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)

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STATISTICAL ANALYSIS PLAN

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).**

PROTOCOL NUMBER: BO42355 (PRM-151G-101)

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STATISTICAL ANALYSIS PLAN APPROVAL

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1. BACKGROUND

Myelofibrosis (MF) (including primary MF, post-polycythemia vera [PV] MF and post-essential thrombocythemia [ET] MF) is a clonal myeloproliferative 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 curative treatment for MF, but the procedure is associated with high morbidity and mortality (Stewart et al. 2010; Ballen 2012). Bone marrow fibrosis resolves in subjects after successful transplant as early as one month (Przepiorka et al. 1998).

Before 2011, there was no approved medical therapy for MF and most symptomatic subjects were managed with various combinations of growth factors, immunomodulatory agents, cytotoxic chemotherapy, and steroids. For many subjects, these therapies were not effective at all or were associated with transient alleviation of certain symptoms of the disease. Ruxolitinib is a Janus kinase inhibitor, approved in the United States (US) and European Union (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. However, ruxolitinib is not believed to be disease modifying and does not have convincing effects on bone marrow fibrosis (Verstovsek et al. 2012). Futhermore, >20% of subjects discontinue ruxolitinib due to intolerance or lack of efficacy within the first year of therapy (Palandri et al. 2020). Other Janus kinase inhibitors are in clinical development and fedratinib was approved by US Food and Drug Administration (USFDA) in 2019 (Blair 2019). There is a clear unmet medical need for new therapies for MF, in particular therapies that are potentially disease modifying and improve bone marrow function.

Pentraxin-2 (PTX-2), also known as serum amyloid protein 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. rhPTX-2 (recombinant human pentraxin-2, RO7490677) is a recombinant version of human pentraxin-2 (rhPTX-2). Similar to endogenous PTX-2, rhPTX-2 circulates as a non-covalent, homo-pentameric glycoprotein. Pre-clinical and clinical data support the investigation of rhPTX-2 in the treatment of fibrotic diseases (Murray et al. 2010; Pilling et al. 2007; Raghu et al. 2018; Verstovsek et al. 2016; Duffield et al. 2010).

Study BO42355 was developed to examine the efficacy and safety of rhPTX-2 in intermediate-1, intermediate-2, and high risk subjects with PMF, post-PV MF, or post-ET MF subjects. More details regarding the study are provided in the Appendix 1, Appendix 2, Appendix 3, and Appendix 4 (Protocol Synopses for the various study stages).

Of note, rhPTX-2 was developed by Promedior and acquired by Roche in 2020. Detailed Statistical Analysis Plans (SAPs) (Stage 1 Version 2.0: 11 April 2019; Stage 2 Version 2.0: 5 March 2018) were prepared by Promedior and signed prior to the respective Stage 1 and Stage 2 primary database lock (DBL) and analyses. This present SAP was prepared by Roche and signed before the final DBL of the Stage 1 and Stage 2 open label extensions (OLEs) of the study. The aim of this SAP is to highlight the analyses that will be performed for the final analysis and reported in a Clinical Study Report (CSR) for both main Stage 1 and Stage 2, and inclusive of their respective OLEs.

2. STUDY DESIGN

Study BO42355 is a Phase II study, divided into 2 stages: Stage 1 and Stage 2, each with a respective OLE.

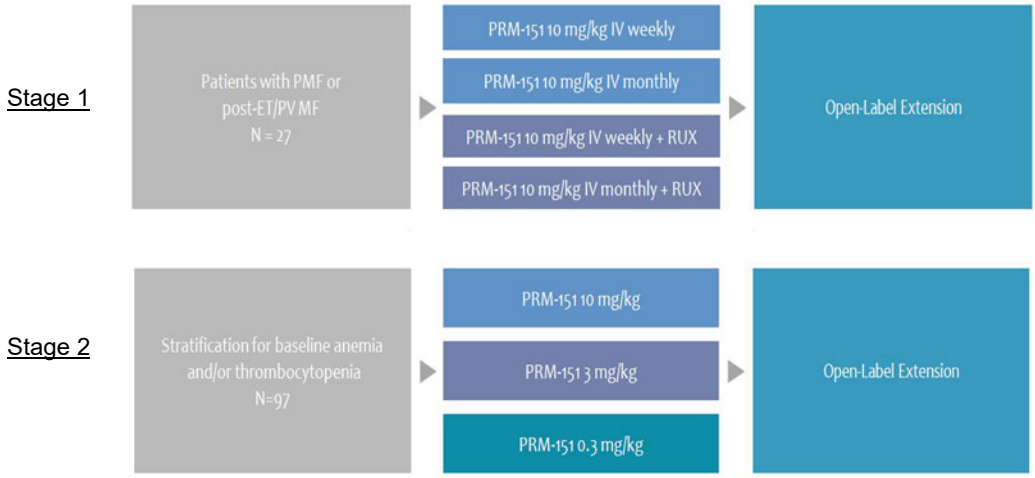
The objective of Stage 1 was to evaluate the efficacy of two different dose schedules of rhPTX-2 in subjects with DIPSS defined intermediate-1, intermediate-2, or high risk PMF, post-PV MF, or post ET-MF. The two dosing schedules were tested as monotherapy and as an add-on therapy to subjects on a stable dose of ruxolitinib for at least three months.

