Official Title:	**A Double-Blind, Double-Dummy Phase 2 Randomized Study to Evaluate the Efficacy and Safety of Ruxolitinib Versus Anagrelide in Subjects With Essential Thrombocythemia Who Are Resistant to or Intolerant of Hydroxyurea**
NCT Number:	NCT03123588
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Clinical Study Protocol

INCB 18424-272

A Double-Blind, Double-Dummy Phase 2 Randomized Study to Evaluate the Efficacy and Safety of Ruxolitinib Versus Anagrelide in Subjects with Essential Thrombocythemia Who Are Resistant to or Intolerant of Hydroxyurea

Product:	**INCB018424**
IND Number:	**77,456**
Phase of Study:	**2**
Sponsor:	**Incyte Corporation 1801 Augustine Cut-Off Wilmington, DE 19803**
Original Protocol (Version 0):	**22 JUL 2016**
Amendment (Version) 1:	**21 DEC 2016**
Amendment (Version) 2:	**02 AUG 2019**

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 18424-272 Protocol Amendment 2 (Version 2 dated 02 AUG 2019) 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: INCB018424 (Ruxolitinib), JAKAFI®

Throughout this Protocol, ruxolitinib or ruxolitinib placebo will be used to designate the drug substance (ruxolitinib phosphate) and drug product (ruxolitinib phosphate tablets) and matching placebo.

Title of Study: A Double-Blind, Double-Dummy Phase 2 Randomized Study to Evaluate the Efficacy and Safety of Ruxolitinib Versus Anagrelide in Subjects With Essential Thrombocythemia Who Are Resistant to or Intolerant of Hydroxyurea

Protocol Number: INCB 18424-272	**Study Phase:** 2

Indication: Essential thrombocythemia that is resistant to or intolerant of hydroxyurea.

Primary Objective:

- To compare efficacy of ruxolitinib versus anagrelide as measured by the proportion of subjects demonstrating platelet and white blood cell (WBC) control.

Secondary Objectives:

- To evaluate the safety and tolerability of ruxolitinib compared with anagrelide in subjects with essential thrombocythemia (ET).
- To compare complete remission (CR) and partial remission (PR) rates of ruxolitinib and anagrelide in subjects with ET.
- To evaluate the duration of response.
- To evaluate the proportion of subjects demonstrating platelet control.
- To evaluate the proportion of subjects demonstrating WBC control.

[redacted]

Primary Endpoint:

- Proportion of subjects who achieve a simultaneous reduction of platelet counts to $< 600 \times 10^9$/L with a reduction of WBC counts to $< 10 \times 10^9$/L for at least 80% of biweekly measurements for a consecutive 12-week period between Weeks 32 and 52.

Secondary Endpoints:

- Safety and tolerability of ruxolitinib measured by adverse events (AEs) and laboratory values.
- Proportion of subjects who discontinue study treatment because of AEs.
- Time to treatment discontinuation.

- Proportion of subjects who achieve CR or PR at Week 32 based on European LeukemiaNet (ELN) 2013 response criteria.
  - Analyses completed for subjects achieving CR plus PR.
  - Analyses completed for subjects achieving CR.
  - Analyses completed for subjects achieving PR.
- Duration of response as measured from the onset of response to the loss of response for responders. Response is defined the same as in the primary endpoint.
- Proportion of subjects who achieve reduction of platelet counts to $< 600 \times 10^9$/L for at least 80% of biweekly measurements for a consecutive 12-week period between Weeks 32 and 52.
- Proportion of subjects who achieve a reduction of WBC counts to $< 10 \times 10^9$/L for at least 80% of biweekly measurements for a consecutive 12-week period between Weeks 32 and 52.

[redacted]

Overall Study Design:

This is a Phase 2, randomized, double-blind, double-dummy study in subjects with ET who are resistant to or intolerant of hydroxyurea (HU; according to modified ELN criteria) with a screening platelet count $\geq 650 \times 10^9$/L and WBC count $\geq 11.0 \times 10^9$/L. Subjects will be randomized in a 1:1 ratio, stratified by Janus kinase (JAK) V617 mutation status (positive vs negative), platelet count at screening ($\geq 1000 \times 10^9$/L or $< 1000 \times 10^9$/L), and prior anagrelide use (yes vs no) to the following 2 treatment groups:

- Group A: ruxolitinib at a dose of 10 mg twice daily (BID) orally and anagrelide-placebo.
- Group B: anagrelide at a dose of 1 mg BID orally and ruxolitinib-placebo.

Subjects will receive blinded study treatment for 52 weeks.

Crossover and open-label extension: After individual subjects reach the Week 52 visit (and data have been entered and cleaned), cross over to an open-label extension may occur. Subjects originally randomized to ruxolitinib who are receiving benefit from therapy will continue receiving open-label ruxolitinib until the study is concluded. Subjects originally randomized to anagrelide will be evaluated for eligibility to cross over to the open-label treatment phase according to investigator's decision, after consultation with the sponsor.

Study Population:

Individuals, aged 18 years or older, who have been diagnosed with ET who are resistant to or intolerant of HU, with a platelet count ≥ 650 × 10^9/L and WBC count ≥ 11.0 × 10^9/L.

Key Inclusion Criteria:

- Men and women, aged 18 or older.
- Subjects diagnosed with ET according to revised WHO 2016 criteria.
- Subjects who are resistant to or intolerant of HU, that is, fulfilling at least 1 of the following criteria:
  - Platelet count > 600 × 10^9/L after 3 months of at least 2 g/day of HU (2.5 g/day in subjects with a body weight over 80 kg) OR at the subject's maximally tolerated dose if that dose is < 2 g/day.
  - Platelet count > 400 × 10^9/L and WBC count < 2.5 × 10^9/L or hemoglobin < 10 g/dl at any dose of HU.
  - Presence of leg ulcers or other unacceptable muco-cutaneous manifestations at any dose of HU.
  - HU-related fever.
- Platelet count ≥ 650 × 10^9/L at screening.
- WBC ≥ 11.0 × 10^9/L at screening.
- ECOG performance status 0 to 2.
- Known status of JAKV617F mutation.
- 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 ≥ 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:

- Subjects who have previously been treated with JAK inhibitors.
- Subjects being treated concurrently with anagrelide or HU.
  - Prior anagrelide use is allowed provided the reason for discontinuation is not AE-related and anagrelide is stopped at least 28 days before the start of study medications (ie, Day 1).
  - Treatment with HU can be stopped at any time once one of the inclusion criteria for HU refractoriness or resistance have been met, and up to the day before the first dose of study treatment (ie, Day 1).
- Subjects with inadequate liver function at screening and Day 1 (before drug administration) as demonstrated by:
  - Total bilirubin > 1.5 × upper limit of normal (ULN)
  - Aspartate aminotransferase or alanine aminotransferase > 1.5 × ULN
  - Hepatocellular disease (eg, cirrhosis)
- Subjects with inadequate renal function at screening as demonstrated by creatinine clearance < 40 mL/min calculated by Cockcroft-Gault equation.

- Subjects with clinically significant cardiovascular disease including uncontrolled cardiac disease, including unstable angina; acute myocardial infarction within 6 months from 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 (New York Heart Association Class III or IV).
- History or presence of an abnormal electrocardiogram that, in the investigator's opinion, is clinically meaningful.
- Subjects with impairment of gastrointestinal (GI) function or active GI disease that may significantly alter absorption of ruxolitinib or anagrelide (eg, active ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, and small bowel obstruction).
- Inability to swallow and retain oral medication.
- Subjects with clinically significant bacterial, fungal, parasitic, or viral infection that requires therapy:
  - Subjects with acute bacterial infections requiring antibiotic therapy should delay screening/enrollment until the course of antibiotic therapy has been completed.
  - Subjects on chronic antibiotics for prophylaxis are allowed.
- 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.
- Subjects with diagnosed primary immunodeficiency syndromes, such as X-linked agammaglobulinemia and common variable immune deficiency.
- Subjects with peripheral blood blast count of > 0% at screening.
- Subjects with an active malignancy over the previous 2 years except treated cervical intraepithelial neoplasia, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or completely resected papillary thyroid and follicular thyroid cancers.
- Pregnant or breastfeeding women.
- Use of any potent cytochrome P450 3A4 inhibitors or inducers and CYP1A2 inhibitors within 14 days or 5 half-lives (whichever is longer) before the first dose of ruxolitinib or anagrelide or their anticipated use during the study (does not apply to topical ketoconazole).
- Use of concomitant treatment of fluconazole at a dose > 200 mg.
- Subjects being treated concurrently with any prohibited medications.
- Subjects being treated concurrently with any medications that may prolong QTc interval of the electrocardiogram.
- Subjects being treated concurrently with any investigational agent or who have had previously participated in an investigational study within 30 days before to the first dose of study drug or within 5 half-lives of the previous investigational product, whichever is longer.
- Subjects who are unable to comprehend or are unwilling to sign an informed consent form.
- Subjects who are unwilling or incapable of complying with the requirements of the study.
- Subjects with active alcohol or drug addiction that would interfere with their ability to comply with the study requirements.
- 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.

INCB018424/Study Drug, Dosage, and Mode of Administration:

Ruxolitinib or ruxolitinib-placebo will be administered orally BID at a starting dose of 10 mg BID without regard to food.

Reference Therapy, Dosage, and Mode of Administration:

Anagrelide or anagrelide-placebo will be administered orally BID at a starting dose of 1 mg BID without regard to food. Use of anagrelide will be consistent with approved prescribing information.

Dose Titration Criteria (for Both Study Drug and Reference Therapy):

Doses should be taken morning and evening, approximately 12 hours apart and without regards to food.

Dose escalations up to the maximum allowed dose for ruxolitinib (25 mg BID) and anagrelide (2.5 mg BID) are permitted. When modifications are made to the ruxolitinib dose, the dose of anagrelide will be modified concurrently. A dose increase of 5 mg BID up to a maximum dose of 25 mg BID is permitted after 2 weeks of treatment for ruxolitinib, and a dose increase of 0.5 mg/day per week up to a maximum dose of 2.5 mg BID is permitted for anagrelide.

Each dose escalation must be at least 1 week apart, and subjects must meet all of the following criteria:

1. Platelet count $\geq 150 \times 10^9$/L.
2. Hemoglobin ≥ 9 g/dL.
3. ANC $\geq 1500 \times 10^9$/L
4. One or more of the following:
    a. Platelet count $> 600 \times 10^9$/L.
    b. WBC count $> 10 \times 10^9$/L.
    c. Minimal improvement, no change, or worsening of vasomotor symptoms including headache, lightheadedness, syncope, atypical chest pain, acral paresthesia, livedo reticularis, erythromelalgia, and transient visual disturbances (eg, amaurosis fugax, scintillating scotomata, ophthalmic migraine).

NOTE: Dose decreases or interruptions for safety are required at any time throughout the study in accordance with Protocol requirements.

A maximum of 8 weeks of dose interruption is permitted in the study; subjects who cannot tolerate the study medications must discontinue from the study.

Study Schedule/Procedures:

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

Core Treatment Period

Subjects will be randomized to receive blinded treatment with ruxolitinib plus anagrelide-placebo or anagrelide plus ruxolitinib-placebo on Day 1. There is a 52-week dose administration period, but efficacy assessments will be measured between Weeks 32 and 52.

Subjects will have regularly scheduled study visits at the clinical site at screening, baseline, Day 1 (before first dose intake), Day 8, Day 15, Day 22, Day 28, then Day 7 every 4 weeks from Week 4 through Week 32, where blood samples will be collected and assessments conducted.

An efficacy assessment period will be defined by collection of blood samples (for hematology assessments of platelet count and WBC) every 2 weeks between Weeks 32 and 52 (Day 7 of Weeks 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, and 52). Subjects will either have a brief laboratory visit at the clinic laboratory or at local laboratory (or as described in the laboratory manual).

Study visits for clinical assessment will be performed every 4 weeks between Weeks 32 and 52.

Hematology laboratory assessments and clinical assessments will occur on Day 7 of Week 56 and every 12 weeks thereafter for subjects continuing treatment after Week 52.

All subjects will be required to have a bone marrow biopsy. Bone marrow biopsy will be conducted at baseline and again at the Weeks 32 and 52 and/or end-of-treatment visits. Optional additional biopsies will be requested at Week 104 and Week 156.

[redacted]

[redacted] liver size will be measured at screening, baseline, and every study visit beginning at Week 4. The edge of the [redacted] liver shall be determined by palpation, [redacted] and liver length measured in centimeters using a soft ruler, from the costal margin to the point of greatest splenic protrusion.

An end-of-treatment visit should be conducted when subjects are discontinued from study treatment, followed by a follow-up visit 30 to 37 days after the last dose of study drug.

All hematology laboratory assessments, serum chemistries, and coagulation parameters will be analyzed by local laboratories. Serology, urinalysis, and lipid panel will be analyzed by a central laboratory.

Additional hematology assessments will be required if the subject has a dose modification or as clinically indicated.

Options for the Open-Label Treatment Phase

Subjects originally randomized to ruxolitinib with anagrelide placebo (Group A) who are receiving benefit from therapy can 1) continue receiving open-label ruxolitinib until the study is concluded or they meet discontinuation criteria, or 2) choose to discontinue therapy.

Subjects originally randomized to receive anagrelide plus ruxolitinib placebo (Group B) have 3 options: 1) they may cross over to begin receiving ruxolitinib if they meet eligibility criteria after consultation with the sponsor and may then continue until the study is concluded or they meet discontinuation criteria; 2) they may continue receiving anagrelide until the study is concluded or they meet discontinuation criteria; or 3) they can choose to discontinue therapy. Note that subjects originally randomized to Group B may cross over to receive ruxolitinib at any time during the open-label part of the study.

Subjects who will continue with the same active agent to which they were randomized will have a study visit at Week 56, at which time study drugs will switch over to open-label supplies (ruxolitinib or anagrelide) and then study visits every 12 weeks (Week 68, 80, etc). Subjects who were originally randomized to anagrelide (Group B) and who cross over to ruxolitinib will begin receiving ruxolitinib at the Week 56 visit. These subjects will have study visits at Weeks 1, 2, 3, 4, and every 4 weeks up to 52 weeks, then every 12 weeks thereafter. Subjects who initially remain on anagrelide after unblinding but choose to cross over to receive ruxolitinib at a later time will have study visits at Weeks 1, 2, 3, 4, and every 4 weeks up to 52 weeks, then every 12 weeks thereafter.

[redacted]

Estimated Duration of Participation:

Individual subject participation is expected to average 24 to 36 months, which includes the following:

Screening period (Day -35 to Day -8): Up to 28 days.

Baseline (pretreatment) period (Day -7 to Day -1): 7 days before the first dose of treatment (required for all eligible subjects to complete the daily symptom diary for 7 days before the first dose of study medication.

Treatment period (Day 1 through Week 52): Begins with first dose of either ruxolitinib plus anagrelide-placebo or anagrelide plus ruxolitinib-placebo (Day 1). The efficacy assessment period will be defined by collection of blood samples every 2 weeks between Weeks 32 and 52.

Crossover and extension period: Treatment with open-label ruxolitinib will continue until the study is concluded for subjects originally randomized to ruxolitinib who are receiving benefit from treatment or subjects originally randomized to anagrelide who cross over after unblinding treatment.

Follow-up period: 30 to 37 days after last dose of blinded study treatment or open-label study treatment.

Estimated Number of Subjects: Approximately 120 subjects will be randomized in a 1:1 manner to 1 of 2 treatment groups (approximately 60 subjects per group). Approximately 85 clinical sites will be used in the United States.

Principal Coordinating Investigator: [redacted], MD, PhD, MD [redacted]

Statistical Methods:

When the last subject reaches Week 52 or discontinues, the database will be cleaned, locked and the final analyses will be conducted.

Selection of Sample Size

Based on a literature search and the Incyte Phase 2 study (INCB 18424-256) and a difference in response rate of 25% (30% vs 5%), a total of approximately 120 subjects (60 subjects per group) would provide approximately 90% power to detect a treatment difference of 25% in the primary endpoint at 2-sided chi-square test with an alpha level of 0.05.

Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects who achieve a simultaneous reduction of platelet counts to $< 600 \times 10^9$/L with a reduction of WBCs to $< 10 \times 10^9$/L for at least 80% of biweekly assessments for 12 consecutive weeks between Weeks 32 and Week 52. The proportion of subjects who meet the response criteria will be estimated with a 95% confidence interval. The Cochran-Mantel-Haenszel test stratified by JAK2V617F mutation status, screening platelet count, and prior anagrelide use will be applied to compare the 2 treatment groups. The test will be 2-sided at 5% significant level. The overall stratum-adjusted odds ratio, along with its 95% confidence interval, will be presented.

In the analysis of the primary efficacy endpoint, subjects who discontinue study treatment without meeting the response criteria will be considered as nonresponders. Subjects who meet the primary endpoint criteria of a response but discontinue treatment before Week 52 will be considered as responders.

Secondary Efficacy Analyses

- Proportion of subjects who achieve CR or PR at Week 32, as defined by ELN 2013 response criteria. The analysis will be conducted in the same fashion as the primary analysis.
- Duration of responses for subjects who achieve primary response as defined in the primary efficacy endpoint will be estimated using the Kaplan-Meier method. The start of a response will be the first visit where both platelet control (defined as a reduction to $< 600 \times 10^9$/L) and WBC control (defined as a reduction to $< 10 \times 10^9$/L) are achieved. Loss of response will be defined as 2 consecutive visits where either platelet count is $\geq 600 \times 10^9$/L or WBC is $\geq 10 \times 10^9$/L. The earlier of the 2 consecutive visits will be used as the end of response time.

- Proportion of subjects who achieve a reduction of platelet count to < 600 × 10^9/L for at least 80% of biweekly assessments for a consecutive 12-week period between Weeks 32 and 52 will be estimated along with their 95% confidence interval.
- Proportion of subjects who achieve a reduction of WBC counts to < 10 × 10^9/L for at least 80% of biweekly measurements for a consecutive 12-week period between Weeks 32 and 52 will be summarized along with their 95% confidence interval.

[redacted]

All applicable efficacy parameters after crossover will be tabulated.

Safety Analyses

All clinical safety data (vital signs, laboratory tests and adverse events) will be tabulated and listed.

The safety data collected after crossover will be summarized separately.

Level of Significance and Testing Procedures

The family wise alpha level will be controlled at 0.05 and will be controlled using a fixed sequential testing procedure. The proportion of subjects who achieve CR or PR at Week 32, as defined by ELN 2013 response criteria, will only be formally tested if the hypothesis for the primary endpoint is rejected.

The duration of response for responders in both treatments will be estimated with 95% confidence intervals without comparison. No alpha adjustment will be applied for the remaining endpoints.

Data Monitoring Committee:
An independent Data Monitoring Committee will be formed that consists of qualified individuals who are not involved in the conduct of the study. The roles, responsibilities, and composition of the committee will be established in a charter.

