each AE term is associated with a 5-point severity scale. MedDRA v12.0.

APPENDIX J: STAGE 2 EXTENSION STUDY

Sponsor: Promedior, Inc.
Name of Finished Product: Recombinant human Pentraxin-2; PRM-151
Study Title: A Phase 2, - Prospective Study of PRM-151 In Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera MF (post-PV MF), or Post-Essential Thrombocythemia MF (post-ET MF)
Study Number: PRM-151G-101
Study Phase: Phase 2
Investigational Product; Dose; and Mode of Administration: PRM-151 10 mg/kg intravenous
Comparator; Dose; and Mode of Administration: Not applicable
Primary Objective(s): To provide subjects in the parent study an opportunity to remain on treatment and to allow all subjects to switch to an open label extension utilizing the 10 mg/kg dose after completing 9 cycles of the originally assigned treatment. **Secondary Objective(s):** • To collect long term safety data of subjects receiving PRM-151 • To collect additional efficacy data on duration of response beyond 36 weeks of treatment • To collect efficacy data on the change of PRM-151 dose level in subjects not achieving a response
Study Design: This is an open-label extension of study PRM-151G-101 to provide continued access to subjects in the parent study. All subjects completing 9 cycles of the originally assigned

treatment may switch to an open label extension and receive PRM-151 10mg/kg every 4 weeks. The first cycle of the open label phase contains a loading dose of 10mg/kg on days 1,3 and 5. This will allow for subjects from all three dosing cohorts to receive a loading dose of 10mg/kg while maintaining the blind. Additionally, subjects who have entered the open label extension study prior to the approval of this amendment may receive a loading dose (10 mg/kg on days 1, 3, and 5), to be administered on their next scheduled cycle after approval of this protocol amendment. This will allow for these subjects to receive any potential pharmacologic benefit of the loading dose.

Study Duration:

Subjects may continue with PRM-151 dosing in the absence of disease progression or toxicity warranting discontinuation of therapy until drug is made available in another way. Cycle numbers will continue from the parent protocol, with cycle 9 Day 29 of the parent protocol becoming Cycle 10 Day 1 of the extension study.

Response Assessments:

In addition to the schedule of assessments listed below, response assessments will be done on Day 1 of every third cycle (every 12 weeks) beginning on Day 1 of Cycle 13 and may include the following, as described below:

Bone Marrow Biopsies:

An optional bone marrow biopsy will be performed every 12 weeks.

MPN SAF and EORTC QLQ-C30:

Symptoms will be assessed using the MPN SAF and EORTC QLQ-C30 on Day 1 on every cycle.

Physical Exam and Spleen Measurement:

An abbreviated physical exam and spleen measurement by palpation will be done on Day 1 of every cycle.

PET-CT or CT or MRI:

These will be performed every 24 weeks.

Stage 2 Extension Study **SCHEDULE OF ASSESSMENTS**	**Cycle 10[11]** **(Cycle 9, Day 29)**			**Extension Cycles** **28 Day Cycle Length**
	Day 1 (+/-3 days)			Day (+/- 3 days)
	1	3	5	1

Informed Consent	x			
AE/SAE assessment (1)	x	x	x	x
Physical Exam (2)	x			x
Prior/Con Meds	x	x	x	x
Special list of excluded medications	x	x	x	x
Vital Signs (3)	x	x	x	x
Weight (kg)	x			x
ECOG Performance Score	x			x
Urine Pregnancy Test	x			x
Complete Blood Count (4)	x			x
Chemistry, BUN/creatinine (5)	x			x
Coagulation (6)	x			x
Review transfusion diaries	x			x
Bone Marrow (7)	x			x
MPN-SAF score (7)	x			x
EORTC-QLQC30 (7)	x			x
PET-CT Scan of CT or MRI (8)	x			x
Anti-pentraxin 2 antibodies, pre-dose (9)	x			x
Pentraxin-2 levels, pre-dose (9)	x			x
Access IRS (10)	x	x	x	x

