Mayo Clinic Cancer Center

MC138F: Phase II Study of P1101 in Myelofibrosis

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Statistician: [redacted]

Drug Availability
Drug Company Supplied: P1101 - *IND# 125,065*

√Study contributor(s) not responsible for patient care
*IND holder has changed as of MCCC Amendment 3

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Addendum 1	12Aug2015
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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/ interruptions/ adjustments, dose modifications, adverse events,forms completion and submission	[redacted]
Protocol document, consent form, regulatory issues	
Serious Adverse Events	

*No waivers of eligibility per NCI

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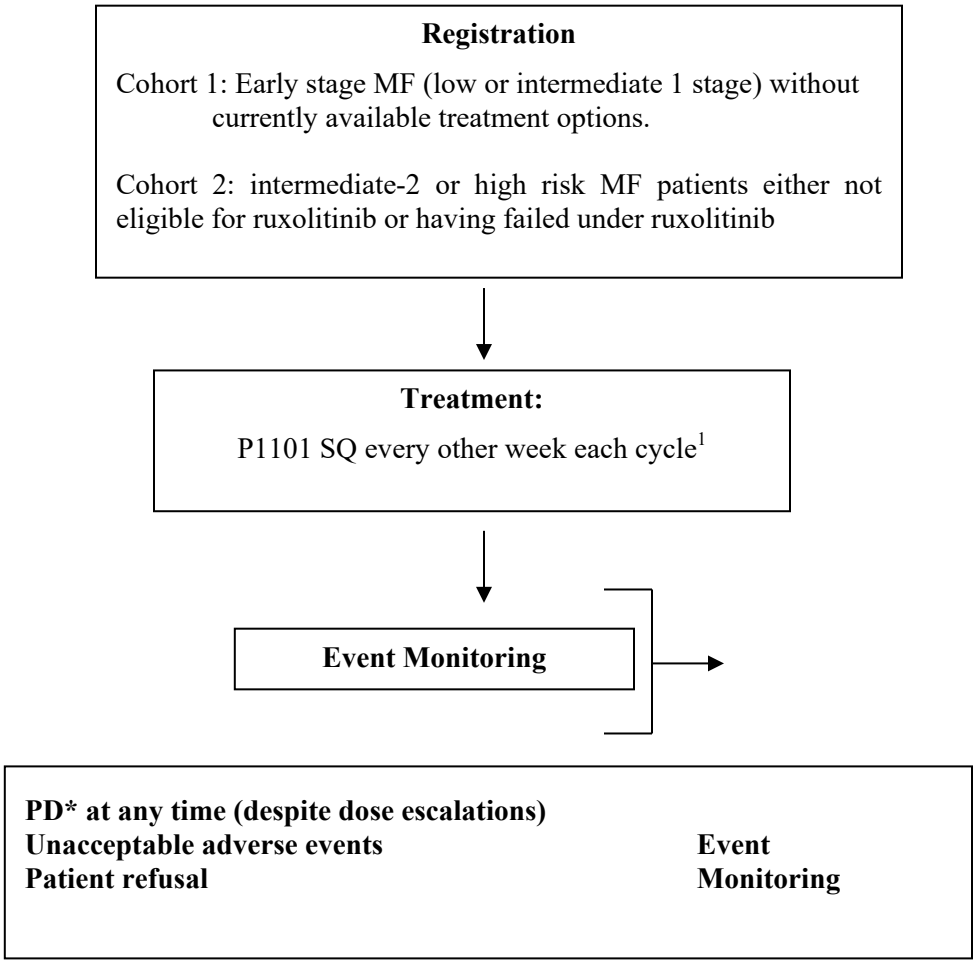
Schema



*PD=Progressive Disease

1. Cycle length 28 days

If a patient is deemed ineligible or a cancel, please refer to Section 13.0 for follow-up information.

Generic name: P1101 Brand name(s): Mayo Abbreviation: P1101 Availability: PharmaEssentia

1.0 Background

1.1 Myelofibrosis Unmet Clinical Needs

Myelofibrosis (MF) is a clonal myeloproliferative neoplasm (along with ET, PV, and CML) that can arise de novo, as primary myelofibrosis, or following essential thrombocytosis or polycythemia vera. Median age at diagnosis is 67 years old. Myelofibrosis is characterized by clonal stem cell proliferation, inefficient hematopoiesis, bone marrow fibrosis, and increased marrow vascularity. Bone marrow fibrosis and cytokine overexpression contribute to the cytopenias, extramedullary hematopoiesis (resulting in hepatosplenomegaly), and constitutional symptoms that are hallmarks of the disease. These associated symptoms can have considerable adverse effects on quality of life. Myelofibrosis is a heterogeneous disease that can follow an indolent course lasting years or a rapidly progressive course with attenuated survival. The Dynamic International Prognostic Scoring System- plus (DIPSS Plus) is a risk stratification system used to predict survival in primary MF. Early primary MF is defined as low or intermediate-1 risk and can be distinguished from advanced stages of the disease by evidence of residual hematopoiesis and grade 1 or 2 fibrosis on bone marrow biopsy.

Myelofibrosis is associated with a high morbidity and mortality resulting from marrow failure, massive splenomegaly, and leukemic transformation. Current drug therapies are not curative and have minimal impact on the natural history of the disease. Allogeneic stem cell transplant is the only known therapy with curative potential, however, advanced age at diagnosis and poor performance status prevent most patients from being transplant eligible.

1.2 Current available treatment

Current available treatments for primary MF target both the abnormal clonal stem cell proliferation and the pathologic bone marrow fibrosis. Unfortunately, bone marrow changes become irreversible in advanced stages of the disease, when patients become symptomatic and warrant treatment. Hydroxyurea has historically been shown to decrease hepatosplenomegaly, improve leukocytosis or thrombocytosis, and decrease constitutional symptoms in MF, however, it can cause cytopenias, is potentially leukemogenic, and effectiveness seems related to JAK2V617F mutation presence.

