Official Title:	**An Open-Label Phase 2 Study of Itacitinib (INCB039110) in Combination With Low-Dose Ruxolitinib or Itacitinib Alone Following Ruxolitinib in Subjects With Myelofibrosis**
NCT Number:	NCT03144687
Document Date:	Clinical Study Protocol: 14 August 2017

Clinical Study Protocol

INCB 39110-209

An Open-Label Phase 2 Study of Itacitinib (INCB039110) in Combination With Low-Dose Ruxolitinib or Itacitinib Alone Following Ruxolitinib in Subjects With Myelofibrosis

Product:	**Itacitinib (INCB039110)**
IND Number:	[redacted]
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Date of Protocol:	**22 MAR 2017**
Date of Amendement 1:	**14 AUG 2017**

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 11, 50, 54, 56, and 312, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have read the INCB 39110-209 Protocol Amendment 1(dated 14 AUG 2017) 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)

SYNOPSIS

Name of Investigational Product: Itacitinib (INCB039110)

Title of Study: An Open-Label Phase 2 Study of Itacitinib (INCB039110) in Combination With Low-Dose Ruxolitinib or Itacitinib Alone Following Ruxolitinib in Subjects With Myelofibrosis

Protocol Number: INCB 39110-209	**Study Phase:** 2

Indication: Primary and secondary myelofibrosis (MF)

Primary Objective	**Primary Endpoint**
To evaluate preliminary efficacy of itacitinib (INCB039110) on spleen volume reduction (SVR) from baseline at Week 24 in the 2 following cohorts of MF subjects: • **Cohort A**: in combination in subjects with ruxolitinib low dose (less than 20mg daily). • **Cohort B**: as monotherapy in subjects who progressed (per revised European LeukemiaNet [ELN] 2013 response criteria for MF) after initial reduction in spleen on ruxolitinib or discontinued for hematologic toxicities.	Change and percentage change in SVR as measured by magnetic resonance imaging [MRI] (computed tomography [CT] scan in subjects who are not candidates for MRI or when MRI is not readily available) at Week 24 when compared with baseline.
Secondary Objectives (Cohorts A and B)	**Secondary Endpoints**
To evaluate preliminary safety and tolerability of itacitinib alone.	Safety and tolerability through assessment of frequency, severity, and duration of adverse events (AEs); changes in clinical safety assessments; and changes in clinical laboratory parameters.
To evaluate preliminary safety and tolerability of itacitinib in combination with ruxolitinib.	
To evaluate preliminary efficacy of itacitinib alone or in combination with ruxolitinib on SVR from baseline at Week 12.	Change and percentage in SVR from baseline through Week 12 as measured by MRI (or CT scan in applicable subjects).
To evaluate preliminary efficacy of itacitinib alone or in combination with ruxolitinib on spleen length reduction from baseline at Week 12 and Week 24.	Change and percentage change on spleen length reduction from baseline through Week 12 and Week 24 as measured by palpation.
To evaluate preliminary efficacy of itacitinib alone or in combination with ruxolitinib with respect to MF symptoms at Week 12 and Week 24.	Change and percentage change in Total Symptom Score (TSS) from baseline through Week 12 and Week 24 as measured by the Myelofibrosis Symptom Assessment Form version 2.0 (MFSAF v2.0) symptom diary and by the Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF).
	Patient Global Impression of Change score at each visit where the variable is measured.
To evaluate preliminary efficacy of itacitinib using International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria.	Number of subjects with responses according to the 2013 IWG-MRT consensus criteria for treatment response.

Secondary Objectives (Cohorts A and B) (Cont'd)	Secondary Endpoints (Cont'd)
To assess the pharmacokinetics (PK) of itacitinib and ruxolitinib.	Calculation of the PK parameters such as AUC, CL/F, C_{max}, and t_{max} along with summarization of the observed concentration data by timepoint will be performed for both ruxolitinib and itacitinib.
[redacted]	

Overall Study Design:

This is an open-label Phase 2 study with 2 cohorts:

- **Cohort A**: MF subjects who are tolerating a ruxolitinib dose of less than 20 mg daily will receive a combination of the JAK1 inhibitor itacitinib at the dose of 200 mg once daily (QD) and the JAK1/2 inhibitor ruxolitinib.
- **Cohort B**: MF subjects who progressed after initial reduction in spleen with ruxolitinib treatment or discontinued for hematologic toxicities will receive treatment with JAK1 inhibitor itacitinib alone at the dose of 600 mg QD.

Subjects will continue study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment are met. Subjects who are receiving benefit will continue receiving study treatment until withdrawal criteria are met.

All subjects will be followed for safety (eg, reporting of AEs and serious AEs) 30 to 35 days after last dose of study treatment.

Study Population:

Male or female subjects aged 18 years or older who have been diagnosed with MF (either primary myelofibrosis [PMF] or secondary MF [post–polycythemia vera myelofibrosis {PPV-MF} or post–essential thrombocythemia myelofibrosis {PET-MF}]) and who can tolerate only less than 20 mg daily dose of ruxolitinib or subjects who either discontinued for hematological toxicities or progressed on ruxolitinib after initial reduction in spleen.

Key Inclusion Criteria:

Cohort A only

- Receiving ruxolitinib dose of less than 20 mg daily with no dose increase or no dose modification in the last 8 weeks before screening visit.

Cohort B only

- Must have had initial reduction in spleen on ruxolitinib treatment (response is defined by any spleen length or volume reduction, by palpation or MRI/CT assessment, from baseline while on previous ruxolitinib treatment per IWG-MRT ELN 2013 guidelines):
  - Followed by documented evidence of progression in spleen length or volume OR
  - Discontinued ruxolitinib for hematologic toxicities, after the initial reduction in spleen length or volume.

All subjects

- Men and women, aged 18 years or older.
- Confirmed diagnosis of PMF, PPV-MF, or PET-MF according to revised WHO 2016 criteria.
- Must have palpable spleen of $\geq$ 5 cm below the left subcostal margin on physical examination at the screening visit. (If spleen is not palpable due to body habitus, spleen enlargement must be documented by other means [eg, ultrasound or MRI] and study sponsor medical monitor be contacted for acceptance).
- ECOG performance status of 0, 1, or 2.
- Screening bone marrow biopsy specimen available or willingness to undergo a bone marrow biopsy at screening/baseline; willingness to undergo bone marrow biopsy at Week 24.
- Life expectancy of at least 24 weeks.
- Willingness to avoid pregnancy or fathering children based on the following criteria:
  - Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR $\geq$ 12 months of amenorrhea and at least 50 years of age).
  - Woman of childbearing potential who has a negative serum pregnancy test at screening and negative urinary test before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
  - Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.

Key Exclusion Criteria:

All subjects

- Lack of recovery from all toxicities from previous therapy (except ruxolitinib) to Grade 1 or better.
- Previous treatment with itacitinib or JAK1 inhibitors (JAK1/JAK2 inhibitor ruxolitinib is permitted).
- Inability to swallow food or any condition of the upper gastrointestinal tract that precludes administration of oral medications.
- Unwillingness to be transfused with blood components.
- Recent history of inadequate bone marrow reserve as demonstrated by the following:
  - Platelet count $< 50 \times 10^9$/L in the 4 weeks before screening or platelet transfusion within 8 weeks before screening.
  - Absolute neutrophil count levels $< 0.5 \times 10^9$/L in the 4 weeks before screening.
  - Peripheral blood blast count of > 10% at the screening or baseline hematology assessments.

- Inadequate liver function at screening and baseline visits as demonstrated by the following:
  - Direct bilirubin $\geq 2.0 \times$ the upper limit of laboratory normal (ULN). (NOTE: direct bilirubin may be assumed to be within limits if total bilirubin is $\leq 2.0 \times$ ULN).
  - Alanine aminotransferase or aspartate aminotransferase $> 2.5 \times$ ULN.
- Inadequate renal function at screening and baseline visits as demonstrated by creatinine clearance < 40 mL/min measured or calculated by Cockroft-Gault equation, or glomerular filtration rate < 40 mL/min/1.73 m^2 as calculated using the Modification of Diet in Renal Disease formula.
- Active bacterial, fungal, parasitic, or viral infection that requires therapy. Subjects with acute infections requiring treatment should delay screening/enrollment until the course of therapy has been completed and the event is considered resolved. Prophylactic antibiotics will be permitted.
- Evidence of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or risk of reactivation: HBV DNA and HCV RNA must be undetectable. Subjects cannot be positive for hepatitis B surface antigen or anti–hepatitis B core antibodies. Subjects who have positive anti-HBs as the only evidence of prior exposure may participate in the study provided that there is both 1) no known history of HBV infection and 2) verified receipt of hepatitis B vaccine.
- Known human immunodeficiency virus infection.
- Clinically significant or uncontrolled cardiac disease, including unstable angina; acute myocardial infarction within 6 months of Day 1 of study drug administration; New York Heart Association Class III or IV congestive heart failure; and arrhythmia requiring therapy unless approved by medical monitor/sponsor.
- Active invasive malignancy over the previous 2 years except treated basal or squamous carcinomas of the skin, completely resected intraepithelial carcinoma of the cervix, and completely resected papillary thyroid and follicular thyroid cancers. Subjects with malignancies with indolent behavior such as prostate cancer treated with radiation or surgery may be enrolled as long as they have a reasonable expectation to have been cured with the treatment modality received.
- Splenic irradiation within 6 months before receiving the first dose of itacitinib.
- Use of any prohibited concomitant medications.
- Active alcohol or drug addiction that would interfere with their ability to comply with the study requirements.
- Use of any potent/strong cytochrome P450 3A4 inhibitors within 14 days or 5 half-lives (whichever is longer) before the first dose of itacitinib or anticipated during the study.
- Use of concomitant treatment of fluconazole at a dose > 200 mg (for ruxolitinib subjects treated in Cohort A only).
- Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
- Currently breastfeeding or pregnant.
- Inability to comprehend or unwilling to sign the informed consent form.
- Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.

Itacitinib/Study Drug, Dosage, and Mode of Administration:

Itacitinib is formulated as 100 mg sustained-release tablet. Itacitinib will be administered orally QD in the morning on an outpatient basis as follows:

- **Cohort A only**: 200 mg QD, without regard to food, for the combination treatment with ruxolitinib.
- **Cohort B only**: 600 mg QD, without regard to food, for the monotherapy treatment.

Reference Therapy, Dosage, and Mode of Administration:

- **Cohort A only**: Ruxolitinib will be administered orally, twice daily (BID), approximately 12 hours apart using the stable dose of less than 20 mg daily established before entering the study.
- **Cohort B only**: Not applicable.

Study Schedule/Procedures:

Subjects will have a regularly scheduled study visit at screening, baseline, Day 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 and every 12 weeks thereafter if continuing on treatment, where assessments, including blood samples and spleen measurements, will be obtained. All laboratory parameters (serology, lipid profile, urinalysis, blood chemistry, hematology, and coagulation) will be assessed using local laboratories. Blood [redacted] PK samples will be collected and analyzed by the sponsor or sponsor's designee.

Additional laboratory assessments may be performed at investigator's discretion, including following changes in dose, or if laboratory parameters are at Grade 3 or Grade 4 levels based on the CTCAE v4.03.

Subjects will have an MRI of the upper and lower abdomen and pelvis to determine the spleen volume at baseline, at Week 12 and Week 24, and every 12 weeks thereafter. Computed tomography scan will be substituted for subjects who are not candidates for MRI or when MRI is not readily available. Patient Global Impression of Change questionnaire will be completed at each study visit from Week 4. Determination of spleen length below the left costal margin will be measured by palpation at each study visit using a flexible ruler.

Subjects will complete an electronic symptom diary (MFSAF v2.0) daily from baseline through the Week 24 visit (total of 25 weeks).

Subjects will complete the MPN-SAF at baseline; at Weeks 12 and 24; and every 12 weeks thereafter.

Estimated Duration of Participation:

Screening: Up to 21 days.

Baseline: 7 days before first dose of itacitinib.

Treatment: Begins with the first dose of itacitinib (Day 1). Treatment will continue as long as the regimen is tolerated and the subject does not meet discontinuation criteria.

Safety follow-up: 30 days to 35 days after the last dose of medication is taken.

It is estimated that an individual subject will participate for approximately 32 weeks.

Estimated Number of Subjects:

Approximately 21 subjects will be included in each dose cohort for a total of 42 subjects. Approximately 20 clinical sites will be used.

Principal Coordinating Investigator: TBD

Statistical Methods:

The primary endpoint of change and percentage change of SVR (as measured by MRI or CT) from baseline at Week 24 will be summarized by cohort. Within each cohort, the sign test will be used to evaluate median percentage of SVR and a 90% confidence interval for the median percentage SVR will be calculated using the exact binomial confidence interval method. If the percentage of SVR at Week 24 is normally distributed with mean 11.4 and standard deviation 14.5, the test has 85% power to indicate additional development is warranted with a sample size of 21 subjects per cohort. The percentage of SVR will be summarized descriptively at Week 12 by cohort.

Safety data, including laboratory values, AEs, and vital signs, will be summarized. Adverse events of special interest include Grade 4 thrombocytopenia, Grade 2 or higher anemia, and Grade 2 or higher hemorrhagic events, as measured by CTCAE v4.03.

Secondary efficacy endpoints for percentage change from baseline in 7-day MFSAF TSS and MPN-SAF TSS will be summarized at Week 12 and Week 24 by cohort, and 90% confidence intervals for the

median percentage change will be estimated. [redacted] Change and percentage change in spleen length from baseline as measured by palpation at each visit where the parameter is assessed through Week 24 will be tabulated by cohort with summary statistics. Patient Global Impression of Change will be summarized by visit. Subject data will be summarized by cohort and final titrated dose of itacitinib. Additional correlative analyses will be conducted comparing the distribution of percentage change in spleen volume, TSS scores, [redacted] to PGIC. [redacted]

Based on the primary endpoint of percentage change from baseline in spleen volume (by MRI/CT scan), further enrollment in a cohort will be terminated if 7 or more subjects within the cohort fail to illustrate SVR at Week 24. Subjects will have failed to illustrate spleen reduction if they either 1) discontinue before the Week 24 assessment or 2) have an SVR ≤ 0 at the Week 24 assessment.