The objective of the Stage 2 was to determine the effect size of three different doses of monotherapy of rhPTX-2 on reduction in bone marrow fibrosis by $>$ 1 grade at any time during the study in DIPSS intermediate-1, intermediate-2, and high risk subjects with PMF, post-PV MF, or post ET-MF who are anemic and/or thrombocytopenic and who are ineligible for, intolerant of, or have had an inadequate response to ruxolitinib.

Please see study design in

Figure 1 and more details in Appendix 1, Appendix 2, Appendix 3 and Appendix 4 (protocol synopses for the various study stages).

Figure 1 Study Design



PMF=Primary myelofibrosis; Post-ET=Post-Essential Thrombocythemia; PV MF=Polycythemia vera Myelofibrosis; RUX= Ruxolitinib.
Note: For Stage 1 and Stage 2 Open-Label Extension, subjects received rhPTX-2 10mg/kg.

In this document, reference to Stage 1 and Stage 2 will correspond to the main stage; otherwise, it will specify (i.e. OLE).

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis for each stage and OLE are in Appendix 1, Appendix 2, Appendix 3 and Appendix 4. For the Schedule of Assessments see Appendix 5 and Appendix 6.

2.2 EFFICACY ENDPOINTS

2.2.1 Primary Efficacy Endpoint

Stage 1:

The primary endpoint for Stage 1 is the Overall Response Rate (ORR). Response rate is defined as the percent of subjects with a response as per International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria (assessed by the investigator), is defined as either:

- achieving clinical improvement (CI), partial remission (PR), or complete remission (CR) at a post-baseline assessment of treatment response

OR

- having at least stable disease (SD) for three consecutive end-of-cycle response assessments (e.g. Day 1 of the subsequent cycle) in conjunction with improvement in the bone marrow fibrosis score (as determined by adjudicated

review) relative to baseline by at least one grade at any time point during the period of stable disease.

Stage 2:

The primary endpoint for Stage 2 is the bone marrow response rate (BMRR). Response rate is defined as the percent of subjects with a reduction in bone marrow fibrosis by at least one grade according to World Health Organization (WHO) criteria (see Appendix D of the protocol) from baseline to any time during the study as determined by a central adjudication panel of expert hematopathologists, blinded to subject, treatment, and time of biopsy.

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows for:

Stage 1:

- Bone Marrow MF grade shifts relative to baseline over time
- Modified Myeloproliferative Neoplasm-Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) changes from baseline over time

Stage 2:

- Bone Marrow improvement:
  - Bone marrow (BM) response rate (MF Grade) at each visit (reduction of 1 grade versus baseline)
  - Duration of BM response defined for responding subjects as time from first decrease from baseline of one grade to time of return to baseline levels. If no return to baseline levels or worse than baseline then duration will be censored at the last BM assessment.
- Hemoglobin improvement (number and percentage of subjects):
  - For red blood cell transfusion dependent subjects at baseline (at least 2 units every 4 weeks for 12 weeks prior to Cycle [C]1Day [D]1), improvement is defined as either:

    1) absence of any packed red blood cells (PRBC) transfusion during any consecutive 12 weeks interval with hemoglobin level of ≥80g/L

    OR

    2) at least a 50% reduction in PRBC transfusions for 12 consecutive weeks with hemoglobin level of ≥80g/L

  - For red blood cell transfusion independent subjects improvement is defined as:

    ≥10 g/L increase in hemoglobin level for 12 consecutive weeks without transfusions
- Platelet improvement (number and percentage of subjects)

- For transfusion dependent subjects at baseline, improvement is defined as either:

  1) becoming transfusion independent for 12 consecutive weeks

  OR

  2) reduction in transfusions need ≥50% from baseline for 12 consecutive weeks

- For transfusion independent subjects with baseline platelet count below 100^9/L,, improvement is defined as:

  ≥50% increase in the number of platelet for 12 consecutive weeks or normalization of platelet count (above lower limit normal)

- Symptom improvement:

  Percent of subjects with 50% reduction in MPN-SAF TSS from baseline over time(Tefferi 2013)

- Percent of subjects with complete response, partial response, clinical improvement, stable disease and progressive disease according to IWG-MRT criteria.

2.2.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows for:

Stage 1:

- Bone marrow biopsy results for:
  - Myeloblasts (%), at each time point and change from baseline
  - Cellularity (%), at each time point and change from baseline
  - Collagen and reticulin grade shifts relative to baseline over time
- Modified MPN-SAF TSS
- Spleen size over time

Stage 2:

- Proportion of subjects with bone-marrow MF Grade 0 or 1 at 12, 24, and 36 weeks
- Proportion of subjects with 30% decrease, 30% increase, and stable (< 30% change) cellularity at 12, 24, and 36 weeks compared to baseline
- Change from baseline to Week 36 in hemoglobin for subjects with baseline < 100 g/L
- Number of units transfused in prior 12 weeks at baseline and Week 36 for transfusion dependent subjects
- Change from baseline to Week 36 in number of units transfused in prior 12 weeks for transfusion dependent subjects
- Proportion of subjects with increase from baseline to week 36 in hemoglobin (Hgb) from < 100 g/L to ≥ 100 g/L without transfusions
- Proportion of subjects with increase in Hgb from < 100 g/L at baseline to ≥ 100 g/L without transfusions for ≥ 12 consecutive weeks

