Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

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Clinical Study Protocol

Title:	A Phase 1/2, Open-Label Study of the JAK2 Inhibitor INCB018424 Administered Orally to Patients with Primary Myelofibrosis (PMF) and Post Polycythemia Vera/Essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)
Protocol Number:	INCB 18424-251
Product:	INCB018424 Phosphate Tablets
Phase of Study:	Phase 1/2
Sponsor:	Incyte Corporation Route 141 & Henry Clay Road Building E336 Wilmington, DE 19880 United States
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1.0 PROTOCOL SYNOPSIS: INCB 18424-251

Title	A Phase 1/2, Open-Label Study of the JAK2 Inhibitor INCB018424 Administered Orally to Patients with Primary Myelofibrosis (PMF) and Post Polycythemia Vera/Essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)
Study Number	INCB 18424-251
Investigator(s), Study Site(s)	2-4 Sites Srdan Verstovsek MD, PhD, M.D. Anderson Cancer Center, Houston, TX Ayalew Tefferi, MD, Mayo Clinic, Rochester, MN
Study Phase	Phase 1/2
Study Objectives and Endpoints	**Objectives:** • To determine the safety and tolerability of oral INCB018424 in patients with Primary Myelofibrosis (PMF) and Post Polycythemia Vera/Essential Thrombocythemia Myelofibrosis (Post-PV/ET MF). • To determine the Dose Limiting Toxicity (DLT) and the Maximum Tolerated Dose (MTD) of oral INCB018424 in patients with PMF and Post-PV/ET MF. • To determine a therapeutic dose for the expanded cohort. • To study preliminary effectiveness of oral INCB018424 in a patient population diagnosed with PMF and Post-PV/ET MF. • To determine the pharmacokinetics (PK) of oral INCB018424. • To assess pharmacodynamic activity, including phosphorylation status of signal transducer and activator of transcription (STAT) protein in blood cells and determination of plasma protein marker and cytokine levels. • To evaluate alternative dosing schedules to potentially improve safety, tolerability and efficacy. • To obtain preliminary data on changes in symptoms of myelofibrosis (MF) and changes in quality of life. • To obtain preliminary data on changes in daily voluntary physical activity and exercise capacity as assessed by Stepwatch™ Activity Monitor (SAM) and the six minute walk test (6MWT), respectively. • To obtain preliminary data on changes in body composition, grip strength and quadriceps size. • To obtain preliminary data on correlation between MRI-based assessment of spleen and liver volume and organ size assessed by palpation • To determine the duration of maintenance of spleen volume reduction as measured by MRI. • To obtain preliminary data on the effect of dose modifications on an individual patient basis as appropriate.

Study Objectives and Endpoints (Cont'd)	**Trial Endpoints**: • Safety and tolerability will be assessed by monitoring frequency, duration and severity of adverse events, physical exams, evaluating changes in vital signs and ECGs, and through clinical laboratory blood and urine sample evaluation. • Efficacy endpoints include: o Clinical response o ECOG status o Distance walked in the 6MWT o Total number and average number of steps taken over a period of time as measured by the SAM accelerometer. o Body composition (including total body water, extracellular water, intracellular water and estimates of lean body mass and of body cell mass) (by tracer dilution) o Grip Strength (by dynamometer) o Quadriceps size (by MRI) o Spleen and liver volumes (by MRI) o Durability of spleen volume decrease by MRI o Reduction of bone marrow fibrosis o Cytogenetic response o Reduction of JAK2V617F allele burden o Quality of Life assessment o Determination of the PK of INCB018424 by measuring plasma concentration time profiles. o Determination of PD markers including % inhibition of baseline and activated STAT protein phosphorylation in blood cells and changes in plasma protein marker and cytokine levels.
Study Design	This is a multicenter, open-label, non-randomized, dose escalation study of INCB018424, a small molecule Janus kinase (JAK) inhibitor, administered orally to patients with PMF or Post-PV/ET MF. The study is comprised of 3 parts: **Part 1, Dose escalation and Expansion** was planned to examine up to seven dose levels in successive cohorts of 50, 100, 200, 350, 500, 700 and 900 mg/day administered orally in two divided doses following a 3 + 3 design. A dose of 25 mg BID was identified as the maximum tolerated dose (MTD), and additional patients have been enrolled at this dose to further evaluate safety and tolerability. Enrollment in Part 1 is complete. **Part 2, Alternative Dosing Schedules (A, B and C): three alternative dosing schedules will be studied.** **Schedule A: Once daily (QD) dosing regimens.** Design follows a standard 3 + 3 dose escalation design with continuous daily (QD) dosing in 28 day cycles with the exception of the first 25 mg cohort, in which 6 patients are enrolled concurrently. A total of up to four dose levels in successive cohorts of 25, 50, 100 and 200 mg/day administered orally as single daily dose will potentially be studied. **Schedule B: Low dose regimen of 10 mg po BID.** If after 3 cycles (12 weeks) of therapy, there is an inadequate response in spleen size, defined as decrease in spleen size of ≤ 50% from baseline, then the patient will be

Study Design (Cont'd)	eligible to be switched to a higher dose of 25 mg po BID or a dose determined to be effective based on emerging safety and efficacy data from alternative dosing schedules examined in Schedule A. **Schedule C**: **Induction/maintenance regimen**. Patients will be treated for 2 cycles (56 days) at 25 mg po BID followed by a lower maintenance dosing. Six patients will be initially treated at 25 mg po BID and observed for 2 cycles (8 weeks). Patients will be switched to the lower dose of 10 mg BID and will be maintained at this dose unless the patient progresses, in which case the patient dose will be switched to 25 mg po BID daily dose or to a dose determined to be effective based on emerging safety and efficacy data from alternative dosing schedules. Sequence of enrollment of Part 2: Order of preference for enrollment is Schedule A followed by B and then C. Schedule B and C will be enrolled whenever Schedule A enrollment is closed during the observation period of the first 28 days. **Part 3, Group I, II and III** Part 3 will be studied in three separate groups of patients to further evaluate the safety and efficacy of selected starting dose levels and to explore dose modification on an individual patient basis as appropriate. Additional response measures will also be determined on patients in Part 3 as part of Amendment 4 (symptoms and quality of life assessments) and Amendment 5 (daily physical activity, body composition, grip strength, spleen, liver and quadriceps measurements via MRI). Patients will enroll in Part 3, Group I first, followed by enrollment into Group II and Group III. Amendment 5 provides for an additional 50 patients (total now = 70 patients) to be enrolled into Group III. **Group I** is planned to enroll up to 30 patients to one or more of the following dose levels: a) 10 mg BID, b) 25 mg BID, c) 25 mg QD, and d) 50 mg QD. Enrollment in Group I will start in parallel with Part 2 if the following conditions are met: a) The selected dose from Part 1 has been determined to be safe; b) Enrollment in Part 2 Schedule A 25 mg cohort and 50 mg cohorts is complete; c) At least 6 patients have been enrolled in Part 2 Schedule B, and have completed at least one 28-day cycle of continuous therapy; d) At least 6 patients have been enrolled Part 2 Schedule C; e) In all instances enrollment is opened only during the interval when Part 2 Alternative Schedule A is temporarily closed for the 28-day observation period. This rule does not apply if enrollment in Part 2 Schedule A is complete or has been stopped. Doses to be examined have been selected by the investigators in collaboration with the sponsor based on available information from Part 1 and 2, and are 10 mg BID and 50 mg QD. **Group II** is planned to enroll up to 20 additional patients once 6 patients in

Study Design (Cont'd)	the Part 2 Alternative Schedule A have been treated at 100 mg po daily for at least one cycle (or 3 patients at 100 mg daily and 3 patients 200 mg daily to a total of 6 patients for at least one cycle) and at least 6 patients enrolled in Part 2 Schedule B have completed a minimum of two 28 day-cycles of therapy. The 20 patients in this group can be enrolled at any of the doses listed above under Group I or at 100 mg po QD if 100 mg QD is determined to be a viable and safe dose for further evaluation. **Group III**: Up to 70 patients may be enrolled. Starting dose will be determined based on the baseline platelet count as follows: • Patients with baseline platelet count > 200 K/μL will begin dosing at 15 mg BID • Patients with baseline platelet count ≤ 200 K/μL will begin dosing at 10 mg BID Dose interruptions for safety, dose decreases for safety and dose increases for inadequate efficacy are defined in terms of platelet count and ANC levels observed during the study (see Section 5.3, Dose Adjustments). If additional data become available prior to starting, or during enrollment of Part 3, Group III and indicate that the therapeutic window for QD regimens is superior to BID regimens, then Part 3 Group III could be conducted with two QD regimens defined by platelet count. Dose adjustments for patients enrolled prior to the institution of Amendment 5 are provided, and are summarized in Section 5.3, Dose Adjustments. Optional dose de-escalation (maintenance therapy) for patients on stable therapy may be applied to patients enrolling in Part 3 Group III, as well as to eligible patients participating in Parts 1, 2 and 3, Group I and II (see Section 5.3, Dose Adjustments). If a decision is made to discontinue or interrupt therapy, consideration of instituting a tapering strategy is recommended as discussed under Patient Discontinuation and Dose Tapering Strategy Sections 5.2.4 and 5.3.4.
Number of Patients	Total Patients: up to 206 patients Part 1: up to 32 patients Part 2: up to 54 patients Schedule A: up to 30 patients total (5 cohorts) Schedules B and C: 6 patients in each with an option to expand one or both schedules up to 12 patients. Part 3: up to 120 patients Group I: up to 30 patients Group II: up to 20 patients Group III: up to 70 patients
Number of Treatment Arms	Part 1: Dose escalation and Expanded cohort, BID dosing Part 2: Alternative dosing schedules (A, B and C) Part 3: Three independent patient groups (Group I, II and III)
Summary of Entrance Criteria	**Inclusion Criteria:** 1. Must be at least 18 years of age with life expectancy of at least 12 weeks. 2. Must be diagnosed with PMF or Post-PV/ET MF irrespective of

Summary of Entrance Criteria (Cont'd)	JAK2 mutation status. 3. Patients with myelofibrosis requiring therapy, including those previously treated by myelofibrosis directed therapy who have subsequently relapsed or are refractory; or if newly diagnosed should be intermediate or high risk according to Lille (Dupriez) Scoring System (adverse prognostic risk factors are: Hgb < 10 g/dL, WBC < 4 or > 30 x 10^9/L; risk group: 0 factor=low, 1 factor = intermediate, 2 factors = high); or with symptomatic splenomegaly that is > 10 cm below costal margin. 4. Must have palpable spleen measuring 10 cm or greater below the costal margin (Patients in Part 3, Group III only). However, with permission of the sponsor, patients with spleen size of ≤ 10 cm, or in rare cases, with prior splenectomy, but ongoing hepatomegaly, may be enrolled in Part 3, Group III. 5. Have adequate bone marrow reserve as demonstrated by: a) absolute neutrophil count (ANC) that is > 1500/μL b) platelet count that is > 100,000/μL without the assistance of growth factors. 6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 in Part 1, Part 2, Part 3 Group I and II and status of 1 or 2 in Part 3 Group III. 7. Have adequate liver and renal function. a) Total bilirubin ≤ 2.0 mg/dL. b) Alanine aminotransferase (ALT) ≤ 2.5x institutional upper limit of normal (ULN) or ≤ 5x institutional upper limit of normal if the liver is involved by malignancy as judged by the treating physician and the Investigator with documented justification. c) Creatinine ≤ 2.5 mg/dL. 8. A female of childbearing potential must have a negative serum pregnancy test at Screening. 9. Females will be either postmenopausal for at least 1 year with documented FSH > 30 IU/L or surgically sterile for at least 3 months OR females of childbearing potential who must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from Screening through Follow-Up. (Note: Permitted methods are at least 99% effective in preventing pregnancy should be communicated to the patients and their understanding confirmed.) For all females, the pregnancy test result must be negative at Screening. Males must agree to take appropriate precautions to avoid fathering a child (with at least 99% certainty) from Screening through Follow-Up. (Note: Permitted methods are at least 99% effective in preventing pregnancy should be communicated to the patients and their understanding confirmed.) 10. Is able to comprehend and is willing to sign an informed consent form. **Exclusion Criteria:** 1. Females who are pregnant or are currently breastfeeding. 2. Patients who received any anticancer medications or investigational

Summary of Entrance Criteria (Cont'd)	therapy in the 14 days (28 days for Busulfan and pegylated interferon) prior to receiving their first dose of study medication. 3. Patients receiving therapy with intermediate or high dose steroids greater than the equivalent of 10 mg prednisone per day are not allowed. 4. Patients diagnosed with another malignancy unless disease free. Patients with early stage squamous cell carcinoma of the skin, basal cell carcinoma of the skin or cervical intraepithelial neoplasia may be eligible for participation at the Investigator's discretion. 5. Patients with known active hepatitis A, B, C or who are HIV-positive. Evidence for active hepatitis includes elevation of ALT and AST, and other clinical evidence of active hepatitis infection. 6. Patients with any unresolved toxicity greater or equal to Grade 2 from previous anticancer therapy, except for stable chronic toxicities not expected to resolve, such as peripheral neurotoxicity. 7. Patients with New York Heart Association Criteria Class IV impairments (Part 3, Group III only). Patients with Class III impairments may only be enrolled if in the judgment of the investigator, the potential benefits outweigh the potential risks (Appendix XIV). This exclusion does not apply to subjects enrolling in the study under Amendment 7. 8. Patients with incomplete recovery from any prior surgical procedures or who have had surgery within 4 weeks prior to study entry, excluding the placement of vascular access. 9. Presence of acute active infection requiring antibiotics. 10. Patients with uncontrolled intercurrent illness or any concurrent condition that, in the Investigator's opinion, would jeopardize the safety of the patient or compliance with the protocol. 11. Any current or planned therapy with CYP3A4 and CYP1A2 inhibitors or inducers (including smoking) unless approved by the Sponsor. 12. Prior treatment with another oral JAK inhibitor is not permitted unless agreed to by both the Investigator and the Sponsor. Any prior oral JAK inhibitor therapy must have been completed at least 14 days or 6 half-lives, whichever is longer, prior to the first dose of study medication. Additional Exclusions for 6MWT (Part 3, Group III). The following will preclude participation by the patient in the 6MWT, and if occurring at the Screening Visit from participation in the study except with Sponsor's approval. 1. History of or current unstable angina. 2. History recent (within 2 years) myocardial infarction. 3. Patients unable to walk. 4. Patients with unstable gait that persists with the use of assistive device (cane or walker) 5. Resting heart rate > 120 beats per minute. 6. Resting systolic blood pressure > 180 mm Hg. 7. Resting diastolic blood pressure > 100 mm Hg.

Dose and Mode of Administration	INCB018424 tablets (5 and 25 mg) will be administered as oral doses with water in an outpatient setting. Doses will range from 5 mg BID to 50 mg BID, and from 15 mg QD to 200 mg QD. Dosing will use QD and BID regimens, as defined within the protocol for specific subgroups in the study.
Duration of Treatment	Patients may continue on therapy indefinitely if they do not meet any of the withdrawal criteria, do not have disease progression and are receiving some clinical benefit.
Duration of Study	Enrollment: Approximately 12-24 months Treatment & Follow-up: Approximately 12 additional months
Indication	Myeloproliferative Disorders
Statistical Methods	• All clinical safety data (vital signs, ECGs, routine laboratory tests and adverse events) will be tabulated and listed. • Efficacy analyses will be exploratory in nature. All efficacy measures will be estimated with 95% confidence intervals by study part and/or dose schedule/group. • All efficacy and QoL variables will be tabulated with summary statistics. Change from baseline to each visit for selected variables will be assessed using Wilcoxon Sign Rank test. • The PK parameters of INCB018424 will be summarized for each dose group using descriptive statistics, and the log-transformed INCB018424 PK parameters will be compared among the dose groups using a 1-factor analysis of variance. If the PK data are sufficiently robust, the dose-proportionality of INCB018424 C_{max} and AUC may be evaluated using a power function regression model (eg, $C_{max} = \alpha \bullet Dose^{\beta}$). The mean values of the PK parameters may be compared to historical data in healthy volunteers to determine if the INCB018424 PK profile is different between patients with PMF and Post-PV/ET MF and healthy patients. • The percent change from Baseline of stimulated and unstimulated STAT3/5 and IL-6 blood concentrations and other plasma PD biomarkers at Baseline and during treatment cycles will be estimated with a 95% confidence interval.

2.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
6MWT	Six-minute walk test
AE	Adverse event/experience
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
$AUC_{0\text{-}12h}$	Area under the plasma concentration vs. time curve over one steady-state dosing interval
BID	Two times per day
BUN	Blood urea nitrogen
CBC	Complete blood count
CDER	Center for Drug Evaluation and Research
CIB	Clinical Investigator's Brochure
Cl/F	Apparent oral-dose clearance
cm	Centimeter
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum (trough) steady-state plasma concentration
CFR	Code of Federal Regulations
CI	Clinical improvement
CNS	Central nervous system
CR	Complete remission
CRF	Case report form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-30	European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire
ERC	Ethics Review Committee

2.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (Continued)

ET	Essential Thrombocythemia
FDA	Food and Drug Administration
GALT	Gut associated lymphoid tissue
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
hERG	Human-ether-a-go-go related gene
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IgM	Immunoglobin M
IRB	Institutional Review Board
IWG-MRT	International Working Group – Myelofibrosis Research and Treatment
JAK	Janus kinase
MF	Myelofibrosis
MFSAF	Modified Myelofibrosis Symptom Assessment Form
MPD	Myeloproliferative disorder
mg	Milligram
mL	Milliliter
mm	Millimeter
µM	Micromolar
MTD	Maximum tolerated dose
nM	Nanomolar
NOAEL	No-Observed-Adverse-Effect-Level
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PMF	Primary Myelofibrosis
Post-PV/ET MF	Post Polycythemia Vera/Essential Thrombocythemia Myelofibrosis
PR	Partial remission

2.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS (Continued)

PV	Polycythemia Vera
QD	Once daily
RH	Relative humidity
SAE	Serious adverse event/experience
SAM	Stepwatch™ Activity Monitor
STAT	Signal transducers and activators of transcription
T_{max}	Time of maximum plasma concentration
ULN	Upper limit of normal
WBC	White blood cell count

3.0 INTRODUCTION

3.1 Background

INCB018424 phosphate is an inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs) that is currently under development for treatment of myeloproliferative disorders (MPD). JAKs play an important role in signal transduction following cytokine and growth factor binding to their receptors. In addition, JAKs activate a number of downstream pathways implicated in the proliferation and survival of malignant cells including the STATs (signal transducers and activators of transcription), a family of important latent transcription factors. Aberrant activation of JAKs has been associated with increased malignant cell proliferation and survival (Valentino and Pierre, 2006). In particular, a causal role for JAK2 has recently been suggested for the majority of patients with Philadelphia chromosome negative MPD.

3.1.1 Inhibition of JAKs as a Target for Myeloproliferative Disorders

The MPDs are a group of clonal hematologic diseases that include chronic myeloid leukemia, polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis with myeloid metaplasia. Myelofibrosis with myeloid metaplasia (MMM) has been known by a variety of names including agnogenic myeloid metaplasia. In this protocol, more recent nomenclature of primary myelofibrosis (PMF) and post polycythemia vera/essential thrombocythemia myelofibrosis (post-PV/ET MF) will be used (Mesa et al, 2007). This disease, as this new terminology indicates, may occur as a primary disorder or it may follow a preceding disease course with PV or ET. The clinical course in this disease is characterized by bone marrow fibrosis, hepatosplenomegaly, progressive anemia, extramedullary hematopoiesis, leukoerythroblastic peripheral blood findings and constitutional symptoms. Overall median survival is 5 years and causes of premature death include leukemic transformation, infections, thrombosis, cardiac failure, hepatic failure, respiratory failure and portal hypertension. For a small subset of patients who are young, otherwise healthy and have a histocompatible donor, allogeneic stem cell transplantation may provide a curative option, although a risk of significant mortality is

associated with the procedure. There are no treatments that are known to increase the survival of the larger population but a number of therapies may provide symptomatic improvement such as drugs (hydroxyurea, thalidomide, lenalidomide), splenectomy, and involved field radiation at a site of extramedullary disease.

Until recently, little was known about the etiology of these Philadelphia chromosome negative MPDs. The finding that peripheral blood from MPD patients is capable of forming erythroid and megakaryocyte colonies in the absence of exogenous factors (which signal through JAKs) suggests that cells from these patients are intrinsically different than normal cells. Indeed, work from a number of laboratories led to the identification of multiple somatic mutations in genes associated with cytokine and growth factor signaling. These include a mutation in the pseudo-kinase domain of JAK2V617F (amino acid 617, valine to phenylalanine) that results in constitutive activation of JAK2 and downstream STATs. This mutation was found in > 90% of all PV patients and in approximately 50% of all ET and MMM patients. More recently, other mutations have been identified in MPD patients lacking the JAK2V617F mutation. For instance, additional activating mutations in JAK2, as well as a mutation in the thrombopoietin receptor (MPL), result in constitutive ligand-independent JAK activation (Scott et al, 2007 and Pikman et al, 2006). Importantly, ectopic expression of each of theses mutant genes has been demonstrated to be sufficient to cause MPD-like syndromes in mice. Moreover, even in MPD patients lacking a confirmed JAK2 mutation, the detection of STAT activation suggests dysregulated JAK activity. In fact, regardless of the mutational status of JAK2, the malignant cells expectedly retain their responsiveness to JAK activating cytokines and/or growth factors; hence, they may benefit from JAK inhibition. These findings, in addition to the limited life span of these patients and lack of beneficial therapies for the treatment of PMF and post-PV/ET MF, clearly support the evaluation of JAK inhibition in these diseases.

3.1.2 INCB018424 Phosphate

INCB018424 phosphate, referred to herein as INCB018424, is a substituted pyrrolopyrimidine compound that acts as a potent and selective inhibitor of the Janus kinase family of enzymes.

3.1.2.1 *In Vitro* Pharmacology of INCB018424

INCB018424 is a novel, potent, and selective inhibitor of the JAKs with modest selectivity for JAK2. INCB018424 potently (IC_{50} values < 5 nM) inhibits JAKs, yet it does not significantly inhibit (<30% inhibition) a broad panel of 26 other kinases when tested at 200 nM (approximately 100 times the average IC_{50} value for JAK enzyme inhibition). Moreover, in cell-based assays relevant to the pathogenesis of MPDs, such as JAK-STAT signaling and the growth of cytokine-dependent lines, INCB018424 demonstrated excellent potency (IC_{50} values of 80-141 nM). This effect was not due to general cytotoxicity, because INCB018424 (up to 25 μM) had no significant effect on the growth of cytokine-independent cell lines transformed by the Bcr-Abl oncogene. In addition, INCB018424 inhibited JAK/STAT signaling and growth of a cell line expressing the JAK2 mutant variant (JAK2V617F) that has been implicated in the pathogenesis of the majority of Philadelphia chromosome negative MPD. Additional details as to the *in vitro* pharmacology of INCB018424 may be found in the Clinical Investigator's Brochure (CIB).

3.1.2.2 *In Vivo* Pharmacology of INCB018424

INCB018424 was evaluated in two mouse models where either a cytokine-dependent multiple myeloma cell line, INA-6, or a cell line, BaF3, engineered to express JAK2V617F was inoculated. The ability of INCB018424 to inhibit JAK pathway signaling as well as tumor cell survival and growth was assessed *in vivo*. *In vitro* cell biology experiments have demonstrated that the potency of INCB018424 is very similar between the cytokine-dependent INA-6 myeloma cells, with wild type JAKs, and the BaF3 cells expressing a clinically relevant mutant JAK2. As such, the *in vivo* studies described herein characterize the ability of INCB018424 to inhibit wildtype JAK2 (using

the INA-6 xenograft model) and MPD-related mutant JAK2 (using a mouse model of splenomegaly driven by cells expressing the mutant JAK2V617F).

Treatment of mice with orally administered INCB018424 resulted in a dose-dependent suppression of STAT3 phosphorylation and tumor growth in the cytokine-dependent INA-6 xenograft model at doses ≥ 10 mg/kg BID. Moreover, oral administration of INCB018424 inhibited the dramatic splenomegaly in mice resulting from intravenous inoculation of the BaF3-JAK2V617F cells. Additional details as to the *in vivo* pharmacology of INCB018424 may be found in the Clinical Investigator's Brochure (CIB).

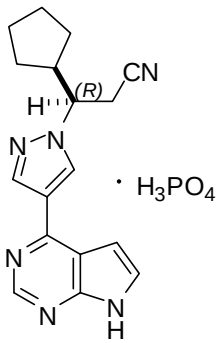
In summary, pharmacological data obtained in both *in vitro* and *in vivo* model systems support the potential utility of orally administered INCB018424 in the treatment of malignancies, including MPD such as PMF and Post-PV/ET MF.

3.2 Physical, Chemical, and Pharmaceutical Properties and Formulation

3.2.1 Chemistry

The chemical name of INCB018424 phosphate is (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate (Figure 1). INCB018424 phosphate has a molecular formula of $C_{17}H_{21}N_6O_4P$ and a molecular weight of 404.36.

Figure 1 INCB018424 Phosphate Structural Formula



3.2.2 Physical Properties

INCB018424 phosphate drug substance is a white to off-white powder, and is referred to herein as INCB018424.