Recombinant interferon has shown efficacy in other myeloproliferative neoplasms (ET, PV) but dosing schedules were inconvenient and side effects limited use. Interferon α has induced cytogenetic and hematologic remissions in CML (another MPN) with evidence of reduction of marrow fibroblasts and bone marrow progenitor cells in vivo suggesting it may be effective in primary MF. (Gilbert HS. Cancer. 1998). Pegylated IFNα-2a has demonstrated efficacy, better tolerability, and a more reasonable dosing schedule. Hematologic responses are durable, and there has been no proven association with transformation to leukemia. A single institution study at Mayo Clinic showed rIFNα -2b monotherapy resulted in both hematologic and molecular responses in MF (Gowin Haematologica. 2012) A prospective single institution study of recombinant IFNα in 18 early MF patients (Silver Blood. 2011) showed an 80% rate of clinical benefit or stability with acceptable toxicities. JAK2 inhibitors have been approved for use in patients with intermediate or high risk MF and effectively reduce spleen size, improve constitutional symptoms, anemia, and quality of life. These medications appear best suited for patients with debilitating constitutional symptoms or severe symptomatic splenomegaly as opposed to patients with early stage myelofibrosis. Pegylated IFNα -2b has been studied in the treatment of hepatitis.

1.3 P1101

The study drug P1101 is a long acting pegylated interferon alpha-2b that has not yet been studied in MF. Preclinical safety data supports safe use of P1101 in humans. Clinical effects are expected to be similar to those of other approved Peg-IFNα products. Three clinical studies have looked at safety, efficacy, and maximum tolerated dose including one study in polycythemia vera patients. In this study, the MTD was found to be 540 µg subcutaneously every two weeks. Among 34 evaluable patients, overall hematological response rate was 90% with complete response rates of 46% after one year of treatment. Sixteen serious adverse events have been reported. The incidence of treatment related emergent adverse events with P1101 was no higher than with Pegasys®. Adverse events were mostly mild to moderate in severity and resolved spontaneously. Injection site erythema was the most common adverse event and headache was second.

Other reported adverse events included myalgia, decreased neutrophil count, back pain, increased body temperature, decreased white blood cell count, arthralgia, chills, fatigue, eye pain, feeling cold, nausea, transaminitis, somnolence, upper respiratory tract infection, feeling hot, decreased appetite, and pyrexia.

1.4 Rational

Patients with primary MF have a shortened life span and can have a significantly compromised quality of life as a result of progressive disease. Disease treatment earlier may delay progression of disease, prolong overall survival, and improve quality of life.
We propose an open label nonrandomized pilot study of P1101 in patients with MF with the hypothesis that P1101 might have an impact in either early MF or in those with MF who are not eligible or failed ruxolitinib.

2.0 Goals

2.1 Primary

2.11 The primary objective in this study will be to evaluate for clinical response (complete remission [CR], partial remission [PR], or clinical improvement [CI]) as defined by IWG-MRT criteria (Tefferi et al. Blood. 2013) in a cohort of intermediate-2/high risk MF patients. Response in a second cohort of early stage MF patients will also be described.

2.2 Secondary

2.21 To evaluate the adverse event profile of P1101 in patients with myelofibrosis by cohort (early vs intermediate-2/high risk)

2.22 To evaluate the tolerability of P1101 in patients with myelofibrosis by cohort (early vs intermediate-2/high risk)

2.3 Exploratory and Correlative Research

2.31 To evaluate quality of life (QOL) and patient-reported symptoms using the MPN-SAF with P1101 for patients with myelofibrosis. (Emanuel et al. J Clin Oncol. 2012) by cohort (early vs intermediate-2/high risk)

2.32 To evaluate the impact of P1101 on bone marrow and histological features of myelofibrosis including cytogenetics, blast percentage, fibrosis, and JAK2-V617F allele burden by cohort (early vs intermediate-2/high risk)

3.0 Patient Eligibility

Overall: The study will enroll patients into two parallel cohorts – cohort 1, corresponding to the "early MF" definition, and the cohort 2, representing a "typical" MF patient. Enrollment will occur simultaneously for both cohorts , until the planned sample size will be achieved.

3.1 Inclusion Criteria

3.10 Evaluable myelofibrosis by IWG-MRT criteria including one or more of the following:

- Spleen ≥5cm below the left costal margin
- MPN-SAF TSS >10 at baseline
- Hemoglobin <10 g/dL

3.11 Age ≥18 years.

3.12 Confirmed diagnosis of myelofibrosis (primary myelofibrosis or myelofibrosis secondary to essential thrombocythemia or polycythemia vera) by WHO diagnostic criteria (3 major and 2 minor criteria: Major criteria: megakaryocyte proliferation and atypia with either reticulin and/or collagen fibrosis, not meeting criteria for CML, PV, MDS, or other myeloid neoplasm, JAK2V617F or other clonal marker or no evidence of reactive marrow fibrosis. Minor criteria: leukoerythroblastosis, increased LDH, anemia, palpable splenomegaly).

3.13 For cohort 1: Early stage MF (low or intermediate 1 stage as defined by DIPSS, see Appendix VI) without currently available treatment options.

For cohort 2: intermediate-2 or high risk MF patients as defined by DIPSS (see Appendix VI) either not eligible for ruxolitinib or having failed under ruxolitinib

3.14 No prior treatment for myelofibrosis (for Cohort 1 only)

3.15 ECOG Performance Status (PS) 0, 1 or 2 (Appendix I).

3.16 The following laboratory values obtained ≤_14 days prior to registration.

- Platelet count ≥100,000/mm^3
- Absolute Neutrophil Count (ANC) ≥1000/mm^3
- Aspartate transaminase (AST) ≤2.5 x ULN
- Alanine aminotransferase (ALT) ≤2.5 x ULN
- Calculated creatinine clearance must be ≥50 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$

Creatinine clearance for females = $\frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$

3.17 Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.18 Ability to complete questionnaire(s) by themselves or with assistance.

3.19a Provide informed written consent.