PRM-151 Administration(11))(12)	x	x	x	x

1. Pre-treatment adverse events, including serious adverse events will be collected from the time of informed consent and after the medical history has been obtained.
2. Abbreviated physical exam and spleen measurement by palpation will be done day 1 of every cycle.
3. Vital signs (including temperature, blood pressure, pulse rate, and respiratory rate) will be performed before and immediately after PRM-151 infusion, and at the conclusion of the one hour observation period.
4. CBC includes red blood cell count (RBC), hemoglobin, hematocrit, white blood cell count with differential, absolute neutrophil count (ANC), reticulocyte count, last count, and platelets.
5. Blood chemistry lab parameters include lactic dehydrogenase (LDH), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), direct and indirect bilirubin, alkaline phosphatase, creatinine phosphokinase (CPK), uric acid, calcium, phosphorus, sodium, potassium, chloride, albumin, bicarbonate, BUN, creatinine, and glucose.
6. Coagulation testing at screening for all subjects to include prothrombin time (PT), and partial thromboplastin time (PTT). For subjects receiving warfarin, the PT, PTT and international normalized ratio (INR) must be obtained. Abnormal INRs will be tested twice weekly until the INR is stable for one month, followed by monthly monitoring of INRs
7. MPN-SAF EORTC QLQ-C30, will be performed on Day 1 of every cycle. Bone marrow biopsy window +/- 6 weeks.
8. PET-CT Scan or CT or MRI will be performed every 24 weeks.
9. Blood sample for pentraxin-2 and anti-pentraxin 2 antibodies should be drawn pre-dose every 12 weeks. If the subject experiences an infusion related reaction, a blood sample for anti-pentraxin 2 antibodies should be drawn prior to any subsequent PRM-151 infusions. A blood sample for cytokines and anti-pentraxin 2 antibodies may be obtained in the event of a suspected adverse reaction as well.
10. For consistency, the unblinded pharmacist will continue to access IRS to confirm occurrence of dosing on Day 1 of each Cycle.
11. Subjects will be observed one hour after each dose.
12. Loading dose of 10 mg/kg on Days 1, 3 and 5. Alternative loading dose schedule is Days 1, 3 and 6 when days 1, 3 and 5 are not possible. Additionally, subjects who have entered the open label extension study prior to the approval of this amendment may receive a loading dose (10 mg/kg on days 1, 3, and 5), to be administered on their next scheduled cycle after approval of this protocol amendment.

APPENDIX K: SYNOPSIS: STAGE 1

Sponsor: Promedior, Inc.
Name of Finished Product: Recombinant human Pentraxin -2; PRM-151
Study Title: A Phase 2, Open-Label, Prospective Study Of PRM-151 In Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera MF (post-PV MF), Or Post-Essential Thrombocythemia MF (post-ET MF)
Study Number: PRM-151G-101
Study Phase: Phase 2
Investigational Product; Dose; and Mode of Administration: PRM-151 10 mg/kg intravenous
Comparator; Dose; and mode of Administration: Not applicable
Primary Objective(s): • To evaluate the efficacy of two different dose schedules of PRM-151 in intermediate -1, intermediate -2, or high risk subjects with PMF, post-PV MF, or post ET-MF who are not receiving therapy for MF, and in subjects with PMF, post-PV MF, or post ET-MF on a stable dose of ruxolitinib for at least three months.
Secondary Objective(s): • To evaluate the safety and tolerability of two different dose schedules of PRM-151 in intermediate-1, intermediate -2, or high risk subjects with PMF, post-PV MF, or post ET-MF who are not receiving therapy other than transfusions, and the safety and tolerability of two different dose schedules of PRM-151 in subjects with PMF, post-PV MF, or post ET-MF on a stable dose of ruxolitinib • To assess the effect of PRM-151 on bone marrow fibrosis • To measure the duration of response • PK of PRM-151 in subjects receiving single agent PRM-151 and in subjects receiving ruxolitinib. **Exploratory Objectives** • To evaluate the effect of PRM-151 on plasma cytokine levels comparing baseline on Cycle 1, Day 1 to Day 1 of Cycles 2, 3, 4 and Day 29 of Cycle 6

- To evaluate the effect of PRM-151 on PBMC mRNA and miRNA expression levels comparing baseline on Cycle 1, Day 1 to Day1 of Cycles 2, 3, 4 and Day 29 of Cycle 6
- To evaluate the correlation of baseline PTX-2 levels with outcomes.

Study Endpoints:

Primary:

- The overall response rate (ORR), defined as a clinical improvement (CI), partial remission (PR), and complete remission (CR) according to the International Working Group (IWG) Criteria (Appendix B)
- Stable disease with improvement in bone marrow fibrosis score by at least one grade according to the European Consensus on Grading of Bone Marrow Fibrosis (Appendix D) will also be considered a response (bone marrow response).

Secondary:

- Incidence of adverse events (AEs), serious adverse events (SAEs), and changes in laboratory test results
- Change in bone marrow fibrosis
- Change in the modified Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF) Score (Appendix G)
- Duration of response
- PK parameters including C_{max} (maximum drug concentration), t_{max} (time to maximum concentration, AUC, clearance, and volume of distribution.

Exploratory:

- Changes in levels of circulating plasma cytokine levels including but not limited to CRP, IL-1ra, MIP-1β, TNFα, IL-6 and VEGF comparing baseline on Cycle 1, Day 1 to Day 1 of Cycles 2, 3, 4 and Day 29 of Cycle 6
- Changes in levels of PBMC mRNA and miRNA expression levels comparing baseline on Cycle 1, Day 1 to Day 1 of Cycles 2, 3, 4 and Day 29 of Cycle 6.
- Correlation of baseline PTX-2 levels with outcomes.