3.2.3 Stability

INCB018424 phosphate drug substance has been shown to be stable for six months at 40ºC/75% RH, and up to twelve months when stored at 25ºC/60% RH. Stability studies for 5 mg and 25 mg tablet formulations are being conducted at 25ºC/60% RH and 40ºC/75% RH. The tablet formulations have been shown to be stable for at least six months at 25ºC/60%RH and 40ºC/75% RH.

3.2.4 Formulation

INCB018424 drug product will be provided as 5 mg and 25 mg strength tablets. The tablet formulation contains the active ingredient along with commonly used excipients. All excipients are of compendial grade.

3.3 Trial Rationale

INCB018424 is an inhibitor of the Janus kinases (JAKs) that is under development for the treatment of Myeloproliferative Disorders (MPD). As noted above, there is good reason to believe that JAK2-inhibitors will be efficacious in a variety of MPD related diseases. Based on the results of the animal toxicology studies and single and multiple dose pharmacokinetic studies in healthy, human volunteers, INCB018424 is expected to be safe and well-tolerated at the doses and regimens proposed in this study. Study INCB 18424-251 is the first study of INCB018424 in patients diagnosed with PMF and Post-PV/ET MF.

In Part 1 of this study, significant and sustained reductions in spleen size have been demonstrated at doses of 25 mg BID. While the 25 mg BID dose has been tolerated by many patients receiving that dose, it is associated with clinically significant declines in platelets and/or hemoglobin in about 25% of patients treated with this dose that lead to

dose interruptions, or, less often, study discontinuation. Therefore, it is important to study other doses and dose regimens in order to define the dosing options that best combine efficacy benefits, while minimizing the negative impact on hematological parameters. Part 2 and 3 of this study explores alternative dosing schedules, including once-daily (QD) regimens, lower dose BID regimens, induction/maintenance regimens, and regimens defined and individually modified by, baseline and on study platelet and ANC levels.

Previously, Protocol Amendment 4 to the study was implemented to add a third part (Part 3) of the study in order to expand enrollment for selected dose levels and to provide for quality of life assessment instruments to be used to monitor patient's symptoms. Importantly, patients with MF report a variety of symptoms and limitations that effect conduct of daily activities, such as fatigue, lack of energy, difficulty walking, and altered body image reflecting both splenomegaly and, in some cases, cachexia. Protocol Amendment 5 expands the study endpoints further to include additional assessments of functional exercise capacity, measurement of spleen volume, liver volume and quadriceps size by MRI, evaluation of body composition, and measurement of grip strength. These additional assessments will allow the determination of the impact of INCB018424 therapy on key symptoms and daily life activities in the treated patients. The additional functional and quality of life measures together with expanded dosing paradigms will provide a robust data set of doses and resultant safety, tolerability and efficacy endpoints that will allow dose selection for future studies in the MF population.

Amendment 6 provides an update to the potential risks of INCB018424 based upon newly acquired clinical safety information, and incorporates protocol changes that recommend considering utilization of a tapering strategy when discontinuing or interrupting therapy (See Sections 5.2.4, Patient Discontinuation and Section 5.3.4, Dose Tapering Strategy).

Amendment 7 provides an update to the potential risks of INCB018424 based on updated safety information from this ongoing study, and updated preclinical safety information. Amendment 7 also incorporates additional MRI assessment of the abdomen every 6 months for subjects enrolled under Amendment 5 and Amendment 6 who have Baseline MRIs, and who are willing to have additional MRI scans performed. Subjects who do not sign consent for additional MRIs will not be precluded from continued participation in the study. The available data suggests that subjects who attain a spleen length decrease as measured by palpation also show a decrease in spleen volume by MRI; quantitatively, a 50% decrease in spleen length is associated with a 35% reduction in spleen volume. Amendment 7 will allow additional long term follow-up of spleen size reductions in subjects using the objective MRI measurement of spleen volume to determine the durability of spleen volume reduction.

3.4 Potential Risks and Benefits

3.4.1 INCB018424 Preclinical Safety

The toxicologic and toxicokinetic profiles of INCB018424 were characterized in single and repeat oral dose studies of up to 6 months in duration in rats and dogs. Genetic toxicology, safety pharmacology, and embryo-fetal toxicology studies have also been conducted.

In a 6 month study in rats, doses up to 60 mg/kg/day were evaluated. An adverse decrease in body weight gain was noted in male, but not in female rats. A dose related decrease in lymphocytes was noted. Minimal-to-mild lymphoid depletion in spleens and in mandibular lymph nodes was noted at the 60 mg/kg/day dose level; at lower doses, lymphoid tissues were within normal histologic limits. The no-observed-adverse-effect level (NOAEL) for oral administration of INCB018424 for 26 weeks was 30 mg/kg/day for the males (unbound AUC 0.119 μM*h), related to adverse effects on body weight at 60 mg/kg/day, and 60 mg/kg/day for female rats (unbound AUC 4.64 μM*h). (Lower parent drug levels in male rats are related to male rat specific isozymes 2C11, 2C13

and CYP3A2 which metabolize INCB018424 to active metabolites). Additional details on rat toxicology studies are available in the IB.

In the 6 month dog study, doses studied included 0.5, 2.5, 5, and 10 mg/kg/day. Demodectic mange, lymphopenia, eosinopenia, decreases in erythron parameters, moderate to severe cellular depletion of lymphoid tissues, bacterial pneumonia, viral-induced papillomas, microscopic invasive demodectic mange, and prostate hypoplasia/atrophy were seen in high dose dogs. Deaths attributed to bacterial pneumonia occurred in 3 of 14 dogs given 10 mg/kg/day. Demodectic mange was observed in several animals given 5 mg/kg/day and, microscopically, in one animal given 2.5 mg/kg/day. These events most likely reflect a response to the immunosuppressive effects of INCB018424. All tissues were normal in the 0.5 mg/kg/day group. The NOAEL dose was defined at 2.5 mg/kg/day (unbound AUC 0.76 μM*h) due to minimal findings, which were not present in recovery animals. The low dose, 0.5 mg/kg/day, was defined as the no-observed effect-level (NOEL). Additional details regarding dog toxicology studies are available in the IB.

INCB018424 was not genotoxic in the bacterial mutagenicity assay, the *in vitro* chromosome aberration assay, or the *in vivo* micronucleus assay in rats. In embryo-fetal assessments in rat and rabbit, maternal toxicity and minimal embryo-fetal toxicity were noted at the highest doses evaluated. INCB018424 was not teratogenic in either rat or rabbit. The NOAEL dose for the rat and rabbit study was 30 mg/kg/day. Additional toxicology and safety pharmacology information is available in the IB.

3.4.2 Clinical Pharmacology of INCB018424

Following oral, single-dose administration of INCB018424 capsules in the fasted state, INCB018424 was absorbed rapidly, typically attaining peak plasma concentrations within 1 to 3 hours after administration for all doses. After attaining C_{max}, the INCB018424 plasma concentrations declined with a mean terminal-phase disposition $t_{1/2}$ of approximately 3-5 hours. The mean INCB018424 C_{max} and 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. Therefore, INCB018424 can be dosed without regard to meals.

No accumulation was seen following administration of repeated oral doses of 15 to 50 mg INCB018424 twice daily (BID), and 50 to 100 mg INCB018424 once daily for 10 days. PK parameters were similar to those seen following the administration of single doses. INCB018424 is metabolized in the liver by the cytochrome (CYP) P450 metabolizing enzyme system, predominantly by the 3A4 isozyme. The effects of the potent CYP3A4 inhibitor ketoconazole on the pharmacokinetics (PK) and pharmacodynamics (PD) of INCB018424 administered as single oral doses shows that with concomitant dosing of ketoconazole, the observed AUC increase is approximately 2-fold, and the calculated Equivalent Constant Concentration (ECC) for the pSTAT3 PD effect was also increased approximately 2-fold. Thus, a dose reduction of ~ 50% for INCB018424 is appropriate for subjects who take ketoconazole or other potent CYP3A4 inhibitors as concomitant medication (see Section 10.6). A more modest effect on the PK parameters of INCB018424 was demonstrated with concomitant dosing of the moderate CYP3A4 inhibitor erythromycin. No dose adjustments are necessary when INCB018424 is co-administered with erythromycin, or by extension, with other moderate or weak inhibitors of CYP3A4, including grapefruit juice. Additional details as to the clinical pharmacology of INCB018424 may be found in the IB.

An open-label study to assess the effect of CYP3A4 inducers on INCB018424 pharmacokinetics and pharmacodynamics revealed that, as expected, rifampin significantly decreased the exposure to INCB018424. However, essentially no difference in cytokine-induced STAT3 phosphorylation was observed with or without rifampin induction. This suggests that CYP3A4 induction with rifampin results in metabolism of INCB018424 to active metabolites which also inhibit JAKs. Increased levels of active metabolites were seen with rifampin dosing. These data indicate that the dose of INCB018424 need not be modified when dosed with CYP3A4 inducers. However, during

the study, use of CYP3A4 inducers is discouraged, and investigators should seek alternatives where possible (see Section 10.6)

INCB018424 was given as a single 25 mg dose to subjects with varying degrees of renal function, including normal (calculated creatinine clearance (ClCr) >80 mL/min), mild (ClCr 50-80 mL/min), moderate (ClCr 30-49 mL/min) and severe (ClCr<30 mL/min) renal impairment as well as subjects on dialysis and the PK and PD parameters measured. There was no statistically significant effect of mild to severe impairment of renal function on the PK or PD parameter; subjects requiring dialysis showed decreased INCB018424 clearance. Subjects with serum creatinine exceeding 2.5 mg/dL will be excluded from the study.

3.4.3 INCB018424 Clinical Safety in Healthy Volunteers

INCB018424 has been administered in single or multiple doses to over 90 healthy subjects. INCB018424 was examined in a 10-day multiple dose study in a total of 71 healthy volunteers in 6 cohorts who received doses of 50 mg QD, 100 mg QD, 15 mg BID, 25 mg BID or 50 mg BID of INCB018424 or placebo (Study INCB 18424-132). INCB018424 was well tolerated in the study, with most adverse events reported by both INCB018424-treated and placebo-treated subjects. Adverse events were, in general, mild, assessed as unrelated to study drug and resolved without intervention. Subjects receiving 15 mg BID, 50 mg QD or 100 mg QD did not report any treatment-related adverse events. At the other doses, headache, dizziness and nausea that were assessed as treatment related events occurred in subjects dosed with placebo at the same or higher frequency as in subjects receiving INCB018424. Neutropenia as an adverse event was noted in 3 subjects receiving the highest dose of INCB018424, 50 mg BID. Neutropenia at the Grade 4 level, assessed as severe, led to study drug discontinuation on Day 5 in one subject, and was reported as a Serious Adverse Event (SAE). There was a decline in mean absolute neutrophil count (ANC) and to a lesser extent, mean white blood cell count (WBC) values with INCB018424 doses of 15 mg BID or higher. In general, these declines in ANC or WBC were observed early during the 10-day dosing period with BID

regimens; did not worsen with continued dosing, and returned to Baseline levels within 1 to 2 days following the last dose of study drug, suggestive of a neutrophil margination effect. Doses of 25 mg BID and 100 mg QD were determined to be maximum tolerated doses (MTDs) in this study. For additional details, consult the IB.

3.4.4 INCB018424 Clinical Safety in Phase 2

INCB018424 has been well tolerated by this aged population with advanced disease. Most adverse events were mild to moderate in severity, considered unrelated to study drug administration and not dose dependent. Related adverse events occurring in at least 5 of the 152 subjects (3%) included in the safety database through February 11, 2009 were restricted to anemia (20 subjects), thrombocytopenia (32 subjects), diarrhea (8 subjects), fatigue (9 subjects), headache (5 subjects) and clinically insignificant QT abnormality that was not present after correction for heart rate (5 subjects). Both anemia and thrombocytopenia represent JAK-inhibitor myelosuppression, and are therefore not unexpected. In study subjects, thrombocytopenia of Grade 3 severity occurred in 3.4% of subjects receiving 10 mg BID of INCB018424, 0% of subjects receiving 15 mg BID of INCB018424, 23% of subjects receiving 25 mg BID of INCB018424, 60% of subjects receiving 50 mg BID of INCB018424, 0% of subjects receiving 25 mg QD of INCB018424, 23% of subjects receiving 50 mg QD of INCB018424 and 17% of subjects receiving 100 mg QD of INCB018424. Thrombocytopenia of Grade 4 severity occurred in 0% of subjects receiving 10 mg BID of INCB018424, 0% of subjects receiving 15 mg BID of INCB018424, 6.4% of subjects receiving 25 mg BID of INCB018424, 20% of subjects receiving 50 mg BID of INCB018424, 0% of subjects receiving 25 mg QD of INCB018424, 4.5% of subjects receiving 50 mg QD of INCB018424 and 0% of subjects receiving 100 mg QD of INCB018424. For the 25 mg BID dose group, subjects exhibiting these Grade 3 or 4 declines in platelets had, in general, entered the study with platelet counts below 200,000/μL. For nearly all subjects, thrombocytopenia was rapidly reversible and manageable with dose interruption and/or reduction. Anemia, though dose dependent, largely reflects the low hemoglobin status at baseline in this disease population.

Because of the advanced disease present in many of the participants in Study INCB 18424-251, there are a number of SAEs that have been reported that were assessed as unrelated to study drug. Of related SAEs reported in the study to date, the most frequent are those reflecting inhibition of bone marrow function(s) (eg, thrombocytopenia) and activation of inflammatory cytokines when the inhibitory influence of INCB018424 is removed due to drug interruption or discontinuation. See the IB for complete details on INCB018424 clinical study findings.

3.4.5 INCB018424 Potential Risks

The primary clinical risks with INCB018424 treatment are the potential sequelae of decreased hematopoiesis, myelopoiesis, thrombopoiesis and decreased levels of circulating cytokines and growth factors, all of which are secondary to the inhibition of growth factor pathways by JAK2 antagonism. Dose-dependent, reversible thrombocytopenia has been observed in Study INCB 18424-251 in subjects with MF (see Section 3.4.7, Justification of Route, Dose Regimen and Treatment Period). Two cases of mild epistaxis in a thrombocytopenic patient considered possibly related to INCB018424 treatment have occurred out of approximately 150 treated 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 this study, decreases in platelet count have led to dose interruptions or dose adjustments; the overall rate and severity of thrombocytopenia appears dose proportional. It is not yet known if dose adjustments instituted with early signs of incipient thrombocytopenia may alter the development of thrombocytopenias that are assessed as Grade 3 or 4; however the preliminary data with subjects enrolled under Amendment 5 and 6, in which well defined dose reduction and restart rules were implemented is encouraging; none of the 34 subjects enrolled to start at doses of 15 mg BID have had a Grade 3 or Grade 4 thrombocytopenia event. Hematologic parameters will be closely monitored for all patients during this study, and therapy will be withdrawn or dosing held or reduced until resolution if there are clinically relevant declines.

A few subjects have had an apparent worsening of their pre-morbid disease symptoms following rapid cessation of INCB018424 therapy and a gradual tapering and use of steroids in fragile subjects, and subjects with significant cardiopulmonary impairment, may be prudent when stopping INCB018424 therapy. Additional information is available in the INCB018424 IB.

3.4.6 INCB018424 Benefits

The initial efficacy results of Study INCB 18424-251 are notable. Improvements in spleen size have been significant, with approximately > 50% of patients achieving 50% reduction or more in spleen size with doses of 15 mg BID or higher. Patients have reported improvements in their quality of life and their performance status has generally improved. Evaluation of pharmacodynamic markers has shown 1) reduction in JAK2 V617F allele burden noted in peripheral blood and bone marrow, 2) normalization of JAK signaling in circulating leukocytes, 3) reduction in plasma levels of inflammatory, prothrombotic, and angiogenic cytokines, and 4) increases in hematopoietic growth factor levels, consistent with the mechanism of action of INCB018424.

3.4.7 Description and Justification of Route, Dose Regimen and Treatment Period

INCB018424 is being developed for oral administration, a route of administration that is widely used and helps promote patient compliance to medication dosing. Both BID and QD regimens will be explored; because of the short plasma half life of INCB018424, there is little accumulation of INCB018424 or active metabolites. The treatment period consists of multiple 28-day cycles, with patients continuing in the study indefinitely provided withdrawal criteria are not met, and there is continuing evidence of clinical benefit.

Initially (Part 1), the study was planned evaluate the safety, tolerability, PK and PD of up to seven rising oral doses of INCB018424 (50, 100, 200, 350, 500, 700, and 900 mg total per day, given as divided doses in a BID regimen), ie, 25 mg BID, 50 mg BID, etc. The top planned dose of 900 mg/day was less than the human equivalent dose of 960 mg,

which is 10 times the safe clinical starting dose. The initial dose level of 25 mg BID was determined based on clinical safety results from previous Phase 1 single and multiple dose escalation studies in healthy volunteers (INCB 18424-131 and -132). The 50 mg BID dose was not well tolerated; the MTD was therefore defined as 25 mg BID, and further dose escalation was not performed.

Although many patients tolerate 25 mg BID, and the effects on spleen size, cytokine parameters and quality of life assessments are significant, declines in platelet count, or, less often, ANC levels occur in about one quarter of the patients receiving this dose. These Grade 3 and 4 declines have led to dose interruptions, dose de-escalations and, occasional early terminations from the study. Therefore, it is important to study other doses and dose regimens in order to define optimal dose options that combine efficacy benefits, while minimizing the negative impact on hematological parameters. Part 2 of this study explores three such alternative dosing regimens. Schedule A evaluates the safety, tolerability, clinical response, PK and PD of up to four rising oral doses of INCB018424 (25, 50, 100, and 200 mg total per day), administered continuously once daily (QD). These dosing regimens are designed to assess if higher doses can reduce spleen size and JAK mutant allele burden and also improve quality of life symptoms while decreasing the average daily fraction of time that JAK-mediated myelosuppression occurs. Schedule B will evaluate the safety, tolerability, clinical response, PK and PD of a BID dose regimen lower than the MTD. In Schedule B INCB018424 is administered at 10 mg BID. Schedule C evaluates the safety, tolerability, clinical response, PK and PD using an induction/maintenance regimen. The initial dose is 25 mg po BID for 2 cycles (8 weeks) followed by a maintenance dose of 10 mg po BID. This regimen explores the possibility that efficacy can be maintained at doses lower, and potentially more tolerable than, those required for initial effects. Doses examined in Schedules A and B of Part 2 will be assessed in an expanded number of patients in Groups I and II of Part 3 of the study.

Available data for BID doses of 10 mg and 25 mg show that the two doses differ in both efficacy (as determined by spleen size reduction) and safety/tolerability (as determined by proportions of patients developing thrombocytopenia) as summarized in Table 2.

Table 2 Spleen Size Reduction and Incidence of Thrombocytopenia at Doses of 10 mg BID and 25 mg BID in Study INCB 18424-251

Parameter	25 mg BID	10 mg BID
N as of February 11, 2009	47	29
Proportion achieving at least 50% reduction in spleen size[a]	56% (22 of 39)	33% (8 of 24)
Proportion with Grade 3 or 4 thrombocytopenia	30%	3.4%

[a] Only subjects with a palpable spleen at Baseline and at least 2 months of spleen size data are included in the spleen reduction analysis.

Similarly, pharmacodynamic data derived from healthy volunteers suggests that for inhibition of pSTAT, doses of 10 mg and 25 mg lie on the linear portion of the dose response curve. When potential risk factors for patients who develop thrombocytopenia are assessed, it was found that entering the study with a relatively low platelet count (eg, less than 200 K/μL), is, not surprisingly, associated with a higher incidence of thrombocytopenia. Based on these preliminary efficacy and safety data, an optimal dose is likely to be between 10 mg BID and 25 mg BID, with baseline platelet count favoring the lower end of the dose range. Therefore, Part 3 Group III explores 15 mg BID as the starting dose, for all patients entering the study with a platelet count > 200 K/μL, and 10 mg BID as the starting dose for all patients entering the study with platelet count between 101 K/μL and 200 K/μL. Up to two dose increases for inadequate efficacy are provided for, while maintaining the daily dose within the range of 10 mg BID to 25 mg BID, inclusive. Mandatory dose decreases for safety reasons are dictated by platelet count levels. These dose increases and decreases are summarized in Section 5.3, Dose Adjustments, and Section 10.4, Dose Interruptions. These dose modification strategies will be applied to all ongoing patients enrolled in the study, as outlined in Section 5.3, Dose Adjustments. When a decision is made to discontinue the patient or interrupt the therapy, then the recommendation is to consider instituting a tapering strategy based on

the investigator's clinical judgment (See Patient Discontinuation, Section 5.2.4 and Dose Tapering Strategy, Section 5.3.4).

As of February 11, 2009, 34 subjects have been enrolled under Amendment 5 and 6 to start at a dose of 15 mg BID. Approximately one fourth of these subjects have had a mandatory dose increase to 20 mg BID after 4 weeks of therapy, and 10% of the subjects in the 15 mg BID cohort have had a second dose increase to 25 mg BID. Of 28 subjects with available spleen size data for at least 2 months, 54% have achieved decreases in spleen size by palpation of at least 50% relative to baseline; of subjects with MRI values at Baseline and 3 or 6 months of therapy, approximately 50% have achieved a reduction in spleen volume, measured by MRI of 35%. To date, no subjects assigned to the 15 mg BID dose group have had a Grade 3 or Grade 4 thrombocytopenia event. The data suggests that initial doses of 15 mg BID are very well tolerated, while providing efficacy similar to that observed at the higher 25 mg BID dose.

If, as additional data become available prior to starting, or during enrollment of Part 3 Group III, it becomes clear that once daily dosing provides a greater therapeutic window for therapy, eg, efficacy of a QD regimen is equal to that seen at 25 mg BID, but the incidence of thrombocytopenia with that same QD dose is similar to that seen at 10 mg BID, then Group III could be conducted with two QD regimens defined by platelet count. The criteria to implement this option are further described in Section 5.2, Trial Design. Dose escalation for inadequate efficacy, dose decreases for safety and dose restarts would still be applied.

3.5 Statement of Good Clinical Practices

The study will be conducted in accordance with Good Clinical Practices (GCP). As such, all of the regulations stipulated in the Code of Federal Regulations (CFR) Title 21 CFR, Parts 50, 56 and 312, and in the International Conference on Harmonisation (ICH) guidance on GCP (ICH E6[R1]) must be satisfied.

3.6 Study Population

The study population will consist of patients diagnosed with PMF and Post-PV/ET MF who are at least 18 years of age with life expectancy of at least 12 weeks or longer. Up to 206 patients will be enrolled.

Part 1: Up to 32 patients will be enrolled

Three to six patients will be enrolled in each cohort for the dose escalation part of the study and 21 additional patients will be enrolled at the recommended therapeutic dose in the expanded cohort of the study to a total of 32 patients.

Part 2 Alternative Schedules A, B, C: Up to 54 patients will be enrolled

Schedule A: up to 30 patients total (4 cohorts)

Schedule B and C: up to 6 patients in each with an option to expand one or both schedules to up to 12 patients each

Part 3 Three independent Groups of Patients: Up to 120 patients will be enrolled

Group I: up to 30 patients

Group II: up to 20 patients

Group III: up to 70 patients

4.0 STUDY OBJECTIVES

Objectives:

- To determine the safety and tolerability of oral INCB018424 in patients with PMF and Post-PV/ET MF.
- To determine the Dose Limiting Toxicity (DLT) and the Maximum Tolerated Dose (MTD) of oral INCB018424 in patients with PMF and Post-PV/ET MF.
- To determine a therapeutic dose for the expanded cohort.
- To study preliminary effectiveness of oral INCB018424 in a patient population diagnosed with PMF and Post-PV/ET MF.

- To determine the pharmacokinetics (PK) of oral INCB018424.
- To assess pharmacodynamic activity, including phosphorylation status of signal transducer and activator of transcription (STAT) protein in blood cells and determination of plasma protein marker and cytokine levels.
- To evaluate alternative dosing schedules to potentially improve safety, tolerability and efficacy.
- To obtain preliminary data on changes in symptoms of myelofibrosis (MF) and changes in quality of life.
- To obtain preliminary data on changes in daily voluntary physical activity and exercise capacity as assessed by Stepwatch™ Activity Monitor (SAM) and the six minute walk test (6MWT), respectively.
- To obtain preliminary data on changes in body composition, grip strength and quadriceps size.
- To obtain preliminary data on correlation between MRI-based assessment of spleen and liver volume and organ size assessed by palpation.
- To determine the duration of maintenance of spleen volume reduction as measured by MRI.
- To obtain preliminary data on the effect of dose modifications on an individual patient basis as appropriate.

5.0 INVESTIGATIONAL PLAN

5.1 Trial Endpoints

The endpoints will include:

- Safety and tolerability will be assessed by monitoring frequency, duration and severity of adverse events, physical exams, evaluating changes in vital signs, ECGs, and through clinical laboratory blood and urine sample evaluation.

