Clinical Study Protocol

INCB 18424-258 / NCT01348490

An Open Label Assessment of Safety and Efficacy of Ruxolitinib (INCB018424) in Subjects With Primary Myelofibrosis, Post Essential Thrombocythemia-Myelofibrosis and Post Polycythemia Vera-Myelofibrosis Who Have Platelet Counts of 50 × 10^9/L to 100 × 10^9/L

Product:	**Ruxolitinib**
IND Number:	**77,456**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **Route 141 & Henry Clay Road** **Building E336** **Wilmington, DE 19880 US**
Date of Protocol:	**29 MAR 2011**
Date of Protocol Amendment 1:	**17 AUG 2011**
Date of Protocol Amendment 2:	**09 AUG 2013**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 50, 54 56, 312, and Part 11 as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for ruxolitinib. I have read the INCB 18424-258 Protocol Amendment 2 and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

1. SYNOPSIS

Name of Investigational Product: ruxolitinib

Throughout this protocol, ruxolitinib will be used to designate the drug substance (ruxolitinib phosphate) and drug product (ruxolitinib phosphate tablets)

Title of Study: An open label assessment of safety and efficacy of ruxolitinib (INCB018424) in subjects with primary myelofibrosis, post essential thrombocythemia-myelofibrosis and post polycythemia vera-myelofibrosis who have platelet counts of 50 x 10^9/L to 100 x 10^9/L

Protocol Number: INCB 18424-258	**Study Phase: 2**

Primary Objectives:

- To determine the effects of ruxolitinib on spleen volume and symptomatic burden in patients with primary myelofibrosis (PMF), post polycythemia vera-myelofibrosis (PPV-MF) and post essential thrombocythemia-myelofibrosis (PET-MF) who have baseline platelet count of 50 x 10^9/L to 100 x 10^9/L.
- To determine the safety and tolerability of ruxolitinib in patients with PMF, PPV-MF, and PET-MF who have a baseline platelet count of 50 x 10^9/L to 100 x 10^9/L.

Secondary Objective:

- To determine appropriate dosing for patients with low platelets.
- To determine the long-term safety and efficacy effects of ruxolitinib in patients with PMF, PPV-MF and PET-MF who have baseline platelet count of 50 x 10^9/L to 100 x 10^9/L.

Overall Study Design:

This is an open label study of ruxolitinib in patients with PMF, PPV-MF, and PET-MF. The study is comprised of 4 phases:

Screening:	Up to 21 days
Baseline:	Exactly 7 days
Core Treatment Phase:	24 weeks
Extended Treatment Phase:	132 weeks; subjects receiving benefit will continue ruxolitinib treatment until Week 156
Follow-up Phase:	All subjects will be followed for safety (eg, reporting of AEs and serious AEs) for 30 to 37 days after the last dose of study drug is administered

Study Drug, Dosage and Mode of Administration and dose adjustments:

All subjects will begin dosing at 5 mg bid ruxolitinib. Doses should be taken morning and evening, approximately 12 hours apart, and without regards to food.

During the core treatment phase, doses of ruxolitinib may be increased in 5 mg qd increments up to a dose of 10 mg bid starting at the Week 4 visit and at subsequent study visits (no more than every 4 weeks) if platelet count was always ≥ 40 x 10^9/L since the last scheduled study visit, platelet count, if decreased since the last visit, is decreased by ≤ 20%, no dose decreases or holds for safety have occurred during the preceding 4 week interval, no ≥ Grade 2 hemorrhage events have occurred since initiating treatment and ANC is > 1000/μL. Doses may not exceed 10 mg bid except in subjects who continue to meet the above dose escalation criteria, and who have, in addition, a PGIC score of minimally worse, much worse or very much worse while receiving 10 mg bid. Such subjects may continue dose escalation to a maximum dose of 15 mg bid.

During the extended treatment phase, doses of ruxolitinib may be increased in 5 mg qd increments up to a dose of 25 mg bid if the subject meets the above dose escalation criteria, or per the investigator's discretion.

Doses may never exceed 25 mg bid.

Subjects will be required to decrease the dose for platelet count < 35 x 10^9/L, and to hold dosing for platelet count < 25 x 10^9/L. Subjects will have the option to restart or re-escalate the dose with improving platelet count.

Subjects will be required to interrupt dosing for any Grade 2 or higher hemorrhage events. Subjects will be able to restart ruxolitinib dosing with resolution of Grade 2 events; restart after a second event requires review and discussion of pertinent data with the sponsor. Restarts of ruxolitinib will only be permitted in some cases of Grade 3 and 4 events, after review and discussion of pertinent data with the sponsor.

Sites will provide information on incidents of Grade 4 thrombocytopenia and Grade 3/ Grade 4 hemorrhage events via FAX to the sponsor or its designee within 24 hours of learning of the event. The overall incidence of these events will be continuously monitored by the sponsor, and with ongoing data review, could result in a temporary hold for further enrollment, a reduction in the maximum allowable dose for subjects in the study, or a protocol amendment to modify dose titration rules.

Duration of Participation:

Up to 4 weeks for screening + baseline phases

Up to 24 weeks for the core treatment phase

Up to 132 weeks for the extended treatment phase (to Week 156)

Up to 37 days for follow-up

Total: 165 weeks, 2 days

Study Population:

Male or female individuals, aged 18 years or older who have been diagnosed with myelofibrosis (either PMF, PPV-MF or PET-MF), with a platelet count between 50 and 100 × 10^9/L and for whom treatment of MF is indicated may enroll. Subjects must score at least 1 point according to the DIPSS prognostic criteria (Passamonti et al 2010). Enrolled subjects must have a life expectancy of > 6 months.

Key Inclusion Criteria:

Must be diagnosed with PMF, PPV-MF or PET-MF as confirmed by bone marrow biopsy. Must have platelet count between 50 and 100 × 10^9/L at the screening and/or baseline visit. Must score at least 1 point on the DIPSS scale for prognostic risk factors, have active symptoms of MF and have peripheral blast count < 5% at both screening and baseline laboratory assessments. Subjects must discontinue all drugs used to treat underlying MF disease no later than Day -14. Subjects must not have INR > 1.5, or PTT value > 1.5 × ULN. Subjects must have hemoglobin levels at least 6.5 g/dL at screening, and be willing to accept transfusions to treat low hemoglobin levels.

Key Exclusion Criteria:

Females who are pregnant or breastfeeding, and males and females who cannot comply with requirements to avoid fathering a child or becoming pregnant. Subjects with confirmed platelet count < 50 × 10^9/L or ANC < 1 × 10^9/L at the screening visit. Inadequate liver or renal function, clinically significant concurrent infections requiring therapy, using potent or moderate CYP 3A4 inhibitors at screening, unstable cardiac function, gastric or esophageal varices, (subjects with a history of an incidental finding of small varices (< 5 mm) may be permitted in the study with sponsor approval), hemorrhagic strokes, intracranial bleeds or invasive malignancy over the previous 2 years except treated early stage carcinomas of the skin completely resected intraepithelial carcinoma of the cervix and completely resected papillary thyroid and follicular thyroid cancers.

Planned Number of Subjects: Approximately 150

Study Schedule/Procedures:

There will be study visits and laboratory-only visits in the study.

Core Treatment Phase:

Subjects will have a regularly scheduled study visit at screening, baseline, Day 1, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24, where blood samples, assessments, spleen measurements, etc. will be obtained. Optional dose increases may occur at these monthly study visits. All hematology labs and coagulation parameters will be analyzed by local laboratories. Serum chemistries, serology, and lipid panel will be analyzed by a central laboratory.

Subjects will have laboratory-only visits to collect hematology lab samples at Week 1, Week 2, Week 3, Week 5, Week 6, Week 7, Week 10, Week 14, and Week 18. The laboratory visits at Week 14 and Week 18 may be skipped for subjects who do not increase their dose at Week 12 or Week 16, and who have maintained platelet counts > 75 x 10^9/L since the last hematology assessment. Additional blood draws for hematology assessment will be required if platelet count falls below 35 x 10^9/L.

Subjects will have an MRI of the upper and lower abdomen and pelvis to determine the spleen volume at baseline and Week 24. CT scan will be substituted for subjects who are not candidates for MRI, or when MRI is not readily available. Patients Global Impression of Change (PGIC) questionnaire will be completed monthly. Measurement of spleen length below the left costal margin will be measured by palpation at each study visit.

Subjects will complete an electronic symptom diary (the Modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0) from baseline thru the Week 24 visits (total of 25 weeks).

Extended Treatment Phase:

Subjects will have a study visit every 12 weeks (eg, Weeks 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, and 156) through Week 156 where blood samples, clinical assessments, and palpable spleen measurements will be obtained. Subjects will have laboratory-only visits to collect hematology samples 6 weeks after the Week 24 visit (eg, Week 30), then after each extended treatment phase visit (eg, Weeks 42, 54, 66, 78, 90, 102, 114, 126, 138, and 150). Additional hematology assessments will be required if the subject has a dose modification or as clinically indicated.

Co-Primary Endpoints:

- Correlation of % change in spleen volume at Week 24 compared to baseline versus final titrated dose.
- Correlation of % change in Total Symptom Score as measured by the modified MFSAF v2.0 diary at Week 24 compared to baseline versus final titrated dose.

Safety Endpoint:

- Safety and tolerability will be assessed by monitoring the frequency, duration and severity of adverse events, performing physical examinations, collecting vital signs, collecting laboratory data for hematology, serum chemistry, and coagulation parameters through Week 156. In addition, analyses will include:
  - Proportion of subjects with new onset Grade 4 thrombocytopenia events as assessed by CTCAE v4.03.
  - Proportion of subjects with new onset Grade 2 or higher hemorrhage as assessed by CTCAE v4.03

Secondary Endpoints:

- Percent change in spleen volume at Week 24 compared to Baseline
- Percent change in Total Symptom Score as measured by the modified MFSAF v2.0 diary at Week 24 compared to baseline.
- Proportion of subjects with ≥ 35% reduction in spleen volume at Week 24 compared to baseline.
- Proportion of subjects with ≥ 10% reduction in spleen volume at Week 24 compare to baseline.
- Proportion of subjects with ≥ 50% improvement in total symptom score as measured by the modified MFSAF v2.0 diary at Week 24 compared to baseline.
- Long-term efficacy of ruxolitinib will be assessed by monitoring change and percent change in spleen length, as measured by palpation, and change in PGIC score from baseline to each visit where the variables are measured through Week 156.

[redacted]

Planned Number of Study Sites: approximately 60 sites that have previous experience with MF patients

Estimated Study Duration:

Estimated date first subject enrolled: May 2011

Estimated date last subject completed: September 2020

Statistical Methods:

The correlation between final titrated dose and % change of spleen volume measured by MRI, and % change in Total Symptom Score from baseline to Week 24 will each be calculated, and the null hypothesis of no correlation will be tested with the t test for correlation. In addition, the overall effect size (drug effect over all patients) will be estimated with 95% confidence intervals.

Safety data will be tabulated from baseline through Week 156 including AE, labs, and vital signs. Proportion of subjects with new onset of Grade 4 thrombocytopenia events, and proportion of subjects with new onset of Grade 2 or higher hemorrhage, as measured by CTCAE will be tabulated with summary statistics. The hazard functions of time to onset of the above two safety measures will be estimated using life table method.

The percent change in spleen volume at Week 24 compared to Baseline, the percent change in total symptom score as measured by the modified MFSAF v2.0 diary at Week 24 compared to Baseline, the proportion of subjects with ≥ 35% reduction in spleen volume at Week 24 compared to Baseline, proportion of subjects with ≥ 10% reduction in spleen volume at Week 24 compared to Baseline and the proportion of subjects with ≥ 50% improvement in total symptom score as measured by the

modified MFSAF v2.0 diary at Week 24 compared to Baseline will be tabulated with summary statistics. Change and percentage change in spleen length from baseline as measured by palpation at each visit where the parameter is assessed through Week 156 will be tabulated with summary statistics. The data will be summarized as one group and by the final titrated dose.

Data Monitoring Committee:

An independent data monitoring committee will be formed, consisting of qualified individuals who are not involved in the conduct of the study. The roles, responsibilities and composition of the committee will be established in a charter.

2. TABLE OF CONTENTS

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3. LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this study protocol.

Table 1: Abbreviations and Special Terms

Term	Explanation
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
bid	twice daily
CBC	complete blood count
C_{max}	maximum observed plasma concentration
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DIPSS	Dynamic International Prognostic Scoring System
dL	deciliter
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report forms
ECOG	Eastern Cooperative Oncology Group
ET	essential thrombocythemia
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWG-MRT	International Working Group for Myelofibrosis Research and Therapy
JAK	Janus kinase

Table 1: Abbreviations and Special Terms (Continued)

Term	Explanation
MF	myelofibrosis
MFSAF v2.0	Modified Myelofibrosis Symptom Assessment Form v2.0 (electronic symptom diary)
mg	milligram
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
PD	pharmacodynamic
PET-MF	post essential thrombocythemia myelofibrosis
PGIC	Patient Global Impression of Change
PI	Principal Investigator
PK	pharmacokinetics
PMF	primary myelofibrosis
PV	polycythemia vera
PPV-MF	post polycythemia vera myelofibrosis
PR	partial remission
PTT	partial thromboplastin time
qd	once daily
Ruxolitinib	Ruxolitinib phosphate or ruxolitinib phosphate tablets, based on context
SAE	serious adverse event
STAT	signal transduction and activator of transduction
ULN	upper limit of normal
WBC	white blood cells

4. INTRODUCTION

The four classic myeloproliferative neoplasms (MPNs) include chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). Myelofibrosis (MF) can present as a de novo disorder (PMF) or evolve secondarily from previous PV or ET (post-PV-MF or post ET-MF). Regardless of whether MF is a primary or secondary disorder, it is characterized by a clonal stem cell proliferation associated with production of elevated serum levels of multiple inflammatory and proangiogenic cytokines, a characteristic bone marrow stromal pattern that includes varying degrees of collagen fibrosis, osteosclerosis and angiogenesis and a peripheral blood smear showing a leukoerythroblastic pattern with varying degrees of circulating progenitor cells. Clinically, MF is characterized by progressive anemia, leukopenia or leukocytosis, thrombocytopenia or thrombocythemia and multi-organ extramedullary hematopoiesis most prominently involving the liver and spleen. Patients may experience severe constitutional symptoms, sequelae of massive splenomegaly (pain, limitations of movement, early satiety and shortness of breath, hepatic obstruction, and splenic infarction), a hypermetabolic state with cachexia, progressive hematopoietic failure, progression to leukemia, and premature death.

The median age at diagnosis is approximately 60 to 65 years. The incidence of PMF has been estimated at 1.5 cases per 100,000 people. Survival in MF varies with the presence or absence of specific risk factors. A prognostic scoring system based on a time-dependent risk evaluation has been developed: the Dynamic International Prognostic Scoring System (DIPSS) for PMF (Passamonti et al 2010), age of greater than 65 years, presence of constitutional symptoms, anemia (Hemoglobin less than 100 g/L), leukocytosis (white blood cell count (WBC) greater than 25 x10^9/L), and a circulating blast percentage of 1% or higher were assessed for their impact on survival when analyzed as time-dependent covariates in a multivariate Cox proportional hazard model. The approach showed that acquisition of anemia over time affects survival with a hazard ratio roughly double that of other parameters; anemia was therefore assigned a score of 2, while the other 4 factors were assigned scores of 1. Four risk categories with non-overlapping survival curves have been described:

Total Risk Score	Risk Category	Median Survival (months)
0	Low	not reached
1 or 2	Intermediate-1	170
3 or 4	Intermediate-2	48
5 or 6	High	18

For a subset of patients who are younger (generally less than 65 years), otherwise healthy and have a histocompatible donor, allogeneic stem cell transplantation may provide a curative option, although with substantial (10-20%) risks of mortality, (Deeg et al 2003). Drug therapies used, including hydroxyurea, busulfan, 6-mercaptopurine, anagrelide, thalidomide, lenalidomide, interferon, corticosteroids, and erythropoiesis stimulating agents or growth factors, have not been shown to improve survival. Some can increase the risk of leukemic transformation, and/or are poorly tolerated, and all have limited effectiveness in improving splenomegaly and constitutional symptoms. Splenectomy, performed in approximately 10% of the patient cohort reported by (Cervantes et al 2009), is associated with significant morbidity and mortality. Splenic irradiation

is also employed to reduce symptoms secondary to splenomegaly, but symptomatic improvement is variable and short-lived; moreover, transient and life-threatening pancytopenia and an approximate 20% treatment-related mortality have been noted.

Thrombocytopenia, although not found to be an independent variable in the multivariate analyses of prognostic factors proposed by the International Working Group for Myelofibrosis Research and Treatment (Cervantes et al 2009, Passamonti et al 2010), is considered to be an adverse risk factor by the Mayo Clinic group, (Elliott et al 2007). More recently, low platelet count ($< 100 \times 10^9$/L), was shown to be a Dynamic International Prognostic Scoring System (DIPSS)-independent factor for survival and leukemia-free survival (Gangat et al 2011). Apart from being an indicator of diminished bone marrow reserve, thrombocytopenia may also be a limiting factor with regards to therapy intensity with multiple agents including ruxolitinib, whose DLT is thrombocytopenia. Therefore, thrombocytopenic patients are often excluded from investigational studies despite having MF requiring therapy.

Within the past 5 years it was discovered that approximately 95% of patients with PV and about 50% of patients with PMF and ET have a somatic gain-of function mutation in the Janus Kinase 2 (JAK2) gene resulting in substitution of phenylalanine for valine at position 617 (JAK2 V617F) within the pseudokinase domain of the encoded protein. JAK 2 is one of four Janus kinases along with JAK1, JAK 3 and TYK 2. Together the Janus kinases are responsible for transduction of cell signaling from Type I and II cytokine receptors families because these receptors do not possess catalytic kinases to activate downstream signal transduction. Under physiologic conditions, the JAKs associate with the intracellular domain of the cytokine receptors in response to cytokine binding. They then undergo autophosphorylation resulting in conformational changes which enable them to transduce intracellular signaling by phosphorylating and activating transcription factors called Signal Transduction and Activator of Transduction (STAT) proteins. The activated STATs translocate to the nucleus where they regulate transcription of a number of genes involved in cellular activation, proliferation and survival. JAKs associate with the intracellular domain of the Type I and II receptors in pairs, which may be homodimers (eg, two JAK2s) or heterodimers (eg, a JAK 1 and a JAK2). Erythropoeitin (EPO), which is responsible for stimulating erythropoiesis, thrombopoietin (TPO) which is responsible for stimulating thrombopoiesis and GM-CSF have been shown to signal only through receptors which utilize JAK2 homodimers. A large number of other inflammatory mediators are known to signal primarily through receptors that utilize JAK heterodimers. It is also apparent that MF, as well as ET and even PV occur in the absence of the JAK2 V617F mutation. In a minority of patients other mutations in the JAK -STAT pathway have been identified but in many patients the mutations have not been identified yet or don't exist. However it appears that majority of patients with MF have over-activation of the JAK STAT pathway, regardless of JAK2 V617F status. In MF, excessive cytokine signaling through both JAK 1 and JAK2 have been observed both in patients harboring the JAK2V617F mutation and in patients without known mutations. Therefore, JAK inhibitors have the potential to treat some or all of the manifestations of MF, despite the potential for mechanism-based myelosuppression, given the role of JAK kinases in normal bone marrow function.