Study Design:

This is an open-label, Simon two stage, Phase 2 study to determine the efficacy and safety of two different dose schedules of PRM-151 in subjects with PMF and post ET/PV MF. There are two treatment cohorts, each assigned to one of two dose schedules of PRM-151. Subjects will be assigned to a weekly or every four week dosing schedule by the investigator based on their ability to visit the study site on a weekly basis. This is an adaptive design as defined in FDA Draft guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics, February 2010. Modifications to dose levels, schedule, or regimen may be made in Stage 2 based on data from Stage 1.

Stage 1:

Cohort 1: Approximately 12 subjects with intermediate -1, intermediate -2, or high risk MF who have received no treatment for MF in at least two weeks will be enrolled and assigned to treatment with single agent PRM-151 at a dose of 10 mg/kg IV on Days 1, 3, 5, 8, 15, and 22 of Cycle 1 and Days 1, 8, 15 and 22 of each subsequent 28 day cycle for six cycles, OR single agent PRM-151 at a dose of 10 mg/kg administered IV on Days 1, 3, and 5 of Cycle 1 and Day 1 of each subsequent 28 day cycle for six cycles. Subjects responding to therapy may continue receiving it as long as there is a benefit.

Cohort 2: Approximately 12 subjects with intermediate -1, intermediate -2, or high risk MF on a stable dose of ruxolitinib for at least 12 weeks, with no improvement in spleen during the last four weeks will be enrolled. Subjects will be assigned to receive PRM-151 in combination with ruxolitinib either at a dose of 10 mg/kg administered IV on Days 1, 3, 5, 8, 15, and 22 of Cycle 1 and Days 1, 8, 15 and 22 of each subsequent 28 day cycle for six cycles, OR in combination with ruxolitinib at a dose of 10 mg/kg administered IV on Days 1, 3, 5 of Cycle 1 and Day 1 of each subsequent 28 day cycle for six cycles. Subjects responding to therapy may continue receiving it as long as there is a benefit.

Stage 2:

If at least one response is seen in any arm of either cohort in Stage 1, an additional 20 subjects may be enrolled and treated on that dosing schedule. All non-responding arms will be closed. Subjects responding to therapy may continue receiving it as long as there is a benefit.

Enrolled subjects will be considered evaluable for response if they are on study drug for at least four weeks.

Study Duration:

Each subject will participate in the study for approximately 32 weeks. Participation will include a screening evaluation within four weeks before the first PRM-151 administration, six study cycles of four weeks each, and an end of study visit four weeks after the end of the last cycle. Subjects may continue with PRM-151 dosing in

the absence of disease progression or toxicity warranting discontinuation of therapy, as long as there is evidence of clinical benefit, as judged by the Investigator.

Subjects who have no benefit in the parent study may switch to a schedule in which responses occur after completing 6 cycles of the originally assigned treatment.

It is estimated that the study will be completed in approximately 18 months.

Study Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Subjects must be > 18 years of age at the time of signing the Informed Consent Form (ICF);

2. Subjects must voluntarily sign an ICF;

3. Subjects must have a pathologically confirmed diagnosis of PMF as per the WHO diagnostic criteria (see Appendix C) or post ET/PV MF (note that all diagnoses must include the presence of at least Grade 2 marrow fibrosis according to the European Consensus on Grading of Bone Marrow Fibrosis (Appendix D) with intermediate -1, intermediate -2, or high risk disease according to the IWG-MRT Dynamic International Prognostic Scoring System (Appendix E);

4. A biopsy must be performed within four weeks prior to Cycle 1 Day 1 treatment to establish the baseline fibrosis score;

5. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance Status of 0-2. (Appendix F);

6. Life expectancy of at least six months;

7. At least two weeks must have elapsed between the last dose of any MF-directed drug treatments for myelofibrosis (including investigational therapies) and study enrollment, except for ruxolitinib for Cohort 2 (see Inclusion Criteria);

8. Recovery to < Grade 1 or baseline of any toxicities due to prior systemic treatments, excluding alopecia;
9. Women of child bearing potential (WCBP), defined as a sexually mature woman not surgically sterilized or not post-menopausal for at least 24 consecutive months if < 55 years or 12 months if > 55 years, must have a negative serum pregnancy test within four weeks prior to the first dose of study drug and must agree to use adequate methods of birth control throughout the study. Adequate methods of contraception include use or oral contraceptives or Depo-Provera, with an additional barrier method (diaphragm with spermicidal gel or condoms with spermicide), double-barrier methods (diaphragm with

spermicidal gel and condoms with spermicide), partner vasectomy, and total abstinence.