- Number of units transfused in prior 12 weeks at baseline and Week 36 for platelet transfusion dependent subjects
- Proportion of subjects with increase from baseline to Week 36 in platelet from < 50 to ≥ 100 without transfusions
- Proportion of subjects with decrease from baseline to Week 36 in peripheral blood blasts from $\geq 1\%$ to $< 1\%$
- Percent of subjects with 10% reduction in spleen volume from baseline by computed tomography (CT) or magnetic resonance imaging (MRI) at each visit
- Percent of subjects with 35% reduction in spleen size volume from baseline by CT or MRI at each visit
- Change from baseline in spleen size volume by CT or MRI at each visit
- Percent of subjects with 10% reduction in liver volume from baseline by CT or MRI at each visit
- Percent of subjects with 35% reduction in liver size volume from baseline by CT or MRI at each visit
- Change from baseline in liver size volume by CT or MRI at each visit
- MPN-SAF total symptom score and change from baseline over time
- Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire (EORTC QLQ-C30) at 36 weeks
- Time to treatment failure (TTF) defined as either:
  - Any discontinuation from the study
  - Progressive disease
  - Study drug permanently stopped
  - Death

2.3 PHARMACOKINETIC ENDPOINTS

In Stage 1, the individual plasma concentration-time data following intravenous infusion of rhPTX-2 will be analyzed to obtain the following pharmacokinetic (PK) parameters, where applicable:

- C_{max} (maximum observed plasma concentration)
- t_{max} (time at which the maximum plasma concentration was observed)
- $AUC_{0\text{-}last}$ (area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration)
- $AUC_{0\text{-}\infty}$ (area under the plasma concentration-time curve from 0-time extrapolated to infinity)
- $t_{1/2}$ (apparent terminal elimination half-life)
- CL (clearance)
- Vd (volume of distribution)

The PK endpoint for Stage 2 subjects is the total PTX-2 level prior to drug administration at the pre-defined timepoints (see Appendix 5 and Appendix 6 Schedule of Assessment). Samples for rhPTX-2 PK analysis were not collected in Stage 2.

2.4 SAFETY OUTCOME MEASURES

Safety parameters to be measured include exposure, adverse events (AE) (including serious adverse events [SAEs], adverse events of special interest [AESI], AE leading to drug discontinuation, and deaths), clinical laboratory results (hematology, chemistry, and anti-drug antibodies), vital signs, electrocardiogram (ECG), and concomitant medication use.

2.5 DETERMINATION OF SAMPLE SIZE

Details regarding the sample size for Stage 1 and Stage 2 are described in the Appendix 1 and Appendix 3 (Protocol Synopsis).

For the OLE, no target sample size was delineated. The sample size was determined by the number of subjects who rollover from the main study. The study was intended to provide access to rhPTX-2 for any subjects in the main study for whom the investigator felt clinical benefit could be realized or extended.

2.6 ANALYSIS TIMING

The full study analysis will be conducted at the completion of the study as defined in the protocol (completion of each stage and OLE). This being an open-label non-inferential study, occasional exploratory analyses may be conducted throughout the study to inform the clinical development plan.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Subjects in Stage 1 were not randomized.

Subjects in Stage 2 were randomized to treatment group with a 1:1:1 randomization ratio. A central randomization system was used. The randomization was stratified according to the subjects' baseline hematologic status: baseline anemia alone (subjects with Hgb $<$ 100 g/L and having received $\geq$ 2 units PRBC in the 12 weeks prior to study entry) or baseline thrombocytopenia (platelet count $<$ 50 x 10^9/L) or baseline anemia associated with baseline thrombocytopenia. The randomization system ensured that at least 50% of the subjects in the final study population have baseline thrombocytopenia from the second stratum (platelet count $<$ 50 x 10^9/L).

3.2 INDEPENDENT REVIEW FACILITY

For Stage 1 and Stage 2, all bone marrow assessments were performed by a committee of expert hematopathologists, who were blinded to subject, dose, and time of biopsy.

The rules for assessment and adjudication are defined in the Central Bone Marrow Review Committee charter.

3.3 DATA MONITORING COMMITTEE

Stage 1 had no Data Monitoring Committee (DMC) in place.

In Stage 2, a DMC was established for purposes of independent assessment of safety during study conduct.

4. STATISTICAL METHODS

Except where specified, all continuous variables will be summarized by treatment group with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum, and maximum). All categorical variables will be summarized with frequency counts and percentages, by treatment group.

4.1 ANALYSIS POPULATIONS

4.1.1 All treated Population

Stage 1:

All subjects who have received at least one dose of rhPTX--2. The primary assessment of all efficacy analyses will be performed on this population.

Stage 2:

The all treated population will consist of subjects:

- randomized and, who have received at least one administration of the drug

In the event of subjects, having received treatments that differed from those assigned according to the randomization schedule, then the efficacy analyses will be conducted according to the randomized treatment (As randomized analysis).