4.1. Background Information on Ruxolitinib Tablets

4.1.1. Pharmacology Summary

Ruxolitinib represents a novel, potent, and selective inhibitor of JAK1 (IC_{50} = 3.3 ± 1.2 nM) and JAK2 (IC_{50} = 2.8 ± 1.2 nM) with modest to marked selectivity against TYK2 (IC_{50} = 19 ± 3.2 nM) and JAK3 (IC_{50} = 428 ± 243 nM), respectively. Ruxolitinib is inactive (ie, < 30% inhibition) against 28 additional kinases when tested at 200 nM.

In cell-based assays relevant to the pathogenesis of MPNs, such as JAK/STAT signaling and growth of the cytokine-dependent tumor cell lines, ruxolitinib demonstrates IC_{50} values of 80-185 nM. This effect is not due to general cytotoxicity, because ruxolitinib (up to 25 μM) had no significant effect on the growth of cells driven by the BCR-ABL oncoprotein. Pharmacological data obtained with in vitro and in vivo model systems supports the potential utility of orally administered ruxolitinib in the treatment of inflammatory diseases such as RA as well as malignancies, including MPNs. See Quintas-Cardama et al 2010 and the Investigator's Brochure (IB) for additional information.

4.1.2. Drug Disposition Summary

Ruxolitinib has high solubility and permeability. It is designated as a Class I molecule in the Biopharmaceutical Classification System and exhibits moderate-to-high clearance, volume of distribution and oral bioavailability in preclinical species. The apparent elimination half-life is short (< 5 hr) in all species. The primary clearance pathway is oxidative metabolism and the metabolism by human liver microsomes is catalyzed predominantly by CYP3A4. In a study using ^{14}C-ruxolitinib in healthy volunteers, unchanged ruxolitinib was the predominant circulating drug-related entity with 2 major circulating metabolites observed, both of which are mono-oxidation products. The metabolites of ruxolitinib retain varying degrees of JAK-related pharmacological activity. Excretion was fairly rapid by both urinary and fecal routes with parent drug accounting for < 1% of the administered dose. Tissue distribution studies in rats indicate rapid and complete elimination of radioactivity in most tissues. Ruxolitinib exhibits high plasma protein binding in humans with an unbound fraction of 3.3%.

PK information is available from single and repeat dose studies in healthy volunteers, an ongoing study in subjects with myelofibrosis (MF), and a study in patients with RA. Ruxolitinib was absorbed rapidly, attaining mean peak plasma concentrations within 1-2 hours after administration. The mean ruxolitinib C_{max} and $AUC_{0-\infty}$ increased approximately proportional to dose over the entire dose range of 5 mg to 200 mg. The mean terminal phase elimination half-life was approximately 3 hours. There was no appreciable accumulation with repeat dosing. Administration of the 25 mg ruxolitinib with a high-fat, high-calorie meal slowed the absorption of ruxolitinib, prolonging the mean T_{max} from 1.3 to 2.7 h, and lowered the mean C_{max} by 24% but did not significantly affect the AUC compared to fasted administration. The overall magnitude of the food effect on ruxolitinib exposure is not expected to be clinically important. Therefore, ruxolitinib can be dosed without regards to meals. PK parameters in patients with RA and MF were similar to those seen in healthy volunteers.

Ruxolitinib was well tolerated in single dose drug-drug interaction studies with inhibitors and an inducer of the CYP P450 family of metabolizing enzymes, when co-administered with methotrexate, in subjects with renal insufficiency, and in subjects with hepatic dysfunction.

Co-administration of methotrexate does not alter the pharmacokinetic parameters of ruxolitinib while administration of erythromycin slightly increases AUC by 26%. Therefore no dose adjustments are required when ruxolitinib is administered together with moderate CYP3A4 inhibitors such as erythromycin, including grapefruit juice, or with methotrexate. Ketoconazole significantly increases the exposure to ruxolitinib when co-administered with ruxolitinib; it is recommended that dosage of ruxolitinib be decreased by 50% when co-administered with systemic ketoconazole, or other potent inhibitors of the CYP3A4 family of metabolizing enzymes. Co-administration with rifampin significantly decreased the exposure to ruxolitinib; however, increases in the relative amount of active metabolites in the presence of this potent inducer of CYP3A4 resulted in nearly identical levels of overall JAK inhibitory activity as assessed by measurement of inhibition of IL-6-induced STAT phosphorylation. Therefore, there is no required dose adjustment when ruxolitinib is co-administered with rifampin or other CYP3A4 inducers, but these agents should be used with caution in combination with ruxolitinib and alternative therapy used if available.

Ruxolitinib pharmacokinetics and pharmacodynamics (as measured by IL-6 induced STAT3 phosphorylation (pSTAT3)) were similar in subjects with normal renal function and with mild, moderate or severe renal impairment. In subjects with end stage renal disease on dialysis ruxolitinib PK parameters were similar to healthy subjects, whether ruxolitinib was dosed prior to or following a dialysis session, but ruxolitinib pharmacodynamics were prolonged in subjects dosed following a dialysis session. Therefore, ruxolitinib may be dosed to subjects with varying degrees of renal impairment without dose adjustment with the exception of subjects with end stage renal disease receiving hemodialysis. In a hepatic impairment study, there was an 88% increase in AUC in mild, 29% increase in moderate, and a 66% increase in severe hepatic disease (based on the Childs-Pugh classification) and the terminal elimination half-life ranged from 4.6 hours in mild, 4.1 hours in moderate, and 5.1 hours in severe hepatic impairment subjects compared to 2.8 hours in healthy subjects. No significant differences in pharmacodynamics were observed among subjects with mild or moderate hepatic dysfunction compared to healthy subjects. In subjects categorized as having severe hepatic impairment, the inhibition of IL-6 induced pSTAT3 levels appeared to be prolonged following a single dose of ruxolitinib. In subjects with hepatic impairment, it is suggested to reduce the initial starting dose (total daily dose) of ruxolitinib by 25% to 50% compared to the recommended therapeutic starting dose. Subjects should be carefully monitored and the dose titrated accordingly.

See the IB for additional information regarding the disposition of ruxolitinib.

4.1.3. Nonclinical Toxicology Summary

Effects noted in multiple dose toxicity studies in mice (up to 4 weeks), rats (up to 6 months), and dogs (up to 12 months) were primarily those associated with the mechanism of action of ruxolitinib, a potent and reversible inhibitor of JAK-STAT signaling. Decreases in red blood cells, reticulocytes, eosinophils and lymphocytes have been observed along with lymphoid depletion in bone marrow and lymphoid organs. In addition, in dogs, demodectic mange, bacterial pneumonia and viral-induced papillomas, expected consequences of the pharmacology of JAK inhibition, were noted.

In a respiratory safety pharmacology study, an adverse decrease in minute volume was noted in female but not in male rats at the highest dose, 150 mg/kg. In a cardiovascular evaluation of

ruxolitinib in dogs, electrocardiogram (ECG) parameters were unaffected at all doses. Administration of ruxolitinib at the highest dose evaluated (30 mg/kg) resulted in an adverse lowering of blood pressure along with an increase in heart rate compared to vehicle control. The IC_{50} for inhibition of the hERG channel was determined to be 131.6 μM.

Ruxolitinib was not mutagenic or clastogenic nor did it demonstrate potential for carcinogenicity in a 6 month study in Tg.rasH2 mice.

In embryo-fetal assessments in rat and rabbit, maternal toxicity and minimal embryo-fetal toxicity were noted at the highest doses evaluated. Ruxolitinib was not teratogenic in either rat or rabbit. In an evaluation of fertility and early embryonic development, no effects were noted on reproductive performance or fertility in male or female rats. Increases in post-implantation loss were noted at the higher doses. In a pre- and post-natal development and maternal function study in rats, no adverse effects were noted. Ruxolitinib passed into the milk of lactating rats with an exposure that was 13-fold higher than maternal plasma exposure. See the IB for additional information.

4.1.4. Clinical Summary

Ruxolitinib has been administered to over 180 healthy volunteers as single, repeat single, or multiple doses of up to 10 days duration. Ruxolitinib has been administered to approximately 450 subjects with MF for periods of up to > 24 months, and over 100 subjects with prostate cancer, multiple myeloma, polycythemia vera or essential thrombocythemia for periods of up to > 24 months.

In healthy volunteer studies, a transient, reversible decrease in neutrophil count has frequently been seen following dosing, which reverses after 12 to 24 hours off drug, suggestive that the neutropenia may reflect an effect of ruxolitinib blocking IL-6 signaling and causing neutrophil margination on blood vessel walls. In a repeat dose healthy volunteer study, neutropenia of any severity grade was seen in 22% of placebo subjects, 11% of subjects receiving 50 mg qd, 67% of subjects receiving 100 mg qd, 13% of subjects receiving 15 mg bid, 33% of subjects receiving 25 mg bid and 67% of subjects receiving 50 mg bid. Importantly, these neutropenia events were of Grade 1 or Grade 2 severity with a single instance of severe Grade 4 neutropenia that led to discontinuation of study drug in 1 subject receiving ruxolitinib at 50 mg bid (highest dose). The maximum tolerated dose in healthy volunteers was determined to be 25 mg bid and no dose limiting toxicities (DLT) were seen at 100 mg qd.

A definitive QT study was carried out in 50 healthy volunteers, evaluating the effects of single doses of 25 mg or 200 mg ruxolitinib compared with placebo and 400 mg moxifloxacin (positive control). The overall conclusion was that there appeared to be no adverse impact on ventricular repolarization (no increase in QTcF) and little change in heart rate, QRS duration, and a slight, non-clinically significant, increase in PR interval with the administration of ruxolitinib.

In an ongoing study in subjects with myelofibrosis (MF) where median time on drug is ~ 15 months (N=154), ruxolitinib was well tolerated by this elderly population (median age 65) with advanced disease. The DLT was thrombocytopenia. Initial dose ranging established an MTD of 25 mg bid and 100 mg qd in the MF population. Most adverse events were mild to moderate in severity and considered unrelated to administration of study drug. Related adverse events occurring in at least 5% (8 subjects) of the 154 subjects included in the safety database

through December 31, 2009 were restricted to anemia (45 subjects), thrombocytopenia (66 subjects), weight increased (11 subjects), diarrhea (10 subjects) and fatigue (8 subjects). Both anemia and thrombocytopenia represent JAK-inhibitor induced myelosuppression. Forty (40) subjects (26% of study population) had a Grade 3 or Grade 4 decline in platelet count during the study (31 Grade 3 events, 9 Grade 4 events). Subjects with Grade 3 or 4 thrombocytopenia entered the study, in general, with platelet counts less than 200 x 10^9/L, although there are exceptions to this trend. Twenty percent of Grade 3 + 4 thrombocytopenia events occurred in the first 4 weeks of dosing, just under half (48%) of Grade 3 + 4 events occurred in the first 16 weeks of treatment. The incidence of thrombocytopenia was dose dependent, as anticipated. For most subjects, thrombocytopenia was rapidly reversible and manageable with ruxolitinib dose interruption and/or dose reduction.

The risk of spontaneous hemorrhage in patients as a result of thrombocytopenia generally does not become manifest until platelet counts fall below 10 to 20 x10^9/L (Slichter 2004). In Study INCB 18424-251, the lowest platelet counts observed (grade 4 thrombocytopenia events) ranged from 6-22 x 10^9/L. There was one patient with associated petechiae and no events of hemorrhage in the 9 patients with grade 4 platelet declines.

There were 2 deaths in study INCB 18424-251 where the primary cause of death was related to hemorrhage (upper gastric and cerebral hemorrhage). In the case of upper gastric hemorrhage, the patient had emergency surgical repair of a bleeding duodenal ulcer and died of post-operative complications. The PLT count was 447 x 10^9/L and there was a history of antecedent aspirin use and epistaxis. The event was considered unrelated to ruxolitinib. In the case of cerebral hemorrhage, the patient had normal PLT count (201 x 10^9/L), normal coagulation tests, and a history of hypertension. The event was assessed as possibly related to ruxolitinib.

Other SAEs in study INCB 18424-251 that involved hemorrhage of any kind have been examined. One patient was admitted to the hospital with a PLT count of [redacted] x 10^9/L and ultimately required splenectomy, following which a post-operative hemorrhage was noted in the surgical drains. The patient was discharged from the hospital but chose to discontinue study drug. Another patient had [redacted] episodes of lower gastrointestinal hemorrhage that were assessed as unrelated to ruxolitinib. No information about PLT counts during the course of the event was provided. A patient suffered from gastrointestinal hemorrhage of unknown source with a PLT count of [redacted] x 10^9/L. One patient had hematuria due to [redacted] surgery; the PLT count was [redacted] x 10 /L. Another patient suffering from splenomegaly developed an intra-abdominal hematoma adjacent to the spleen, with a PLT count of [redacted] x 10^9/L. One patient was hospitalized for melena with a PLT count of [redacted] x10^9/L. Thus overall hemorrhage events in subjects on ruxolitinib in Study INCB 18424-251 were not associated with drug-induced thrombocytopenia.

Ruxolitinib has demonstrated marked reduction in spleen size in the ongoing study in patients with MF, and without regard to presence of the JAK2 V617F mutation (Verstovsek et al 2010). In addition to spleen size reduction, Eastern Cooperative Oncology Group (ECOG) scores and symptoms thought to be related to splenomegaly, as well as symptoms related to elevated cytokine levels, all show improvement with ruxolitinib treatment. As a surrogate marker for functional benefit, exercise capacity was assessed with a standardized six minute walk test (6MWT). Ruxolitinib therapy resulted in improved 6MWT performance after 1, 3 or 6 months of therapy. After an initial small weight loss likely due to resolution of ascites and/or reduction

in splenomegaly, there is an increase in total body weight; importantly, there is weight gain in subjects with low body mass index at entry, ie, cachectic subjects.

Two Phase 3 registrations studies are ongoing. Study INCB 18424-351 is a double blind, placebo controlled study of ruxolitinib in subjects with MF, and Study INCB 18424-352 is an open label comparative study of ruxolitinib versus best available therapy in subjects with MF. In both Phase 3 studies, subjects began dosing at 20 mg bid if Baseline platelet count was $> 200 \times 10^9$/L and at 15 mg bid for platelet count of 100 $\times 10^9$/L to 200 $\times 10^9$/L, inclusive. The data was analyzed when the last subject had completed the Week 24 visit, and at least 50% of subjects remaining in the study had completed the Week 36 visit, and the data base was frozen. The primary endpoint was the response rate defined as the percentage of patients achieving a 35% or greater reduction in spleen volume at 24 weeks as measured by magnetic resonance imaging, or computerized tomography, comparing the rates in patients receiving ruxolitinib or placebo. The primary analysis was recently conducted, and the primary and key secondary endpoints were met. The response rate for spleen volume reduction was 42% in patients randomized to ruxolitinib versus < 1% in patients randomized to placebo (p 0.0001). A significantly larger proportion of subjects in the ruxolitinib group achieved a ≥ 50% improvement from baseline in the modified MFSAF v2.0 diary total symptom score at Week 24 compared with the placebo group (45.9% versus 5.3%, respectively, $P < 0.0001$). At Week 24, the median total symptom scores were 6.6 and 17.6 in the ruxolitinib and placebo groups, respectively. This represents a median improvement (score decrease) of 6.9 in the ruxolitinib group and a worsening (score increase) of 2.0 in the placebo group compared to baseline (Incyte confidential data on file). The safety profile of ruxolitinib was consistent with previous studies, which included reversible thrombocytopenia and anemia. Platelet counts declined over the first 4 weeks of therapy in the ruxolitinib group, however the median count remained in the normal range. Overall, 20 (12.9%) subjects in the INCB018424 group and 2 (1.3%) subjects in the placebo group had a new or worsening Grade 3 or 4 thrombocytopenia, usually as a single occurrence. As in earlier studies, thrombocytopenia was managed with dose reductions and/or interruptions; only 1 subject receiving ruxolitinib discontinued from the study because of thrombocytopenia (Incyte confidential data on file).

See the IB (Incyte Corporation) for additional details on clinical development of ruxolitinib.

4.1.5. Interim Analysis Data from Study INCB 18424-258

In Study INCB 18424-258, subjects with platelet counts of 50 to 100 x 10^9/L were enrolled to begin administration of ruxolitinib at 5 mg BID, which is a dose that represents a conservatively low starting dose, that data from earlier studies suggested should have a limited impact on platelet count. Subjects could then titrate their dose to an appropriate dose that offers benefit (eg, symptomatic and/or spleen size improvements) with cautious monitoring to avoid levels of thrombocytopenia associated with higher risk of spontaneous hemorrhage. Ruxolitinib administration was interrupted for a platelet count below 25 x 10^9/L or for Grade 2 or higher hemorrhage events.

The study is currently in the enrollment phase; however, an interim analysis was conducted based on a data cutoff when it was expected that at least 20 subjects would have completed 24 weeks of treatment. At the time of the interim analysis, a total of 50 subjects had enrolled in the study. Of the 50 subjects enrolled, 33 (66.0%) subjects completed the Week 24 visit,

8 (16.0%) discontinued prior to Week 24, and 9 (18.0%) subjects remained on study and had not yet completed their Week 24 visit.

Most subjects were titrated to a ruxolitinib dose of 10 mg BID or higher by Week 24 and 20.0% of subjects had a ≥ 35% reduction in spleen volume at Week 24. This is consistent with the proportion of subjects in Study INCB 18424-351 who had a ≥ 35% reduction in spleen volume at Week 24 who initiated treatment at a dose of 15 mg BID (21.8%), and substantially higher than that observed for placebo-treated subjects in Study INCB 18424-351 (1.7%). In addition, Mesa et al (2011) has shown that a spleen volume reduction of ≥ 10% is associated with meaningful improvements in symptoms and other measures of patient-perceived benefit (Patient Global Impression of Change [PGIC] and Myelofibrosis Symptom Assessment Form [MFSAF v2.0]).

In Study INCB 18424-258, the proportion of ruxolitinib-treated subjects achieving a ≥ 50% improvement in TSS at Week 24 was 34%. This is consistent with the proportion of subjects in Study INCB 18424-351 who had a ≥ 50% improvement in TSS at Week 24 who initiated treatment at a dose of 15 mg BID (31.4%). Although this was an unblinded study, the gradual time course of improvement is consistent with the gradual dose escalation in the study. The proportion of subjects who achieved a ≥ 50% improvement in TSS gradually increased over time through approximately Week 13, which is consistent with the time that the majority of subjects reached 10 mg BID at Week 13. This is in contrast with the rapid improvement seen in Study INCB 18424-351, suggesting that the observed effect is related to ruxolitinib titration.