10. Ability to adhere to the study visit schedule and all protocol requirements;

11. For Cohort 2 (PRM-151 added to ruxolitinib) Subjects only;

12. Must have been on a stable dose of ruxolitinib treatment for at least 12 weeks with no further improvement in splenomegaly for at least four weeks;

13. Must have adequate organ function as demonstrated by the following:

    - ALT (SGPT) and or AST/ (SGOT) < 3 x upper limit of normal (ULN), or < 4 x ULN (if upon judgement of the treating physician, it is believed to be due to extramedullary hematopoiesis [EMH] related to MF);

    - Direct bilirubin < 1.5 x ULN; or < 2 x ULN (if upon judgement of the treating physician, it is believed to be due to EMH related to MF);

    - Serum creatinine ≤ 2.5 mg/dL OR serum creatinine < 2.5 x ULN.

Exclusion Criteria:

1. Other invasive malignancies within the last 3 years, except non-melanoma skin cancer and localized cured prostate and cervical cancer;

2. History of strike, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months;

3. Presence of active serious infection;

4. Any serious, unstable medical or psychiatric condition that would prevent, (as judged by the Investigator) the subject from signing the informed consent form or any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study;

5. Known history of human immunodeficiency virus (HIV), or known active hepatitis A, B, or C infection;

6. Organ transplant recipients other than bone marrow transplant;

7. Women who are pregnant or lactating.

Efficacy Assessments:

Efficacy will be assessed by evaluation of the overall response rate (ORR) categorized according to the International Working Group (IWG) Criteria (APPENDIX B) modified to include stable disease with improvement in bone marrow fibrosis by at least one grade.

Safety Assessments:

Safety will be evaluated from reported adverse events, scheduled physical examinations, vital signs, and clinical laboratory test results.

This Phase 2 clinical trial will have an independent Data Monitoring Committee (DMC) to conduct interim reviews of safety data, and provide an independent evaluation on a predetermined and ad-hoc basis of accumulating safety data. All adverse events reported to Promedior will be considered by Promedior and the DMC regardless of the reported causality by the study site. In assessing adverse events, Promedior and the DMC will consider only treatment emergent adverse events, defined as adverse events that occur after at least one exposure to study drug. The DMC will review all safety data at the following pre-determined times:

- when the first 12 subjects reach Cycle 4, Day 1
- when the first 24 subjects have completed the study

The DMC will review the following events immediately on an ad-hoc basis and will make a recommendation about whether the study may proceed:

- any death
- any event of anaphylaxis
- any SAEs
- any treatment emergent Grade 3 non-hematologic toxicity
- any treatment emergent grade 4 hematological adverse event or a treatment emergent grade 3 hematologic adverse event that represents a change of 2 grades from grade 1, or a doubling of transfusion frequency.

Statistical Methods:

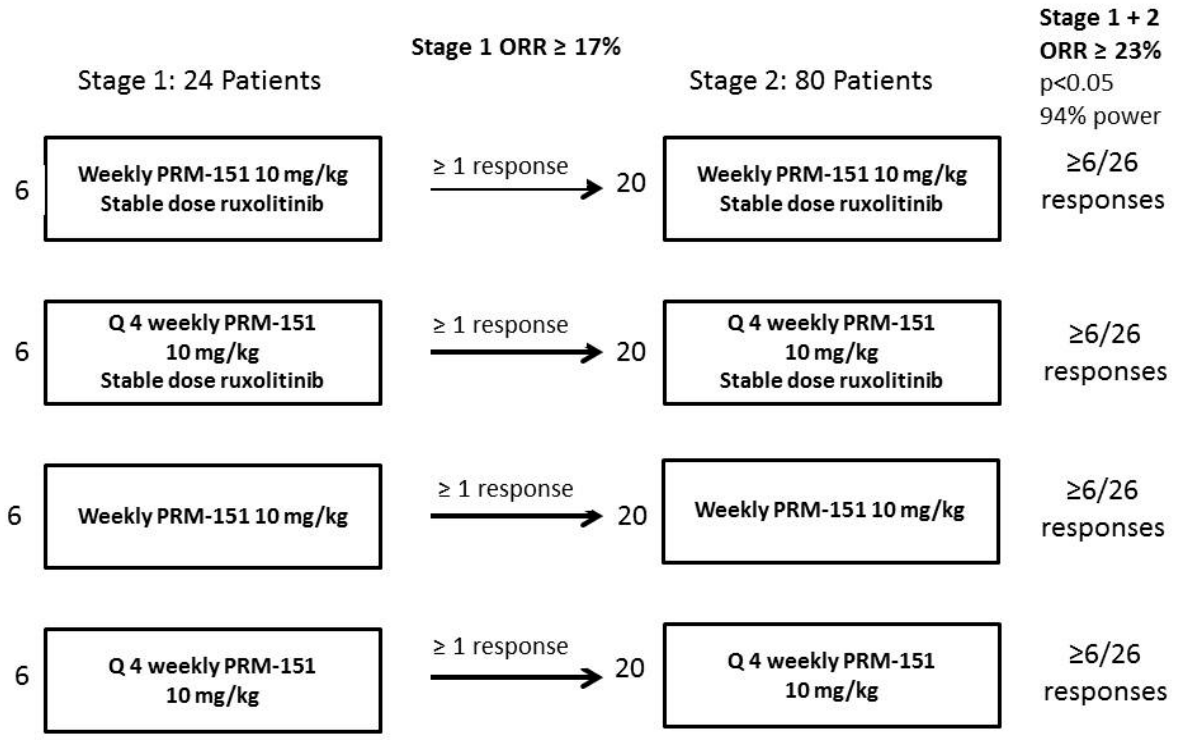
The objective is to demonstrate superiority within each cohort and dose schedule, comparing observed ORR in each arm to a fixed uninteresting level ORR of 0.1. Let π denote population expected value of the primary parameter ORR. The objective of the trial is to reject the null-hypothesis