This population will be the primary population for the efficacy analyses.

4.1.2 Pharmacokinetic Population

Stage 1:

The PK population includes all subjects who have received at least one dose of rhPTX-2 and have at least one measurable post-dose total PTX-2 concentration result.

The PK evaluable population includes all subjects who completed at least 1 cycle and had sufficient total PTX-2 concentration data to accurately estimate at least one PK parameter in at least 1 cycle.

Stage 2:

The PK population includes all subjects who have received at least one dose of rhPTX-2 and have at least one post-dose total PTX-2 concentration result.

4.1.3 Safety Population

For both stages, the safety population consists of subjects who have received at least one dose of study drug.

For Stage 2, in the event of subjects having received treatments that differed from those assigned according to the randomization schedule, then the safety analyses will be conducted according to the treatment actually received (As Treated Analysis).

4.1.4 Open Label Extension Population

For both stages, the OLE population consists of all subjects who received at least one dose of rhPTX-2 during the OLE phase.

4.1.5 Open Label Extension Subjects with Bone Marrow Biopsy Population

For both stages, the OLE patient populations with BM biopsy consist of all subjects who received at least one dose of rhPTX-2 during the OLE phase and have at least one BM biopsy result available during the OLE.

4.2 ANALYSIS OF STUDY CONDUCT

All analyses will be performed by study stage separately. The number of subjects who are enrolled and/or randomized (Stage 2 only) will be tabulated by treatment group, center and country. Major eligibility exceptions, major protocol deviations and reasons for study discontinuation will be summarized by treatment group for all subjects.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Descriptive summaries will be provided for all baseline characteristics. The summaries will be provided for both stages separately. Demographic and baseline variables that will be summarized by treatment group include at least:

- Stratification factors (Stage 2 only):
  - Baseline anemia (Hgb < 100 g/L and having received > 2 units PRBC in 12 weeks prior to study entry) alone
  - Baseline thrombocytopenia (platelet count $< 50 \times 10^9$ /L) alone
  - Baseline anemia associated with baseline thrombocytopenia
- Demographics for both Stages:
  - Gender
  - Age at consent (continuous and categorical)
  - Race
  - Ethnicity (if available)
  - Weight at baseline

Should country policy prohibit the collection of race and/or age information, subjects will appear in the missing category of summary tables.

- MF history for Stage 1:
  - Number of years since diagnosis
  - Bone marrow fibrosis grade at baseline
  - Spleen size below left costal margin at baseline
  - Type of MF (PMF, post-PV MF or post-ET MF)
  - Risk group with PMF (low, intermediate-1, intermediate-2, or high)
  - Red blood cell transfusion history 3 months prior to first dose
  - Number of subjects transfused (PRBC, Platelets, Fresh frozen plasma)
  - Number of subjects with baseline hemoglobin $<$ 100 g/L at baseline
  - Number of subjects with platelets < 50 g/L and <25 g/L at baseline
  - Number of units of platelet and RBC transfusions
  - Number of subjects previously treated with ruxolitinib
- MF history for Stage 2:
  - Number of years since diagnosis
  - Bone marrow fibrosis grade at baseline
  - Spleen size measured by CT, positron emission tomography-CT (PET-CT) or MRI at baseline
  - Type of MF (PMF, post-PV MF or post-ET MF)
  - Risk group with MF (DIPSS low, intermediate-1, intermediate-2, or high)
  - Number of subjects with at least one transfusion in 12 weeks prior to baseline (RBC and platelet)
  - Number of subjects with baseline hemoglobin $<$ 100 g/L at baseline
  - Number of subjects with platelets < 50 g/L and <25 g/L at baseline
  - Number of units of platelet and RBC transfusions
  - Number of subjects previously treated with ruxolitinib

In addition, for both stages, ruxolitnib history will be presented.

4.4 EFFICACY ANALYSIS

All analyses will be performed separately for each stage.

4.4.1 Primary Efficacy Endpoint

Stage 1:

The ORR will be compared against a fixed level of 10% using one-proportion Z-test.

The hypothesis test will be performed separately in each of the 4 treatment groups and overall, each at the 5% significance level (one-sided; statistical significance will be concluded if the lower bound of the 2-sided 90% CI is above 10%).

Subjects with no post-baseline IWG response assessments will be considered non-responders.

Stage 2:

The BMRR will be described as the percent of subjects with a reduction in bone marrow fibrosis score by at least one grade from baseline to any time of the study.

The BMRR will be presented within each treatment group with the corresponding 95% CI.

The BMRR will be analyzed using a logistic regression with bone marrow response at any time during the study (yes/no) as response variable and treatment group as explanatory variable. The analysis will be adjusted on randomized stratum. Pairwise comparisons between the 3 treatment groups will be performed.

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 demonstrate superiority and therefore, will use an adjusted two-sided level of significance of 0.025. 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 two-sided 0.05 level of significance.