Subjects also showed improvement based on the PGIC, which is an assessment of overall impression of treatment benefit. In Study INCB 18424-258 as early as Week 4, 36.6% of subjects rated themselves as much improved or very much improved, and at Week 24, 53.7% of subjects rated themselves as much improved or very much improved.

There were no unexpected safety signals during this study. The most common nonhematologic adverse events (AEs) were diarrhea (28.0%), peripheral edema (26.0%), nausea (24.0%), abdominal pain (24.0%), and fatigue (22.0%). Most nonhematologic AEs were Grade 1 or 2. The majority of subjects were able to escalate to a dose of 10 mg BID and maintain platelet counts above 35 x 10^9/L. Subjects who had dose decreases or interruptions per protocol showed recovery of platelet counts. Based on laboratory values, 8 subjects (16%) had a Grade 4 decreased platelet count (< 25 x 10^9/L). One subject withdrew from the study because of thrombocytopenia.

The gradual increase in dose from 5 mg BID in Study INCB 18424-258 seemed to avoid the initial drop in hemoglobin seen in Study INCB 18424-351, in which subjects began therapy with 15 mg or 20 mg BID. In addition, in Study INCB 18424-258, a maximum dose of 10 mg BID was not associated with significant changes in hemoglobin through Week 24 in subjects who did not receive transfusions through the study.

These preliminary findings suggest that a dosing strategy starting with lower doses of ruxolitinib with subsequent dose optimization is efficacious and well tolerated in subjects who have platelet counts of 50 to 100 x 10^9/L at treatment initiation. In most subjects, ruxolitinib could be titrated to 10 mg BID, which provided clinically meaningful reductions in spleen volume and TSS. Thrombocytopenia was manageable with dose reduction or dose interruption and mean hemoglobin levels remained stable throughout the study. Although this study is ongoing, data

from this interim analysis will help support individualized ruxolitinib dosing strategies in subjects with MF and lower platelet counts.

4.2. Trial Rationale

As noted in the Introduction, the ongoing phase 1/2 study INCB 18424-251 in MF patients examined twice daily dose regimens ranging from 10 mg bid to 50 mg bid, and once daily dosing regimens ranging from 25 mg qd to 200 mg qd; doses of 50 mg bid and 200 mg qd were not well tolerated; 25 mg bid and 100 mg qd were designated maximum tolerated doses. To date, all patients enrolling in this study, or in the ongoing Phase 3 studies, have been required to have a pre-study platelet count of at least 100 $x10^9$/L. However, there is a significant population of MF patients who have chronic mild or moderate thrombocytopenia, with platelet counts in the range of 50 $x10^9$/L to 100 $x10^9$/L. Based on epidemiology data (Mesa et al 2007), 16.5% of all MF patients are reported to have PLT counts < 100 $x10^9$/L at diagnosis. According to chart reviews of nearly 800 subjects with PMF at the Mayo Clinic, the proportion of subjects with platelets below 100 $x10^9$ in various risk categories based on the Dynamic International Prognostic Scoring system (DIPSS) ranged from 7% for low risk to 32% in intermediate-2 risk groups (Gangat et al 2011). While JAK inhibition is clearly, and not unexpectedly, associated with decreasing platelet counts, emergent thrombocytopenia is easily detected, and can be managed with dose decreases or brief drug interruptions. A Phase 1 /2 study with another JAK inhibitor, CYT387, is being conducted in subjects with platelet counts as low as 50 $x10^9$/L (http://clinicaltrials.gov, identifier: NCT00935987, Pardanani et al 2011).

An exploratory analysis of subjects who enrolled in the Phase 1/2 study with platelet counts < 150 $x10^9$/L who had extended (many weeks) periods of Grade 1 or 2 platelet decline, was carried out in order to identify the dose(s) associated with stable platelet counts in the range of 50 $x10^9$/L to 100 $x10^9$/L. Fourteen subjects were identified that fit these criteria; 9 of the subjects maintained platelet counts between 50,000/µL and 100,000/µL while receiving 5 mg bid, 2 subjects maintained platelets in this range taking 10 mg bid, one subject was receiving 10 mg PM/5 mg AM, one was receiving 5 mg qd and one was receiving 10 mg qd. Importantly, splenomegaly and/or symptom improvements were maintained in 11 of the 14 subjects at a level similar to that observed with their initial, higher dose regimen. These data suggest that a dose of 5 mg bid, with dose escalation and reductions in response to platelet count response may be associated with symptom and spleen size improvements, while allowing platelet counts to be maintained near or above the 50 $x10^9$/L level. In the present study, patients with Grade 1 and 2 thrombocytopenia, having platelet counts of 50 $x10^9$/L to 100 $x10^9$/L will be enrolled to begin dosing at 5 mg bid, and titrated to an appropriate dose that offers benefit (symptomatic and/or spleen size improvements) balanced with risk (worsening thrombocytopenia).

4.3. Potential Risks and Benefits of the Treatment Regimen

4.3.1. Potential Risks

No specific findings in nonclinical repeat dose toxicity studies identify clinical risks other than noting that consequences of immunosuppression may occur. Hypotension and increases in heart rate were noted at a high dose in a cardiovascular preclinical study. However, these findings have not been recapitulated in a clinical setting.

The primary clinical risks with ruxolitinib treatment are the potential sequelae of decreased hematopoietic proliferation secondary to the inhibition of growth factor pathways by JAK2 inhibition. Dose-dependent, reversible thrombocytopenia has been observed in subjects with MF and represents the DLT. The risk of spontaneous hemorrhage in patients as a result of thrombocytopenia generally does not become manifest until platelet counts fall below 10 x 10^9/L (Slichter 2004); platelet counts below 25 x 10^9/L (Grade 4) were not observed in any subjects initiating ruxolitinib at starting doses of 10 mg bid or 15 mg bid in the ongoing phase 1 /2 study. In the current study, dosing must be interrupted for platelet count below 25 x 10^9/L, or for Grade 2 or higher hemorrhage events that are assessed as at least possibly related to ruxolitinib therapy.

Anemia and, less frequently, neutropenia have also been observed in patients with MF treated with ruxolitinib. Increased rates of infection and anemia are potential risks of myelosuppression, and there are multiple sequelae of anemia including the burden and risks of transfusion. A few subjects have had an apparent worsening of their pre-morbid disease symptoms following rapid cessation of ruxolitinib therapy and a gradual tapering and use of steroids in fragile subjects may be considered when stopping ruxolitinib therapy.

4.3.2. Potential Benefits

The clinical efficacy results of ruxolitinib that have emerged from the ongoing Phase 1/2 and Phase 3 studies are notable, including marked reduction in splenomegaly, improvement in symptoms, performance status and activity level, and reduction in plasma levels of inflammatory, prothrombotic and angiogenic cytokines. In those subjects with prolonged exposure to ruxolitinib (median of 15 months therapy), these positive effects have been maintained. In the present study, it is anticipated that individualized dose optimization from the starting level of 5 bid will be associated with reductions in splenomegaly, MF-associated symptoms and inflammatory cytokine levels.

5. STUDY OBJECTIVES AND PURPOSE

5.1. Primary Objective

- To determine the effects of ruxolitinib on spleen volume and symptom burden in patients with primary myelofibrosis (PMF), post polycythemia vera-myelofibrosis (PPV-MF) and post essential thrombocythemia-myelofibrosis (PET-MF) who have Baseline platelet count of 50 x 10^9/L to 100 x 10^9/L.
- To determine the safety and tolerability of ruxolitinib in patients with PMF, PPV-MF and PET-MF who have Baseline platelet count of 50 x 10^9/L to 100 x 10^9/L.

5.2. Secondary Objectives

- To determine an appropriate dosing strategy for patients with low platelets.
- To determine the long-term safety and efficacy effects of ruxolitinib in patients with PMF, PPV-MF, and PET MF who have a baseline platelet count of 50 x 10^9/L to 100 x 10^9/L.

6. SUBJECT ELIGIBILITY

6.1. Study Population

Male or female individuals, aged 18 years or older who have been diagnosed with myelofibrosis (either PMF, PPV-MF or PET-MF), who have platelet counts between 50 and 100 x10^9/L and for whom treatment of MF is indicated may enroll. Subjects must score at least 1 point according to the DIPSS prognostic criteria (Passamonti et al 2010). Enrolled subjects must have a life expectancy of > 6 months.

6.2. Subject Inclusion Criteria

All subjects must meet the following inclusion criteria:

1. Subjects who are able to understand and sign an informed consent document.
2. Subjects 18 years of age or older.
3. Subjects must be diagnosed with PMF, PPV-MF or PET-MF, according to the investigator's expert judgment, guided by the criteria outlined in the 2008 World Health Organization criteria (see Appendix 1) for PMF, and the proposed criteria for PPV-MF and PET-MF outlined by the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) (see Appendix 2) irrespective of *JAK2* mutation status. A bone marrow biopsy will provide the relevant information; subjects without a prior biopsy report obtained in the 2 months prior to screening for review must have a biopsy at screening or baseline or will not be able to enroll in the study.
4. Subjects with MF requiring therapy must have at least 1 point using the DIPSS prognostic criteria developed by the IWG-MRT (Passamonti et al 2010), using the information from laboratory assessments and ongoing medical history recorded at the screening visit. The prognostic variables and assigned point values are:

Prognostic Variable	Value		
	0 Points	**1 Point**	**2 Points**
Hemoglobin[a]	≥ 10 g/dL		< 10 g/dL
Age, Years	< 65	≥ 65	
White Blood Cell Count	≤ 25 x 10^9/L	> 25 x 10^9/L	
Peripheral Blood Blasts	< 1%	≥ 1%	
Constitutional Symptoms[b]	No	Yes	

[a] A hemoglobin value < 10 g/dL must be demonstrated during the screening visit for subjects who are not transfusion dependent. Subjects receiving at least 2 units of packed red blood cells in the 12 weeks prior to Screening will be considered to have hemoglobin < 10 g/dL for the purpose of evaluation of risk factors.

[b] Constitutional symptoms are defined as any of the following: 10% or more weight loss in the 6 months prior to screening, night sweats, unexplained fever (> 37.5°C).

5. Subjects in whom treatment of MF is indicated based on the Investigator's expert judgment.
6. Subjects with active symptoms of MF at the screening Visit as demonstrated by presence of one symptom score of at least 5 or two symptom scores of at least 3 using the Screening Symptom Assessment Form (Appendix 7).
7. Subjects who have platelet counts between 50 and 100 x 10^9/L at the screening and/or baseline visits. Platelet counts must be without the assistance of growth factors, thrombopoietic factors, or platelet transfusions.
8. Subjects with hemoglobin value at the screening visit ≥ 6.5 g/dL and who are willing to receive red blood cell transfusions to treat low hemoglobin levels.
9. Subjects must have discontinued all drugs used to treat underlying MF disease no later than Day -14.
10. Subjects must not currently have the option of stem cell transplantation, either because they are not a candidate, or because a suitable donor is not available.
11. Subjects with an ECOG performance status of 0, 1, 2 or 3 (Appendix 5) at the screening visit.
12. Subjects with peripheral blood blast count of < 5% at both screening and baseline visits.

6.3. Subject Exclusion Criteria

Any of the following are causes for exclusion from the study, and must be demonstrated not to be present at the screening visit (historical data for measurements or labs may not be used):

1. Subjects with a life expectancy of less than 6 months.
2. Subjects in whom MF disease is well controlled with current therapy.
3. Females who are pregnant or are currently breastfeeding.
4. Subjects of childbearing potential who are unwilling to take appropriate precautions (from screening through follow-up) to avoid becoming pregnant or fathering a child.
    - Females of non-childbearing potential are defined as women who (a) are ≥ 55 years of age with history of amenorrhea for 1 year, OR (b) are surgically sterile for at least 3 months.
    - For females of childbearing potential, or for males, appropriate precautions are those that are at least 99% effective in preventing the occurrence of pregnancy. These methods should be communicated to the subjects and their understanding confirmed (Appendix 3).
5. Subjects with inadequate bone marrow reserve as demonstrated by:
    - Absolute neutrophil count (ANC) that is < 1 x 10^9/L at the screening or baseline visits **or** had ANC levels < 500/µL in the month (30 days) prior to screening. Subjects must not have received growth factors for at least 1 month (30 days) prior to receiving the first dose of study drug.

- Confirmed platelet count that is < 50 x 10^9/L or subjects with a known history of platelet counts < 25,000/µL, in the absence of cytoreductive therapy.

6. Subjects with platelet count > 100 x 10^9/L at BOTH screening and baseline visits.
7. Subjects with recent (within 12 months of screening) major bleed requiring transfusion(s) or resulting in a decrease in hemoglobin by 3 g/dL or more.
8. Subjects with inadequate coagulation parameters as follows: INR > 1.5 or PTT > 1.5 x upper limit of laboratory normal (ULN).
9. Subjects with known history of esophageal or gastric varices, or any intracranial bleeding. Subjects with a history of an incidental finding of small varices (< 5 mm) may be permitted in the study with Sponsor approval.
10. Subjects with inadequate liver or renal function at screening and baseline visits as demonstrated by:
    - Direct bilirubin ≥ 2 x ULN (NOTE: direct bilirubin will only be determined if total bilirubin is ≥ 2.0 x ULN).
    - Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) > 2.5 x ULN.
    - Serum creatinine > 2.0 mg/dL or creatinine clearance < 30 mL/min measured or calculated by Cockroft-Gault Equation.
11. Subjects with clinically meaningful, active bacterial, fungal, parasitic or viral infection which require therapy, or who are HIV positive
12. Subjects with acute bacterial infections requiring antibiotic use should delay screening/enrollment until the course of antibiotic therapy has been completed and the event is considered resolved.
13. Subjects who are currently receiving therapy with a moderate or potent CYP3A4 inhibitor (Appendix 8). Subjects may enter the screening phase when therapy with the moderate or potent CYP3A4 inhibitor is completed, and use of moderate inhibitors during the study will be permitted.
14. Subjects with an invasive malignancy over the previous 2 years except treated early stage carcinomas of the skin completely resected intraepithelial carcinoma of the cervix and completely resected papillary thyroid and follicular thyroid cancers.
15. Subjects with recent severe or unstable cardiac disease.
16. Subjects who have had splenic irradiation within 6 months prior to Day 1.
17. Subjects who have previously received treatment with a JAK inhibitor.
18. Subjects being treated concurrently with any prohibited medications (see Section 8.9.2 for specific prohibited medications and the associated timeframe over which they are prohibited).
19. Subjects with active alcohol or drug addiction that would interfere with their ability to comply with the study requirements.

20. Subjects with any concurrent condition that, in the investigator's opinion, would jeopardize the safety of the subject or compliance with the protocol.
21. Subjects who are unable to complete the daily symptom diary, which is available in English and Spanish versions.

6.4. Subjects Who Fail to Meet Screening Criteria

A subject who has a laboratory test result(s), vital signs, or ECG finding(s) that does not satisfy the entrance criteria may have the test(s) repeated once. These tests may be repeated as soon as the investigator believes that the retest result is likely to be within the acceptable range to satisfy the entrance criteria, but must be completed within the 3 week screening phase (Days -28 to -8). In this case, the subject will not be required to sign another ICF, and the original subject identification number will be used. In the event that the laboratory test(s) cannot be performed within the screening period, or the re-test(s) do not meet the entrance criteria or the subject's medical condition has changed significantly during the screening phase so that inclusion/exclusion criteria are no longer met, the subject is considered a screen failure, and must be withdrawn from the study. Therefore, sites should consider the testing schedule carefully so that any potential retests are accomplished in the 3 week time frame. If the subject and investigator agree to re-screening, the subject must sign a new ICF, a new subject identification number will be assigned, and all required screening activities must be performed when the subject is re-screened for participation in the study (except bone marrow biopsy if already performed at screening). An individual subject may only re-screen once for the study.

If all screening activities cannot be completed in the screening phase because of an event unrelated to a laboratory finding, ECG finding, or medical history finding, including scheduling difficulties at the clinic site, the subject may retain the original subject number and complete the remaining screening activities as soon as possible, within a maximum of 42 days (6 weeks) from the original screening visit date. A blood draw for hematology and serum chemistry must be taken at the time the subject returns for completion of screening activities, and will be used to determine eligibility.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is an open label study of ruxolitinib in patients with PMF, PPV-MF, and PET-MF. The study is comprised of 4 phases:

Screening:	Up to 21 days
Baseline:	Exactly 7 days
Core Treatment Phase:	24 weeks
Extended Treatment Phase:	132 weeks; subjects receiving benefit will continue ruxolitinib treatment until Week 156
Follow-up Phase:	All subjects will be followed for safety (eg, reporting of AEs and SAEs) for 30 to 37 days after the last dose of study drug is administered

Core Treatment Phase:

During the core treatment phase, there will be study visits and laboratory-only visits. Subjects will have a regularly scheduled study visit at screening, baseline, Day 1, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24, where blood samples, assessments, spleen measurements, etc. will be obtained. All hematology labs and coagulation parameters will be analyzed by local laboratories. Serum chemistries, serology, and lipid panel will be analyzed by a central laboratory.

Subjects will have laboratory-only visits to collect hematology lab samples at Week 1, Week 2, Week 3, Week 5, Week 6, Week 7, Week 10, Week 14, and Week 18. The laboratory visits at Week 14 and Week 18 may be skipped for subjects who do not increase their dose at Week 12 or Week 16, and who have maintained platelet counts > 75 x 10^9/L since the last hematology assessment. Additional, at least weekly laboratory-only visits to collect hematology lab samples will be required if platelet count falls below 35 x 10^9/L; more frequent monitoring is recommended if counts fall below 25 x 10^9/L. These laboratory visits can occur at the study site laboratory, or any local laboratory that can provide the data and appropriate certificates and normal laboratory ranges to the study site for review for subject management in a timely fashion.

Subjects will have an MRI of the upper and lower abdomen and pelvis to determine the spleen volume at baseline and Week 24. A CT scan will be substituted for subjects who are not candidates for MRI, or when MRI is not readily available. Patients Global Impression of Change (PGIC) questionnaire will be completed monthly. Measurement of spleen length below the left costal margin will be measured by palpation at each study visit.

Subjects will complete an electronic symptom diary from baseline through the Week 24 visits (total of 25 weeks). Subjects will be trained on the use and care of the diary, and symptom diary data will be transmitted automatically each night wirelessly or using the diary docking station provided to subjects**.**

Extended Treatment Phase:

Subjects will have a study visit every 12 weeks (eg, Weeks 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, and 156), through Week 156 where blood samples, clinical assessments, and palpable spleen measurements, etc. will be obtained. Subjects will have laboratory-only visits to collect hematology samples 6 weeks after the Week 24 visit (eg, Week 30), then after **each** extended treatment phase visit (eg, Weeks 42, 54, 66, 78, 90, 102, 114, 126, 138, and 150). Additional hematology assessments will be required if the subject has a dose modification or as clinically indicated.