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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
AML	acute myeloid leukemia
AMP	adenosine monophosphate
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BAT	best available therapy
BID	twice daily
CALR	calreticulin
CFR	Code of Federal Regulations
[redacted]	[redacted]
CMH	Cochran-Mantel-Haenszel
CML	chronic myeloid leukemia
CMML	chronic myelomonocytic leukemia
COX-1	cyclo-oxygenase–1
CR	complete remission
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
ELN	European LeukemiaNet
EOT	end of treatment
ET	essential thrombocythemia
[redacted]	[redacted]
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
HBV	hepatitis B virus

Abbreviation	Definition
HCV	hepatitis C virus
HDPE	high-density polyethylene
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HU	hydroxyurea
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IN	Investigator Notification
IRB	institutional review board
ITT	intent-to-treat
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
IXRS	interactive voice/web response system
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MPL	myeloproliferative leukemia
MPN	myeloproliferative neoplasm
MPN-SAF	Myeloproliferative Neoplasm–Symptom Assessment Form
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamic
PDEIII	phosphodiesterase III
PET-MF	post–essential thrombocythemia myelofibrosis
[redacted]	[redacted]
[redacted]	[redacted]
PMF	primary myelofibrosis
PPV-MF	post–polycythemia vera myelofibrosis
PR	partial remission
PRO	patient-reported outcome
pSTAT	phosphorylated signal transducer and activator of transcription
PV	polycythemia vera
QD	once daily
RNA	ribonucleic acid

Abbreviation	Definition
SAE	serious adverse event
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TXA2	thromboxane A2
TYK2	tyrosine kinase 2
ULN	upper limit of normal
WBC	white blood cells

1. INTRODUCTION

Ruxolitinib (previously known as INCB018424 phosphate, INC424, ruxolitinib phosphate) is a novel, potent, and selective inhibitor of Janus kinase (JAK) 1 and JAK2 with modest to marked selectivity against tyrosine kinase 2 (TYK2) and JAK3, respectively. Ruxolitinib has been granted marketing authorisation approval for the treatment of myelofibrosis (MF) and polycythemia vera (PV) and is currently in development for the treatment of myeloproliferative neoplasms (MPNs; MF, PV, and essential thrombocythemia [ET]) and other hematologic malignancies.

For a thorough discussion of the pharmacology of ruxolitinib, refer to the Investigator's Brochure (IB).

1.1. Background and Overview on Essential Thrombocythemia

The chronic MPNs are classified into subgroups, of which 4 are well characterized: chronic myeloid leukemia (CML), PV, primary myelofibrosis (PMF), and ET. Essential thrombocythemia is alone among the chronic MPNs in that it is diagnosed by excluding causes of reactive thrombocytosis and by excluding presence of the other MPNs (Arber et al 2016, Tefferi and Barbui 2015).

Essential thrombocythemia represents one of the Philadelphia-chromosome negative MPNs and is associated with a mutation in the JAK2 tyrosine kinase domain estimated to be present in approximately 50% of ET patients (Levine et al 2007). The majority of patients with essential thrombocytosis have mutations in 1 of 3 genes: JAK2, calreticulin (CALR), or myeloproliferative leukemia (MPL) virus oncogene. Rare cases involve mutations in the thrombopoietin gene, which are associated with autosomal dominant hereditary thrombocytosis, and somatic mutations in tet methylcytosine dioxygenase 2 (NIH 2016, Rumi et al 2014). Essential thrombocythemia is characterized by persistent thrombocytosis (median platelet and white blood cell [WBC] counts at the time of diagnosis has been reported to range from 716 to 1000 $\times 10^9$/L and 8.6 to 9.6 $\times 10^9$/L, respectively), excessive proliferation of megakaryocytes in the bone marrow (hyperplasia of enlarged mature with hyperlobulated nuclei megakaryocytes), splenomegaly (palpable spleen, enlargement below the costal margin in 16% to 25% of subjects at diagnosis; Montanaro et al 2014, Tefferi et al 2014a, Tefferi et al 2014b, Passamonti et al 2012, Barbui et al 2011a) normal erythrocyte mass, the absence of bone marrow fibrosis and a clinical course complicated by thrombotic or hemorrhagic episodes, or both (Colombi et al 1991). Although uncommon, thrombosis and hemorrhage are the life-threatening complications of ET. Leukocytosis (WBC counts > 11 $\times 10^9$/L) also increases the risk of thrombotic events and reduces survival in subjects with ET. Predictors of arterial thrombosis include age > 60 years, history of thrombosis, presence of cardiovascular risk factors (eg, tobacco use, hypertension, diabetes mellitus), WBC count > 11 $\times 10^9$/L, and presence of the JAK2V617F mutation. The risk of significant bleeding is also associated with extreme thrombocytosis (platelet count > 1000 $\times 10^9$/L), the use of aspirin in doses > 325 mg/day, or following treatment with nonsteroidal anti-inflammatory drugs (NSAIDs; Gangat et al 2007, Griesshammer et al 1997, Colombi et al 1991, Bellucci et al 1986).

Leukemic and myeloid transformation into PV, PMF, or acute myeloid leukemia (AML) is another risk for patients with ET (Barbui et al 2011a, Cervantes et al 2002, Colombi et al 1991, Chistolini et al 1990, Fenaux et al 1990, Bellucci et al 1986) that is relatively low but increasing substantially after 10 years and 20 years (Wolanskyj et al 2006).

Incidence of symptoms in ET is ill-defined, but reported to be in the range of 34% to 70% (Mesa et al 2007, Tefferi et al 2001, Fenaux et al 1990). There exists a wide range in the reported incidence rates of symptoms in ET because of interstudy differences in patient selection and the definition of what constitutes a "vasomotor symptom." Vasomotor manifestations include headache, lightheadedness, syncope, atypical chest pain, acral paresthesia, livedo reticularis, erythromelalgia, and transient visual disturbances (eg, amaurosis fugax, scintillating scotomata, and ophthalmic migraine). These events are usually controlled by treatment with low or standard doses of aspirin (Pascale et al 2012, Michiels et al 2006, Michiels et al 1993). However, vasomotor symptoms in some patients may be resistant to antiplatelet therapy and may require cytoreductive therapy (Ruggeri et al 1998).

The median age at diagnosis is approximately 50 to 60 years, and as many as 20% of the patients may be younger than 40 years of age (Tefferi et al 2015, Mehta et al 2014). Five- and 10-year survival rates of 53% to 93% and 60% to 84%, respectively, have been reported in ET (Price et al 2014, Hultcrantz et al 2012, Maynadié et al 2013, Wolanskyj et al 2006). The incidence rate for ET ranges from 0.2 to 3 new cases/100,000 in the population per year.

Patients with ET can live many years after diagnosis but may have a reduced life expectancy compared with the normal population, particularly subjects with characteristics associated with an increased risk of thrombotic events or bleeding complications (Montanaro et al 2014, Hultcrantz et al 2012, Barbui et al 2011b, Finazzi and Barbui 2008, Schafer 2006). The goal of cytoreductive therapy is the reduction and maintenance of the platelet and WBC counts to the normal range, which is associated with a reduction in the risk of hemorrhage or thrombosis (Tefferi and Barbui 2015, Campbell et al 2012, Regev et al 1997, Fenaux et al 1990).

Hydroxyurea (HU), with or without aspirin, is considered first-line therapy in most subjects with ET (Cortelazzo et al 1995, Harrison et al 2005). Side effects of HU, which include oral ulcers, hyperpigmentation, skin rash, and nail changes, may lead to discontinuation of therapy and the need for alternative cytoreductive therapy. A small percentage of subjects will develop leg ulcers, nausea, diarrhea, or alopecia (Gisslinger et al 2013, Barbui and Finazzi 2005, Latagliata et al 2012). Thus, many subjects cannot remain on HU and require alternative cytoreductive therapies.

Anagrelide is an oral imidazoquinazoline derivative that may interfere with megakaryocyte proliferation and maturation, resulting in platelet underproduction (Tomer 2002, Mazur et al 1992). Anagrelide is approved by the FDA for the treatment of patients with thrombocythemia, secondary to myeloproliferative disorders, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombo-hemorrhagic events. In general, the drug is capable of reducing the platelet count to $< 600 \times 10^9$/L in more than 80% of previously treated and untreated subjects in a similar manner to HU (Gisslinger et al 2013, Harrison et al 2005, Petitt et al 1997, Chintagumpala et al 1995, Balduini et al 1992). Anagrelide has minimal effect on WBCs that may also be an important mediator of thrombotic risk (Harrison et al 2005, Bouchard and Tracy 2001, Falanga et al 2000). Anagrelide also does not appear to stop the progression of bone marrow fibrosis and hypercellularity in ET or

PV (Hultdin et al 2007). Toxicity of anagrelide is mainly related to the drug's direct vasodilatory and inotropic effects (Spencer and Brogden 1994, Abe Andes et al 1984). Anagrelide use in patients with ET has been associated with acquired idiopathic cardiomyopathy and must be given with caution in patients with known or suspected heart disease, which may limit its utility in the older patient (Jurgens et al 2004, Amabile and Spencer 2004). Thus, anagrelide is not tolerated or poorly tolerated in many subjects who would benefit from alternative options for platelet control.

Alpha interferon controls the thrombocytosis associated with all MPNs, including ET. An overview of the reported literature indicates a 75% to 88% hematologic response rate, associated with a 32% rate of reduction in spleen size (Kiladjian et al 2011, Kiladjian et al 2008, Saba et al 2005, Radin et al 2003, Gilbert 1998, Elliott and Tefferi 1997). The overall benefit to patients, compared with current treatment that usually consists of HU and low dose aspirin, is unknown. Similar efficacy along with marginally less toxicity has been observed with the use of the pegylated interferons alpha-2b and alpha-2a, which provide prolonged activity compatible with once weekly dose administration (Quintás-Cardama et al 2009, Jabbour et al 2007, Samuelsson et al 2006, Sacchi et al 1998). Because of the toxicity issues, alpha interferon in ET should not be used in high-risk women of childbearing age and in those who are pregnant. Considering the decreased tolerability associated with interferon therapy, a controlled study is needed before endorsing treatment with interferon as standard therapy in ET.

Low-dose aspirin is especially effective in treating the vasomotor symptoms of ET, such as acral paresthesias and erythromelalgia (Fröhli et al 1983, Michiels et al 1993). The optimal dose regimen of aspirin in ET is not known. Whereas low-dose aspirin given once daily (QD) is known to inhibit platelet thromboxane A2 (TXA2) synthesis by approximately 97% to 99% in healthy subjects through the irreversible inhibition of platelet cyclo-oxygenase–1 (COX-1), the same aspirin regimen is unable to fully inhibit TXA2 production in approximately 80% of patients with ET (Pascale et al 2012, Dragani et al 2010, Patrignani et al 1982). This may be attributable to increased platelet turnover in ET, with the emergence of young platelets with intact COX-1 activity in the 24 hours between aspirin doses.

Busulfan, in an uncontrolled study of 21 PV and 15 ET patients who were resistant to or intolerant of HU, was shown to be effective, but a significant rate of transformation was observed (Alvarez-Larrán et al 2014). Radiophosphorus (32P) and plateletpheresis are alternative treatments for a limited number of subjects with ET because of the high rate of leukemic transformation following 32P and the transient results obtained by pheresis (reserved for those with limited life expectancy or acute, serious, thrombotic, or hemorrhagic events).

1.2. Product Information and Overview of Ruxolitinib

1.2.1. Pharmacology

Ruxolitinib (previously known as INCB018424 phosphate, INC424, ruxolitinib phosphate) is a novel, potent, and selective inhibitor of JAK1 (inhibition concentration 50% [IC_{50}] = 3.3 ± 1.2 nM) and JAK2 (IC_{50} = 2.8 ± 1.2 nM) with modest to marked selectivity against TYK2 (IC_{50} = 19 ± 3.2 nM) and JAK3 (IC_{50} = 428 ± 243 nM), respectively. Ruxolitinib interferes with the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function.

Ruxolitinib efficacy was demonstrated in several *in vitro* and *in vivo* models relevant to the increased inflammatory cytokine profile observed in patients with MF. When combining ruxolitinib with the pan-deacetylase inhibitor panobinostat in a mouse model of JAK2V617F-driven PV-like disease, there was an added benefit on a number of endpoints. Efficacy was also demonstrated in mouse xenograft/allograft models, including models in which the most common mutation in MPNs, the JAK2V617F mutation, was expressed (Quintás-Cardama et al 2010).

Ruxolitinib inhibited the splenomegaly and morbidity/mortality in mice resulting from intravenous inoculation of cells expressing the same mutated JAK2V617F implicated in the pathogenesis of the majority of Philadelphia chromosome–negative MPNs. Ruxolitinib inhibited erythroid colony formation from mononuclear cells derived from PV subjects (IC_{50} of 223 nM compared with 407 nM for normal donors). Growth factor–independent colony formation, a unique characteristic of PV and other MPNs, was inhibited more potently with an IC_{50} of 67 nM for ruxolitinib in cells bearing the JAK2V617F mutation compared with cells bearing the wild-type JAK2.

Effects of ruxolitinib noted in 6-month rat and 12-month dog repeat-dose toxicology studies were primarily myelosuppressive in nature and are believed to be associated with the mechanism of action of ruxolitinib (inhibitor of JAK–signal transducer and activator of transcription [STAT] signaling). Genetic toxicology assessments (evaluations of ruxolitinib in the bacterial mutagenicity assay, *in vitro* chromosome aberration assay, and *in vivo* micronucleus assay) in rats were negative. In safety pharmacology evaluations, an adverse decrease in minute volume in a respiratory study in female rats only was noted at the highest dose. In a cardiovascular evaluation of ruxolitinib in dogs, electrocardiogram (ECG) parameters and ventricular repolarization were unaffected at all doses, whereas the compound lowered blood pressure and increased heart rate compared with vehicle control at the highest dose evaluated. In embryo-fetal assessments in rat and rabbit, maternal toxicity and minimal embryo-fetal toxicity were noted at the highest doses evaluated. Ruxolitinib was not teratogenic in either rat or rabbit. No effects were noted on reproductive performance or fertility in male or female rats. Increases in postimplantation loss were noted at the higher doses.

More detailed information on the pharmacology of ruxolitinib, single- and multiple-dose pharmacokinetic (PK) studies conducted in multiple species, and nonclinical safety evaluations can be found in the IB.

1.2.2. Nonclinical Drug Metabolism and Pharmacokinetics

After oral single-dose administration of ruxolitinib capsules in the fasted state, ruxolitinib was absorbed rapidly, typically attaining peak plasma concentrations within 1 to 3 hours after administration for all doses. After attaining the maximum plasma concentration (C_{max}), the ruxolitinib plasma concentrations declined, with a mean terminal-phase disposition half-life of approximately 3 to 5 hours. The mean ruxolitinib C_{max} and area under the curve (AUC) increased with approximately linear proportionality to dose for the entire dose range evaluated of 5 to 200 mg. There was no significant food effect on absorption or exposure.

Ruxolitinib is metabolized in the liver by the cytochrome P450 (CYP) metabolizing enzyme system, predominantly by the 3A4 isozyme. Systemic exposure of ruxolitinib was appreciably increased (AUC 2-fold higher) when given in combination with ketoconazole, a potent CYP3A4

inhibitor, with a similar effect observed on the pharmacodynamic (PD) activity (cytokine-induced STAT3 phosphorylation). Cytochrome P450 3A4 inducers significantly decreased the exposure to ruxolitinib, with essentially no difference observed on the PD activity (cytokine-induced STAT3 phosphorylation). This suggests that CYP3A4 induction with rifampin results in metabolism of ruxolitinib to active metabolites that also inhibit JAK.

Ruxolitinib was given as a single 25 mg dose to subjects with varying degrees of renal function (Study INCB 18424-142) and to subjects with varying degrees of hepatic dysfunction or with normal hepatic function (Study INCB 18424-137). Mild, moderate, or severe impairment of renal function had no statistically significant effect on PK or PD parameters; subjects requiring dialysis showed prolonged PD activity without a demonstrable effect on ruxolitinib clearance. The mean total AUCs of ruxolitinib were 87%, 28%, and 65% higher, respectively, in subjects with mild, moderate, and severe hepatic impairment than in subjects with normal hepatic function. Terminal half-life of ruxolitinib was increased in subjects with hepatic impairment by approximately 2-fold compared with healthy controls. The subjects with severe hepatic impairment showed modestly protracted PD activity compared with the other hepatically impaired subjects who displayed PD activity similar to the healthy controls.

Additional details about clinical pharmacology of ruxolitinib may be found in the IB.

1.2.3. Clinical Safety Summary

1.2.3.1. Healthy Volunteers Study

Ruxolitinib has been administered to over 180 healthy volunteers as single dose, repeat-single dose, or multiple doses of up to 10 days duration. The clinical database (safety set) in solid tumor and hematologic malignancies consists of 787 subjects treated in 6 studies evaluating subjects with MF (n = 679), prostate cancer (n = 22), multiple myeloma (n = 13), and ET and PV (n = 73), of whom 617 received ruxolitinib.

In healthy volunteer studies, a transient, reversible decrease in neutrophil count has been seen after doses of 25 mg to 50 mg, which reverses 12 to 24 hours after stopping ruxolitinib. These neutropenia events were of Grade 1 or Grade 2 severity, with a single instance of severe Grade 4 neutropenia that led to study drug discontinuation in 1 subject receiving 50 mg ruxolitinib twice daily (BID; highest dose). The maximum tolerated dose in healthy volunteers was determined to be 25 mg BID or 100 mg QD.

In a thorough cardiac QT study, it was shown that increasing plasma concentrations of ruxolitinib are not associated with increases in the QT interval.

For a thorough review of ruxolitinib clinical safety, refer to the IB.

1.2.3.2. Clinical Safety Data

In the randomized period of the 2 pivotal studies in MF, COMFORT-I and COMFORT-II (cutoff 01 MAR 2011, median duration of exposure = 10.8 months), discontinuation due to adverse events (AEs) regardless of causality was observed in 11.3% of subjects. The most frequently reported adverse drug reactions were thrombocytopenia and anemia. Hematological adverse reactions (any CTCAE Grade) included anemia (82.4%), thrombocytopenia (69.8%), and neutropenia (16.6%). Anemia, thrombocytopenia, and neutropenia are dose-related effects.

The 3 most frequent nonhematological adverse reactions were bruising (21.6%), dizziness (15.3%), and headache (14.0%). The 3 most frequent nonhematological laboratory abnormalities were raised alanine aminotransferase (ALT; 27.2%), raised aspartate aminotransferase (AST; 18.6%) and hypercholesterolemia (16.9%).

Long-term follow-up in subjects with MF (including 615 subjects treated with ruxolitinib during the controlled and extension period of studies INCB 18424-251 [cutoff 01 OCT 2012], COMFORT-I [02 SEP 2013], and COMFORT-II [cutoff 12 OCT 2015]) has shown that, as expected, the numbers and proportions of AEs and serious AEs (SAEs) has increased; however, no new safety signals have emerged (median duration of exposure for this population = 27.6 months, 1345.78 patient-years of exposure).

Study INCB 18424-258 established 5 mg BID as a safe starting dose in patients with PMF, post–polycythemia vera myelofibrosis (PPV-MF), and post–essential thrombocythemia myelofibrosis (PET-MF) who have platelet count between 50 and 100 × 10^9/L.

Study INCB 18424-261 showed that 10 mg BID was an effective starting dose by providing symptomatic benefit and reducing palpable spleen length in the majority of subjects while having less of an impact on hematologic parameters than seen in the pivotal Phase 3 studies.

In Study INCB 18424-260, a sustained release formulation as administered provided safety and efficacy results generally comparable to results reported previously for the immediate release (IR) formulation.

Up to Week 32 of the randomized portion in the RESPONSE trial (cutoff 25 SEP 2014, median duration of exposure = 7.8 months), ruxolitinib was generally well-tolerated in subjects with PV, and only a small proportion of subjects discontinued ruxolitinib due to AEs (6.4%). Most of the AEs have been managed by dose modifications and/or supportive care. Hematological toxicities were less frequent and less severe in patients with PV than those observed in patients with MF. Analysis of Week 80 data did not identify any new safety findings, and the frequency of AEs remained comparable to Week 48 data.