- Efficacy endpoints include:
    - Clinical response
    - ECOG status
    - Distance walked in the 6MWT
    - Total number and average number of steps taken over a period of time as measured by the SAM accelerometer
    - Body composition (including total body water, extracellular water, intracellular water and estimates of lean body mass and of body cell mass) (by tracer dilution)
    - Grip Strength (by dynamometer)
    - Quadriceps size (by MRI)
    - Spleen and liver volumes (by MRI)
    - Durability of spleen volume decrease by MRI
    - Reduction of bone marrow fibrosis
    - Cytogenetic response
    - Reduction of JAK2V617F allele burden
    - Quality of Life assessment
    - Determination of the PK of INCB018424 by measuring plasma concentration time profiles
    - Determination of PD markers including % inhibition of baseline and activated STAT protein phosphorylation in blood cells and changes in plasma protein marker and cytokine levels

5.2 Trial Design

This is a multicenter, open-label, non-randomized, dose escalation study of INCB018424, a small molecule Janus kinase (JAK) inhibitor, administered orally to patients with PMF or Post-PV/ET MF. The study is comprised of three parts. Upon completion of the Part 1 dose escalation phase including enrollment of the expanded cohort, Part 2 enrollment for the alternative dosing schedules will begin. Enrollment in Part 3 Groups I and II will begin in parallel with ongoing Part 2, once the selected dose or doses have been determined to be safe and well tolerated. A dose is considered to be safe for selection when six patients have completed a dose level with zero or one DLTs or three patients have completed a dose level with no DLTs and either three patients have completed the next dose level with no DLT or 6 patients have completed the next dose level with no more than one DLT. Enrollment in Part 3, Group III will begin with the approval of Protocol Amendment 5 of Study INCB 18424-251.

5.2.1 Part 1: Dose escalation and expansion

Sequential cohorts consisting of 3 to 6 patients were to be enrolled in the dose escalation part of the study to determine the dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) of the INCB018424. Each of seven planned cohorts was to be assigned to receive escalating doses of INCB018424, starting with a total daily dose of 50 mg administered in two divided doses, ie, BID (at least 10 and no more than 14 hours apart). Dose escalation followed a modified Fibonacci series with the exception that the two initial doses were in 100% increments. The planned dose levels were:

- Cohort A: 50 mg INCB018424 total daily dose
- Cohort B: 100 mg INCB018424 total daily dose
- Cohort C: 200 mg INCB018424 total daily dose
- Cohort D: 350 mg INCB018424 total daily dose
- Cohort E: 500 mg INCB018424 total daily dose
- Cohort F: 700 mg INCB018424 total daily dose
- Cohort G: 900 mg INCB018424 total daily dose

The dose levels could have been decreased from these intended dose levels, but could not be increased without a protocol amendment. A cohort could be dosed with a once daily regimen based on emerging safety, PK and PD data; however, the once daily dose could not exceed the next planned dose that would have been given twice daily. For example, following successful completion of the 100 mg BID dose level (200 mg total daily dose), the next cohort may be dosed up to 175 mg once daily, instead of the intended next dose level of 175 mg BID (350 mg total daily dose).

Three patients were to be initially enrolled (fourth patient enrollment for all cohorts is optional at the discretion of the Investigator and Sponsor) at a starting total daily dose of 50 mg/day as the divided dose 25 mg BID. The patients were to receive INCB018424 tablets twice daily continuously for 28 days in an outpatient setting. This 28-day period constitutes one treatment cycle. Cycles can be repeated at the discretion of the treating physician. Prior to each clinic visit, each patient will be evaluated for development of AEs. The decision whether to expand a cohort to 6 patients or to treat the next cohort of 3 patients at the next higher dose-level was to be based on the occurrence of any DLTs. The escalation rules will be applied 28 days after the final patient in a given cohort receives the first treatment with INCB018424. Evaluable patients will be those who experience a DLT or complete 28 days without a DLT and have received at least 75% of planned doses during their first cycle of therapy. The second dose examined, 50 mg BID was not well tolerated. The MTD was defined as a dose of 25 mg BID. Further dose escalation did not occur. Enrollment is complete for Part 1.

5.2.2 Part 2: Alternative Dosing Schedules A, B, C

Three alternative dosing schedules will be studied.

Schedule A Once daily (QD) dosing regimens: follows a standard 3 + 3 dose escalation design with continuous daily (QD) dosing in 28 day cycles with the exception that the first 25 mg QD cohort will enroll 6 patients. Up to four dose levels in successive cohorts of 25, 50, 100 and 200 mg/day administered orally as single daily doses will potentially be studied. Immediately following enrollment of the 25 mg QD cohort, three

new patients will be enrolled at 50 mg QD. If none of the 3 patients enrolled at the 50 mg dose experience a DLT for the first 28-day cycle of treatment, then 3 new patients will be enrolled at the 100 mg QD dose. If none of the 3 patients enrolled at the 100 mg dose experience a DLT for the first 28-day cycle of treatment, then 3 new patients will be enrolled at the 200 mg QD dose. If one DLT is experienced amongst 3 patients in a given dose group, the cohort is expanded to 6 patients. If 2 or more DLTs are now found in the 6 patients at this dose level then dose escalation is stopped and the next lower dose will be expanded to 6 patients, if that had not previously occurred, so that 6 evaluable patients are dosed for one 28-day cycle before that dose is considered safe and tolerated. If a DLT occurs in 2 of first 3 patients in a cohort, the MTD will have been exceeded. The maximum tolerated dose (MTD) will have been reached when at least 6 patients have received a dose for one 28-day cycle with no more than 1 patient experiencing any DLTs. An additional 6 patients may be entered at the MTD to further evaluate safety, tolerability and efficacy of the MTD. If the MTD for QD dosing is not established (ie, DLT defining MTD are not encountered at the highest dose of 200 mg QD), then 3 additional patients will be enrolled at 200 mg QD. If 0 or 1 patient experiences a DLT, this will be defined as the highest once daily dose that will be used in this study. Additional patients may then be enrolled at any QD dose up to the MTD or 200 mg QD for a maximum total of 30 patients over the 4 doses.

The escalation rules will be applied 28 days after the last patient in a given cohort receives the first treatment with INCB018424. Evaluable patients will be those who experience a DLT or complete 28 days without a DLT and have received at least 75% of planned doses during their first cycle of therapy. Dose escalations for inadequate response, dose de-escalations for low platelet counts, and dose adjustments to lower maintenance doses are summarized below (Section 5.3, Dose Adjustments).

Schedule B Low dose regimen of 10 mg BID: A total of six patients will be enrolled concurrently at 10 mg po BID. This dosing regimen is designed to determine if a lower dose of 10 mg po BID is effective in reduction of spleen size with possible improvement

in cytopenias relative to the previously studied BID regimen of 25 mg. Dose escalations for inadequate response, dose de-escalations for low platelet counts, and dose adjustments to lower maintenance doses are summarized below (Section 5.3, Dose Adjustments).

Schedule C Induction/maintenance regimen: Six patients will be treated at the 25 mg BID dose level for 2 cycles (8 weeks). Patients will then be switched to the lower dose of 10 mg BID and will be maintained at this dose. Dose escalations for inadequate response or progression, and dose de-escalations for low platelet counts, are summarized below (Section 5.3, Dose Adjustments). For this cohort, inadequate response or disease progression will be based on worsening from the new baseline established at the end of two cycles of treatment at 25 mg BID.

Sequence of enrollment for Part 2: Order of preference for enrollment is Schedule A followed by B and then C. Schedule B and C will be enrolled whenever Schedule A enrollment is closed during the observation period of the first 28 days. Enrollment is complete for Part 2.

5.2.3 Part 3: Groups I, II and III

Part 3 will be comprised of three separate groups of patients to further evaluate safety and efficacy of selected dose levels, to explore dose selection and modification based on platelet count values, to evaluate quality of life and symptoms of MF using EORTC QLQ-C30 (Appendix XI) and modified Myelofibrosis Symptom Assessment Form (MFSAF, Appendix XII), and to evaluate other measures such as activity and exercise capacity assessments, body composition, organ and muscle size and grip strength as summarized in Section 5.4, Response Assessment.

Group I is planned to enroll up to 30 patients to one or more of the following dose levels: a) 10 mg BID, b) 25 mg BID, c) 25 mg QD, and d) 50 mg QD.

Enrollment in Group I will start in parallel with Part 2 if the following conditions are met:

a) The selected dose from Part 1 has been determined to be safe;
b) Enrollment in Part 2 Schedule A 25 mg cohort and 50 mg cohorts is complete;
c) At least 6 patients have been enrolled in Part 2 Schedule B, and have completed at least one 28-day cycle of continuous therapy;
d) At least 6 patients have been enrolled in Part 2 Schedule C;
e) In all instances enrollment is opened only during the interval when Part 2 Alternative Schedule A is temporarily closed for the 28-day observation period. This rule does not apply if enrollment in Part 2 Schedule A is complete or has been stopped.

Doses to be examined have been selected by the investigators in collaboration with the sponsor based on available information from Part 1 and 2, and are 10 mg BID and 50 mg QD.

Group II: is planned to enroll up to 20 additional patients once 6 patients in the Part 2 Alternative Schedule A have been treated at 100 mg po daily for at least one cycle (or 3 patients at 100 mg daily and 3 patients 200 mg daily to a total of 6 patients for at least one cycle) and at least 6 patients enrolled in Part 2 Schedule B have completed a minimum of two 28 day-cycles of therapy. The 20 patients in this group can be enrolled at any of the doses listed above under Group I or at 100 mg po QD if 100 mg QD is determined to be a viable and safe dose for further evaluation.

Group III: Up to 70 patients may be enrolled. Starting dose will be determined based on the baseline platelet count as follows:

- Patients with baseline platelet count > 200 K/μL will begin dosing at 15 mg BID
- Patients with baseline platelet count ≤ 200 K/μL will begin dosing at 10 mg BID

If, prior to initiation of Group III, data are available from at least 12 patients receiving 50 mg QD demonstrating that the risk of Grade 2 or higher thrombocytopenia is not higher than the risk at 10 mg BID and if 12 patients completing one cycle demonstrating that 100 mg QD appears to be at least as effective in reducing spleen size as 25 mg BID and data from at least 6 patients receiving 200 mg QD for at least one cycle results in a frequency of Grade 2 or higher thrombocytopenia no higher than with 25 mg BID, then the study team consisting of the sponsor and the primary investigators at each site will have the option to perform Group III using once daily regimens instead of twice daily regimens. If consensus is reached to switch to once daily dosing the starting dose for

patients with baseline platelet count > 200,000/ μL will be 75 mg QD and the starting dose for patients with baseline platelet counts ≤ 200,000/ μL will be 50 mg QD. Unless each of these conditions is met and the study team reached consensus to switch to QD dosing, the BID regimens listed above will be used.

Dose interruptions for safety, dose decreases for safety and dose increases for inadequate efficacy are defined in terms of platelet count and ANC levels observed during the study (see Section 5.3, Dose Adjustments).

Dose adjustments for patients enrolled prior to the institution of Amendment 5 are provided, and are summarized in Section 5.3, Dose Adjustments.

Optional dose de-escalation (maintenance therapy) for patients on stable therapy may be applied to patients enrolling in Part 3 Group III, as well as to eligible patients participating in Parts 1, 2 and 3, Group I and II (see Section 5.3, Dose Adjustments).

5.2.4 Part 1, 2, 3: Patient Discontinuation

When a decision is made to discontinue INCB018424 therapy, it is recommended that a tapering strategy be considered. The tapering strategy should be considered based on evaluation of the condition of the patient, current dosing regimen and the clinical judgment of the investigator (see Section 5.3.4 Dose Tapering Strategy and Section 10.4, Dose Interruption). If a decision has been made to discontinue the patient without a taper, INCB018424 may be restarted up to 2 weeks later in order to institute a tapering strategy. Tapering of INCB018424 therapy is to be considered for all patients enrolled in the study regardless of time of enrollment, starting dose or duration of their participation (see Section 5.3.4, Dose Tapering Strategy). If considered to be medically necessary, the investigator may use any treatment to manage withdrawal from INCB018424 including, but not limited to, the management of events which may be secondary to discontinuation, interruption or reduction or administration of INCB018424. Short-term courses of corticosteroids, at equivalent doses of greater than 10 mg/day of prednisone have been

used to moderate withdrawal from INCB018424 and may be considered as part of a tapering strategy. Corticosteroids may be started prior to, or concurrent with, INCB018424 tapering in anticipation of the possibility of occurrence of withdrawal symptoms. When a decision has been made to discontinue the patient with utilization of a tapering strategy, regardless of the use of concomitant medications, safety data will continue to be assessed in accordance with the protocol.

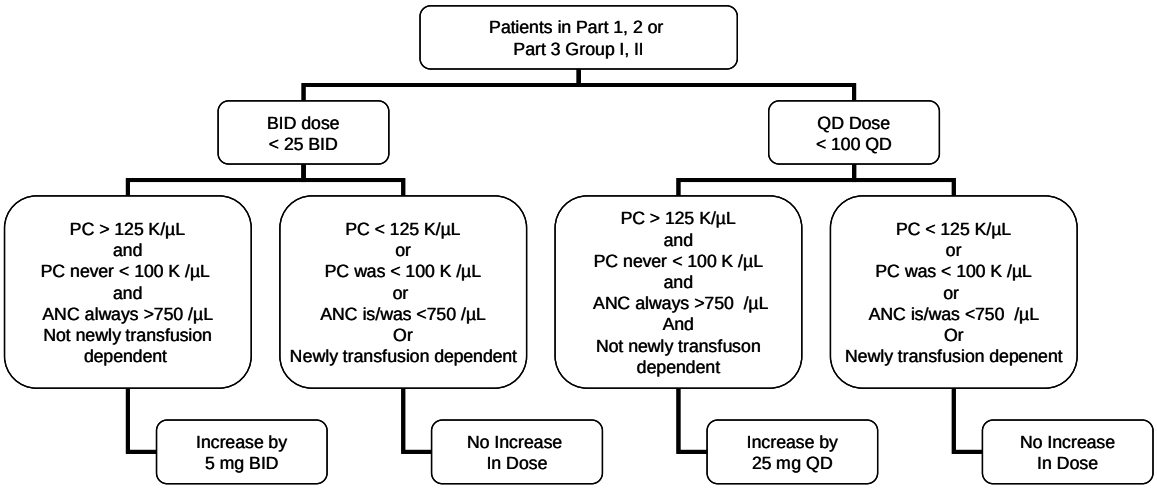
5.3 Dose Adjustments

5.3.1 Dose Increases for Inadequate Efficacy

5.3.1.1 Patients in Part 1, Part 2, Part 3 Groups I and II

Dose increases for inadequate efficacy are optional for all patients enrolled *prior to* Amendment 5. However, if spleen size reductions are < 50% after at least 2 28-day cycles of therapy, and if, in the expert opinion of the Investigator, and the opinion of the patient, less than adequate symptomatic improvement has been observed, a dose increase may be considered. Dose increases may only be undertaken if platelet count and ANC levels are adequate as described in Flow Chart 1 below. For patients currently on BID regimens less than 25 mg BID, dose escalation may proceed in increments of 5 mg BID, allowing at least 1 28-day cycle to elapse before any additional dose increase. In no case may doses escalate to beyond 25 mg BID. For patients currently on a QD regimen less than 100 mg QD dose escalation may proceed in increments of 25 mg QD, allowing at least 1 28-day cycle to elapse before an additional dose increase. In no case may doses escalate to beyond 100 mg QD*. Patients may not switch from BID regimens to QD regimens as part of an efficacy inadequacy-based dose increase.

Flow Chart 1 Strategies for Dose Increases due to Inadequate Efficacy for Patients in Part 1, Part 2 or Part 3 Groups I and II



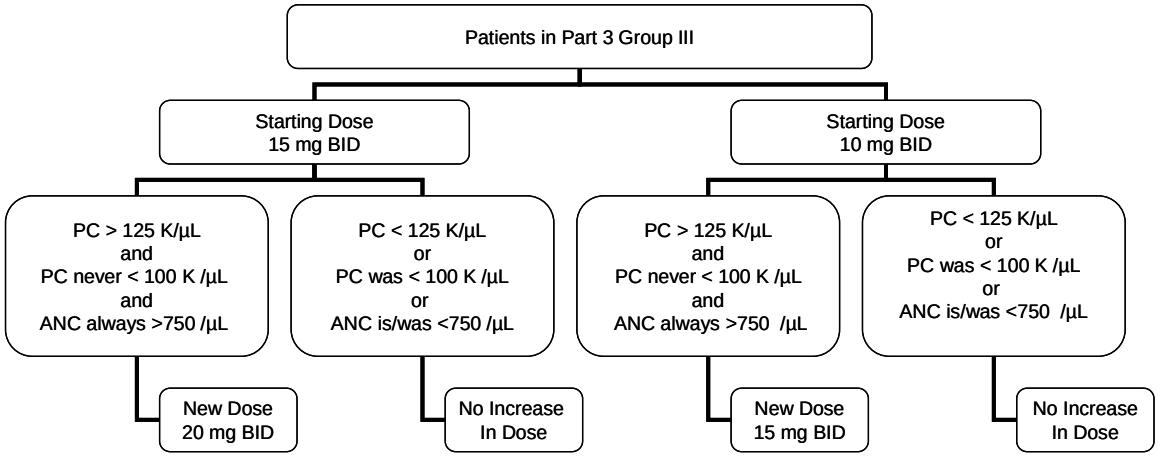
PC=Platelet count

* If at least 6 patients receiving 200 mg QD for at least one cycle in Part 2 Schedule A results in a frequency of Grade 2 or higher thrombocytopenia no higher than with 25 mg BID, patients on a dose of 100 mg QD may undergo a single escalation to 125 mg QD for inadequate efficacy.

5.3.1.2 Patients in Part 3, Group III

As indicated above (Section 3.4.6 Description and Justification of Route, Dose Regimen and Treatment Period), the doses for Part 3, Group III are determined by the baseline platelet count value. After one 28-day cycle of therapy, doses *MUST* be increased by 5 mg BID for patients who demonstrate inadequate efficacy, and who meet all of the conditions illustrated in Flow Chart 2. For the purposes of dose adjustments after one 28-day cycle of therapy, inadequate efficacy will be defined as a palpable spleen length reduced by less than 30% relative to baseline *AND*, in the judgment of the Investigator and the patient, inadequate symptomatic improvement.

Flow Chart 2 Strategies for First Dose Increase due to Efficacy Inadequacy for Part 3 Group III

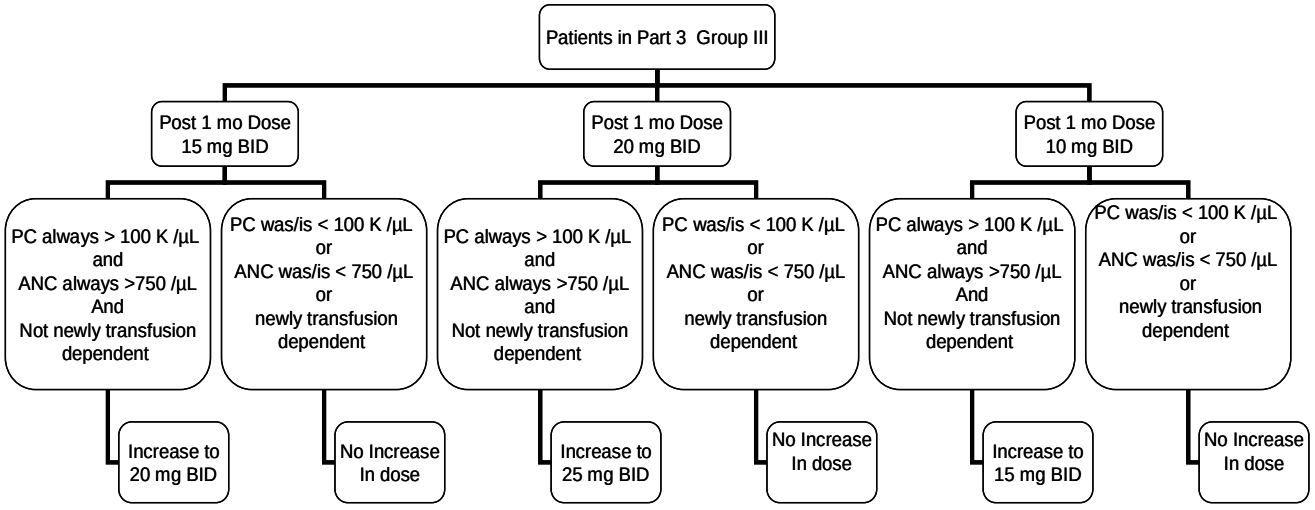


PC = Platelet count

After two 28-day cycles of therapy, doses *MAY* be increased by 5 mg BID, either for the first time, or for the second time for those patients who increased dose after one 28-day cycle of therapy, for continued inadequate efficacy. For the purposes of dose adjustments after two 28-day cycles of therapy, inadequate efficacy will be defined as a palpable spleen length reduced by less than 50% relative to baseline after *OR*, in the judgment of the Investigator and the patient, inadequate symptomatic improvement. In addition to meeting ANC and platelet count criteria for this dose increase, the patient may not have become newly transfusion dependent. For these purposes, newly transfusion dependent will be taken to mean that since beginning to receive therapy, one or more transfusions (unrelated to bleeding or hemorrhage due to trauma) have been required by the patient.

Note that as a result of these 2 possible dose increases, the maximum dose that patients in Part 3 Group III may attain is 25 mg BID (for those patients starting the study with platelet count > 200 K/µL) or 20 mg BID (for those patients starting the study with platelet count ≤ 200 K/µL. Criteria for this second, and final dose increase are summarized in Flow Chart 3.

Flow Chart 3 Strategies for Second Dose Increases due to Inadequate Efficacy for Part 3 Group III



PC = platelet count

If Group III is instead performed using the QD doses defined in Section 5.2.3, dose changes for inadequate efficacy will be made in increments of 25 mg QD instead of 5 mg BID. The maximum possible dose for a patient beginning at a dose of 75 mg QD would therefore be 125 mg QD, and the maximum possible dose for a patient beginning at a dose of 50 mg QD would be 100 mg QD.

5.3.2 Dose Reductions for Safety

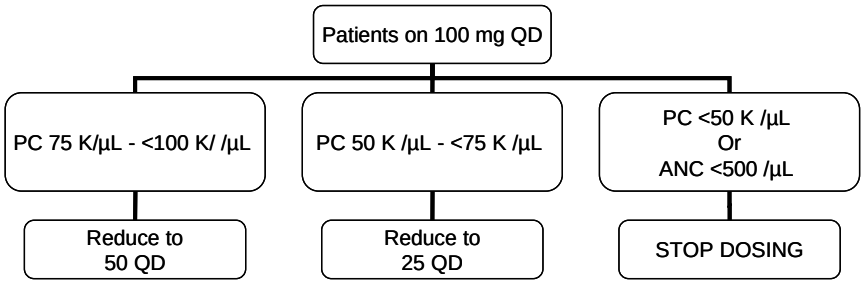
For all patients participating in the study, dose reductions are required for platelet count reductions to specified levels. Dosing must be discontinued if platelet counts decline below 50 K/µL (Grade 3 laboratory abnormality by CTCAE v. 3.0), or if ANC falls below 500/µL, unless approved otherwise by the Sponsor. As for other instances where dosing of INCB018424 is stopped or interrupted, a recommendation is made that a tapering strategy be considered. Therapy will be restarted after dose interruptions for safety following recovery in platelet levels. Flow Charts 4 to 9 and 10 to 13 below

illustrate the criteria for and required dose reductions in patients in Part 1,2 3 Groups I and II and Part 3 Group III, respectively, who exhibit declines in platelet count during the study, and subsequent strategies for restarting dosing. Note that not all parts of the dosing strategy for restarting doses may be applicable depending on the dose at the time of the safety issue.

5.3.2.1 Patients in Part 1, Part 2, Part 3 Groups I and II

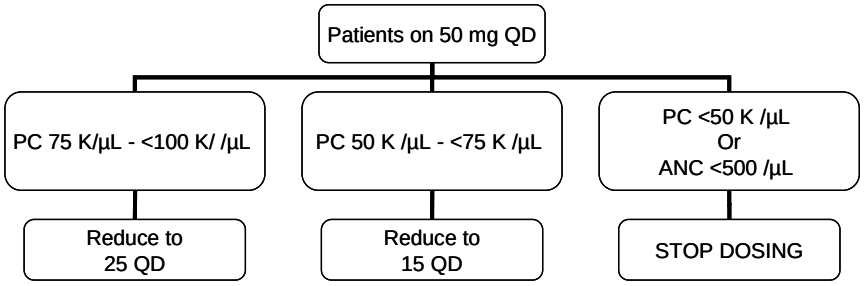
Patients receiving QD regimens in Part 1, Part 2 or Part 3, Groups I and II will undergo dose reductions in the increments illustrated in Flow Charts 4-6.