Follow-Up Phase:

All subjects will be followed for safety (eg, reporting of AEs and serious AEs) for 30 to 37 days after the last dose of study drug is administered.

7.2. Study Endpoints

7.2.1. Co-Primary Endpoints

- Correlation of % change in spleen volume at Week 24 compared to baseline versus final titrated dose.
- Correlation of % change in Total Symptom Score as measured by the modified MFSAF v2.0 diary at Week 24 compared to baseline versus final titrated dose.

7.2.2. Safety Endpoints:

- Safety and tolerability will be assessed by monitoring the frequency, duration and severity of adverse events, performing physical examinations, collecting vital signs, collecting laboratory data for hematology, serum chemistry, and coagulation parameters through Week 156. In addition, analyses will include:
  - Proportion of subjects with new onset Grade 4 thrombocytopenia events as assessed by CTCAE v4.03.
  - Proportion of subjects with new onset Grade 2 or higher hemorrhage as assessed by CTCAE v4.03.

7.2.3. Secondary Endpoints

- Percent change in spleen volume at Week 24 compared to Baseline.
- Percent change in Total Symptom Score as measured by the modified MFSAF v2.0 diary at Week 24 compared to baseline.
- Proportion of subjects with ≥ 35% reduction in spleen volume at Week 24 compared to baseline.
- Proportion of subjects with ≥ 10% reduction in spleen volume at Week 24 compared to baseline.
- Proportion of subjects with ≥ 50% improvement in total symptom score as measured by the modified MFSAF v2.0 diary at Week 24 compared to baseline.

- Long-term efficacy of ruxolitinib will be assessed by monitoring change and percent change in spleen length, as measured by palpation, and change in PGIC score from baseline to each visit where the variables are measured through Week 156.

7.3. Measures Taken to Avoid Bias

This is an open label study. Measurement of spleen volume by MRI (or CT scan in applicable subjects) and determination of thrombocytopenia grade (by CTCAE criteria) are objective responses.

7.4. Number of Subjects

Approximately 150 subjects may be enrolled.

7.5. Criteria for Study Termination

Both the Sponsor and the Investigator reserve the right to terminate the study, according to the terms specified in the study contract. The Investigator is to notify the IRB/IEC in writing of the study's completion or early termination, and send a copy of the notification to the Sponsor or Sponsor's designee and retain one copy for the site study regulatory file.

8. TREATMENT OF SUBJECTS

8.1. Treatment Arms and Study Drug Administration

All subjects will begin dosing at 5 mg bid ruxolitinib. Doses should be taken morning and evening, approximately 12 hours apart, and without regards to food.

Dose increases will be allowed for subjects with adequate platelet counts, and mandatory dose reductions and interruptions will be required for declining platelet counts, declining ANC levels or Grade 2 and higher hemorrhage events. See Section 8.6, Dose Adjustments.

8.2. Treatment Compliance

Subjects will bring all bottles of unopened, empty, and opened/partially used study drug with them to each study visit. Investigative site staff will perform a count of returned pills to assess compliance, and this information will be entered on the eCRF. Study drug, including all bottles of unopened, partially opened or empty bottles cannot be returned to the depot until a monitor reviews and verifies all pill counts for compliance.

8.3. Randomization and Blinding

Not applicable, study is open label and single arm.

8.4. Duration of Treatment and Subject Participation

Participation will be for approximately 165 weeks and 2 days, including the screening and baseline phases (see Section 9.1), core treatment phase (see Section 9.2), extended treatment phase (see Section 9.3), and follow-up phase (see Section 9.5).

8.5. Considerations for Dose Modifications

Inhibition of JAKs by a JAK 1/2 inhibitor such as ruxolitinib is associated with thrombocytopenia and anemia in subjects with MF. See the Investigator's Brochure for additional details on hematologic consequences of JAK inhibition. Platelet count, ANC and hemoglobin levels will be assessed on a regular basis. Complete blood count (CBC) will be monitored more frequently in the first few weeks of the study, and more frequent monitoring may be done at the Investigator's discretion at any time.

8.6. Dose Adjustments

The goal of dose modifications in the study is to permit individual dose optimization for subjects to obtain maximum benefit, while maintaining a stable platelet count > 25 x 10^9/L, and an ANC > 0.5 x 10^9/L.

8.6.1. Dose Increases

Dose increases are optional.

During the core treatment phase, doses of ruxolitinib may be increased in 5 mg qd increments up to a dose of 10 mg bid starting at the Week 4 visit and at subsequent study visits. Dose increases can occur no more frequently than every 4 weeks, and only if:

- Platelet count was always ≥ 40 x 10^9/L since the last scheduled study visit
- Platelet count, if decreased since the last scheduled study visit, is decreased by no more than 20% of the platelet count at the last scheduled visit
- No dose decreases or holds for safety have occurred during the preceding 4-week interval
- ANC > 1.0 x 10^9/L since the last scheduled study visit.
- For subjects with prior ≥ Grade 2 hemorrhage events, please see below under Section 8.6.3.4, Restarting with Resolution of Hemorrhage Events

Doses may not exceed 10 mg bid except in subjects who continue to meet the above dose escalation criteria, and who have, in addition, a PGIC score of 3 (minimally improved) to 7 (very much worse) while receiving 10 mg bid. Such subjects may continue dose escalation to a maximum dose of 15 mg bid. Note that when a 5 mg qd increment is added, creating a regimen such as 5 mg/10 mg, the higher dose should be taken in the evening and the lower dose in the morning.

During the extended treatment phase, doses of ruxolitinib may be increased in 5 mg qd increments up to a dose of 25 mg bid if the subject meets the above dose escalation criteria, or per the investigator's discretion.

Doses may never exceed 25 mg bid.

8.6.2. Mandatory Dose Interruptions, Dose Discontinuations and Dose Reductions

Dosing must be held if any of the following occur:

- Platelet counts decline below 25 x 10^9/L (dosing must be interrupted immediately. A repeat assessment should be performed as soon as feasible, but follow-up platelet values to trigger the restart guidelines from Section 8.6.3 may only follow beginning at least 3 days later).
- ANC declines to < 0.5 x 10^9/L.
- Ongoing Grade 2 or higher hemorrhage event, regardless of causality.

The dose must be reduced for a confirmed platelet count < 35 x 10^9/L as follows:

- An observation of platelets between 25 x 10^9/L and 35 x 10^9/L should trigger a repeat laboratory measurement of platelet counts. Dosing need not be adjusted until the results of the confirmatory test are known.
- The reduction will be based on the current dose, and on the rapidity with which counts declined to the < 35 x 10^9/L level and are ≥ 25 x 10^9/L (see Table 2).
- Subjects who have implemented a dose reduction because of platelets falling below 35 x 10^9/L DO NOT need to further decrease their dose provided the platelet count remains ≥ 25 x 10^9/L even if they remain below 35 x 10^9/L.
- Mandatory dose reductions are summarized in Table 2.

Table 2: Mandatory Dose Reductions and Dose Holds for Safety

Thrombocytopenia	
Platelet Count at Time of Decline	Action with Respect to Dose
≥ 35 x 10^9/L throughout study	Continue on dose established according to Section 8.6.1
< 35 x 10^9/L and ≥ 25 x 10^9/L (confirmed by repeat lab), and platelet count decline is >20% from prior visit	Decrease current dose level by 5 mg bid or to a dose of 5 mg qd if currently receiving 5 mg bid. If current dose is 5 mg qd, can continue at that dose.
< 35 x 10^9/L and ≥ 25 x 10^9/L (confirmed by repeat lab), and platelet count decline is ≤ 20% from prior visit	Decrease current dose level by 5 mg qd or to a dose of 5 mg qd if currently receiving 5 mg bid. If current dose is 5 mg qd, can continue at that dose.
< 25 x 10^9/L	Must hold dosing
Active Hemorrhage	
Worst CTCAE Grade	Action with Respect to Dose
Grade 1	May continue dosing (frequent platelet counts recommended)
Grade ≥ 2	Must hold dosing
Neutropenia	
ANC at Time of Decline	Action with Respect to Dose
< 0.5 x 10^9/L	Must hold dosing

NOTE: Investigators may also decrease the dose for any reason based on their clinical judgment, including taking a more conservative approach to hematological abnormalities or because of nonhematologic safety findings. Dose re-escalation will follow the guidelines provided in Section 8.6.1 (Dose Increases).

8.6.3. Restarting or Increasing Ruxolitinib after Recovery of Platelet or ANC Levels or Resolution of Hemorrhage

Note that the restarting and re-escalation doses in this section are the maximum allowed under this protocol. Individual investigators may elect to adopt a more cautious approach to restarting or escalating doses at their discretion, but they may not restart sooner or re-escalate more rapidly than outlined in this section.

8.6.3.1. Restarting or Re-Escalating with Improving Platelet Counts

For subjects who had never previously increased their dose above 5 mg bid, and have a platelet count decline necessitating drug hold, ruxolitinib may be restarted as follows:

- Ruxolitinib may be restarted at 5 mg qd when the platelet count has risen above 35 x 10^9/L.
- After no less than 2 weeks, and provided there are at least 2 consecutive platelet count results, at least 3 days apart, of ≥ 40 x 10^9/L, the dose may be increased to 5 mg bid. No further increase in dose is allowed.
- A second platelet decline below 25 x 10^9/L will necessitate a second drug hold. Ruxolitinib may be restarted at 5 mg qd when the platelet count has risen above 35 x 10^9/L. No further increase in dose is allowed.
  - The subject may remain on 5 mg qd provided platelet counts remain ≥ 25 x 10^9/L.

For subjects who had previously increased their dose to a level above 5 mg bid, and have a platelet count decline necessitating drug hold, ruxolitinib may be restarted as follows:

- Ruxolitinib may be restarted at 5 mg qd when the platelet count has risen above 35 x 10^9/L.
- After no less than 2 weeks, and provided there are at least 2 consecutive platelet count results, at least 3 days apart, of ≥ 40 x 10^9/L, the dose may be increased to a dose up to the highest dose that previously qualified for further dose increases according to Section 8.6.1 (Dose Increases). For example, if a subject tolerated 10 mg bid ruxolitinib and qualified for a dose increase, but the platelet counts fell sharply at the increased dose of 10 mg AM/15 mg PM, and drug was halted; the highest dose this subject may now use is the previously tolerated dose of 10 mg bid.
- A second platelet decline below 25 x 10^9/L will necessitate a second drug hold. Ruxolitinib may be restarted at 5 mg qd when the platelet count has risen above 35 x 10^9/L, and may be increased to 5 mg bid after ≥ 2 weeks with at least 2 consecutive measures above 40 x 10^9/L at least 3 days apart. No further increase in dose is allowed.

For subjects who previously decreased dose, but never held dose, dose increases using the dose increase guidelines in Section 8.6.1 may be implemented once platelet counts are ≥ 40 x 10^9/L on at least 2 consecutive measurements at least 3 days apart, however, the maximum dose may not exceed the higher of a dose of 5 mg bid or a dose that is 5 mg qd less than the dose at the time the decline to below 35 x 10^9 first began.

8.6.3.2. Use of Platelet Transfusions

Platelet transfusions may be used at Investigator's discretion to treat thrombocytopenia. Dosing restart or increase decisions may not be based on platelet count values observed within 7 days of a platelet transfusion.

8.6.3.3. Restarting or Re-Escalating with Improving ANC

For subjects who had never previously increased their dose above 5 mg bid, and have an ANC decline necessitating drug hold, ruxolitinib may be restarted as follows:

- The dose may be restarted at 5 mg qd when ANC levels are > 0.75 x 10^9/L.
- After no less than 2 weeks, and provided there are at least 2 consecutive ANC levels ≥ 1.0 x 10^9/L at least 3 days apart, the dose may be increased to 5 mg bid. No further increase in dose is allowed.
- A second ANC decline below 0.5 x 10^9/L will necessitate a second drug hold. Ruxolitinib may be restarted at 5 mg qd when the ANC is > 0.75 x 10^9/L. No further increase in dose is allowed

For subjects who had previously increased their dose to a level above 5 mg bid, and have an ANC decline necessitating drug hold, ruxolitinib may be restarted as follows:

- The dose may be restarted at 5 mg qd when ANC levels are > 0.75 x 10^9/L.
- After no less than 2 weeks, and provided there are at least 2 consecutive ANC levels ≥ 1.0 x 10^9/L at least 3 days apart, the dose may be increased to a dose up to the highest dose that previously qualified for further dose increases according to Section 8.6.1 (Dose Increases).
- A second ANC decline below 0.5 x 10^9/L will necessitate a second drug hold. Ruxolitinib may be restarted at 5 mg qd when the ANC is > 0.75 x 10^9/L, and may be increased to 5 mg bid with at least 2 consecutive measures, at least 3 days apart of ≥ 1.0 x 10^9/L. No further increase in dose is allowed.

In order to provide sufficient data to make the dose restart decisions, it is recommended that hematology parameters be obtained at least 2 times weekly for platelet count < 25 x 10^9/L, or for ANC levels < 0.5 x 10^9/L.

8.6.3.4. Restarting with Resolution of Hemorrhage Event

- For Grade 2 hemorrhage events of any causality, dosing may be restarted at the prior level once the event is resolved to Grade 0, and its underlying cause has been alleviated or resolved, as long as platelet count and ANC do not preclude a restart at that dose level. Restart of dosing after a second Grade 2 hemorrhage event may only occur following discussion with the sponsor taking into account causality, resolution of the bleeding and underlying etiology and likelihood of recurrence, in order to reach agreement that the potential benefits of a restart at an appropriate dose outweigh risks of recurrent hemorrhage.
- For Grade 3 or 4 hemorrhage events of any causality, dosing may only be restarted provided: platelet count and ANC do not preclude a restart, the event has resolved to Grade 0, and the underlying cause has been alleviated or resolved, and following discussion with the sponsor taking into account causality, resolution of the bleeding and underlying etiology and likelihood of recurrence, in order to reach agreement that the potential benefits of a restart at an appropriate dose outweigh risks of recurrent hemorrhage. Further dose escalations in these subjects will also require discussion with the sponsor.

Note that if more than one finding (thrombocytopenia, neutropenia or hemorrhage) was the cause for the dose reduction or interruption, improvements in all parameters must be considered in restarting ruxolitinib and the lowest calculated dose must be used.

8.6.4. Possible Changes in Study Conduct Because of Frequent Hemorrhage or Thrombocytopenia Events

Events of Grade 4 thrombocytopenia and > Grade 2 hemorrhage will be reported by Investigators to sponsor on a continuous basis, and this data will be reviewed by sponsor on an ongoing basis. A Data Monitoring Committee (DMC) will also review this data. The protocol may be modified on the basis of this ongoing safety monitoring. See Section 11.7, Data Safety Monitoring for a

complete description of study safety monitoring for Grade 4 thrombocytopenia, and > Grade 2 hemorrhage events, and possible changes in study conduct.

8.6.5. Management of Anemia

Subjects with a hemoglobin level < 6.5 g/dL must receive red cell transfusion(s) to maintain a level of ≥ 6.5 g/dL. Erythropoietin (EPO) use is discouraged, but is permitted at the Investigator's discretion, although use is not permitted in lieu of transfusions for hemoglobin below 6.5 g/dL.

8.6.6. Optional Dose Tapering Strategy

In ongoing clinical studies with ruxolitinib, exacerbation of underlying cardiopulmonary disease and return of MF symptoms has been occasionally observed in subjects after drug discontinuation. When a decision is made to permanently discontinue ruxolitinib therapy for reasons other than low platelet counts or ANC levels, tapering of ruxolitinib dosage may be considered, based on evaluation of the condition of the subject, current dose regimen and the clinical judgment of the investigator. Doses of ruxolitinib may be very slowly lowered until the subject is completely off drug. If medically indicated, doses of ruxolitinib may be temporarily restarted after they have been discontinued. If considered to be medically necessary, the investigator may use any treatment to manage withdrawal from ruxolitinib including, but not limited to, the management of events which may be secondary to discontinuation, and interruption or reduction of dose administered of ruxolitinib. Short-term courses of high-dose corticosteroids, equivalent to doses of > 10 mg/day of prednisolone have been used to moderate the withdrawal of ruxolitinib and may be considered as part of a tapering strategy. Corticosteroids may be started prior to, or concurrent with, ruxolitinib tapering in anticipation of the possibility of occurrence of withdrawal symptoms. When a decision has been made to discontinue the subject with utilization of a tapering strategy, regardless of the use of concomitant medications, safety data will continue to be assessed in accordance with the protocol. An end of study and subsequent follow-up visit must be scheduled.

8.6.7. Procedures for Interruption of Study Medication

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse experiences that may have an unclear relationship to study drug. Except in cases of emergency, it is recommended that the Investigator consult with the Sponsor Medical Monitor (or other representative of the Sponsor) before temporarily interrupting therapy for reasons other than protocol mandated medication holds for platelet or ANC counts. Additionally, the Investigator must notify the sponsor's medical monitor and study project manager via email before restarting study drug that was temporarily discontinued for an adverse experience.

8.6.8. Procedures for Permanent Discontinuation of Study Drug

In the event that any subject discontinues the study drug and subsequently withdraws from the study prior to completion, regardless of reason, reasonable efforts should be made to have the subject return for an early termination visit and have the end-of-treatment procedures completed as described in Section 9.4.

The date the subject discontinued the study drug and the specific reason for discontinuation will be recorded in the eCRF. This will include reasons such as discontinuation due to treatment failure or withdrawn due to adverse event. This information will be used to summarize the reasons for study discontinuation and treatment failure.

8.7. Withdrawal of Subjects from the Study

8.7.1. Withdrawal Criteria

Subjects may choose to withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled. Every reasonable effort should be made to determine the reason a subject withdraws prematurely, and this information should be recorded in the eCRF.

A subject **may** be withdrawn from the study, if, in the investigator's expert medical judgment, the subject is non-compliant with the study requirements. Subjects may be withdrawn at the discretion of the Food and Drug Administration (FDA) or the investigator.

Subjects **must** be discontinued from study drug and withdrawn from the study for the following reasons:

- In the Investigator's medical judgment, further participation would be injurious to the subject's health or well-being
- Positive urine pregnancy test, confirmed by positive serum pregnancy (serum human chorionic gonadotropin) test results
- Consent is withdrawn
- Termination of the study by the sponsor, local health authority, or IRB/IEC.
- The subject requires splenic irradiation.
- The subjects exhibits leukemic transformation (as evidenced by bone marrow blast counts of at least 20%, or peripheral blast counts of at least 20% lasting at least 8 consecutive weeks).
- The subject cannot maintain platelet counts of at least 25 x 10^9/L over a given 4 week interval at the lowest possible dose of 5 mg qd.
- The subject experiences 3 or more Grade 2 hemorrhage events. Note withdrawal after a second Grade 2 hemorrhage event may occur following the sponsor and investigator review of pertinent data.
- The subject experiences 2 hemorrhage events of ≥ Grade 2, at least one of which is Grade 3 or Grade 4, and believed to be from the same source or etiology.