The protocol proposed a threshold of 10% as the lower limit for clinically relevant response. For the 3 mg/kg and 10 mg/kg groups, the lower limit of the 97.5% two-sided confidence interval will be compared to this threshold of 10%. If the lower limit of the confidence interval is above 10%, the corresponding dose will be claimed to have demonstrated clinically relevant efficacy.

For subjects with no readable post-baseline BM biopsy results available, the conservative rule to consider them as non-responders will be used.

4.4.2 Secondary Efficacy Endpoints

Stage 1:

For Stage 1, no formal hypothesis testing will be performed for the secondary efficacy endpoints. All summaries will be presented by treatment group and overall.

The bone marrow biopsy results will be analyzed as:

- Myelofibrosis grade shifts relative to baseline at Weeks 12 and 24.
- Myeloblasts and cellularity will be presented at baseline, Weeks 12 and 24 as well as change from baseline
- Collagen grade shifts relative to baseline at Weeks 12 and 24.

The modified MPN-SAF TSS will be presented descriptively at baseline and at the beginning of each cycle (Cycle 2 onward). In addition, the number of subjects with ≥ 25% and ≥ 50% reduction relative to baseline at the beginning of each cycle (Cycle 2 onward) will be presented.

Stage 2:

Duration of effect of the three doses on reduction in bone marrow fibrosis:

- To assess the duration of effect of the three doses on bone marrow improvement a Kaplan-Meier plot will be provided. Duration of BM improvement will be defined for responding subjects as time from first decrease from baseline of one grade to time of return to baseline levels. If no return to baseline levels then duration will be censored at the last BM assessment
- Effect and duration of effect of the three doses on disease related anemia, thrombocytopenia, and constitutional symptoms: For patients with improvement, the duration of improvement is defined as the number of weeks of improvement from the first12 weeks of improvement period.

IWG-MRT response will be summarized by treatment group at each visit by percent of subjects with complete response, partial response, clinical improvement, stable disease and progressive disease according to IWG-MRT criteria.

4.4.3 Exploratory Efficacy Endpoints

The exploratory endpoints will be summarized using tables, listings and graphs as appropriate.

4.4.4 Sensitivity Analyses

For Stage 2, a non-stratified analysis of BMRR will be computing as a sensitivity analysis.

4.4.5 Subgroup Analyses

Stage 1:

- Primary endpoint results will be presented by risks groups (intermediate-1, intermediate-2, or high risk subjects).

Stage 2:

- Primary endpoint results will be presented:
  - by risks groups (intermediate-1, intermediate-2, or high risk subjects)
  - for each strata separately (baseline anemia alone, baseline thrombocytopenia alone, baseline anemia and thrombocytopenia)
  - by transfusion status at baseline with transfusion dependency defined as: ≥ 2 units PRBC every 4 weeks for 12 weeks prior to or after C1D1
  - by PTX-2 level at baseline classify by High/Low category (median as the cutoff)

The platelet improvement analyses will be presented by platelet levels (subjects with platelet <50 x10^9/L at baseline and subjects with platelet <25 x10^9/L at baseline)

4.5 PHARMACOKINETIC ANALYSES

The Stage 1 PK analysis will be reported in a dedicated report.

For all Stage 2 subjects, pre-dose plasma concentrations of total PTX-2 will be presented descriptively at each time point by treatment group, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

4.6 BIOMARKER ANALYSES

All biomarker data will be presented in a dedicated report.

4.7 SAFETY ANALYSES

The safety analysis population will be used for all safety analyses. Analyses will be performed for both stages separately, as well as for the OLE phases.

4.7.1 Exposure to Study Medication

Information on study drug administration will be summarized by duration, starting dose, and cumulative dose. In addition, treatment exposure will be summarized, including the percentage of the planned dose given at each cycle.

Withdrawals of subjects from study treatment will be reported as listings and summary tables.

4.7.2 Adverse Events

Coding of all adverse events will be done using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). As part of the safety data transfer to Roche, the adverse events will be re-coded in legacy coding domain after database lock. Consequently, no queries are planned to be raised for any discrepancies in MedDRA Preferred Terms (PTs). This might result in some event terms that are vague (for example - 'heart problems') to be coded to less accurate, more high level concepts (eg Cardiac disorder for the example given). All AEs and routine laboratory parameters will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI CTCAE) version 4.0 grading system.

For AEs, the most extreme intensity will be used for reporting. All AEs occurring during or after the first treatment will be described by summary tables divided by body system, NCI CTCAE grade, and relation to study treatment. In tables showing the overall incidence of AEs, subjects who experienced the same event on more than one occasion are counted only once in the calculation of the event frequency and the AE with the most extreme severity will be included.

For selected events of particular interest (Infusion Related Reaction[IRR]) more detailed analyses will be conducted. The analyses will depend on the specific question of interest for that particular AE. IRR will be presented by anti-drug antibody status. In addition, the IRR event frequency and severity will be included in the analysis. Treatment discontinuations due to IRR will be listed.

AE leading to treatment discontinuations and early study withdrawals will be summarized by treatment group and by reason. In addition, all serious AE will be summarized.

Deaths reported during the study treatment period and those reported during follow-up (i.e. follow-up is 4 week after the last visit cycle) after treatment completion or discontinuation will be summarized by treatment group.