Flow Chart 4 Dose Reductions for Safety for 100 mg QD Regimen



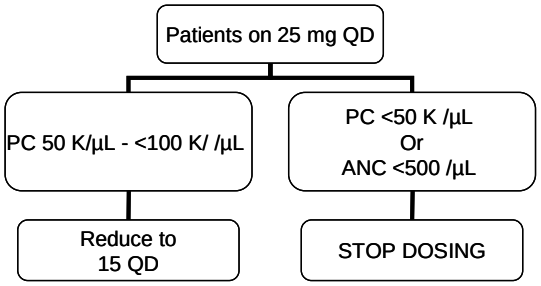
PC = platelet count

Flow Chart 5 Dose Reductions for Safety for 50 mg QD Regimen



PC = platelet count

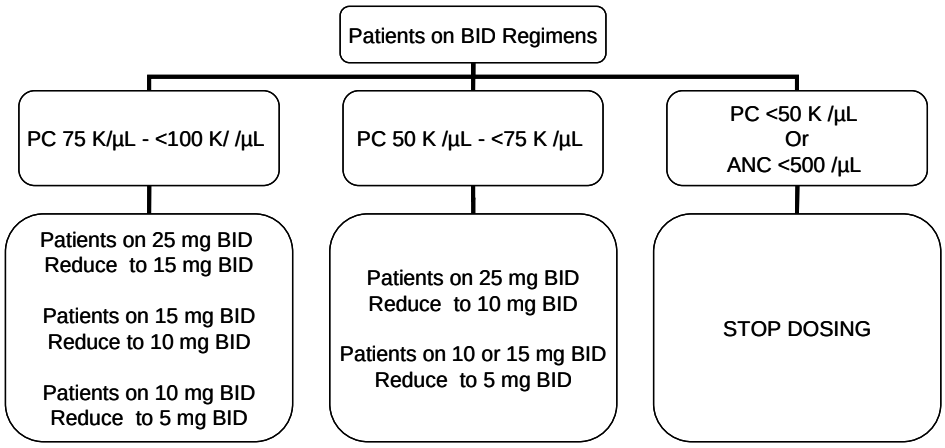
Flow Chart 6 Dose Reductions for Safety for 25 mg QD Regimen



PC = platelet count

For patients receiving BID regimens, doses must be reduced when platelet count is 75 K/µL to <100 K/µL to a dose of 15 mg BID, if the original dose was 25 mg BID or 5 mg BID if the original dose was 10 mg BID. The exception is for patients with starting platelet counts 100 K/µL to 125 K/µL who are at 10 mg BID, who will remain at this dose until platelet count falls to below 75 K/µL. If the platelet count is reduced to 50 K/µL to <75 K/µL, the dose must be further reduced. Dosing will be held if platelet count falls below 50 K/µL, or if ANC drops below 500/µL, except with permission from Sponsor. This dose reduction strategy is illustrated in Flow Chart 7.

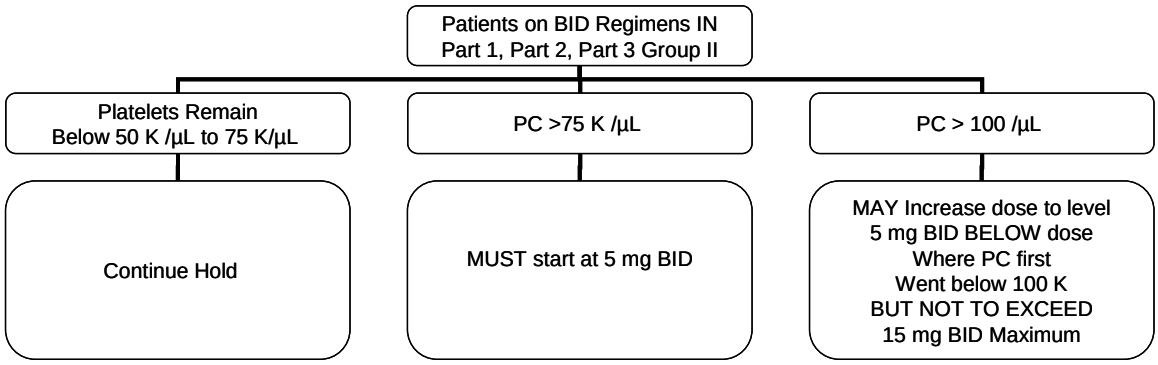
Flow Chart 7 Dose Reductions for Safety for BID Regimens in Part 1, Part 2 and Part 3 Group II



PC = platelet count
The exception is for patients with starting platelet counts 100 K/µL to 125 K/µL who are at 10 mg BID, who will remain at this dose until platelet count falls to below 75 K/µL

Doses may be restarted or increased with platelet count recovery to above 75 K/µL as diagrammed in Flow Charts 8 and 9 below, provided ANC levels have also increased above 500/µL. Note that the maximum dose allowed for BID regimens with restarting after thrombocytopenia is 15 mg BID.

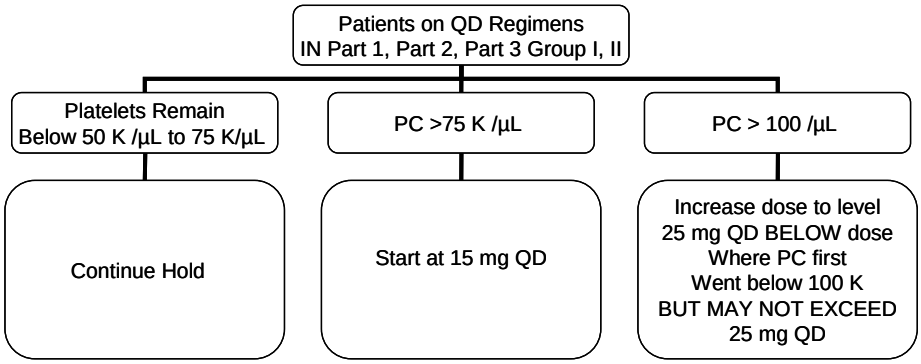
Flow Chart 8 Restarting Doses after Safety Interruptions or De-Escalations for Patients in Part 1, Part 2, Part 3 Group II Using BID Regimens



PC = platelet count

For patients In Part 1, Part 2 or Part 3 Groups I, II, on QD regimens, restarting after thrombocytopenia will be allowed; the maximum dose allowed will be 25 mg QD (Flow Chart 9).

Flow Chart 9 Restarting Doses after Safety Interruptions or De-Escalations for Patients in Part 1, Part 2, Part 3 Group I or II



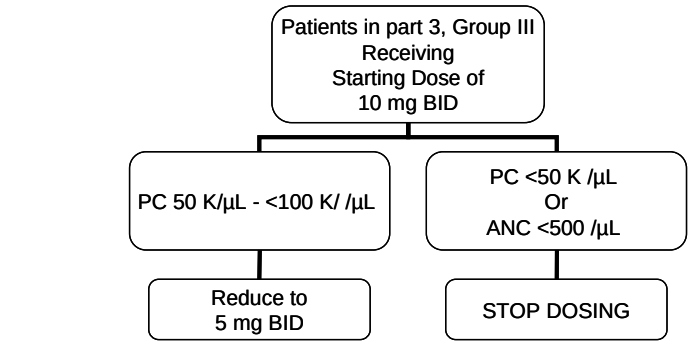
PC = platelet count

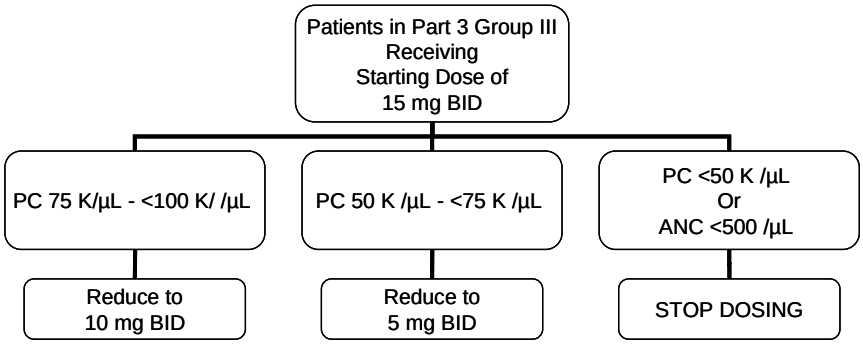
ANC levels < 500/µL dictate immediate dose interruption. ANC level recovery to above 750 /µL but less than 1000/µL will allow dosing to be restarted at 5 mg BID or 15 mg QD. ANC level increases to above 1000/µL will allow a further dose increase to the dose level lower than the level that precipitated the initial ANC < 500/µL observation, but this final dose may not exceed 15 mg BID or 25 mg QD.

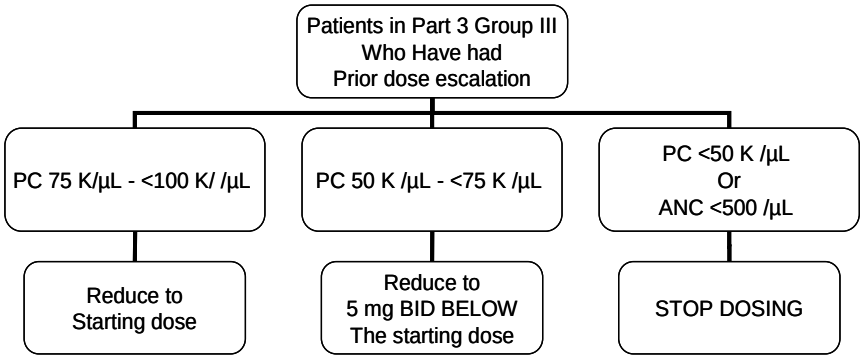
5.3.2.2 Patients in Part 3 Group III

As noted above (Section 5.3.1.2), patients may increase dose up to two times (at a 28-day cycle interval) for inadequate efficacy. All patients in Group III must have doses decreased or held for low platelet counts according to Flow Charts 10, 11 and 12.

Flow Charts 10-12 Dose Reductions for Safety in Part 3 Group III





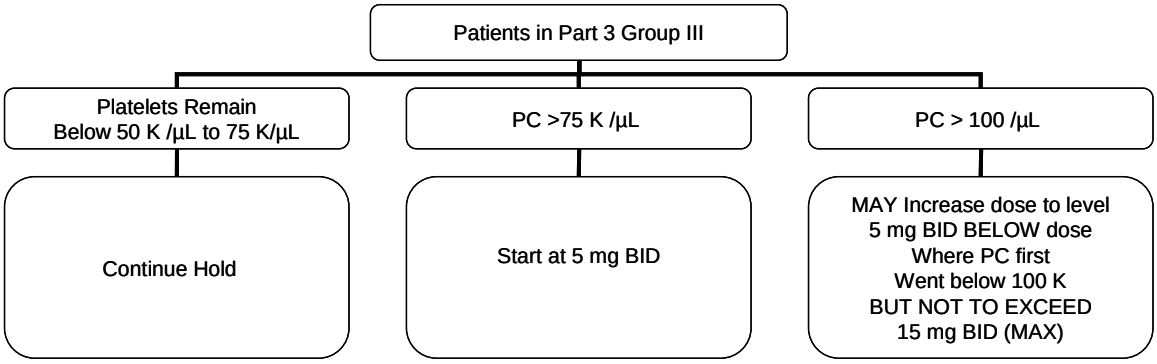


PC = platelet count
Exception: Patients at 10 mg BID with baseline PC <125 K/µL will remain on 10 mg BID until PC drops below 75 K/µL.

Dosing may be restarted or increased following recovery of platelet counts to acceptable levels as defined in the flow charts below, provided ANC levels have recovered to values

> 500/µL. After restarting, BID dose regimens may not exceed 15 mg BID maximum. Doses must be held with platelet count < 50 K/µL unless otherwise approved by the Sponsor.

Flow Chart 13 Restarting Doses after Safety Interruptions or De-Escalations for Patients in Part 3 Group III



PC = platelet count

If Group III is performed with a QD regimen, doses would be reduced in increments of 25 mg QD, and reinitiation of therapy after platelet count level recovery would occur with increments of 25 mg QD, but may not exceed 50 mg QD.

ANC levels < 500/µL dictate immediate dose interruption. ANC level recovery to above 750 /µL but less than 1000/µL will allow dosing to be restarted at 5 mg BID. ANC level increases to above 1000/µL will allow a further dose increase to a dose 5 mg BID lower than the level that precipitated the initial ANC < 500/µL observation, but this final dose may not exceed 15 mg BID.

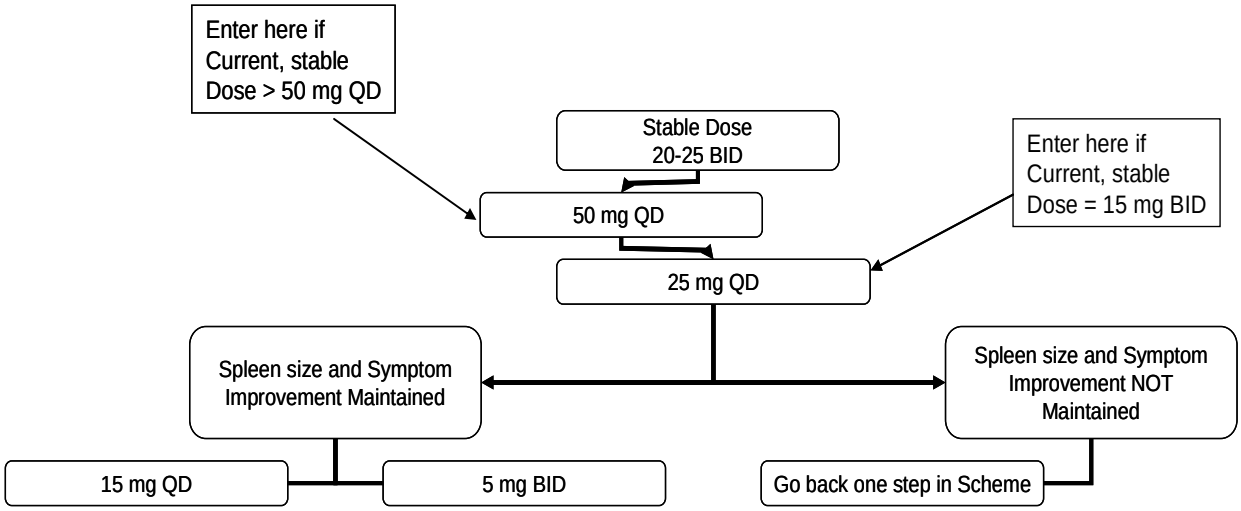
5.3.3 Dose Adjustments for Maintenance Therapy

5.3.3.1 Patients in Part 1, Part 2, Part 3 Groups I, II

Patients on a stable dose of at least 15 mg BID or of at least 50 mg QD enrolled prior to the implementation of Amendment 5 have the option of reducing their dose level to a maintenance dose to attempt to increase red blood cell production and eliminate

transfusion dependence. Flow Chart 14 illustrates the recommended dose strategy, recommended, where entrance into the chart varies with the starting stable dose. As indicated in the chart, 20 to 25 mg BID doses are successively reduced from BID to 50 mg QD to 25 mg QD; patients already on 50 mg QD or 15 mg BID enter the reduction scheme as indicated by arrows. Patients receiving BID dose regimens higher than 15 mg BID and QD regimens higher than 50 mg QD therefore eventually reach the same 25 mg QD dose in the scheme; splenomegaly and symptom improvement relative to the study visit prior to the dose changes will then be used to determine if doses lower than 25 mg QD should be used.

Flow Chart 14 Dose Adjustments for Maintenance Dosing Part 1, Part 2 and Part 3 Groups I, II

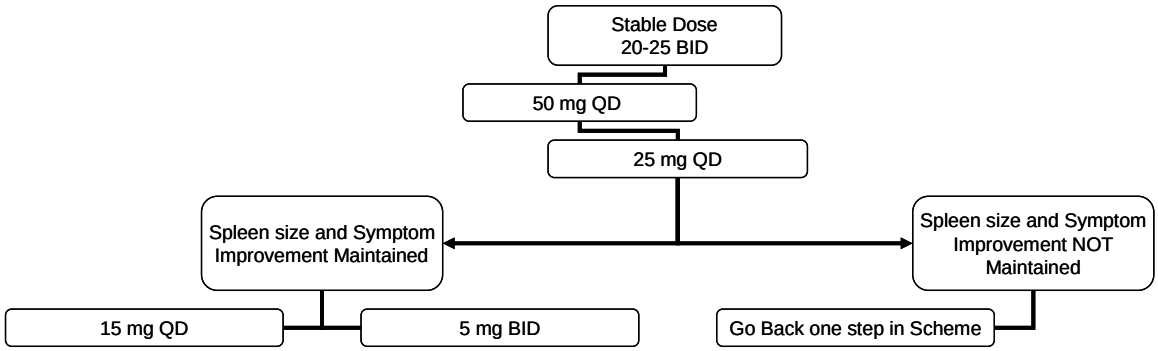


5.3.3.2 Patients in Part 3, Group III

For patients on a stable dose of 15 mg BID or higher for a minimum of 3 28-day cycles who either remain or have become transfusion dependent, or who maintain a hemoglobin level of less than 10 g/dL without transfusion, an attempt to reduce the dose with the aim of improving red blood cell production is allowed. A secondary goal is to allow transition to a once daily (QD) regimen. Flow Chart 15 illustrates the recommended dose strategy to dose reduce to a maintenance dose regimen. In the strategy, dose reduction

occurs in successive steps to 25 mg QD. Splenomegaly and symptom improvement then dictate if further dose reductions should be attempted.

Flow Chart 15 Maintenance Dose Strategy for Part 3 Group III



If the QD dosing regimen is used in Group III, a maintenance strategy would require that patients dose reduce in increments of 25 mg QD to the 25 mg QD dose level; Flow Chart 15 then provides additional dose reduction strategy. It is recommended that if patients experience a bothersome increase in symptoms, or a growth in palpable spleen length, then the patient should be put back on the previously established stable dose as soon as reasonably possible. Additionally, if a patient becomes transfusion independent, the highest dose that maintains transfusion independence, acceptable symptom management and absence of spleen re-growth should be considered the maintenance dose. Once daily maintenance doses are preferred if they are an effective option for the patient.

5.3.4 Dose Tapering Strategy

When a decision is made to discontinue the patient or interrupt INCB018424 therapy, it is recommended that a tapering strategy be considered, except in instances where there are protocol defined dose reduction algorithms (see Section 5.3.2). Utilization of a tapering strategy is based on condition of the patient, the current dosing regimen and the investigator's clinical judgment as discussed in Section 5.2.4, Patient Discontinuation and

Section 5.3, Dose Adjustments, detailing gradual dose reductions and re-starts. The strategy may vary case-by-case and/ or within an individual case to include one or more aspects of dosing schedule eg, daily dose regimen, dosing interval, frequency of dose or overall duration of administration of the therapy as well as concomitant treatments to manage any untoward symptoms. The course of management of the patient is at discretion of the investigator as determined in the best interest of the patient. For patients who do not require dose interruption but have thrombocytopenia or neutropenia and no other serious safety concerns, the protocol defined dose reduction algorithms (see Section 5.3.2) should continue to be followed.

5.4 Response Assessments

5.4.1 Overall Response Assessment

Overall response assessment will be graded according to the International Working Group (IWG) consensus criteria for treatment response in PMF and Post-PV/ET MF (Tefferi et al, 2006). Recently published response criteria developed by the International Working Group on Myelofibrosis will be utilized in this study (Tefferi et al, 2006) and are defined as follows:

1. **Complete remission (CR):** Requires all of the following in the absence of both transfusion and growth factor support;

   i) Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly.

   ii) Peripheral blood count remission defined as hemoglobin > 11 g/dL, platelet count $\geq 100 \times 10^9$/L, and absolute neutrophil count $\geq 1.0 \times 10^9$/L.

   iii) Normal leukocyte differential including disappearance of nucleated red blood cells and immature myeloid cells in the peripheral smear, in the absence of splenectomy.*****

iv) Bone marrow histological remission defined as the presence of age-adjusted normocellularity, < 5% myeloblasts, and an osteomyelofibrosis grade of ≤ 1.**

2. **Partial remission (PR):** Requires all of the above criteria for CR except the requirement for bone marrow histological remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.

3. **Clinical improvement (CI):** Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment *(CI response is validated only if it lasts for ≥ 8 weeks).*

i) A ≥ 2 g/dL increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of < 10 g/dL).

ii) Either a ≥ 50% reduction in palpable splenomegaly of a spleen that is ≥ 10 cm at baseline or a spleen that is palpable at > 5 cm at baseline becomes not palpable.

iii) A ≥ 100% increase in platelet count and an absolute platelet count of ≥ 50,000 x 10^9/L. (applicable only for patients with baseline platelet count of < 50 x 10^9/L).

iv) A ≥ 100% increase in ANC and an ANC of ≥ 0.5 x 10^9/L (applicable only for patients with baseline absolute neutrophil count of < 1 x 10^9/L).

4. **Progressive disease:** Requires one of the following;

i) Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at > 5 cm below the left costal margin or a ≥ 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a ≥ 50% increase in palpable distance for baseline splenomegaly of > 10 cm.

ii) Leukemic transformation confirmed by a bone marrow blast count of ≥ 20%.

iii) An increase in peripheral blood blast percentage to ≥ 20% that lasts for ≥ 8 weeks.

5. **Stable disease:** None of the above.

6. **Relapse:** Loss CR, PR, and CI. In other words, a patient with CR or PR is considered to have undergone relapse when he or she no longer fulfils the criteria for even CI.

Footnotes

**Because of subjectivity in peripheral blood smear interpretation, CR does not require absence of morphological abnormalities of red cells, platelets, and neutrophils.*

*** In patients with CR, a complete cytogenetic response is defined as failure to detect a cytogenetic abnormality in cases with a pre-existing abnormality. A partial cytogenetic response is defined as 50% or greater reduction in abnormal metaphases. In both cases, at least 20 bone marrow- or peripheral blood-derived metaphases should be analyzed. A major molecular response is defined as the absence of a specific disease-associated mutation in peripheral blood granulocytes of previously positive cases. In the absence of a cytogenetic/molecular marker, monitoring for treatment-induced inhibition of endogenous myeloid colony formation is encouraged. Finally, baseline and post-treatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process.*

[§]Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the last month for a hemoglobin of < 8.5 g/dL that was not associated with clinically overt bleeding. Similarly, during protocol therapy, transfusions for a hemoglobin of ≥ 8.5 g/dL is discouraged unless it is clinically indicated.

[§§]In splenectomized patients, palpable hepatomegaly is substituted with the same measurements.

¶*It is acknowledged that worsening cytopenia might represent progressive disease but its inclusion as a formal criterion was avoided because of the difficulty distinguishing disease-associated from drug-induced myelosuppression. However, a decrease in hemoglobin of ≥ 2 g/dL, a 100% increase in transfusion requirement, and new development of transfusion dependency, each lasting for more than 3 months after the discontinuation of protocol therapy can be considered disease progression.*

Determination of the overall response assessment are required during the Screening phase and on Day 1 of Cycles 2, 3, and 4 and then every 3 28-day cycles thereafter. Individual efficacy measures will be determined at various intervals, but in general will be assessed prior to dosing, and after 1, 3 and 6 28-day cycles of therapy.

5.4.2 Additional Response Assessments

Preliminary efficacy will be assessed using the following methods:

1. **JAK2V617F allele burden** in the estimated 50% of patients enrolling in the study with evidence of a JAK2 mutation will be monitored. Analysis will be conducted at pre-dose (Screening or C1D1), and after each 28-day cycle of treatment in patients with the mutant allele present pre-dose. Bone marrow aspirates will be used for the analysis where available; peripheral blood samples collected for PK/PD may be used when available, if bone marrow aspirate samples cannot be obtained. See Section 8.8, Bone marrow Aspiration, Biopsy and Cytogenetics for general assay description, and Appendix X for sample collection, processing, storage and shipment for this assessment.
2. **Cytogenetic profile** in patients enrolling with a cytogenetic abnormality will be performed pre-dose (Screening ± 7 days), and after 3, 6 and subsequent 6 28-day cycle intervals of therapy. See Section 8.8, Bone marrow Aspiration, Biopsy and Cytogenetics for general assay description.
3. **Bone marrow fibrosis** is a component of the Consensus Criteria, but will also be analyzed separately. Bone marrow aspiration and biopsy will be conducted pre-

dose (Screening ± 7 days), and after 3, 6 and subsequent 6 28-day cycle intervals of therapy. See Section 8.8, Bone marrow Aspiration, Biopsy and Cytogenetics for general assay description, and Appendix VIII for consensus grading for this assessment. If unable to obtain BM aspirate, cytogenetics may also be done on peripheral blood collected for PD/PK analysis.

4. **Quality of life and symptoms of MF** will be assessed in all patients in Part 3 of the study at pre-dose (C1D1), after 2 weeks, and after each 28-day cycle of therapy for the first 4 cycles, and then at Study Visits indicated in the Description of Study Visits (Section 7.3), for patients participating in Part 3 using EORTC QLQ-C30 (See Section 8.14, Quality of Life Assessments and Appendix XI) and modified Myelofibrosis Symptom Assessment Form (MFSAF, see Section 8.14, Quality of Life Assessments and Appendix XII).

5. **Sub-maximal exercise capacity will be measured using a six minute walk test (6MWT).** 6MWT assessments will be done using a modification of the American Thoracic Society ATS Statement: Guidelines for the Six-Minute Walk Test, 2002, for all patients enrolled under Amendment 5 at pre-dose (Screening and/or C1D1), and after 1, 3 and 6 28-day cycles of therapy. The 6MWT will be performed twice prior to receiving the first dose of study medication because of the potential for 'training effects' in walk performance. The duplicate tests may be conducted at the Screening visit, at C1D1 or one test may be conducted at each visit. A 6MWT will also be conducted for patients who withdraw early from the study. Note that patients must be evaluated for additional eligibility criteria prior to administering the 6MWT each time (see Section 6.3 Exclusion Criteria for 6MWT). Not meeting any of the eligibility criteria will preclude the patient from taking the 6MWT. Patients who are excluded from the 6MWT at Screening because of the criteria listed in Section 6.3, will not be enrolled in the study except with approval of the Sponsor. Detailed directions for conducting the 6MWT will be provided in a Reference Manual. 6MWT will not be conducted beyond the C7D1 visit. 6MWT will not be conducted for subjects enrolling under Amendment 7.