In INCB 18424-256, a Phase 2, open-label dose-ranging clinical study to determine the safety and efficacy of INCB018424 in subjects with advanced ET refractory to or intolerant of hydroxyurea, subjects with ET were randomized to receive oral ruxolitinib at a dose of 10 mg BID (n = 8), 25 mg BID (n = 9), or 50 mg QD (n = 9). No unexpected safety signals were observed compared with treatment in subjects with MF. Exposure-response analyses and population PK/PD models were developed for dose change and time courses in platelet count, absolute neutrophil count (ANC), WBC count, and hematocrit to support the starting dose selection. The majority of subjects in the 25 mg BID and 50 mg QD groups did not have dose increases over their starting dose, suggesting that total daily of 50 mg may be a maximum tolerated dose for this population. However, subjects receiving starting doses of 2 mg BID or 50 mg QD commonly required dose reduction for anemia, suggesting that 10 mg BID is an appropriate starting dose.

No new safety signals emerged from a study in pancreatic cancer in combination with capecitabine.

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.

1.2.3.3. Clinical Efficacy Data

As of 22 FEB 2016, approximately 10,350 patients had been evaluated in sponsored clinical studies and 5932 patients in third-party studies, and an estimated 37,166 patient-years of postmarketing experience have accrued since the initiation of global marketing of ruxolitinib (refer to the Ruxolitinib Development Safety Update Report).

More than 70 interventional or observational studies sponsored by third parties are ongoing or completed. These indications include the following:

- Hematologic malignancies: PV, Chuvash PV, MF (in combination with either panobinostat, azacytidine, danazol, lenalidomide, or pomalidomide), MF patients eligible for allogeneic hematopoietic stem cell transplantation, high-risk ET patients resistant to or intolerant of HU, MPNs in accelerated or blast phase (in combination with decitabine), MDS (single treatment or in combination with azacytidine), AML, CML (single treatment or in combination with nilotinib), chronic myelomonocytic leukemia, relapsed or refractory leukemia, relapsed or refractory Hodgkin lymphoma, B- or T-cell non-Hodgkin lymphoma, or chronic lymphocytic leukemia.
- Solid malignancies: phosphorylated STAT3 positive breast cancer, triple-negative breast cancer, ER-positive advanced breast cancer (in combination with exemestane), EGFR-mutant lung adenocarcinoma (in combination with erlotinib), advanced solid cancers (in combination with afatinib), or cancer-related cachexia.

Ruxolitinib is also being examined in pediatric patients with hematologic malignancies.

The results from 2 Phase 3 studies in MF (COMFORT-I, Verstovsek et al 2012; COMFORT-II, Harrison et al 2012) demonstrate the effectiveness of ruxolitinib in subjects with PMF, PPV-MF, and/or PET-MF. The results of these 2 studies were consistent, demonstrating statistically significant ($p < 0.0001$) differences in the proportion of subjects who demonstrated ≥ 35% spleen volume reduction, when compared with either placebo or an investigator's selection of best available therapy (BAT). Ruxolitinib was associated with prolonged survival compared with placebo (COMFORT-I) and BAT (COMFORT-II).

Consistent with its activity in MF, ruxolitinib demonstrated efficacy in a related MPN, PV, in the RESPONSE study (Vanucchi et al 2015). A significantly greater proportion of subjects who were randomized to ruxolitinib met the primary endpoint of the study, which was a composite endpoint of hematocrit control in the absence of phlebotomy and spleen volume reduction ≥ 35%, when compared with subjects randomized to BAT (22.7% vs 0.9%, $p < 0.0001$). Of the subjects meeting the primary endpoint at Week 32, 88% maintained their response at Week 48, and 80% maintained their response for at least 48 weeks from initial response.

An open-label Phase 2 dose regimen ranging clinical study to determine the safety and efficacy of ruxolitinib with advanced PV or ET refractory to HU (Study INCB 18424-256) is currently

ongoing in United States and Italy. The last ET subject was randomized on 07 APR 2009. As of 22 FEB 2016, 39 subjects with ET were enrolled in the study, and 19 subjects (48.7%) withdrew from the study. The median duration of exposure was 358.6 weeks (range: 13-384 weeks), and the most frequently reported reasons for withdrawal from the study for subjects with ET was lack of response (17.9%) and AEs (17.9%). In this study, ruxolitinib is well-tolerated and is associated with platelet and WBC control in most subjects. The median baseline platelet count in subjects with ET is 849×10^9/L, with 35 subjects (89.7%) having counts $> 600 \times 10^9$/L. The median baseline WBC count was 8.15×10^9/L with 11 subjects (28.2%) having counts $> 10 \times 10^9$/L. Of the subjects with baseline platelet count $> 600 \times 10^9$/L, 60.0% achieved platelet count $\leq 600 \times 10^9$/L at the Week 32 visit and 57.1% at the Week 192 visit, which was similar at Week 364 (56.3%) and demonstrating durability of response. In the initial (dose-finding) portion of the study, subjects were randomized to receive oral ruxolitinib at a dose of 10 mg BID (n = 8), 25 mg BID (n = 9), or 50 mg QD (n = 9). The majority of ET subjects received ruxolitinib in total daily doses of 10 mg to 20 mg BID or of 30 mg to 50 mg QD.

1.2.3.4. Proposed Indications

The FDA approved ruxolitinib in the United States under the trade name, 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.

The most commonly observed adverse drug reactions in subjects with MF taking ruxolitinib were anemia and thrombocytopenia. The most commonly observed nonhematological adverse drug reactions were dizziness and headache, which were mainly CTCAE Grade 1. Incyte successfully collaborated with the FDA to develop and implement a 'fit for purpose' patient-reported outcome (PRO) instrument (modified Myelofibrosis Symptom Assessment Form version 2.0) used in a Phase 3, double-blind, placebo-controlled registration trial (COMFORT-I) to evaluate the safety and effectiveness of ruxolitinib in subjects with MF. This resulted in the inclusion of symptom improvement data in the Jakafi label. In a pivotal Phase 3 study (CINC424B2301; The RESPONSE Trial), the most common nonhematologic AEs for PV subjects (incidence >10%) were headache, abdominal pain, diarrhea, dizziness, fatigue, pruritus, dyspnea, and muscle spasms.

In MAR 2010, orphan-drug designations for ruxolitinib were granted by the FDA for the "Treatment of Essential Thrombocythemia" (22 MAR 2010). In the present study, Jakafi (ruxolitinib) tablets will be used for the treatment of subjects with ET who are resistant to or intolerant of HU.

1.3. Product Information and Overview of Anagrelide

1.3.1. Anagrelide

1.3.1.1. Product Name and Application Number

Anagrelide hydrochloride, USP is a platelet-reducing agent. Its chemical name is 6,7-dichloro-1,5-dihydroimidazo[2,1-b] quinazolin-2(3H)-one monohydrochloride monohydrate, and it has the following structural formula: $C_{10}H_7Cl_2N_3O \cdot HCl \cdot H_2O$ M.W. 310.56.

Anagrelide is approved by the FDA for the treatment of patients with thrombocythemia, secondary to MPNs, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombo-hemorrhagic events.

The mechanism by which anagrelide reduces blood platelet count is still under investigation. Studies in subjects support a hypothesis of dose-related reduction in platelet production resulting from a decrease in megakaryocyte hypermaturation. In blood withdrawn from normal volunteers treated with anagrelide, a disruption was found in the postmitotic phase of megakaryocyte development and a reduction in megakaryocyte size and ploidy. At therapeutic doses, anagrelide does not produce significant changes in white cell counts or coagulation parameters and may have a small, but clinically insignificant, effect on red cell parameters. Anagrelide inhibits cyclic adenosine monophosphate (AMP) phosphodiesterase III. Phosphodiesterase III inhibitors can also inhibit platelet aggregation. However, significant inhibition of platelet aggregation is observed only at doses of anagrelide higher than those required to reduce platelet count.

Anagrelide is metabolized at least in part by CYP1A2. It is known that CYP1A2 is inhibited by several medicinal products, including fluvoxamine, and that such medicinal products could theoretically adversely influence the clearance of anagrelide. Anagrelide demonstrates some limited inhibitory activity towards CYP1A2, which may present a theoretical potential for interaction with other coadministered medicinal products sharing that clearance mechanism (eg, theophylline).

Anagrelide is an inhibitor of cyclic AMP PDEIII. The effects of medicinal products with similar properties such as inotropes milrinone, enoximone, amrinone, olprinone, and cilostazol may be exacerbated by anagrelide.

At fasting and at a dose of 0.5 mg of anagrelide, the plasma half-life is 1.3 hours. The available plasma concentration time data at steady state in subjects showed that anagrelide does not accumulate in plasma after repeated administration. Food has no clinically significant effect on the bioavailability of anagrelide.

Two major metabolites have been identified (RL603 and 3-hydroxy anagrelide).

Refer to the anagrelide label for complete detailed information on the product (Agrylin 2013).

1.4. Study Rationale

Essential thrombocythemia is a chronic MPN, which may result in a reduced life expectancy in subjects compared with the normal population. Multiple risk factors impacting overall survival of individuals with ET have been described (Tefferi et al 2014a, Tefferi et al 2014b). Subjects at increased risk for thrombosis or bleeding, particularly those with a history of thrombosis, and

high platelet and WBC counts, are treated with cytoreductive therapies. Hydroxyurea is effective and tolerated in most subjects with ET, but many require alternative cytoreductive therapy because of inadequate efficacy or poor tolerability of HU. Anagrelide is an FDA approved standard of care for ET but is associated with intolerable short- and long-term side effects. In addition, anagrelide has minimal effect on WBCs, which may also be an important mediator of thrombotic risk and does not appear to stop the progression of bone marrow fibrosis and hypercellularity in ET or PV.

Ruxolitinib may represent an effective, better-tolerated treatment than anagrelide, and the present study is proposing to compare ruxolitinib with anagrelide therapy in subjects with ET who are candidates for anagrelide therapy.

1.4.1. Essential Thrombocythemia Symptoms and Treatment

Essential thrombocythemia patients with specific characteristics such as age ≥ 60 years, extreme thrombocytosis, leukocytosis, or previous thrombo-hemorrhagic complications are treated with cytoreductive therapy, with the goal of normalizing platelet counts to reduce the risk of complications.

Anagrelide is approved by the FDA for the treatment of patients with thrombocythemia, secondary to MPNs, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms, including thrombo-hemorrhagic events.

Essential thrombocythemia patients who are candidates for cytoreductive therapy as described above are eligible for anagrelide therapy. In general, the drug is capable of reducing the platelet count to less than 600×10^9/L in more than 80% of subjects. Anagrelide would be an appropriate comparator.

1.4.2. Rationale for Study Design and Treatment and Dose Selection

In order to optimize the benefit-risk for patients, a dose titration approach is necessary. In Study INCB 18424-256, ruxolitinib treatment at doses of 10 to 25 mg BID resulted in improvements in platelet and WBC count and disease-related symptoms in subjects with ET who were hydroxyurea-refractory/intolerant, with no unexpected safety signals compared with treatment in subjects with MF. However, subjects who received starting doses of 25 mg Bid or 50 mg QD commonly required dose reduction for anemia, supporting 10 mg BID as a starting dose of ruxolitinib.

In the currently approved US label for Agrylin® capsules, dose modification guidelines recommend that the starting dose should be 0.5 mg 4 times daily or 1 mg BID and maintained for at least 1 week.

- The starting dose in Treatment Group A is ruxolitinib 10 mg BID and anagrelide-placebo capsules BID.
- The starting dose in Treatment Group B is anagrelide 1 mg BID orally and ruxolitinib-placebo.

This study is proposed to establish clinical benefit using a composite primary endpoint of durable control of platelet and WBC counts. Secondary [redacted] endpoints were chosen to systematically evaluate and compare safety and tolerability to anagrelide. Symptom

amelioration will also be assessed in subjects who have symptoms related to ET at baseline, such as pruritus, which presents in approximately 34% to 70% of ET patients (Mesa et al 2007, Tefferi et al 2001, Fenaux et al 1990). The rate of thrombo-hemorrhagic events will also be assessed.

1.4.2.1. Double-Dummy Design

Patients and investigators in open-label clinical studies are aware of treatment assignment, and therefore this approach is not suitable for clinical studies investigating efficacy of a compound with a reference treatment and the relief of symptoms using PRO instruments. This is because patients and their healthcare providers who know that they are on a particular therapy may overestimate the symptom benefit. To avoid this, a double-blinded clinical study is necessary that includes a placebo and an active drug in each group. Therefore the patient-reported symptoms are collected without the influence of the knowledge of study treatment assignment by the subjects and their health care providers. This study is designed as a double-blind, double-dummy, randomized study in which the blind is maintained until the subjects have reached Week 52, marking the timepoint for comparative analyses of the primary and secondary endpoints. Therefore, 1-way crossover to ruxolitinib for individual subjects originally randomized to anagrelide is allowed after Week 52 according to investigator's decision after consultation with the sponsor. Subjects initially assigned to Group A (ruxolitinib) receiving benefit from therapy will be assessed for durability of their responses in the open-label portion of the study.

However, unblinding for medical emergency purposes may be performed at any time during a subject's participation in the study.

1.4.2.2. Prior Anagrelide Use

While the original study design excluded subjects who have previously used even a limited course of anagrelide, Amendment 2 allows for participation of these subjects provided that anagrelide was not discontinued as a result of an AE. Prohibiting prior anagrelide use severely limited the number of subjects who needed alternative therapies permitted to participate in this study. This revision is intended to be more inclusive and allow for a greater number of subjects to participate. To avoid bias, subjects will be stratified based on prior anagrelide use.

1.5. Potential Risks and Benefits of the Treatment Regimen

1.5.1. Risks Related to Ruxolitinib

No specific findings in nonclinical repeat-dose toxicity studies identify clinical risks other than noting that consequences of immunosuppression may occur. Hypotension and increases in heart rate were noted at a high dose in a cardiovascular preclinical study. However, these findings have not been recapitulated in a clinical setting at doses up to 25 mg BID.

The primary clinical risks with ruxolitinib treatment are the potential sequelae of decreased hematopoietic proliferation secondary to the inhibition of growth factor pathways with JAK2 inhibition. Dose-dependent, reversible thrombocytopenia has been observed in the ongoing study of subjects with MF. Anemia and, less frequently, neutropenia have also been observed in the ongoing study of MF subjects. Increased rates of infection and anemia are potential risks of

myelosuppression, and there are multiple sequelae of anemia, including the burden and risks of transfusion. In healthy volunteers, rheumatoid arthritis patients, and hormone-refractory prostate cancer patients with greater bone marrow reserve, the effects on hematopoietic proliferation appear to be less pronounced.

Long-term ruxolitinib treatment was well-tolerated in subjects with ET (ongoing Study INCB 18424-256, cutoff date 22 FEB 2016). The majority of treatment-emergent AEs (TEAEs) were mild or moderate. Three subjects (7.6%) with ET died during the study (SAE of unrelated cardiac failure after 3 years of treatment; SAE of unrelated osteolytic lesions from vulva Paget's disease after 6 years of treatment; and SAE of unrelated multiorgan failure after 4 years). Fifteen subjects (38.4%) had at least 1 SAE. The most frequently reported TEAE was anemia and the most frequently reported nonhematologic TEAE were cough and increased weight. One case of unrelated basal cell carcinoma and 1 case of possibly related Kaposi's sarcoma were reported after 7 years of treatment. Headache, leukopenia, and pain in extremity were also reported in this study. There were no patterns among clinical hematology or chemistry parameters that were indicative of new safety concerns during long-term treatment with ruxolitinib in subjects with ET. Refer to the IB for full details.

1.5.2. Risks Related to Anagrelide

Anagrelide therapy requires close clinical supervision of the patient. While the platelet count is being lowered (usually during the first 2 weeks of treatment), blood counts (hemoglobin, WBCs), and renal function (serum creatinine, blood urea nitrogen) should be monitored. Cases of clinically significant hepatotoxicity (including symptomatic ALT and AST elevations and elevations > 3 × upper limit of normal [ULN]) have been reported in postmarketing surveillance. Liver function tests (ALT, AST) should be performed before initiating anagrelide treatment and during therapy.

Refer to the anagrelide label for complete detailed information on the product (Agrylin 2013).

1.5.3. Potential Benefits of Ruxolitinib

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

2.1. Study Objectives

2.1.1. Primary Objective

- To compare efficacy of ruxolitinib versus anagrelide as measured by the proportion of subjects demonstrating platelet and WBC control.

2.1.2. Secondary Objectives

- To evaluate the safety and tolerability of ruxolitinib compared with anagrelide in subjects with ET.
- To compare complete remission (CR) and partial remission (PR) rates of ruxolitinib and anagrelide in subjects with ET.
- To evaluate the duration of response.
- To evaluate the proportion of subjects demonstrating platelets control.
- To evaluate the proportion of subjects demonstrating WBC control.

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Proportion of subjects who achieve a simultaneous reduction of platelet counts to $< 600 \times 10^9$/L with a reduction of WBC counts to $< 10 \times 10^9$/L for at least 80% of biweekly measurements for a consecutive 12-week period between Weeks 32 and 52.

2.2.2. Secondary Endpoints

- Safety and tolerability of ruxolitinib measured by AEs and laboratory values.
- Proportion of subjects who discontinue study treatment because of AEs.
- Time to treatment discontinuation.
- Proportion of subjects who achieve CR or PR at Week 32 based on European LeukemiaNet (ELN) 2013 response criteria.
  - Analyses completed for subjects achieving CR plus PR.
  - Analyses completed for subjects achieving CR.
  - Analyses completed for subjects achieving PR.
- Duration of response as measured from the onset of response to the loss of response for responders. Response is defined the same as in the primary endpoint.
- Proportion of subjects who achieve reduction of platelet counts to $< 600 \times 10^9$/L for at least 80% of biweekly measurements for a consecutive 12-week period between Weeks 32 and 52.
- Proportion of subjects who achieve a reduction of WBC counts to $< 10 \times 10^9$/L for at least 80% of biweekly measurements for a consecutive 12-week period between Weeks 32 and 52.

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:

1. Men and women, aged 18 or older.
2. Subjects diagnosed with ET according to revised WHO 2016 criteria (Appendix A; Arber et al 2016).
3. Subjects who are resistant to or intolerant of HU (Appendix B), that is, fulfilling at least 1 of the following criteria:
    a. Platelet count > 600× 10^9/L after 3 months of at least 2 g/day of HU (2.5 g/day in subjects with a body weight over 80 kg) OR at the subject's maximally tolerated dose if that dose is < 2 g/day.
    b. Platelet count > 400 × 10^9/L and WBC count < 2.5 × 10^9/L or hemoglobin (Hgb) < 10 g/dl at any dose of HU.
    c. Presence of leg ulcers or other unacceptable muco-cutaneous manifestations at any dose of HU.
    d. HU-related fever.
4. Platelet count ≥ 650 × 10^9/L at screening.
5. WBC ≥ 11.0 × 10^9/L at screening.
6. ECOG performance status 0 to 2.
7. Known status of JAKV617F mutation.

8. 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. Subjects who have previously been treated with JAK inhibitors.
2. Subjects being treated concurrently with anagrelide or HU.
    a. Prior anagrelide use is allowed provided the reason for discontinuation is not AE-related and anagrelide is stopped at least 28 days before the start of study medications (ie, Day 1).
    b. Treatment with HU can be stopped at any time once one of the inclusion criteria for HU refractoriness or resistance have been met, and up to the day before the first dose of study treatment (ie, Day 1).
3. Subjects with inadequate liver function at screening and Day 1 (before drug administration) as demonstrated by the following:
    a. Total bilirubin > 1.5 × ULN.
    b. AST or ALT > 1.5 × ULN.
    c. Hepatocellular disease (eg, cirrhosis).
4. Subjects with inadequate renal function at screening as demonstrated by creatinine clearance < 40 mL/min calculated by Cockcroft-Gault equation.
5. Subjects with clinically significant cardiovascular disease, including uncontrolled cardiac disease, including unstable angina; acute myocardial infarction within 6 months from 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.
6. History or presence of an abnormal ECG that, in the investigator's opinion, is clinically meaningful.