If a subject is withdrawn from the study:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and eCRF.
- The end-of-treatment/early termination visit should be performed.

- All subjects must be followed for safety until the time of the follow-up evaluation or until study drug related toxicities resolve, return to baseline or are deemed irreversible, whichever is longer.

8.8. Concomitant Medications and Measures

All concomitant medications and treatments must be recorded in the CRF. Any prior medication received up to 30 days prior to the baseline visit will be recorded in the CRF. Concomitant treatments that are required to manage a subject's medical condition during the study will also be recorded in the CRF.

8.9. Restricted and Prohibited Medications and Measures

8.9.1. Restricted Medications and Measures

The following medications have restrictions on use or doses that may be used during this study:

- Aspirin in doses exceeding 81 mg per day is not permitted. Low dose aspirin (81 mg/day or less) is permitted. Acetaminophen and non-steroidal anti-inflammatory agents (eg, ibuprofen, NSAIDs) may be used at over-the-counter doses. Subjects receiving over-the-counter NSAIDs should not exceed the recommended dose and should be encouraged to use gastroprotective agents (antacids, H2 antagonists, or proton pump inhibitors).
- Inducers of CYP3A4 (Appendix 8) may be used with caution, and investigators should seek other options if available.
- Moderate CYP3A4 inhibitors (Appendix 8) may be used with caution. Differences in individual sensitivity and variation in potency of inhibition of various CYP enzymes may result in the need for a reduced dose of ruxolitinib during a period of concomitant medication use. If required for safety, the study drug dose may be reduced from bid to qd in these circumstances. The sponsor's medical monitor may be consulted for advice when using these agents.
- Use of potent inhibitors of CYP3A4 (ketoconazole, clarithromycin, itraconazole, nefazodone or telithromycin, voriconazole or posaconazole, see Appendix 8) and use of fluconazole should be avoided, and if used, a 50% ruxolitinib dose reduction is recommended along with frequent platelet monitoring during the period of co-administration. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole in the study.
- Hematopoietic growth factor receptor agonists (eg, erythropoietin) may be used at investigator's discretion in certain circumstances as described in Section 8.6.5, Management of Anemia.
- If concomitant administration of an anticoagulant/antiplatelet medication is indicated, caution and enhanced monitoring is required. History of thrombocytopenia, and any concurrent ruxolitinib-related thrombocytopenia should be a factor in the choice of anticoagulant and dose. Medications that interfere with coagulation or inhibit platelet function are listed in Appendix 9.

8.9.2. Prohibited Medications and Measures

- Any prior or concomitant use of another JAK inhibitor.
- Any investigational medication other than the study drugs. Use of such medications within 14 days or 6 half-lives, whichever is longer, prior to the first dose of study drug and during the study through the follow-up visit is prohibited.
- Systemic corticosteroid doses greater than the equivalent of 10 mg prednisolone per day are not permitted, unless use is part of a ruxolitinib dose tapering strategy (see Section 8.6.6 Optional Dose Tapering Strategy).
- Romiplostim or eltrombopag are not permitted beginning with the baseline visit (Day -7) through the final dose of ruxolitinib.
- St John's Wort and rifampin are not permitted at any time during participation in the study.
- Use of hydroxyurea, interferon, thalidomide, busulfan, lenalidomide, anagrelide, or any investigational medication used to treat MF is not permitted at any time beginning on Day -14 up until the time that ruxolitinib therapy is permanently discontinued. Use of androgens to treat anemia is permitted.

9. STUDY ASSESSMENTS

All study assessments will be performed as shown in the Table of Assessments (Table 3) and Table of Laboratory Assessments (Table 4). The order of assessments is suggested by the order of mention in the Table of Assessments. For instructions on each assessment, please refer to Section 10.

Table 3: Table of Assessments

Study Phase	Screening & Baseline		Core Treatment Phase			Extended Treatment Phase		End of Treatment & Follow-Up	
	Screening	Baseline	Day 1	Study Visits Weeks 4, 8, 12, 16, 20	Week 24	Study Visits Weeks 36, 48, 60, 72, 84, 96, 108, 120, 132, 144 (q12 weeks)	Week 156	End of Treatment or Early Termination Visit (EOT)	Follow-Up 30-37 days after last dose of study drug
Evaluation/window	**Day -28 to -8[a]**	**Day -7 to -1**	**Day 1**	**± 5 days**	**± 5 days**	**± 5 days**	**± 5 days**	**± 5 days**	
Assign Subject #	X								
Informed consent / eligibility criteria	X	X							
Prior medical & medication history	X	X							
Concomitant medication review		X	X	X	X	X	X	X	X
Transfusion history/status	X[b]	X[b]		X	X	X	X	X	
Discontinue prior MF therapies	X[c]								
Screening Symptom Form	X								
Record AEs	X	X	X	X	X	X	X	X	X
Comprehensive physical examination	X[d]	X			X	X	X	X	
Targeted physical examination[e]			X	X					X
Spleen palpation	X	X		X	X	X	X	X	
Vital signs	X	X		X	X	X	X	X	X
12-lead ECG	X								
BM biopsy	X[f]	X[f]							
MRI of upper and lower abdomen and pelvis		X[g, h]			X			X[i]	
Modified MFSAF v2.0 (see Section 9.1.2)		Diary is completed each evening from Day -7 to the Week 24 visit							
Dispense and/or bring MFSAF v2.0 diary to visit		X	X	X	X				
PGIC (see Appendix 5)				X	X	X	X	X	
ECOG status	X	X		X	X	X	X	X	
[redacted]									
Dispense reminder card[k]		X	X	X	X	X			
Contact IVRS	X		X	X	X	X	X	X	

Table 3: Table of Assessments (Continued)

Study Phase	Screening & Baseline		Core Treatment Phase			Extended Treatment Phase		End of Treatment & Follow-Up	
	Screening	Baseline	Day 1	Study Visits Weeks 4, 8, 12, 16, 20	Week 24	Study Visits Weeks 36, 48, 60, 72, 84, 96, 108, 120, 132, 144 (q12 weeks)	Week 156	End of Treatment or Early Termination Visit (EOT)	Follow-Up 30-37 days after last dose of study drug
Evaluation/window	**Day -28 to -8**	**Day -7 to -1**	**Day 1**	**± 5 days**	**± 5 days**	**± 5 days**	**± 5 days**	**± 5 days**	
Dispense study drug			X[l]	X[m]					
Drug accountability assessment				X	X	X	X	X	

[a] If all screening activities cannot be completed in the screening phase because of an event unrelated to a laboratory finding, ECG finding, or medical history finding, including scheduling difficulties at the clinic site, the subject may retain the original subject number and complete the remaining screening activities as soon as possible, within a maximum of 42 days (6 weeks) from the original screening visit date.

[b] Complete transfusion history should be recorded where possible, but must include at least the 12 weeks prior to screening.

[c] Confirm that all drugs, used to treat the underlying MF disease are discontinued by Day -14, so that at least 1 week will have elapsed between the last dose of medication(s) used to treat MF and the baseline MRI (or CT scan in applicable subjects) and diary dispensing.

[d] Height will be measured at the screening visit only.

[e] The targeted physical examination should include the subject's weight.

[f] A bone marrow biopsy is required at screening or baseline if a biopsy was not previously obtained within the prior 2 months or if all data from the samples are not available.

[g] MRI of the upper and lower abdomen and pelvis will be performed, to assess spleen volumes. CT scan may be performed if subject is not a candidate for MRI, or if MRI is not readily available. The MRI (or CT scan in applicable subjects) should be performed on the first or second day of the baseline period (ie, Day -7 or Day -6), and the site radiologist should send the scan to the central imaging laboratory that same day.

[h] The first MRI may be delayed for up to 2 weeks because of scheduling or other issues at the clinic site, but must be completed within 56 days, maximum from the start of the original Screening Visit date, and this must occur prior to the subject receiving the first dose of study drug.

[i] An MRI should be conducted at the end of treatment visit **only** if treatment was is discontinued prior to Week 24.

[redacted]

[k] Reminder cards will be sent home with subjects to state upcoming visit scheduling, and to record the time subjects took their last dose of study drug prior to each visit.

[l] On Day 1, the first dose of ruxolitinib will be administered to the subject in a fasted state at the site and the exact time of administration will be recorded on the eCRF.

[m] Subject should be instructed NOT to take the morning dose of study drug on the day of the Week 4 study visit, as study drug will be administered to the subject in a fasted state at the clinic.

Table 4: Table of Laboratory Assessments

Study Phase	Screening & Baseline		Core Treatment Phase							Extended Treatment Phase		End of Treatment & Follow-Up	
	Screening	Baseline[a]	Day 1[a]	Lab Only Visits Weeks 1,2, 3,5,6,7,10, 14, 18	Week 4[a]	Week 8	Week 12	Weeks 16 and 20	Week 24[a]	Lab Only Visits[b]	Study Visits[b]	End of Treatment or Early Termination Visit (EOT)	Follow-Up 30-37 days After Last Dose of Study Drug
Evaluation/window	Day -28 to -8	Day -7 to -1	Day 1	± 3 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days
Serum Chemistry	X	X[c]			X	X	X	X	X		X	X	X
Hematology	X	X[c]		X[d]	X	X	X	X	X	X	X	X	X
Coagulation panel	X	X					X		X		X	X	
Lipid Panel		X			X		X		X		X	X	
Serum Pregnancy Test (childbearing females only)	X												
Serology for HIV, HBV, HCV	X												
[redacted]													

[a] For blood samples drawn at baseline, Day 1, Week 4, and Week 24, subjects should arrive in a fasted state after an overnight fast of at least 8 hours or since midnight. Lack of fasting will be noted on the eCRF page regarding blood sampling, but this will not constitute a protocol violation or deviation.

[b] Extended treatment phase visits will occur at Weeks 36, 48, 60, 72, 84, 96, 108, 120, 132, 144 (eg, every 12 weeks). Subjects will have laboratory-only visits to collect hematology samples 6 weeks after the Week 24 visit (eg, Week 30), then after **each** extended treatment phase visit (eg, Weeks 42, 54, 66, 78, 90, 102, 114, 126, 138, and 150). Additional hematology assessments will be required if the subject has a dose modification or as clinically indicated.

[c] Blood samples for hematology and serum chemistry should be taken as close as possible to Day 1. If, on the baseline assessment of serum chemistry and hematology parameters, an exclusionary value is observed, the test may be repeated once, no more than 3 days following the first observation.

[d] The laboratory visits at Week 14 and Week 18 may be skipped for subjects who do not increase their dose at Week 12 or Week 16, and who have maintained platelet counts > 75 x 10^9/L since the last hematology assessment. Additional, twice-weekly laboratory-only visits to collect hematology lab samples will be required if platelet count falls below 35 x 10^9/L.

[redacted]

9.1. Screening + Baseline Phase

The screening + baseline phase may not exceed 28 days (4 weeks), with the exception of delays caused by scheduling issues, see Section 6.4). The length of the screening visit for a given individual subject will be determined by the requirement to discontinue all drugs used to treat MF at least 7 days prior to the first baseline evaluation (ie, must discontinue prior MF therapy by Day -14). Subjects who are not currently taking any drugs to treat their MF may complete all screening activities in a few days, and proceed to the baseline phase.

9.1.1. Screening Assessments

Prospective participants will be scheduled for a screening visit by site staff. A subject number will be assigned by an Interactive Voice Response System (IVRS). All procedures for screening and baseline must be completed within the 21-day screening + 7-day baseline phase, except as noted in Section 6.4. The following procedures will be performed:

Obtain informed consent before any study specific procedures are conducted.

- A subject number will be assigned by IVRS.
- Review of eligibility criteria including discussion of methods known to be at least 99% effective in preventing pregnancy (Appendix 3).
- Review of medical history, prior medication history and prior history of medications used to treat MF (see Section 8.8, Prior and Concomitant Medications). Record medication histories on the eCRF.
- Review of transfusion history. Complete transfusion history should be recorded where possible, but must include at least the 12 weeks prior to Screening. The history should be recorded on the eCRF.
- Confirm that all drugs, used to treat underlying MF disease will be discontinued by Day -14, so that at least 1 week will have elapsed between the last dose of medication(s) used to treat MF and the baseline MRI (or CT scan in applicable subjects) and diary dispensing. Prior MF medication(s) may be discontinued in one of the 3 following ways:
    1. Prior to and independent of considering enrollment in this study (prior to signing the ICF). These subjects can proceed to the baseline visit as soon as screening activities are completed, 7 days have elapsed since the prior MF medications were discontinued and eligibility is verified.
    2. At the time of signing the ICF. These subjects can proceed to the baseline visit 7 days after signing the ICF, if screening activities are completed and eligibility is verified.
    3. After confirming eligibility via the screening symptom form, laboratory assessments, and medical history. These subjects must obtain necessary screening visit results within the first 14 days in order to have 7 days for drug discontinuation prior to baseline (total screening time elapsed = 21 days).

- NOTE: The timing for the screening hematology blood samples should take the possible discontinuation of a prior MF therapy into account, in order to allow time for possible recovery of low platelet count values caused by the prior MF regimen. It is suggested that the hematology blood sample be taken around Day -8, eg, at the end of the possible wash-out period for prior therapy.

- Complete Screening Symptom Form.
- Record adverse events.
- Comprehensive physical examination including body weight and height.
- Measurement of spleen length below the costal margin by palpation.
- Vital signs
- ECOG status assessment.
- 12-lead electrocardiogram (ECG).
- Bone marrow biopsy for confirmation of MF diagnosis. NOTE: a bone marrow biopsy at screening or baseline is required if a biopsy was not previously obtained within the prior 2 months or if all data from the samples are not available for review by the Study Investigator of Study INCB 18424-258. The prior data will need to be entered into the eCRF for this study, with explanation as to the origin of the data (date of biopsy).
- Blood sampling for the following laboratory tests (see Appendix 4):
  - Serum chemistry tests
  - Hematology
  - Coagulation tests
  - Serum pregnancy test (females of childbearing potential only)
  - Serology tests for HIV and hepatitis

9.1.2. Baseline Assessments

The results from the screening visit evaluations will be reviewed to determine if the subject continues to meet the eligibility requirements as specified in the protocol. Subjects who have signed the ICF and meet all the entry criteria (see Section 6) may be enrolled in the study, and will be contacted by clinical site staff to schedule the baseline visit. Subjects will be reminded by site staff that they must arrive for the baseline visit where blood draws for lipid profile will be taken after an overnight fast of at least 8 hours or since midnight.

Subjects will begin completing the evening diary the evening of the first baseline assessment (Day -7). The MRI (or CT scan in applicable subjects) should be conducted on the first or second day to allow ample time for the central imaging laboratory to verify scan quality. Blood samples for hematology and serum chemistry should be taken as close as possible to Day 1, but in ample time for the results to be returned from the central laboratory (or in the case of

hematology and coagulation labs, the local laboratory). If, on the baseline assessment of serum chemistry and hematology parameters, an exclusionary value is observed, the test may be repeated once, no more than 3 days following the first observation.

The following procedures will be performed during the 7-day baseline period and prior to enrollment for all subjects:

- Confirm that the subject continues to meet all eligibility criteria.
- Update medication history and concurrent medications; confirm that all drugs used to treat underlying MF disease have been discontinued for at least 7 days.
- Update transfusion history status.
- Record adverse events.
- Conduct a comprehensive physical examination.
- Measurement of spleen length below the costal margin by palpation.
- Vital signs.
- ECOG status assessment.
- [redacted]
- Bone marrow biopsy (only if not performed at screening and no prior biopsy data are available to the Investigator for review).
- Blood sampling for the following laboratory tests (see Appendix 4):
  - Serum chemistry tests
  - Hematology
  - Coagulation tests
  - Lipid panel
  - [redacted]
  - [redacted]
  - [redacted]
- MRI of the upper and lower abdomen and pelvis will be performed, to assess spleen volumes. CT scan may be performed if subject is not a candidate for MRI, or if MRI is not readily available. The MRI (or CT scan in applicable subjects) should be performed on the first or second day of the baseline period (ie, Day -7 or Day -6), and the site radiologist should send the scan to the central imaging laboratory that same day. Scans can be sent by file transfer protocol (ftp) or by mailing it on a CD-ROM by pre-paid mailer provided for the study. The MRI central reader will assess the quality of the scan and will send a notice of acceptance via FAX and/or email to the site within 48 hours of receipt of the scan at their offices. A notice of acceptance MUST be received by the site before the subject can begin dosing. If a notice of "non-acceptance" is received by the investigator, the subject must have a repeat MRI (or CT in applicable subjects) prior to

receiving the first dose of study drug. This MRI should be performed within 2 weeks of the first MRI. In rare cases, the central imaging laboratory may suggest that CT scan be performed instead of MRI because of subject's abdominal anatomy.

  - NOTE: the first MRI may be delayed for up to 2 weeks because of scheduling or other issues at the clinic site, but must be completed within 56 days, maximum from the start of the original screening visit date, and this must occur prior to the subject receiving the first dose of study drug.
  - In the case where the MRI is delayed for scheduling or other issues, or a repeat MRI is required because of scan quality issues, a repeat hematology assessment should be completed 2 to 7 days prior to the planned Day 1.

- Distribution of modified MFSAF v2.0 diary. Subjects will be issued a hand-held device, and will complete the diary questions each night beginning on Day -7 up to the Week 24 Visit. Subjects will be instructed to place the device on the docking station (also provided), for automatic data transmittal each night after completing the questions. Subjects will be instructed to leave the device in the docking station when not answering the questions so that the unit remains fully charged. Subjects will receive training on the device by study site staff prior to leaving the site. Subjects will bring the device with them to Study Visits on Day 1, Week 4, Week 8, Week 12, Week 16 and Week 20 so that the device charging can be verified, and to download accumulated data. The device will then be returned to the subject at these same visits for continued use each night. Subjects will return the device and the docking station for the final time at the Week 24 Visit, so that all data can be archived. All subjects will complete the diary through Week 24.
- Subjects will be given a reminder card with the date and time of the Day 1 visit. Subjects will be reminded to arrive for the study visit after an overnight fast of at least 8 hours or since midnight.

9.2. Core Treatment Phase

Refer to Table 3, Study Visit Assessments and Table 4, Scheduled Laboratory Assessments for procedures to be performed at on-study visits and laboratory-only visits. Subjects do not need to come in for study visits in the fasted state except for baseline, Day 1, Week 4, and Week 24, when they should arrive for the visit after an overnight fast of at least 8 hours or since midnight.