6. Daily voluntary physical activity and exercise capacity will be assessed for patients participating under Amendment 5 at selected site(s) using the **StepWatch™ Activity Monitor (SAM)** (Orthocare Innovations, Mouthlake Terrace, WA). Patients may be exempted from evaluation of physical activity and exercise capacity as assessed by the SAM with permission of the sponsor. The scope may be expanded to include more patients being enrolled in these Groups and/or sites based on initial data. The SAM accelerometer is a small, durable, impact resistant, waterproof, self-contained device that is impervious to tampering and does not provide any feedback to the patient or encourage performance behavior. The device is worn on the ankle and records the number of steps taken each minute. The device will be worn daily by patients for 9 days during the screening interval and then for the first 9 days following 1 28-day cycle, 3 28-day cycles and 6 28-day cycles of drug therapy. Site staff will download data using a docking station. Detailed directions for use of this accelerometer will be provided in a Reference Manual. SAM activity monitor will not be used beyond the C7D1 visit. SAM activity monitor will not be used for subjects enrolling under Amendment 7.
7. **Body composition** will be assessed on all patients enrolled under Amendment 5. Evaluation of body composition will occur at pre-dose (C1D1) and after 1, 3 and 6 28-day cycles of therapy, by recording an accurate body weight (+/- 0.1 kg) and evaluating total body water (TBW) and extracellular water (ECW) by tracer dilution methods. Body composition will not be assessed beyond the C7D1 visit. Body composition will not be assessed for subjects enrolling under Amendment 7. TBW will be measured by administration of deuterated water (deuterium oxide, $^{2}H_2O$). Deuterium is a safe, stable (non-radioactive) isotope of hydrogen that distributes into the total body water pool. The extent of dilution of the deuterium, determined by analyzing a plasma sample, provides a measure of the TBW (Moore et al 1963). ECW is measured by administration of sodium bromide. Bromide distributes to the extracellular spaces in the same manner as chloride. The extent of bromide dilution provides a measure of the size of the total body

extracellular space. (Kim et al, 1999) From these two measured values, the total volume of intracellular water (ICW) can be calculated (TBW-ECW=ICW), and this value provides an estimate of the body cell mass, which is the sum of metabolically active tissues, the largest component of which is lean body mass. (Pierson et al, 1996) Thus this method evaluates body fluid distribution, and can provide an estimate of lean body mass independent of assumptions of the hydration level of lean tissues. The method is described in Appendix XIII, and is briefly as follows:

- The patient should arrive at the clinic in the morning having fasted since midnight. Body weight will be measured with the patient wearing minimal clothing (hospital gown) and no shoes.
- A 4-mL blood sample will be drawn.
- The patient will consume a small volume of a salty solution (cocktail).
- The patient should then refrain from consumption of any food or beverages (including water) for a 3-hour period. The patient can undergo normal activity and other non-invasive tests during this time.
- At precisely 3 hours after consumption of the cocktail, a second 4-mL blood sample will be drawn. Following this blood sample, the patient can resume eating and drinking *ad libitum*.

8. **Grip strength** will be measured on the dominant arm using a calibrated Jamar Hand Dynamometer for all patients enrolled under Amendment 5. Grip strength will be performed three times at each visit corresponding to Screening, C1D1, and after 1, 3 and 6 28-day cycles of therapy, and the average of the triplicate measurements will be used for data analysis. Grip strength will not be performed beyond the C7D1 visit. Grip strength will not be performed for subjects enrolling under Amendment 7. A grip strength assessment will also be performed for patients who terminate the study early. A calibrated Jamar Hand Dynamometer will be used to measure grip strength in the dominant arm in the standardized recommended position. The reliability and validity of this method has been documented (Peolsson, Hedlund, and Oberg, 2001; Westaway, Stratfor, and Binkley, 1998). On study assessments will be compared to baseline.

A standard position for testing has been recommended by the American Society of Hand Therapists (Richards and Palmiter-Thomas, 1996). Details for positioning of the patient and test conduct will be provided in the Reference Manual. At all visits:

- Patient assumes position above
- Patient grips the dynamometer (see user reference manual)
- Single maximum grip strength at Jamar position "2" (3.8 cm)
- Record time and measurement
- Rest for 15 seconds
- Repeat steps 1 to 5 at each test point 3 times
- Record the time when the test of triplicate dynamometer measurements begin in the source document

Detailed directions for conduct of the grip strength assessment will be provided in a Reference Manual.

9. **Spleen and liver volume**s will be assessed by non-contrast MRI, and correlated to changes noted by palpation in approximately 20 patients who enroll in the study under Amendment 5 or 6 and for whom MRI is not contraindicated. Depending upon emerging data, this subset of patients could be expanded, but will not exceed 50 patients total. MRI measurements will be conducted in these patients at pre-dose (C1D1) and after 1, 3 and 6 28-day cycles of therapy. For subjects with Baseline MRIs, additional MRIs will be performed approximately every 6 months after the C7D1 visit, beginning with the C13D1 visit ± 8 weeks. A new ICF for these additional MRI procedures must be signed prior to have an additional MRI performed. Subjects who do not sign consent for additional MRI will not be precluded from continued participation in the study. Procedure specific training for scanning and image capture will be provided by the Vendor.

10. **Photography** of muscles and/or body areas may be obtained at Screening and after 3 28-day cycles of therapy. Photographs of selected muscles or body areas will be taken only for subjects who provide consent for this voluntary assessment.

All features that might allow identification of the patients will be masked. A user manual will provide instructions and a suitable camera will be provided to the sites.

11. **Cross-sectional area of the left quadriceps** will be measured using MRI in the same sub-set of patients used for spleen and liver volume assessment prior to dosing (C1D1), and after 1, 3 and 6 28-day cycles of therapy. This second scan will use the same coil as used for liver and spleen measurements. Positioning guidelines and anatomical landmarks will be used to reproducibly scan the same area. Cross-sectional area of the right quadriceps may be scanned concurrently with left quadriceps and assessed, if needed. Procedure specific training for scanning and image capture will be provided by the Vendor. Cross sectional area of the quadriceps will not be measured past the C7D1 visit. Cross sectional area of the quadriceps will not be measured on subjects enrolling under Amendment 7.

5.5 Identification of Dose-Limiting Toxicity (DLT)

A dose-limiting toxicity (DLT) is defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to underlying disease, intercurrent illness, or concomitant medications and occurring during the first 28-day treatment cycle that meets the NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE) Grade 3 or 4. Specific clinical situations which modify this DLT definition include:

1. DLT is ≥ Grade 3 diarrhea or vomiting only if it occurs despite treatment with optimal antidiarrheals or antiemetics.
2. If pre-therapy bilirubin or ALT are already abnormally elevated at Grade 2 level, then further elevation will be considered a DLT only if the increase is > 3 times the baseline and the increase is confirmed by repeat testing one week later.
3. Fatigue will be considered a DLT only if ≥ Grade 3.
4. If the patient has a history of hyperuricemia Grade 3 (ULN to 10mg/dL with physiologic consequences), repeated occurrence while on the study medication will not be considered a DLT.

5. Neutropenia will be considered a DLT only a) if ≥ Grade 4 when the ANC is < 500/mm^3 for 7 or more consecutive days or b) if ≥ Grade 4 neutropenia of any duration when associated with fever (> 38.5°C) and/or infection.
6. Thrombocytopenia will be considered a DLT only a) if ≥ Grade 3, platelets are < 50,000 – 25,000/mm^3 for ≥ 7 consecutive days, or b) if ≥ Grade 4, platelets are < 25,000/mm^3 for any duration.
7. Grade 4 toxicity (DLT), as defined by CTCAEv3 criteria, does not automatically imply occurrence of an SAE unless classified as such by the Investigator.

5.6 Measures Taken to Avoid Bias

Patient reported outcomes and quality of life measures will be reported via questionnaires by the patients without guidance or influence by the investigative staff. The study technician administering the 6MWT will not have knowledge of the patients improvement status or spleen size in the study.

6.0 PATIENT ELIGIBILITY

6.1 Inclusion Criteria

1. Must be at least 18 years of age with life expectancy of at least 12 weeks.
2. Must be diagnosed with PMF or Post-PV/ET MF, irrespective of JAK2 mutation status.
3. Patients with myelofibrosis requiring therapy, including those previously treated by myelofibrosis directed therapy who have subsequently relapsed or are refractory; or, if newly diagnosed, should be intermediate or high risk according to Lille (Dupriez) Scoring System (Dupriez et al, 1996), (adverse prognostic risk factors are: Hgb < 10 g/dL, WBC < 4 or > 30 x 10^9/L; risk group: 0 factor=low, 1 factor = intermediate, 2 factors = high); or with symptomatic splenomegaly that is > 10 cm below costal margin.

4. Must have palpable spleen measuring 10 cm or greater below the costal margin (Patients in Part 3, Group III only). However, with permission of the sponsor, patients with spleen size of ≤ 10 cm, or in rare cases, with prior splenectomy, but ongoing hepatomegaly may be enrolled in Part 3, Group III.

5. Have Adequate bone marrow reserve as demonstrated by:

    a. absolute neutrophil count (ANC) that is > 1500/μL

    b. platelet count that is > 100,000/μL without the assistance of growth factors.

6. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 in Part 1, Part 2, Part 3 Group I and II and status of 1 or 2 in Part 3 Group III.

7. Have adequate liver and renal function.

    a. Total bilirubin ≤ 2.0 mg/dL.
    b. Alanine aminotransferase (ALT) ≤ 2.5x institutional upper limit of normal (ULN) or ≤ 5x institutional upper limit of normal if the liver is involved by malignancy as judged by the treating physician and the Investigator with documented justification.
    c. Creatinine ≤ 2.5 mg/dL.

8. A female of childbearing potential must have a negative serum pregnancy test at Screening.

9. Females will be either postmenopausal for at least 1 year with documented FSH > 30 IU/L or surgically sterile for at least 3 28-day cycles OR females of childbearing potential who must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from Screening through Follow-Up. (Note: Permitted methods are at least 99% effective in preventing pregnancy (Appendix IX) should be communicated to the patients and their understanding confirmed.) For all females, the pregnancy test result must be negative at Screening.

Males must agree to take appropriate precautions to avoid fathering a child (with at least 99% certainty) from Screening through Follow-Up. (Note: Permitted methods are at least 99% effective in preventing pregnancy (Appendix IX) should be communicated to the patients and their understanding confirmed.)

10. Is able to comprehend and is willing to sign an informed consent form (ICF).

6.2 Exclusion Criteria

Any of the following are cause for exclusion from the study:

1. Females who are pregnant or are currently breastfeeding.
2. Patients who received any anticancer medications or investigational therapy in the 14 days (28 days for Busulfan and pegylated interferon) prior to receiving their first dose of study medication.
3. Patients receiving therapy with intermediate or high dose steroids greater than the equivalent of 10 mg prednisone per day are not allowed.
4. Patients diagnosed with another malignancy unless disease free. Patients with early stage squamous cell carcinoma of the skin, basal cell carcinoma of the skin or cervical intraepithelial neoplasia may be eligible for participation at the Investigator's discretion.
5. Patients with known active hepatitis A, B, C or who are HIV-positive. Evidence for active hepatitis includes elevation of ALT and AST, and other clinical evidence of active hepatitis infection.
6. Patients with any unresolved toxicity greater or equal to Grade 2 from previous anticancer therapy, except for stable chronic toxicities not expected to resolve, such as peripheral neurotoxicity.
7. Patients with New York Heart Association Criteria Class IV impairments (Patients in Part 3, Group III only). Patients with Class III impairments may only be enrolled if in the judgment of the investigator, the potential benefits outweigh

the potential risks (See Appendix XIV). This exclusion does not apply to subjects enrolling in the study under Amendment 7.

8. Patients with incomplete recovery from any prior surgical procedures or who have had surgery within 4 weeks prior to study entry, excluding the placement of vascular access.
9. Presence of acute active infection requiring antibiotics.
10. Patients with uncontrolled intercurrent illness or any concurrent condition that, in the Investigator's opinion, would jeopardize the safety of the patient or compliance with the protocol.
11. Any current or planned therapy with CYP3A4 and CYP1A2 inhibitors or inducers (including smoking) unless approved by the Sponsor.
12. Prior treatment with another oral JAK inhibitor is not permitted unless agreed to by both the Investigator and the Sponsor. Any prior oral JAK inhibitor therapy must have been completed at least 14 days or 6 half-lives, whichever is longer, prior to the first dose of study medication

6.3 Exclusion Criteria for Participation in the 6MWT

The following will preclude participation by the patient in the 6MWT, and if occurring at the Screening Visit from participation in the study except with Sponsor's approval.

1. History of or current unstable angina.
2. History recent (within 2 years) myocardial infarction.
3. Patients unable to walk.
4. Patients with unstable gait that persists with the use of assistive device (cane or walker)
5. Resting heart rate > 120 beats per minute.
6. Resting systolic blood pressure > 180 mm Hg.
7. Resting diastolic blood pressure > 100 mm Hg.

7.0 SCHEDULE OF OBSERVATIONS

7.1 Part 1: Dose Escalation and Expanded Cohort BID Continuous Dosing

Table 3 Schedule of Observations Flowchart: Part 1

	Screening Phase	Treatment Phase										End-of-Treatment Visit	
		Cycle 1				Cycle 2+3				Subsequent Visits - For details see Footnotes			
Evaluation	**Day -14 to Day -1**	**Day 1**	***Day 8**	**Day 15**	***Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**End of Study**	**Follow-Up**
Informed consent / Eligibility criteria	X	X											
Medical & medication history	X	X											
Physical examination[a,j]	X	X	X[t]	X	X[t]	X				X		X	X
Vital signs[a,j]	X	X	X[t]	X	X[t]	X				X		X	X
Overall response assessment (IWG-MRT)[b]						X				X		X	
ECOG performance status	X					X				X		X	X
Concomitant medication review		X	X	X	X	X				X		X	X
12-lead ECG[c,j]	X	X	X[t]	X	X[t]	X				X		X	
Clinical laboratory tests[d]	X	X	X	X	X	X		X		X		X	X
CBC[e]	X	X	X	X	X	X	X	X	X	X[i]	X[i,]	X	X
Pregnancy test[d]	X					X				X		X	X
PT, PTT[e,k]	X					X				X		X	
FSH test[d]	X												
Serology / HIV laboratory tests[d]	X												
Urinalysis[d]	X	X	X	X	X	X		X		X		X	X
CD34+ cell count in blood	X					X				X		X	X
BM aspiration, biopsy and cytogenetics[f]	X									X			
Molecular test for JAK2 mutation in blood[g]	X					X				X		X	
Administer dose of INCB018424[h]		X		X		X				X			
Dispense INCB018424 study medication[h]		X		X		X				X			
PK sampling		X		X		X							
PD biomarker sampling		X		X		X				X		X	
Adverse event / Intercurrent illness assessment		X	X	X	X	X				X		X	X
Study medication compliance[i]			X	X	X	X				X		X	

* = Cycle 1 Day 8 and Day 22 site clinic visits are optional for the expanded cohort at Investigator's discretion. However, CBC must be done and reviewed on both Day 8 and 22.

a. A complete examination will be performed at Screening, the End-of-Study Visit and the Follow-up Visit. A "targeted" examination will be performed at all other visits. If Screening Visit is within 3 days of Cycle 1 Day 1, then targeted physical examination may not be repeated on Cycle 1 Day 1 at Investigator's discretion. During the treatment phase, weekly visits are required during the 1st cycle of therapy in the dose escalation phase with a review of constitutional symptoms and targeted physical examination, including transfusion requirement. However, physical examination and vital signs are required on Day 1 and Day 15 during the phase II expanded cohort of the study, see footnote "p." During 2nd and 3rd cycles, visits are every 4 weeks, and then every 3 28-day cycles thereafter. All examinations will include body weight. On Day 1 and Day 15 of Cycle 1, the vital signs will be taken predose and once between 1 and 4 hours morning post-dose. On all other clinical visits vital signs are taken once.
b. Overall response assessments will be graded according to the International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia. (Tefferi et al, 2006). Overall response assessments are required on Day 1 of Cycles 2, 3, and 4 and then every 3 28-day cycles thereafter.
c. A 12-lead ECG is required at Screening and Day 1 pre-dose (if Screening Visit is within 3 days of Cycle 1 Day 1, then ECG does not need to be repeated). ECG is required in the dose escalation phase on Day 8 during the 1st cycle of therapy and on Day 15 in the expanded cohort. ECG is required on Day 1 of Cycles 2 and 3 and on Day 1 of each scheduled subsequent visit for both dose escalation and expanded cohort. Final ECG is required at End-of-Study. Additional ECG may be done at the discretion of the Investigator. ECG may also be done at the Follow-up Visit for any patient with a new onset abnormality or change in an existing abnormality at the last "on treatment" evaluation which was considered 'clinically significant' by the Investigator.
d. See Appendix III for specific information on the tests, including serum chemistry, urine analysis, hepatitis and HIV screening and FSH and pregnancy testing. Tests may be done between Day -3 to Day -1 of specified visit(s) at discretion of the Investigator. A serum pregnancy test will be obtained at Screening. Urine pregnancy test is required every 4 weeks during the treatment phase, at the End-of-Study Visit and during the Follow-Up Visit. A serum pregnancy test will be performed to confirm positive results obtained from a urine test. FSH test will only be performed on females who have been amenorrheic for >1 year, and if levels are elevated no further pregnancy testing is required for these female patients. If Screening Visit is within 3 days of Cycle 1 Day 1, laboratory testing may not be repeated at Investigator's discretion on Cycle 1 Day 1. Urine analysis is not required for the expanded cohort during Cycle 1 Day 8 and Day 22; and during Cycle 2 and 3 on Day 15. If specific safety issues arise, additional laboratory analyses may be done at the discretion of the Investigators in consultation with Sponsor and upon IRB notification.
e. Tests may be done between Day-3 and Day -1 of specified visit(s) at discretion of the Investigator. PT and PTT are required at Screening, on Day 1 of Cycle 2, 3 and 4, on Day 1 of every protocol-scheduled subsequent visit, and at the End-of-Study Visit. See Appendix III.
f. Bone marrow aspiration and biopsy will be taken during the Screening phase (± 7 days), and at start of Cycle 4 (± 7 days), Cycle 7 (± 7 days), and thereafter at the start of each 6th subsequent cycle (± 7days). Evaluation will include staining for fibrosis; cytogenetics if abnormal prior to therapy, JAK2 mutation analysis if mutation present prior to therapy. Cytogenetic studies will be repeated only in patients with abnormalities at baseline, on Day 1 of Cycles 4 and 7 and thereafter on Day 1 of each 6th subsequent cycle. If unable to obtain BM aspirate, cytogenetics may also be done on peripheral blood collected for PD/PK analysis.
g. Molecular testing for JAK2 mutation in peripheral blood may be done at Screening Visit or pre-dose on Cycle 1 Day 1 for operational ease of the investigative site. Thereafter, JAK2 mutation analysis will only be done on Day 1 Cycles 2, 3 and 4 and every subsequent visit only if mutation present prior to start of therapy. See Appendix X.
h. The study medication may be dispensed on Day -1 to the entitled qualified patient at discretion of the Investigator for Cycle 1. If the study medication is dispensed on Day -1, patient must be instructed not to take medication prior to pre-dose PK blood draw. In addition, the patient will be instructed that the dose is to be taken at 12-hour intervals at approximately the same times each day. The first dose of each day should be taken in the morning. The second dose must be taken at approximately 12 hours from the morning dose.
i. Study medication compliance should be checked at each scheduled clinical visit. See footnote "j" for the expanded cohort when MTD has been reached.
j. Once MTD is established, physical examination, vital signs and ECG are optional on Cycle 1 Days 8 and 22. Study medication compliance check is not required on Days 8, 15 and 22 of Cycle 1 during the expanded cohort in Part 1.
k. PT (INR) and PTT test results, if done as standard of care by the clinic site prior to amendment 3, will be retrieved.

7.1.1 Part 1 Screening Evaluations (Day -14 to Day -1)

The following procedures will be performed for all cohorts at the Screening Visit:

- Obtain informed consent prior to any study specific procedures being conducted.
- Determine if patient meets the inclusion/exclusion criteria.
- Discuss methods known to be at least 99% effective in preventing pregnancy (Appendix IX).
- Review medical history and medication history.
- Perform comprehensive (complete) physical examination including body weight and height.
- Collect vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be taken in a sitting position after 5 minutes of rest.
- Determine Eastern Cooperative Oncology Group (ECOG) status at Screening (ECOG status must be 0, 1, or 2).
- Perform 12-lead electrocardiogram (ECG) after 5 minutes of rest.
- Collect urine sample for urinalysis (Appendix III).
- Collect blood samples for the following:
  - Serum chemistry tests, CBC, PT, PTT and CD34+
  - Serum pregnancy test (female patients of childbearing potential only (Appendix III)
  - Follicle stimulating hormone (FSH) level (postmenopausal female patients only [Appendix III])
  - HIV and hepatitis tests (Appendix III)
- Perform bone marrow aspiration and biopsy, cytogenetics and JAK2 mutation assay. JAK2 mutation and cytogenetics may be done in peripheral blood if bone

marrow aspirate is insufficient in patients known to have abnormalities or unknown cytogenetic status.

- Collect blood for quantitative molecular test for JAK2 mutation (Appendix X, Note: alternatively, JAK2 mutation in blood draw may be done pre-dose on Cycle 1 Day 1).

7.1.2 On-Treatment Evaluations of Dose Escalation and Expanded Cohort Part 1 BID Continuous Dosing

7.1.2.1 Part 1 Cycle 1

7.1.2.1.1 Part 1 Cycle 1, Day 1

Patients who meet all of the study entrance criteria and none of the exclusion criteria will return to the study site on Day 1. The following procedures will be performed:

- Review of eligibility criteria including laboratory results.
- Review of prior/concomitant medications.
- Targeted (symptom directed) physical examination (may be done between Day -3 and Day -1 at discretion of the Investigator).
- Vital signs will be taken predose and once between 1 and 4 hours morning post-dose.
- 12-lead ECG prior to first dose. Electrocardiogram may be done between Day -3 and Day -1 at discretion of the Investigator.
- Urine collection for urinalysis (may be done between Day -3 and Day -1 at discretion of the Investigator).
- Blood sampling for serum chemistry tests, CBC (may be done between Day -3 and Day -1 at discretion of the Investigator), see Appendix III.
- Blood sample for plasma PK assessment will be drawn pre and post-dose with exact time recorded as defined in the Schedule of Observations. Pharmacokinetic

samples will be collected at pre-dose, 0.5, 1, 1.5, 2, 4, 6 and 9 hours after administration of the morning dose of INCB018424.

- Blood sample for PD will be collected pre-dose, 2, 6, and 9 hours after administration of the morning dose of INCB018424.
- Blood sampling for JAK2 mutation assay, if not done during Screening Visit.
- Administration of the first dose of the INCB018424.
- Intercurrent illness will be assessed pre-dose.
- Adverse events will be assessed postdose.
- Patients will be provided with a diary to record observations. The diary will also include instructions on dosing and contact information for the Investigator and/or designated research staff.
- Study medication for the first 4 weeks of Cycle 1 will be dispensed and the study staff will instruct the patient regarding dosing regimen.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.
- Patients will be asked to return to the clinical site on Day 8 during the dose escalation phase only. Day 8 clinic visit is optional during the expanded phase of the study. Patients will be asked to bring the study medication and the diary with them on the next scheduled clinic visit.

Note: If Screening Visit is within 3 days of Cycle 1 Day 1, then targeted physical examination, ECG and blood and urine clinical laboratory tests need not be repeated on Cycle 1 Day 1 based on Investigator's discretion.

7.1.2.1.2 Part 1 Cycle 1, Days 2 to 7

Patients will self-administer study medication as instructed twice daily at approximately 12-hour intervals in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.1.2.1.3 Part 1 Cycle 1, Day 8 ± 2

The following procedures will be performed:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical (symptom directed) examination and vital signs are required during the dose escalation phase. These procedures are optional during the expanded cohort part of the study at Investigator's discretion.
- 12-lead ECG after 5 minutes of rest for Part 1, dose escalation phase only.
- Urine collection for urinalysis is not required in the expanded cohort.
- Blood sampling for the serum chemistry tests, CBC, see Appendix III.
- Review all safety information and criteria for dosing interruptions (Section 10.4) to determine if patients should receive further doses.
- The study medication tablet count is optional to assess compliance; if count is done, the study medication will be returned to qualified patients.
- Patient diary will be reviewed and returned for recording of observations.

7.1.2.1.4 Part 1 Cycle 1, Days 9 to 14

Patients will self-administer study medication as instructed twice daily at approximately 12-hour intervals in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.1.2.1.5 Part 1 Cycle 1, Day 15 ± 2

The following procedures will be performed:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical examination (symptom directed).
- Vital signs are to be taken predose and once between 1 and 4 hours morning postdose.
- 12-lead ECG after 5 minutes of rest for the expanded cohort.
- Urine sampling for urinalysis (See Appendix III).
- Blood sampling for serum chemistry tests, CBC, see Appendix III.
- Administration of the morning dose of INCB018424.
- Blood sample for plasma PK assessment will be drawn pre- and post-dose with exact time recorded as defined in the Schedule of Observations. For Cycle 1, PK samples to be collected on Day 15 at pre-dose, 0.5, 1, 1.5, 2, 4, 6 and 9 hours after administration of the morning dose of INCB018424.
- Blood sample for PD assessment for Cycle 1 to be collected on Day 15 at pre-dose, 2, 6 and 9 hours after administration of the morning dose of INCB018424.
- The study medication tablet count is optional to assess compliance.
- Patient diary will be reviewed and returned for recording of observations.
- Review all safety information and criteria for dosing interruptions (Section 10.4) to determine if patients should receive further doses.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.