7. Subjects with impairment of gastrointestinal (GI) function or active GI disease that may significantly alter absorption of ruxolitinib or anagrelide (eg, active ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, and small bowel obstruction).
8. Inability to swallow and retain oral medication.
9. Subjects with clinically significant bacterial, fungal, parasitic, or viral infection that requires therapy:
    a. Subjects with acute bacterial infections requiring antibiotic therapy should delay screening/enrollment until the course of antibiotic therapy has been completed.
    b. Subjects on chronic antibiotics for prophylaxis are allowed.
10. 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.
11. Known human immunodeficiency virus infection.
12. Subjects with diagnosed primary immunodeficiency syndromes, such as X-linked gammaglobulinemia and common variable immune deficiency.
13. Subjects with peripheral blood blast count of > 0% at screening.
14. Subjects with an active malignancy over the previous 2 years except treated cervical intraepithelial neoplasia, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or completely resected papillary thyroid and follicular thyroid cancers.
15. Pregnant or breastfeeding women.
16. Use of any potent CYP3A4 inhibitors or inducers or CYP1A2 inhibitors within 14 days or 5 half-lives (whichever is longer) before the first dose of ruxolitinib or anagrelide or their anticipated use during the study (does not apply to topical ketoconazole).
17. Use of concomitant treatment of fluconazole at a dose > 200 mg.
18. Subjects being treated concurrently with any prohibited medications.
19. Subjects being treated concurrently with any medications that may prolong QTc interval of the ECG (see Appendix J).
20. Subjects being treated concurrently with any investigational agent or who have previously participated in an investigational study within 30 days before to the first dose of study drug or within 5 half-lives of the previous investigational product, whichever is longer.
21. Subjects who are unable to comprehend or are unwilling to sign an informed consent form (ICF).
22. Subjects who are unwilling or incapable of complying with the requirements of the study.

23. Subjects with active alcohol or drug addiction that would interfere with their ability to comply with the study requirements.
24. 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 4-week screening period (Days -35 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, then the subject is considered a screen failure and must be withdrawn from the study. Therefore, sites should consider the testing schedule carefully so that any potential retests are accomplished within the 4-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 laboratory finding, ECG finding, or medical history finding, including scheduling difficulties at the clinic site, then the subject may retain the original subject number and complete the remaining screening activities as soon as possible, within a maximum of 42 days (6 weeks) from the original screening visit date. A blood draw for hematology and serum chemistry must be taken at the time that the subject returns for completion of screening activities and will be used to determine eligibility.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

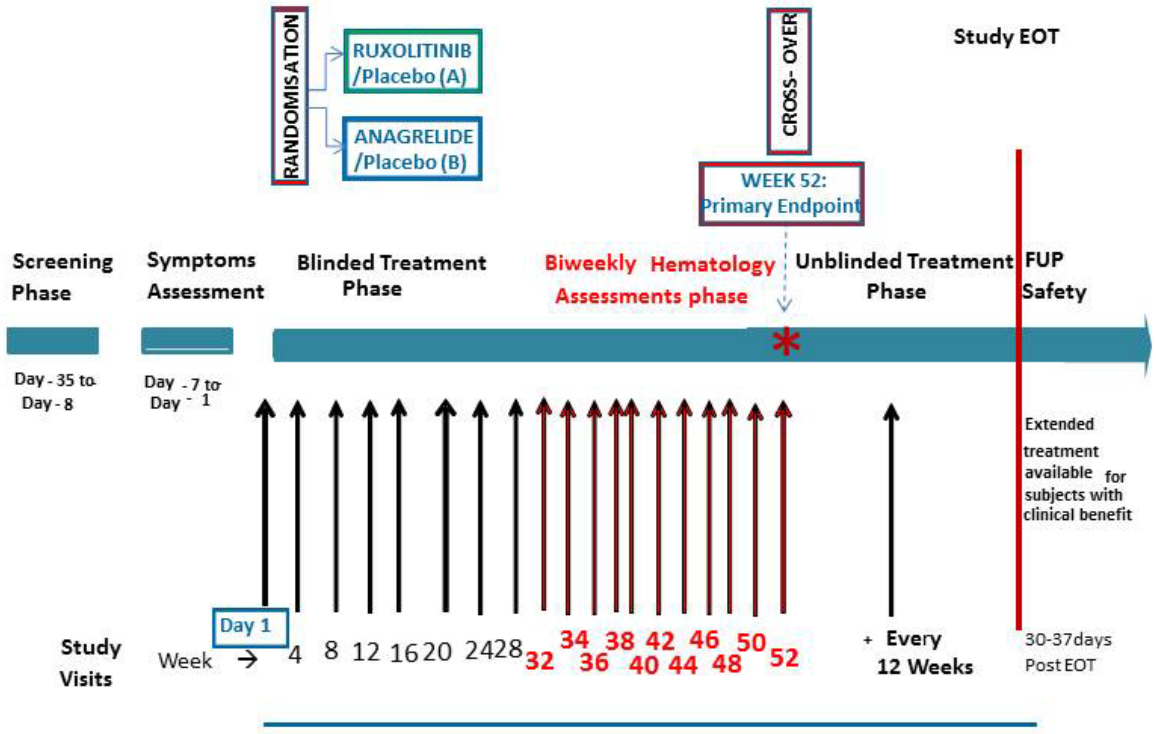
This is a Phase 2, randomized, double-blind, double-dummy study in subjects with ET who are resistant to or intolerant of HU (according to modified ELN criteria) with a screening platelet count ≥ 650 × 10^9/L and WBC count ≥ 11.0 × 10^9/L. Subjects will be randomized in a 1:1 ratio, stratified by JAKV617 mutation status (positive vs negative), platelet count at screening (≥ 1000 × 10^9/L or < 1000 × 10^9/L), and prior anagrelide use (yes vs no) to the following 2 treatment groups:

- Group A: ruxolitinib at a dose of 10 mg BID orally and anagrelide-placebo.
- Group B: anagrelide at a dose of 1 mg BID orally and ruxolitinib-placebo.

The study will enroll approximately 120 subjects. Due to block randomization and stratification, the 2 treatment groups may not each contain exactly the targeted number of subjects (n = 60).

Subjects will receive blinded study treatment for 52 weeks. Options for the open-label treatment phase are detailed in Section 4.1.1. All subjects will be followed for safety (eg, reporting of AEs and SAEs) 30 to 37 days after the last dose of blinded study treatment or open-label study treatment. The overall study design is shown in Figure 1.

Figure 1: Study Design



4.1.1. Options for the Open-Label Treatment Phase

Subjects originally randomized to ruxolitinib with anagrelide placebo (Group A) who are receiving benefit from therapy can 1) continue receiving open-label ruxolitinib until the study is concluded or they meet discontinuation criteria, or 2) choose to discontinue therapy.

Subjects originally randomized to receive anagrelide plus ruxolitinib placebo (Group B) have 3 options: 1) they may cross over to begin receiving ruxolitinib if they meet eligibility criteria after consultation with the sponsor and may then continue until the study is concluded or they meet discontinuation criteria; 2) they may continue receiving anagrelide until the study is concluded or they meet discontinuation criteria; or 3) they can choose to discontinue therapy. Note that subjects originally randomized to Group B may cross over to receive ruxolitinib at any time during the open-label part of the study.

Subjects who will continue with the same active agent to which they were randomized will have a study visit at Week 56, at which time study drugs will switch over to open-label supplies (ruxolitinib or anagrelide) and then study visits every 12 weeks (Week 68, 80, etc). Subjects who were originally randomized to anagrelide (Group B) and who cross over to ruxolitinib will begin receiving ruxolitinib at the Week 56 visit. These subjects will have study visits at Weeks 1, 2, 3, 4, and every 4 weeks up to 52 weeks, then every 12 weeks thereafter. Subjects who initially remain on anagrelide after unblinding but choose to cross over to receive ruxolitinib at a later time will have study visits at Weeks 1, 2, 3, 4, and every 4 weeks up to 52 weeks, then every 12 weeks thereafter.

4.2. Measures Taken to Avoid Bias

This is a randomized, double-blind, placebo-controlled study with a composite primary endpoint, defined as the proportion of subjects who complete at least 52 weeks of treatments and who achieve a simultaneous reduction of platelet count to $< 600 \times 10^9$/L and of WBC count to $< 10 \times 10^9$/L for at least 80% of biweekly measurements for 12 consecutive weeks between Weeks 32 and 52. Subjects will receive blinded study drug (ruxolitinib + anagrelide placebo or anagrelide + ruxolitinib placebo).

Centralized randomization numbers within each stratum will be created for treatment assignment. Subjects will be stratified by presence/absence of the JAK2 V617F mutation, screening platelet count, and prior anagrelide use. Subjects will be assigned to study treatment in accordance with the randomization schedule. Subjects, investigators, and the study team will be blinded to treatment assignment. A sponsor statistician who is not part of the study team will be unblinded and may provide summary-aggregated data by treatment group to the sponsor and/or the Data Monitoring Committee (DMC), but individual subject data will remain blinded.

4.3. Number of Subjects

Approximately 120 subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups (approximately 60 subjects per group).

4.4. Duration of Treatment and Subject Participation

After signing the ICF, subject study participation is estimated to average approximately 24 to 36 months per individual subject:

Screening (Day -35 to Day -8): Up to 28 days.

Baseline (pretreatment) period (Day -7 to Day -1): 7 days before the first dose of treatment (required for all eligible subjects to complete the daily symptom diary for 7 days before the first dose of study medication).

Blinded Treatment Phase (Day 1 through Week 52): Begins with first dose of either ruxolitinib plus anagrelide-placebo or anagrelide plus ruxolitinib-placebo (Day 1). The efficacy assessment period will be defined by collection of blood samples every 2 weeks between Weeks 32 and 52.

Open-Label Treatment Phase (Crossover and Extension Period): After each individual subjects reach the Week 52 study visit (and all data through the Week 52 visit have been entered to the eCRF and the data verified), crossover to an open-label extension may occur. Once Week 52 data completion has been confirmed, the study subject and the investigator will be unblinded to study treatment assignment. The subjects will be brought into the study clinic for the unblinding crossover visit, which is designated as Week 56 in the schedules of assessments (Table 3 and Table 5).

Subjects originally randomized to anagrelide (Group B) will be evaluated for eligibility to cross over to open-label ruxolitinib according to investigator's decision and if subjects meet safety criteria (eg, they do not now meet any exclusion criteria that would have precluded their participation in the study), after consultation with the sponsor. Subjects originally randomized to ruxolitinib (Group A) who are receiving benefit from therapy will continue receiving open-label ruxolitinib until the study is concluded. All subjects will be followed for safety (eg, reporting of AEs and SAEs) 30 to 37 days after last dose of blinded study treatment or open-label study treatment.

Follow-up period: 30 to 37 days after the last dose of blinded study treatment or open-label ruxolitinib.

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The blinded treatment phase is complete and study data analysis can occur for the primary endpoint when all subjects have completed Week 52 or discontinued, and all study data through the Week 52 visit have been entered and the data cleaned and verified. The database will be frozen at this time for the initial data analysis to occur.

The study is completed when the last subject has reached Week 156 (approximately 3 years of treatment). Individual subject participation is expected to average 24 to 36 months.

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, or upon advice of the DMC. 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 interactive voice/web response system (IXRS).

Study sites will enter subject demographic and baseline data into 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 allocate the subject to treatment assignment and obtain the initial study drug assignment. The investigator or designee will select the assigned units of study drug from their stock that correspond to the number provided by the IXRS and dispense the study drug to the subject. All subsequent dispensing of study drug should follow this process. 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 electronic case report form (eCRF) Completion Guidelines for instruction on which eCRFs to complete.

5.1.2. Randomization and Blinding

Subjects will be randomly assigned to either Group A or Group B through central randomization by the IXRS. Full details will be provided in the IXRS manual.

Subjects, investigators, and the sponsor will remain blinded to each subject's treatment assignment throughout the study. Emergency unblinding will occur if an AE requires the investigator to be made aware of the subject's treatment assignment.

5.1.2.1. Blinding and Unblinding

Treatment assignment should remain blinded to the investigators, subjects, and sponsor as long as the blinded treatment period continues for that subject. Unblinding of treatment assignment may occur in 2 different circumstances: emergency unblinding and scheduled unblinding for individual subjects after Week 52.

5.1.2.1.1. Emergency Unblinding

The investigator will, whenever possible, discuss options with the sponsor's medical monitor before initiating the emergency unblinding procedure. If the investigator is unable to contact the sponsor before unblinding, then the investigator must notify the sponsor as soon as possible after the unblinding incident. In addition, the investigator will record the date and reason for revealing the blinded treatment assignment for that subject. Refer to the IXRS manual for detailed emergency unblinding procedures.

If an SAE (as defined in Section 8.3) is reported to the sponsor, then the sponsor may choose to unblind the treatment assignment for the individual subject. If an expedited regulatory report to 1 or more regulatory agencies is required, then the report will identify the subject's treatment assignment. When applicable, a copy of the regulatory report may be sent to investigators in accordance with relevant regulations, the sponsor's policy, or both.

Generally, emergency unblinding will occur only in the case of a serious medical event for which knowledge of the treatment assignment is critical for the acute medical management of the subject's condition. Subjects experiencing this type of event will be withdrawn from study participation for safety reasons.

5.1.2.1.2. Scheduled Unblinding

After each individual subject completes the Week 52 visit, and when all data for each subject have been entered into the eCRFs and cleaned and verified, unblinding for an individual subject can occur. Subjects will be brought to the study clinic for the unblinding/crossover visit, which is designated Week 56 in the schedules of assessments (Table 3 and Table 5). Subjects who will continue receiving the study drug to which they were originally randomized will have subsequent visits every 12 weeks (Week 68, 80, etc).

Subjects who are unblinded and cross over to start ruxolitinib for the first time will have study visits at Weeks 1, 2, 3, 4, and every 4 weeks up to 52 weeks, then every 12 weeks thereafter.

The unblinding of study treatment before Week 52 will only occur for medical emergency purposes (SAE for which unblinding is necessary for medical management) and will result in withdrawal from the study.

5.2. Study Drug

5.2.1. Ruxolitinib

5.2.1.1. Description and Administration

Ruxolitinib or matching placebo will be provided as 5 mg tablets packaged in high-density polyethylene (HDPE) bottles. Ruxolitinib or matching placebo will be self-administered as a BID oral treatment.

Doses of ruxolitinib or matching placebo should be self-administered with approximately 12 hours apart without regards to food.

Note that subjects must be instructed to withhold the morning dose of ruxolitinib or matching placebo until reaching the clinic for each study visit where dose administration will occur. The dose must be reduced or interrupted for declining platelet count, hemoglobin, or ANC as described in Section 5.4 and will be increased or restarted with recovery of hematologic parameters.

5.2.1.2. Supply, Packaging, and Labeling

The study drugs will be dispensed in a kit form in which paired bottles of study drugs will be dispensed to the subject, with instructions of how to self-administer the study drugs.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country.

5.2.1.3. Storage

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

5.2.2. Anagrelide (Non-Incyte Product)

5.2.2.1. Description and Administration

Anagrelide hydrochloride or matching placebo will be provided as 0.5 mg capsules packaged in HDPE bottles.

Anagrelide or matching placebo will be self-administered as a BID oral treatment using the dose designated at the time of the screening visit for each subject.

Doses of anagrelide or matching placebo should be self-administered approximately 12 hours apart without regards to food.

Note that subjects must be instructed to withhold the morning dose of anagrelide or matching placebo until reaching the clinic for each study visit where dose administration will occur. The dose must be reduced or interrupted for declining platelet count or ANC as described in Section 5.4 and will be increased or restarted with recovery of hematologic parameters.

For patient-specific counseling information, refer to the anagrelide label (Agrylin 2013).

5.2.2.2. Supply, Packaging, and Labeling

The study drugs will be dispensed in a kit form in which paired bottles of study drugs will be dispensed to the subject, with instructions of how to self-administer the study drugs.

Anagrelide or matching placebo reference therapies with marketing authorisation must be used in accordance with the storage conditions and shelf life in the manufacturer's approved label.

5.2.2.3. Storage

The bottles of anagrelide or matching placebo capsules should be stored at room temperature, 15°C to 30°C (59°F to 86°F). Stability studies will be conducted on clinical batches to support the clinical study.

5.2.3. Instruction to Subjects for Handling Study Drug Ruxolitinib and Anagrelide and Their Matching Placebo

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 ruxolitinib and/or anagrelide or matching placebo 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 of ruxolitinib and/or anagrelide or matching placebo 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 is missed by more than 4 hours, then that dose should be skipped, and the next scheduled dose taken at the usual time.
- 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 ruxolitinib and/or anagrelide or matching placebo 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, Interruptions, and Adjustments

Subjects randomized to either study group will be receiving both an active drug and a placebo (dummy drug). Neither the investigator nor the subject will know which is the active drug and which is the placebo. Thus, in order to maintain the blind, when dose modification is required, both of the study drugs will be titrated together.

5.4.1. Dose Increases for Inadequate Efficacy

Dose increases will be permitted for inadequate efficacy. Dose increases for subjects meeting prespecified criteria for inadequate efficacy will be permitted after 2 weeks of therapy, and dose decreases for safety are allowed at any time. Doses of both study drugs will be titrated simultaneously using different dose levels as shown in Table 2. Anagrelide or anagrelide placebo and ruxolitinib or ruxolitinib placebo increases are permitted per investigator discretion and taking into account the manufacturer's instructions, labeling, and subject's medical condition.

Each dose escalation must be at least 1 week apart, and subjects must meet all of the following criteria:

1. Platelet count $\geq 150 \times 10^9$/L
2. Hemoglobin ≥ 9 g/dL.
3. ANC $\geq 1500 \times 10^9$/L.
4. One or more of the following:
    a. Platelet count $> 600 \times 10^9$/L.
    b. WBC count $> 10 \times 10^9$/L.
    c. Minimal improvement, no change, or worsening of vasomotor symptoms including headache, lightheadedness, syncope, atypical chest pain, acral paresthesia, livedo reticularis, erythromelalgia, and transient visual disturbances (eg, amaurosis fugax, scintillating scotomata, ophthalmic migraine).

Additionally, it is recommended that safety hematology be performed within 14 days of a dose increase to confirm that a safe dose has not been exceeded. Doses may be increased by 5 mg BID for ruxolitinib or ruxolitinib-placebo. These are per investigator discretion and taking into account the manufacturer's instructions, labeling, and subject's medical condition. The dose of ruxolitinib or ruxolitinib-placebo will never exceed 25 mg BID.

Doses of anagrelide or anagrelide placebo may not be increased by more than 0.5 mg/day per week from the previous dose or to a dose that was not previously tolerated by the subject. The dose of anagrelide or anagrelide placebo should not exceed 2.5 mg BID (and 2.5 mg in a single dose). The maximum dose of anagrelide is 2.5 mg BID (5 mg total per day), which corresponds to a high maintenance dose used in practice.

5.4.2. Dose Interruptions or Decreases for Toxicity

5.4.2.1. Hematologic Toxicities

The following changes in hematologic values will be considered sufficient reason for dose interruption according to the guidelines in Table 1.

Table 1: Dose Interruptions for Hematologic Toxicities

Parameter	Dose Reduction by 1 Dose Level If:	Hold If	Reinstitute Drug at 1 Dose Level Lower When Recovered to
Hematocrit (%)	< 35%	< 30%	≥ 35%
ANC ($\times 10^9$/L)	< 1.5 × 10^9/L	< 1.0 × 10^9/L	≥ 1.25 × 10^9/L
Platelet count ($\times 10^9$/L)	< 150× 10^9/L	< 100× 10^9/L	≥ 125 × 10^9/L

5.4.2.2. Nonhematologic Toxicities

Treatment with study drug should also be withheld for any ≥ Grade 3 nonhematologic toxicity possibly, probably, or definitely related to treatment and only resumed after the toxicity returns to baseline.