Data Monitoring Committee:

Not applicable.

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LIST OF ABBREVIATIONS

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

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BAT	best available therapy
BID	twice daily
[redacted]	[redacted]
CFR	Code of Federal Regulations
CI	clinical improvement
C_{max}	maximum plasma concentration
CML	chronic myeloid leukemia
CR	complete remission
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DIPSS	Dynamic International Prognostic Scoring System
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELN	European LeukemiaNet
EOT	end of treatment
ET	essential thrombocythemia
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
[redacted]	[redacted]
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act of 1996

Abbreviation	Definition
HU	hydroxyurea
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
[redacted]	[redacted]
IN	Investigator Notification
INR	international normalized ratio
IPSS	International Prognostic Scoring System
IRB	institutional review board
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
IXRS	interactive voice/web response system
JAK	Janus kinase
LDL	low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MFSAF v2.0	Myelofibrosis Symptom Assessment Form version 2.0
MPN	myeloproliferative neoplasm
MPN-SAF	Myeloproliferative Neoplasm–Symptom Assessment Form
MRI	magnetic resonance imaging
NA	not applicable
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
[redacted]	[redacted]
PET-MF	post–essential thrombocythemia myelofibrosis
PGIC	Patient Global Impression of Change
PK	pharmacokinetic
PMF	primary myelofibrosis
PPV-MF	post–polycythemia vera myelofibrosis
PR	partial response
PRBC	packed red blood cell
PT	prothrombin time
PTT	partial thromboplastin time
PV	polycythemia vera
QD	once daily

Abbreviation	Definition
RA	rheumatoid arthritis
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reaction
SVR	spleen volume reduction
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
TPO	thrombopoietin
TSS	Total Symptom Score
TYK2	tyrosine kinase 2
ULN	upper limit of normal
WBC	white blood cells

1. INTRODUCTION

Itacitinib (INCB039110) represents a novel, potent, and selective inhibitor of the JAKs with selectivity for JAK1 with low *in vitro* affinity for JAK2 and is proposed for investigation and development for the treatment of MF. For a thorough discussion of the pharmacology of itacitinib, refer to the Investigator's Brochure (IB).

Ruxolitinib, a potent and selective inhibitor of the JAK family of protein tyrosine kinases, JAK1 and JAK2, is approved in multiple jurisdictions for MF, with variations on the specific indication language, and is currently in development for the treatment of MPNs, hematologic malignancies, and solid tumors. For a thorough discussion of the pharmacology of ruxolitinib (INCB018424), refer to the ruxolitinib prescribing information.

1.1. Background and Overview on Myelofibrosis

The classic MPNs include CML, PV, ET, and PMF. Myelofibrosis can present as a *de novo* disorder (PMF) or evolve secondarily from previous PV or ET (PPV-MF or PET-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 multiorgan extramedullary hematopoiesis most prominently involving the liver and spleen. Patients may experience debilitating symptoms (Mesa et al 2007, Mesa et al 2013a), 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 of MF is approximately 60 to 65 years, and the incidence of PMF has been estimated at 4 to 6 cases per 100,000 people in the United States (Stein et al 2015). Survival in MF varies with the presence or absence of specific risk factors. Analysis of risk factors over the past 20 years has resulted in a number of prognostic scoring systems (for a review, refer to Bose and Verstovsek 2015). A prognostic scoring system based on a time-dependent risk evaluation has been developed: the 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 (WBC count $> 25 \times 10^9$/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 hazards model. The approach showed that acquisition of anemia over time affects survival with a hazard ratio roughly double that of other parameters, and therefore anemia was assigned a score of 2, while the other 4 factors were assigned scores of 1. Four risk categories with nonoverlapping survival curves have been described (Table 1).

Table 1: Risk Categories

Total Risk Score	Risk Category	Median Survival (years)
0	Low	not reached
1 or 2	Intermediate-1	14.2
3 or 4	Intermediate-2	4
5 or 6	High	1.4

Although not included in the DIPSS, cytogenetic abnormalities in PMF, JAK V617F allele burden, mutations in exon 9 of the gene encoding CALR and mutations in the gene encoding the TPO receptor (MPL) have been examined for impact on DIPSS score, thrombotic risk, and overall survival and together are grouped as "driver" mutations. These mutations often coexist with several somatic mutations: genes for the epigenetic regulators EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit), ASXL1 (additional sex combs-like 1 transcriptional regulator, the splicing gene SRSF2 (serine/arginine-rich splicing factor), and the genes encoding the Krebs cycle enzymes isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2). These factors are combined into the newest prognostic scoring system, the genetics-based prognostic scoring system, which is currently being validated.

For the subset of patients who are younger (generally < 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 in MF, including HU, 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, can be poorly tolerated, and all have limited effectiveness in improving splenomegaly and constitutional symptoms. 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. Splenectomy, performed in approximately 10% of the patient cohort reported by Cervantes et al (2009), is associated with significant morbidity and mortality.

1.2. Role of JAK Pathway in Myelofibrosis

Within the recent years, it was discovered that approximately 95% of patients with PV and approximately 50% of patients with PMF and ET have a somatic gain-of-function mutation in the JAK2 gene resulting in substitution of phenylalanine for valine at position 617 (JAK2 V617F) within the pseudokinase domain of the encoded protein. Janus kinase 2 is one of 4 members of the JAK family along with JAK1, JAK3, and TYK2. The JAKs are responsible for transduction of cell signaling from Type I and II cytokine receptors families, because these receptors do not possess intrinsic kinase activity 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 that enable them to transduce intracellular signaling by phosphorylating and activating transcription factors called 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. Janus kinases associate with the intracellular domain of the Type I and II cytokine receptors in pairs, which may be homodimers (eg, 2 JAK2s) or heterodimers (eg, a JAK 1 and a JAK2). Erythropoietin, which is responsible for stimulating erythropoiesis, and TPO, which is responsible for stimulating thrombopoiesis, have been shown to signal only through receptors that use JAK2 homodimers. A large number of inflammatory mediators, such as IL-6, interferon γ, and IL-17, are known to signal primarily through receptors that use 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 may not exist. Regardless, it appears that the majority of patients with MF have overactivation of the JAK-STAT pathway. In MF, excessive cytokine signaling through both JAK1 and JAK2 have been observed both in patients harboring the JAK2 V617F mutation and in patients without known mutations. [redacted]

Ruxolitinib, a potent and selective inhibitor of JAK 1 and 2, is approved for use in patients with intermediate- or high-risk MF, including PMF, PPV-MF, and PET-MF. Registration studies showed improvement in spleen size, symptom burden, and overall survival with ruxolitinib use in this patient population (Harrison et al 2012, Cervantes et al 2013, Mesa et al 2013b, Verstovsek et al 2012, Verstovsek et al 2015, Vannucchi et al 2015). The primary AEs observed with ruxolitinib are thrombocytopenia and anemia; both were infrequently the cause of study discontinuation in a double-blind, placebo-controlled Phase III study, and both are due at least in part to JAK2-mediated myelosuppression. It is thus of interest to determine the overall efficacy and hematological limitations of a JAK1-selective inhibitor of the JAK family.

1.3. Product Information and Overview of Itacitinib

Itacitinib adipate, hereafter designated itacitinib, is an inhibitor of the JAK family of protein tyrosine kinases (JAKs) with selectivity for JAK1 and is proposed for the treatment of MPNs, including MF, solid tumors, inflammatory diseases, and B-cell malignancies.

1.3.1. Pharmacology

Itacitinib represents a novel, potent, and selective inhibitor of the JAKs with selectivity for JAK1. There are 4 known JAK family members, JAK1, JAK2, JAK3, and TYK2.

The pharmacology and additional details on toxicology of itacitinib are described in the IB. In brief, itacitinib potently inhibits JAK1 (IC_{50} = 3.6 nM) with 22- to > 500-fold selectivity compared with JAK2, JAK3, and TYK2, and it does not significantly inhibit a broad panel of approximately 60 other kinases. Itacitinib is potent (IC_{50} values 10-100 nM) in cytokine-driven cell-based assays, such as IL-2–stimulated phosphorylation of JAKs and STATs and IL-2–induced proliferation of primary human T cells. Itacitinib inhibits the growth of the cytokine-dependent cell line INA-6, this effect is not due to general cytotoxicity. Itacitinib potently inhibits the phosphorylation of STAT proteins and the production of proinflammatory factors (eg, IL-17, MCP-1) induced by cytokines such as IL-23 and IL-6 (IC_{50} ~30-100 nM). In contrast, itacitinib shows less inhibition in cell-based assays dependent on JAK2 (eg, TPO or prolactin-stimulated STAT phosphorylation) with IC_{50} approximately 1 μM or greater,

suggesting that itacitinib is JAK2-sparing in cells. In *in vivo* models of JAK-dependent malignancy, itacitinib impedes subcutaneous tumor growth of INA-6 cells expressing wild-type JAKs plasma concentrations well below those necessary to inhibit JAK2. Moreover, oral itacitinib improved splenomegaly in a JAK2 V617F–driven neoplasia model of MF.

Administration of itacitinib did not result in QT prolongation or cardiovascular effects. Adverse findings were noted only at high dose (1000 mg/kg) suggesting the primary toxicities are expected to be on-target and these observations are considered to be well beyond the needed safety margin compared to the therapeutic dose.

[redacted]

1.3.2. Nonclinical Drug Metabolism and Pharmacokinetics

In single-dose PK studies in rats, dogs, and monkeys, orally administered itacitinib was rapidly absorbed ($t_{max} \leq 2.0$ hours). The protein binding of itacitinib in plasma and serum from rats, dogs, and humans was moderate (unbound fraction of 29%-43%) and not dependent on itacitinib concentration.

Itacitinib has minimal penetration across the blood-brain barrier in rats. Protein binding in plasma and serum from rats, dogs, and humans was moderate, and the fraction unbound was independent of itacitinib concentration. In rats and dogs, excretion was rapid and complete after a single oral dose of 14C-INCB039110.

The major analyte present in plasma and urine from all species studied was parent compound. CYP3A4 is the major isozyme responsible for the metabolism of itacitinib. Itacitinib did not inhibit or induce CYP activity, suggesting a low potential for drug-drug interactions.

Preliminary PK analysis showed that following multiple-dose administration of itacitinib SR, itacitinib attained peak plasma concentrations with a median t_{max} of 1.89 hours to 3.78 hours. For increasing dose regimens between 100 mg BID and 200 mg BID, itacitinib plasma exposures (C_{max} and AUC) appeared to be dose proportional. The itacitinib AUC for 600 mg QD in subjects with PMF, PPV-MF, and PET-MF was comparable to that of 600 mg QD in subjects with stable, chronic plaque psoriasis.

Additional information on pharmacology, drug disposition, and nonclinical toxicology is available in the itacitinib IB.

1.3.3. Itacitinib Clinical Safety Summary

1.3.3.1. Clinical Studies in Patients

As of the data cutoff date (13 DEC 2016), 752 subjects have been exposed to itacitinib as monotherapy and/or in one of the following combinations:

- Itacitinib in combination with chemotherapeutic agents for the treatment of solid tumors.
- Itacitinib in combination with a novel PI3Kδ inhibitor for the treatment of lymphoid malignancies (INCB040093 or INCB050465).

- Itacitinib in combination with INCB050465 for the treatment of solid tumors.
- Itacitinib in combination with pembrolizumab for the treatment of solid tumors.
- Itacitinib in combination with epacadostat for the treatment of solid tumors.
- Itacitinib in combination with corticosteroids for the treatment of acute GVHD.

Of the subjects exposed to itacitinib, 493 subjects have been exposed to itacitinib monotherapy: 284 of these subjects were healthy volunteers and 209 subjects had underlying disease, such as RA (Study INCB 39110-201), chronic plaque psoriasis (Study INCB 39110-250), or MF (Study INCB 39110-230). Nine Phase 1, 3 Phase 1/2, and 5 Phase 2 clinical studies with itacitinib, including studies of itacitinib in combination with PI3Kδ inhibitors INCB040093 and INCB050465, have either been completed or are ongoing. Additional details regarding the study designs and primary endpoints of these studies are summarized in the itacitinib IB.

In the open-label Phase 2 study INCB 39110-230, the efficacy and safety of 3 dose levels of itacitinib, a potent and selective oral JAK1 inhibitor, were evaluated in patients with intermediate- or high-risk MF and a platelet count $\geq 50 \times 10^9$/L. Of 10, 45, and 32 subjects enrolled in the 100 mg BID, 200 mg BID, and 600 mg QD cohorts, respectively, 50.0%, 64.4%, and 68.8% completed Week 24. A $\geq$ 50% reduction in TSS was achieved by 35.7% and 28.6% of subjects in the 200 mg BID cohort and 32.3% and 35.5% in the 600 mg QD cohort at Week 12 (primary endpoint) and Week 24, respectively. By contrast, 2 subjects (20%) in the 100 mg BID cohort had $\geq$ 50% TSS reduction at Weeks 12 and 24. For the 200 mg BID and 600 mg QD cohorts, the median SVR at Week 12 were 14.2% and 17.4%, respectively. Furthermore, 21 of 39 subjects (53.8%) who required RBC transfusions during the 12 weeks preceding treatment initiation achieved a $\geq$ 50% reduction in the number of RBC units transfused during study Weeks 1 through 24. Only 1 subject discontinued for Grade 3 thrombocytopenia. Nonhematologic AEs were largely Grade 1 or 2; the most common was fatigue. Treatment with itacitinib resulted in clinically meaningful symptom relief, modest SVR, and limited myelosuppression (Mascarenhas et al 2016). Although the primary efficacy endpoints were at 12 and 24 weeks postenrollment, subjects were allowed to continue in the study as long as they are experiencing clinical benefit in the investigator's opinion. As of the data cutoff, 14 subjects are still receiving the study drug.

1.3.4. Ruxolitinib Clinical Safety Summary

1.3.4.1. Clinical Safety Data

Based on the randomized Phase 3 COMFORT I and II and RESPONSE studies, ruxolitinib is indicated for the treatment of intermediate or high-risk MF, including PMF, PPV-MF, PET-MF, and PV patients.