- Patients may be asked to return to the clinic on Day 22 (optional visit) at Investigator's discretion. Patients will be asked to bring all study medication and the diary with them to the next scheduled visit.
- Patients will be asked to withhold their morning dose of study medication on Day 1 of Cycle 2.

7.1.2.1.6 Part 1 Cycle 1, Days 16 to 21

Patients will continue to self-administer study medication per instructions twice daily at approximately 12 hour intervals in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.1.2.1.7 Part 1 Cycle 1, Day 22 ± 2

The following procedures will be performed:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical (symptom directed) examination, vital sign measurements and ECG are optional at Investigator's discretion.
- Urine sampling for urinalysis (Appendix III) is not required in the expanded cohort.
- Blood sampling for serum chemistry tests, CBC, see Appendix III.
- The study medication tablet count to assess compliance is optional to assess compliance; if count is done, the study medication will be returned to qualified patients following the tablet count.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.

- Patients will be asked to return to the clinic on Day 1 of Cycle 2 (Day 28 ± 3 of Cycle 1). Patients will be asked to bring all study medication and the diary with them to the next scheduled visit.
- Patients will be asked to withhold their morning dose of study medication on Day 1 of Cycle 2.
- Review all safety information and criteria for dosing interruptions (Section 10.4) to determine if patients should receive further doses.

7.1.2.1.8 Part 1 Cycle 1, Days 23 to 27

Patients will continue self-administering study medication per instructions twice daily at approximately 12 hour intervals in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.1.2.2 Part 1 Cycles 2 and 3

7.1.2.2.1 Part 1 Cycles 2 and 3, Day 1 ± 3

The following procedures will be performed:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical (symptom directed) examination and vital signs.
- ECOG performance status.
- 12-lead ECG after 5 minutes of rest.
- Urine collection for urinalysis and pregnancy test on females of childbearing potential only. If urine pregnancy test is positive, then serum pregnancy test will be done.
- Blood sampling for the following:
  - Serum chemistry tests, CBC, PT, PTT and CD34+, see Appendix III

- PK analysis sample collection pre-dose
- PD marker analysis sample collection pre-dose

- Overall response assessment (IWG-MRT).
- Blood collection for quantitative molecular test JAK2 mutation (Appendix X) for patients with positive results at Screening.
- Administration of the morning dose of INCB018424.
- A study medication tablet count will be done to assess compliance. If the patient qualifies for continued dosing, he/she will be provided with study medication for the next 4 weeks of Cycle 2.
- Patient diary will be reviewed and returned for recording of observations.
- Patients will be asked to return to the clinic on Day 1 of Cycle 3 (Day 28 of Cycle 2 ± 3 days). Patients will be asked to bring all study medication and the diary with them to the visit.
- Patients will be asked to withhold their morning dose of study medication on Day 1 of Cycle 3.
- All procedures listed above, including dispensing of study medication for next 4 weeks of Cycle 3, if patient qualifies for continued dosing, will be performed on Day 1 of Cycle 3 ± 3 days. Patients will be asked to return to the clinic on Day 1 of Cycle 4 (Day 28 of Cycle 3 ± 3 days). Patients will be asked to bring all study medication with them to the visit.
- Review all safety information and criteria for dosing interruptions (Section 10.4) to determine if patients should receive further doses.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.

7.1.2.2.2 Part 1 Cycles 2 and 3, All Other Days

- Patients will be instructed to have the following tests done at their local clinical laboratory at the frequency listed below:
  - CBC, weekly ie, Days 8, 15 and 22 of both Cycles 2 and 3 (Appendix III)
  - Serum chemistry (Appendix III) every two weeks ie, Day 15 of both Cycles 2 and 3.
  - Urine collection for urinalysis every two weeks ie, Day 15 of both Cycles 2 and 3. Urinalysis is not required for Part 1, expanded cohort on Day 15 of both Cycles 2 and 3.
- Review all safety information and criteria for dosing interruptions (Section 10.4) to determine if patients should receive further doses.
- The Investigator and/or research staff will immediately contact the patient to notify him/her to interrupt study medication if the laboratory test results meet either of the interruption criteria (Section 10.4). The Investigator will continue to review the laboratory test results and inform the patients about how to proceed regarding study medication (ie, restarting or continue to hold).
- Patients will continue to self-administer study medication per instructions twice daily at approximately 12 hour intervals in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.1.2.3 Part 1 Each Subsequent Visit, Day 1 ± 5

- All study visit specific observations as outlined in the Schedule of Observations and described for Day 1 of Cycles 2 and 3 will be done for each subsequent visit on Day 1. Each subsequent visit comprises three 28-day cycles.
  - In addition, on Day 1 of Cycle 4 the following procedures will be done:
  - Bone marrow aspiration, biopsy and cytogenetics will be done (Cycle 4, Cycle 7 and each sixth subsequent cycle)

  - Peripheral blood will be collected, in accordance with the Schedule of Observations for
    - Quantitative molecular test for JAK2 mutation (only if positive at the Screening Visit, see Appendix X)
    - PD biomarkers, analysis, sample collection pre-dose
    - Cytogenetics (if bone marrow aspiration is inadequate)
    - No blood sampling is done for PK assessments.

- A 3-28-day cycle supply of study medication will be dispensed on Day 1 of each subsequent visit to qualified patients who have not met any interruption criteria and are showing some clinical benefit from the therapy.
- Patients will be instructed to return to the site every three 28-day cycles (± 5 days) following Day 1 of Cycle 4 and bring their study medication including empty containers and the diary with them.
- Patient diary will be reviewed and returned. Patients will be provided with a new diary at each subsequent Day 1 visit to record observations. The diary will also include instructions on dosing and contact information for the Investigator and/or designated research staff.
- Patients will be instructed to go every two weeks ie, Day 15 of each subsequent cycle, for the next three 28-day cycles to their local laboratory to have blood drawn for CBC, see Appendix III.
- Patients will be asked to withhold their morning dose of study medication on Day 1 of each subsequent visit.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.

7.1.2.4 Part 1 Each Subsequent Visit, All Other Days

- Review all safety information and criteria for dosing interruptions (Section 10.4) on a regular and ongoing basis to determine if patients should receive further doses.
- The Investigator and/or research staff will immediately contact the patient to notify him/her to interrupt study medication if the laboratory test results meet either of the interruption criteria (Section 10.4). The Investigator will continue to review the laboratory test results and inform the patients about how to proceed regarding study medication (ie, restarting or continue to hold).
- The Investigator and/or research staff will contact the patient on a regular monthly basis to assess the patient's overall well-being, any new or worsening signs and/or symptoms, compliance with study medication and dosing instructions, compliance with the local laboratory schedule and to answer any questions that the patient might have. The Investigator and/or research staff will remind the patient of their next scheduled visit and how to prepare for it (ie, withhold their morning dose of study medication.) The research staff will send a notification card to the patient to remind them of the date and time of their next scheduled visit to the clinic. The Investigator and research staff will be responsible for ensuring that all relevant information resulting from these monthly contacts is documented in the patient's medical record and case report form, as appropriate.
- Patients will record any signs and/or symptoms on the diary provided.

7.1.2.5 Part 1 End of Study or Early Termination Visit

- All study visit specific observations as outlined in the "Schedule of Observations" and described above for Day 1 of Cycles 2 and 3 will be done except:
    - Study medication will not be dispensed.
    - Blood draw for PK sampling will not be done.
    - Diary will be reviewed and returned to the patient.

7.1.2.6 Part 1 Follow-Up Visit

All enrolled patients are required to have a Follow-up visit. Follow-up visit interval will be determined from the End-of-Study Visit or the last actual dose of the study drug for patients who were discontinued using the tapering strategy. The following evaluations will be performed 30 to 35 days after the completion of the End of Study or early termination Visit:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Complete physical examination and vital signs.
- ECOG performance status.
- Urine collection for urinalysis and pregnancy test. If urine pregnancy test is positive, then serum pregnancy test will be done.
- Blood sampling for the serum chemistry tests, CBC, and CD34+, see Appendix III.

7.2 Part 2: Alternative Dosing Schedule A, B and C

Table 4 Part 2 Schedule of Observations Flowchart

	Screening Phase	Treatment Phase										End-of-Treatment Visit	
		Cycle 1				Cycle 2 and 3				Subsequent Visits - For details see Footnotes			
Evaluation	**Day -14 to Day -1**	**Day 1**	***Day 8**	**Day 15**	***Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**End of Study**	**Follow up**
Informed consent/ Eligibility criteria	X	X											
Medical & medication history	X		X	X	X	X				X[b]		X	X
Physical examination[a]	X	X		X		X				X[c]		X	X
Vital signs[a]	X	X		X		X				X[c]		X	X
Overall response assessment (IWG-MRT)[b]						X				X[d]		X	
ECOG performance status	X					X				X[e]		X	X
Concomitant medication review		X	X	X	X	X				X[f]		X	X
12-lead ECG[c]	X	X		X		X				X[g]		X	
Clinical laboratory tests[d]	X	X	X	X	X	X		X		X[h]		X	X
CBC[e]	X	X	X	X	X	X	X	X	X	X[i]	X[i]	X	X
PT and PTT[e]	X					X				X		X	
Pregnancy test[d]	X					X				X[h]		X	X
FSH test[d]	X												
Serology / HIV laboratory tests[d]	X												
Urinalysis[d]	X	X		X		X				X[h]		X	X
CD34+ cell count in blood	X					X				X[j]		X	X
BM aspiration, biopsy and cytogenetics[f]	X									X[k]			
Molecular test for JAK2 mutation in blood[g]	X					X				X[l]		X	
Administer dose of INCB018424[h]		X		X		X				X			
Dispense INCB018424 study medication[h]		X				X				X[m]			
PK sampling				X		X							
PD biomarker sampling		X		X		X				X[o]		X	
Adverse event / Intercurrent illness assessment		X	X	X	X	X				X[p]		X	X
Study medication compliance						X				X[q]		X	

* = Cycle 1 Day 8 and Day 22 site clinic visits are optional at Investigator's discretion. However, CBC must be done and reviewed on both Day 8 and 22.

a. A complete examination will be performed at Screening, the End-of-Study Visit and the Follow-up Visit. A "targeted" examination will be performed at all other scheduled clinic visits. Note: Physical examination and vital signs are optional on Days 8 and 22 of Cycle 1 based on the Investigator's discretion. If Screening Visit is within 3 days of Cycle 1 Day 1, then targeted physical examination may not be repeated on Cycle 1 Day 1 at Investigator's discretion. During the treatment phase, biweekly visits are required during 1st cycle of therapy with a review of constitutional symptoms and targeted physical examination, including transfusion requirement. During 2nd and 3rd cycle visits are every 4 weeks, and then every 3 28-day cycles thereafter. All examinations will include body weight. On Day 1 and Day 15 of Cycle 1, the vital signs will be taken predose and once between 1 and 4 hours morning post-dose. On all other clinical visits vital signs are taken once.
b. Overall response assessments will be graded according to the International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia. (Tefferi et al, 2006). Overall response assessments are required on Day 1 of Cycles 2, 3, and 4 and then every 3 28-day cycles thereafter.
c. A 12-lead ECG is required at Screening, on Day 1 pre-dose (if Screening Visit is within 3 days of Cycle 1 Day 1, then ECG does not need to be repeated) and on Day 15 during the 1st cycle of therapy; and then on Day 1 of Cycles 2 and 3 and on each scheduled subsequent visit. Final ECG is required at End-of-Study. Additional ECG may be done at the discretion of the Investigator. ECG may also be done at the Follow-up Visit for any patient with a new onset abnormality or change in an existing abnormality at the last "on treatment" evaluation which was considered 'clinically significant' by the Investigator.
d. See Appendix III for specific information on the tests, including serum chemistry, urine analysis, Hepatitis and HIV screening and FSH and pregnancy testing. Tests may be done between Day -3 to Day -1 of specified visit(s) at discretion of the Investigator. A serum pregnancy test will be obtained at Screening. Urine pregnancy test is required every 4 weeks during the treatment phase, at the End-of-Study Visit and during the Follow-Up Visit. A serum pregnancy test will be performed to confirm positive results obtained from a urine test. FSH test will only be performed on females who have been amenorrheic for >1 year, and if levels are elevated no further pregnancy testing is required for these female patients. If Screening Visit is within 3 days of Cycle 1 Day 1, laboratory testing may not be repeated at Investigator's discretion on Cycle 1 Day 1. Urine analysis is not required during Cycle 1 Day 8 and Day 22; and during Cycle 2 and 3 on Day 15. If specific safety issues arise, additional laboratory analyses may be done at the discretion of the Investigators in consultation with Sponsor and upon IRB notification.
e. Complete blood count (CBC including differential, platelets and reticulocytes) required weekly for Cycles 1, 2 and 3. For subsequent visits these tests are done biweekly. Tests may be done between Day-3 and Day -1 of specified visit(s) at discretion of the Investigator. PT and PTT are required at Screening, on Day 1 of Cycle 2, 3 and 4, on Day 1 of every scheduled subsequent visit, and at the End-of-Study Visit. See Appendix III.
f. Bone marrow aspiration and biopsy will be taken during the Screening Phase (± 7 days), and at start of Cycle 4 (± 7 days), Cycle 7 (± 7 days), and thereafter start of each 6th subsequent cycle (± 7 days). Evaluation will include staining for fibrosis; cytogenetics if abnormal prior to therapy, JAK2 mutation analysis if mutation present prior to therapy. Cytogenetic studies will be repeated only in patients with abnormalities at baseline, on Day 1 of Cycles 4 and 7 and thereafter on Day 1 of each 6th subsequent cycle. If unable to obtain BM aspirate, cytogenetics may also be done on peripheral blood collected for PD/PK analysis.
g. Molecular testing for JAK2 mutation in peripheral blood may be done at Screening Visit or pre-dose on Cycle 1 Day 1 for operational ease of the investigative site. Thereafter, JAK2 mutation analysis will only be done on Day 1 Cycle 2, 3 and 4 and every subsequent visit only if mutation present prior to start of therapy. See Appendix X.
h. The study medication may be dispensed on Day -1 to the entitled qualified patient at discretion of the Investigator for Cycle 1. If the study medication is dispensed on Day -1, patient must be instructed not to take medication prior to pre-dose PK blood draw. In addition, instruct the patient that the dose is to be taken at 24 or 12 hour interval at approximately the same times each day based on their individual Schedule of enrollment. The first dose of each day should be taken in the morning. The second dose for Schedules B and C must be taken at approximately 12 hour interval from the morning dose.
i. Study medication compliance should be checked on Day 1 of each cycle or at each scheduled Subsequent clinic site visit.

7.2.1 Part 2 Screening and Baseline Evaluations: Alternative Schedules A, B and C

7.2.1.1 Part 2 Screening Evaluations (Day -14 to Day -1)

It is recommended that patients come to the clinic after a fast of 2 hours from food and 1 hour from beverages. The following procedures will be performed for all cohorts at the Screening Visit:

- Obtain informed consent prior to any study specific procedures being conducted.
- Determine if patient meets the inclusion/exclusion criteria.
- Discussion of methods known to be at least 99% effective in preventing pregnancy (Appendix IX).
- Review of medical history and medication history.
- Comprehensive (complete) physical examination including body weight and height.
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- Eastern Cooperative Oncology Group (ECOG) status must be 0, 1, or 2.
- 12-lead electrocardiogram (ECG) after 5 minutes of rest.
- Urine sampling for urinalysis (Appendix III).
- Blood sampling for the following:
  - Serum chemistry tests, CBC, PT, PTT and CD34+.
  - Serum pregnancy test (females of childbearing potential only (Appendix III).
  - Follicle stimulating hormone (FSH) level (postmenopausal females only [Appendix III]).
  - HIV and hepatitis tests (Appendix III).

- Bone marrow aspiration and biopsy, cytogenetics and JAK2 mutation assay. JAK2 mutation assay cytogenetics may be done in peripheral blood if bone marrow aspirate is insufficient in patients known to have abnormalities or unknown cytogenetic status.
- Quantitative molecular test for JAK2 mutation in blood (Appendix X, Note: alternatively, JAK2 mutation in blood draw may be done pre-dose on Cycle 1 Day 1).

7.2.2 Part 2 On-Treatment Evaluations of Alternative Schedules A, B, C

7.2.2.1 Part 2 Cycle 1

7.2.2.1.1 Part 2 Cycle 1, Day 1

Patients who meet all of the study entrance criteria and none of the exclusion criteria will return to the study site on Day 1. The following procedures will be performed:

- Review of eligibility criteria including laboratory results.
- Review of prior/concomitant medications.
- Targeted (symptom directed) physical examination (may be done between Day -3 and Day -1 at discretion of the Investigator).
- Vital signs will be taken predose and once between 1 and 4 hours morning post-dose.
- 12-lead ECG prior to first dose. ECG may be done between Day -3 and Day -1 at discretion of the Investigator.
- Urine collection for urinalysis (may be done between Day -3 and Day -1 at discretion of the Investigator).
- Blood sampling for serum chemistry tests, CBC (may be done between Day -3 and Day -1 at discretion of the Investigator), Appendix III.

- Blood sample for PD will be collected pre-dose, before administration of the first morning dose of INCB018424.
- Blood sampling for JAK2 mutation assay, if not done during Screening Visit.
- Administration of the first dose of the INCB018424.
- Intercurrent illness will be assessed pre-dose.
- Adverse events will be assessed post-dose.
- Patients will be provided with a diary to record observations. The diary will also include instructions on dosing and contact information for the Investigator and/or designated research staff.
- Study medication will be dispensed based on Dosing Schedule A, B, C for the first 4 weeks of Cycle 1 and the study staff will instruct the patient regarding the dosing schedule based on their Schedule or Group of enrollment.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.
- Patients will be asked to bring the study medication and the diary with them to the next scheduled clinic visit.

Note: If Screening Visit is within 3 days of Cycle 1 Day 1, then targeted physical examination, ECG and blood and urine clinical laboratory tests need not be repeated on Cycle 1 Day 1 based on Investigator's discretion.

7.2.2.1.2 Part 2 Cycle 1, Days 2 to 7

Patients will self-administer study medication once or twice daily as instructed at approximately 24-hour or 12-hour intervals, in accordance with their Schedule or Group of enrollment, in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.2.2.1.3 Part 2 Cycle 1, Day 8 ± 2

The visit is optional to study clinic per schedule of observations. However, the following procedures will be performed:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical (symptom directed) examination and vital signs are optional based on Investigator's discretion.
- Blood sampling for serum chemistry tests, CBC, Appendix III.
- Review all safety information and criteria for dosing interruptions (Section 10.4) to determine if patients should receive further doses.

7.2.2.1.4 Part 2 Cycle 1, Days 9 to 14

Patients will self-administer study medication as instructed once or twice daily based on the dosing schedule, at approximately 24 or 12 hour intervals in accordance with their Schedule or Group of enrollment in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.2.2.1.5 Part 2 Cycle 1, Day 15 ± 2

The following procedures will be performed:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical examination.
- Vital signs are to be taken predose and once between 1 and 4 hours morning postdose.
- 12-lead ECG prior to first dose.
- Urine sampling for urinalysis (See Appendix III).
- Blood sampling for serum chemistry tests, CBC, see Appendix III.

- Administration of the morning dose of INCB018424.
- Blood sample for plasma PK assessment will be drawn pre- and post-dose with exact time recorded as defined in the Schedule of Observations. PK samples are to be collected on Day 15 at pre-dose, 0.5, 1, 1.5, 2, 4, 6 and 9 hours after administration of the morning dose of INCB018424.
- Blood sample for PD assessment for Cycle 1 to be collected on Day 15 at pre-dose (0 hour), 2 and 6 hours after administration of the morning dose of INCB018424.
- Review all safety information and criteria for dose interruptions or modification (Sections 10.4 and 10.5) to determine if patient's dose should be modified or they continue with their assigned dose level. If patient qualifies for continued dosing, he/she will be asked to continue with study medication based on their enrollment Schedule or Group or at the new assigned modified dose.
- Patient diary will be reviewed and returned for recording of observations.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.
- At Investigator's discretion the patient may be asked to return to the clinic on Day 22. Patients will be asked to bring the diary with them to the next scheduled visit.

7.2.2.1.6 Part 2 Cycle 1, Days 16 to 21

Patients will self-administer study medication as instructed once daily (Schedule A), based on the dosing schedule, at approximately 24 or 12 hour intervals in accordance with their schedule or group of enrollment in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.2.2.1.7 Part 2 Cycle 1, Day 22 ± 2

The visit is optional to study clinic per schedule of observations. However, the following procedures will be performed:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical (symptom directed) examination and vital signs are optional based on Investigator's discretion.
- Blood sampling for serum chemistry tests, CBC (Appendix III).
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.
- Patients will be asked to return to the clinic on Day 1 of Cycle 2 (Day 28 ± 3 of Cycle 1). Patients will be reminded to bring all study medication and the diary with them to the visit.
- Patients will be asked to withhold their morning dose of study medication on Day 1 of Cycle 2.
- Review all safety information and criteria for dosing interruptions (Section 10.4) to determine if patients should receive further doses.

7.2.2.1.8 Part 2 Cycle 1, Days 23 to 27

Patients will self-administer study medication as instructed once daily or twice, based on the dosing schedule, at approximately 24 or 12 hour intervals in accordance with their schedule or group of enrollment in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.2.2.2 Part 2 Cycles 2 and 3

7.2.2.2.1 Part 2 Cycles 2 and 3, Day 1 ± 3

The following procedures will be performed:

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical (symptom directed) examination and vital signs.
- ECOG performance status.
- 12-lead ECG after 5 minutes of rest.
- Urine collection for urinalysis and pregnancy test on females of childbearing potential only. If urine pregnancy test is positive, then serum pregnancy test will be done.
- Blood sampling for the following:
  - Serum chemistry tests, CBC, PT, PTT and CD34+
  - PK analysis sample collection pre-dose
  - PD marker analysis sample collection pre-dose
- Overall response assessment (IWG-MRT).
- Blood collection for quantitative molecular test JAK2 mutation (Appendix X) for patients with positive results at Screening.
- Administration of the morning dose of INCB018424.
- A study medication tablet count will be done to assess compliance. If the patient qualifies for continued dosing, he/she will be provided with study medication for the next 4 weeks in accordance with their schedule. Those patients where dose has been or may be modified will receive study medication consistent with the modified prescribed dose.

- Patient diary will be reviewed and returned for recording of observations.
- Patients will be asked to return to the clinic on Day 1 of Cycle 3 (Day 28 of Cycle 2 ± 3 days). Patients will be asked to bring all study medication and the diary with them to the visit.
- Patients will be asked to withhold their morning dose of study medication on Day 1 of Cycle 3.
- **Study medication dispensing Cycle 3, Day 1:**

  Schedule C: Dosing regimen will be adjusted to lower dose of 10 mg po BID.

  Schedule A, B, C: If patient qualifies for continued or adjusted dosing, all procedures listed above, including dispensing of study medication corresponding to the Alternative Schedule A, B or C for the next 4 weeks of Cycle 3 will be performed on Day 1 of Cycle 3 ± 3 days. Those patients where dose has been or may be modified will receive study medication consistent with the modified prescribed dose.
- Patients will be asked to return to the clinic on Day 1 of Cycle 4 (Day 28 of Cycle 3 ± 3 days). Patients will be asked to bring all study medication with them to the visit.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.

7.2.2.2.2 Part 2 Cycles 2 and 3, All Other Days

- Patients will be instructed to have the following tests done at their local clinical laboratory at the frequency listed below:
  - CBC, weekly ie, Days 8, 15 and 22 of both Cycles 2 and 3.
  - Serum chemistry, every two weeks ie, Day 15 of both Cycles 2 and 3.

- Review all safety information and criteria for dose interruptions and dose reduction (Sections 10.4 and 10.5) to determine if patients should continue further doses.
- The Investigator and/or research staff will immediately contact the patient to notify him/her to interrupt or reduce the study medication if the laboratory test results meet either of the interruption criteria or require dose modification (Sections 10.4 and 10.5). The Investigator will continue to review the laboratory test results and inform the patients about how to proceed regarding study medication (ie, modification, restarting or continue to hold).
- Patients will continue to self-administer study medication per instructions daily corresponding with their dosing regimen at approximately 24-hour interval or 12-hour interval consistent with the current modified dose level or based on their schedule in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.2.3 Part 2 Subsequent Visits

7.2.3.1 Part 2 Each Subsequent Visit, Day 1 ± 5

- All study visit specific observations as outlined in the "Schedule of Observations" and described for Day 1 of Cycles 2 and 3 will be done for each subsequent visit on Day 1. Each subsequent visit comprises three 28-day cycles.
- Patients will remain on their respective dosing regimen in accordance with their respective schedule.
- In addition, Day 1 of Cycle 4 the following procedures will be done:
    - Bone marrow aspiration, biopsy, JAK2 mutation assay and cytogenetics will be done (Cycle 4, Cycle 7 and each sixth subsequent cycle)
    - Peripheral blood will be collected, in accordance with the "Schedule of Observations" for

- Quantitative molecular test for JAK2 mutation (only if positive at the Screening Visit, see Appendix X).
- PD biomarkers, analysis, sample collection pre-dose
- Cytogenetics (if bone marrow aspiration is inadequate).
- Blood draw for PK sampling will not be done.