Hematological and nonhematological toxicities should be reviewed by the investigator with the subject in person, by telephone, or by e-mail at least weekly. Drug may be withheld up to 4 weeks at a time up to a maximum of 8 weeks, but if hematology parameters do not return to the level for reinstituting drug by that time, or if another nonhematological form of toxicity does not return to baseline grade, then the subject will be discontinued from the study. Erythropoietin is not allowed during the study. [redacted]

Doses of both study drugs are titrated simultaneously following the guidelines in Table 2.

Table 2: Dose Levels for Ruxolitinib and Anagrelide and Dose Reduction/Restart Guidelines

Ruxolitinib					Anagrelide				
		Dose (mg)					Dose (mg)		
Dose Level	Week	AM	PM	Total Daily Dose (mg)	Dose Level	Week	AM	PM	Total Daily Dose (mg)
DL 4	W 2	25	25	50	DL 4	W 2	2.5	2.5	5
	W 1	25	25	50		W 1	2	2.5	4.5
DL 3	W 2	20	20	40	DL 3	W 2	2	2	4
	W 1	20	20	40		W 1	1.5	2	3.5
DL 2	W 2	15	15	30	DL 2	W 2	1.5	1.5	3
	W 1	15	15	30		W 1	1	1.5	2.5
DL 1 - STARTING DOSE		**10**	**10**	**20**	**DL 1 - STARTING DOSE**		**1**	**1**	**2**
DL -1	W 1	10	5	15	DL -1	W 1	1	0.5	1.5
	W 2	10	5	15		W 2	1	0.5	1.5
DL -2	W 1	5	5	10	DL -2	W 1	0.5	0.5	1
	W 2	5	5	10		W 2	0.5	0.5	1
DL -3	W 1	5	0	5	DL -3	W 1	0.5	0	0.5
	W 2	5	0	5		W 2	0.5	0	0.5

5.4.2.3. Dose Reductions With Concomitant Cytochrome P450 Inhibitors

5.4.2.3.1. Cytochrome P450 3A4 Inhibitors

Ruxolitinib is metabolized in the liver by the CYP-metabolizing enzyme system, predominantly by the 3A4 isozyme. With concomitant treatment of potent CYP3A4 inhibitors such as systemic ketoconazole (see Appendix H), plasma exposure of ruxolitinib increases by approximately 2-fold. Thus, a dose reduction of approximately 50% for study treatment is appropriate for subjects who take systemic ketoconazole or other potent CYP3A4 inhibitors systemically as concomitant medication. This dose reduction should be accomplished by reducing doses of ruxolitinib or ruxolitinib-placebo from BID to QD.

Potent inhibitors of CYP3A4 include systemic ketoconazole, posaconazole, voriconazole, clarithromycin, itraconazole, nefazodone, and telithromycin (see Appendix H). Dose reductions are not required for topical ketoconazole.

NOTE: Once the course of therapy using a CYP3A4 inhibitor has been completed, the subject may resume his/her previous BID dose regimen of study treatment beginning the next day.

5.4.2.3.2. Cytochrome P450 1A2 Inhibitors

Anagrelide is metabolized at least in part by CYP1A2. Anagrelide is an inhibitor of cyclic AMP PDEIII. Thus, a dose reduction of approximately 50% for study treatment is appropriate for subjects who take potent CYP1A2 inhibitors systemically as concomitant medication (see Appendix H). This dose reduction should be accomplished by reducing doses of anagrelide or anagrelide-placebo from BID to QD.

NOTE: Once the course of therapy using a CYP1A2 inhibitor has been completed, the subject may resume his/her previous BID dose regimen of study treatment beginning the next day.

Investigators may refer to anagrelide label for further detailed information of potential interactions.

5.4.3. Dose Discontinuation of Ruxolitinib or Ruxolitinib Placebo/Anagrelide or Anagrelide Placebo

5.4.3.1. Discontinuation of Study Drugs for Hematologic Toxicity

Study drug (ruxolitinib, anagrelide, or matching placebos) MUST be permanently discontinued if any 1 of the following Grade 3 or 4 hematologic toxicities (National Cancer Institute [NCI] CTCAE v 4.03) fails to resolve to ≤ Grade 2 within 8 weeks of study drug interruption or if a lower restart dose or administration schedule subsequent to any of the following recurrent Grade 3 hematologic toxicities is either not available or likely to be clinically ineffective:

- Hgb < 8.0 g/dL (Grade 3).
- Platelet count < 25×10^9/L (Grade 4).
- ANC < 0.5×10^9/L (Grade 4).

5.4.3.2. Discontinuation of Study Drug for Nonhematologic Toxicity

Study drug (ruxolitinib, anagrelide, or matching placebos) MUST be permanently discontinued if any 1 of the following AEs fails to resolve to ≤ Grade 2 within 8 weeks of study drug interruption or if a lower restart dose or administration schedule subsequent to any of the following nonhematologic toxicities is either not available or likely to be clinically ineffective:

- The occurrence of a Grade 4 laboratory or nonlaboratory abnormality attributable to study treatment (ruxolitinib, anagrelide, or matching placebo).
- The occurrence of a Grade 3 laboratory or nonlaboratory abnormality attributable to study treatments (ruxolitinib, anagrelide, or matching placebo) that remains at Grade 3 or worse for > 7 days duration and, for laboratory abnormalities, is deemed clinically significant in the judgment of the investigator.

5.4.3.3. Dose Reduction Tapering Strategy (Optional)

Following discontinuation of study drugs, symptoms from MPNs may return to pretreatment levels over a period of approximately 1 week.

When discontinuing or interrupting therapy for reasons other than thrombocytopenia or neutropenia, consider tapering the dose of study drugs gradually rather than discontinuing abruptly. A dose-tapering strategy may be considered, based on evaluation of the condition of the subject, current dosing regimen, and the clinical judgment of the investigator.

5.4.4. Dose Modifications for Subjects Receiving Open-Label Treatment

The dose increase, decrease, and discontinuation rules described in Sections 5.4.1, 5.4.2, and 5.4.3 will be followed for subjects receiving open-label anagrelide or open-label ruxolitinib. Table 2 should be used to identify dose levels for the individual study medications.

5.5. Withdrawal of Subjects From Study Treatment

In the event that any subject permanently discontinues the study treatment, regardless of reason, reasonable efforts should be made to have the subject return to have the end-of-treatment (EOT) and follow-up evaluations completed as described in Section 6.6.

The date that the subject discontinued the study treatment and the specific reason for withdrawal will be recorded in the eCRF. This information will be used to summarize the reasons for study withdrawal.

5.5.1. Withdrawal Criteria

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

- Toxicities occur as noted in Section 5.4.3.
- Treatment is interrupted for ≥ 8 weeks, unless approved by medical monitor.
- Subject is unblinded before Week 52 for safety reasons.
- 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 FDA or the investigator.

5.5.2. Withdrawal Procedures

In the event that the decision is made to permanently discontinue the study treatment, the subject will be withdrawn from the study and the end-of-treatment 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 and the subject is withdrawn from the study, reasonable efforts should be made to have the subjects return for a follow-up visit for safety until the time of the follow-up visit or until study treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

If the subject discontinues study treatment and actively withdraws consent for collection of follow-up data (safety follow-up or disease assessment), then no additional data collection should occur; however, subjects will have the option of withdrawing consent for study treatment but continuing in the follow-up period of the study for safety/efficacy assessments.

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 randomization 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. [redacted]

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.

All randomized subjects should receive low dose aspirin (75 mg to 125 mg daily) unless medically contraindicated. In this case, other prophylactic antithrombotic agents may be used.

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 restricted during the study:

1. Aspirin in doses exceeding 125 mg per day is not permitted. Low-dose aspirin is permitted. Acetaminophen and nonsteroidal anti-inflammatory agents (eg, ibuprofen, NSAIDs) may be used at over-the-counter doses. Subjects receiving over-the-counter NSAIDs should not exceed the recommended dose and should be encouraged to use gastroprotective agents (antacids, H2 antagonists, or proton pump inhibitors).
2. Inducers of CYP3A4 (Appendix H) may be used with caution, and investigators should seek other options if available.
3. 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 during a period of concomitant medication use. If required for safety, the study drug dose may be reduced from BID to QD in these circumstances. The sponsor's medical monitor may be consulted for advice when using these agents.
4. Use of potent inhibitors of CYP3A4 and CYP1A2 should be avoided where possible. See Section 5.4.2.3 for required dose reductions and Appendix H for included CYP inhibitors.
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.

5.6.3. Prohibited Medications

The following medications are prohibited during the study:

1. Any prior or concomitant use of another JAK inhibitor.
2. Concurrent use of anagrelide or HU.
    a. Prior anagrelide use is allowed provided the reason for discontinuation is not AE-related and anagrelide is stopped at least 28 days before the start of study medications (ie, Day 1).
    b. Treatment with HU can be stopped at any time once one of the inclusion criteria for HU refractoriness or resistance have been met, and up to the day before the first dose of study treatment (ie, Day 1).
3. Any investigational medication (other than ruxolitinib) that is not approved for any indication.
    a. 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.

4. Steroid doses greater than the equivalent of 10 mg prednisone per day. During study participation, if a subject requires steroids for a comorbid condition, then continuation in the study will be considered on an individual basis by the sponsor and the investigator (unless part of study treatment dose-tapering strategy).
5. Use of busulfan, interferon alpha, pegylated interferon, or any investigational medication used to treat ET is not permitted at any time beginning on Day -30 up until the time that ruxolitinib therapy is permanently discontinued. Use of androgens to treat anemia is permitted.

[redacted]

7. Erythropoietin is not allowed during the study.
8. Romiplostim or eltrombopag are not permitted beginning with the baseline visit (Day -7) through the final dose of ruxolitinib.
9. St John's Wort and rifampin are not permitted at any time during participation in the study.
10. Any medications that may prolong QTc interval of the ECG.

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

See Appendix J for a list of drugs that may cause prolongation of QT interval.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (Table 3), and all laboratory assessments will be performed as indicated in Table 4. The schedule of assessments and laboratory assessments for subjects in Group B (anagrelide) who cross over to open-label ruxolitinib after Week 52 are provided in Table 5 and Table 6. Table 7 presents a summary of clinical laboratory analytes to be assessed. 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 3: Schedule of Assessments

				Blinded Treatment (All Subjects)						Open-Label Treatment				
										Subjects Who Do Not Cross Over	Subjects Who Cross Over			
		Screening	Baseline	W1-W3				W4-W52 q4w	W34-W50 q4w (lab only)	W56 + q12w	W56+ q12w	EOT	Safety Follow-Up 30-37d After Last Dose	Notes
	Section	Days -35 to -8	Days -7 to -1	D1	D8 (±2d)	D15 (±2d)	D22 (± 2d)	D7 (± 3d)	D7 (± 3d)	D7 (± 7d)				
Informed consent	7.1	X									See Table 5			
Contact IXRS	7.2	X		X				X		X		X		
Review inclusion and exclusion criteria	7.5.1	X		X										
Demography, medical history	7.3	X												
Prior/concomitant medications	7.4	X	X	X	X	X	X	X		X		X	X	
Vital signs	7.5.4	X	X	X	X	X	X	X		X		X	X	Vital signs collected after 5 min rest in recumbent, semirecumbent, or sitting position.
Physical examination, body weight, height	7.5.3	X*		X	X	X	X	X		X		X*	X	* Comprehensive examination at screening and EOT visits, targeted physical examination at all other indicated visits. Height at screening only.
ECOG status	7.7.1	X*		X*				X		X		X		* Performance status must be 0, 1, or 2 at baseline.
[redacted]/liver palpation	7.6.3	X	X					X		X		X	X	Using flexible ruler provided for study.
Complete MPN-SAF questionnaire	7.7.4		X					X*				X*		*Weeks 32 and 52 and/or EOT visits.
Overall response assessment	7.6.2							X*				X*		* Weeks 32 and 52 and/or EOT visits.
12-lead ECG	7.5.5	X						X*				X		* Week 52.

Table 3: Schedule of Assessments (Continued)

				Blinded Treatment (All Subjects)						Open-Label Treatment				
										Subjects Who Do Not Cross Over	Subjects Who Cross Over			
		Screening	Baseline	W1-W3				W4-W52 q4w	W34-W50 q4w (lab only)	W56 + q12w	W56+ q12w	EOT	Safety Follow-Up 30-37d After Last Dose	Notes
	Section	Days -35 to -8	Days -7 to -1	D1	D8 (±2d)	D15 (±2d)	D22 (± 2d)	D7 (± 3d)	D7 (± 3d)	D7 (± 7d)	D7 (± 7d)			
Laboratory tests	7.5.6	X	X	X	X	X	X	X*	X*	X	See Table 5	X	X	* Weeks 32-52 are evaluation period for primary endpoint. Should ALL be carefully monitored by sites.
[redacted]														
Review AEs	7.5.2	X	X	X	X	X	X	X		X		X	X	
Transfusion history/status	7.4	X	X	X				X		X		X	X	
Drug dispensed	7.10.2			X				X		X				
Drug accountability	7.10.3							X		X		X		

MPN-SAF = Myeloproliferative Neoplasm–Symptom Assessment Form (paper/pencil format).

Table 4: Schedule of Laboratory Assessments

				Blinded Treatment (All Subjects)						Open-Label Treatment				
										Subjects Who Do Not Cross Over	Subjects Who Cross Over			
		Screening	Baseline	W1-W3				W4-W52 q4w	W34-W50 q4w (lab only)	W56+ q12w	W56+ q12w	EOT	Safety Follow-Up 30-37d After Last Dose	Notes
	Section	Days -35 to -8	Days -7 to -1	D1	D8 (±2d)	D15 (± 2d)	D22 (± 2d)	D7 (± 3d)	D7 (± 3d)	D7 (± 7d)	D7 (± 7d)			
Local laboratory assessments											See Table 6			
Hematology	7.5.6	X	X*	X*	X	X	X	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. ** Weeks 32-52 are evaluation period for primary endpoint: Should ALL be carefully monitored by sites.
Ferritin level	7.5.6		X											
Coagulation panel	7.5.6	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.
Serum chemistries	7.5.6	X	X*	X*	X	X	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.
Urine pregnancy test	7.5.6.1			X				X		X				Females of childbearing potential. Test should be repeated if required by local regulations. Not needed if FSH elevated or amenorrheic > 1 year.

Table 4: Schedule of Laboratory Assessments (Continued)

				Blinded Treatment (All Subjects)						Open-Label Treatment				
										Subjects Who Do Not Cross Over	Subjects Who Cross Over			
		Screening	Baseline	W1-W3				W4-W52 q4w	W34-W50 q4w (lab only)	W56+ q12w	W56+ q12w	EOT	Safety Follow-Up 30-37d After Last Dose	Notes
	Section	Days -35 to -8	Days -7 to -1	D1	D8 (±2d)	D15 (± 2d)	D22 (± 2d)	D7 (± 3d)	D7 (± 3d)	D7 (± 7d)	D7 (± 7d)			
Bone marrow biopsy and analysis	7.6.4	X*						X**		X***	See Table 6	X		Local laboratory evaluation and pathology report. * Predose biopsy not required if previous biopsy and report from 2 months before screening are available. ** Weeks 32 and 52 only. *** Optional at Week 104 and 152 for ruxolitinib-treated subjects only.
Central laboratory samples														The central laboratory is the sponsor or designee.
Bone marrow biopsy and analysis	7.6.4	X*						X**		X***		X		Samples sent for banking to central laboratory. See notes for local laboratory collections above.
Lipid panel	7.5.6	X		X*	X	X	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.
Serology hepatitis A, B, and C	7.5.6	X												
Urinalysis	7.5.6	X		X		X		X		X		X	X	

Table 4: Schedule of Laboratory Assessments (Continued)

				Blinded Treatment (All Subjects)						Open-Label Treatment				
										Subjects Who Do Not Cross Over	Subjects Who Cross Over			
		Screening	Baseline	W1-W3				W4-W52 q4w	W34-W50 q4w (lab only)	W56+ q12w	W56+ q12w	EOT	Safety Follow-Up 30-37d After Last Dose	Notes
	Section	Days -35 to -8	Days -7 to -1	D1	D8 (±2d)	D15 (± 2d)	D22 (± 2d)	D7 (± 3d)	D7 (± 3d)	D7 (± 7d)	D7 (± 7d)			
Serum pregnancy	7.5.6.1	X									See Table 6	X		Not needed if FSH elevated or amenorrheic > 1 year. Test should be repeated if required by local regulations.
FSH	7.5.6.1	X												To document hormonal menopause.
[redacted]														

FSH = follicle-stimulating hormone

Table 5: Schedule of Assessments for Subjects From Group B Who Cross Over to Open-Label Ruxolitinib

	Section	Crossover Eligibility Visit	Crossover Treatment Phase						Notes
			W1-W3 After Crossover				W4-W52 q4w After Crossover	W56+ q12w After Crossover	
		Day -1	D1	D8 (± 2d)	D15 (± 7d)	D22 (± 2d)	D7 (± 3d)	D7 (± 7d)	
Contact IXRS	7.2	X					X	**X**	
Review inclusion and exclusion criteria	7.5.1	X							To determine eligibility for crossover.
Prior/concomitant medications	7.4	X		X	X	X	X	X	
Vital signs	7.5.4	X		X	X	X	X	X	Vital signs collected after 5 min rest in recumbent, semirecumbent, or sitting position.
Physical examination, body weight	7.5.3	X		X	X	X	X	X	Comprehensive examination at the crossover eligibility visit and EOT; targeted examination at all other visits.
ECOG status	7.7.1	X*			X		X	X	* Must be 0, 1, or 2 to start ruxolitinib.
[redacted]/liver palpation	7.6.3	X			X		X	X	Using flexible ruler provided for study.
12-lead ECG	7.5.5	X					X*		* Week 52
Laboratory tests	7.5.6	X		X	X	X	X	X	See Table 6 and Table 7.
Review AEs	7.5.2	X		X	X	X	X	X	
Transfusion history/status	7.4	X							
Open-label ruxolitinib dispensed	7.10.2	X*					X	X	* Open-label ruxolitinib may be dispensed at the crossover eligibility visit.
Record first day of open-label ruxolitinib dosing	7.10.1	X							
Drug accountability	7.10.3						X	X	

Table 6: Schedule of Laboratory Assessments for Subjects From Group B Who Cross Over to Open-Label Ruxolitinib

	Section	Crossover Eligibility Visit	Crossover Treatment Phase						Notes
			W1-W3 after Cross Over				W4-52 q4w After Crossover	W56 + q12w After Crossover	
		Day -1	D1	D8 (± 2d)	D15 (± 2d)	D22 (± 2d)	D7 (± 3d)	D7 (± 3d)	
Local laboratory assessments									
Hematology	7.5.6	X		X	X	X	X	X	
Coagulation panel	7.5.6	X							
Serum chemistries	7.5.6	X		X	X	X	X		
Urine pregnancy test	7.5.6.1	X					X	X	Females of childbearing potential if required by local regulations. Test should be repeated if required by local regulations.
Central laboratory samples*									* The central laboratory is the sponsor or designee.
Lipid panel	7.5.6	X					X	X	
Urinalysis	7.5.6	X					X	X	

Table 7: Laboratory Tests: Required Analytes

Serum 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 Red blood cell 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 Low density lipoprotein High density lipoprotein	Hepatitis B surface antigen Hepatitis B surface antigen antibody Hepatitis A, B core antibody HBV-DNA HCV antibody HCV-RNA	PT aPTT INR **Pregnancy Testing** Female subjects of childbearing potential only require a serum test at screening and EOT and a urine pregnancy test at each study visit when the test is requested. Pregnancy tests (serum or urine) should be repeated if required by local regulations. FSH

Note: Additional tests may be required, as agreed by investigator and sponsor, based on emerging safety data.