$H_0: \pi < 0.1$

in favor of the alternative hypothesis

$$H_A: \pi > 0.4$$

The design will be two-staged within each arm based on Simon (Simon 1989) as shown in the figure below:



The design maintains the type I error probability at 3.4 % which is less than 5 %. Furthermore, for $\pi > 0.4$, there is a high probability of at least 94 % to demonstrate superiority. The probability under H_0 to stop after stage 1 is 53 %, which implicit consequence that the expected number of subjects is 15, compared to a maximum number of subjects of 26.

Date of Original Protocol: Version 1.0 17 Jan 2013

APPENDIX L: SYNOPSIS: STAGE 1 OPEN LABEL EXTENSION STUDY

Sponsor: Promedior, Inc.
Name of Finished Product: Recombinant human Pentraxin -2; PRM-151
Study Title: A Phase 2, Open-Label, Prospective Study Of PRM-151 In Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera MF (post-PV MF), Or Post-Essential Thrombocythemia MF (post-ET MF)
Study Number: PRM-151G-101
Study Phase: Phase 2
Investigational Product; Dose; and Mode of Administration: PRM-151 10 mg/kg intravenous
Comparator; Dose: and Mode of Administration: Not applicable
Primary Objective(s): To provide subjects achieving clinical benefit as determined by the investigator in the parent study an opportunity to remain on treatment and to allow subjects not achieving a benefit to switch to a potentially more effective schedule of PRM-151 Secondary Objective(s): To collect long term safety data of subjects receiving PRM-151 To collect additional efficacy data on duration of response beyond 6 months of treatment To collect efficacy data on the change of PRM-151 schedule in subjects not achieving a response
Study Design: This is an open-label, extension of study PRM-151G-101 to provide access to subjects in the parent study who have achieved benefit in the parent study. Additionally, subjects who have no benefit in the parent study may switch to a schedule of PRM-151 in which responses have occurred after completing 6 cycles of the originally assigned treatment. Subjects may switch schedules of PRM-151 and/or drop ruxolitinib in the extension but subjects are not allowed to add ruxolitinib if they were in Cohort 1. After study completion and data analysis, all subjects remaining on PRM-151 in this extension will switch to the dose selected for future clinical development.
Study Duration: Subjects may continue with PRM-151 dosing in the absence of disease progression or toxicity warranting discontinuation of therapy, as long as there is evidence of clinical benefit or until

drug is made available in another way. Cycle numbers will continue from the parent protocol, with Cycle 6 Day 29 of the parent protocol becoming Cycle 7 Day 1 of the extension study.

Response Assessments:
In addition to the schedule of assessments listed below, response assessments will be done on Day 1 of every third cycle (every 3 months) beginning on Day 1 of Cycle 10 and may include the following, as described below:

Bone Marrow Biopsies:
A bone marrow biopsy will be performed only to determine or confirm a change in response category. This will be done at the following time points depending on the subjects' response category at the time of the most recent bone marrow biopsy:

- CR: Bone marrow biopsy will be done only if there is a change in status indicating potential disease progression.
- PR: For subjects with bone marrow histological remission, bone marrow biopsy (BMB) will be done only if there is a change in status indicating disease progression. For subjects without bone marrow histological remission BMB will be done every 6 months until CR is documented or until indication of potential disease progression.
- CI: BMB will be done if the clinical status changes from CI to PR or PD
- Stable disease with improvement in bone marrow fibrosis: BMB will be done if the clinical status changes from SD to CI, PR, or PD.