- Schedule B patients only: Spleen size evaluation to determine continuation of assigned dosing regimen of 10 mg po BID or a need for dose adjustment will be done. Patient's dosing regimen will continue at 10 mg po BID or will be adjusted based on reduction in spleen size in accordance with Section 3.4.6.
- A 3-28-day cycle supply of study medication will be dispensed on Day 1 of each subsequent visit to qualified patients who have not met any interruption or dose modification criteria (Sections 10.4 and 10.5) and are showing some clinical benefit from the therapy. The dose of study medication unless modified will be consistent with Part 2, Alternative dose schedule
- Patients will be instructed to return to the site every three 28-day cycles (± 5 days) following Day 1 of Cycle 4 and bring their study medication including empty containers and the diary with them.
- Patient diary will be reviewed and returned. Patients will be provided with a new diary at each subsequent Day 1 visit to record observations. The diary will also include instructions on dosing and contact information for the Investigator and/or designated research staff.
- Patients will be instructed to go every two weeks ie, Day 15 of each subsequent cycle, for the next three 28-day cycles to their local laboratory to have blood drawn for CBC.
- Patients will be asked to withhold their morning dose of study medication on Day 1 of each subsequent visit.

- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.

7.2.3.2 Part 2 Each Subsequent Visit – All Other Days

- Review all safety information and criteria for dose interruptions or modification (Sections 10.4 and 10.5) on a regular and ongoing basis to determine if patient's dose should be modified or interrupted or continued at the assigned dose level.
- The Investigator and/or research staff will immediately contact the patient to notify him/her to interrupt or modify the dose of the study medication if the laboratory test results meet either of the dose modification or interruption criteria (Section 10.4). The Investigator will continue to review the laboratory test results and inform the patients about how to proceed regarding study medication (ie, dose modification, restarting or continue to hold).
- The Investigator and/or research staff will contact the patient on a regular monthly basis to assess the patient's overall well-being, any new or worsening signs and/or symptoms, compliance with study medication and dosing instructions, compliance with the local laboratory schedule and to answer any questions that the patient might have. The Investigator and/or research staff will remind the patient of their next scheduled visit and how to prepare for it (ie, withhold their morning dose of study medication). The research staff will send a notification card to the patient to remind them of the date and time of their next scheduled visit to the clinic. The Investigator and research staff will be responsible for ensuring that all relevant information resulting from these monthly contacts is documented in the patient's medical record and case report form, as appropriate.
- Patients will continue to self-administer study medication as instructed once or twice daily based on the dosing schedule, at approximately 24 or 12 hour intervals in accordance with their schedule or group of enrollment in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.2.4 Part 2 End of Study or Early Termination Visit

- All study visit specific observations as outlined in the "Schedule of Observations" and described above for Day 1 of Cycles 2 and 3 will be done EXCEPT:
- Study medication will not be dispensed.
- Blood draw for PK sampling will not be done.
- Diary will be reviewed and will not be returned to the patient.

7.2.5 Part 2 Follow-up Visit

All enrolled patients are required to have a Follow-up visit. Follow-up visit interval will be determined from the End-of-Study Visit or the last actual dose of the study drug for patients who were discontinued using the tapering strategy. The following evaluations will be performed 30 to 35 days after the completion of the End of Study or early termination visit:

- Review of medical history and concomitant medication
- Review of any adverse events
- Complete physical examination and vital signs
- ECOG performance status
- Urine collection for urinalysis and pregnancy test. If positive then serum pregnancy test will be done.
- Blood sampling for serum chemistry tests, CBC, and CD34+.

7.3 Part 3: Groups I, II and III

Table 5 Part 3 Schedule of Observations Flowchart

	Screening Phase	Treatment Phase												End-of-Treatment Visit	
		Cycle 1				Cycle 2 and 3				Cycle 4		Subsequent Visits			
Evaluation	**Day -14 to Day -1**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**End of Study**	**Follow up**
Informed consent / Eligibility criteria	X	X													
Medical & medication history	X			X		X				X		X		X	X
Physical examination, including spleen and liver size by palpation[a]	X	X	X[a]	X	X[a]	X				X		X		X	X
Vital signs[a]	X	X		X		X				X		X		X	X
Overall response assessment (IWG-MRT)						X				X		X		X	
ECOG performance status	X					X				X		X		X	X
Concomitant medication review		X		X		X				X		X		X	X
12-lead ECG[b]	X	X		X		X				X		X		X	
Clinical laboratory tests[c]	X	X	X	X	X	X		X		X		X		X	X
CBC[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT and PTT	X					X				X		X		X	
Pregnancy test[c]	X					X				X		X		X	X
FSH test[c]	X														
Serology / HIV laboratory tests[c]	X														
Urinalysis[c]	X	X		X		X				X		X		X	X
CD34+ cell count in blood	X					X				X		X		X	X
BM aspiration, biopsy and cytogenetics[e]	X									X		X			
MRI of spleen, liver,		X				X(C2)				X		X[k]			
MRI of thigh		X				X (C2)				X		X[k]			
Molecular test for JAK2 mutation in blood[e]	X	X				X				X		X		X	
Administer dose of INCB018424[f]		X		X		X				X		X			
Dispense INCB018424 study medication[f]		X				X				X		X			
PK sampling				X		X									
PD biomarker sampling	X	X		X		X				X		X		X	
Adverse event / Intercurrent illness assessment[g]		X	X	X	X	X				X		X		X	X

	Screening Phase	Treatment Phase												End-of-Treatment Visit	
		Cycle 1				Cycle 2 and 3				Cycle 4		Subsequent Visits			
Evaluation	**Day -14 to Day -1**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**End of Study**	**Follow up**
Study Medication Compliance						X				X		X		**X**	
EORTC QLQ-C30		X		X		X				X		X		**X**	X
Modified MFSAF		X		X		X				X		X		X	X
Six-minute Walk Test [h]	X	X				X(C2)				X		X(C7)			
StepWatch™ Activity Monitor Assessment[i]	X					X(C2)		X[i]		X	X[i]	X(C7)	X[i]		
Body composition[d]		X				X(C2)				X		X(C7)			
Grip strength[d]	X	X				X(C2)				X		X(C7)			
Photographing of body[j]	X									X					

a. A complete examination will be performed at Screening, the End-of-Study Visit and the Follow-up Visit. A "targeted" examination will be performed at all other scheduled clinic visits. Note: Physical examination and vital signs are optional on Days 8 and 22 of Cycle 1 based on the Investigator's discretion. All examinations will include body weight, spleen and liver size. On Day 1 and 15 of Cycle 1 and Day 1 of Cycle 2, the vital signs will be taken predose and once between 1 and 4 hours morning post-dose. On days when the 6MWT will be conducted, vital signs (HR and BP only) will also be taken before the 6MWT. If a second 6MWT is to be conducted that day, HR and BP must be measured prior to the second test.

b. A 12-lead ECG is required at Screening, on Day 1 pre-dose (if Screening Visit is within 3 days of Cycle 1 Day 1, then ECG does not need to be repeated) and on Day 15 during the 1st cycle of therapy; and then on Day 1 of Cycles 2 and 3 and on each scheduled subsequent visit. Final ECG is required at End-of-Study. Additional ECG may be done at the discretion of the Investigator. ECG may also be done at the Follow-up Visit for any patient with a new onset abnormality or change in an existing abnormality at the last "on treatment" evaluation which was considered 'clinically significant' by the Investigator.

c. See Appendix III for specific information on the tests, including serum chemistry, urine analysis, Hepatitis and HIV screening and FSH and pregnancy testing. Tests may be done between Day -3 to Day -1 of specified visit(s) at discretion of the Investigator. If Screening Visit is within 3 days of Cycle 1 Day 1, laboratory testing may not be repeated at Investigator's discretion on Cycle 1 Day 1. If specific safety issues arise, additional laboratory analyses may be done at the discretion of the Investigators in consultation with Sponsor and upon IRB notification. A serum pregnancy test will be obtained at Screening. Urine pregnancy test is required every 4 weeks during the treatment phase, at the End-of-Study Visit and during the Follow-Up Visit. A serum pregnancy test will be performed to confirm positive results obtained from a urine test. FSH test will only be performed on females who have been amenorrheic for >1 year, and if levels are elevated no further pregnancy testing is required for these female patients

d. Tests may be done between Day-3 and Day -1 of specified visit(s) at discretion of the Investigator.

e. Bone marrow aspiration and biopsy evaluation will include staining for fibrosis; cytogenetics if abnormal prior to therapy, JAK2 mutation analysis if mutation present prior to therapy. Cytogenetic studies will be repeated only in patients with abnormalities at baseline. If unable to obtain BM aspirate, cytogenetics may also be done on peripheral blood collected for PD/PK analysis.

f. The study medication may be dispensed on Day -1 to the entitled qualified patient at discretion of the Investigator for Cycle 1. If the study medication is dispensed on Day -1, patient must be instructed not to take medication prior to pre-dose PK blood draw. In addition, instruct the patient that the dose is to be taken at 24 or 12 hour interval at

approximately the same times each day based on their individual Schedule of enrollment. The first dose of each day should be taken in the morning. The second dose must be taken at approximately 12 hour interval from the morning dose.

g. Troubling adverse events will be reported to the Clinical Site by telephone between Study Visits.

h. Six minute walk test (6MWT) will be performed twice prior to receiving the first dose of INCB018424 because of the potential for 'training effects' in walk performance. The pre-dose test may be done twice on the same day at least 30 minutes apart and only after the measured HR has returned to within 10% of the pre first-test value. Vitals signs (HR and BP) may be repeated as needed every 15 minutes until the required HR level has been attained. If the walk test is performed once at the Screening visit then it will be repeated once on C1D1 predose. Vital signs (HR and BP only) will be recorded before the walk test is conducted. Note: there is a specific eligibility criteria (Section 6.2) for patients to be qualified to take the 6MWT. The eligibility criteria must be reviewed each time prior to administering the test. Test may be done between Day -3 and Day -1 of specified visit(s) at discretion of the Investigator.

i. Patients will bring the device back after the Screening monitoring period when they return for the Baseline visit. For other visits, patient must mail the device back after the 9-day monitoring period. Pre-labeled overnight envelopes will be provided. Site coordinators will download data according to the instructions in the Reference Manual. The device will be re-issued to patients for the next testing period.

j. A subgroup of subjects will have portions of their body photographed, prior to receiving study medication and after 3 28-day cycles of therapy. Participation in this assessment is strictly voluntary.

k. Spleen and liver volumes will be assessed by non-contrast MRI, and correlated to changes noted by palpation in approximately 20 patients who enroll in the study under Amendment 5 or 6 and for whom MRI is not contraindicated. Depending upon emerging data, this subset of patients could be expanded, but will not exceed 50 patients total. MRI measurements will be conducted in these patients at pre-dose (C1D1) and after 1, 3 and 6 28-day cycles of therapy. MRI For subjects with Baseline MRIs, additional MRIs will be performed approximately every 6 months after the C7D1 visit, beginning with the C13D1 visit ± 8 weeks. A new ICF for these additional MRI procedures must be signed prior to have an additional MRI performed. Subjects who do not sign consent for additional MRI will not be precluded from continued participation in the study.

7.3.1 Part 3 Screening and Baseline Evaluations: Groups I, II and III

7.3.1.1 Part 3 Screening Evaluations (Day -14 to Day -1)

It is recommended that patients come to the clinic after a fast of 2 hours from food and 1 hour from beverages. The required procedures may need to be scheduled over a 1 to 4 day period (or longer if approved by the sponsor). A light meal or snack should be provided to patients 1 hour prior to the 6MWT and grip strength assessment. Eligibility Criteria for the 6MWT must be consulted prior to the test (Section 6.3). The following procedures will be performed for all groups at the Screening Visit:

- Obtain informed consent prior to any study specific procedures being conducted.
- Determine if patient meets the inclusion/exclusion criteria.
- Discussion of methods known to be at least 99% effective in preventing pregnancy (Appendix IX).
- Review of medical history and medication history.
- Comprehensive (complete) physical examination including body weight and height. Spleen and liver measurement will include whether the organs are palpable and the centimeters below the left costal margin.
- Subjects who consent to having portions of their muscles or body photographed will have these pictures taken.
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- Eastern Cooperative Oncology Group (ECOG) status must be 0, 1, or 2.
- 12-lead electrocardiogram (ECG) after 5 minutes of rest.
- Urine sampling for urinalysis (Appendix III).
- Blood sampling for the following:

- Serum chemistry tests, CBC, PT, PTT and CD34+.
- Serum pregnancy test (females of childbearing potential only. (Appendix III)
- Follicle stimulating hormone (FSH) level (postmenopausal females only [Appendix III]).
- HIV test and hepatitis tests for subjects with evidence of active hepatitis infection (Appendix III).

- Blood sample collected for PD analysis.
- Bone marrow aspiration and biopsy, cytogenetics and JAK2 mutation assay. JAK2 mutation assay cytogenetics may be done in peripheral blood if bone marrow aspirate is insufficient in patients known to have abnormalities or unknown cytogenetic status.
- Quantitative molecular test for JAK2 mutation in blood (Appendix X, Note: alternatively, JAK2 mutation in blood draw may be done pre-dose on Cycle 1 Day 1).
- Provide a light meal or snack 1 hour prior to the 6MWT, grip assessment and accelerometer training.
- 6MWT to be performed by the patient after 10 mins of rest in the seated position (Group III only). Vital signs (HR and BP only) will be recorded 5 minutes prior to the 6MWT. A second 6MWT will be performed approximately 30 minutes later, or when the HR has returned to within 10% of the HR measured before the first 6MWT. Vital signs may be repeated every 15 minutes until the target HR is observed. Alternatively, the second 6MWT may be performed at the Baseline visit (C1D1), prior to taking the first dose of INCB018424. Detailed instructions are provided in the Reference Manual.
- Daily voluntary physical activity will be assessed using a SAM accelerometer for a 9 day period at the participating site(s) (Group III only). Each SAM unit will be prelabeled with patient's initials before unit is given to patient. The patient must be trained on the use and will need to be instructed how to wear it around the

ankle. The patient will receive a leaflet with basic instructions and a SAM diary to record the times the unit is placed on the ankle and removed each day. If the device is not worn the diary must be marked "not worn" for that day. The patient will need to take the SAM accelerometer off at bedtime and during bathing. The patient needs to be instructed to place the SAM accelerometer at a place in their house ie, next to their alarm clock, or next to their coffee maker, so they can remember to put it back on every day and after finishing their bath. The patient should be instructed to bring the device back with them along with the SAM diary at the next visit to the clinic site. Patients should also be supplied with pre-labeled priority overnight envelopes to ship the SAM accelerometer back to the site should there be any need to do so (if patient missed their visit or upon Sponsor request to the site). The accelerometer needs to be put on at the clinic, and the site staff needs to check that the accelerometer blinks once for every stride the patient takes (ask patient to take 10-15 strides and make sure it blinks every time the leg with monitor on it is used) and the patient should wear it every day from that day on according to the instructions. The day of this visit is Day 1 on the SAM 9-day clock. Detailed instructions are provided in the Reference Manual.

- A calibrated Jamar Hand Dynamometer will be used to measure grip strength in the dominant arm in the standardized recommended position (Group III only). Grip strength will be measured three times, and the average value of the measurements will be used for data analysis. Detailed instructions are provided in the Reference Manual.

7.3.2 Part 3 On-Treatment Evaluations of Groups I, II and III

7.3.2.1 Part 3 Cycle 1

7.3.2.1.1 Part 3 Cycle 1, Day 1

Patients who meet all of the study entrance criteria and none of the exclusion criteria will return to the study site on Day 1 having fasted since 12 midnight. The patient should

avoid strenuous exercise and alcohol consumption on the day prior to the visit. The required procedures may need to be scheduled over a 1 – 2 day period. A light meal or snack should be provided to patients 1 hour prior to the 6MWT and grip strength assessment. Eligibility Criteria for the 6MWT must be consulted prior to the test (Section 6.3). The following procedures will be performed:

- Review of eligibility criteria including laboratory results.
- Review of concomitant medications.
- Body composition testing should begin as soon as the patient arrives at the clinic, having fasted since midnight (Group III only). The testing will consist of recording a body weight, and measuring body water using a tracer dilution method. Following the initiation of the test (see Appendix XIII) the patient must refrain from consumption of any food or beverages (including water) for a 3-hour period. The patient can undergo normal activity and other non-invasive tests during this time. Following the conclusion of the test, the patient can resume eating and drinking *ad libitum*.
- Briefly give overview of the completion instructions and allow time for completion:
- EORTC QLQ-C30 questionnaire must be completed by the patient consistent with the EORTC guideline or standard guideline for completion of QOL questionnaires (see Appendix XI).
- MFSAF questionnaire must be completed by the patient consistent with the standard guideline for completion of QOL questionnaires (see Appendix XII).

Note: Completed EORTC and MFSAF must be placed in a sealed envelope. Where feasible the EORTC QLQ-C30 and MFSAF questionnaire should be administered prior to any study-specific procedures.

- Targeted (symptom directed) physical examination (may be done between Day -3 and Day -1 at discretion of the Investigator). Spleen and liver size will be assessed by palpation below the costal left margin.
- Vital signs will be taken (predose).
- 12-lead ECG prior to first dose. ECG may be done between Day -3 and Day -1 at discretion of the Investigator.
- Urine collection for urinalysis (may be done between Day -3 and Day -1 at discretion of the Investigator).
- Blood sampling for serum chemistry tests, CBC (may be done between Day -3 and Day -1 at discretion of the Investigator), Appendix III.
- Blood sample for PD will be collected pre-dose.
- Blood sampling for JAK2 mutation assay, if not done during Screening Visit.
- MRI of the spleen, liver, and left thigh will be performed on a subset of up to 20-25 patients (Group III only). Depending upon emerging data, this subset could be expanded, but will not exceed 50 patients.
- Provide a light meal or snack 1 hour prior to the 6MWT and/or grip assessment.
- 6MWT will be performed after collection of vital signs and after 10 mins of rest in the seated position only if a second test was not completed at the Screening visit (Group III only). Vital signs (HR and BP only) must be recorded 5 minutes prior to the 6MWT.
- A calibrated Jamar Hand Dynamometer will be used to measure grip strength in the dominant arm in the standardized recommended position (Group III only). Grip strength will be measured three times consistent with manufacturer's user manual, and the average value of the measurements will be used for data analysis.
- The SAM accelerometer along with the SAM diary will be returned at this visit and data will be downloaded by the site staff (Group III only). The SAM will be returned to the patient in Cycle 2.

- Administration of the first dose of the INCB018424.
- Intercurrent illness will be assessed pre-dose.
- Adverse events will be assessed post-dose.
- Vital signs will be taken 1 to 4 hours post-dose.
- Study medication for the first 28 days will be dispensed.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity. These adverse events will be recorded on the CRF.
- Patients will be asked to bring the study medication, and the diary with them to the next scheduled clinic visit.

Note: Any tests such as targeted physical examination, ECG and blood and urine clinical laboratory tests done within 3 days of Cycle 1 Day 1 need not be repeated on Cycle 1 Day 1 based on Investigator's discretion.

7.3.2.1.2 Part 3 Cycle 1, Days 2 to 7

Patients will self-administer study medication once or twice daily as instructed at approximately 24-hour or 12-hour intervals, in accordance with their Group of enrollment, in an outpatient setting. Patient will record any signs and/or symptoms on the diary provided.

7.3.2.1.3 Part 3 Cycle 1, Day 8 ± 2

Patients will be instructed to go to their local clinical laboratory to have a blood sample drawn for CBC, Platelets and Differential on Cycle 1, Day 8 ± 2. Patients are encouraged to use the same off-site testing laboratory for off-site testing. Physical examination is at Investigator's discretion.

7.3.2.1.4 Part 3 Cycle 1, Days 9 to 14

Patients will self-administer study medication as instructed once or twice daily based on the dosing schedule, at approximately 24 or 12 hour intervals in accordance with their Group of enrollment in an outpatient setting. Patients will continue to record any signs and/or symptoms in the diary provided.

7.3.2.1.5 Part 3 Cycle 1, Day 15 ± 2

The following procedures will be performed:

- EORTC QLQ-C30 questionnaire must be completed by the patient consistent with the EORTC guideline or standard guideline for completion of QOL questionnaires (see Appendix XI).
- MFSAF questionnaire must be completed by the patient consistent with the standard guideline for completion of QOL questionnaires (see Appendix XII).

Note: Completed EORTC and MFSAF must be placed in a sealed envelope. Where feasible, the EORTC QLQ-C30 and MFSAF questionnaire should be administered prior to any study-specific procedures.

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical examination.
- Vital signs will be taken (pre-dose).
- 12-lead ECG prior to dose.
- Urine sampling for urinalysis (See Appendix III).
- Blood sampling for serum chemistry tests, CBC, see Appendix III.
- Blood sample for INCB018424 PK (pre-dose)
- Blood sample for PD will be collected on C1D15 at pre-dose.
- Administration of the morning dose of INCB018424.

- Vital signs will be taken 1 to 4 hours post-dose.
- Blood sample for plasma PK assessment will be drawn 2 hours post-dose with exact time recorded.
- Review all safety information and criteria for dose interruptions (Section 10.4) or adjustments (Section 5.3) to determine if patient's dose should be modified or they continue with their assigned dose level. If patient qualifies for continued dosing, he/she will be asked to continue with study medication based on their assigned or modified dose.
- Patient diary will be reviewed and returned for recording of observations.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.
- At Investigator's discretion the patient may be asked to return to the clinic on Day 22. Patients will be asked to bring the diary with them to the next scheduled visit.

7.3.2.1.6 Part 3 Cycle 1, Days 16 to 21

Patients will self-administer study medication as instructed once or twice daily based on the dosing schedule, at approximately 24 or 12 hour intervals in accordance with their group of enrollment in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.3.2.1.7 Part 3 Cycle 1, Day 22 ± 2

Patients will be instructed to go to their local clinical laboratory to have a blood sample drawn for CBC, differential and platelets. Physical examination is at Investigator's discretion.

7.3.2.1.8 Part 3 Cycle 1, Days 23 to 27

Patients will self-administer study medication as instructed once daily or twice, based on the dosing schedule, at approximately 24 or 12 hour intervals in accordance with their group of enrollment in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

Prior to the Cycle 2, Day 1 visit, the patient should be contacted and reminded to avoid strenuous exercise and alcohol consumption on the day prior to the visit. Patients will be asked to withhold their morning dose of study medication on Day 1 of Cycle 2 for the Study Visit.

7.3.2.2 Part 3 Cycles 2 and 3

7.3.2.2.1 Part 3 Cycle 2 Day 1 ± 3

Patients will return to the study site on Day Cycle 2 Day 1 having fasted since 12 midnight. The patient should avoid strenuous exercise and alcohol consumption on the day prior to the visit. The required procedures may need to be scheduled over a 1 to 4 day period (or longer if approved by the sponsor). A light meal or snack should be provided to patients 1 hour prior to the 6MWT and grip strength assessment (Group III only). Eligibility Criteria for the 6MWT must be consulted prior to the test (Section 6.3). The following procedures will be performed:

- Review of medical history and concomitant medication.
- Body composition testing should begin as soon as the patient arrives at the clinic, having fasted since midnight (Group III only). The testing will consist of recording a body weight, and measuring body water using a tracer dilution method. Following the initiation of the test (see Appendix XIII) the patient must refrain from consumption of any food or beverages (including water) for a 3-hour period. The patient can undergo normal activity and other non-invasive tests during this time. Following the conclusion of the test, the patient can resume eating and drinking *ad libitum*.

- EORTC QLQ-C30 questionnaire must be completed by the patient consistent with the EORTC guideline or standard guideline for completion of QOL questionnaires (see Appendix XI).
- MFSAF questionnaire must be completed by the patient consistent with the standard guideline for completion of QOL questionnaires (see Appendix XII).

Note: Completed EORTC and MFSAF must be placed in a sealed envelope. Where feasible the EORTC QLQ-C30 and MFSAF questionnaire should be administered prior to any study- specific procedures.

- Targeted physical (symptom directed) examination and vital signs. NOTE: coordinate vital signs with 6MWT.
- ECOG performance status.
- Overall response assessment (IWG-MRT).
- Vital signs will be taken (pre-dose).
- 12-lead ECG after 5 minutes of rest.
- Urine collection for urinalysis and pregnancy test on females of childbearing potential only. If urine pregnancy test is positive, then serum pregnancy test will be done.
- Blood sampling for the following:
  - Serum chemistry tests, CBC, PT, PTT and CD34+
  - PK analysis sample collection pre-dose.
  - PD marker sample collection pre-dose.
  - PK sample collection post-dose.
- Blood collection for quantitative molecular test JAK2 mutation (Appendix X) for patients with positive results at Screening.

- MRI of the spleen, liver, and left thigh will be performed on a subset of up to 20-25 patients (Group III only). Depending upon emerging data, this subset could be expanded, but will not exceed 50 patients.