The most common hematological adverse reactions based on these studies are myelosuppression (thrombocytopenia, anemia, and neutropenia) and increase of ALT/AST, hypercholesterolemia and hypertriglyceridemia. Nonhematologic adverse reactions are bruising, dizziness, headache, urinary tract infection, and weight gain.

The AE profile of the compound has been assessed in more than 370 healthy volunteers, in subjects with various degrees of renal (n = 32) or hepatic (n = 24) impairment, and in subjects

with RA (n = 59) receiving ruxolitinib: AEs were, in general, mild and resolved without interventions.

A thorough QT study was conducted in 50 healthy subjects. There was no indication of a QT/QTc-prolonging effect of ruxolitinib in single doses up to a supratherapeutic dose of 200 mg, indicating that ruxolitinib has no effect on cardiac repolarization.

For complete information on ruxolitinib, refer to the prescribing information.

1.3.4.2. Ruxolitinib Indications

The FDA approved ruxolitinib in the United States under the tradename, JAKAFI®, in NOV 2011 for the treatment of patients with intermediate- or high-risk MF, including PMF, PPV-MF, and PET-MF. This approval was based on the demonstration in 2 Phase 3 studies (COMFORT-I and COMFORT-II) that treatment with ruxolitinib in all 3 subtypes of MF (PMF, PPV-MF, and PET-MF) resulted in rapid, significant, and durable reduction in spleen size and improvement in disease-related symptoms when compared with either placebo in COMFORT-I or BAT in COMFORT-II. On 04 DEC 2014, ruxolitinib was approved for the treatment of patients with PV who have had an inadequate response to or are intolerant of HU. This approval was based on data from the pivotal Phase 3 RESPONSE trial, which was conducted under a Special Protocol Assessment and demonstrated superior hematocrit control and reductions in spleen volume compared with BAT. In addition, a greater proportion of subjects in the ruxolitinib treatment group achieved complete hematologic remission, which was defined as achieving hematocrit control and lowering platelet and WBC counts.

1.4. Study Rationale

Despite statistically significant improvements in signs and symptoms of MF and overall survival rates, compared with either placebo or BAT demonstrated in the registration studies, there are patients for whom ruxolitinib monotherapy fails to provide adequate and/or sustained response.

A subgroup analysis of the ruxolitinib COMFORT-1 study, did not identify subgroups (age, MF subtype, IPSS risk group, baseline ECOG score, baseline platelet or hemoglobin level, baseline spleen volume quartile, baseline symptom burden quartile or presence/absence of V617F mutation) that did not benefit from ruxolitinib therapy (Verstovsek et al 2013); however a subgroup of subjects were only able to sustain a dose of ruxolitinib < 10 mg BID which has been identified to be less active than the dose ≥ 10mg BID as shown in COMFORT I and II.

This small subgroup of subjects (n = 5) still experienced some percentage of reduction in their spleen volume along with minimal changes in their symptoms score. It is possible that for those subjects, declining hemoglobin or platelet counts associated with ruxolitinib use preclude maintenance at optimal ruxolitinib dosages. As 10 mg BID was an effective dose in the COMFORT-I and -II studies, a lower dose of ruxolitinib might need to be associated with another therapy for efficacy for those subjects in need of treatment maintenance. [redacted] Little or no JAK2 inhibition is observed at the low dose of itacitinib of 200 mg QD (see IB). In the study INCB 39110-230, itacitinib at the dose of 100 mg BID (200 mg per day) demonstrated some

efficacy on SVR and some degree of symptoms improvement with limited hematological and nonhematological AE rate, although this dose was not maximally effective.

Some patients treated with ruxolitinib have required interruptions in therapy for either hematological toxicities or have experienced a nondurable spleen response and discontinued ruxolitinib due to disease progression. Itacitinib may represent a second-line therapy option for these patients with good performance status. Itacitinib at the dose of 600 mg QD may demonstrate good tolerability and efficacy on symptoms improvement and some SVR for these patients.

Thus, this study is proposing to administer itacitinib in 2 distinct cohorts:

- Cohort A subjects will receive a combination of the JAK1 inhibitor itacitinib at the dose of 200 mg QD and the JAK 1/2 inhibitor ruxolitinib, and
- Cohort B subjects will receive the JAK1 inhibitor itacitinib as monotherapy at the dose of 600 mg QD.

The study will thus evaluate the effects of selective JAK1 inhibition in MF, in combination with a low dose of ruxolitinib (less than 20 mg daily) or as a monotherapy after ruxolitinib treatment in subjects who initially had some reduction in spleen followed by progression or discontinued for hematologic toxicities. The impact on spleen size and MF symptoms (using palpation and MRI or CT and using symptom diary, respectively) along with the possible benefits of lowered anemia and thrombocytopenia incidence will be assessed.

1.5. Potential Risks and Benefits of the Treatment Regimen

1.5.1. Risks Related to Itacitinib

Clinical experience with itacitinib as of 13 DEC 2016 is based on administration to 777 safety evaluable subjects. This population includes 493 subjects who received itacitinib as monotherapy, including healthy subjects (n = 284) and subjects with MF (n = 87), chronic plaque psoriasis (n = 38), and RA (n = 84). Also, 64 subjects with solid tumors received itacitinib in combination with chemotherapy; 78 subjects with lymphoid malignancies received itacitinib in combination with the PI3Kδ inhibitor, INCB040093; 38 subjects with solid tumors or lymphoid malignancies received itacitinib in combination with pembrolizumab; 40 subjects with solid tumors received itacitinib in combination with epacadostat; and 29 subjects with aGVHD disease received itacitinib in combination with corticosteroids. Additional details on each of these studies can be found in the itacitinib IB.

Adverse events that have been reported by more than 5% of healthy subjects receiving itacitinib in an individual study included fatigue, headache, neutropenia, nausea, contact dermatitis, ecchymosis, reticulocyte count decreased, excoriation, and nasal congestion.

Because of the potential for myelosuppression, subjects will have hematologic parameters closely monitored during clinical studies. If there are clinically relevant declines in hematology parameters, then therapy may be interrupted until resolution or discontinuation. As itacitinib also has the potential to cause WBC margination (ie, a transient decrease in ANC), assessment of hematology parameters should be performed before study drug administration and at all applicable study visits.

Adverse events reported by more than 10% of subjects in the MF study included anemia, fatigue, thrombocytopenia/platelet count decreased, upper respiratory tract infection, nausea, constipation, diarrhea, cough, peripheral edema, pyrexia, dyspnea, dizziness, pain in extremity, night sweats, abdominal pain, arthralgia, contusion, headache, pruritus, and vomiting. The only adverse event reported by more than 10% of itacitinib-treated subjects with an inflammatory condition was nasopharyngitis in a psoriasis study; there were no TEAEs reported by more than 10% of subjects with RA.

1.5.2. Risks Related to Ruxolitinib

The safety of ruxolitinib was assessed in 617 subjects in 6 clinical studies with a median duration of follow-up of 10.9 months, including 301 subjects with MF in 2 Phase 3 studies. In a double-blind randomized, placebo controlled study of ruxolitinib, among the 155 subjects treated with ruxolitinib, the most frequent adverse drug reactions were thrombocytopenia and anemia. Thrombocytopenia, anemia, and neutropenia are dose-related effects. The most frequent nonhematologic adverse reactions were bruising, dizziness, and headache.

Some symptoms such as infections with herpes zoster or multifocal leukoencephalopathy (PML), symptom exacerbation following interruption or discontinuation of treatment with ruxolitinib, and nonmelanoma skin cancer have occurred.

For a description of the full risks of ruxolitinib, refer to the prescribing information.

1.5.3. Risks for the Combination of Itacitinib and Ruxolitinib

Inhibition of JAK1 and JAK2 by ruxolitinib is associated with a potential risk of developing serious bacterial, mycobacterial, fungal, and viral infections. It is not known whether inhibition primarily of JAK1, such as with itacitinib, will be associated with increased risk of infections. Subjects with active serious infections will not be allowed to enroll in the study. Investigators should carefully observe subjects receiving itacitinib for signs and symptoms of infections and initiate appropriate treatment.

1.5.4. Potential Benefits of Itacitinib and Ruxolitinib

1.5.4.1. Itacitinib Potential Benefits

Janus kinase inhibition by itacitinib may result in reductions in spleen size and symptoms.

1.5.4.2. Ruxolitinib Potential Benefit

The clinical efficacy results of ruxolitinib that have emerged from the ongoing studies 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 5 years therapy), these positive effects have been maintained, given the closely related pathophysiology of MPNs.

2. STUDY OBJECTIVES AND ENDPOINTS

Study objectives and endpoints are presented in Table 2.

Table 2: Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To evaluate preliminary efficacy of itacitinib on SVR from baseline at Week 24 in the 2 following cohorts of MF subjects: • **Cohort A**: in combination in subjects with ruxolitinib low dose (less than 20mg daily). • **Cohort B**: as monotherapy in subjects who progressed (per revised ELN 2013 response criteria for MF) after initial reduction in spleen on ruxolitinib or discontinued for hematologic toxicities.	Change and percentage change in SVR as measured by MRI (CT scan in subjects who are not candidates for MRI or when MRI is not readily available) at Week 24 when compared with baseline.
Secondary Objectives (Cohorts A and B)	**Secondary Endpoints**
To evaluate preliminary safety and tolerability of itacitinib alone.	Safety and tolerability through assessment of frequency, severity, and duration of AEs; changes in clinical safety assessments; and changes in clinical laboratory parameters.
To evaluate preliminary safety and tolerability of itacitinib in combination with ruxolitinib.	
To evaluate preliminary efficacy of itacitinib alone or in combination with ruxolitinib on SVR from baseline at Week 12.	Change and percentage in SVR from baseline through Week 12 as measured by MRI (or CT scan in applicable subjects).
To evaluate preliminary efficacy of itacitinib alone or in combination with ruxolitinib on spleen length reduction from baseline at Week 12 and Week 24.	Change and percentage change on spleen length reduction from baseline through Week 12 and Week 24 as measured by palpation.
To evaluate preliminary efficacy of itacitinib alone or in combination with ruxolitinib with respect to MF symptoms at Week 12 and Week 24.	Change and percentage change in TSS from baseline through Week 12 and Week 24 as measured by the MFSAF v2.0 symptom diary and by the MPN-SAF.
	PGIC score at each visit where the variable is measured.
To evaluate preliminary efficacy of itacitinib using IWG-MRT criteria.	Number of subjects with responses according to the 2013 IWG-MRT consensus criteria for treatment response.
To assess the PK of itacitinib and ruxolitinib.	Calculation of the PK parameters such as AUC, CL/F, C_{max}, and t_{max} along with summarization of the observed concentration data by timepoint will be performed for both ruxolitinib and itacitinib.

Table 2: Study Objectives and Endpoints (Continued)

3. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

3.1. Subject Inclusion Criteria

A subject who meets all of the following criteria may be included in the study:

Cohort A only

1. Receiving ruxolitinib dose of less than 20 mg daily with no dose increase or no dose modification in the last 8 weeks before screening visit.

Cohort B only

2. Must have had initial reduction in spleen on ruxolitinib treatment (response is defined by any spleen length or volume reduction, by palpation or MRI/CT assessment, from baseline while on previous ruxolitinib treatment per IWG-MRT ELN 2013 guidelines, Appendix B):
    a. Followed by documented evidence of progression in spleen length or volume OR
    b. Discontinued ruxolitinib for hematologic toxicities, after the initial reduction in spleen length or volume.

All subjects

3. Men and women, aged 18 years or older.
4. Confirmed diagnosis of PMF, PPV-MF, or PET-MF according to revised WHO 2016 criteria (Appendix A).

5. Must have palpable spleen of ≥ 5 cm below the left subcostal margin on physical examination at the screening visit (if spleen is not palpable due to body habitus, spleen enlargement must be documented by other means [eg, ultrasound or MRI] and study sponsor medical monitor be contacted for acceptance).
6. ECOG performance status of 0, 1, or 2.
7. Screening bone marrow biopsy specimen available or willingness to undergo a bone marrow biopsy at screening/baseline; willingness to undergo bone marrow biopsy at Week 24.
8. Life expectancy of at least 24 weeks.
9. Willingness to avoid pregnancy or fathering children based on the following criteria (Appendix G):
    a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 50 years of age).
    b. Woman of childbearing potential who has a negative serum pregnancy test at screening and negative urinary test before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
    c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.

3.2. Subject Exclusion Criteria

A subject who meets any of the following criteria will be excluded from the study:

1. Lack of recovery from all toxicities from previous therapy (except ruxolitinib) to Grade 1 or better.
2. Previous treatment with itacitinib or JAK1 inhibitors (JAK1/JAK2 inhibitor ruxolitinib is permitted).
3. Inability to swallow food or any condition of the upper gastrointestinal tract that precludes administration of oral medications.
4. Unwillingness to be transfused with blood components.
5. Recent history of inadequate bone marrow reserve as demonstrated by the following:
    a. Platelet count < 50×10^9/L in the 4 weeks before screening or platelet transfusion within 8 weeks before screening.
    b. ANC levels < 0.5×10^9/L in the 4 weeks before screening.
    c. Peripheral blood blast count of > 10% at the screening or baseline hematology assessments.