MPN SAF Score:
The subjects MPN symptoms will be assessed using the MPN SAF every 3 months.

Physical Exam and Spleen Measurement:
An abbreviated physical exam and spleen measurement by palpation will be done every 3 months.

STAGE 1 OPEN LABEL EXTENSION STUDY		
SCHEDULE OF ASSESSMENTS	Weekly Dosing Extension Cycles	Q4 Weekly Dosing Extension Cycles

	28 Day Cycle Length				28 Day Cycle Length
	Day (+/- 3 days)				Day (+/- 3 days)
	1	8	15	22	Day 1
Informed Consent	x				x
Prior/Con Meds	x	x	x	x	x
AE/SAE assessment (1)	x	x	x	x	x
Vital Signs (2)	x	x	x	x	x
Weight (kg)	x				x
ECOG Performance Score	x				x
Urine Pregnancy Test	x				x
Complete Blood Count (3)	x				x
Chemistry, BUN/creatinine (4)	x				x
Transfusion History over past 3 months or since last visit	x				x
Special list of excluded medications	x				x
Anti-pentraxin 2 antibodies, pre dose (5)	x				x
PRM-151 Administration	x	x	x	x	x
Response Assessments (6)	x				x

1. Pre-treatment adverse events, including serious adverse events will be collected from the time of informed consent and after the medical history has been obtained
2. Vital signs (including temperature, blood pressure, pulse rate, and respiratory rate) will be performed before infusions.
3. CBC includes red blood cell count (RBC), hemoglobin, hematocrit, white blood cell count with differential, absolute neutrophil count (ANC), and platelets. Results should be reviewed prior to PRM-151 infusion. CBC can be drawn up to 7 days prior to PRM-151 infusion.
4. Blood chemistry lab parameters include lactic dehydrogenase (LDH), serum alanine aminotransferase (ALT), serum aspartamine aminotransferase (AST), direct and indirect bilirubin, alkaline phosphatase, creatinine phosphokinase (CPK), uric acid, calcium, phosphorus, sodium, potassium, chloride, bicarbonate, BUN, creatinine, and glucose.

5. Blood sample for anti-pentraxin 2 antibodies should be drawn pre-dose every 12 weeks. If the subject experiences an infusion related reaction, a blood sample for anti-pentraxin 2 antibodies should be drawn prior to any additional PRM-151 infusions.
6. The following components of response assessment will begin on Cycle 10, Day 1 and continue on Day 1 of every third cycle thereafter: Abbreviated physical exam and spleen measurements, MPN-SAF, and Investigator Response Assessment based on IWG-MRT criteria. Bone marrow biopsies will be performed only to determine or confirm a change in response category as described above.

APPENDIX M: Summary of Protocol Changes from Version 5

Section(s)	Change	Rationale
Cover Page	Added the following: • Added Country Specific Amendments • Amendment 5 Version 6 information. • EudraCT Number • New Medical Director [redacted] MD, PhD • The last protocol version was erroneously referred to as Amendment 5, Version 5 but has been corrected to Amendment 4, Version 5,	• Administrative Clarifications
Synopsis: Stage 2 Study Design,	• Added a loading dose for in subjects in Stage 2 open label extension study • Provided additional safety information from the IPF trial. • Referred to Appendix J for Stage 2 OLE • Referred to Appendix L for Stage 1 OLE.	• This will allow for subjects from all three dosing cohorts to receive a loading dose of 10 mg/kg while maintaining the blind. Additionally, subjects who have entered the open label extension study prior to the approval of this amendment may receive a loading dose (10 mg/kg on days 1, 3, and 5), to be administered on their next scheduled cycle. This will allow for these subjects to receive any potential pharmacologic benefit of the loading dose. • Added clarification that, based on available data through NOV 14, in patients with IPF receiving a loading dose in an open label study, no incremental risk has been reported. • Clarification on the Stage 2 OLE loading dose schedule and Stage 1 OLE study