3.19b Willing to return to enrolling institution for follow-up per section 4.0

3.19c Willing to provide blood samples for correlative research purposes (see Sections 6.2 and 14.0)

3.2 Exclusion Criteria

3.21 Patients who have had chemotherapy or radiation ≤2 weeks of registration.

3.22 For Cohort 1 only: Patients with evidence of Intermediate 2 or High risk disease (according to DIPSS, see Appendix VI).

3.23 For Cohort 1 only: Patients with a bone marrow biopsy with <15% cellularity,evidence of collagen fibrosis, osteosclerosis, or blasts > 10% in peripheral blood or marrow (demonstrating advanced disease).

3.24 Patients who have received a prior stem cell transplant

3.25 Patients who have received radiation to the spleen within 3 months prior to registration

3.26 Patients with intolerance to compounds similar to pegylated interferon alpha-2b.

3.27 Patients with evidence of ≥grade 2 peripheral sensory neuropathy.

3.28 Any of the following, because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.29a Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.29b Immunocompromised patients or patients known to be HIV positive and currently receiving antiretroviral therapy.

3.29c Uncontrolled simultaneous illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac

arrhythmia, history of depression, or psychiatric illness/social situations that would limit compliance with study requirements.

3.29d Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.29e History of myocardial infarction ≤6 months prior to registration, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.29f History of significant or major fundoscopic findings including, but not limited to, retinal exudates, hemorrhage, detachment, neovascularization, papilloedema, optic atrophy, micro-aneurysm or macular changes.

3.29g Other active malignancy at time of registration. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix.

4.0 Test Schedule

Cycle = 28 days

	Prior to Registration	**Active Monitoring**					
Parameter	≤14 days	**Cycle 1** Day 1	**Cycle 1** Days 8, 15, 22 ±2 days	**Cycle 2 and Cycle 3 Day 15**	**Prior to Treatment Cycle 2 Day 1 and Beyond**	**Prior to Treatment Cycles 2, 3, 6, 9 & 12 and every 3 cycles thereafter** Day 1 ±3 days	**At Treatment Discon-tinuation** ±7 days
Medical History	X						
Prior Diagnosis/Prior Treatment	X						
Height (pre-study only)	X						
Weight, ECOG PS	X					X	X
Physical Examination	X					X	X
Serum pregnancy test(HCG)[3]	X						
Vital Signs	X	X[7]				X	X
CBC with Differential and peripheral blood smear (Can be from home lab for interval monitoring)	X		X[7]	X[7]	X[2]		X
Chemistries (Sodium, potassium, creatinine, chloride, SGOT (AST), SGPT (ALT), Alkaline Phosphatase, Total bilirubin, glucose)	X		X[7]	X[7]	X[2]		X
JAK2, BCR-ABL, CALR, & MPL	X[6]					X[6]	
Treatment Evaluation (see Section 11)						X	X
EKG	X						
Transfusion Assessment	X				X[5]	X	X
Symptom Assessment Package (Patient Questionnaire Booklet)	X					X[1]	X

	Prior to Registration	**Active Monitoring**					
Parameter	≤14 days	**Cycle 1** Day 1	**Cycle 1** Days 8, 15, 22 ±2 days	**Cycle 2 and Cycle 3 Day 15**	**Prior to Treatment Cycle 2 Day 1 and Beyond**	**Prior to Treatment Cycles 2, 3, 6, 9 & 12 and every 3 cycles thereafter** Day 1 ±3 days	**At Treatment Discon-tinuation** ±7 days
Clinical measurement of spleen and liver by physical exam	X					X	X
Research Blood Samples		X[7]			X[7, 8]		
Adverse Event monitoring	X	X[7]	X[7]		X[5, 7]	X	X
Bone marrow biopsy and aspirate including cytogenetics[4]	X					X	

Footnotes:

1. To be completed prior to treatment on Day 1. Patient questionnaire booklet must be used; copies are not acceptable for this submission.
2. To be completed on Day 1 of Cycles 4, 5, 7, 8, 10 and 11 at local MD office and faxed to study team
3. Pregnancy test must be completed ≤7 days prior to registration
4. ≤90 days prior to registration. Repeat at cycle 6 and 12 only.
5. Patients can be contacted by telephone for adverse event assessment when not seen in the clinic.
6. Must be completed at least 90 days prior to registration. Any positive results at baseline will be repeated again every three cycles (Cycle 3, 6, 9, *etc*).
7. Must be completed prior to treatment.
8. Research blood samples only collected on C1D1, C2D1, and C3D1 prior to treatment.

5.0 Grouping Factor:

Cohort: Cohort 1 (early stage MF) versus Cohort 2 (intermediate-2 or high risk MF)

6.0 Registration/Randomization Procedures

6.1 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted] If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.2 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19c and 14.0).

6.3 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Prior to accepting the registration, registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form

- Existence of a signed authorization for use and disclosure of protected health information

6.5 At the time of registration, the following will be recorded:
- Patient has/has not given permission to store and use his/her sample(s) for future research of Myelofibrosis at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.6 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.

6.7 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.8 All required baseline symptoms (see Section 10.51) must be documented and graded.

6.9 Treatment on this protocol must commence at Mayo Clinic Arizona under the supervision of a hematologist or healthcare professional.

6.9a Study drug is available on site.

6.9b Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

7.0 Protocol Treatment

7.1 Treatment Schedule (Both Cohorts)

Dose level	Agent	Dose	Route	Day
-2	P1101	50 micrograms (mcg)	SQ	Day 1
-1	P1101	50 micrograms (mcg)	SQ	Day 1 and 15
0*	P1101	100 micrograms (mcg)	SQ	Day 1 and 15
1	P1101	150 micrograms (mcg)	SQ	Day 1 and 15
2	P1101	200 micrograms (mcg)	SQ	Day 1 and 15
3	P1101	250 micrograms (mcg)	SQ	Day 1 and 15
4	P1101	300 micrograms (mcg)	SQ	Day 1 and 15

*starting dose level

7.2 **All patients will be started at dose level 0 every other week, and then dose will be titrated up by 50mcg increments to a maximum dose of 300mcg every other week as**

tolerated.