4.7.3 Laboratory Data

Laboratory values will be listed for subjects individually, with flagging of values outside the normal range. Shift tables will be used to present the number and percentage of subjects with changes in grade based on the NCI CTCAE version 4.0 grading system.

The frequency and percentage of positive, negative and untested serological laboratory parameters will be reported by cycle and treatment group.

4.7.4 Vital Signs

Vital signs (absolute and change from baseline) will be summarized according to treatment group over time without any replacement for missing data.

Electrocardiogram and physical exam abnormalities will be listed.

4.8 OLE STUDY ANALYSES

The OLE analyses will be performed separately for the OLE Stage 1 and Stage 2.

The listings will include the treatment regimen the patient received during the main stage and during the OLE.

For Stage 1, OLE begins with the first infusion of Cycle 7. As with the main study, cycles are 28 days in length. The “OLE Baseline” consists of assessments at the end of Cycle 6 / beginning of Cycle 7 (pre-dose).

For Stage 2, OLE begins with the first infusion of Cycle 10. As with the main study, cycles are 28 days in length. The “OLE Baseline” consists of assessments at the end of Cycle 9 / beginning of Cycle 10 (pre-dose).

The synopses for the OLE are in Appendix 2 and Appendix 4.

The primary and secondary endpoints for both stages, will be also produced on the OLE population when applicable. The OLE tables will be classified as per the original dose

received on the main stage and overall. For subjects who change doses, improvement will be analyzed.

4.9 MISSING DATA

All available efficacy and safety data will be included in data listings and tabulations. No imputation of values for missing data will be performed. Subjects with missing post baseline response data, for any reason, will be counted as non responders.

4.10 INTERIM ANALYSES

No efficacy interim analyses are planned. This SAP aims to define the analyses to be produced for the final analysis.

5. REFERENCES

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Appendix 1
Protocol Synopsis – Stage 1

APPENDIX K: SYNOPSIS: STAGE I

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 Day 1 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, 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.

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 (see 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 of 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) ≤ 3x 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 ≤ 2x ULN (if upon judgment of the treating physician, it is believed to be due to EMH related to MF);
    - Serum creatinine ≤ 2.5 mg/dL 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 stroke, 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

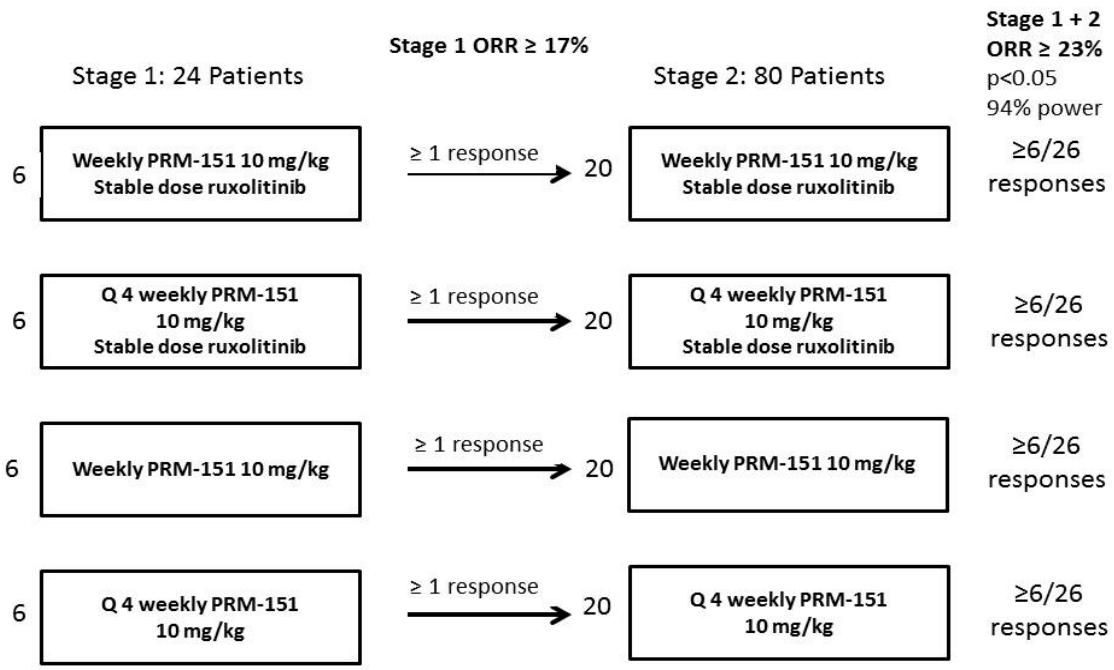
Statistical Methods:
The objective is to demonstrate superiority within each cohort and dose schedule, comparing observed ORR in each arm to a fixed uninteresting level ORR of 0.1. Let π denote population expected value of the primary parameter ORR. The objective of the trial is to reject the null-hypothesis

$H_0: \pi \leq 0.1$

in favor of the alternative hypothesis

$$: \pi > 0.4$$

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 π>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%, with 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 2 OLE Synopsis – Stage 1

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		
	Weekly Dosing	Q4 Weekly Dosing

SCHEDULE OF ASSESSMENTS	Extension Cycles 28 Day Cycle Length				Extension Cycles 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 3- Protocol Synopsis – Stage 2

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; 3mg/kg and 10 mg/kg intravenous
Comparator; Dose; and Mode of Administration: Not applicable
Primary Objective(s): • To determine the effect size of three different doses 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.
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 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 **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 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)

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 > 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 ≥ 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 < 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 ≥ 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 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

Stage 2 Study Design:

This is a randomized, double-blind Phase 2 study to determine the efficacy and safety of three different doses 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 ≥ 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 10mg/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) ≤ 3x 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 ≤ 2x ULN (if upon judgment of the treating physician, it is believed to be due to EMH 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

Appendix 4 OLE Synopsis – Stage 2

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 10mg/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 PRM151G-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 on every cycle.