Synopsis: 4 Inclusion Criteria # 12; 5.1.1.	• Added clarification for contraception and adding highly effective methods to align with IB v10 and country amendment 5.1.	• To align with IB v10 and the country specific amendments.
Synopsis: Inclusion Criteria # 14; 5.1.1.	• Modified units of measurement of serum creatinine to: "≤ 2.5 x ULN"	• Updated the unit of measurement for clarification.
Synopsis: Endpoints, 3.3	• Clarified that spleen size is measured by CT or MRI and removed "(in subjects with palpable spleen at baseline)"	• Clarification that the use of MRI to measure spleen size, for patients not receiving PET-CT, was intended to be allowed as an alternative to CT.
1.1 Overview	• Added "PRM-151 is a recombinant human PTX-2".	• Per IRB request.
1.5 Rationale for Stage 2 Changes, 7. Study Procedures	• Added a loading dose for subjects in Stage 2 open label extension study. • Referred to Appendix K and L for Stage 1 and Stage 1 OLE information.	• This will allow for subjects from all three dosing cohorts to receive a loading dose of 10 mg/kg while maintaining the blind. Additionally, subjects who have entered the open label extension study prior to the approval of this amendment may receive a loading dose (10 mg/kg on days 1, 3, and 5), to be administered on their next scheduled cycle. This will allow for these subjects to receive any potential pharmacologic benefit of the loading dose. • Added reference for additional information on Stage 1 and Stage 1 OLE.
4.1.1 Study Design	• Added a loading dose for in subjects in Stage 2 open label extension study.	• This will allow for subjects from all three dosing cohorts to receive a loading dose of 10 mg/kg while maintaining the blind. Additionally, subjects who have entered the open label extension study prior to the approval of this amendment may receive a loading dose (10

		mg/kg on days 1, 3, and 5), to be administered on their next scheduled cycle. This will allow for these subjects to receive any potential pharmacologic benefit of the loading dose.
6.2 Treatment(s) Administered	• Clarified that PRM-151 can be resumed when adverse event has resolved to Grade 1 or baseline.	• To account for adverse events that may return to baseline but not Grade 1 (eg hemoglobin; platelets).
6.3 Dose for Each Subject	• Removed dosing for Stage 2 OLE and referred to Appendix J for dosing information.	• To provide clarification and consistency throughout the document.
7.8 Investigation Product Administration; 7.13.1.1	Provided clarification on premedication for IRR: a. Diphenhydramine 50 mg IV "or clemastine 2 mg IV or an equivalent antihistaminic" b. Dexamethasone 10 mg IV "or an equivalent corticosteroid"	• To provide additional options for premedication for IRR.
7.10. Exploratory Laboratory Assessments	• Added clarification that DNA sampling is not mandatory for subjects and they can still enroll in the trial if they opt out of the sampling. • Revised for clarification "week 36" to "Cycle 9 Day 29" • Added clarification that the baseline blood sample for DNA sampling will also be used for the cytogenetic analysis.	• Updates added for clarification on exploratory assessments.
7.11.1 Bone Marrow Biopsy	• Revised the title by removing "and Aspirate". • Removed cytogenetic analysis on marrow biopsy/aspirate	• Obtaining an aspirate was never intended, and not implemented. • It was never intended or implemented to obtain a bone marrow aspirate for cytogenetic testing. The exploratory endpoint of cytogenetic testing is performed on peripheral blood.
7.11.3.2. Imaging	• Added "MRI" • Updated title to "Imaging"	• Clarification that the use of MRI to measure spleen size, for patients not receiving PET-CT, was intended to be

		allowed as an alternative to CT. • Clarification to title as other imaging procedures can be performed.
7.11.6 Response Assessments	• Added this section to help clarify the IWG-MRT response assessment.	• To provide clarification on the IWG-MRT response assessment.
7.12.3 Clinical Laboratory Tests	• Added clarification on which labs are central laboratory or local.	• To provide clarification on the laboratory assessments.
7.12.4 Pregnancy Test	• Added information regarding pregnancy testing requirements for clarification.	• To provide clarification on pregnancy testing.
7.12.6 Immune Response Assessment	• Added anti-pentraxin 2 antibodies collection for IRR and anti-pentraxin 2 antibodies and cytokines in the event of an suspected adverse reaction.	• To provide additional options to monitor IRR/suspected adverse reactions
7.13.1.4 Data Monitoring Committee	• Added clarification on the data to be reviewed by the DMC.	• To provide clarification that unblinded safety data will be reviewed by the DMC, to align with the DMC charter
7.13.2.2 Reporting Serious AEs	• Removed "Only serious Treatment Emergent AEs (TEAEs), defined as adverse events occurring after at least one dose of study drug, will be recorded." All AEs will be recorded.	• To provide clarification that all AEs are collected.
7.13.3 Reporting Pregnancies	• Added reporting clarification for reporting pregnancies.	• To provide clarification on pregnancy reporting.
8.0 Stage 2 Study Procedures	• Clarifications on the process for local labs use when a central lab result is not reliable.	• To provide clarification for sites on the process for when a test result cannot be determined in the central lab.
8.1 Screening, 8.2 Cycle 1, Day 1, 8.5 Cycle 9, Day 29	Clarification was added on: • When IWG-MRT DIPPS (risk assessment) is assessed • Which assessment are done at central labs • That bone marrow biopsy at screening is obtained <4 weeks prior to first dose	• To provide clarification on risk assessment, laboratory assessments and bone marrow biopsy.
8.2 Cycle 1, Day 1	Clarification was added for: • option for MRI	• To provide clarification on laboratory assessments and imaging assessment.