7.3 Patients can be instructed in administration techniques and granted treatment independence with nursing staff approval. Patients should complete the Medication Diary (Appendix II) and be instructed to complete the Transfusion Diary (Appendix V).

7.3 For this protocol, the patient must return to the consenting institution for evaluation at least every 4 weeks during treatment through cycle 3 day 1, and then will return every 3 cycles.

7.5 Local Medical Doctor (LMD) treatment:
After cycle 3, day 1 and if the patient is tolerating therapy without excessive toxicity at a stable dose level, the patient may be seen by their Local Medical Doctor (LMD). Patients will need to return to Mayo Clinic Arizona at least every 3 cycles for assessment (refer to Section 4.0). The registering physician retains responsibility for the patient.

In this case, a written statement outlining drug dosage, method of administration, follow-up tests required, and telephone number to call to discuss any questions with the responsible investigator must be sent with the patient to provide necessary information to the LMD.

8.0 Dosage Modification Based on Adverse Events

Treatment modifications are based on adverse events. All adverse events should be graded according to the CTEP Common Terminology Criteria for Adverse Events (CTCAE v4.0). Dose modification recommendations listed below are general guidelines, and appropriate dose adjustments for patient safety should be done as deemed necessary by the treating physician or his representative.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

Dose Modifications for P1101 (Based on Adverse Events in Tables 8.2)

Starting Dose	Dose level -1	Dose level -2	Dose level -3	Dose level -4	Dose level -5	Dose level -6	Dose level -7
100 micrograms (mcg)	50 micrograms (mcg) Days 1 and 15	50 micrograms (mcg) Day 1 only	Discontinue				
150 micrograms (mcg)	100 micrograms (mcg)	50 micrograms (mcg) Days 1 and 15	50 micrograms (mcg) Day 1 only	Discontinue			
200 micrograms (mcg)	150 micrograms (mcg)	100 micrograms (mcg)	50 micrograms (mcg) Days 1 and 15	50 micrograms (mcg) Day 1 only	Discontinue		
250 micrograms (mcg)	200 micrograms (mcg)	150 micrograms (mcg)	100 micrograms (mcg)	50 micrograms (mcg) Days 1 and 15	50 micrograms (mcg) Day 1 only	Discontinue	
300 micrograms (mcg)	250 micrograms (mcg)	200 micrograms (mcg)	150 micrograms (mcg)	100 micrograms (mcg)	50 micrograms (mcg) Days 1 and 15	50 micrograms (mcg) Day 1 only	Discontinue

Table 8.2: Dose modification guidelines for P1101 related adverse events (with an attribution of possible, probable or definite)

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*** ← ←

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
BASED ON INTERVAL ADVERSE EVENTPRIOR TO DAY 15 EACH CYCLE			
Investigations	Grade 3 Platelet count decreased	P1101	Omit Day 15 treatment until platelet count resolves to grade 2 or less. Treatment may be restarted at the next lower dose level
	Grade 4 Neutrophil count decreased	P1101	Omit Day 15 treatment until neutrophil count resolves to grade 2 or less. Treatment may be restarted at the next lower dose level
	Grade 3 Alanine aminotransferase (ALT) increased	P1101	Omit Day 15 treatment until ALT resolves to grade 2 or less. Treatment may be restarted at the next lower dose level
	Grade 3 Aspartate aminotransferase (AST) increased	P1101	Omit Day 15 treatment until AST resolves to grade 2 or less. Treatment may be restarted at the next lower dose level
Non Hematologic	All other Non-Hematologic Toxicities Grade ≥3 (With the exception of nausea, vomiting or diarrhea controlled with appropriate medications.)	P1101	Omit Day 15 treatment and re-check weekly, when returns to ≤ grade 2 resume treatment at next lower dose level.
AT TIME OF RETREATMENT ON DAY 1 OF EACH CYCLE			
Investigations	Grade 3 Platelet count decreased	P1101	Hold treatment until platelet count resolves to grade 2 or less, checking labs weekly. Treatment may be restarted at the next lower dose level. Contact study chair if treatment is held beyond 28 days.
	Grade 4 Neutrophil count decreased	P1101	Hold treatment until neutrophil count resolves to grade 2 or less, checking labs weekly. Treatment may be restarted at the next lower dose level. Contact study chair if treatment is held beyond 28 days.

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
	Grade 3 Alanine aminotransferase (ALT) increased	P1101	Hold treatment until ALT resolves to grade 2 or less, checking labs weekly. Treatment may be restarted at the next lower dose level. Contact study chair if treatment is held beyond 28 days.
	Grade 3 Aspartate aminotransferase (AST) increased	P1101	Hold treatment until AST resolves to grade 2 or less, checking labs weekly. Treatment may be restarted at the next lower dose level. Contact study chair if treatment is held beyond 28 days.
Non Hematologic	All other Non-Hematologic Toxicities Grade ≥ 3 (With the exception of nausea, vomiting or diarrhea controlled with appropriate medications.)	P1101	Hold treatment and re-check weekly, when returns to ≤ grade 2 resume treatment at next lower dose level.

* Located at [redacted]

** Use the following to describe actions in the Action column:

- ☐ Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- ☐ Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- ☐ Discontinue = The specified drug(s) are totally stopped.

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further adverse events >Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time, in the following cycles.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (42) Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Clinical Practice Guidelines. J Clin Oncol 18(20): 3558-3585, 2000.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.
If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed.
Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics
CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
[redacted]

Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Important: Expedited adverse event reporting requires submission of an AdEERS Multiple Agent Template found at [redacted]

10.11 Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.52 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

- **NOTE:** A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected

- The determination of whether an AE is expected is based on the agent-specific information provided in Section 15.0 of this protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.