6. Inadequate liver function at screening and baseline visits as demonstrated by the following:
   a. Direct bilirubin $\geq 2.0 \times$ ULN. (NOTE: direct bilirubin may be assumed to be within limits if total bilirubin is $\leq 2.0 \times$ ULN).
   b. ALT or AST $> 2.5 \times$ ULN.
7. Inadequate renal function at screening and baseline visits as demonstrated by creatinine clearance < 40 mL/min measured or calculated by Cockroft-Gault equation, or glomerular filtration rate < 40 mL/min/1.73 m^2 as calculated using the Modification of Diet in Renal Disease formula.
8. Active bacterial, fungal, parasitic, or viral infection that requires therapy. Subjects with acute infections requiring treatment should delay screening/enrollment until the course of therapy has been completed and the event is considered resolved. Prophylactic antibiotics will be permitted.
9. Evidence of HBV or HCV infection or risk of reactivation: HBV DNA and HCV RNA must be undetectable. Subjects cannot be positive for hepatitis B surface antigen or anti–hepatitis B core antibodies. Subjects who have positive anti-HBs as the only evidence of prior exposure may participate in the study provided that there is both 1) no known history of HBV infection and 2) verified receipt of hepatitis B vaccine.
10. Known human immunodeficiency virus infection.
11. Clinically significant or uncontrolled cardiac disease, including unstable angina; acute myocardial infarction within 6 months of Day 1 of study drug administration; New York Heart Association Class III or IV congestive heart failure; and arrhythmia requiring therapy unless approved by medical monitor/sponsor.
12. Active invasive malignancy over the previous 2 years except treated basal or squamous carcinomas of the skin, completely resected intraepithelial carcinoma of the cervix, and completely resected papillary thyroid and follicular thyroid cancers. Subjects with malignancies with indolent behavior such as prostate cancer treated with radiation or surgery may be enrolled as long as they have a reasonable expectation to have been cured with the treatment modality received.
13. Splenic irradiation within 6 months before receiving the first dose of itacitinib.
14. Use of any prohibited concomitant medications.
15. Active alcohol or drug addiction that would interfere with their ability to comply with the study requirements.
16. Use of any potent/strong cytochrome P450 3A4 inhibitors within 14 days or 5 half-lives (whichever is longer) before the first dose of itacitinib or anticipated during the study.
17. Use of concomitant treatment of fluconazole at a dose > 200 mg (only for subjects treated in Cohort A with ruxolitinib).
18. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
19. Currently breastfeeding or pregnant.

20. Inability to comprehend or unwilling to sign the ICF.
21. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful.
22. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.

3.3. Subjects Who Fail to Meet Screening Criteria

A subject who has a laboratory test result, vital sign assessment, or ECG finding that does not satisfy the entrance criteria may have the tests 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 they must be completed within the 3-week screening period (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. If the laboratory tests cannot be performed within the screening period, if the retests do not meet the entrance criteria, or if the subject's medical condition has changed significantly during the screening period such that inclusion/exclusion criteria are no longer met, the subject will be 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 within the 3-week timeframe. If the subject and investigator agree to rescreening, then 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 rescreened for participation in the study (except bone marrow biopsy if already performed at screening). An individual subject may only rescreen once for the study.

If all screening activities cannot be completed during the screening period because of an event unrelated to a medical finding (for example, scheduling difficulties for MRI), then the 21-day screening period may be extended to as much as 42 days, with the subject retaining the original subject number. A repeat of screening tests for hematology and blood chemistry may be necessary to determine eligibility.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label Phase 2 study with 2 cohorts:

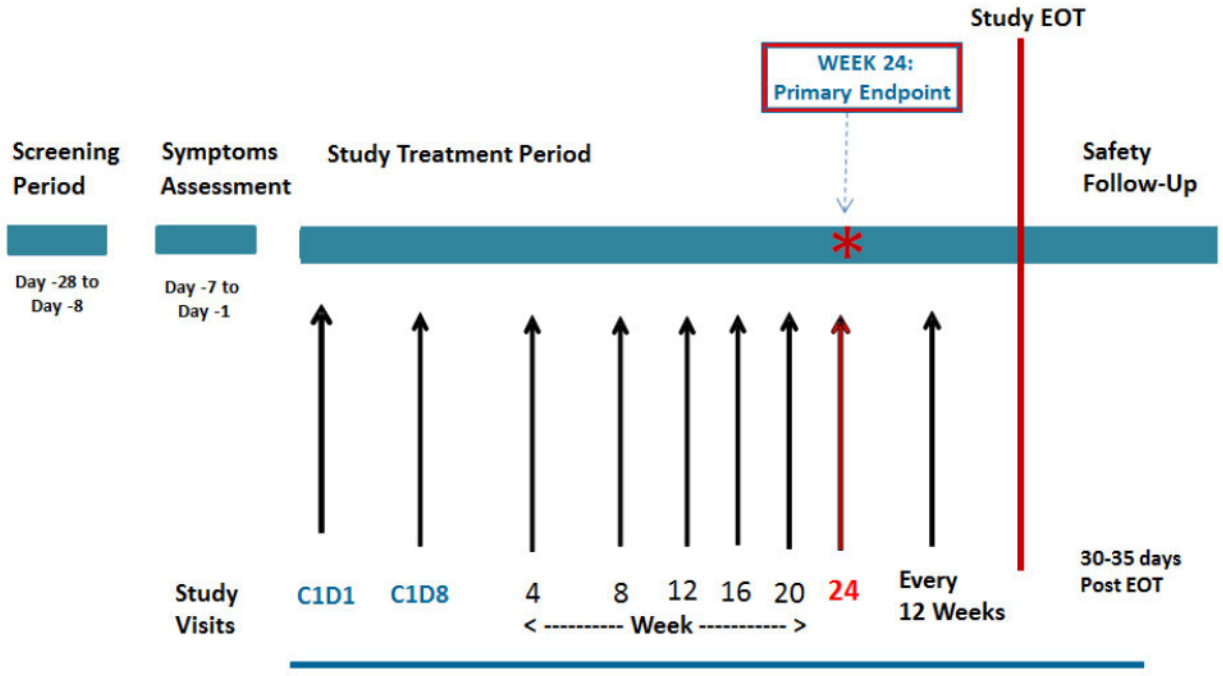
- **Cohort A**: MF subjects who are tolerating a ruxolitinib dose of less than 20 mg daily with no dose increase or no dose modification in the last 8 weeks before screening visit will receive a combination of the JAK1 inhibitor itacitinib at the dose of 200 mg QD and the JAK 1/2 inhibitor ruxolitinib.
- **Cohort B**: MF subjects who, after an initial reduction in spleen with ruxolitinib treatment, progressed or discontinued for hematologic toxicities, will receive treatment with JAK1 inhibitor itacitinib alone at the dose of 600 mg QD.

Subjects will continue study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other Protocol-specified criteria to stop treatment are met. Subjects who are receiving benefit from the therapy will continue receiving study treatment until withdrawal criteria are met.

All subjects will be followed for safety 30 to 35 days after the last dose of study treatment (eg, reporting of AEs and SAEs).

The overall study design is shown in Figure 1.

Figure 1: Study Design



4.2. Measures Taken to Avoid Bias

This is an open-label study; no comparisons will be made between subjects or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made.

4.3. Number of Subjects

Approximately 21 subjects will be included in each dose cohort for a total of 42 subjects.

4.4. Duration of Treatment and Subject Participation

After signing the ICF, subject study participation is estimated to average approximately 32 weeks per individual subject, exclusive of long-term follow-up period:

- **Screening period** (Day -28 to Day -8): Up to 21 days.
- **Baseline (pretreatment) period** (Day -7 to Day -1): 7 days before the first dose of itacitinib (required for all eligible subjects to complete the daily symptom diary for 7 days before the first dose of study medication).
- **Treatment period** (starts at Day 1 through EOT): Begins with the first dose of itacitinib (Day 1). Treatment will continue as long as the regimen is tolerated and the subject does not meet discontinuation criteria.
- **Safety follow-up period**: 30 to 35 days after the last dose of itacitinib is taken.

4.5. Overall Study Duration

The study will begin when the first subject enters screening, and the end of the study will occur when all subjects have completed treatment or discontinued study drug and have completed applicable follow-up assessments. Individual subject participation is expected to average 32 weeks per individual subject.

4.6. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the institutional review board (IRB)/independent ethics committee (IEC) in writing of the study's completion or early termination, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively, if required by regulatory decision. If the study is terminated prematurely, then the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Each subject will be identified in the study by a subject ID number, which is a combination of the site ID and subject number (see Section 7.2).

Enrollment will be controlled by an IXRS.

Study sites will register study subjects in the IXRS in order to receive a subject number and treatment allocation.

All subject numbers will be 6 digits; the first 3 digits will be the site number, and the last 3 digits will be the subject's number. This subject number will be maintained throughout the study and will not be reassigned. Subjects who withdraw consent or discontinue from the study after being assigned a subject number will retain their initial number.

Site staff will contact the IXRS to obtain the initial study drug assignment. Refer to the IXRS manual for detailed information.

If a subject is mistakenly given a bottle of study drug that is not the bottle assigned by the IXRS, then the IXRS help desk must be notified immediately. The reason for the misallocation of the study drug must be documented by the study site and reported to the IRB/IEC.

For subjects who signed an ICF but are not allocated and for subjects who are allocated but were not treated, refer to the eCRF Completion Guidelines for instruction on which eCRFs to complete.

5.1.2. Randomization and Blinding

Not applicable.

5.2. Study Drug

5.2.1. Itacitinib

5.2.1.1. Description and Administration

5.2.1.1.1. Cohort A subjects

Itacitinib will be self-administered as a 200 mg QD oral treatment in the form of 100 mg tablets, in addition to their current ruxolitinib treatment. Doses of itacitinib should be self-administered without regards to food. Note that subjects must be instructed to withhold the morning dose of itacitinib until reaching the clinic for each study visit where dose administration will occur.

5.2.1.1.2. Cohort B subjects

Itacitinib will be self-administered as a 600 mg QD oral treatment in the form of 100 mg tablets. Note that subjects must be instructed to withhold the morning dose of itacitinib until reaching the clinic for each study visit where dose administration will occur.

5.2.1.2. Supply, Packaging, and Labeling

Itacitinib will be provided as 100 mg SR tablets packaged in high-density polyethylene bottles. All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

5.2.2. Ruxolitinib

5.2.2.1. Description and Administration

5.2.2.1.1. Cohort A subjects

Ruxolitinib will be self-administered as an oral treatment at the stable dose of less than 20 mg daily established before entering the study.

Doses of ruxolitinib should be self-administered approximately 12 hours apart without regard to food.

Note that subjects must be instructed to withhold the morning dose of ruxolitinib until reaching the clinic for each study visit where dose administration will occur (see Section 6.3).

5.2.2.1.2. Cohort B subjects

Not applicable.

5.2.2.2. Supply, Packaging, and Labelling

Refer to the ruxolitinib prescribing information for supply, packaging, and labeling information.

5.2.3. Storage

The bottles of tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F).

The subject must be instructed in the handling of study drugs as follows:

- To store study drugs at room temperature.
- To only remove from the bottle of itacitinib or ruxolitinib the number of tablets needed at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- To report any missed doses at the next study visit.
- If the subject vomits after taking study drug(s), then the subject should not take another dose.

- If a dose of study drug itacitinib is missed by more than 8 hours, then that dose should be skipped, and the next scheduled dose taken at the usual time, except on Week 2 Day 8 for PK sample management. (For Cohort A subjects, ruxolitinib should be taken BID every 12 hours but no less than 8 hours apart).
- To keep study drug in a safe place and out of reach of children.
- To bring all used and unused study drug kits to the site at each visit.

5.3. Treatment Compliance

Compliance with all study-related treatments should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with itacitinib will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Subjects will be instructed to bring all study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

5.4. Treatment Modifications: Increases, Decreases, and Interruptions

5.4.1. Dose Increases for Inadequate Efficacy

For Cohort A and Cohort B, itacitinib will be given at a fixed starting dose (200 mg or 600 mg QD), and no increase will be allowed for inadequate efficacy.

5.4.2. Dose Modification for Toxicity

Adverse event data and laboratory data should be reviewed by the investigator with the subject (either in person or by telephone or email) at least weekly. Data will also be monitored by the sponsor on an ongoing basis in order to observe any emerging trends. Laboratory data should be used to guide dose modifications for individual subjects as described in this section.

5.4.2.1. Laboratory Findings That Require Dose Modification

The goal of the dose titration is to administer the highest dose that can be tolerated while maintaining the following specific safety parameters:

1. Platelet counts should remain above 35×10^9/L (50×10^9/L is desirable).
2. ANC should remain $\geq 0.5 \times 10^9$/L.
3. ALT, AST, bilirubin, and creatinine values should not exceed Grade 3.
4. The subject should not experience new or worsening anemia. For the purposes of this Protocol, new or worsening anemia is defined as follows:
   a. For subjects who are transfusion-dependent* at baseline:
      – Received the same total number of packed RBC (PRBC) units transfused between study start Day 1 through Day 42 as was observed during the 12 weeks before study start; OR

- An increase by more than 50% in total number of PRBC units compared with the 12 weeks before the study start.

b. For subjects who are transfusion-independent** at baseline:

- A decline in hemoglobin of at least 2 g/dL to a level < 8.0 g/dL (not resulting from a bleed caused by acute trauma), if confirmed by a repeat laboratory assessment within 7 days without intervening change in dose, use of an erythropoiesis stimulant, or receipt of a transfusion.

* Baseline transfusion-dependent is defined as transfusions of at least 6 units of PRBCs in the 12 weeks before study enrollment, or a hemoglobin level of < 8.5 g/dL, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days before study enrollment.

** Subjects not meeting the definition of transfusion-dependent at baseline are considered transfusion-independent.

5. Additionally, significant AEs or laboratory abnormalities other than those specified may precipitate a dose adjustment or interruption if judged by the investigator to be at least possibly related to study drug.

5.4.2.2. Permitted Dose Levels

Permitted dose levels are only those shown in Table 3.

Table 3: Permitted Dose Levels by Cohort

	Dose Level 1	Dose Level 2	Dose Level 3	Dose Level 4
Cohort A	200 mg QD	100 mg QD	Interrupt	N/A
Cohort B	600 mg QD	300 mg QD	200 mg QD	Interrupt

5.4.2.3. Dose Adjustment Guidelines and Managing Toxicity

Hematologic or blood chemistry findings may result in mandatory reductions or interruptions in itacitinib administration as shown in Table 4. Guidelines are provided for dose reductions, interruptions, restarts, and re-escalations in order to provide consistency in the dose titration strategy; however, not all possible cases may be anticipated by these guidelines. The investigator may use a more cautious approach to dose interruption, restart, or re-escalation if deemed in the subject's best interest, but may not use doses that exceed the guidelines described here unless approved by the medical monitor.

In general, toxicities are to be managed by dose reductions or interruptions. Medications may be used to manage emerging toxicities if needed; however, please see Sections 5.6.2 and 5.6.3 for restricted and prohibited medications. Erythropoietin is not allowed during the study. Granulocyte growth factors are not allowed while study medication is being administered but may be used for severe neutropenia at the investigator's discretion while study medication is interrupted.