6.1. Screening

Screening is the interval between signing the ICF and the day that the subject is randomized in the study (Cycle 1 Day 1). Informed consent must be obtained, in writing, before performing any study-specific procedures. Screening may not exceed 28 days (from Day -35 to Day -8).

Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process. 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 35 days of Cycle 1 Day 1). All information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before randomization. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening process (to include repeating the informed consent process) if the investigator believes that there has been a change in eligibility status (eg, after recovery from an infection). For screening assessments that are repeated, the most recent available result before randomization will be used to determine subject eligibility.

6.2. Baseline

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 ET in the [redacted] diary (see Appendix E). 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 least 4 of 7 diary entries have been completed. The subjects will also bring the device along to every study visit to verify the device charging and 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.

6.3. Blinded Treatment

The blinded treatment period begins on the day that the subject receives the first dose of study treatment (Day 1of treatment) – and normally also the day of randomization – through the Week 52 visit or an earlier point at which the investigator determines that the subject will be permanently discontinued from study treatment. Day 1 of treatment must be no more than 35 days after the subject has signed the ICF and no more than 7 days after the date of randomization. Dates for subsequent study visits will be determined based on this day and should occur within ± 2 or 3 days of the scheduled date unless delayed for safety reasons. On Day 1 of treatment, results from screening visit evaluations should be reviewed to determine

whether the subject continues to meet the eligibility requirements, as specified in the Protocol, excepting platelet and WBC counts if they differ from screening evaluation.

Study treatment will be given continuously.

After 2 weeks of treatment, subjects may have the dose of ruxolitinib/ruxolitinib-placebo or anagrelide/anagrelide-placebo increased because of inadequate efficacy. At this visit or any time during the study, the dose may be adjusted for hematologic safety, following the guidelines described in Section 5.4. The individual study visit descriptions describe activities that must occur to support and document these dose changes.

This study schedule is designed to closely monitor symptom response to ruxolitinib or ruxolitinib-placebo and anagrelide/anagrelide-placebo. In addition, the doses of study treatment will need modifications for hematologic parameters. Every effort must be made to ensure that the visit assessment data as well the hematology data are obtained at each scheduled study visit and laboratory-only visit, and repeat laboratory assessments should be conducted if WBC counts and/or platelet count data are not obtained from the initial blood collection conducted as part of the visit procedures. If at any time during the study a subject experiences unexpected signs or symptoms, additional safety evaluations should be conducted at a regular study visit or unscheduled visit.

Study visits during the blinded treatment period will be conducted on the following days:

- Day 1; Day 8 (± 2 days); Day 15 (± 2 days); Day 22 (± 2 days).
- Day 7 every 4 weeks beginning with Week 4 and ending with Week 52 (± 3 days).

Laboratory-only visits during the blinded treatment period will be conducted every 4 weeks beginning with Week 34 and ending at Week 50.

Note: Assessment period from Weeks 32 through Week 52 will be closely monitored to ensure that requested laboratory assessments for evaluation have been completed.

6.3.1. Transition Period Before Open-Label Period

Upon completion of the Week 52 study visit for each individual subject, a period of approximately 2 to 4 weeks will be used to perform eCRF entry and cleaning of clinical data up to and including the Week 52 visit. During this period, the subject should continue on blinded study treatment (unless interrupted for safety reasons). When the data cleaning process is complete (procedure to be detailed in the Study Manual), the sponsor will authorize the unblinding of the subject's treatment assignment via the IXRS system (see Section 5.1.2.1) and perform the following actions:

- Contact the IXRS for treatment management.
- Schedule subject to return to clinic to begin the open-label treatment period or EOT visit.
- Conduct an unscheduled visit if necessary to perform safety assessments for determining eligibility to begin open-label treatment.

This period will end when the subject either begins receiving open-label treatment or is withdrawn from the study. It may be necessary to delay initiating the open-label treatment

period treatment once reaching Week 52 of the blinded treatment in order for the subject to meet these eligibility criteria (see Section 3). A delay of up to 4 weeks is permitted for this purpose. Additional study visits will be scheduled for all subjects the first 4 weeks after open-label ruxolitinib is initiated to permit safety evaluations and dose modification. Afterward, the regular study schedule will be resumed for the patients initially treated with ruxolitinib. Subjects initially treated in the anagrelide arm will follow a specific crossover study schedule (see Table 5 and Table 6). Subjects not willing or eligible to continue in the open-label treatment period will be withdrawn from the study.

6.4. Open-Label Treatment

Subjects randomized to either Group A (ruxolitinib and anagrelide-placebo) or Group B (anagrelide and ruxolitinib-placebo) will return to the clinic to turn in study treatment dispensed during the blinded treatment period and receive new study treatment (see Section 4.1.1). Subjects from Group A (ruxolitinib and anagrelide-placebo) will continue on the same dose used during the blinded treatment period.

Subjects not willing or not eligible to continue will be scheduled for the EOT visit and follow-up evaluations and will discuss further therapeutic options with their treating physician.

6.4.1. Visits After Week 52

Subjects who continue with the same active agent to which they were randomized will have a study visit at Week 56, at which time study drugs will switch over to open label supplies (ruxolitinib or anagrelide) and then study visits every 12 weeks (Week 68, 80, etc). Subjects who were originally randomized to anagrelide (Group B) and who cross over to ruxolitinib will begin receiving ruxolitinib at the Week 56 visit. These subjects will have study visits at Weeks 1, 2, 3, 4, and every 4 weeks up to 52 weeks, then every 12 weeks thereafter. Subjects who initially remain on anagrelide after unblinding but choose to cross over to receive ruxolitinib at a later time will have study visits at Weeks 1, 2, 3, 4, and every 4 weeks up to 52 weeks, then every 12 weeks thereafter.

6.5. End of Treatment

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.

6.6. 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 37 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 be instructed to document this contact in the source.

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 28-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 screening period. Upon determining that the subject is eligible for randomization, the IXRS will be contacted to obtain the treatment 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 ET diagnosis, prior therapies, and phlebotomy history, 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 randomization and up to the end of study 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 packed red blood cells, 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 and Targeted Physical Examinations

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.

A targeted physical examination will be performed as indicated in Table 3 and Table 5 will always include liver and spleen. In addition, it will include body systems as indicated by subject symptoms.

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, serum chemistries, and coagulation parameters will be analyzed by local laboratories. Serology, urinalysis, and lipid panel will be analyzed by a central laboratory. Samples for hematology, serum 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 4 and Table 6. 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 > 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 4 and Table 6, 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. Measurement of Platelet and White Blood Cell Control Between Weeks 32 and 52

Platelet and WBC control will be measured by the performance of blood collection for hematologic assessment (complete blood count) every 2 weeks between Weeks 32 and 52.

Subjects will be closely monitored by their treating physicians and reminded (diary with appointments) to perform these assessments in a timely manner. A window of ± 3 days is allowed for the performance of the test. Subjects should closely follow the schedule of blood test assessments and provide copies of local laboratory hematological results at each clinical study visit.

Sites should closely follow-up with subjects by phone call to ensure that those tests are performed in a timely manner and to provide subjects support if appropriate, as subjects should not miss blood testing in this timeframe. A detailed description of the procedures for the collection of hematologic blood tests is provided in the Study Reference Manual.

7.6.2. Overall Response Assessment

Overall response assessment (Appendix C) will be assessed at Weeks 32 and 52.

[redacted]

7.6.4. Bone Marrow Biopsy

A bone marrow biopsy should be obtained as outlined in Table 4. The local site laboratory/pathology laboratory will be responsible for obtaining and analyzing the biopsy and collecting samples of tissue and aspirate. The marrow should be evaluated for histomorphologic abnormalities as well as the presence of cytogenetic abnormalities and mutations associated with ET. A quantitative evaluation for the JAK2V617F mutation is recommended**. If the marrow has been evaluated in the 2 months before screening, then the pretreatment examination does not need to be repeated**. Biopsy samples at Weeks 32 and 52 (and baseline with the caveat above) are required; biopsy samples at Weeks 104 and 152 are optional only, and only for subjects receiving open-label ruxolitinib (they may provide additional data regarding changes in bone marrow parameters while on treatment). Samples of the bone marrow biopsy materials will be sent to the central laboratory for archiving and retrospective analyses by the sponsor or its designee.

7.7. Performance and Quality-of-Life Assessments

7.7.1. Eastern Cooperative Oncology Group Performance Status

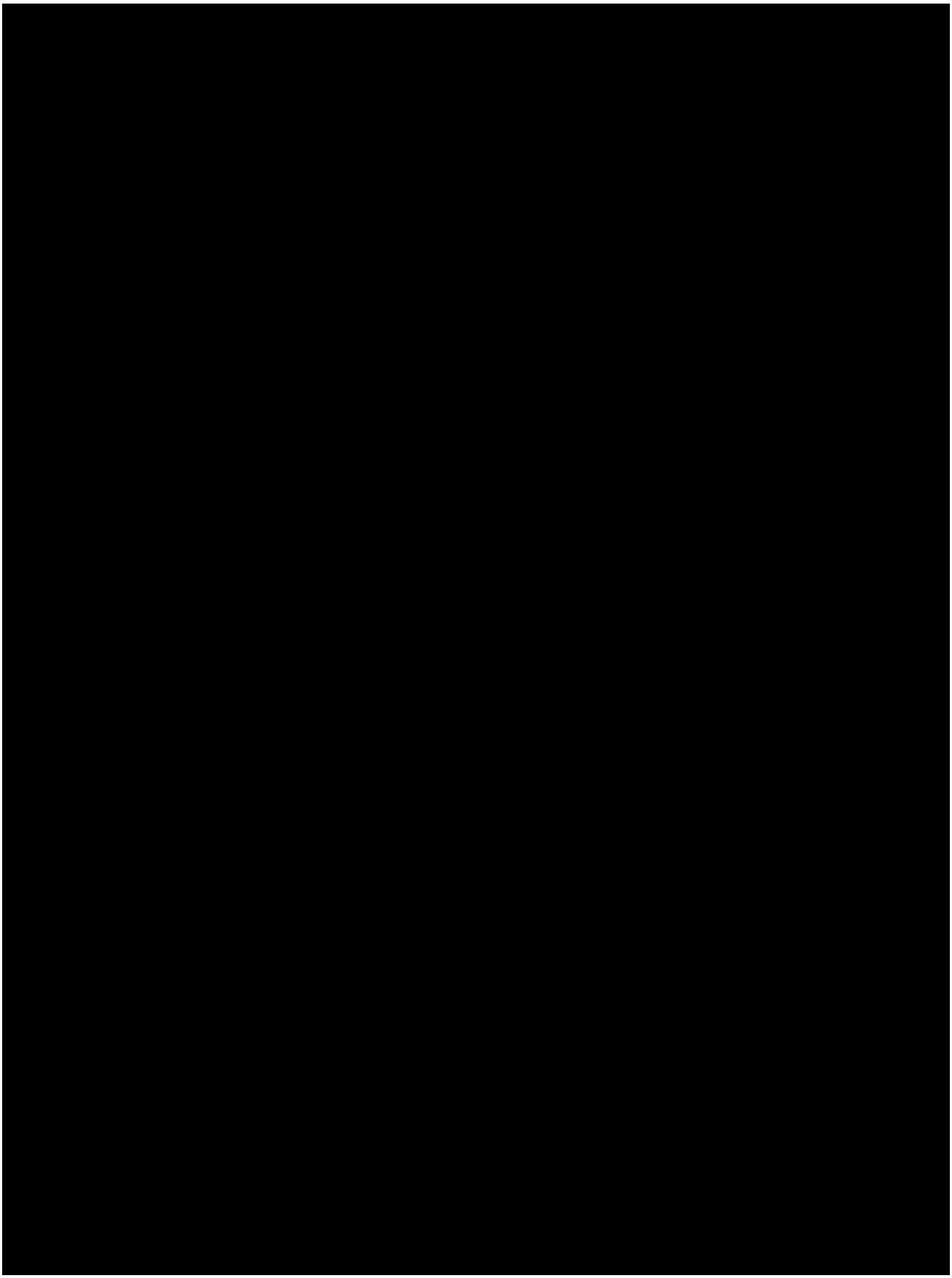
The ECOG performance status will be assessed as shown in Table 3 and Table 5 (Appendix D).

[redacted]

7.7.4. MPN-SAF Questionnaire

The MPN-SAF questionnaire (see Appendix I) will be completed at baseline, Week 32 and Week 52, and/or the EOT visits so that the overall response assessment can be determined and reported. This questionnaire will be on a paper/pencil format.

[redacted]



[redacted]

7.10. Other Study Procedures

7.10.1. Administration of Study Treatment

Subjects will take their dose of ruxolitinib or ruxolitinib-placebo in the morning and in the evening, approximately 12 hours apart, without regard to food.

Anagrelide or anagrelide-placebo 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.

7.10.2. Dispensing of Study Treatment

Site staff will contact the IXRS to obtain the initial subject study treatment assignment, as well as for subsequent dispensing of study treatment. Kits containing paired bottles of ruxolitinib or ruxolitinib-placebo plus anagrelide or anagrelide-placebo will be used during the blinded treatment period, and bottles of ruxolitinib will be used during the open-label treatment period. The investigator or designee will select the assigned study drug kits or bottles from their stock that correspond with the number provided by IXRS and dispense the medication. The investigator will enter the kit numbers in the eCRF. Full details will be provided in the IXRS Manual.

7.10.3. 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.

7.10.4. 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 [redacted] as well as an area indicating laboratory assessments scheduled for the period of evaluation between Weeks 32 and 52 of treatment.

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 4).
- 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 or 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

The procedure for emergency unblinding is provided in the study reference manual. This option may be used ONLY if the subject's well-being requires the investigator to be aware of the subject's treatment assignment.

The investigator should make every effort to contact the sponsor's (or its designee's) clinical research physician or medical monitor before unblinding a subject's treatment assignment; however, this is not mandatory. If a subject's treatment assignment is unblinded, the sponsor or its designee must be notified immediately by telephone.

If an investigator, site personnel performing assessments, or subject is unblinded, the subject must be withdrawn from the study treatment. In cases where there are ethical reasons to have the subject remain in the study, the investigator must obtain specific approval from the sponsor's (or

its designee's) clinical research physician or medical monitor for the subject to continue in the study.

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 Investigator's Brochure (IB). 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

An independent DMC will be formed. The DMC will consist of qualified individuals who are not involved with the conduct of the study. The establishment, composition, roles, duties, and responsibilities of the DMC are addressed in the approved DMC charter.

8.8. Adverse Events of Special Interest

All reported AEs will be collected. [redacted]

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 intent-to-treat (ITT) population will include subjects randomized in the study. Treatment groups for this population will be defined according to the treatment assignment at randomization.

The per protocol population will include those ITT subjects who are considered to be sufficiently compliant with the Protocol. The criteria will be detailed in the SAP, and this population is defined for use in supportive sensitivity analyses for the primary efficacy endpoint.

The safety evaluable population will include randomized subjects who received at least 1 dose of study drug.

[redacted]

9.2. Selection of Sample Size

Based on a literature search and the Incyte Phase 2 study (INCB 18424-256) and a difference in response rate of 25% (30% vs 5%), a total of approximately 120 subjects (60 subjects per group) would provide approximately 90% power to detect a treatment difference of 25% in the primary endpoint at 2-sided chi-square test with an alpha level of 0.05.

9.3. Level of Significance

The level of significance for the primary endpoint is 2-sided 0.05.

The family wise alpha level will be controlled at 0.05 and will be controlled using a fixed sequential testing procedure. The proportion of subjects who achieve CR or PR at Week 32, as defined by the ELN 2013 response criteria, will only be formally tested if the hypothesis for the primary endpoint is rejected.

The duration of response for responders in both treatments will be estimated with 95% confidence intervals without comparison. No alpha adjustment will be applied for the remaining endpoints.

9.4. Statistical Analyses

When the last subject reaches Week 52 or discontinues, the database will be cleaned and locked, and the final analyses will be conducted.

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

The primary efficacy endpoint is the proportion of subjects who achieve a simultaneous reduction of platelet counts to $< 600 \times 10^9$/L with a reduction of WBCs to $< 10 \times 10^9$/L for at least 80% of biweekly assessments for 12 consecutive weeks between Week 32 and Week 52. This analysis will be based on the ITT population according to the treatment assigned at randomization. The proportion of subjects who meet the response criteria will be estimated with a 95% confidence interval. The Cochran-Mantel-Haenszel (CMH) test stratified by JAK2V617F mutation status (positive or negative), screening platelet count ($\geq 1000 \times 10^9$/L or $< 1000 \times 10^9$/L), and prior anagrelide use (yes vs no) will be applied to compare the 2 treatment groups. The test will be 2-sided at 5% significant level. The overall stratum-adjusted odds ratio, along with its 95% confidence interval, will be presented.

In the analysis of the primary efficacy endpoint, subjects who discontinue study treatment without meeting the response criteria will be considered as nonresponders. Subjects who meet the primary endpoint criteria of a response but discontinue treatment before Week 52 will be considered as responders.

The primary endpoint will also be analyzed based on per protocol population as sensitivity analysis.

9.4.1.2. Secondary Efficacy Analyses

Secondary efficacy analyses will be conducted for the ITT population.

- Proportion of subjects who achieve CR or PR at Week 32, as defined by ELN 2013 response criteria, will be estimated with a 95% confidence interval. The CMH test stratified by JAK2V617F mutation status (positive or negative), screening platelet count ($\geq 1000 \times 10^9$/L or $< 1000 \times 10^9$/L), and prior anagrelide use (yes vs no) will be applied to compare the 2 treatment groups. The overall stratum-adjusted odds ratio along with its 95% confidence interval will be presented.

- Proportion of subjects who achieve CR or those who achieve PR (separate analyses) at Week 32, as defined by ELN 2013 response criteria, will be estimated with a 95% confidence interval. The CMH test stratified by JAK2V617F mutation status (positive or negative), screening platelet count ($\geq 1000 \times 10^9$/L or $< 1000 \times 10^9$/L), and prior anagrelide use (yes vs no) will be applied to compare the 2 treatment groups. The overall stratum-adjusted odds ratio along with its 95% confidence interval will be presented.
- Duration of responses for subjects who achieve primary response as defined in the primary efficacy endpoint is defined as the time from the start of response until the end of response. The start of a response will be the first visit where both platelet control (defined as a reduction to $< 600 \times 10^9$/L) and WBC control (defined as a reduction to $< 10 \times 10^9$/L) are achieved. Loss of response will be defined as 2 consecutive visits where either platelet count is $\geq 600 \times 10^9$/L or WBC is $\geq 10 \times 10^9$/L. The earlier of the 2 consecutive visits will be used as the end of response time. Duration of response will be estimated using the Kaplan-Meier method.
- Proportion of subjects who achieve reduction of platelet count to $< 600 \times 10^9$/L for at least 80% of biweekly assessments for a consecutive 12-week period between Weeks 32 and 52 will be summarized along with their 95% confidence interval.
- Proportion of subjects who achieve reduction of WBC counts to $< 10 \times 10^9$/L for at least 80% of biweekly assessments for a consecutive 12 weeks period between Weeks 32 and 52 will be summarized along with their 95% confidence interval.

[redacted]

9.4.2. Safety Analyses

The safety analyses will be conducted for the safety evaluable population. Safety data collected after crossover will be summarized separately.

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.