NOTE: "Unexpected adverse experiences" means any adverse experience that is

neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 **Special Situations for Expedited Reporting**

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report or notification form may not be required for specific Grade 1, 2, 3 and 4 Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supersede the standard Expedited Adverse Event Reporting Requirements (Note: These adverse events must still be reported through the routine reporting mechanism [i.e. Nadir/adverse events form]; see footnote 1):

System Organ Class (SOC)	**Adverse event/Symptoms**	CTCAE Grade at which the event will not be expeditedly reported.
General disorders and administrations site conditions	Fatigue	Grade 3
	Malaise	
Investigations	White blood cell decreased	Grade 3 and Grade 4
	Platelet count decreased	
	Neutrophil count decreased	
Blood and lymphatic system disorders	Anemia	Grade 3 and Grade 4

1. These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event, except in the event of a hospitalization (follow reporting instructions for section 10.4).

10.311 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial

disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.312 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

    - Death attributable to a CTCAE term.

    - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

    - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.313 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported via AdEERS. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
    - Myelodysplastic syndrome (MDS)
    - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.314 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS.

10.4 Expedited Reporting Requirements:

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below using the AdEERS Multiple Agent Template [redacted]

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		7 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.31 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via paper Adverse Event Expedited Report – Single Agent or Multiple Agents within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.[3]
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.[3]

Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Effective Date: May 5, 2011

10.42 General reporting instructions

The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form [redacted] for investigational agents or commercial/investigational agents on the same arm.

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.4 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.44. Reporting of SAEs to PharmaEssentia

SAE reporting forms should be faxed or emailed directly to:

[redacted]

10.5 Other Required Reporting

10.51 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System/Organ/Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	White blood cell decreased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
Gastrointestinal Disorders	Diarrhea		X
	# of stools	X	
	Nausea	X	X
	Vomiting	X	X

10.52 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.51

10.521 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.522 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.53 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

Revised International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) as defined by IWG-MRT criteria (Tefferi et al. Blood. 2013)

Table 11.1

Response categories	Required criteria
Complete Remission (CR)	*Bone marrow:** Age-adjusted normocellularity; <5% blasts; ≤Grade 1 myelofibrosis**, AND *Peripheral blood:* Hemoglobin ≥100 g/L and <UNL; Neutrophil count ≥1 x 109/L and <UNL; Platelet count ≥100 x 10^9/L and <UNL; <2% immature myeloid cells***, AND *Clinical:* Resolution of disease symptoms; Spleen and liver not palpable; No evidence of EMH
Partial Remission (PR)	*Peripheral blood:* Hemoglobin ≥100 g/L and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥100 x 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 myelofibrosis**, AND *Peripheral blood:* Hemoglobin ≥85 but <100 g/L and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥50 but <100 x 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 CT showing ≥35% spleen volume reduction (optional)*
Symptoms response	A ≥50% reduction in the Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (MPN-SAF TSS)
Progressive Disease ¥ (PD)	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 to 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 x 10(9)/L that lasts for at least two weeks

Stable Disease (SD)	Belonging to none of the above listed response categories
Relapse (REL)	No longer meeting criteria for at least CI after achieving CR, PR or CI, OR Loss of anemia response persisting for at least one month, OR Loss of spleen response persisting for at least one month

Key: UNL, upper normal limit; LCM, left costal margin; MRI, magnetic resonance imaging; CT, computed tomography; EMH, extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven non-hepatosplenic EMH) ;

*Baseline and post-treatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

**Grading of myelofibrosis is according to the European classification (*Thiele et al. Haematologica 2005;90:1128*) . It is underscored that the consensus definition of "a complete remission bone marrow" is to be used only in those patients where all other criteria, including resolution of leukoerythroblastosis, are met. 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 histological remission.

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

See table 11.1 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 pre-treatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pre-treatment baseline, in platelet count or absolute neutrophil count, according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In addition, assignment to clinical improvement (CI) requires a minimum platelet count of ≥25,000 x 10(9)/L and absolute neutrophil count of ≥0.5 x 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 below), but have received transfusions within the previous month, the pre-transfusion 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

Optional, Spleen or liver responses can be confirmed by imaging studies where a ≥35% reduction in spleen volume, assessed by magnetic resonance imaging (MRI) or computed tomography (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 Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (MPN-SAF TSS).17 The MPN-SAF TSS is assessed by the patients themselves and 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-to-100 scale). Symptoms response requires ≥50% reduction in the MPN-SAF TSS.

Optional, Progressive disease assignment for splenomegaly requires confirmation my MRI or CT showing a ≥25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pre-treatment baseline and not to post-treatment measurements.

12.0 Descriptive Factors

12.1 Prior ET/PV disease specific therapy (including drugs, or splenectomy): Yes vs no.

12.2 Prior bleeding events felt to be related to underlying disease: Yes vs no.

12.3 Prior thrombosis: Yes vs no.

12.4 Type of Myelofibrosis at registration: Primary Myelofibrosis (PMF) vs. Post ET Myelofibrosis vs. Post PV Myelofibrosis.

12.5 MF DIPSS Risk at time of registration (Appendix VI): Low vs. Int-1 vs. Int-2 vs. high

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are without progression will continue treatment per protocol.

13.2 Patients who develop PD while receiving therapy will go to the event-monitoring phase.

13.3 Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 18.0.

13.4 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the end of active treatment/cancel notification form must be submitted. Nor further data submission is necessary.

13.5 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. Event monitoring will be required per Section 18.0 of the protocol.

13.6 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Prior to Treatment on C1D1, C2D1, C3D1	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Banking	Mandatory	Serum	Red	10 mL (1)	X	yes	Freeze

14.2 Blood/Blood Products Handling

14.21 All samples must be collected **Monday-Friday ONLY.**

14.22 Label specimen tube(s) with protocol number, patient study ID number, and time and date blood drawn.

14.23 Collect and processing

14.231 Serum specimens will be collected per schedule as outlined in Section 14.1. Collect 10 mLs of No Additive blood and allow the blood to clot at room temperature x 30 minutes. Centrifuge the blood at 3000 rpm x 10 minutes. Carefully aliquot the 1.0 mL of serum into three aliquots and 0.5 mL into the 4th aliquot and freeze at - 80°C freezer until requested.