Dose decisions should be made in conjunction with the sponsor's medical monitor when special cases exist. These guidelines could be revised based on emerging safety data. The sponsor will provide any relevant safety updates to the investigator.

Table 4: Dose Interruptions or Reductions for Toxicity

Laboratory Finding or Adverse Event	Action Taken with Itacitinib Dose	Required Duration of Dose Reduction or Interruption
COHORT A		Restart or re-escalation is permitted after ≥ 2 weeks IF:
	Start: Dose Level 1 **First Reduction: Dose Level 2**	↓
Platelet count 25 to < 35 × 10^9/L	Reduce to or maintain Dose Level 2.	Platelets recover to ≥ 50 × 10^9/L on 2 consecutive measures ≥ 7 days apart.
Platelet count < 25 × 10^9/L	Interrupt dose.	Platelets stabilize at ≥ 35-50 × 10^9/L on 2 consecutive measures ≥ 7 days apart (restart allowed only at Dose Level 2) OR Platelets recover to 50 × 10^9/L on 2 consecutive measures ≥ 7 days apart.
ANC < 0.5 × 10^9/L	Interrupt dose.	ANC recovers to ≥ 0.5 × 10^9/L on 2 consecutive measures ≥ 7 days apart.
Protocol-defined anemia	Reduce 1 level from current dose.	Hemoglobin stabilized for at least 4 weeks at ≥ 9 g/dL.
Confirmed Grade 4[a] increase in ALT, AST, bilirubin, or creatinine	Interrupt dose.	Laboratory abnormality resolves to Grade 2 or better.
Other nonhematologic toxicities	Study drug may be interrupted at the discretion of the investigator.	Consult sponsor's medical monitor before restarting.
COHORT B		Restart or re-escalation is permitted after ≥ 2 weeks IF:
	Start: Dose Level 1 **First Reduction: Dose Level 2** **Second Reduction: Dose Level 3**	↓
Platelet count 25 to < 35 × 10^9/L	Reduce 1 level from current dose OR maintain dose if at Dose Level 3.	Platelets recover to ≥ 50 × 10^9/L on 2 consecutive measures ≥ 7 days apart.
Platelet count < 25 × 10^9/L	Interrupt dose.	Platelets stabilize at ≥ 35-50 × 10^9/L on 2 consecutive measures ≥ 7 days apart (restart permitted only at Dose Level 3) OR Platelets recover to ≥ 50 × 10^9/L on 2 consecutive measures ≥ 7 days apart.
ANC < 0.5 × 10^9/L	Interrupt dose.	ANC recovers to ≥ 0.5 × 10^9/L on 2 consecutive measures ≥ 7 days apart.
Protocol-defined anemia	Reduce 1 level from current dose.	Hemoglobin stabilized for at least 4 weeks at ≥ 9 g/dL.
Confirmed Grade 4[a] increase in ALT, AST, bilirubin, or creatinine	Interrupt dose.	Laboratory abnormality resolves to Grade 2 or better.
Other nonhematologic toxicities	Study drug may be interrupted at the discretion of the investigator.	Consult sponsor's medical monitor before restarting.

[a] According to the CTCAE v4.03.

5.4.2.4. Guidelines for Dose Restart or Re-escalation

It is recommended that any laboratory findings or AEs precipitating a dose decrease or interruption be monitored at least twice weekly until recovered. The dose interruption or reduction should be at least 2 weeks in duration, after which study drug may be rechallenged (ie, restarted or re-escalated) IF the criterion shown in Table 4 has been met.

The rechallenge may utlize the dose that precipitated the reduction or interruption, unless otherwise specified in Table 4. If recovery is prolonged or the abnormality is very pronounced, consider rechallenging at the next lower dose, if one is available. The decision to rechallenge at the dose precipitating the event or at a lower available dose level should depend on the duration and severity of the abnormality; discussion with the medical monitor is recommended. In the case that rechallenge is conducted at a decreased dose, the dose may be re-escalated subsequently (after ≥ 2 weeks) if safety parameters permit.

Any given dose may be rechallenged a maximum of twice. Subsequently, any rechallenge must utilize the next lower dose for that cohort (Table 3). (Exceptions may be granted by the sponsor's medical monitor if the precipitating events are separated by long periods of stable counts.) If the lowest allowable dose has been rechallenged twice and is found to be not tolerated, OR if the study drug cannot safely be restarted at the lowest available dose level within 21 days, the subject should be withdrawn from the study (see Section 5.5.1)

5.4.3. Interruption of Ruxolitinib (Cohort A Only)

Dose reductions of ruxolitinib to daily doses below 5 mg BID are not permitted and will result in the discontinuation of the subject from the study. All changes in dose should be recorded in the eCRF, and the subject should be notified by phone with written follow-up in cases where laboratory data subsequent to a study visit indicate that a dose change is required.

Dose modification or temporary interruption (for no more than 8 weeks) of ruxolitinib for safety reasons is at the discretion of the investigator with approval from the medical monitor.

5.5. Withdrawal of Subjects From Study Treatment

5.5.1. Withdrawal Criteria

Subjects **must** be withdrawn from study treatment for the following reasons:

- If toxicity requiring itacitinib interruption is not resolved sufficiently to permit study drug administration to resume with 21 days.
- Treatment with itacitinib is interrupted for more than 21 days for any reason other than toxicity.
- If the lowest allowable dose (based on cohort) has been rechallenged twice and was not tolerated.
- Cohort A: Treatment with ruxolitinib is interrupted for ≥ 8 weeks, unless approved by the medical monitor, or if ruxolitinib is reduced to a dose below 5 mg QD.
- The subject requires splenic irradiation.

- The subject 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 becomes pregnant (positive urine pregnancy test, confirmed by positive serum pregnancy [serum human chorionic gonadotropin] test results).
- Consent is withdrawn.
- Further participation would be injurious to the subject's health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A subject **may** be discontinued from study treatment as follows:

- 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 that a subject withdraws prematurely, and this information should be recorded in the eCRF.
- If, during the course of the study, a subject is found not to have met eligibility criteria, then the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study (see Section 10.5, Protocol Adherence).
- A subject may be withdrawn from the study if, in the investigator's expert medical judgment, the subject is noncompliant with the study requirements. The sponsor should be consulted for instruction on handling the subject. Subjects may be withdrawn at the discretion of the health authorities or the investigator.

5.5.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study treatment (itacitinib) the EOT visit should be conducted. Reasonable efforts should be made to have the subject return for a follow-up visit. These visits are described in Section 6. The last date of the last dose of study treatment and the reason for subject withdrawal will be recorded in the eCRF.

If a subject is withdrawn from the study treatments:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the eCRF.
- The EOT visit should be performed, including diary completion.
- The date of the EOT visit should be recorded in the IXRS.
- In the event that a decision is made to permanently discontinue the study treatment, reasonable efforts should be made to have the subject return for a follow-up visit for safety and, if possible, should be followed until study treatment-related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

5.6. Concomitant Medications

5.6.1. Permitted Medications

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

Antibiotic prophylaxis for chronic treatment is permitted; subjects requiring acute antibiotic treatment at the time of screening must delay screening/enrollment until the course of antibiotic therapy is completed.

The subject needs to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant nondrug therapies (including physical therapy and blood transfusions) administered after the subject starts treatment with study drug must be listed on the Concomitant Medications/Significant Nondrug Therapies After Start of Study Drug eCRF.

5.6.2. Restricted Medications

The following medications are prohibited during the study:

1. Aspirin in doses exceeding 81 mg per day in the United States, 125 mg in Europe or standard dose for prophylaxis is not permitted. Low-dose aspirin is permitted.
2. Acetaminophen and NSAIDs (eg, ibuprofen) 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).
3. Inducers of CYP3A4 (Appendix H) may be used with caution, and investigators should seek other options if available.
4. Mild/moderate CYP3A4 inhibitors (Appendix H) 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/or itacitinib during a period of concomitant medication use. If required for safety, ruxolitinib 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.
5. If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then 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.
6. Granulocyte growth factors are not allowed while study medication is being administered but may be used for severe neutropenia at the investigator's discretion while study medication is interrupted
7. If a subject requires steroids for a comorbid condition during study participation, then continuation in the study will be considered on an individual basis by the sponsor and the investigator.

5.6.3. Prohibited Medications

1. Any investigational medication (a drug that is not approved for any indication) other than the study drug is prohibited. Use of such medications within 30 days or 5 half-lives, whichever is longer, before the first dose of study drug and during the study through the safety follow-up visit is prohibited.
2. Use of any medication used to treat MF (eg, HU, interferon, thalidomide, busulfan, lenalidomide, anagrelide, other cytotoxics or immune modulators, other JAK1 inhibitors, or any investigational agent) is not permitted at any time beginning at Day 1 up until the time that itacitinib therapy is permanently discontinued. Investigators must determine that the subject is able to withdraw current therapy without it being likely to lead to significant deterioration of the subject's condition in order for the subject to qualify for the study.
3. Use of TPO receptor agonists (romiplostim, eltrombopag) is not permitted from screening to the safety follow-up visit.
4. Use of erythropoietin is not permitted from screening.
5. Use of rifampin and St John's Wort, is not permitted at any time during participation in the study from screening to safety follow-up visit.
6. Use of potent/strong CYP3A4 inhibitors (boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole) is prohibited. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole in the study.

See Appendix H for a list of CYP inhibitors and inducers.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (see Table 5 and Table 6), and all laboratory assessments will be performed as indicated in Table 7 and Table 8. Required laboratory analytes are listed in Table 9. The order of assessments is suggested by the order of mention within the schedule. See Section 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

Table 5: Schedule of Assessments for Cohort A and B (Screening Through Week 12)

Visit Day (Range)	Section	Screening Day -28 to Day -8	Baseline Day -7 to Day -1	D1	W2 (D8)	W4 (D29), W8 (D57) ± 5d	W12 (D85) ± 5d	Notes
Informed consent	7.1	X						
Contact IXRS	7.1	X		X		X	X	
Inclusion/exclusion criteria	3	X	X					
Prior medical and medication history	7.3	X	X					
Concomitant medication review	7.4		X	X		X	X	
Transfusion history/status	7.3	X	X	X		X	X	
Record AEs	7.5.2	X	X	X	X	X	X	
Comprehensive physical examination	7.5.3.1	X*		X				*Includes height (screening only).
Targeted physical examination	7.5.3.2					X	X	
Spleen palpation and measure/liver palpation	7.6.2	X	X			X	X	
Vital signs	7.5.4	X	X	X	X	X	X	
12-lead ECG	7.5.5	X						
MRI/CT of the upper and lower abdomen and pelvis	7.6.3		X				X	
ECOG status	7.7.1	X						
PGIC (Appendix F)	7.7.2					X	X	
IWG-MRT assessment*	7.8							*Response assessment starts at Week 24
Dispense and/or bring MFSAF v2.0 diary to visit	7.6.4		X	X	X	X	X	
Modified MFSAF v2.0 diary (Appendix D)	7.6.4		Completed every evening from baseline through Week 24 (25 weeks in total)					
MPN-SAF (Appendix E)	7.7.3		X				X	
Laboratory assessments*	7.5.6	X	X	X	X	X	X	*See Table 7 and Table 8.
Dispense reminder card	7.11.4		X	X		X	X	
Administer study drug during visit	7.11.1			X	X	X	X	
Dispense study drug	7.11.2			X		X	X	
Drug accountability assessment	7.11.3				X	X	X	

Table 6: Schedule of Assessments for Cohort A and B (Week 16 Through Follow-Up)

Visit Day (Range)	Section	W16 (D113), W20 (D141) ± 5d	W24 (D169) ± 5d	Extension Visits (Q12W After W24) ± 7d	EOT/Early Termin. Visit + 7d of discon.	Safety Follow-Up 30-35d After Last Dose of Itacitinib	Notes
Informed consent	7.1						
Contact IXRS	7.1	X	X	X	X		
Inclusion/exclusion criteria	3						
Prior medical and medication history	7.3						
Concomitant medication review	7.4	X	X	X	X	X	
Transfusion history/status	7.3	X	X	X	X	X	
Record AEs	7.5.2	X	X	X	X	X	
Comprehensive physical examination	7.5.3.1		X			X	
Targeted physical examination	7.5.3.2	X		X	X		
Spleen palpation and measure/liver palpation	7.6.2	X	X	X	X	X	
Vital signs	7.5.4	X	X	X	X	X	
12-lead ECG	7.5.5				X		
MRI/CT of the upper and lower abdomen and pelvis	7.6.3		X	X			
ECOG status	7.7.1		X			X	
PGIC (Appendix F)	7.7.2	X	X	X	X		
IWG-MRT assessment	7.8		X*	X*			*Q24W
Dispense and/or bring MFSAF v2.0 diary to visit	7.6.4	X	X				
Modified MFSAF v2.0 diary (Appendix D)	7.6.4	Completed every evening from baseline through Week 24 (25 weeks in total)					
MPN-SAF (Appendix E)	7.7.3		X	X*			*Q12W
Laboratory assessments*	7.5.6	X	X	X	X	X	*See Table 7 and Table 8.
Dispense reminder card	7.11.4	X	X	X			
Administer study drug during visit	7.11.1	X	X				
Dispense study drug	7.11.2	X	X	X			
Drug accountability assessment	7.11.3	X	X	X	X		

Table 7: Schedule of Laboratory Assessments for Cohort A and B (Screening Through Week 12)