[redacted]

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. The following summaries will be produced for the laboratory data:

- Number and percentage of subjects with worst postbaseline CTCAE grade (regardless of baseline value). Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst postbaseline value using CTCAE grade.
- 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.

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 9), 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 9: 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	> 38ºC	< 35.5ºC
Respiratory rate	> 24/min	< 8/min

[redacted]

9.5. Analyses for the Data Monitoring Committee

Preplanned analyses of safety will be provided to an independent DMC as specified in the DMC charter. The DMC will review safety data of the ongoing study at close, regular intervals as specified in the DMC charter. Such safety will be summarized by treatment group. The process by which the DMC will make recommendations and decisions will be documented in the DMC charter.

9.6. Interim Analysis

No interim analysis for efficacy is planned.

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 if 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.

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APPENDIX A. REVISED WHO 2016 CRITERIA FOR ESSENTIAL THROMBOCYTHEMIA

Diagnosis of essential thrombocythemia requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion:

Major criteria
1. Platelet count $\geq 450 \times 10^9$/L.
2. Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (Grade 1) increase in reticulin fibers.
3. Not meeting WHO criteria for BCR-ABL1+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms.
4. Presence of JAK2, CALR, or MPL mutation.
Minor criterion
Presence of a clonal marker or absence of evidence for reactive thrombocytosis.

CALR = calreticulin; CML = chronic myeloid leukemia; JAK2 = Janus kinase 2; PMF = primary myelofibrosis; PV = polycythemia vera.
Source: Arber et al 2016.

APPENDIX B. DEFINITION OF MODIFIED CLINICAL RESISTANCE OR INTOLERANCE TO HYDROXYUREA

Hydroxyurea (HU)-resistant or HU-intolerant subjects should demonstrate at least 1 of the following criteria:

- Platelet count greater than 600×10^9/L after 3 months of at least 2 g/day of HU (2.5 g/day in subjects with a body weight over 80 kg); OR at the subject's maximally tolerated dose if that dose is less than 2 g/day;
- Platelet count greater than 400×10^9/L and white blood cell count less than 2.5×10^9/L or hemoglobin less than 10 g/dl, at any dose of HU;
- Presence of leg ulcers or other unacceptable muco-cutaneous manifestations at any dose of HU;
- HU-related fever.

Source: Barosi et al 2007, Verstovsek et al 2014a, Verstovsek et al 2014b.

APPENDIX C. RESPONSE CRITERIA FOR ESSENTIAL THROMBOCYTHEMIA

	Criteria
Complete remission	
A	Durable[a] resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement,[b] AND
B	Durable[a] peripheral blood count remission, defined as platelet count ≤ 400 × 10^9/L, WBC count < 10 × 10^9/L, and absence of leukoerythroblastosis, AND
C	Without signs of progressive disease and absence of any hemorrhagic or thrombotic events, AND
D	Bone marrow histological remission defined as disappearance of megakaryocyte hyperplasia and absence of > Grade 1 reticulin fibrosis.
Partial remission	
A	Durable[a] resolution of disease-related signs including palpable hepatosplenomegaly, and large symptoms improvement,[b] AND
B	Durable[a] peripheral blood count remission, defined as platelet count ≤ 400 × 10^9/L, WBC count < 10 × 10^9/L, absence of leukoerythroblastosis, AND
C	Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND
D	Without bone marrow histological remission, defined as the persistence of megakaryocyte hyperplasia.
No response	Any response that does not satisfy partial remission.
Progressive disease	Transformation into PV, post-ET myelofibrosis, myelodysplastic syndrome, or acute leukemia.[c]

ET = essential thrombocythemia; IWG-MRT = International Working Group-Myeloproliferative Neoplasms Research and Treatment; MPN-SAF TSS = Myeloproliferative Neoplasm–Symptom Assessment Form Total Symptom Score; PV = polycythemia vera; WBC = white blood cell.

Note: Molecular response is not required for assignment as complete response or partial response. Molecular response evaluation requires analysis in peripheral blood granulocytes. Complete response is defined as eradication of a pre-existing abnormality. Partial response applies only to subjects with at least 20% mutant allele burden at baseline. Partial response is defined as ≥ 50% decrease in allele burden.

[a] Lasting at least 12 weeks.

[b] Large symptom improvement (≥ 10-point decrease) in MPN-SAF TSS.

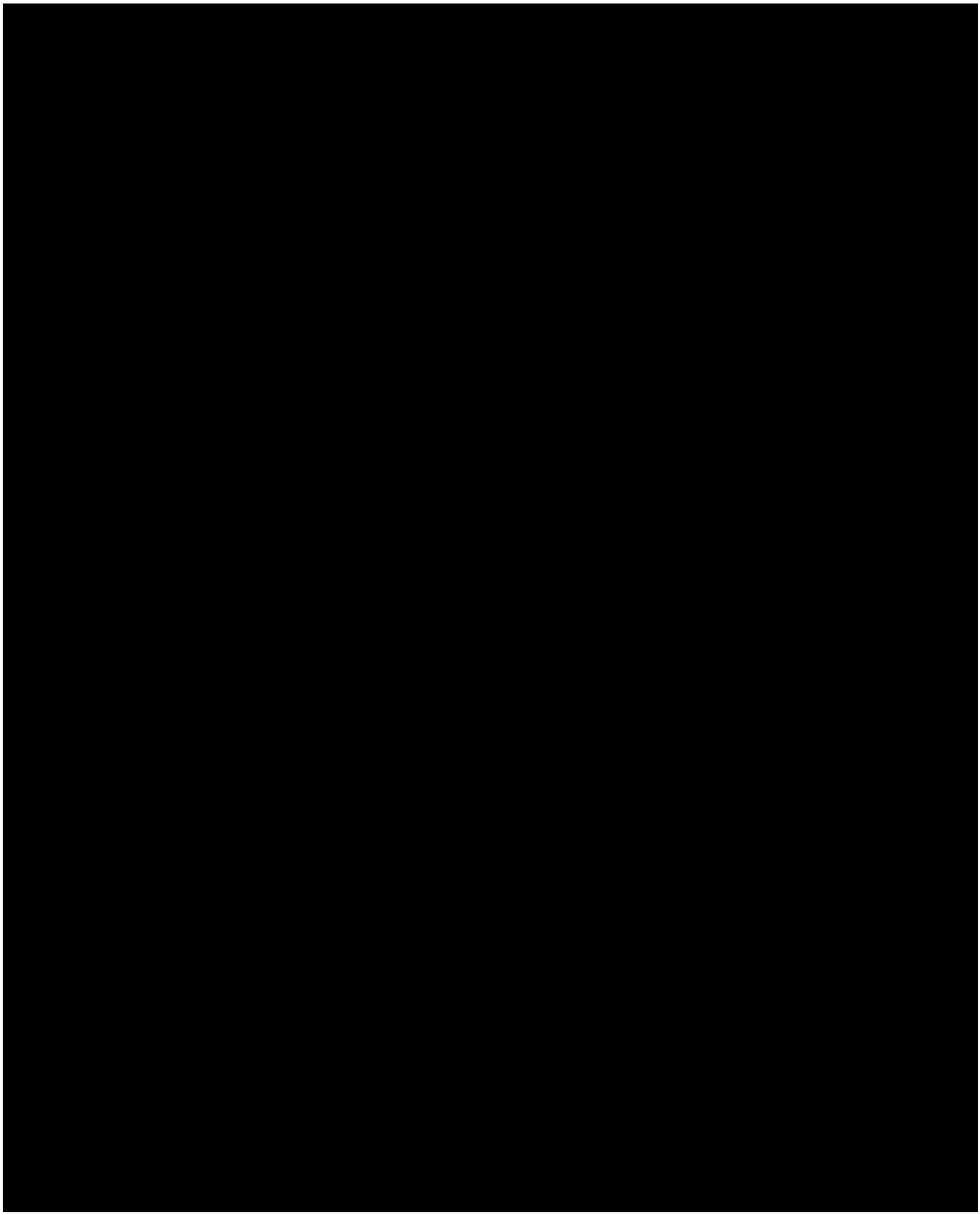
[c] For the diagnosis of PV, see the WHO 2016 criteria 13; for the diagnosis of post-ET myelofibrosis, see the IWG MRT criteria12; for the diagnosis of myelodysplastic syndrome and acute leukemia, see the WHO criteria.

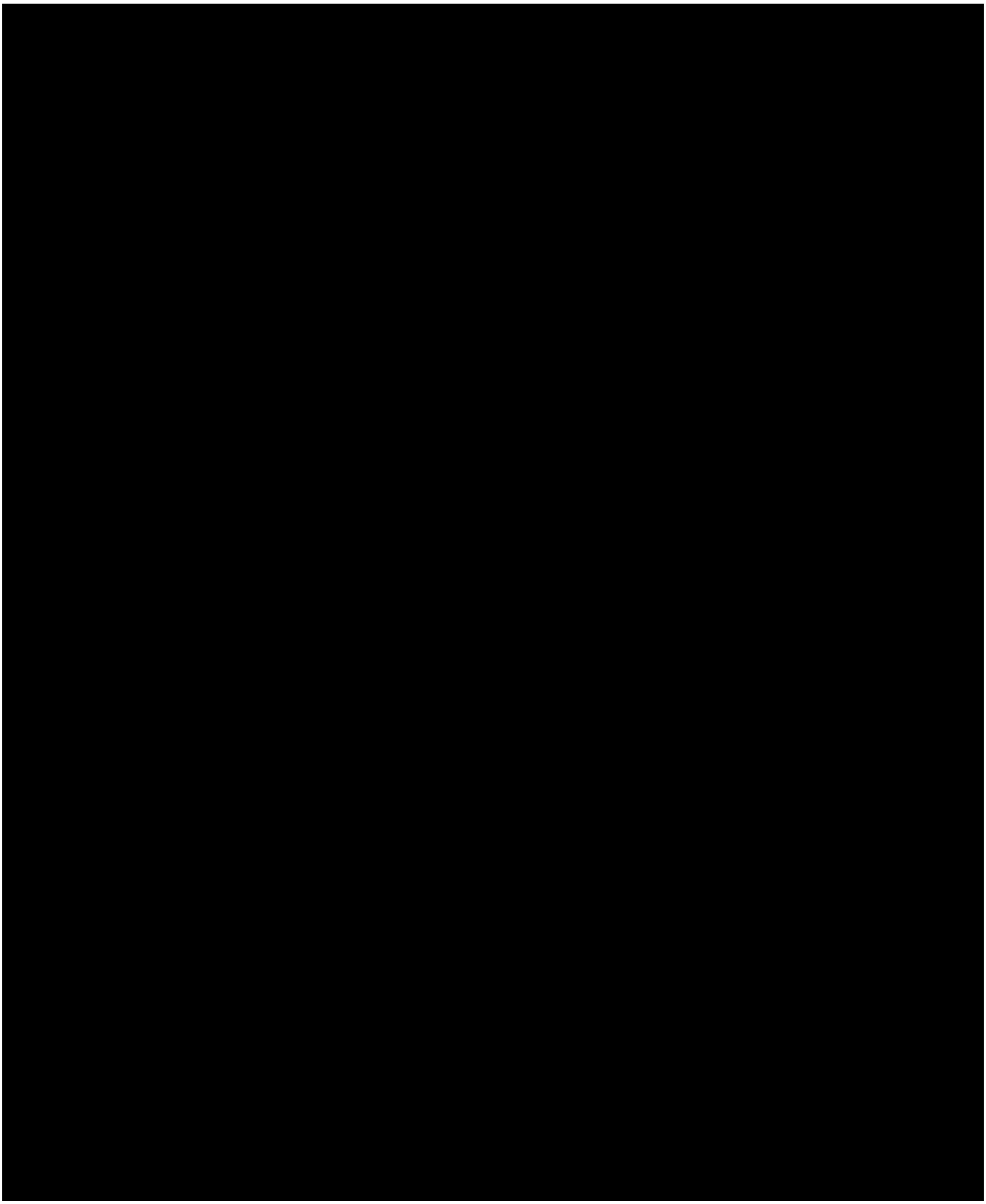
Source: Barosi et al 2013.

APPENDIX D. 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 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 INHIBITORS AND INDUCERS

CYP 3A4 Inhibitors

Inhibitor	Therapeutic Class
Potent CYP3A Inhibitors	
VIEKIRA PAK	Antivirals
Indinavir /RIT	Protease inhibitors
Tipranavir/RIT	Protease inhibitors
Ritonavir	Protease inhibitors
Cobicistat (GS-9350)	None
Ketoconazole	Antifungals
Indinavir	Protease inhibitors
Troleandomycin	Antibiotics
Telaprevir	Antivirals
Danoprevir/RIT	Antivirals
Elvitegravir/RIT	Treatments of AIDS
Saquinavir/RIT	Protease inhibitors
Lopinavir/RIT	Protease inhibitors
Itraconazole	Antifungals
Voriconazole	Antifungals
Mibefradil	Calcium channel blockers
LCL161	Cancer treatments
Clarithromycin	Antibiotics
Posaconazole	Antifungals
Telithromycin	Antibiotics
Grapefruit juice DS	Food products
Conivaptan	Diuretics
Nefazodone	Antidepressants
Nelfinavir	Protease inhibitors
Saquinavir	Protease inhibitors
Ribociclib	Kinase inhibitors
Idelalisib	Kinase inhibitors
Boceprevir	Antivirals

Inhibitor	Therapeutic Class
Moderate CYP3A Inhibitors	
Erythromycin	Antibiotics
Fluconazole	Antifungals
Atazanavir/RIT	Protease inhibitors
Darunavir	Protease inhibitors
Diltiazem	Calcium channel blockers
Darunavir/RIT	Protease inhibitors
Dronedarone	Antiarrhythmics
Crizotinib	Kinase inhibitors
Atazanavir	Protease inhibitors
Letermovir	Antivirals
GSK2647544	Alzheimer's disease & dementia treatments
Aprepitant	Antiemetics
Casopitant	Antiemetics
Amprenavir	Protease inhibitors
Faldaprevir	Antivirals
Imatinib	Antineoplastic agents
Verapamil	Calcium channel blockers
Netupitant	Antiemetics
Nilotinib	Kinase inhibitors
Grapefruit juice	Food products
Tofisopam	Benzodiazepines
Cyclosporine	Immunosuppressants
ACT-178882	Renin inhibitors
Ciprofloxacin	Antibiotics
Magnolia vine (Schisandra sphenanthera)	Herbal medications
Isavuconazole	Antifungals
Cimetidine	H-2 receptor antagonists
FK1706	Central nervous system agents

Inhibitor	Therapeutic Class
Weak CYP3A Inhibitors	
Tabimorelin	Hormone replacement
Amlodipine	Calcium channel blockers
Ranolazine	Cardiovascular drugs
Breviscapine	Herbal medications
Lomitapide	Other antilipemics
Fosaprepitant (IV)	Antiemetics
Seville orange (Citrus aurantium) juice	Food products
Amiodarone	Antiarrhythmics
Diosmin	Herbal medications
Chlorzoxazone	Muscle relaxants
M100240	Antihypertensive agents
Fluvoxamine	Antidepressants
Ranitidine	H-2 receptor antagonists
Goldenseal	Herbal medications
Clotrimazole	Antifungals
Tacrolimus	Immunosuppressants
Palbociclib	Kinase inhibitors
Cilostazol	Antiplatelets
Ticagrelor	Antiplatelets
Peppermint oil	Food products
Ivacaftor	Cystic fibrosis treatments
GSK2248761	Transcriptase inhibitors
Guan Mai Ning	Herbal medications
Osilodrostat	Adrenal steroidogenesis inhibitors
AZD2327	Depression treatments
Piperine	Food products
Resveratrol	Food products
Roxithromycin	Antibiotics
Suvorexant	Hypnotics - sedatives
Propiverine	Anticholinergics
Isoniazid	Antibiotics
Berberine	Herbal medications
Oral contraceptives	Oral contraceptives
Delavirdine	NNRTIs
Daclatasvir	Antivirals

Inhibitor	Therapeutic Class
Weak CYP3A Inhibitors	
Simeprevir	Protease inhibitors
Atorvastatin	HMG CoA reductase inhibitors (statins)
Tolvaptan	Vasopressin antagonists
Almorexant	Hypnotics - sedatives
GSK1292263	Other antilipemics
Evacetrapid	CETP inhibitors
Linagliptin	Dipeptidyl peptidase 4 inhibitors
Grazoprevir *(ingredient of Zepatier)*	Antivirals
Lacidipine	Calcium channel blockers
Cranberry juice	Food products
Pazopanib	Kinase inhibitors
Fostamatinib	Other
Everolimus	Immunosuppressants
Blueberry juice	Food products
Flibanserin	Central nervous system agents
Lapatinib	Kinase Inhibitors
Brodalumab	Immunomodulators biologics
AMD070	Fusion inhibitors
Alprazolam	Benzodiazepines
Tong Xin Luo	Herbal medications
Glecaprevir and pibrentasvir	Antivirals
Bicalutamide	Antiandrogens
Sitaxentan	Endothelin receptor antagonists
Azithromycin	Antibiotics
Obeticholic acid	Miscellaneous agents
Ginkgo	Herbal medications
Teriflunomide	Other immunomodulators

CYP 3A4 Inducers

Inducers	Therapeutic class
Potent CYP3A Inducers	
Rifampin	Antibiotics
Mitotane	Other Antineoplastics
Avasimibe	Other Antilipemics
Rifapentine	Antibiotics
Apalutamide	Antiandrogens
Phenytoin	Anticonvulsants
Carbamazepine	Anticonvulsants
Enzalutamide	Antiandrogens
St John's Wort extract	Herbal medications
Lumacaftor	Cystic fibrosis treatments
Rifabutin	Antibiotics
Phenobarbital	Anticonvulsants
Moderate CYP3A Inducers	
Ritonavir and St. Johns wort	None
Semagacestat	Alzheimer's treatments
Efavirenz	NNRTIs
Tipranavir and ritonavir	Protease inhibitors
Dabrafenib	Kinase inhibitors
Lesinurad	Antigout and uricosuric agents
Bosentan	Endothelin receptor antagonists
Genistein	Food products
Thioridazine	Antipsychotics
Nafcillin	Antibiotics
Talviraline	NNRTIs
Lopinavir	Protease inhibitors
Modafinil	Psychostimulants
Pf-06282999	Myeloperoxidase inactivators
Etravirine	NNRTIs
Lersivirine	NNRTIs
Telotristat ethyl	Antidiarrheals

Inducers	Therapeutic class
Weak CYP3A Inducers	
Eslicarbazepine	Anticonvulsants
Telaprevir	Antivirals
Daclatasvir and asunaprevir and beclabuvir	Antivirals
Amenamevir	Antivirals
Garlic	Food products
Bexarotene	Other antineoplastics
Sarilumab	Immunomodulators biologics
Artesunate and mefloquine	Antimalarials
Amprenavir (fosamprenavir)	Protease inhibitors
Raltegravir	HIV-integrase strand transfer inhibitors
Vemurafenib	Kinase inhibitors
Troglitazone	Thiazolidinediones
Dicloxacillin	Antibiotics
Sorafenib	Kinase inhibitors
Rufinamide	Anticonvulsants
Sirukumab	Immunomodulators biologics
Pleconaril	Antivirals
Ginseng	Herbal medications
Boceprevir	Antivirals
Sulfinpyrazone	Antigout and uricosuric agents
Ginkgo	Herbal medications
Vinblastine	Vinca alkaloids
Nevirapine	NNRTIs
Armodafinil (R-modafinil)	Psychostimulants
Ticagrelor	Anticoagulants and antiplatelets
LCL161	Cancer treatments
Vicriviroc and ritonavir	Treatments of AIDS
Ritonavir	Protease inhibitors
Prednisone	Corticosteroids
Oxcarbazepine	Anticonvulsants
Danshen	Herbal medications
Clobazam	Benzodiazepines
Echinacea	Herbal medications
Ticlopidine	Anticoagulants and antiplatelets
Isavuconazole	Antifungals
Brivaracetam	Anticonvulsants
Stribild	Treatments of AIDS