15.0 Drug Information

15.1 P1101 (PEG-P-IFNa-2b)

15.11 Background:
P1101 is a long-acting interferon that has only one major form as opposed to the 8-14 isomers of other FDA approved pegylated interferon products that are indicated for the treatment of hepatitis B and C. With P1101, it is anticipated that a reduced dosing frequency will be possible (once every two or more weeks) compared to that required with other pegylated interferon products. P1101 was shown to have slightly longer half-life but maintain serum 2'5'-oligoadenylate synthetase (OAS) activity longer than the other pegylated interferon products.

15.12 Formulation: P1101 will be supplied in a pre-filled syringe containing 500 micrograms ropeginterferon alfa-2b, sodium chloride, sodium acetate, acetic acid, benzyl alcohol, polysorbate 80 and water for injection

15.13 Storage: Syringes are shipped in cooled containers. Syringes must be refrigerated at 2°C-8°C immediately upon receipt to ensure optimal retention of physical and biochemical integrity and should remain refrigerated until just prior to use. Temperature logs must be maintained (in accordance with local pharmacy practice) to ensure proper storage conditions. Do not use medication beyond the

expiration date stamped on the vial. If a temperature deviation from the allowed 2°C-8°C is found either during shipment or storage then please contact the Sponsor to determine if the drug is still available for use. Refrigerated syringes at 2°C-8°C must have the following conditions adhered to: Do not freeze. Do not shake. Keep syringe in outer carton; protect from light.

Study medication labels will contain the following information: site number, subject number, visit number, product description, dosage strength, dosing instruction, expiry date, lot number, storage conditions, and caution statements.

15.14 Administration: P1101should be given by subcutaneous injections in the abdomen around but not within two inches of the navel. If the abdomen appears inappropriate according to the investigator's judgment, then study drug can be injected subcutaneously to the thigh.

15.15 Pharmacokinetic information: Mean P1101 serum concentration time curves were comparable across treatment groups and reached a peak at approximately 3 to 5 days after dosing and then declined gradually, with elimination half-lives of 60 to 118 hours. Single dose pharmacokinetic parameters (Cmax, AUC and AUC0-t) for P1101 increased with dose. The results of the power model analysis of dose proportionality for P1101 suggested more than proportional kinetics with increasing dose, as the slopes of the power model ranged from 1.19 to 1.36. The lack of dose proportionality for P1101 in this study may be attributed partly due to the high intersubject pharmacokinetic variability, and the small number of subjects.

15.16 **Potential Drug Interactions:** No information available.

15.17 Known potential toxicities: Adverse events reported most frequently (>10% of subjects) in either treatment in the ***single dose*** study include injection site erythema, headache, myalgia, decreased neutrophil count, back pain, increased body temperature, decreased white blood cell count, arthralgia, chills, fatigue, eye pain, feeling cold, nausea, increased alanine aminotransferase, somnolence, upper respiratory tract infection, feeling hot, decreased appetite, and pyrexia.

Adverse events reported in the ***repeated dose*** study have so far been mild to moderate. These include anemia, dizziness, dry mouth, dry skin, dyspnea, ear pain, epigastralgia, epistaxis, fatigue, fidget, flank pain, headache, myalgia, pruritus, respiratory distress, skin allergy, skin erythema, somnolence, sore throat, UTI, WBC decrease.

Investigators should also be informed of published data on marketed pegylated interferon. Subjects receiving ***repeated doses*** of interferon α-2b, have reported adverse events that include influenza-like symptoms, fever, headache, fatigue, rigors, musculoskeletal pain, arthralgia, back pain, injection site disorders (bruising, itching, and irritation), dry mouth, nausea/vomiting, diarrhea, abdominal pain, anorexia, weight, dizziness, impaired concentration, impaired memory, depression, anxiety/emotional lability/irritability, insomnia, alopecia, pruritus, dermatitis, rash, increased sweating, dyspnea, cough, and hypothyroidism. Common laboratory adverse events include neutropenia,

thrombocytopenia, increases in triglycerides and total cholesterol, abnormalities indicative of altered thyroid and liver function. Ten to fifteen percent of patients develop antibodies to interferon.

Serious adverse events that have been reported with this class of drugs include suicide attempt, suicidal ideation, severe depression, relapse of drug addiction/overdose, nerve palsy (facial, oculomotor), cardiomyopathy, myocardial infarction, retinal ischemia, retinal vein thrombosis, transient ischemic attack, supraventricular arrhythmias, loss of consciousness, neutropenia, infection (pneumonia, abscess), autoimmune thrombocytopenia, hyperthyroidism, rheumatoid arthritis, interstitial nephritis, lupus-like syndrome, aggravated psoriasis and urticaria.

15.18 Drug procurement: Drug is supplied by PharmaEssentia and provided free of charge to study subjects.

15.19 Nursing Guidelines:

15.191 Patients may experience injection site reactions including pain, erythema.

15.192 Monitor LFT's, report increases to the study team.

15.193 Monitor CBC w/diff. Leukopenia and neutropenia have been seen with agent.

15.194 Patients may experience fever. Treat symptomatically and monitor for effectiveness.

15.195 Arthralgias, and back pain were common. Treat symptomatically and monitor for effectiveness.

15.196 Given the similarity between this agent and pegylated IFN, patients may experience similar reactions and side effects. Carefully review those with patients based on the published data for pegylated IFN. Additionally this information is found in section 15.17 of the protocol.

16.0 Statistical Considerations and Methodology

16.1 Overview: This protocol will assess the efficacy of P1101in patients with myelofibrosis using a two-stage phase II study design. Cohort 2 will be formally analyzed for safety and efficacy as described by the decision rules below. Cohort 1 analysis will be descriptive only; no formal efficacy decision rules will be applied. Recruitment occurs separately for cohort 1 and cohort 2. **We currently plan to enroll and complete Stage 1. The protocol will be amended to expand to Stage 2.**

16.11 Primary Endpoint (Cohort 1 & 2): The primary endpoint of this trial is best overall response. An evaluable patient will be classified as a treatment success for the primary endpoint if the patient's best overall response is CR, PR or CI (Clinical Improvement) as determined by International Working Group Criteria [detailed in Section 11.0] over all cycles of study treatment. All patients meeting the eligibility

criteria who have signed a consent form, have begun treatment, and have not experienced a major treatment violation within the first cycle of treatment will be evaluable for response. Any evaluable patient not meeting the definition for treatment success will be deemed as having a treatment failure. The primary endpoint will be formally tested based on the decision rules below for cohort 2. For cohort 1, the primary endpoint will be summarized for descriptive purposes only.