	Section	Screening Day -28 to Day -8	Baseline Day -7 to Day -1	D1	W2 (D8)	W4 (D29), W8 (D57)	W12 (D85)	Notes
Window		**The window for laboratory visits is ± 3 days**						
Local Laboratory Assessments								
Blood chemistries	7.5.6	X	X*	X*		X	X	*Should be taken as close as possible to Day 1 but may be drawn up to 3 days before first dose. Only 1 sample for baseline/Day 1 is required.
Hematology	7.5.6	X	X*	X*		X	X	*Should be taken as close as possible to Day 1 but may be drawn up to 3 days before first dose. Only 1 sample for baseline/Day 1 is required.
Coagulation panel	7.5.6	X					X	
Urine pregnancy test*	7.5.6.1			X**				*All female subjects of childbearing potential. **Pregnancy tests should be conducted more often if required by local regulations.
Bone marrow biopsy/aspirate and analysis	7.5.6		X*					*Requirement for baseline biopsy/aspirate may be fulfilled by prior standard-of-care assessment within 2 months of Day 1 if data are made available to the investigator and sponsor.
Lipid panel (requires overnight fast)	7.5.6	X					X	
Serology - hepatitis*	7.5.6	X						*HBV, HCV
Urinalysis	7.5.6	X					X	
Serum pregnancy*	7.5.6.1	X						*All female subjects of childbearing potential.
FSH*	7.5.6.1	X						*To document hormonal menopause.
Central Laboratory Assessments*								*The central laboratory is the sponsor or sponsor's designee.
Cohort A and B* PK samples	7.9				X**	X***		*Cohort A, see Table 10. Cohort B, see Table 11. **For Cohort A, itacitinib should be administered after last PK collection; see Table 10. *** Week 4 only.
Correlative plasma	7.10.2			X	X	X*	X	*Week 4 only
[redacted]								

Table 8: Schedule of Laboratory Assessments for Cohort A and B (Week 16 Through Follow-Up)

	Section	W16 (D113), W20 (D141)	W24 (D169)	Extension Visits (Q12W After W24)	EOT/Early Termin. Visit + 7d of discon.	Safety Follow-Up 30-35d After Last Dose of Itacitinib	Notes
Window		**The window for laboratory visits is ± 3 days**					
Local Laboratory Assessments							
Blood chemistries	7.5.6	X	X	X	X	X	
Hematology	7.5.6	X	X	X	X	X	
Coagulation panel	7.5.6		X	X	X	X	
Urine pregnancy test*	7.5.6.1						*All female subjects of childbearing potential.
Bone marrow biopsy/aspirate, and analysis	7.5.6		X	X*			*Required Q24W.
Lipid panel (requires overnight fast)	7.5.6		X	X*	X	X	*Required Q12W.
Serology* - hepatitis	7.5.6						*HBV, HCV
Urinalysis	7.5.6		X	X*		X	*Required Q12W.
Serum pregnancy*	7.5.6.1				X		*All female subjects of childbearing potential.
FSH*	7.5.6.1						*To document hormonal menopause.
Central Laboratory* Assessments							*The central laboratory is the sponsor or sponsor's designee.
Cohort A and B* PK samples	7.9						*Cohort A, see Table 10. Cohort B, see Table 11.
Correlative plasma	7.10.2		X	X**			**Week 36 and 48 only
[redacted]							

Table 9: Local Laboratory Tests: Required Analytes

Blood Chemistry	Hematology	Urinalysis With Microscopic Examination	Hepatitis Screening	Coagulation
Albumin Alkaline phosphatase ALT AST Bicarbonate Blood urea nitrogen Calcium Chloride Creatinine Ferritin Glucose Lactate dehydrogenase Phosphate Potassium Sodium Total bilirubin Direct bilirubin (if total bilirubin is elevated above ULN) Total protein Uric acid	Complete blood count, including reporting of % blasts Hemoglobin Hematocrit Platelet count RBC count WBC count Differential count, including: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Absolute values must be provided for: WBC differential laboratory results: Lymphocytes Neutrophils	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Urobilinogen **Lipid Panel** Total cholesterol Triglycerides LDL HDL	Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis A, B core antibody HBV-DNA HCV antibody HCV-RNA	PT PTT INR **Pregnancy Testing** Female subjects of childbearing potential only require a serum test at screening and EOT and a urine pregnancy test before the first dose on Cycle 1 Day 1. Pregnancy tests (serum or urine) should be repeated if required by local regulations. FSH

HDL = high-density lipoprotein; INR = international normalized ratio; LDL = low-density lipoprotein; PT = prothrombin time; PTT = partial thromboplastin time.
Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.

Table 10: Schedule of Pharmacokinetic Sampling for Cohort A (Itacitinib and Ruxolitinib)

Week 2 (Day 8)	Week 4
Subject arrives having withheld both itacitinib and ruxolitinib	Subject arrives having withheld both itacitinib and ruxolitinib
Predose sample = Time 0 sample	Predose sample = Time 0 sample
Administer ruxolitinib	Administer itacitinib plus ruxolitinib
Timed samples:	Timed samples:
1 hour postdose (± 15 min)	1 hour postdose (± 15 min)
2 hours postdose (± 30 min)	2 hours postdose (± 30 min)
5 hours postdose (± 60 min)	5 hours postdose (± 60 min)
8 hours postdose (± 60 min)[a]	8 hours postdose (± 60 min)
Administer itacitinib	

[a] Eight-hour postdose samples on Week 2 should only be collected if the subject is still in clinic at the scheduled time of collection (ie, at least 7 h postdose). If the subject will be released before the start of the collection window (7 h postdose), the sample is not required. The subject should receive itacitinib Week 2 after collection of the last PK sample at either 5 or 8 hours postdose. The Week 4 eight-hour postdose sample is required.

Table 11: Schedule of Pharmacokinetic Sampling for Cohort B (Itacitinib Alone)

Week 2 (Day 8)	Week 4
Subject arrives having withheld itacitinib	Subject arrives having withheld itacitinib
Predose sample = Time 0 sample	Predose sample = Time 0 sample
Administer itacitinib	Administer itacitinib
Timed samples:	Timed samples:
1 hour postdose (± 15 min)	1 hour postdose (± 15min)
2 hours postdose (± 30 min)	2 hours postdose (± 30min)
5 hours postdose (± 60 min)	5 hours postdose (± 60min)
8 hours postdose (± 60 min)[a]	8 hours postdose (± 60min)

[a] Eight-hour postdose samples on Week 2 should only be collected if the subject is still in clinic at the scheduled time of collection (ie, at least 7 h postdose). If the subject will be released before the start of the collection window (7 h postdose), the sample is not required. The Week 4 eight-hour postdose sample is required.

6.1. Screening

Screening is the interval between signing the ICF and the beginning of the 7-day baseline period (ie, Day -28 to Day -7). Screening may not exceed 21 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Subjects should arrive for the screening visit after an overnight fast of at least 8 hours or since midnight. A subject who has not fasted should be scheduled for the screening assessment blood draws on a morning when he/she can arrive after an overnight fast of at least 8 hours or since midnight.

Procedures conducted as part of the subject's routine clinical management (eg, blood count, bone marrow biopsy) and obtained before signing of informed consent may be used for screening purposes provided that the procedure meets the Protocol-defined criteria and has been performed

in the timeframe of the study (ie, within 28 days of Cycle 1 Day 1). All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Bone marrow biopsy (and additional aspirate collection) for confirmation of MF diagnosis and degree of fibrosis must be performed at the screening or baseline visit intervals. NOTE: Subjects without circulating blasts at the screening hematology assessment may use a historical biopsy obtained within 2 months before screening if all data and reports are available for investigator's review. Subjects without a prior biopsy report as indicated above must have a biopsy at screening or baseline or will not be able to enroll in the study. 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/aspirate).

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment.

6.2. Baseline

Subjects who have signed the ICF and meet all the entry criteria (see Section 3) may be eligible in the study and will be contacted by clinical site staff to schedule the baseline visit. The baseline interval corresponds to the 7 days before initiating treatment with itacitinib and during which the baseline MRI (or CT scan in applicable subjects) and symptom diary will be initiated.

- Subjects who meet all eligibility criteria may begin the baseline period of this study (7 days before Day 1 study start). During the baseline period, all eligible subjects will be issued a handheld device (eDiary) on which to record symptoms of MF in the MF-SAF diary (see Appendix D). Subjects will receive training on the device by study site staff before leaving the site. The investigative site staff must ensure that the diary is completed each night beginning on at least Day -7 in order to provide 1 complete week of data entries before the Day 1 visit. Subjects will bring the device along to the Day 1 visit to confirm that at the diary entries have been completed. The Day 1 visit should not be scheduled for any subject who has not completed at least 4 days of diary entries. The subjects will also bring the device along to every study visit to verify the device charging and to download accumulated data. The device will then be returned to the subject upon visit completion for continued use each night. Subjects will return the device and its docking station for the final time at the EOT visit so that all data can be archived. NOTE: The diary may be distributed as early as the screening visit in order to accommodate subject visit schedules during the baseline period.
- The MRI (or CT scan in applicable subjects) should be conducted on the first or second day of the baseline interval to allow ample time to verify scan quality.
- Blood samples for hematology and chemistry analyses should be taken as close as possible to Day 1 but may be drawn up to 3 days before the first dose of itacitinib. This blood sample will serve as the pre-itacitinib baseline sample; a Day 1 sample is not required if the baseline sample is within 3 days of the first dose of itacitinib.

6.3. Treatment

The treatment period begins with the first dose of itacitinib (Day 1) through the point at which the investigator determines the subject will be permanently discontinued from study drug.

There will be study visits with laboratory assessments in the study. Table 5, Table 6, Table 7, and Table 8 provide the scheduled assessments for each study visit.

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 and every 12 weeks thereafter if continuing on treatment, where blood samples, spleen measurements, and other assessments will be obtained. There is also a study visit at Week 2 for PK sampling, AE assessment, and hematology blood draws. The visit window is ± 5 days for visits through Week 24 and ± 7 days for visits thereafter. The timing for study visits will be based on the date of the Day 1 visit when treatment with itacitinib is initiated.

Blood [redacted] PK samples will be collected and analyzed by the sponsor or sponsor's designee. Subjects will arrive for all study visits having withheld the morning dose of itacitinib and ruxolitinib if applicable and in the fasted state; administration will occur in the clinic. Subjects should be told to bring a snack or small meal to the study visits, as they will arrive for the visits in the fasted state.

Subjects will have laboratory assessments performed during study visits to collect hematology lab samples as noted in Table 7 and Table 8. The window for laboratory visits is ± 3 days. Additional laboratory assessments may be performed at the investigator's discretion, including following changes in dose, or if laboratory parameters are at Grade 3 or Grade 4 levels based on the CTCAE v4.03.

Subjects will complete an electronic symptom diary (MFSAF v2.0) daily from baseline through the Week 24 visit (total of 25 weeks; Appendix D).

Subjects will complete the MPN-SAF in a e-diary (Appendix E) at visits noted in Table 5 and Table 6.

6.4. End of Treatment

There is not a predefined EOT. If a decision is made that the subject will withdraw from study participation, then an EOT visit should be conducted within 7 days after the last dose of study treatment. If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The subject should be encouraged to return for the follow-up visit.

If a study withdrawal occurs, or if the subject fails to return for visits, then the investigator must determine the primary reason for a subject's premature withdrawal from the study and record this information in the eCRF.

The investigator must contact the IXRS system to register the subject's discontinuation.

6.5. Follow-Up

6.5.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 30 to 35 days after the EOT visit (or after the last dose of study treatment if the EOT visit was not performed). Adverse events and SAEs must be reported up until 30 days after the last dose of study treatment, the date of the follow-up visit, or until study treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this period. If the subject cannot return to the site for the safety follow-up visit (eg, lives far away), then the subject should be contacted by telephone for assessing AEs and SAEs. Sites should document this contact in the source.

6.6. End of Study

The end of study for each subject is considered to have occurred when the subject is deceased, when the study is completed, or when the subject is permanently lost to follow up.

6.7. Unscheduled Visits

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed (eg, laboratory or clinical assessments) at those visits should be recorded in the eCRF.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

Prospective participants will be scheduled for a screening visit by site staff. A subject number will be assigned by an IXRS. All procedures for screening and baseline must be completed within the 21-day screening + 7-day baseline period, except as noted in Section 6.1). The procedures in this section will be performed.

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures using an ICF approved by the local IRB/IEC that contains all 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; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation.

7.2. Interactive Response Technology Procedure

The IXRS will be contacted to obtain a subject ID number when a subject enters the screening period. Upon determining that the subject is eligible, the IXRS will be contacted to obtain the treatment cohort assignment. Additionally, the IXRS will be contacted at each regular study visit to update the study treatment supply and at the EOT visit to record subject discontinuation from the study treatment (see Section 5.1.1).

7.3. Demography and Medical History

Demographic data and a complete medical and medication history will be collected at screening. The subject's date of birth, race, ethnicity, medical and surgical history, and concurrent illnesses assessed using CTCAE v4.03 (NCI 2010) will be recorded. Documentation of disease history, including details of MF diagnosis, and prior bone marrow biopsy data with respect to fibrosis stage will be recorded. All treatments for MF, including a complete history of ruxolitinib usage, phlebotomy history, and all transfusions of RBC products or platelets from at least 12 weeks before the screening visit will also be collected.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. All concomitant medications and measures must be recorded in the eCRF, and any medication received or procedure performed within 30 days before enrollment and up to the safety follow-up (30-35 days after EOT) will be recorded in the eCRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the eCRF. Transfusions of PRBCs, platelets, or other blood product must be recorded in the eCRF.

7.5. Safety Assessments

Safety examinations must be performed by a suitably trained, medically qualified individual such as a licensed physician, physician's assistant, or an advanced registered nurse practitioner, as local law permits.

7.5.1. Review Inclusion and Exclusion Criteria

All safety data and other eligibility assessments must be reviewed during the screening period to confirm the subject's eligibility.

7.5.2. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and 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 eCRFs regardless of the assumption of a causal relationship with the study treatment. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.5.3. Physical Examinations

7.5.3.1. Comprehensive Physical Examination

The comprehensive physical examination will include height (at screening) and body weight, and assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat;

thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes, as well as a brief neurological examination. The comprehensive physical examination should also include an assessment of body fluid abnormalities, including ascites and edema.

7.5.3.2. Targeted Physical Examinations

A targeted physical examination will be a symptom-directed evaluation and will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings as determined by the investigator or designee. A targeted physical examination must include a measurement of the subject's body weight (within 1 lb. or 0.5 kg), an assessment of body fluid abnormalities of edema and ascites, and an evaluation of any AEs or symptoms that the subject has had previously.