PET-CT or CT or MRI:

These will be performed every 24 weeks.

Stage 2 Extension Study SCHEDULE OF ASSESSMENTS	Cycle 10, Day 1 (Cycle 9, Day 29)			Extension Cycles 28 Day Cycle Length
	Day 1 (+/- 3 days)			Day 1 (+/- 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
Completion of transfusion diaries	x			x
Bone Marrow(7)	x			x
MPN-SAF score(7)	x			x
EORTC-QLQC30(7)	x			x
PET-CT Scan or 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-SAFEORTC 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 5 Schedule of Assessments-Stage 1

APPENDIX A Schedules of Events

Table 6: Schedule of Events: Cohorts 1 and 2, Weekly Dosing

	Screening ≤ 28 days	Cycle 1 28 Day Cycle Length						Cycle 2, 3, 4, 5, 6 28 Day Cycle Length				Cycle 6, Day 29 (+/- 1 day)	~28 days after Cycle 6, Day 29 or withdrawal from study
		Day (+/- 1 day)						Day (+/- 1 day)					
		1	3	5	8	15	22	1	8	15	22		
Informed Consent	x												
Demographics	x												
Past Medical History	x												
Inclusion/Exclusion	x	x											
Bone Marrow Biopsy (1)	x							x(11)				x(11)	
Physical Exam (2)	x	x				x		x				x	x
Response Assessment								x					
Prior/Concomitant Medications	x	x	x	x	x	x	x	x	x	x	x	x	x
AE/SAE Assessment (3)	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs (4)	x	x	x	x	x	x	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	x		x		x	x
Pregnancy Test (5)	x	x						x					
Complete Blood Count (6)	x	x			x	x	x	x	x	x	x	x	x
Chemistry, BUN/creatinine (7)	x	x			x	x	x	x		x		x	x
Coagulation (8)	x	x				x		x				x	
12 lead ECG (13)	x	x						x		x			
ExploratoryLaboratory		x						x				x	

	Screening ≤ 28 days	Cycle 1 28 Day Cycle Length						Cycle 2, 3, 4, 5, 6 28 Day Cycle Length				Cycle 6, Day 29 (+/- 1 day)	~28 days after Cycle 6, Day 29 or withdrawal from study
		Day (+/- 1 day)						Day (+/- 1 day)					
		1	3	5	8	15	22	1	8	15	22		
Assessments (9)													
Transfusion History over past 3 months or since last visit	x	x			x	x	x	x				x	x
Ruxolitinib dose over last 3 months	x	x											
Special list of excluded medications	x	x			x	x	x	x		x		x	x
Pharmacokinetic samples (10)		x	x	x	x	x	x	x	x	x	x	x	
Anti-pentraxin 2 antibodies, pre-dose		x				x	x	x				x	
MPN-SAF score	x	x						x				x	x
PRM-151 Administration		x	x	x	x	x	x	x	x	x	x		
Review ruxolitinib self-administration log – Cohort 2 ONLY (12)		x						x				x	x

1. Bone marrow biopsy must have been performed within 4 weeks prior to first infusion of PRM-151; subsequent bone marrow biopsies performed +/- 3 days of scheduled visit

2 Abbreviated physical exam including spleen measurement by palpation at all timepoints

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 for all subjects receiving at least one dose of PRM-151

4. Vital signs (including temperature, blood pressure, pulse rate, and respiratory rate) will be performed before, immediately after, and every hour during the four hour observation periods, and before, immediately after, and at the conclusion of all one hour observation periods. Four hour observation periods are required through Cycle 2 Day 1 and subsequent observation periods are 1

hour.5. Serum pregnancy test within 4 weeks prior to the first dose of study drug; urine pregnancy tests for all subsequent tests; see 8.2.

6. 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.

7. 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

8. Coagulation testing at screening for all patients and include prothrombin time (PT), and partial thromboplastin time (PTT). For patients 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. Plasma samples will be analyzed for changes in the levels of cytokines including but not limited to CRP, IL-1ra, MIP-1β, TNFα, IL-6 and VEGF. PBMC will also be isolated and analyzed for changes in levels of mRNA and miRNA to determine a PRM-151 response signature. Blood samples for exploratory laboratory assessments to be obtained on Day 1 of Cycles 1, 2, 3 and 4, and Day 29 of Cycle 6.