16.2 Statistical Design:

16.21 Decision Rule(Cohort 2 only) : The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 10%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 30%. The following two-stage Fleming design (1982) uses 12 or 35 patients to test the null hypothesis that the true success proportion in a given patient population is at most 10%.

16.211 STAGE 1(Cohort 2 only): Enter 12 patients into the study. If 0 successes are observed in the first 12 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. If 4 or more successes are observed in the first 12 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population (a decision to complete the planned accrual specified by the design will be based on availability of budget, assuming no safety concerns). Otherwise, if the number of successes is 1, 2, or 3, we will consider a protocol amendment to expand to Stage 2. In cohort 2, after the first 3 patients are enrolled a recruitment pause will occur as asafety precaution measure. Safety/toxicity data will be analyzed in these 3 patients and a decision to continue the study will be made by the Principal Investigator, statistician and study team. .

16.212 STAGE 2(Cohort 2 only): Enter an additional 23 patients into the study. If 6 or fewer successes are observed in the first 35 evaluable patients, we will consider this regimen ineffective in this patient population. If 7 or more successes are observed in the first 35 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

16.213 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients is discussed in Section 16.34.

16.22 Sample Size: The two-stage study design to be utilized is fully described in Section 16.21. A minimum of 12 and a maximum of 35 evaluable patients will be accrued onto this phase II (Cohort 2 only) study unless undue toxicity is encountered. **We are currently planning to enroll to Stage 1 only.** We anticipate accruing an additional 1 patient to Stage 1 to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual to Stage 1 is therefore **13 patients for cohort 2**. Anticipated enrollment in cohort 1 is expected to be low, therefore a maximum of 6 patients will be

enrolled in cohort 1. Cohort 1 will be analyzed for descriptive purposes only, Total sample size is a maximum of 19 patients in both cohorts for Stage 1.

16.23 Accrual Time and Study Duration: The anticipated accrual rate is approximately 1 patient per month. Therefore, the accrual period for Stage 1 of this phase II study is expected to be 19 months. The Stage 1 analysis can begin approximately 25 months after the trial begins, i.e., as soon as the last patient has been followed for 6 months.

16.24 Power and Significance Level (Cohort 2 only): Assuming that the number of successes is binomially distributed, the significance level is >/=10% and the probability of declaring that this regimen warrants further studies (i.e., statistical power) under various success proportions and the probability of stopping accrual after the first stage can be tabulated as a function of the true success proportion as shown in the following table. These computations assume that the study is carried out in its entirety (i.e., accrual continues to Stage 2 if indicated by the responses observed in Stage 1).

If the true success proportion is . . .	0.10	0.15	0.20	0.25	0.30	0.35
then the probability of declaring that the regimen warrants further studies is . . .	0.07	0.28	0.58	0.81	0.93	0.98
and the probability of stopping (and rejecting H_a) at stage 1 is . . .	0.28	0.14	0.07	0.03	0.01	<0.01
and the probability of stopping at stage 1 is . . .	0.31	0.23	0.27	0.38	0.52	0.66

16.25 Other Considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan: The analysis for this trial will commence at planned time points (see Section 16.2) and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is approximately 19 months after the trial begins, i.e., as soon as the last patient has been followed for 6 months.

16.31 Primary Endpoint (Both Cohorts)

16.311 Definition: The primary endpoint of this trial is the best overall response rate where a response is defined in Section 16.11.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner (1987).

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals as though they were accrued in the final stage.

16.32 Definitions and Analyses of Secondary Endpoints (Both Cohorts)

16.321 Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier (1958).

16.322 Adverse events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.33 Exploratory & Correlative Endpoints (Both Cohorts)

16.331 Patient-reported outcomes: Patient-reported outcomes will be an exploratory component of this trial. Patient-reported symptoms and quality of life (QOL) will be described at each time point using the mean, confidence interval, median, and range. The MPN-SAF will be analyzed using published scoring algorithms. For the MPN-SAF, we will investigate changes in individual symptoms, changes in a symptom scale composed of symptoms specific to MF patients (night sweats, itching, abdominal discomfort, abdominal pain, early satiety, and bone pain) similar to the subset of symptoms used in the COMFORT clinical trials, and changes in the MPN Total Symptom Score (MPN-TSS, Emanuel et al, J Clin Oncol 2012 [in press]). Interpretation will take into consideration that the MPN-TSS includes symptoms potentially irrelevant to this MF population. Graphical procedures will include stream plots of individual patient scores and plots of average values over time. Correlational analyses will be done to determine the relationships among patients-reported symptoms and QOL, as well as with clinical outcomes (best overall response and overall survival) and clinician-assessed symptoms (NCI CTCAE v4). Such correlations will be done at single data time points.

16.4 Data & Safety Monitoring:

16.41 The study chair(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.42 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. The stopping rule applies to the

overall study, irregardless of cohort. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following:

- if 2 or more patients in the first 6 treated patients in either cohort (or 30% after the first 6 treated patients have been accrued) experience a grade 4 or higher non-hematologic adverse event.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 19 months after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has completed treatment.