7.5.4. Vital Signs

Vital sign measurements include blood pressure, pulse, respiratory rate, and body temperature. Blood pressure and pulse will be taken with the subject in the recumbent, semirecumbent, or sitting position after 5 minutes of rest. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.5. Electrocardiograms

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

The 12-lead ECGs will be interpreted by the investigator at the site to be used for immediate subject management. The decision to include or exclude a subject or withdraw a subject from the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.6. Laboratory Assessments

All hematology laboratory assessments, blood chemistries, coagulation, lipid panel, serology, and urinalysis parameters will be analyzed by local laboratories. Samples for hematology, blood chemistry, serology, coagulation tests, pregnancy, and FSH tests and urinalysis will be prepared using standard procedures. A complete list of laboratory assessments is shown in Table 7 and Table 8. Refer to the Laboratory Manual for further details and specifications for sample handling, processing, and shipping. Additional laboratory assessments may be conducted at investigator's discretion to understand safety findings or to support dose modifications

7.5.6.1. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential at screening and at the EOT visit. An FSH test will be performed on females who have been amenorrheic for $\geq$ 1 year. If FSH levels are elevated to postmenopausal range, no pregnancy testing is required for these female subjects. Urine pregnancy tests will be conducted as outlined in Table 7, as medically indicated, or per country-specific requirement. Urine pregnancy tests will be performed locally.

If a urine pregnancy test is positive, then the results should be confirmed with a serum pregnancy test. If the serum pregnancy test is negative after a urine test was positive, then the investigator will assess the potential benefit/risk to the subject and determine whether it is in the subject's best interest to resume study treatment and continue participation in the study.

7.6. Efficacy Assessments

7.6.1. Bone Marrow Biopsy

Bone marrow biopsy (and additional aspirate collection) will be collected as outlined in Table 7 and Table 8. Subjects without circulating blasts at the screening hematology assessment may use a historical biopsy obtained within the 2 months before screening, if all data and reports are available for investigator's review. The previous data will need to be entered into the eCRF for this study, with explanation as to the origin of the data (date of biopsy/aspirate). Subjects without a previous biopsy report as indicated above must have a biopsy at screening or baseline or they will not be able to enroll in the study. Collection, processing, and staining of bone marrow samples will be performed in accordance with standard procedures at the investigative sites. The bone marrow biopsy and optional aspirate should be assessed by an experienced hematopathologist using his/her standard examination.

[redacted]

7.6.2. Spleen and Liver Palpation

Spleen size should be determined at every physical examination with the subject in the recumbent (not left decubitus) position. The edge of the spleen will be determined by palpation, measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion. The measurements should be noted and the site at which it was determined listed (eg, anterior axillary line, midclavicular line, and/or subxiphoid).

Liver palpation will be performed as part of the physical examination described in Section 7.5.3.

7.6.3. Imaging

The primary measure of spleen size will be by MRI (or CT scan in applicable subjects). An MRI of the upper and lower abdomen and pelvis will be performed as outlined in Table 5 and Table 6. An MRI will be performed with a body coil because the objective is to measure organ volume, not to find very small lesions. The 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.

An 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 (eg, because of the presence of metal clips in the body, because of claustrophobia) or if MRI is not readily available. Computed tomography 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 vs CT) must be used for all visits for a given subject unless a new contraindication to the use of MRI occurs (eg, pacemaker insertion).

7.6.4. Symptom Diary

Symptoms of MF will be assessed using a symptom diary (modified MFSAF v2.0 diary; Appendix D). 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 as outlined in Table 5 and Table 6 so that the device charging can be verified and the accumulated data can be downloaded. 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 that 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. French and Spanish translations of the modified MFSAF v2.0 diary will be available.

7.7. Performance and Quality-of-Life Assessments

7.7.1. Eastern Cooperative Oncology Group Performance Status

The ECOG performance status will be assessed as shown in Table 5 and Table 6 (Appendix C).

7.7.2. Patient Global Impression of Change

Subjects will complete the 1-question assessment form (Appendix F) at study visits shown in Table 5 and Table 6. Instructions will be provided as a separate document.

7.7.3. Myeloproliferative Neoplasms Symptom Assessment Form

The MPN-SAF questionnaire (see Appendix E) will be completed at baseline; at Weeks 12 and 24; and at every 12-week visit thereafter so that the overall symptoms response assessment can be determined and reported.

7.8. IWG-MRT Assessment

Overall response assessment will be graded according to the IWG consensus criteria for treatment response in PMF and PPV/ET-MF (Appendix B, Tefferi et al 2013).

7.9. Pharmacokinetic Assessments

7.9.1. Blood Sample Collection

Pharmacokinetic samples are to be collected on each of the study visit days specified in the laboratory assessment schedule (see Table 7 and Table 8) before the morning treatment dose. The site must ensure that the subject is instructed NOT to take the dose of study treatment on the day of the PK sampling visit, as study treatment will be administered in the clinic at that visit with sampling. Reminder cards will be used and sent home with subjects to state upcoming visit dates and provide a place for subjects to record the time that they took their last dose before each visit (previous evening dose). Use of the reminder cards by site staff is mandatory, and they will be retained in the subject's records. The exact date and time of the PK blood draws will be recorded in the eCRF, along with the date and time of the last dose of study treatment preceding the blood draw and date and time of last meal. Instructions for sample preparation and shipping will be provided in the Laboratory Manual.

[redacted]

7.9.2. Bioanalytical Methodology and Analysis

The plasma samples will be analyzed for ruxolitinib by a validated liquid chromatography tandem mass chromatography method, carried out by Incyte Corporation (Wilmington, DE) or Incyte's designee. Samples may also be used for incurred sample reanalysis (the details will be documented in a sample analysis plan). [redacted]

[redacted]

[redacted]

7.11. Other Study Procedures

7.11.1. Administration of Study Treatment

Cohort A and B: Subjects will take their dose of itacitinib in the morning.

Cohort A only: Ruxolitinib will be administered orally as directed by the local prescribing information. In the United States, updated information can be found at http://dailymed.nlm.nih.gov/dailymed/about.cfm.

7.11.2. Dispensation of Study Treatment

Site staff will contact the IXRS to obtain the initial subject study treatment assignment, as well as for subsequent dispensations of study treatment. The investigator or designee will select the assigned study drug bottles from their stock that correspond with the number provided by IXRS and dispense the medication. The investigator will enter the bottle numbers in the eCRF. Full details will be provided in the IXRS Manual.

7.11.3. Assessment of Compliance With Study Drug

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.

7.11.4. Distribution of Subject Reminder Cards

Subjects will be provided with reminder cards at each visit. The subject reminder cards will indicate the date/time of the next visit and include any special instructions for that visit. This card will have an area for the subject to record the date and time of the last dose taken before the study visit and the time of their last meal (required for PK visits). On days when study drug is NOT to be taken at home in advance of the study clinic, reminder cards will indicate this.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, that occurs after a subject provides informed consent. 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 the study drug(s).

8.1.2. Reporting

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events form of the eCRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History form in the eCRF. Monitoring for the occurrence of new AEs should be continued for at least 30 days after the last dose of study drug Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

The term "disease progression" should be recorded as an AE/SAE only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported 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. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the eCRF.

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

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

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF 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. To the extent possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 5).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per serious adverse event (SAE) definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements (see Section 8.3.2).

All AEs should be treated appropriately. If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event form and the treatment should be specified on the Prior/Concomitant Medications or Procedures and Non-Drug Therapy form in the eCRF.

Once an AE is detected, it should be followed until it has resolved 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 drug, the interventions required to treat the event, and the outcome.

When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves. For example, 2 separate AEs will be reported if a subject has Grade 1 diarrhea, meeting the definition of an AE that lasts for 3 days before worsening to a Grade 3 severity. The Grade 1 event will be reported as an AE with a start date equal to the day the event met the Grade 1 AE definition and a stop date equal to the day that the event increased in severity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an AE, with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date equal to the day that the event either changed severity again or resolved.

8.2. Laboratory Test Abnormalities

Laboratory abnormalities that constitute an AE in their own right (considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug) should be recorded on the Adverse Event form in the eCRF. 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 test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory 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 and Grade 4 AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.4) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

An SAE is defined as an event that meets at least 1 of the following criteria:

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
  - Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

Every SAE, regardless of suspected causality (eg, relationship to study drug(s) or study procedure or disease progression), occurring after the subject has signed the ICF through the last study visit (or 30 days after the last dose of study drug, whichever is later) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. Any SAEs occurring more than 30 days after the last dose of study drug should be reported to the sponsor or its designee only if the investigator suspects a causal relationship to the study drug.

Information about all SAEs is collected and recorded on the Adverse Event form of the eCRF. The investigator must assess and record the causal relationship of each SAE to the study treatment.

The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

The contact information of the sponsor's study-specific representatives is listed in the investigator manual provided to each site. The original copy of the SAE Report Form and the confirmation sheet must be kept at the study site.

Investigational site personnel must report any new information regarding the SAE within 24 hours of becoming aware of the information in the same manner that the initial SAE Report Form was sent. Follow-up information is recorded on an amended or new SAE Report Form, with an indication that it is follow-up to the previously reported SAE and the date of the original report. The follow-up report should include information that was not provided on the previous SAE Report Form, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or subject disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee 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.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a subject during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure subject safety:

- The study drug must be discontinued immediately (female subjects only; see Section 5.5.1 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy 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 Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy must be recorded on the SAE report form and submitted to the sponsor or designee.

8.6. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the itacitinib Investigator's Brochure (IB) and ruxolitinib prescribing information. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (INs). Any important new safety information should be discussed with the subject during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

8.7. Data Monitoring Committee

Not applicable.

8.8. Adverse Events of Special Interest

All reported AEs will be collected. The incidence of specific safety events including major thrombosis, hemorrhagic events, leukemia, or myeloid transformation will be tabulated.

8.9. Product Complaints

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

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 8.1.2 of this Protocol.

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

9. STATISTICS

9.1. Study Populations

The FAS includes all subjects enrolled in the study who received at least 1 dose of study drug (itacitinib). The FAS will be used in the analyses of demographic, baseline, and efficacy data.

The safety population includes all enrolled subjects who received at least 1 dose of study drug.

The per protocol population includes all enrolled subjects who were sufficiently compliant with the Protocol. Specific criteria for this population will be defined in the SAP.

The PK/PD evaluable population includes all subjects who received at least 1 dose of study drug and provided at least 1 sample for PK/PD.

9.2. Selection of Sample Size

Up to 21 subjects will be enrolled in each of the 2 dose cohorts (Cohort A and Cohort B) for a total of 42 subjects overall. The sign test will be used to evaluate percentage change from baseline in spleen volume by MRI or CT at Week 24 in applicable subjects with a 1-sided Type I error of 0.05. If 15 or more out of 21 subjects observe a > 0% SVR at Week 24, then further development of itacitinib as monotherapy or in combination with ruxolitinib may be considered. If the percentage of SVR at Week 24 is normally distributed with mean 11.4 and standard deviation 14.5, the test has 85% power to indicate that additional development is warranted.

9.3. Level of Significance

The level of significance for detecting a difference from a 0% median percentage SVR in each cohort is 5% (1-sided). In other words, under the null hypothesis of subjects receiving itacitinib having a true median percentage SVR of 0%, there is a 5% chance of declaring a given cohort as having a median percentage SVR > 0%. Note that this level of significance does not account for testing of multiple cohorts.

9.4. Statistical Analyses

A full description of all analyses will be included in the SAP document.

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

The primary endpoint of change and percentage of SVR (as measured by MRI or CT) at Week 24 will be summarized by cohort. Within each cohort, the sign test will be used to evaluate median percentage of SVR, and a 90% confidence interval for the median percentage SVR will be calculated using the exact binomial confidence interval method. Percentage SVR will be summarized descriptively at Week 12 by cohort.

9.4.1.2. Secondary Efficacy Analyses

Secondary efficacy analyses will be conducted for the FAS population. Change and percentage change from baseline in quantitative variables will be summarized by cohort using descriptive statistics. Frequencies and percentages for categorical variables will be provided by cohort.

Change and percentage change in spleen length from baseline as measured by palpation at each visit where the parameter is assessed through Week 24 will be tabulated by cohort with summary statistics.

Percentage change from baseline in 7-day MFSAF TSS and MPN-SAF TSS will be summarized at Week 12 and Week 24 by cohort, and 90% confidence intervals for the median percentage change will be estimated.

Patient Global Impression of Change will be summarized by visit. Subject data will be summarized by cohort and final titrated dose of itacitinib.

The number of subjects with responses according to the 2013 IWG consensus criteria will be tabulated.

9.4.1.2.1. Derivation of MFSAF TSS

The TSS for the MFSAF v2.0 diary will be determined as follows (NOTE: scores for inactivity and fatigue will not be included in TSS determinations):

- The Daily Total Score will be defined as the sum of 6 individual symptom scores (nights sweats, itchiness, abdominal discomfort, pain under left ribs, early satiety, bone/muscle pain, each with a 0 to 10 point scale) collected on the same day; the score will be missing if there are any missing individual scores. Note that the diary is completed at the end of each day.
- The Baseline Total Score will be defined as the average of Daily Total Scores from the baseline period. If there are more than 7 days of baseline symptom data recorded (because of a delay in treatment start), the last 7 days before enrollment will be used. The Baseline Total Score will be missing if there are fewer than 4 days of Baseline Daily Total Scores.
- The Week 12 (24) Total Score will be defined as the average of Daily Total Scores from the last 7 days of symptom scores before the Week 12 (24) visits. The Week 12 (24) Total Score will be missing if there are fewer than 4 days of Week 12 (24) Daily Total Scores.
- The percentage change will be calculated as follows:

  % Change = 100 × (Week 12 Total Score – Baseline Total Score) / Baseline Total Score

9.4.2. Safety Analyses

The safety analyses will be conducted for the safety evaluable population.

9.4.2.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v4.03 using Grades 1 through 5.

The subset of AEs considered by the investigator to have a relationship 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, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

9.4.2.2. Clinical Laboratory Tests

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Laboratory data will be classified into Grades 1 through 5 using CTCAE v4.03 or similar criteria where clinical intervention is required for CTCAE grading. Shift tables from baseline to the worst postbaseline CTCAE grade will be provided for laboratories using CTCAE grading criteria. For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges will be provided.

9.4.2.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, pulse, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 12), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 12: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 40 bpm
Temperature	> 38°C	< 35.5°C
Respiratory rate	> 24/min	< 8/min

9.4.2.4. Electrocardiograms

Electrocardiogram abnormalities, both at baseline and postbaseline visits, will be tabulated by treatment group. Subjects exhibiting clinically notable ECG abnormalities will be listed.