The site must ensure that the subject is instructed NOT to take the dose of study drug on the day of the Week 4 study visit, as study drug will be administered in the clinic at that visit [redacted] Reminder cards will be used to send home with subjects to state upcoming visit scheduling, and to record the time subjects took their last dose prior to each visit. Use of the reminder cards by site staff is mandatory, and they will be retained in the subject's records.

The procedures are summarized as follows:

Day 1

- Record adverse events
- Update concomitant medications

- Complete a targeted physical examination
- Administration of first dose of ruxolitinib, exact time recorded on eCRF.
- [redacted]
- Study drug will be dispensed via IVRS.
- MFSAF v2.0 diary collection, data downloading and return to subject.
- Dispense reminder card to record time of dose on the day prior to Week 4 visit, and to remind subject NOT to take their morning dose the day of the Week 4 visit, to arrive for the visit after an overnight fast of at least 8 hours or since midnight, and to provide visit scheduling details.

Weeks 1, 2, 3, 5, 6, 7, 10, 14, and 18 (± 3 days)

- Subjects will go to the study site laboratory, or a local laboratory for blood draws for hematology assessments.
- The laboratory visits at Week 14 and Week 18 may be skipped for subjects who do not increase their dose at Week 12 or Week 16, and who have maintained platelet counts > 75 x 10^9/L since the last hematology assessment. Additional, twice-weekly laboratory-only visits to collect hematology lab samples will be required if platelet count falls below 35 x 10^9/L.

Week 4 (± 5 days)

- Review concomitant medications.
- Review transfusion status.
- Record adverse events.
- Complete a targeted physical examination.
- Measurement of spleen length below the costal margin by palpation.
- Vital signs.
- Complete PGIC question (Appendix 5).
- ECOG status assessment.
- [redacted].
- Reminder card will be distributed to record the time of the dose taken the day of the Week 8 visit, to record the time of the meal prior to the visit, and to provide visit scheduling details.

- Dispense study drug via IVRS.
- Perform study drug accountability assessment.
- MFSAF v2.0 diary collection, data downloading and return to subject.
- Blood sampling for the following laboratory tests (see Appendix 4):
  - Serum chemistry tests
  - Hematology
  - Lipid panel
  - [redacted]
- [redacted]
- Administration of ruxolitinib, exact time recorded on eCRF.
- [redacted]

Week 8 (± 5 days)

- Review concomitant medications.
- Review transfusion status.
- Record adverse events.
- Complete a targeted physical examination
- Measurement of spleen length below the costal margin by palpation.
- Vital signs.
- Complete PGIC question (Appendix 5).
- ECOG status assessment.
- Dispense reminder card with Week 12 visit scheduling details.
- Dispense study drug via IVRS.
- Perform study drug accountability assessment.
- MFSAF v2.0 diary collection, data downloading and return to subject.
- Blood sampling for the following laboratory tests (see Appendix 4):
  - Serum chemistry tests
  - Hematology
  - Sample for plasma level of ruxolitinib (prior meal/dose times will be recorded)

Week 12 (± 5 days)

- Review concomitant medications.
- Review transfusion status.
- Record adverse events.
- Complete a targeted physical examination.
- Measurement of spleen length below the costal margin by palpation.
- Vital signs.
- Complete PGIC question (Appendix 5).
- ECOG status assessment.
- [redacted].
- Reminder card will be distributed with Week 16 visit scheduling details.
- MFSAF v2.0 diary collection, data downloading and return to subject.
- Dispense study drug via IVRS.
- Perform study drug accountability assessment.
- Blood sampling for the following laboratory tests (see Appendix 4):
  - Serum chemistry tests
  - Hematology
  - Lipid panel
  - [redacted]
  - Coagulation panel

Week 16 (± 5 days)

- Review concomitant medications.
- Review transfusion status.
- Record adverse events.
- Complete targeted physical examination.
- Measurement of spleen length below the costal margin by palpation.
- Vital signs.
- Complete PGIC question (Appendix 5).
- ECOG status assessment.
- Reminder card will be distributed with Week 20 visit scheduling details.
- MFSAF v2.0 diary collection, data downloading and return to subject.

- Dispense study drug via IVRS.
- Perform study drug accountability assessment.
- Blood sampling for the following laboratory tests (see Appendix 4):
  - Serum chemistry tests
  - Hematology

Week 20 (± 5 days)

- Review concomitant medications.
- Review transfusion status.
- Record adverse events.
- Complete targeted physical examination.
- Measurement of spleen length below the costal margin by palpation.
- Vital signs.
- Complete PGIC question (Appendix 5).
- ECOG status assessment.
- Reminder card will be distributed to remind subjects to arrive for the Week 24 visit after an overnight fast of at least 8 hours or since midnight, and with Week 24 visit scheduling details.
- MFSAF v2.0 diary collection, data downloading and return to subject.
- Dispense study drug via IVRS.
- Perform study drug accountability assessment.
- Blood sampling for the following laboratory tests (see Appendix 4):
  - Serum chemistry tests
  - Hematology

Week 24 (± 5 days)

- Review concomitant medications.
- Review transfusion status.
- Record adverse events.
- Perform comprehensive physical examination.
- Measurement of spleen length below the costal margin by palpation.
- Vital signs.
- MRI (or CT scan in applicable subjects).
- Complete PGIC question (Appendix 5).

- ECOG status assessment.
- [redacted].
- Collect MFSAF v2.0 diary and all cords and charging stations.
- Dispense reminder card for subsequent visit scheduling, if subject will continue to receive study drug.
- Dispense study drug via IVRS if subject will continue to receive study drug.
- Perform study drug accountability assessment.
- Blood sampling for the following laboratory tests (see Appendix 4):
  - Serum chemistry tests
  - Hematology
  - Coagulation tests
  - Lipid panel
  - [redacted]
  - [redacted]
  - [redacted]

9.3. Extended Treatment Phase

Visits will occur every 12 weeks (eg, Weeks 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, and 156) beginning with Week 36 (± 5 days). Subjects will have laboratory-only visits to collect hematology samples 6 weeks after the Week 24 visit (eg, Week 30), then after **each** extended treatment phase visit (eg, Weeks 42, 54, 66, 78, 90, 102, 114, 126, 138, and 150). Additional hematology assessments will be required if the subject has a dose modification or as clinically indicated.

The following procedures will be performed every 12 weeks:

- Review concomitant medications.
- Review transfusion status.
- Record adverse events.
- Measurement of spleen length below the costal margin by palpation.
- Perform comprehensive physical examination.
- Vital signs.
- Complete PGIC question (Appendix 5).
- ECOG status assessment.
- [redacted].
- Reminder card will be distributed with subsequent visit scheduling details.

- Dispense study drug via IVRS.
- Perform study drug accountability assessment.
- Blood sampling for the following laboratory tests (see Appendix 4):
  - Serum chemistry tests
  - Hematology
  - Lipid panel
  - [redacted]
  - Coagulation panel

Week 156 (± 5 days)

- Review concomitant medications.
- Review transfusion status.
- Record adverse events.
- Perform comprehensive physical examination.
- Measurement of spleen length below the costal margin by palpation.
- Vital signs.
- Complete PGIC question (Appendix 5).
- ECOG status assessment.
- [redacted].
- Update subject status in IVRS.
- Perform study drug accountability assessment.
- Blood sampling for the following laboratory tests (see Appendix 4):
  - Serum chemistry tests
  - Hematology
  - Coagulation tests
  - Lipid panel
  - [redacted]

9.4. End of Treatment (± 5 days)

If a decision is made that the subject will withdraw from study participation, the end-of-treatment visit (EOT) should be conducted. If the EOT Visit coincides with a regular study visit, the end-of-treatment evaluations will supersede those of that scheduled visit, the data should be entered in the end of treatment visit in the CRF. The subject should be encouraged to return for the follow-up visit. The following will be performed:

- Review concomitant medications.
- Review transfusion status.
- Record adverse events.
- Perform complete physical examination.
- Measurement of spleen length below the costal margin by palpation.
- Vital signs.
- MRI (or CT scan in applicable subjects) should only be performed at the EOT visit if the subject discontinues treatment **prior** to Week 24.
- Complete PGIC question (Appendix 5).
- ECOG status assessment.
- Perform study drug accountability assessment.
- Blood sampling for the following laboratory tests (see Appendix 4):
  - Serum chemistry tests
  - Hematology
  - Coagulation tests
  - Lipid panel
  - [redacted]
- Contact IVRS to register subject discontinuation.

9.5. Follow-Up Phase

The follow-up phase is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 37 days following the EOT visit (or following the last dose of study drug if the EOT visit was not performed). If no follow-up visit is performed the follow-up phase is considered to be 30 days past the last dose of study drug. Reasonable efforts should be made to have the subject return for the follow-up visit, and report any AEs that may occur during this phase. The following procedures will be performed:

- Review concomitant medications.
- Record adverse events.
- Perform a targeted physical examination.

- Vital signs.
- Blood sampling for the following laboratory tests (see Appendix 4):
  - Serum chemistry tests
  - Hematology

9.6. Unscheduled Visits

Unscheduled visits for laboratory assessments may be conducted anytime at the Investigator's discretion. [redacted]

10. STUDY ASSESSMENT PROCEDURES

10.1. Demographics and Medical History

Demographic data and a complete medical and medication history will be collected at screening, after informed consent has been signed. Height and body weight measurements will be performed; body mass index will be calculated automatically in the eCRF. Complete transfusion history should be collected at the screening visit where possible, but must include at least 12 weeks prior to screening. All medical, medication and transfusion history will be recorded in the eCRF.

10.2. Order of Assessments

Multiple assessments are scheduled during the study visits. In order to standardize the visits, a suggested order of assessments is implied by the ordering of events in the description of study visits. Where feasible, vital signs and ECG measurements should be collected prior to blood draws. [redacted] Site staff should discuss the importance of the Subject Reminder Cards with the subject at the Day 1 visit so that the subject will be compliant with its return each visit. If the subject does not bring the reminder card, or it is blank, the site staff will discuss the prior dose timing with the subject, and will record the information in the subjects chart (site may use a blank reminder card for the specified visit).

10.3. Safety Assessments

10.3.1. Adverse Events

Adverse events will be monitored from the time the subject signs informed consent. Subjects will be instructed to report all AEs during the study and subjects will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and case report forms regardless of the

assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 11.

10.3.2. Physical Examination

A comprehensive physical examination will be performed at the times indicated on the Table of Assessments (Section 9). The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver, spleen); extremities, lymph nodes, assessment for edema and/or ascites, measurement of weight and a brief neurological exam. Height will be measured at the Screening visit only. Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant or advanced Registered Nurse Practitioners as local law permits. Clinically significant findings will be recorded in the eCRF.

10.3.2.1. Targeted Physical

A targeted physical examination will be a symptom-directed evaluation. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AE, or other findings as determined by the Investigator or designee. The targeted physical examination should also include an assessment of the subject's weight.

10.3.3. Vital Signs

Vital sign measurements (blood pressure, heart rate, body temperature) will be collected on the days and times noted in the Table of Assessments (Section 9). Vital signs will be taken with the subject in the sitting position after 5 minutes of rest. Vital signs will be recorded in the eCRF.

10.3.4. Concomitant Medications

Concomitant medications will be collected on the days and times noted in the Table of Assessments (Section 9) and recorded in the eCRF.

10.3.5. Twelve-Lead Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent position after 5 minutes of rest.

The screening ECG will be interpreted by the Investigator or another appropriately trained individual at the site. If ECG abnormalities that are clinically meaningful are present, they will be recorded on the eCRF. Normal ECG findings or non-clinically meaningful abnormal ECG findings will not be recorded on the eCRF, other than data indicating the ECG was performed.

Twelve-lead ECGs may be conducted during the study at the Investigator's discretion. ECGs that are identified as abnormal and clinically meaningful compared to the Screening assessment should be reported as AEs. For such AEs, the findings of the abnormal ECGs and the corresponding baseline ECG findings must be reported in the eCRF, and copies of the abnormal tracings and corresponding baseline tracings will also be sent to the Sponsor and CRO for their records. For Sponsor:

[redacted] MD
[redacted] (FAX)

10.3.6. Laboratory Assessments

A central laboratory or as instructed in the lab manual will perform the clinical laboratory tests except for hematology and coagulation panel which will be performed by the local laboratory. Samples for serum chemistry, lipid panel, serology, [redacted] and serum pregnancy test will be prepared using standard procedures. All subjects will have samples of blood collected on the days and times noted in the Table of Laboratory Assessments (Table 4) for analysis of serum chemistry and hematology. Appendix 4 provides a complete list of laboratory tests that will be performed. Please refer to the laboratory manual for further details and specifications for sample handling, processing and shipping.

10.3.6.1. Hematology

Hematology assessments, including complete blood count (CBC) with manual differential will be performed by the local laboratory during study visits, and may be performed at this same laboratory, or at a local laboratory identified by the subject and investigator for laboratory-only visits as outlined in Table 4, and any other time additional hematology monitoring is deemed necessary. The investigator is responsible for obtaining the data from such local laboratories, as well as the normal lab ranges used by that laboratory. A standardized local laboratory range will be used in analysis of hematology lab data.

10.3.6.2. Chemistry

Chemistry labs will be analyzed by a central laboratory.

10.3.6.3. Pregnancy and Fertility Testing

Blood will be collected during screening for females of childbearing potential to conduct a pregnancy test. Females of non-childbearing potential are defined as women who are:

- At least 55 years of age with history of amenorrhea for 1 year OR
- Are surgically sterile for at least 3 months

Subsequently, pregnancy tests will be conducted only as medically indicated. A positive urine pregnancy test will be confirmed by a serum pregnancy test. Pregnancy status will be documented at each visit on the eCRF.

10.3.6.4. Serology

Serology labs will be analyzed by a central laboratory.

10.4. Efficacy Assessments

- **Imaging.** The primary measure of spleen size will be by MRI (or CT scan in applicable subjects). MRI of the upper and lower abdomen and pelvis will be performed at baseline and Week 24. MRI will be performed with a body coil because the objective is to measure organ volume, not to find very small lesions. MRIs will be read initially by local radiologists who will assess the scan for quality, and send all scans (MRI or CT) to the central imaging laboratory the same day, if at all possible. The scans from an individual subject will be read by a central reader. Spleen and liver volume will be obtained by outlining the circumference of the organ and

determining the volume using the validated technique of least squares. The MRI will not determine spleen length below the costal margin, as there are no validated approaches for determining this measurement. Procedure specific training for scanning and image capture will be provided by the Vendor.

MRI is the preferred method for obtaining spleen volume data. However, CT scans may be performed at the visits where MRI is designated if the subject is not a candidate for MRI (because of the presence of metal clips in the body, or because of claustrophobia, for example), or if MRI is not readily available. CT scans will be similarly processed by the same central laboratory as used for MRIs. Procedure specific training for scanning and image capture will be provided by the Vendor. NOTE: The same method (MRI versus CT) must be used for both visits for a given subject unless a new contraindication to the use of MRI (eg, pacemaker insertion) occurs.

- **Spleen length.** Spleen length will be assessed by manual palpation as outlined in Table 3. Investigators will be provided with a soft centimeter ruler so that palpable spleen length is measured in centimeters and not in finger breadths. The edge of the spleen shall be determined by palpation, and measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion. Spleen length must be recorded on the eCRF.

10.5. Symptom and Quality of Life Assessments

- **Symptom Diary.** Symptoms of MF will be assessed using a symptom diary (modified MFSAF v2.0 diary). Subjects will be issued a hand-held device on which to record answers to queries regarding MF symptoms. Symptoms assessed will include filling up quickly/early satiety, abdominal discomfort, abdominal pain, inactivity, night sweats, itching, and bone/muscle pain. The modified MFSAF v2.0 diary will be completed by subjects each night beginning at Day -7 (first day of Baseline), and continuing to the Week 24 visit (25 weeks total). Subjects will bring the device to the study site at Study visits on Day 1, Week 4, Week 8, Week 12 and Week 16, so that the device charging can be verified, and to download accumulated data. NOTE: subjects who will have overnight stays associated with their Study Visit must also bring their docking station so that their device can be fully charged at all times, and so they can complete the evening diary entries. The device will then be returned to the subject at these same visits for continued use each night. The subject will return the device and the docking station for the final time at the Week 24 visit so that the data can be archived. Detailed directions for the administration of the modified MFSAF v2.0 diary will be provided in a Reference Manual. Spanish translations of the modified MFSAF v2.0 diary will be available.
- Patient Global Impression of Change will be administered at each visit beginning with Week 4, and consists of a single question to which the subject responds with answer on a scale of 1 to 7. See Appendix 5.

[redacted]

10.9. Other Study Procedures

10.9.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject prior to conducting any study-specific procedures. The granting of informed consent for participation in the study must be documented in writing, using an ICF that contains all the elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed, and a copy of the signed ICF must be provided to the study subject.

Subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy or fathering a child in order to participate in the study (Appendix 3).

10.9.2. IVRS/IWRS Procedures

An IVRS system will be used to assign subject numbers and to dispense study drug. Procedures to be followed will be provided in an IVRS manual.

10.9.3. Study Drug Administration

Subjects will take their dose of ruxolitinib morning and evening, approximately 12 hours apart, and without regards to food.

10.9.4. Study Drug Dispensation

Site staff will contact an IVRS to obtain the subject study drug assignment. The investigator or designee will select the assigned bottles from their stock that correspond to the number provided by IVRS and dispense the medication. The investigator will enter the bottle numbers in the eCRF. At subsequent medication dispensing visits, the investigator or designee will follow the same procedures as described above. Full details will be provided in the IVRS manual.

10.9.5. Assessment of Study Drug Compliance

Compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee (tablet counts). The objective is 100% compliance and investigators and their staff should evaluate compliance at each visit, and take appropriate steps to optimize compliance. For the purpose of subgroup analyses, subjects with at least 80% compliance over the total duration of dosing from the first day of dosing to the analysis of the study will be considered to be compliant.

10.9.6. Distribution of Subject Reminder Cards and Diaries

Subjects will be provided with subject reminder cards at each visit. The subject reminder cards will indicate the date/time of the next visit, and will also remind the subject when they should not take their morning dose of study drug, and when they should arrive for the visit after an overnight fast of at least 8 hours or since midnight. The reminder cards will have an area on which the date and time of the last dose taken prior to each study visit will be recorded by the subject, and to record time of last meal (certain visits only).

11. SAFETY MONITORING AND REPORTING

11.1. Adverse Events

11.1.1. Definitions and Reporting

An Adverse Event (AE) for the purposes of this protocol is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after a subject's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in study drug(s).