	• Added when blood sample for infusion related cytokines (pre-dose) occurs for clarification • Added anti-pentraxin 2 antibodies collection for infusion related reactions • Removed "Blood samples for exploratory laboratory assessments" to specify collection is for "genetic analysis". • Specified which labs are to be done at central lab	
8.3 Cycle 1, Days 3 and 5	• Specified which labs are to be done at central laboratory.	• To provide clarification on laboratory assessments.
8.4 Cycle 2 through 9, Day 1	Clarification was added for: • Modified +/- 1days to +/- 3 days window • Specified which labs are to be done at central laboratory. • Added IWG-MRT Response Assessment for clarification • Clarified pentraxin levels • Clarified anti-pentraxin-2 sample should be taken "pre-dose" • Updated language of recording of transfusion diary to reviewing	• To allow for a wider visit window. • To provide clarification on window for visit, laboratory assessments, transfusion diary and response assessments.
8.5 Cycle 9, Day 29 (week 36)	Clarification was added for: • Modified +/- 1-3 days to +/- 3 days window • Added MRI as an option. • Removed "Blood samples for exploratory laboratory assessments" to specify collection is for "genetic analysis". • Clarified pentraxin levels • Clarified anti-pentrxin-2 sample should be taken "pre-dose"	• To allow for a wider visit window • To provide clarification on window for visit, imaging procedures and laboratory assessments.
8.6 End of Study	Clarification was added for:	• To allow for a winder visit window. • To provide clarification on the window allowed

	• Modified +/- 1-3 days to +/- 3 days window • Specified which labs are to be done at central laboratory. • Updated language on recording of transfusion diary to reviewing	for visit, lab collection and transfusion diary recording.
Appendix A Schedule of Events	Modified Schedule of Events Table to align with protocol: • Revised "Completion of" to "Review" transfusion diaries • Modified +/- 1days to +/- 3 days • Added MRI as an option • Removed language "On Cycle 1 Day 1, in addition to the blood sample for central lab, blood sample for local lab must be done for hemoglobin and/or platelet to confirm eligibility by the Investigator prior to dosing." • Added clarification to footnote # 10; MRI (within 2 weeks prior to C1D1) • Added clarification to footnote #11"cytogenetics" and removed list of "exploratory laboratory assessments" • Added footnote # 15 "Subjects will be observed one hour after each dose." for clarification. • Added IWG-MRT DIPSS (risk assessment) and IWG-MRT Response • Added anti-pentraxin 2 antibodies to collection for IRR.	• To align with the updates in the body of the protocol and add clarification in the schedule of events.
Appendix J Stage 2 Extension Study	Clarifications were added: Study Design: • Added clarification on dosing schedule. Response Assessments: • Added MRI as an option • Removed language for every 12 weeks and added Day 1 of every cycle for clarification.	• To align with updates in the body of the protocol amendment.

	Modified Schedule of Events Table: • Modified +/- 1 day to +/- 3 days for Cycle 1 Day 1 • Added Days 1, 3, and 5 for Cycle 10 • Removed from footnote # 4 "Results should be reviewed prior to PRM-151 infusion CBC can be drawn up to 7 days prior to PRM-151 infusion." • Added to footnote # 7 the bone marrow biopsy window and clarification that assessment of MPN-SAF and EORTC QLQ-C30 is performed at Day 1 of every cycle. • Added to footnote # 8 "MRI" • Added to footnoate # 9 "A blood sample for cytokines and anti-pentraxin 2 antibodies may be obtained in the event of a suspected adverse reaction as well." • Added footnote # 11 "Subjects will be observed one hour after each dose." • Added footnote # 12 " Loading dose of 10 mg/kg on Days 1, 3 and 5. Alternative loading dose schedule is Days 1, 3 and 6 when days 1, 3 and 5 are not possible. Additionally, subjects who have entered the open label extension study prior to the approval of this amendment may receive a loading dose (10 mg/kg on days 1, 3, and 5), to be administered on their next scheduled cycle after approval of this protocol amendment."	
Appendix L	Added Synopsis: Stage 1 Open Label Extension Study and added Schedule of Events Stage 1 Open Label Extension Study to provide clarification for subjects still in the Stage 1 OLE.	• To provide clarification for subjects in the Stage 1 OLE.
Appendix M	Updated Summary of Protocol Changes from Amendment 4, Version 5	• To easily refer to updates made from the previous protocol amendment.
Throughout	Formatting updates and minor corrections/clarifications to text.	• Grammatical updates.