9.4.2.5. Adverse Events of Special Interest

Adverse events of special interest include Grade 4 thrombocytopenia, Grade 2 or higher anemia, and Grade 2 or higher hemorrhagic events, as measured by CTCAE v4.03. These AEs will be tabulated individually and summarized.

[redacted]

9.4.3. Pharmacokinetic Analyses

Plasma concentrations of itacitinib and ruxolitinib will be analyzed using standard noncompartmental analysis methods. Observed concentration data of INCB039110 and ruxolitinib will also be summarized by timepoint. If warranted by the data, a model-based approach may also be used for PK analysis.

[redacted]

9.5. Analyses for the Data Monitoring Committee

No Data Monitoring Committee for safety analysis is planned.

9.6. Interim Analysis

Although no formal interim analysis for efficacy is planned, further enrollment in a cohort will be terminated if 7 or more subjects within the cohort fail to illustrate SVR at Week 24 based on the primary endpoint of percentage change from baseline in spleen volume (by MRI/CT scan). Subjects will have failed to illustrate spleen reduction if they either 1) discontinue before the Week 24 assessment or 2) have an SVR ≤ 0 at the Week 24 assessment.

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

This study will be performed in accordance with ethical principles that originate in the Declaration of Helsinki and conducted in adherence to the study Protocol; GCPs as defined in Title 21 of the US CFR Parts 11, 50, 54, 56, and 312; ICH E6 GCP consolidated guidelines; and local regulatory requirements as applicable to the study locations.

The investigator will be responsible for:

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and subject records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all subjects.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.
- Obtaining informed consent and ensuring that the study subjects' questions have been answered and the subjects fully understand study procedures:
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the subject. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records.

- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling subjects who have met the specified eligibility criteria.

  The IRB/IEC that granted original approval, or the IRB/IEC 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/IEC to the sponsor or CRO and retain the original in the site study regulatory file.

  Major eligibility deviations must be reported to the IRB/IEC in accordance with the IRB/IEC 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 whether the subject should be withdrawn from the study.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure that the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All eCRF 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 eCRF data and audit trail.

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; 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 drug 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 drug 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 the sponsor.

10.3. Data Management

10.3.1. Data Collection

The investigator will be provided with an eCRF for each subject. Entries made in the eCRF must be verifiable against source documents; any discrepancies should be explained and documented. 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. The investigator is responsible for the review and approval of all responses.

10.3.2. Data Management

Data management will be performed in a validated database via an Electronic Data Capture (EDC) system. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database will be authorized for lock once all defined procedures are completed.

10.4. 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 eCRFs

- 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 eCRFs and office, hospital, and laboratory records supporting the participation of each subject in the study. The eCRFs 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 (eCRFs, subject medical and laboratory records, and other pertinent data). The study monitor will verify the eCRF 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.

10.5. 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 ICF 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/IEC. Each investigator is responsible for enrolling subjects who have met the protocol inclusion and exclusion criteria. The IRB/IEC that granted original approval, or the IRB/IEC 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/IEC to the sponsor or CRO and retain the original in the site study regulatory file.

Major eligibility deviations must be reported to the IRB/IEC in accordance with the IRB/IEC 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.

10.6. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data privacy laws and regulations. The investigator and the sponsor or its designee 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.

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the eCRF, where permitted; if the subject's 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 or its designee. 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 or its designee, IRB or 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.

10.7. 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.

10.8. Quality Control and Quality Assurance

10.8.1. 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. Before 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 eCRFs and other study-related documents.

10.8.2. 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 eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

10.9. Data Handling and Recordkeeping

10.9.1. 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.

10.9.2. 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 after 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 the sponsor. 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, the sponsor 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 eCRF 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 eCRF data and audit trail.

10.9.3. Confidentiality

Subject names will not be supplied to the sponsor. Only the subject number and subject initials will be recorded in the eCRF, and if the subject name appears on any other document (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.

10.10. 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. Study results will be published in accordance with applicable local and national regulations. 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 the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

11. REFERENCES

Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-2405.

Bose P, Verstovsek S. The evolution and clinical relevance of prognostic classification systems in myelofibrosis. Cancer 2016;122:681-692.

Cervantes F, Dupreiz B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International working Group for Myelofibrosis Research and Treatment. Blood 2009;113:2895-2901.

Cervantes F, Vannucchi AM, Kiladjian JJ, et al. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. Blood 2013;122:4047-4053.

Clinical Trial Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. 2014. http://www.hma.eu/ctfg.html. Accessed July 15, 2016.

Deeg HJ, Gooley TA, Flowers ME, et al. Allogenic hematopoietic stem cell transplantation for myelofibrosis. Blood 2003;102:3912-3918.

Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med 2012;366:787-798.

INC424 (INCB018424) Ruxolitinib Investigator's Brochure (IB). Basel, Switzerland: Novartis.

INCB039110 Investigator's Brochure (IB). Wilmington, DE: Incyte Corporation.

Mascarenhas JO, Talpaz M, Gupta V, et al. Primary analysis of a phase II open-label trial of INCB039110, a selective JAK1 inhibitor, in patients with myelofibrosis, Haematologica 2016;151126.

Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. Cancer 2007;109:68-76.

Mesa RA, Gotlib J, Gupta V, et al. Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patient-reported outcomes in COMFORT-I: a randomized, double blind, placebo-controlled trial. J Clin Oncol 2013a;31:1285-1292.

Mesa RA, Shields A, Hare T, et al. Progressive burden of myelofibrosis in untreated patients: assessment of patient-reported outcomes in patients randomized to placebo in the COMFORT-1 study. Leuk Res 2013b;37:911-916.

National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events version 4.03. 2010. http://ctep.cancer.gov/reporting/ctc.html. Accessed July 15, 2016.

Oken MM, Creech RH, Tormey DC. Toxicity and response criteria of the Eastern Cooperative Oncology Group. J Clin Oncol 1982;5:649-655.

Passamonti F, Cervantes F, Vannuchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT. Blood 2010;115:2703-1708.

Stein BL, Gotlib J, Arcasoy M, et al. Historical views, conventional approaches, and evolving management strategies for myeloproliferative neoplasms. J Natl Compr Canc Netw 2015;13:424-434.

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

Thiele J, Kvasnicka HM, Facchetti F, Franco V, van der Walt J, Orazi A. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica 2005;90:1128-1132.

Vannucchi AM, Kantarjian HM, Kiladjian JJ, et al. A pooled analysis of overall survival in COMFORT-1 and COMFORT-II, 2 randomized phase III trials of ruxolitinib for the treatment of myelofibrosis. Haematologica 2015;100:1139-1145.

Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366:799-807.

Verstovsek S, Mesa RA, Gotlib J, et al. The clinical benefit of ruxolitinib across patient subgroups: analysis of a placebo-controlled, Phase III study in patients with myelofibrosis. Br J Haematol 2013;161:508-516.

Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I. Haematologica 2015;100:479-488.

APPENDIX A. REVISED WHO 2016 CRITERIA FOR MYELOFIBROSIS

Table 13: WHO Pre–Primary Myelofibrosis Criteria

Major Criteria
1. Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1[a], accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis 2. Not meeting the WHO criteria for *BCR-ABL1*$^+$ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms 3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,[b] or absence of minor reactive BM reticulin fibrosis[c]
Minor Criteria
Presence of at least 1 of the following, confirmed in 2 consecutive determinations: a. Anemia not attributed to a comorbid condition b. Leukocytosis $\geq 11 \times 10^9$/L c. Palpable splenomegaly d. LDH increased to above upper normal limit of institutional reference range
Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion

[a] See Table 15.
[b] In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.
[c] BM fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Table 14: WHO Overt Primary Myelofibrosis Criteria

Major Criteria
1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3[a] 2. Not meeting WHO criteria for ET, PV, BCR-ABL1+ CML, myelodysplastic syndromes, or other myeloid neoplasms 3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker,[b] or absence of reactive myelofibrosis[c]
Minor Criteria
Presence of at least 1 of the following, confirmed in 2 consecutive determinations: a. Anemia not attributed to a comorbid condition b. Leukocytosis $\geq 11 \times 10^9$/L c. Palpable splenomegaly d. LDH increased to above upper normal limit of institutional reference range e. Leukoerythroblastosis
Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion

[a] See Table 15.
[b] In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.
[c] BM fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Table 15: Myelofibrosis Grading

Myelofibrosis Grading	
MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal BM
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis[a]
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis[a]

[a] In grades MF-2 or MF-3 an additional trichrome stain is recommended.
Source: Arber et al 2016.

APPENDIX B. INTERNATIONAL WORKING GROUP–MYELOPROLIFERATIVE NEOPLASMS RESEARCH AND TREATMENT CRITERIA

Response Categories	Required Criteria (for All Response Categories, Benefit Must Last for ≥ 12 Weeks to Qualify as a Response)
CR	Bone marrow[a]: Age-adjusted normocellularity; < 5% blasts; ≤ Grade 1 MF[b] and
	Peripheral blood: Hemoglobin ≥ 100 g/L and < UNL; neutrophil count ≥ 1×10^9/L and < UNL;
	Platelet count ≥ 100×10^9/L and < UNL; < 2% immature myeloid cells[c] and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
PR	Peripheral blood: Hemoglobin ≥ 100 g/L and < UNL; neutrophil count ≥ 1×10^9/L and < UNL; platelet count ≥ 100×10^9/L and < UNL; < 2% immature myeloid cells[c] and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or
	Bone marrow:[a] Age-adjusted normocellularity; < 5% blasts; ≤ Grade 1 MF[b]; and peripheral blood: hemoglobin ≥ 85 g/L but < 100 g/L and < UNL; neutrophil count ≥ 1×10^9/L and < UNL; platelet count ≥ 50×10^9/L but < 100×10^9/L and < UNL; < 2% immature myeloid cells[c] and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
CI	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia[d]
Anemia response	Transfusion-independent patients: a ≥ 20 g/L increase in hemoglobin level[e]
	Transfusion-dependent patients: becoming transfusion-independent[f]
Spleen response[g]	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable[h] or
	A baseline splenomegaly that is palpable at > 10 cm, below the LCM, decreases by ≥ 50%[h]
	A baseline splenomegaly that is palpable at < 5 cm, below the LCM, is not eligible for spleen response
	A spleen response requires confirmation by MRI or CT showing ≥ 35% spleen volume reduction
Symptoms response	A ≥ 50% reduction in the MPN-SAF TSS[i]
Progressive disease[j]	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or
	A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or
	A 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm or
	Leukemic transformation confirmed by a bone marrow blast count of ≥ 20% or

Response Categories	Required Criteria (for All Response Categories, Benefit Must Last for ≥ 12 Weeks to Qualify as a Response)
	A peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1×10^9/L that lasts for at least 2 weeks
Stable disease	Belonging to none of the above-listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or
	Loss of anemia response persisting for at least 1 month or
	Loss of spleen response persisting for at least 1 month

CI = clinical improvement; CR = complete response; CT = computed tomography; EMH = extramedullary hematopoiesis; LCM = left costal margin; MF = myelofibrosis; MPN-SAF TSS = Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; MRI = magnetic resonance imaging; PR = partial response; PRBC = packed red blood cell; UNL = upper normal limit.

[a] Baseline and post-treatment bone marrow slides are to be interpreted at 1 sitting by a central review process. [redacted]

[b] Grading of MF is according to the European classification (Thiele et al 2005). It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.

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

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

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

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

[g] In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy.

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

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

[j] Progressive disease assignment for splenomegaly requires confirmation by MRI or CT showing a ≥ 25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to posttreatment measurements.

Source: Tefferi et al 2013.

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

Source: Oken et al 1982.

APPENDIX D. MODIFIED MYELOFIBROSIS SYMPTOM ASSESSMENTS FORM VERSION 2.0

Please complete this diary at night before bedtime. The diary asks about your MF symptoms during the past 24 hours. There is no right or wrong answer. Please give the answer that best reflects your opinion.

1. During the past 24 hours, 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 24 hours, 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 24 hours, 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 24 hours, 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 24 hours, 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 24 hours, 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 24 hours, 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)

APPENDIX E. MYELOPROLIFERATIVE NEOPLASMS SYMPTOM ASSESSMENT FORM

Subject Number _____ _____

Symptom	1 to 10 (0 if absent) ranking - 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours.	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes, during the past week, how much difficulty you had with each of the following symptoms	
Night sweats	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse, not joint pain or arthritis)	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (> 100°F)	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Unintentional weight loss in the last 6 months	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Filling up quickly when you eat (early satiety)	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - compared to prior to my MPD	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
	TSS: _____
MD Signature/Date	Per IWG-MRT 2013 Criteria: TSS to include fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers.
Staff Signature/Date	

APPENDIX F. PATIENT GLOBAL IMPRESSION OF CHANGE

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 G. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Source: CTFG 2014.

APPENDIX H. CYTOCHROME P450 AND P-GLYCOPROTEIN INHIBITORS AND CYTOCHROME P450 INDUCERS

In clinical studies with CYP3A4 inhibitors, elevated levels of INCB018424 of approximately 2-fold have been observed after oral administration. Additionally, simulations using physiologically based pharmacokinetic models suggested that fluconazole (a dual CYP3A4 and CYP2C9 inhibitor) increases steady-state ruxolitinib AUC by approximately 1- to 3-fold after oral administration. Thus, these concomitant medications should not be taken by subjects beginning 2 weeks or 5 half-lives (whichever is longer) before the first application of study drug until the last administration (either Week 24 or Week 48); however, topical use of these agents if the systemic bioavailability is low may be permitted on a case-by-case basis. The following is a list of potent CYP3A4 inhibitors and fluconazole. The sponsor should be contacted with any questions regarding concomitant medications that might be considered potent CYP3A4 inhibitors but are not on this list.

boceprevir

clarithromycin

cobicistat

conivaptan

danoprevir

elvitegravir

fluconazole

grapefruit juice

idelalisib

indinavir

itraconazole

ketoconazole

LCL161

lopinavir

mibefradil

nefazodone

nelfinavir

posaconazole

ritonavir

saquinavir