Inducers	Therapeutic class
Weak CYP3A Inducers	
Pioglitazone	Thiazolidinediones
VIEKIRA PAK	Antivirals
Dexamethasone	Corticosteroids
Terbinafine	Antifungals
Quercetin	Food products
Glycyrrhizin	Herbal medications
Aprepitant	Neurokinin-1 receptor antagonists
Pretomanib (PA-824)	Antibiotics
Safinamide	MAO-B inhibitors
Oritavancin	Antibiotics
AZD 7325	Anxiolytics
Methylprednisolone	Corticosteroids
Topiramate	Anticonvulsants

CYP1A2 Inhibitors

Inhibitor	Therapeutic Class
Strong CYP1A2 Inhibitors	
Ciprofloxacin	Antibiotics
Cinafloxacin	Antibiotics
Enoxacin	Antibiotics
Fluvoxamine	Serotonin reuptake inhibitor
Oltiprza	Cancer chemotherapy
Rofecoxib	NSAID
Zafirlukast	Anti-asthmatic
Angelica root – Bai Zhi	Herbal medication
Moderate CYP1A2 Inhibitors	
Etintidine	H=2 Receptor antagonist
Genistein	Food product
Idrocilamide	Muscle relaxant
Methoxsalen	Anti-psoriasis
Mexiletine	Anti-arrhythmic
Osilodrostat	Adrenal steroidogenesis inhibitor
Oral contraceptives	Oral contraceptives
Phenylpropaholamine	Vasoconstrictor
Pipemidic acid	Antibiotics
Propafenone	Anti-arrhythmic
Propranolol	Beta adrenergic blocker
Troleandomcin	Antibiotics
Vemurafenib	Kinase inhibitors

Inhibitor	Therapeutic Class
Weak CYP1A2 Inhibitors	
Acyclovir	Antivirals
Antofloxacin	Antibiotics
Artemisinin	Antimalerials
Caffeine	Methylxanthines
Cimetidine	H-2 Receptor antagonists
Curcumin	Food product
Deferasirox	Miscellaneous
Disulfiram	Alcohol deterrent
Echinacea	Herbal medicine
Famotidine	H-2 Receptor antagonist
Glecaprevir and pibrentasvir	Antivirals
Grapefruit juice	Food product
Grepafloxacin	Antibiotics
Hormone replacement therapy	Hormone replacement therapy
Interferon alpha	Immunomodulator
Interferon beta	Immunomodulator
Norfloxacin	Antibiotics
Obeticholic acid	Other
Pefloxacin	Antibiotics
Peg interferon alpha 2a	Immunomodulator
Peperine	Food product
Safinamide	MAO-B inhibitor
Simeprevir	Antivirals
Sirukumab	Immunomodulator
Terbinafine	Antifungals
Thiabendazole	Antiparasitics
Ticlopidine	Anticoagulants and Antiplatelets
Verapamil	Calcium Channel Blocker
Viloxazine	Other antidepressants
Zileuton	Anti-asthmatics

APPENDIX I. MYELOPROLIFERATIVE NEOPLASMS SYMPTOM ASSESSMENT FORM (MPN-SAF)

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 J. DRUGS THAT MAY PROLONG QT INTERVAL

NOTE: This list is not complete; investigators should review all concomitant medications for possible QT effects.

Psychiatric Medications	**Antihistamines**	**Cardiovascular Agents**
Thioridazine	Diphenhydramine	Quinidine
Haloperidol	Astemizole	Procainamide
Chlorpromazine	Loratidine	Disopyramide
Pimozide	Terfanadine	Flecainide
Aiprasidone	Azelastine	Encainide
Iloperidone	Clemastine	Sotalol
Quetiapine		Amiodarone
Citalopram	**Anti-infectives**	Bepridil
Escitalopram	Amantadine	Nicardipine
Amitryptyline	Clarithromycin	Israpidine
Imipramine	Chloroquine	Indapamide
Maprotiline	Foscarnet	Moesipril/HCTZ
Nortriptyline	Halofantrine	
Despipramine	Hydroxychloroquine	**Other**
Clomipramine	Quinine	Cisapride
Trimipramine	Mefloquine	Salmeterol
Ventafaxine	Erythromycin	Zolmitriptan
Mirtazapine	Azithromycin	Naratriptan
Risperidone	Mofloxacin	Sumatriptan
Doxepin	Sparfloxacin	Tizanidine
Lithium	Ciprofloxacin	Fosphenytoin
	Pentamidine	Felbamate
	Trimethoprim-sulfamethoxazole	
	Ketoconazole	

Sources:
1. Dietle A. QTc Prolongation with Antidepressants and Antipsychotics. US Pharm 2015;40:HS34-HS40.
2. FDA. Drug-induced QT prolongation and Torsades de Pointes. https://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_01_ruskin.ppt.

APPENDIX K. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	21 DEC 2016
Amendment (Version) 2:	02 AUG 2019

Amendment 2 (02 AUG 2019)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to revise the prior medication restrictions. Under Amendment 2, prior anagrelide will be allowed, provided it was not discontinued because of adverse events. Any prior anagrelide must be discontinued no later than 28 days before the anticipated start of study medications. This revision is intended to allow for a greater number of subjects to participate in the study without making significant changes to the previous SPA agreement by allowing prior anagrelide use; the requirement for high WBC and high platelet counts severely limited possible enrollees, and prohibiting prior anagrelide use further restricted the number of subjects allowed to participate.

Additional changes to the Protocol that had been communicated to the study sites via previous administrative change letters were also incorporated. These include multiple clarifications/corrections of typographical errors to the schedules of assessments, addition of an appendix listing drugs that may prolong the QT interval, clarifying the options available for crossover for subjects completing 52 weeks of treatment, and options for discontinuing HU.

1. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design**

   Description of change: Changed required WBC and platelet count from $> 650 \times 10^9$/L and $> 11.0 \times 10^9$/L to $\geq 650 \times 10^9$/L and $\geq 11.0 \times 10^9$/L, respectively.

   Rationale for change: Correct typographical error in original Protocol.

2. **Synopsis; Section 1.4.2.2, Prior Anagrelide Use; Section 3.2, Subject Exclusion Criteria; Section 5.6, Concomitant Medications**

   Description of change: Revised to allow prior anagrelide use provided the reason for discontinuation is not AE-related. Added language to indicate that anagrelide must be stopped at least 28 days before the first dose of study treatment.

   Rationale for change: To increase the available pool of potential participants in the study, while avoiding enrolling subjects who might be more susceptible to AEs related to anagrelide based on prior experience with the drug.

3. **Synopsis; Section 1.4.2.2, Prior Anagrelide Use; Section 4.1, Overall Study Design; Section 4.3, Measures Taken to Avoid Bias, Section 9.4.1, Efficacy Analysis**

   Description of change: Addition of wording to indicate that subjects will be stratified by prior anagrelide use.

   Rationale for change: To ensure equivalent enrollment of subjects with prior anagrelide use into both treatment groups to decrease potential bias.

4. **Synopsis; Section 2.2.2, Secondary Endpoints, Section 9.4.1.2, Secondary Efficacy Analysis**

   Description of change: Reworded endpoint to allow for analysis of CR and PR both together and separately.

   Rationale for change: FDA request.

5. **Appendix H, Cytochrome P450 Inhibitors and Inducers**

   Description of change: Replaced appendix with updated version.

   Rationale for change: To provide updated information.

The following changes are from Administrative Change 3 (dated 09 NOV 2017):

6. **Synopsis; Section 3.2, Exclusion Criteria; Section 5.6, Concomitant Medications**

   Description of change: Clarified that HU can be discontinued once one of the criteria for HU refractoriness or resistance have been met (as described in inclusion criterion 3) and up to the day before the first dose of study treatments.

   Rationale for change: To clarify when HU can be stopped before the start of the study.

7. **Section 3.2, Subject Exclusion Criteria; Section 5.6.3, Prohibited Medications; Appendix J, Drugs That Prolong QT Interval**

   Description of change: Exclusion criterion 19 and Section 5.6.3 revised to include a cross-reference to the new Appendix J, which lists QT-prolonging drugs that are prohibited.

   Rationale for change: To provide guidance on concomitant medications.

The following changes are from Administrative Change 2 (dated 29 AUG 2017):

8. **Section 6, Study Assessments (Table 5, Schedule of Assessments for Subjects From Group B Who Cross Over to Open-Label Ruxolitinib)**

   Description of change: Assessments were added for the visits beginning 56 weeks after crossover and continuing every 12 weeks.

   Rationale for changes: Addition of missing assessments.

The following changes are from Administrative Change 1 (dated 07 APR 2017):

9. **Synopsis; Section 4.1.1, Options for the Open-Label Treatment Phase; Section 4.4, Duration of Treatment and Subject Participation; Section 5.1.2.1.2, Scheduled Unblinding; Section 6, Study Assessments (Table 3, Schedule of Assessments; Table 4, Schedule of Laboratory Assessments; Table 5, Schedule of Assessments for Subjects From Group B Who Cross Over to Open-Label Ruxolitinib); Section 6.4, Open-Label Treatment**

   Description of change: Treatment options were added for the open-label crossover period.

   Rationale for change: To clarify treatment options after unblinding.

10. **Synopsis, Section 3.2, Subject Exclusion Criteria**

    Description of change: In Synopsis and Section 3.2, Criterion 16 was revised to include CYP1A2 inhibitors. In Section 3.2, criteria 19 and 20 are the same, and criteria 24 and 25 are the same. The duplicate criteria were deleted.

    Rationale for change: Correction of typographical errors and to be consist with Section 5.4.2.3.2 (Cytochrome P450 1A2 Inhibitors).

11. **Section 5.4.4, Dose Modifications for Subjects Receiving Open-Label Treatment**

    Description of change: A subsection was added to indicate that subjects receiving open-label ruxolitinib or open-label anagrelide will follow the same rules for dose modifications as described in Sections 5.4.1, 5.4.2, and 5.4.3.

    Rationale for change: To clarify treatment modification options after unblinding.

12. **Section 5.6.1, Permitted Medications; Section 5.6.2, Restricted Medications**

    Description of change: The maximum allowed dose of aspirin was changed to 125 mg per day (instead of 150 mg per day).

    Rationale for change: Correction of a typographical error.

13. **Section 6, Study Assessments (Table 4, Schedule of Laboratory Assessments)**

    a. **Description of change:** The time frame for Screening was changed to Days -35 to -8 (instead of Days -28 to -8).

       Rationale for change: Correction of typographical error.

    b. **Description of change:** JAK2V617F assessment: the X was moved from the baseline column to the screening column.

       Rationale for change: Correction of a typographical error. The status of JAK2V617F must be known at screening per inclusion criteria and will be used for stratification (not an additional laboratory assessment).

    [redacted]

    d. **Description of change:** Urinalysis assessment: an X was added at W56 + q12w in the open-label treatment column for subjects who do not cross over.

       Rationale for change: Correction of a typographical error.

    e. **Description of change:** FSH testing and blood sample for mutations testing: the X in the baseline column was moved to the screening column.

       Rationale for change: Correction of a typographical error.

14. **Section 6, Study Assessments (Table 4, Schedule of Laboratory Assessments); Section 7.6.4, Bone Marrow Biopsy**

    Description of change: In Table 4 under central laboratory samples, the third note for bone marrow biopsy and analyses (***) was revised to indicate Week 152 instead of Week 156 and to specify only subjects treated with open-label ruxolitinib. In addition, bone marrow biopsy and analyses was added under local laboratory assessments (for local laboratory evaluation and pathology report) in addition to central laboratory assessments (central samples for banking). Section 7.6.4 was revised to specify that

samples of tissue/aspirate will be initially analyzed at the site's local laboratory and stored at a central vendor for potential future central pathology reading.

Rationale for change: To allow the bone marrow biopsy to be performed during a subject's visit every 12 weeks and to specify ruxolitinib subjects only as the table now includes anagrelide- and ruxolitinib-treated subjects, and clarification of sample management specifications.

15. **Section 6, Study Assessments (Table 7, Laboratory Tests: Required Analytes)**

    Description of change: Under Hematology, "including reporting of % blasts" was added after the complete blood count. Under Coagulation, PTT was replaced with aPTT. Pregnancy testing was revised to indicate a serum test at both screening and EOT and a urine pregnancy test at each study site visit if the test is requested.

    Rationale for change: The % of blasts is already part of the complete hematology blood count and has been specified in writing, aPTT is the generic term for this assessment, and the pregnancy testing information was updated to be consistent with Table 4 and Table 6.

17. **Section 8.1.2, Reporting; Section 8.2, Laboratory Test Abnormalities; Section 9.4.2.1, Adverse Events**

    Description of change: In Sections 8.1.2 and 9.4.2.1, the severity of adverse events assessed using CTCAE v4.03 was updated to include up to Grade 5 (death due to AE). In Section 8.2, the parenthetical "severe" after Grade 4 was deleted.

    Rationale for change: To align with sponsor safety reporting process update.

18. **Appendix E, Essential Thrombocythemia Symptom Assessments Diary**

    Description of change: A column has been added to increment the numbering of the questions from 1 to 18, and the title of the last subsection was corrected to "modified BPI item" instead of "Physical weakness item."

    Rationale for change: To facilitate readability of the questions for the subjects in the electronic device and correct a typographical error.

19. **Incorporation of other administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 1 (21 DEC 2016)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update the Protocol based on feedback from FDA. Updates include but are not limited to adding a rationale for the ruxolitinib 10 mg twice daily (BID) starting dose, updating the dose modification guidelines for anagrelide, and updating and laboratory guidelines for absolute neutrophil count (ANC) and white blood cell (WBC) count.

This amendment includes the changes to Protocol INCB 18424-272 (22 JUL 2016) summarized below. A redline version of the amendment depicting updated and previous text is also provided.

1. **Synopsis; Section 2.1.2, Secondary Objectives [redacted] Section 2.2.2, Secondary Endpoints [redacted] Section 9.4.1.2, Secondary Efficacy Analysis; Section 9.4.1.3, Other Analyses**

   [redacted]

2. **Synopsis; [redacted] Section 5.6.1, Permitted Medications; Section 9.4.2.1, Adverse Events**

   [redacted]

3. **Synopsis; Section 4.1, Overall Study Design; Section 1.2.3.2, Clinical Safety Data; Section 1.4.2, Rationale for Study Design and Treatment and Dose Selection**

   Description of change: The starting dose for ruxolitinib has been revised from 20 mg BID to 10 mg BID, and the rationale for this change has been added.

   Rationale for change: Revision to the starting dose was made based on FDA feedback in response to question 2a in the SPA No Agreement response dated September 8, 2016. FDA agreement with the 10 mg BID starting dose was indicated in the Meeting Preliminary Comments dated December 15, 2016.

4. **Synopsis; Section 1.4.3, Double-Dummy Design; Section 4.1, Overall Study Design; Section 4.4, Duration of Treatment and Subject Participation; Section 5.1.2.1.2, Scheduled Unblinding; Section 6, Study Assessments (Table 5, Schedule of Assessments for Crossover Subjects From Group B; Table 6, Schedule of Laboratory Assessments for Crossover Subjects From Group B); Section 6.3.1, Transition Period Before Open-Label Period; Section 6.4, Open-Label Treatment; Section 9.4.1.3, Other Analyses; Section 9.4.2, Safety Analyses**

   Description of change: A crossover open-label extension has been added after the Week 52 visit and will allow subjects originally randomized to anagrelide to be evaluated for eligibility to cross over to the open-label treatment phase according to investigator's decision, after consultation with the sponsor. For Group A, study assessments during the open-label phase will be every 12 weeks instead of 8 weeks. Specific schedules of assessments for Group B during the open-label phase have been added. All other relevant sections have been updated accordingly.

   Rationale for change: Crossover was added to address an additional comment from FDA (in Clinical section of additional comments on the meeting minutes dated May 9, 2016, and feedback from investigators. FDA agreement on crossover was indicated in the Meeting Preliminary Comments dated December 15, 2016.

5. **Synopsis; Section 3.2, Subject Exclusion Criteria; Section 5.6.3, Prohibited Medications**

   Description of change: A new exclusion criterion #18 was added to exclude subjects being treated concurrently with any medications that may prolong QTc interval of the electrocardiogram. Section 5.6.3 was updated to prohibit medications that may prolong QTc interval of the electrocardiogram.

   Rationale for change: Exclusion criterion was added to address a clinical comment from FDA in clinical comments 2 on SPA No Agreement response dated September 8, 2016, and agreed upon by FDA in the Meeting Preliminary Comments dated December 15, 2016.

6. **Synopsis; Section 5.4, Treatment Modifications: Increases, Interruptions, and Adjustments; Section 6.3, Blinded Treatment**

   Description of change: The guidelines and criteria for dose modification for anagrelide, for dose increases for inadequate efficacy and for hematologic/nonhematologic toxicities have been updated. Table 1 (Dose Interruptions for Hematologic Toxicities) has been updated with revised ANC and platelet count criteria, and Tables 2 and 3 (Dose Levels for Ruxolitinib and Anagrelide, respectively) have been replaced with a new Table 2 (Dose Levels for Ruxolitinib and Anagrelide and Dose Reduction/Restart Guidelines).

   Rationale for change: These changes address the response to question 2b from SPA letter, dated September 8, 2016: the anagrelide dose modification has been adjusted to reflect the Agrylin® Prescribing Information (2b/c); ANC and platelet count criteria have been updated to include FDA suggestions of counts cutoff for lack of efficacy/symptoms improvement (2b/a; b). Changes were indicated as generally acceptable in the Meeting Preliminary Comments dated December 15, 2016.

7. **Synopsis; Section 6, Study Assessments (Table 4, Schedule of Laboratory Assessments); Section 7.6.4 Bone Marrow Biopsy**

   Description of change: Optional additional bone marrow biopsies will be requested at Week 104 and Week 156.

   Rationale for change: These samples have been added as optional only as they may provide additional data regarding changes in bone marrow parameters while on treatment.

8. **Synopsis; Section 6, Study Assessments (Table 4, Schedule of Assessments);**

10. **Synopsis; Section 9.4.1.1, Primary Efficacy Analyses**

    Description of change: The definition of nonresponders for the primary efficacy endpoint was revised to subjects who discontinue treatment without meeting the response criteria.

    Rationale for change: To address the question 4b on SPA no agreement response dated September 8, 2016, to clarify the definition of nonresponder subjects.

11. **Section 4.5, Overall Study Duration; Section 6.3, Blinded Treatment**

    Description of change: Timing for the blinded treatment phase and study completion has been updated.

    Rationale for change: To clarify the overall study duration.

12. **Section 5.1.2.1.2, Scheduled Unblinding; Section 5.5.1, Withdrawal Criteria**

    Description of change: Updated to indicate that subjects who are unblinded before Week 52 will be withdrawn from the study.

    Rationale for change: To clarify subjects accounted for the primary analysis if not reaching Week 52 timepoint interval used for primary endpoint and address FDA comment 2 on statistics on SPA No Agreement response dated September 8, 2016.

13. **Section 5.2, Study Drug**

    Description of change: The tablet and capsule counts per bottle for ruxolitinib and anagrelide, respectively, have been deleted.

    Rationale for change: The count per bottle has been removed as it has not been defined yet for the blinded kits logistics preparation.

15. **Incorporation of administrative changes.** Other minor, administrative changes, including rewording for clarity, have been incorporated throughout the Protocol and are noted in the redline version of the amendment.