Adverse Events that begin or worsen after informed consent should be recorded in the Adverse Events section of the CRF. Conditions that were already present at the time of informed consent should be recorded in the medical history section of the CRF. Adverse Event monitoring should be continued through the follow-up visit or for at least 30 days following the last dose of study treatment, whichever comes later. Adverse Events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

Adverse Events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. If CTCAE grading is not used for a study, the severity of mild, moderate, severe, and life-threatening, or Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected as an outcome of the event. The occurrence of AEs should be sought by non-directive questioning of the subject during the screening process after signing informed consent and at each visit during the study. Adverse Events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1-4)
- Reasonable possibility that AE is related to the study treatment: (no, yes)
- Reasonable possibility that AE is related to a study procedure: (no, yes)
- Start and end dates, unless unresolved at final exam
- Action taken with respect to study medication (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
- Whether it is serious, as per Serious Adverse Event (SAE) definition provided in Section 11.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements, see Section 11.3.2.

All AEs should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the AE CRF as well as the Prior/Concomitant medications CRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study medication, the interventions required to treat it, and the outcome.

Disease progression should not be regarded or reported as an AE itself, unless it is associated with a separate AE.

11.2. Laboratory Test Abnormalities

11.2.1. Definitions and Reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the AE CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (eg, anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) event, as per CTCAE, does not automatically indicate a SAE unless it meets the definition of serious, as defined below, and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in Section 8.6 and should not contribute to the designation of a laboratory test abnormality as a SAE.

11.3. Serious Adverse Events

11.3.1. Definitions

Serious Adverse Event (SAE) is defined as one of the following:

- Is fatal or life-threatening (ie, immediate risk of dying)
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly or birth defect
- Is clinically meaningful, (ie, defined as an event that jeopardizes the subject or requires potential medical or surgical intervention to prevent 1 of the outcomes listed above). Considered meaningful by the Investigator as an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is due to:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.
  - Social reasons and respite care, in the absence of any deterioration in the subject's general condition.
  - Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, and whether there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere.

11.3.2. Reporting

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has signed the informed consent form (ICF) and until (at least) the Follow-up Visit or 30 days after the subject has stopped study treatment (whichever comes later) must be reported to the Sponsor or designee within 24 hours of learning of its occurrence. Any SAEs experienced after this period of at least 30 days should only be reported to the Sponsor, or designee, if the Investigator suspects a causal relationship to the study mediation. Recurrent episodes, complications, or progression of the initial SAE must be reported as the follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. Serious AE collection begins after the subject has signed the ICF. If a subject experiences an SAE after signing the ICF, but prior to receiving study medication, the event will **not** be collected unless the Investigator feels the event may have been caused by a protocol procedure. Previously planned (prior to signing the ICF) surgeries should not be reported as SAEs unless the underlying medical condition worsens over the course of the study.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The Investigator must assess and record the relationship of each SAE to each specific study medication (if there is more than 1), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the Sponsor (or designee). The investigator must assess if there is a Reasonable possibility that the SAE is related to the study treatment: no (unrelated), yes (related).

SAEs related to unblinded comparator drugs or concomitant medications/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The telephone and facsimile number of the Sponsor's contact persons, specific to the study, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation or if study medication was interrupted or discontinued.

If the SAE is not previously documented in the Investigator's Brochure for the study medication (new occurrence) and is thought to be related to the Sponsor's study drug, a Sponsor's associate may urgently require further information from the Investigator for reporting to Health Authorities.

The Sponsor may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. If the study is open-label, no special unblinding procedures are needed for exceptional circumstances or medical emergencies.

11.4. Emergency Unblinding of Treatment Assignment

Not applicable, study is open label.

11.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive medication or method. The procedures that will be followed based on whether a pregnancy is confirmed by a positive serum or urine test result are listed below:

- Investigator and subject must notify each other immediately
- Investigator must notify the Sponsor immediately
- Study medication must be discontinued immediately
- Subject must be withdrawn from the study
- Perform the required End-of-treatment Visit evaluations
- Investigator must complete and submit the Pregnancy Initial and Follow-up report forms to the Sponsor

- A serum pregnancy test must be performed to confirm the urine test result. (The serum test should be performed at the investigative site to ensure the test will be performed promptly and the result available immediately for review.)

If a negative serum test does not confirm the urine test result, then:

- The Investigator will use his/her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine if it is in the subject's best interest to resume study drug and continue participation in the study.

To ensure subject safety, each pregnancy in a subject during maternal or paternal exposures to study medication must be reported within 24 hours of learning of its occurrence. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation. The pregnancy should be followed-up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the Investigator to the Sponsor. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Sponsor's study medication of any pregnancy outcome and follow-up to the first well-baby visit. **Any SAE experienced during pregnancy must be reported on the SAE Report Form and needs to be reported to Incyte Corporation.**

11.6. Warnings and Precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (INs). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

11.7. Data Safety Monitoring

11.7.1. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be formed. It will consist of qualified individuals who are not involved with the conduct of the study. The establishment, composition, roles, duties and responsibilities of the DMC will be addressed in an approved DMC charter. The timing of data review by the DMC will be specified in the charter, but at a minimum, will include review of safety data with an emphasis on events of thrombocytopenia and hemorrhage at least 28 days after 20 subjects have been enrolled into the study and 28 days after 40 subjects have been enrolled into the study.

11.7.2. Reporting of Grade 4 Thrombocytopenia Events and > Grade 2 Hemorrhage Events During the Study

The study is designed to assess the efficacy and safety of ruxolitinib in a myelofibrosis patient population with platelet counts of 50 to100 x 10^9/L. As these patients are potentially at higher risk for greater degrees of thrombocytopenia and bleeding, events of Grade 4 thrombocytopenia

and > Grade 2 hemorrhage will be monitored on an ongoing basis. Investigators will be required to notify the sponsor via FAX of any Grade 4 thrombocytopenia event and any Grade 3 or Grade 4 event of hemorrhage, regardless of suspected causality. The notification must occur within 24 hours of the time the site first becomes aware of the event. All such events occurring after a subject has signed informed consent and received at least one dose of study drug up to the follow-up visit (or at least 30 days after the last dose of study drug is taken) must be reported. The notification form (supplied by sponsor) will require the site to provide information regarding dosing history, platelet count, event description and any other information pertinent to the event.

11.7.3. Safety Reviews

As ruxolitinib has been studied extensively in the myelofibrosis population in Phase II and III trials, its safety profile is generally well characterized in patients with platelet counts above 100 x 10^9/L. Because this trial is designed to assess the efficacy and safety of ruxolitinib in a myelofibrosis patient population with platelet counts of 50 to100 x 10^9/L, there will be a review of safety with an emphasis on events of thrombocytopenia and hemorrhage at regularly scheduled intervals corresponding to when:

1. 20 patients have been enrolled
2. 40 patients have been enrolled

Additional safety reviews as deemed necessary by the DMC or the sponsor may be conducted at any time

11.7.3.1. Review After Enrollment of 20th Subject

When the 20th patient is enrolled, additional screening of subjects will be paused for at least 28 days and up to approximately 42 days. Subjects in screening at that time will be allowed to enroll if they are found to be eligible. During this period, enrolled subjects will be allowed to continue on study per protocol. At least twenty eight days from the enrollment of the 20th subject, safety data will be assessed by the DMC and the sponsor. Subjects will be analyzed if they have completed at least 28 days on the study or have discontinued the study due to Grade 4 thrombocytopenia or > Grade 2 hemorrhage. If fewer than 33% of the subjects had an event of Grade 4 thrombocytopenia and fewer than 10% of these subjects had an event of > Grade 2 hemorrhage, the study may resume enrollment without amendment. If these criteria are not met, or other safety concerns are reveled, a recommendation will be made for one of the following actions:

1. Stop the trial
2. Recommend amendments and suspend enrollment until the amendments can be implemented
3. Continue enrollment with a new dosing cap (with subsequent amendment of the protocol)
4. Continue the trial without amendment (must be agreed upon by both the Sponsor and the DSMC)

11.7.3.2. Review After Enrollment of 40th Subject

At least 28 days from the enrollment of the 40th subject, safety data will be assessed by the DMC and the sponsor. Since the first dose escalation opportunity in the study is at Day 28 and the starting dose for all subjects of 5 mg bid will have been adequately assessed for safety at the first safety review after the enrollment of 20 patients, screening will not be suspended following enrollment of the 40th subject. If safety of the 5 mg bid dose is not clear from this first data review, the DMC and sponsor may mandate a hold on screening at the review that occurs with enrollment of the 40th subject. Subjects will be analyzed if they have completed at least 28 days on the study or discontinued due to grade 4 thrombocytopenia or > Grade 2 hemorrhage. If 33% or fewer of the subjects had an event of Grade 4 thrombocytopenia and 10% or fewer of these subjects had an event of > Grade 2 hemorrhage, the study may resume enrollment without amendment. If these criteria are not met, or other safety concerns are reveled, a recommendation will be made for one of the following actions:

1. Stop the trial
2. Recommend amendments and suspend enrollment until the amendments can be implemented
3. Continue enrollment with a new dosing cap (with subsequent amendment of the protocol)
4. Continue the trial without amendment (must be agreed upon by both the Sponsor and the DSMC)

The DMC and the sponsor will also specifically evaluate the event rates for Grade 4 thrombocytopenia and > Grade 2 hemorrhage in subjects from the initial cohort of 20 subjects who have had longer follow-up and opportunities for dose escalation.

11.7.4. Continuous Safety Monitoring

Events of Grade 4 thrombocytopenia and > Grade 2 hemorrhage will be monitored continuously. Subjects will be analyzed if they have completed at least 28 days on the study or discontinued due to Grade 4 thrombocytopenia or > Grade 2 hemorrhage. If at any time > 33% of these subjects have an event of Grade 4 thrombocytopenia, or > than 10% of the subjects have an event of > Grade 2 hemorrhage, the sponsor will temporarily hold further screening and seek consultation with the DMC. A recommendation will be made for one of the following actions:

1. Stop the trial
2. Recommend amendments and suspend enrollment until the amendments can be implemented
3. Continue enrollment with a new dosing cap (with subsequent amendment of the protocol)
4. Continue the trial without amendment (must be agreed upon by both the Sponsor and the DMC).

11.8. Product Complaints

Incyte collects product complaints on study medications and drug delivery systems used in clinical studies in order to ensure the safety of study participants, to monitor quality, and to facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by Incyte or its designee will be reported.

The Investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- Recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- Faxing the completed product complaint form within 24 hours to Incyte or its designee.

If the Investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

12. STATISTICS

12.1. Study Population

Intent-to-treat (ITT): includes all subjects enrolled in the study.

Per-protocol (PP): includes subjects who are considered to be sufficiently compliant with the protocol.

Safety Evaluable: includes subjects who received at least 1 dose of study drug.

[redacted]

12.2. Statistical Analyses

12.2.1. Primary Analyses

Co-Primary Endpoints:

- Correlation of % change in spleen volume at Week 24 compared to baseline versus final titrated dose.
- Correlation of % change in Total Symptom Score as measured by the modified MFSAF v2.0 diary at Week 24 compared to baseline versus final titrated dose.

The null hypothesis is that the correlation between percent change in spleen volume or total symptom score and final titrated dose is zero. The test will be based on the t test for a product-moment correlation coefficient:

$$t = r_{xy} \sqrt{(n - 2)} / \sqrt{(1 - r_{xy}^2)}$$

(Cohen 1988, Formula 3.1.1)

A two-sided alpha of 5% will be used. With a sample size of 150, the critical correlation that is needed to reject H_0 is 0.16. if the absolute value of the observed correlation is 0.16 or higher, H_0 will be rejected. In order to keep the overall alpha at 5%, a sequential testing procedure will be used: First we will test the correlation with % change in spleen volume, and only if the null hypothesis of no correlation can be rejected will we continue to test the correlation with % change in Total Symptom Score.

Safety Endpoints:

Safety and tolerability will be assessed by monitoring the frequency, duration and severity of adverse events, performing physical examinations, collecting vital signs, collecting laboratory data for hematology, serum chemistry, coagulation parameters, and lipid panel through Week 156.

Change in platelet count from baseline to each visit where the variables are measured will be tabulated with summary statistics.

Proportion of subjects with new onset of Grade 4 thrombocytopenia events, and proportion of subjects with new onset of Grade 2 or higher hemorrhage, as measured by CTCAE will be tabulated with summary statistics. The hazard functions of time to onset of the above two safety measures will be estimated using life table method.

Adverse events will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA®) preferred term and by system organ class. Severity of AEs will be based on the CTCAE scale as indicated in Section 11.1.1.

The subset of AEs that are considered by the Investigator to be related to study drug will be considered to be treatment-related AEs. If the Investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

Clinical Laboratory Tests

The clinical laboratory data will be analyzed using summary statistics (eg, means and frequencies), and no formal statistical comparisons among the treatments are planned.

Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (body temperature, respiratory rate, blood pressure and heart rate) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities according to the criteria shown below; subjects exhibiting clinically notable vital sign abnormalities will be listed.

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 160 mm Hg	< 85 mm Hg
Diastolic blood pressure	> 100 mm Hg	< 50 mm Hg
Respiratory Rate	> 24 per minute	< 8 per minute
Heart rate	> 100 bpm	< 45 bpm
Note: mm Hg = millimeters of mercury; bpm = beats per minute.		

12.2.2. Secondary Analyses

Secondary Endpoints

- Percent change in spleen volume at Week 24 compared to Baseline
- Percent change in Total Symptom Score as measured by the modified MFSAF v2.0 diary at Week 24 compared to baseline
- Proportion of subjects with ≥ 35% reduction in spleen volume at Week 24 compared to baseline
- Proportion of subjects with ≥ 10% reduction in spleen volume at Week 24 compare to baseline
- Proportion of subjects with ≥ 50% improvement in total symptom score as measured by the modified MFSAF v2.0 diary at Week 24 compared to baseline

Long-term efficacy of ruxolitinib will be assessed by monitoring change and percent change in spleen length, as measured by palpation, and change in PGIC score from baseline to each visit where the variables are measured through Week 156. The percent change in spleen volume at Week 24 compared to baseline, the percent change in Total Symptom Score as measured by the modified MFSAF v2.0 diary at Week 24 compared to baseline, the proportion of subjects with ≥ 35% reduction in spleen volume at Week 24 compared to baseline, proportion of subjects with ≥ 10% reduction in spleen volume at Week 24 compared to baseline, and the proportion of subjects with ≥ 50% improvement in total symptom score as measured by the modified MFSAF v2.0 diary at Week 24 compared to baseline will be tabulated with summary statistics. Change and percentage change in spleen length from baseline as measured by palpation at each visit where the parameter is assessed through Week 156 will be tabulated with summary statistics. The data will be summarized as one group and by the final titrated dose. The final titrated dose will be based on dosing data up to Week 24.

[redacted]

12.3. Interim Analysis

Interim data review focused on thrombocytopenia and hemorrhage events will occur as described in Section 11.7 Data Safety Monitoring.

12.4. Selection of Sample Size

Approximately 150 subjects will be enrolled. Using an alpha of 5% (two-sided), this sample size gives a power of 96% to reject the null hypothesis of no dose-effect correlation if the true correlation is 0.30. The power is 87% if the true correlation is 0.25, and the power is 69% if the true correlation is 0.20. These calculations are based on (Cohen 1988, Formula 12.3.4).

In addition, the mean percent change of spleen volume measured by MRI, and mean percent change in Total Symptom Score from baseline to Week 24 will each be estimated with a 95% confidence interval. With 150 subjects, the half-length of the 95% confidence interval of the spleen volume change from baseline to Week 24 is about 3%. This is based on the Phase III study (INCB 18424-351), where the standard deviation of the percent change of spleen volume from baseline to Week 24 was 19%.

12.5. Level of Significance

All confidence intervals will be 95% and tests will be performed at two sided 0.05% level. Since this is an exploratory study, no multiplicity adjustment will be performed.

13. STUDY DRUG MATERIALS AND MANAGEMENT

13.1. Investigational Product Description

Ruxolitinib Phosphate tablets will be provided as 5 mg tablets packaged as 60 count in high-density polyethylene bottles.

13.1.1. Study Drug Packaging, Labeling and Preparation

All bottles of Incyte investigational product contain the following language: "Caution: New Drug—Limited by Federal law to investigational use."

13.1.2. Study Drug Storage and Stability

Ruxolitinib Phosphate 5 mg tablets are packaged as 60-count in high-density polyethylene (HDPE) bottles. The bottles of tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F). Stability studies will be conducted on clinical batches to support the clinical trial.

13.2. Study Drug Accountability, Handling, and Disposal

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

The Investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study medication until the end of the study. The Investigator or designee must maintain records that document:

- investigational product delivery to the study site
- the inventory at the site
- use by each subject including pill/unit counts from each supply dispensed
- return to the Investigator or designee.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study subjects.

The investigational product must be used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the subjects were provided the correct study medication specified.

Completed accountability records will be archived by the site. At the completion of the study, the Investigator or designee will oversee shipment of any remaining study drug back to the Sponsor or Sponsor's designee for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from Incyte.

14. STUDY ADMINISTRATION

14.1. Data Management

14.1.1. Data Collection

The Investigator will be provided with an eCRF for each subject. Entries made in the eCRF must be verifiable against source documents, or, in certain circumstances, as directed by the Sponsor, have been directly entered into the eCRF, in which case the entry in the eCRF will be considered as the source data. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. The Investigator will be responsible for reviewing all data and eCRF entries and will sign and date the designated pages in each subject's eCRF, verifying that the information is true and correct. Queries generated by Data Management will be sent to the study site for resolution. The Investigator is responsible for the review and approval of all responses.

14.1.2. Data Management

Data management will be performed from electronic case report forms (eCRFs). All eCRF data will be entered into a validated database. Laboratory data will be imported to the database electronically. All data entry, verification and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at Incyte or its designee. The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures completed.

14.2. Study Monitoring

Qualified representatives of the Sponsor or Sponsor designees, "study monitors," will monitor the study according to a predetermined monitoring plan. Monitoring visits provide the Sponsor with the opportunity to:

- Evaluate the progress of the study.
- Verify the accuracy and completeness of CRFs.
- Assure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled.
- Resolve any inconsistencies in the study records.

The Investigator must allow the study monitors to periodically review, at mutually convenient times, during the study and after the study has been completed, all CRFs and office, hospital, and laboratory records supporting the participation of each subject in the study. The CRFs and other documentation supporting the study must be kept up-to-date by the Investigator and the research staff at the investigative site. These study materials must be available for review by the study monitor, and/or other qualified representatives of the Sponsor, at each monitoring visit.

The study monitor will review the various records of the study (CRFs, subject medical and laboratory records, and other pertinent data). The study monitor will verify the CRF data against original source documentation for accuracy and completeness. The study monitor will identify

data discrepancies and collaborate with the Investigator and research staff to resolve the discrepancies in a timely manner. Protocol deviations will also be identified and recorded on a "Protocol Deviation Log." The study monitor will follow an "Issue Escalation" plan in order to ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

14.3. Protocol Adherence

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject informed consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

Each Investigator must adhere to the protocol as described in this document and agree that changes to the protocol, with the exception of medical emergencies, must be discussed and approved, firstly, by the Sponsor and, secondly, by the IRB/EC. Each Investigator is responsible for enrolling subjects who have met the protocol inclusion and exclusion criteria. The IRB/EC that granted original approval, or the IRB/EC currently responsible for overseeing the conduct of the study must be notified of all changes in and deviations from the protocol that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation. The Investigator must send a copy of the approval letter from the IRB/EC to the Sponsor or CRO and retain the original in the site study regulatory file.