16.6 Inclusion of Women and Minorities

16.61 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.62 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.63 The geographical region served by this study, has a population which includes approximately 7% minorities. Based on prior MMC studies involving similar disease sites, we expect about 7% of patients will be classified as minorities by race and about 33% of patients will be women. Expected sizes of racial by gender subsets for patients registered to this study are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

	Sex/Gender			
Ethnic Category	**Females**	**Males**	**Unknown**	**Total**
Hispanic or Latino	0	1		1
Not Hispanic or Latino	6	12		18
Ethnic Category: Total of all subjects*	6	13		**19**
Racial Category				
American Indian or Alaska Native	0	0		0
Asian	0	0		0
Black or African American	0	1		1
Native Hawaiian or other Pacific Islander	0	0		0
White	6	12		18
Racial Category: Total of all subjects*	6	13		**19**

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."
Not Hispanic or Latino

Racial Categories: **American Indian or Alaska Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.
Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)
Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

None

18.0 Records and Data Collection Procedures

18.1 Submission Timetables

Initial Material(s) -

Case Report Form (CRF)	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤2 weeks after registration
Adverse Event - Baseline	
Measurement - Baseline	
Bone Marrow and Cytogenetics	
Bone Marrow Biopsy Report including Cytogenetics	
JAK2V617F, BCR/ABL, CALR AND MPL	
Research Blood Submission	
End of Active Treatment/Cancel Notification	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire	≤2 weeks after registration – Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
Booklet Compliance	≤2 weeks after registration – This form **must** be completed only if the [name of booklet(s) – or whatever verbiage you want to use to describe the booklet(s)] contains absolutely **NO** patient provided assessment information.

Test Schedule Material(s)

	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
CRF	At each evaluation during treatment	At end of treatment
Evaluation/Treatment	X	X
Concurrent Transfusion	X	X
Interval Laboratory	X	X
Bone Marrow and Cytogenetics	X[3]	
Bone Marrow Biopsy Report including Cytogenetics	X[3]	
JAK2V617F, BCR/ABL, CALR AND MPL	X	
Nadir/Adverse Event	X	X
Measurement	X	X
Research Blood Submission	X (see Section 14.0)	
Patient Questionnaire	X[1]	
Booklet Compliance	X[2]	
End of Active Treatment/Cancel Notification		X
ADR/AER	At each occurrence (see Section 10.0)	

1. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
2. This form must be completed **only** if the booklet contains absolutely **NO** patient provided assessment information.
3. Only required when bone marrow biopsy is performed.

Follow-up Material(s)

	Event Monitoring Phase[1]				
CRF	q. 3 months until PD and/or subsequent treatment[2]	At PD[2]	After PD and/or subsequent treatment q. 6 mos.	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive __3___ years after registration, no further follow-up is required.
2. Submit copy of documentation of response or progression to the MCCC Operations Office, Attention: QAS

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: P1101 study drug is supplied by PharmaEssentia and provided free of charge to study subjects.

19.3 Other budget concerns: none

20.0 References

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Appendix I: ECOG Performance Status Scale

SCORE	DESCRIPTION
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 housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix II: MEDICATION DIARY for Myelofibrosis Patients

Name _____

Patient Medical Record #. _____ Cycle No. _____

Please complete this diary on the days you take the study drugs. Please place the time in the appropriate box indicating that you took the medication. Please also indicate the site, location, where you gave yourself your injection of study drug.

If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

Study Drug: P1101

	Date	Dose Time	Site of injection
Day 1	___ / ___ / ___		
Day 15	___ / ___ / ___		

My next scheduled visit is : _____

If you have any questions, please call: _____

Patient Signature: _____ Date:_____

Area Below Only To Be Completed only by Coordinator

Number of syringes returned_____ Study Coordinator Initials_____

Date_____ Discrepancy Yes____ No_____

Appendix III: Patient Information Sheet

PATIENT INFORMATION SHEET

Patient Completed Quality of Life Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains MPN-SAF (27 questions)

2. Directions on how to complete each set of questions are written on the top of each set.

3. Please complete the booklet during your scheduled clinical visit and return it to your nurse, physician, or research coordinator.

Thank you for taking the time to help us.

Appendix IV: MPN-SAF

Instructions: Please fill out all questions, as best able, reflecting how these symptoms affected you over the **LAST WEEK** unless directed otherwise. Use a scale of 0 to 10, circling "0" of the symptom is absent, "1" being most favorable, and "10" being least favorable.

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0	1	2	3	4	5	6	7	8	9	10
No fatigue										Worst imaginable

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No fatigue										Worst imaginable

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No fatigue										Worst imaginable

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

General activity

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Mood

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Walking ability

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Normal work (includes work both outside the home and daily chores)

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

5. Circle the one number that describes how, over the last week, the following symptoms have affected you.

Filling up quickly when you eat (early satiety)

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Abdominal pain

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Abdominal discomfort

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Inactivity

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Problems with headaches

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Problems with concentration – compared to prior to my MPN

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Dizziness / vertigo / lightheadedness

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Numbness / tingling (in your hands and feet)

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Difficulty sleeping

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Depression or sad mood

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Problems with sexual desire or function

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Cough

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Night sweats

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Itching (pruritus)

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Bone pain (diffuse not joint pain or arthritis)

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Fever (greater than 100ºF / 37.8ºC)

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Unintentional weight loss last 6 months

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

6. What is your overall quality of life?

0	1	2	3	4	5	6	7	8	9	10
As good as it can be										As bad as it can be

Appendix V: TRANSFUSION DIARY

Name _____

Patient Medical Record No. _____

Please complete this diary and bring it with you to your next study visit. Write in the date that you received a transfusion, the type of transfusion you received (platelets, red cells, or any other product), and the number of units.

Date of Transfusion	*Type of Product Received (platelets, red cells, other)	Number of Units Received	Pre-Transfusion HGB or Platelet count

*If other, list the type of product

My next scheduled visit is: _____

If you have any questions, please call: _____

_____ _____

(Date) (Participant's Signature)

Appendix VI: The Dynamic International Prognostic Scoring System (DIPSS) for primary myelofibrosis (PMF)

Each one of these risk factors is assigned 1 adverse point (2 adverse points for hemoglobin lower than 10 g/dL)

- age older than 65 years
- hemoglobin lower than 10 g/dL
- leukocyte count higher than 25 x 10^9/L
- circulating blasts ≥ 1%
- constitutional symptoms

Risk Group:

Low (0 adverse points)
Intermediate-1 (1 or 2 points)
Intermediate-2 (3 or 4 points)
High (5 or 6 points)

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