10. Blood samples for PK analysis (4 mL) will be obtained on Cycles 1, 2 and 6, Day 1 at predose and at end of infusion, 1, 2, 4, and 8 hours post infusion; on Cycle 1, Day 15 at predose, 0.5, 0.75, 1.5, 3 and 6 hours post infusion; at pre-dose on Cycle 1, days 3, 5, 8 and 22; at pre-dose on Cycle 2, Days, 8, 15 and 22; at pre-dose Cycle 6, Day 15; and anytime on Cycle 6, Day 29.

11. Bone marrow biopsy will be done at screening, on Day 1 of Cycle 4, and on Day 29 of Cycle 6.

12. Patient Self-administration form for ruxolitinib

13. ECGs will be obtained pre-treatment and an additional ECG at end of infusion for Cycle 6 only, Days 1 and 15

Table 7: Schedule of Events: Cohorts 1 and 2, Every Four Week Dosing

	Screening ≤ 28 days	Cycle 1 28 Day Cycle Length Day (+/- 1 day)				Cycle 2, 3, 4, 5, 6 28 Day Cycle Length Day (+/- 1 day)		Cycle 6, Day 29 (+/- 1 day)	28 days after Cycle 6, Day 29 or withdrawal from study (+/- 1 day)
		1	3	5	15	1	15		
Informed Consent	x								
Demographics	x								
Past Medical History	x								
Inclusion/Exclusion	x	x							
Bone Marrow Biopsy (1)	x					x(11)		x(11)	
Physical Exam (2)	x	x			x	x		x	x
Response Assessment						x			
Prior/Concomitant Medications	x	x	x	x	x	x		x	x
AE/SAE Assessment (3)	x	x	x	x	x	x		x	x
Vital Signs (4)	x	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	x
Pregnancy test (5)	x	x				x			
Complete Blood Count (6)	x	x			x	x	x	x	x
Chemistry, BUN/creatinine (7)	x	x			x	x	x	x	x
Coagulation (8)	x	x			x	x		x	
12 lead ECG (12)	x	x				x			
Exploratory laboratory assessments (9)		x				x		x	

	Screening	Cycle 1 28 Day Cycle Length				Cycle 2, 3, 4, 5, 6 28 Day Cycle Length		Cycle 6, Day 29 (+/- 1 day)	28 days after Cycle 6, Day 29 or withdrawal from study (+/- 1 day)
		Day (+/- 1 day)				Day (+/- 1 day)			
	≤ 28 days	1	3	5	15	1	15		
Transfusion history over past 3 months or since last visit	x	x			x	x		x	x
Ruxolitinib dose over last 3 months	x	x							
Special list of excluded medications	x	x			x	x		x	x
Pharmacokinetic samples (10)		x	x	x	x	x		x	
Anti-pentraxin 2 antibodies, pre-dose		x			x	x		x	
MPN-SAF score	x	x				x		x	x
PRM-151 Administration		x	x	x		x			
Review ruxolitinib self-administration log – Cohort 2 ONLY (12)		x				x		x	X

1. Biopsy must have been performed within 4 weeks prior to first infusion of PRM-151; subsequent bone marrow biopsies performed +/- 3 days of scheduled visit
2. Abbreviated physical exam including spleen measurement by palpation at all timepoints
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, immediately after, and every hour during the four hour observation periods, and before, immediately after, and at the conclusion of all one hour observation periods. Four hour observation periods are required through Cycle 2 Day 1 and subsequent observation periods are 1 hour. .

5. Serum pregnancy test within 4 weeks prior to the first dose of study drug. Urine pregnancy test at all subsequent time points. See protocol Section 8.1
6. Complete blood count (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.
7. 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.
8. Coagulation testing at screening for all patients and include prothrombin time (PT), and partial thromboplastin time (PTT). For patients 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. Plasma samples will be analyzed for changes in the levels of cytokines, including but not limited to CRP, IL-1ra, MIP-1β, TNFα, IL-6 and VEGF. PBMC will also be isolated and analyzed for changes in levels of mRNA and miRNA to determine a PRM-151 response signature. Blood samples for exploratory laboratory assessments to be obtained on Day 1 of Cycles 1, 2, 3 and 4, and Day 29 of Cycle 6.
10. Blood samples for PK analysis (4 mL) will be obtained on Cycles 1, 2 and 6, Day 1 at predose and at end of infusion, 1, 2, 4, and 8 hours post infusion; at pre-dose on Cycle 1, Days 3 and 5; on Cycle 1, Day 15 at any time, and any time on Cycle 6, Day 29.
11. Bone marrow biopsy will be done at screening, on Day 1 of Cycle 4, and on Day 29 of Cycle 6.
12. Patient Self-administration form for ruxolitinib
13. ECGs will be obtained pre-treatment and an additional ECG at end of infusion for Cycle 6 Day 1 only.

Appendix 6 Schedule of Assessments-Stage 2

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 day)**	**(+/- 3 day)**	**(+/- 3 day)**
		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	

	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 day)	(+/- 3 day)	(+/- 3 day)
		1	3	5	1		
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[12]	x	x			x	x	x
Access IRS [13]	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 timepoints
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 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 of blood smear for 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 accessed 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 event

16 Subjects will be observed one hour after each dose