Major eligibility deviations must be reported to the IRB/EC in accordance with the IRB/EC requirements. During the course of the study, the monitor must notify the Sponsor of subjects found not to have met eligibility criteria. The medical monitor, in collaboration with the Investigator, will determine if the subject should be withdrawn from the study.

14.4. Financial Disclosure

All clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators, are required prior to study initiation to submit a completed Clinical Investigator Financial Disclosure Request Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, clinical investigator is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new investigators or sub-investigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Request Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the Sponsor/designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligation to report to the Sponsor/designee any changes to the financial information previously reported. The clinical investigators will also be reminded that they must report any changes in their financial information for a period of 1 year after completion of the covered clinical study.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Sponsor Audits

At some point during the study, individuals from the Sponsor's Quality Assurance department and/or their authorized representative may visit the Investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the Investigator's adherence to the protocol, applicable regulations, and the Sponsor's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the Investigator will be contacted by the Sponsor to arrange a convenient time for this visit. The Investigator and staff are expected to cooperate with the auditors and allow access to all subject records supporting the CRFs and other study-related documents.

15.2. Inspection by Regulatory Authorities

At some point during the investigational product's development program, a regulatory authority may visit the Investigator to conduct an inspection of the study and the site. The Investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the CRFs and other study related documents. The Investigator must immediately notify the Sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

16. ETHICS

16.1. Ethical Conduct of the Study

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 50, 54 56, 312 and Part 11 as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

16.2. Written Informed Consent

An informed consent form (ICF) that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate verbal and written information about the nature, purpose, and the possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue study medication and withdraw from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures. The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

Preparation of the consent form is the responsibility of the Investigator and must include all elements required by the ICH GCP, and applicable regulatory requirements, and must adhere to the ethical principles that have their origin in the Declaration of Helsinki.

A template will be provided by Incyte. Incyte or its designee must review and approve all changes to site-specific ICFs.

The consent form must include a statement that the Sponsor or designee and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the IRBs and/or IECs must provide the Investigator with written approval/favorable opinion of the written ICF and any other information to be provided to the subjects.

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

The Investigator should inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

16.3. Ethics Review

It is the responsibility of the Investigator to assure that all aspects of the ethics review are conducted in accordance with the Declaration of Helsinki as described in the International Conference on Harmonization (ICH) E6: Guideline for Good Clinical Practice (GCP), and/or local laws, whichever provides the greatest level of protection for the study participants. The protocol and any information supplied to the subject to obtain informed consent including written ICFs, subject recruitment procedures (eg, advertisements), and written information to be provided to subjects (information leaflets) must be reviewed and approved by a qualified IRB/EC prior to enrollment of participants in the study. Prior to initiation of the study, the Sponsor must receive documentation of the IRB/EC approval, which specifically identifies the study/protocol, and a list of the committee members.

The Principal Investigator is responsible for informing the IRB or EC of any amendment to the protocol in accordance with local requirements. Protocol Amendments and revisions to the informed consent must be submitted to and approved by the IRB/EC.

Investigators must submit progress reports to the IRB/EC in accordance with the IRB/EC requirements and local regulations. Annual re-approval of the study must be obtained. Copies of progress reports and annual re-approvals must be sent to the Sponsor.

The Principal Investigator is also responsible for providing the IRB/EC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. Incyte will provide this information to the Principal Investigator.

When the Sponsor provides the Investigator with a safety report, the Investigator must promptly forward a copy to the IRB/EC.

After completion or termination of the study, the Investigator must submit a final report to the IRB/EC and to the Sponsor.

The Investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB/IEC.

Each clinical Investigator is responsible to conduct the study in accordance with the protocol, all applicable laws, regulations, and GCP according to ICH guidelines.

16.4. Data Privacy

The Investigator and Sponsor must adhere to applicable data privacy laws and regulations. The Investigator and Sponsor are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The Investigator must ensure that all records pertaining to the conduct of the clinical study (as listed above) are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal termination of clinical development of the investigational product.

17.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the termination of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

The Investigator must not destroy any records associated with the study without receiving approval from Incyte. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, Incyte must be contacted to arrange alternative record storage options.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable, provided it is legible and is a verified copy of the original document.

All CRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance

with applicable record retention regulations. The Sponsor will retain the original CRF data and audit trail.

17.3. Confidentiality

Subject names will not be supplied to the Sponsor. Only the subject number and subject initials will be recorded in the CRF, and if the subject name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the Sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

18. PUBLICATION POLICY

By signing the study protocol, the Investigator and his or her institution agree that the results of the study may be used by the Sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

The terms regarding the publication of study results are contained in the agreement signed with Incyte or its contract research organization. The signed agreement is retained by Incyte or its contract research organization.

19. LIST OF REFERENCES

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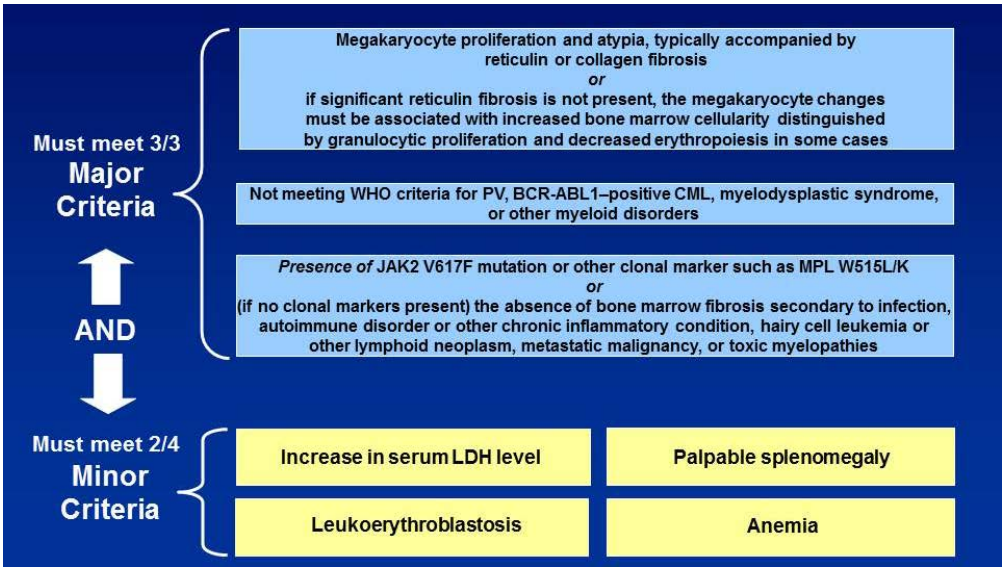
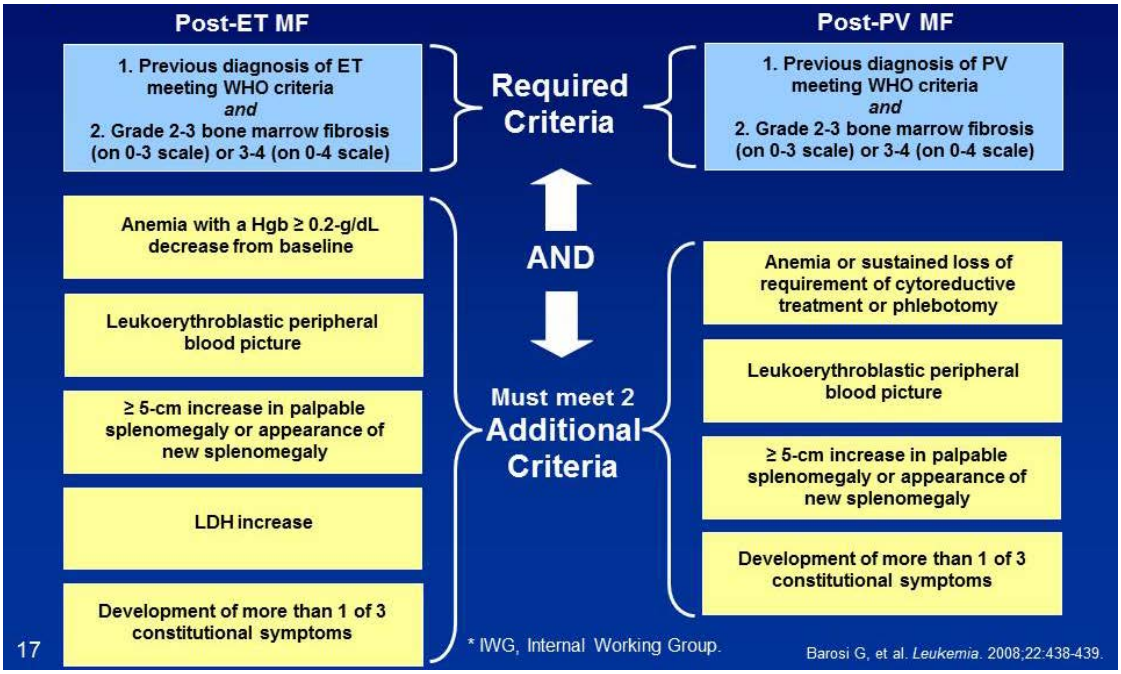
APPENDIX 1. 2008 WORLD HEALTH ORGANIZATION CRITERIA FOR DIAGNOSIS OF PRIMARY MYELOFIBROSIS



Reference: Tefferi and Vardiman 2008.

APPENDIX 2. PROPOSED DIAGNOSTIC CRITERIA FOR PPV-MF AND PET-MF BY THE INTERNATIONAL WORKING GROUP FOR MYELOFIBROSIS RESEARCH AND TREATMENT



Reference: Barosi et al 2008.

APPENDIX 3. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Males Subjects Participating in the Study:

The following methods have been determined to be more than 99% effective (failure rate less than 1% per year, when used consistently and correctly) (Trussell 2004), by the male subject and his partner and are permitted under this protocol:

- Complete abstinence from sexual intercourse
- Double barrier methods
  - condom with spermicide in conjunction with use of an intrauterine device (IUD)
  - condom with spermicide in conjunction with use of a diaphragm
- Oral, injectable, or implanted contraceptives
- Tubal ligation or vasectomy (surgical sterilization)

For Female Subjects Participating in the Study:

The following methods have been determined to be more than 99% effective (failure rate less than 1% per year, when used consistently and correctly) (Trussell 2004), by the female subject and her partner and are permitted under this protocol:

- Complete abstinence from sexual intercourse
- Double barrier methods
  - condom with spermicide in conjunction with use of an IUD
  - condom with spermicide in conjunction with use of a diaphragm
- Tubal ligation or vasectomy (surgical sterilization)
- Oral, injectable, or implanted contraceptives

APPENDIX 4. CLINICAL LABORATORY TESTS

Serum Chemistry	Hematology	Other
Albumin * Alkaline phosphatase* ALT* AST* Bicarbonate BUN* Calcium Chloride Creatinine* Gamma glutamyl transferase* Glucose Iron* Lactate dehydrogenase* Phosphorus Potassium Serum lipase* Sodium Total Bilirubin* Total Protein Uric acid Transferrin Ferritin	Complete Blood Count (CBC) Manual Differential*, including reporting of % blasts Platelets* Reticulocyte count* Hemoglobin* Hematocrit*	Serology*: Hepatitis A virus antibody (IgM) Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis B core antibody Hepatitis C virus antibody HIV Antibody Pregnancy Test*: Female subjects of childbearing potential only; serum test at screening.
Lipid Panel	**Coagulation**	**Immunology**
Total cholesterol* Triglycerides LDL HDL HS-CRP	PT (INR) PTT	[redacted]
	Values denoted with * will be reported to the sponsor. All laboratory data will be retained in source documents.	
ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, PT = prothrombin time, PTT = partial thromboplastin time, HS-CRP = high sensitivity C-reactive protein		

APPENDIX 5. PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Instructions: Circle the answer that is most appropriate.

Since the start of the treatment you've received in this study, your myelofibrosis symptoms are:

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

APPENDIX 6. BONE MARROW BIOPSY EVALUATION

- Grading of bone marrow biopsy fibrosis density

Fibrosis Grade	Description
0	Scattered linear reticulin with no intersections corresponding to normal bone marrow
1	Loose network of reticulin with many intersections, especially in perivascular areas
2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
3	Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis

Note: Fibrosis density should be assessed in hematopoietic areas.
Source: Tefferi et al 2006.

Bone Marrow Biopsy Pathology Reporting Guidelines

The following should be assessed:

- Assessment of cellularity.
- 500-cell differential of aspirate, (if collected) correlated, if possible, with data from appropriate marrow biopsy section. Percentage of pronormoblasts, blasts, normoblasts, myelocytes, metamyelocytes
- Blast percentage, indicating what cellular types are being considered as blast equivalents, and the degree of maturation and dysplastic abnormalities within the neoplastic population should be described.
- Characterization of erythrocyte and megakaryocyte morphology.
- Characterization and gradation of fibrosis within hematopoietic cellular areas.
- Diagnostic interpretation with specific mention of (expected) absence of an infiltrative or granulomatous process
- Pathologist's diagnosis (PMF, PPV-MF, etc.)

APPENDIX 7. SCREENING SYMPTOM FORM

Instructions to Subjects: Please answer all questions to the best of your ability, based on your memory **over the past 7 days (1 week).** There is no right or wrong answer.

1. During the past 7 days, how severe were your worst night sweats (or feeling hot or flushed) due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
2. During the past 7 days, how severe was your worst itchiness due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
3. During the past 7 days, how severe was your worst abdominal discomfort (feel uncomfortable, pressure or bloating) due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
4. During the past 7 days, how severe was your worst pain under the ribs on the left side due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
5. During the past 7 days, what was the worst feeling of fullness (early satiety) you had after beginning to eat, due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
6. During the past 7 days, how severe was your worst bone or muscle pain due to MF (diffuse, not joint or arthritis pain)?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
7. During the past 7 days, what was the worst degree of inactivity (including work and social activities) you had due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Investigators/Site Staff:

Please complete the table below to confirm the criterion used to confirm the subject's eligibility in the trial based on an assessment of his/her active symptoms of myelofibrosis.

ELIGIBILITY CRITERION	CONFIRMATION
A symptom score of at least 5 on at least one of the symptoms	☐ Yes ☐ No
A symptom score of 3 or greater on at least 2 of the symptoms	☐ Yes ☐ No

APPENDIX 8. INHIBITORS AND INDUCERS OF CYTOCHROME – P450 3A4

CYP3A4 Inhibitors

strong A Strong inhibitor.
moderate A Moderate inhibitor.
weak A Weak inhibitor.
others All other inhibitors.

HIV Antivirals:

- indinavir[1]
- nelfinavir[1]
- ritonavir[1]
- saquinavir[1]

- clarithromycin[2]
- itraconazole[2]
- ketoconazole[2]
- nefazodone[2]
- posaconazole[2]
- voriconazole[2]
- telithromycin[2]
- aprepitant
- erythromycin
- fluconazole[2]
- grapefruit juice
- verapamil
- diltiazem
- cimetidine
- amiodarone
- chloramphenicol
- delaviridine
- diethyl-dithiocarbamate
- fluvoxamine
- gestodene
- imatinib
- mibefradil
- mifepristone
- norfloxacin
- norfluoxetine
- starfruit

CYP 3A4 Inducers:*

HIV Antivirals:

efavirenz[1]
nevirapine[1]
barbiturates
carbamazepine
glucocorticoids
modafinil
nevirapine
oxcarbazepine
phenobarbital
phenytoin
pioglitazone
rifabutin
rifampin[3]
St. John's wort[3]

Other Prohibited Medications[3]:

systemic steroids exceeding 10 mg prednisolone equivalents per day except as part of a taper strategy or to prevent reactions to blood component transfusions
aspirin > 81 mg daily
other investigational medication
hydroxyurea
interferon
thalidomide
busulfan
lenalidomide
anagrelide

thrombopoietin receptor agonists (romiplostim, eltrombopag)

*Use of all CYP3A4 inhibitors or inducers is discouraged as they may have effects on ruxolitinib levels, and alternative therapies should be sought if available.
[1] Subjects receiving these medications should not be allowed in the study as HIV+ patients are excluded
[2] Use of these medications should be avoided and if used, a 50% ruxolitinib dose reduction is recommended along with frequent platelet monitoring during the period of co-administration.
[3] These medications are prohibited during this study.

APPENDIX 9. DRUGS THAT INTERFERE WITH COAGULATION OR INHIBIT PLATELET FUNCTION

Antiplatelet Agents[a]	**Anticoagulant Agents**[a]	**Procoagulant Agents**	**Synthetic inhibitors of factor Xa**	**Thrombolytic Agents**	**Direct thrombin inhibitors**	**NSAIDs and Acetaminophen** **PERMITTED AT RECOMMENDED DOSES**[b]	**Food supplements** **PROHIBITED**
Aspirin (> 81 mg) PROHIBITED	Heparin	Aminocaproic Acid	Fondaparinux	Urokinase	Argatroban	Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Flurbiprofen, Oxaprozin, Indomethacin, Sulindac, Etodolac, Ketorolac, Diclofenac, Nabumetone, Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam, Mefenamic acid, Meclofenamic acid, Flufenamic acid, Tolfenamic acid	Nattokinase (extracted and from a Japanese food called natto)
Ticlopidine	Warfarin	Desmopressin	Idraparinux	Streptokinase	Lepirudin		
Clopidogrel	Dicumarol			Anistreplase	Bivalirudin		Lumbrokinase (present in the earthworm *Lumbricus bimastus*)
Prasugrel	Phenprocoumon			Tissue Plasminogen Activator (tPA)	Dabigatran		
Cilostazol	Acenocoumarol						
Abciximab	Anisindione						
Eptifibatide	Dalteparin						
Tirofiban	Danaparoid			Alteplase			
Dipyridamole	Enoxaparin			Reteplase			
Epoprostenol	Tinzaparin			Tenecteplase		Acetaminophen	
	Phenindione						

[a] If concomitant administration of an anticoagulant/antiplatelet medication is indicated, caution and enhanced monitoring is required. History of thrombocytopenia, and any concurrent ruxolitinib-related thrombocytopenia should be a factor in the choice of anticoagulant and dose.

[b] Over-the-counter acetaminophen and NSAIDS (ibuprofen and naproxen) are permitted in this study. All prescription strength NSAIDs are prohibited.

Signature Manifest

Document Number: IC-DEV-PROT-AMEND-0039 **Revision:** 0
Title: INCB 18424-258 Protocol Amendment 2

All dates and times are in Eastern Standard Time.

APPROVAL: 18424-258 Protocol Amend2

Approval and Release

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