- Provide a light meal or snack 1 hour prior to the 6MWT and grip assessment (Group III only).

- 6MWT to be performed by patient after 10 minutes of rest in the seated position (Group III only). Vital signs (HR and BP only) will be collected 5 minutes prior to the walking test.

- A calibrated Jamar Hand Dynamometer will be used to measure grip strength in the dominant arm in the standardized recommended position (Group III only). Grip strength will be measured three times consistent with manufacturer's user manual, and the average value of the measurements will be used for data analysis (see Reference Manual).

- Daily voluntary physical activity will be recorded for the first 9 days of Cycle 2 at participating sites using SAM accelerometer (Group III only). Patients will use the same SAM device worn previously (identified by the label on the device). The accelerometer needs to be put on at the clinic, and the site staff needs to check that the accelerometer blinks once for every stride the patient takes (ask patient to take 10-15 strides and make sure it blinks every time the leg with monitor on it is used) and the patient should wear it every day from that day on according to the instructions. Patients will be given a SAM diary to record when the device was put on and removed each day. If the device is not worn, the diary must be marked "not worn" for that day. Patient needs to be reminded to wear the device except while sleeping at night or bathing. Patients should also be supplied with pre-labeled priority overnight envelopes to ship the SAM accelerometer and the SAM diary back to the site after the 9-day monitoring period has ended. The day of this visit is Day 1 on the SAM 9-day clock. Detailed instructions are provided in the Reference Manual.

- Administration of the morning dose of INCB018424.
- Vital signs collected 1 to 4 hours post-dose.
- PK blood sample to be taken 2 hours post dose, exact time to be recorded.
- A study medication tablet count will be done to assess compliance.
- Platelet count, ANC level, spleen size and overall symptomatic improvement should be reviewed, and dose adjustments planned where appropriate based on Section 5.3, Dose Adjustments.
- Study medication for the next 28 days will be dispensed to qualified patients who have not met any interruption criteria (Section 10.4).
- Patient diary will be reviewed and returned for recording of observations.
- Review of any adverse events.
- Patients will be asked to return to the clinic on Day 1 of Cycle 3 (Day 28 of Cycle 2 ± 3 days). Patients will be asked to bring all study medication and the diary with them to the visit. Patients will be asked to withhold their morning dose of study medication on Day 1 of Cycle 3.

7.3.2.2.2 Part 3 Cycle 3 Day 1 ± 3

The following procedures will be performed:

- EORTC QLQ-C30 questionnaire must be completed by the patient consistent with the EORTC guideline or standard guideline for completion of QOL questionnaires (see Appendix XI).
- MFSAF questionnaire must be completed by the patient consistent with the standard guideline for completion of QOL questionnaires (see Appendix XII).

Note: Completed EORTC and MFSAF must be placed in a sealed envelope. Where feasible the EORTC QLQ-C30 and MFSAF questionnaire should be administered prior to any study- specific procedures.

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Targeted physical (symptom directed) examination and vital signs.
- ECOG performance status.
- Overall response assessment (IWG-MRT).
- 12-lead ECG after 5 minutes of rest.
- Urine collection for urinalysis and pregnancy test on females of childbearing potential only. If urine pregnancy test is positive, then serum pregnancy test will be done.
- Blood sampling for the following:
  - Serum chemistry tests, CBC, PT, PTT and CD34+
  - PD marker sample collection pre-dose
- Blood collection for quantitative molecular test JAK2 mutation (Appendix X) for patients with positive results at Screening.
- Administration of the morning dose of INCB018424.
- A study medication tablet count will be done to assess compliance.
- Platelet count, ANC level, spleen size and overall symptomatic improvement should be reviewed, and dose adjustments planned where appropriate based on Section 5.3, Dose Adjustments.
- Study medication for the next 28 days will be dispensed to qualified patients who have not met any interruption criteria (Section 10.4).
- Patients will be asked to return to the clinic on Day 1 of Cycle 4 (Day 28 of Cycle 3 ± 3 days). Patients will be asked to bring all study medication with them to the visit. Patients will be asked to withhold their morning dose of study medication on Day 1 of Cycle 4.

Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.

7.3.2.2.3 Part 3 Cycles 2 and 3, All Other Days

- Patients will be instructed to have the following tests done at their local clinical laboratory at the frequency listed below:
  - CBC, weekly ie, Days 8, 15 and 22 of both Cycles 2 and 3.
  - Serum chemistry, every two weeks ie, Day 15 of both Cycles 2 and 3.
- During Cycle 2, patients (Group III) will return the SAM accelerometer and the SAM diary to the clinical site using the pre-labeled priority overnight envelope supplied at the last visit. Site coordinators will download the data according to the Reference Manual.
- Investigators will review all safety information and criteria for dose interruptions and dose adjustments (Section 10.4, Section 5.3) to determine if dose modifications or interruptions are required. The Investigator and/or research staff will immediately contact the patient to notify him/her to interrupt or reduce the study medication if the laboratory test results meet these criteria.
- Patients will continue to self-administer study medication per instructions daily corresponding with their dosing regimen at approximately 24-hour interval or 12-hour interval consistent with the current modified dose level or based on their schedule or group of enrollment in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.3.2.3 Part 3 Cycle 4

7.3.2.3.1 Part 3 Cycle 4, Day 1 ± 3

Patients will return to the study site on Day Cycle 4 Day 1 having fasted since 12 midnight. The patient should avoid strenuous exercise and alcohol consumption on the day prior to the visit. The required procedures may need to be scheduled over a 1 to

4 day period (or longer if approved by the sponsor). A light meal or snack should be provided to patients 1 hour prior to the 6MWT and grip strength assessment (Group III only). Eligibility Criteria for the 6MWT must be consulted prior to the test (Section 6.3). The following procedures will be performed:

- Review of medical history and concomitant medication.
- Body composition testing should begin as soon as the patient arrives at the clinic, having fasted since midnight (Group III only). The testing will consist of recording a body weight, and measuring body water using a tracer dilution method. Following the initiation of the test (see Appendix XIII) the patient must refrain from consumption of any food or beverages (including water) for a 3-hour period. The patient can undergo normal activity and other non-invasive tests during this time. Following the conclusion of the test, the patient can resume eating and drinking *ad libitum*.
- EORTC QLQ-C30 questionnaire must be completed by the patient consistent with the EORTC guideline or standard guideline for completion of QOL questionnaires (see Appendix XI).
- MFSAF questionnaire must be completed by the patient consistent with the standard guideline for completion of QOL questionnaires (see Appendix XII).

Note: Completed EORTC and MFSAF must be placed in a sealed envelope. Where feasible the EORTC QLQ-C30 and MFSAF questionnaire should be administered prior to any study- specific procedures.

- Targeted physical (symptom directed) examination.
- Subjects who consent to having portions of their muscles or body photographed will have these pictures taken.
- ECOG performance status.
- Overall response assessment (IWG-MRT).
- Vital signs will be taken.

- 12-lead ECG after 5 minutes of rest.
- Urine collection for urinalysis and pregnancy test on females of childbearing potential only. If urine pregnancy test is positive, then serum pregnancy test will be done.
- Blood sampling for the following:
  - Serum chemistry tests, CBC, PT, PTT and CD34+
  - PD marker sample collection pre-dose
- Blood collection for quantitative molecular test JAK2 mutation (Appendix X) for patients with positive results at Screening.
- Bone marrow aspiration, biopsy, JAK2 mutation assay and cytogenetics will be performed.
- MRI of the spleen, liver, and left thigh will be performed on a subset of up to 20-25 patients (Group III only). Depending upon emerging data, this subset could be expanded, but will not exceed 50 patients.
- Provide a light meal or snack 1 hour prior to the 6MWT and grip assessment (Group III only).
- 6MWT will be performed by patient after 10 minutes of rest in the seated position (Group III only). Vital signs (HR and BP only) will be collected 5 minutes prior to the walking test.
- A calibrated Jamar Hand Dynamometer will be used to measure grip strength in the dominant arm in the standardized recommended position (Group III only). Grip strength will be measured three times consistent with manufacturer's user manual, and the average value of the measurements will be used for data analysis.
- Daily voluntary physical activity will be recorded for the first 9 days of Cycle 4 at participating sites using SAM accelerometer (Group III only). Patients will use the same SAM device worn previously (identified by the label on the device). The accelerometer needs to be put on at the clinic, and the site staff needs to

check that the accelerometer blinks once for every stride the patient takes (ask patient to take 10-15 strides and make sure it blinks every time the leg with monitor on it is used). Patients will be given a SAM diary to record when the device was put on and removed each day. If the device is not worn, the diary must be marked "not worn" for that day. Patient needs to be reminded to wear the device except while sleeping at night or bathing. Patients should also be supplied with pre-labeled priority overnight envelopes to ship the SAM accelerometer and SAM diary back to the site after the 9-day monitoring period has ended. The day of this visit is Day 1 on the SAM 9-day clock. Detailed instructions are provided in the Reference Manual.

- Administration of the morning dose of INCB018424.
- A study medication tablet count will be done to assess compliance.
- Platelet count, ANC level, spleen size and overall symptomatic improvement should be reviewed, and dose adjustments, including implementation of maintenance dosing planned where appropriate based on Section 5.3, Dose Adjustments.
- Three-28-day cycle supplies of study medication will be dispensed to qualified patients who have not met any interruption criteria (Section 10.4).
- Patient diary will be reviewed and returned. The diary will also include instructions on dosing and contact information for the Investigator and/or designated research staff.
- Review of any adverse events.
- Patients will be instructed to go every two weeks ie, Day 15 of Cycle 4, Day 1 of Cycle 5, Day 15 of Cycle 5, etc for the next three 28-day cycles to their local laboratory to have blood drawn for CBC, differential and platelets. Patients will be asked to continue the use of the same local laboratory for their off-site laboratory testing.

- Patients will be instructed to return to the site every three 28-day cycles (± 5 days) following Day 1 of Cycle 4 and to bring their study medication including empty containers and the diary with them. Patients should refrain from taking the morning dose of study medication prior to the Cycle 7 Day 1 visit.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.

7.3.2.3.2 Cycle 4, All Other Days

- Patients will be instructed to have the following tests done at their local clinical laboratory at the frequency listed below:
  - CBC, differentials and platelets on day 15 of Cycle 4
- Patients (Group III only) will return the SAM accelerometer and the SAM diary to the clinical site using the pre-labeled priority overnight envelope supplied at the last visit. Site coordinators will download the data according to the Reference Manual.
- Investigators will review all safety information and criteria for dose interruptions and dose adjustments (Section 10.4, Section 5.3) to determine if dose modifications or interruptions are required. The Investigator and/or research staff will immediately contact the patient to notify him/her to interrupt or reduce the study medication if the laboratory test results meet these criteria.
- Patients will continue to self-administer study medication per instructions daily corresponding with their dosing regimen at approximately 24-hour interval or 12-hour interval consistent with the current modified dose level or based on their group of enrollment in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.3.3 Part 3 Subsequent Visits (every third Cycle after Cycle 4)

7.3.3.1 Part 3 Each Subsequent Visit, Day 1 ± 5

Study visit specific observations are outlined in the "Schedule of Observations" for each subsequent visit Day 1. Each subsequent visit comprises three 28-day cycles (ie, Cycle 7, Cycle 10, Cycle 13, etc).

At Cycle 7, Day 1, Patients will return to the study site having fasted since 12 midnight. The patient should avoid strenuous exercise and alcohol consumption on the day prior to the visit. The required procedures may need to be scheduled over a 1 to 4 day period (or longer if approved by the sponsor). A light meal or snack should be provided to patients 1 hour prior to the 6MWT and grip strength assessment (Group III only, C7D1 only). Eligibility Criteria for the 6MWT must be consulted prior to the test (Section 6.3). The following procedures will be performed:

- Review of medical history and concomitant medication.
- Body composition testing should begin as soon as the patient arrives at the clinic, having fasted since midnight (Group III only). The testing will consist of recording a body weight, and measuring body water using a tracer dilution method. Following the initiation of the test (see Appendix XIII) the patient must refrain from consumption of any food or beverages (including water) for a 3-hour period. The patient can undergo normal activity and other non-invasive tests during this time. Following the conclusion of the test, the patient can resume eating and drinking *ad libitum*. Body composition testing will not continue beyond the C7D1 visit.
- EORTC QLQ-C30 questionnaire must be completed by the patient consistent with the EORTC guideline or standard guideline for completion of QOL questionnaires (see Appendix XI).
- MFSAF questionnaire must be completed by the patient consistent with the standard guideline for completion of QOL questionnaires (see Appendix XII).

Note: Completed EORTC and MFSAF must be placed in a sealed envelope. Where feasible the EORTC QLQ-C30 and MFSAF questionnaire should be administered prior to any study- specific procedures.

- Targeted physical (symptom directed) examination and vital signs. NOTE: coordinate vital signs with 6MWT.
- ECOG performance status.
- Overall response assessment (IWG-MRT).
- Vital signs will be taken.
- 12-lead ECG after 5 minutes of rest.
- Urine collection for urinalysis and pregnancy test on females of childbearing potential only. If urine pregnancy test is positive, then serum pregnancy test will be done.
- Blood sampling for the following:
  - Serum chemistry tests, CBC, PT, PTT and CD34+
  - PD marker sample collection pre-dose
- Bone marrow aspiration, biopsy, JAK2 mutation assay and cytogenetics will be performed.
- MRI of the spleen, liver, and left thigh will be performed on a subset of up to 20-25 patients (Group III only). Depending upon emerging data, this subset could be expanded, but will not exceed 50 patients. MRI of the spleen and liver (but not the thigh) will be performed at visits C7D1, C13D1, C19D1, and every 6 months in subjects with Baseline MRI, who sign consent for additional MRI assessments beyond C7D1. Subject who do not sign consent for additional MRI are not precluded for continued participation in the study.
- Provide a light meal or snack 1 hour prior to the 6MWT and grip assessment (Group III only).

- 6MWT to be performed by the patient after 10 minutes of rest in the seated position (Group III only). Vital signs (HR and BP only) will be collected 5 minutes prior to the walking test. 6MWT will not be performed beyond the C7D1 visit.
- A calibrated Jamar Hand Dynamometer will be used to measure grip strength in the dominant arm in the standardized recommended position (Group III only). Grip strength will be measured three times consistent with manufacturer's user manual, and the average value of the measurements will be used for data analysis. Grip strength will not be assessed beyond the C7D1 visit.
- Daily voluntary physical activity will be recorded for the first 9 days of Cycle 7 at participating sites using SAM accelerometer (Group III only). Patients will use the same SAM device worn previously (identified by the label on the device). The accelerometer needs to be put on at the clinic, and the site staff needs to check that the accelerometer blinks once for every stride the patient takes (ask patient to take 10-15 strides and make sure it blinks every time the leg with monitor on it is used). Patient will be given a SAM diary to record when the device was put on and removed each day. If the device is not worn, the diary must be marked "not worn" for that day. Patient needs to be reminded to wear the device except while sleeping at night or bathing. Patients should also be supplied with priority overnight pre-labeled priority overnight envelope to ship the SAM accelerometer and the SAM diary back to the site after the 9-day monitoring period has ended. The day of this visit is Day 1 on the SAM 9-day clock. Detailed instructions are provided in the Reference Manual. SAM activity monitoring will not be performed beyond the C7D1 visit.
- Administration of the morning dose of INCB018424.
- A study medication tablet count will be done to assess compliance.
- Platelet count, ANC level, spleen size and overall symptomatic improvement should be reviewed, and dose adjustments, including maintenance dose

implementation planned where appropriate based on Section 5.3, Dose Adjustments.

- Three-28-day cycle supplies of study medication will be dispensed to qualified patients who have not met any interruption criteria (Section 10.4).
- Patient diary will be reviewed and returned for recording of observations.
- Review of any adverse events.
- Patients will be instructed to return to the site every three 28-day cycles (± 5 days) following Day 1 of Cycle 7 and bring their study medication including empty containers and the diary with them.
- Patients will be instructed to go every two weeks ie, Day 15 of each subsequent cycle, for the next three 28-day cycles to their local laboratory to have blood drawn for CBC.
- Patients will be asked to withhold their morning dose of study medication on Day 1 of each subsequent visit.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.

At all subsequent visits (ie, Cycle 10, Cycle 13, etc.) the following will be performed:

- Bone marrow aspiration, biopsy, JAK2 mutation assay and cytogenetics will be done on each sixth succeeding cycle (ie, Cycle 13, Cycle 19, etc).
- Blood sample collection for PD analysis at each scheduled visit
- Patients will remain on their respective dosing regimen in accordance with their regimen or dose modification. Platelet count, ANC level, spleen size and overall symptomatic improvement should be reviewed, and dose adjustments, including maintenance dose implementation planned where appropriate based on Section 5.3, Dose Adjustments.

- Three-28-day cycle supplies of study medication will be dispensed to qualified patients who have not met any interruption criteria (Section 10.4).
- Patients will be instructed to return to the site every three 28-day cycles (± 5 days) following Day 1 of Cycle 4 and bring their study medication including empty containers and the diary with them.
- Patient diary will be reviewed and returned. Patients will be provided with a new diary at each subsequent Day 1 visit to record observations. The diary will also include instructions on dosing and contact information for the Investigator and/or designated research staff.
- Patients will be instructed to go every two weeks ie, Day 15 of each subsequent cycle, for the next three 28-day cycles to their local laboratory to have blood drawn for CBC.
- Patients will be asked to withhold their morning dose of study medication on Day 1 of each subsequent visit.
- Patients will be instructed to call the Investigator or designated research staff if they experience any signs and/or symptoms that are of moderate or greater severity.

On Day 1 of each second Study Visit beginning with Cycle 13, in other words, Cycle 19, Cycle 25, Cycle 31, and every 6 28-day cycles, subjects who had a Baseline MRI, and sign an additional consent for further MRI monitoring will undergo additional MRI of the spleen and liver (not of the thigh). These additional MRIs should be scheduled to occur ± 8 weeks from the C13D1, C19D1, C25D1, C31D1, and every 6th 28-day cycle visits. Not signing the consent for additional MRI monitoring will not preclude a subject's participation in the study.

7.3.3.2 Part 3 Each Subsequent Visit – All Other Days

- During Cycle 7, patients (Group III only) will return the SAM accelerometer and the SAM diary to the clinical site using the pre-labeled priority overnight

envelope supplied at the last visit. Site coordinators will download the data according to the Reference Manual.

- Investigators will review all safety information and criteria for dose interruptions or modification (Section 10.4, Section 5.3) on a regular and ongoing basis to determine if dose modifications or interruptions are required. The Investigator and/or research staff will immediately contact the patient to notify him/her to interrupt or reduce the study medication if the laboratory test results meet these criteria.
- The Investigator and/or research staff will contact the patient on a regular monthly basis to assess the patient's overall well-being, any new or worsening signs and/or symptoms, compliance with study medication and dosing instructions, compliance with the local laboratory schedule and to answer any questions that the patient might have. The Investigator and/or research staff will remind the patient of their next scheduled visit and how to prepare for it (ie, withhold their morning dose of study medication). The research staff will send a notification card to the patient to remind them of the date and time of their next scheduled visit to the clinic. The Investigator and research staff will be responsible for ensuring that all relevant information resulting from these monthly contacts is documented in the patient's medical record and case report form, as appropriate.
- Patients will continue to self-administer study medication as instructed once or twice daily based on the dosing schedule, at approximately 24 or 12 hour intervals in accordance with their schedule or group of enrollment in an outpatient setting. Patients will record any signs and/or symptoms on the diary provided.

7.3.4 Part 3 End of Study or Early Termination Visit

The following procedures will be performed:

- EORTC QLQ-C30 questionnaire must be completed by the patient consistent with the EORTC guideline or standard guideline for completion of QOL questionnaires (see Appendix XI).

- MFSAF questionnaire must be completed by the patient consistent with the standard guideline for completion of QOL questionnaires (see Appendix XII).

Note: Completed EORTC and MFSAF must be placed in a sealed envelope. Where feasible the EORTC QLQ-C30 and MFSAF questionnaire should be administered prior to any study- specific procedures.

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Complete physical examination and vital signs. .
- ECOG performance status.
- 12-lead ECG after 5 minutes of rest.
- Urine collection for urinalysis and pregnancy test on females of childbearing potential only. If urine pregnancy test is positive, then serum pregnancy test will be done.
- Blood sampling for the following:
  - Serum chemistry tests, CBC, PT, PTT and CD34+
  - PD marker sample collection pre-dose
- Overall response assessment (IWG-MRT).
- Blood collection for quantitative molecular test JAK2 mutation (Appendix X) for patients with positive results at Screening.
- A study medication tablet count will be done to assess compliance.
- Patients will be asked to return to the clinic 30 to 35 days later for a final Follow-up Visit.

7.3.5 Part 3 Follow-up Visit

All enrolled patients are required to have a Follow-up visit. Follow-up visit interval will be determined from the End-of-Study Visit or the last actual dose of the study drug for

patients who were discontinued using the tapering strategy. The following evaluations will be performed 30 to 35 days after the completion of the End of Study or early termination visit:

- EORTC QLQ-C30 questionnaire must be completed by the patient consistent with the EORTC guideline or standard guideline for completion of QOL questionnaires (see Appendix XI).
- MFSAF questionnaire must be completed by the patient consistent with the standard guideline for completion of QOL questionnaires (see Appendix XII).

Note: Completed EORTC and MFSAF must be placed in a sealed envelope. Where feasible the EORTC QLQ-C30 and MFSAF questionnaire should be administered prior to any study specific procedures.

- Review of medical history and concomitant medication.
- Review of any adverse events.
- Complete physical examination and vital signs.
- ECOG performance status.
- Urine collection for urinalysis and pregnancy test. If positive then serum pregnancy test will be done.
- Blood sampling for serum chemistry tests, CBC, differentials, platelets and CD34+.

7.4 Duration of Participation

The individual patient participation is expected to be approximately 12-24 months; patients may continue on therapy indefinitely if they do not meet any of the withdrawal criteria, do not have disease progression and are receiving some clinical benefit.

8.0 STUDY ASSESSMENTS

8.1 Symptom and Functional Response Assessments

See Section 5.4, Response Assessments for descriptions of planned efficacy assessments and measures.

8.2 Order of Assessments

Multiple assessments are scheduled simultaneously during the treatment period; at study visits where body composition, MRI, 6MWT and grip strength are to be assessed, it is likely that the assessments may need to be scheduled over a one to four day period of time. In order to standardize the study visits, a suggested order of assessments is implied by the ordering of events in the visit descriptions in Section 7.3. Body composition, when analyzed must occur early in the visit since fasting before the procedure and until its completion is required. In order to standardize the previous meal time prior to the 6MWT and grip assessment, a light meal or snack must be provided to the patients 1 hour prior to these assessments. Dosing will occur after these two assessments. In general, vital signs and ECGs should occur prior to blood draws. At all time points, the PK and PD blood samples should be obtained at the scheduled time relative to when the patient was dosed, and the actual time of each dose and blood sampling should be recorded as instructed.

8.3 Clinical Laboratory Assessments

After written informed consent is obtained, demographic data and a complete medical and medication history will be collected at Screening. Height and body weight measurements will be done. Intercurrent illnesses will be updated up until the first dose of study medication, after which adverse events will be recorded.

8.4 Clinical Laboratory Assessments

Site associated laboratory will be used to perform testing for serum and urine chemistry, pregnancy, serology, hematology and coagulation testing. The laboratory's specific procedures will be used for collection, handling, shipment, and processing of blood

samples for this testing. Appendix III provides a complete list of blood chemistry and hematology tests that will be performed.

8.4.1 Pregnancy Test

Blood will be collected during Screening for females of childbearing potential to conduct a pregnancy test to evaluate eligibility. An FSH test will be performed on females who have been amenorrheic for > 1 year. If FSH levels are elevated to post-menopausal range, no further pregnancy testing is required for these female patients. A urine pregnancy test will be performed as in the Schedule of Observations. A positive urine pregnancy test will be confirmed with a serum pregnancy test. Pregnancy status will be documented at each visit when the test is performed, including the Follow-Up Visit.

8.4.2 Serology

Appendix III provides a complete list of serology tests to be performed at the Screening Visit.

8.4.3 Urine Sampling

Appendix III provides a complete list of urinalysis to be performed.

8.5 Physical Examinations

A comprehensive physical examination will be performed at Screening, End of Study and at Follow-up Visits. The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose and throat; thyroid; lungs; cardiovascular; abdomen (liver, spleen); lymph nodes; neurological examination and extremities. The targeted physical examination will always include liver and spleen; in addition it will include assessments of the body systems or organs as indicated by patient symptoms, AEs, prior physical examinations, or other findings as determined by the Investigator.

8.6 Vital Signs

Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature) will be collected on the days and times noted in the Schedule of Observations. Vital signs will be taken with the patient in the sitting position after 5 minutes of rest. Vital signs (BP and HR only) will be taken just prior to the 6MWT. The vital signs will be taken pre-dose and once between 1 and 4 hours morning post-dose during Cycle 1 when PK samples are collected. Vital signs must be repeated between successive 6MWT assessments that are performed on the same day. On all other clinic visits, vital signs will be taken once. Body temperature may be measured orally or via the ear.

8.7 Pharmacokinetic Methods

8.7.1 Blood Collection

For Part 1 and 2, pharmacokinetic blood samples will be obtained pre-dose, 0.5, 1, 1.5, 2, 4, 6 and 9 hours after administration of the morning dose of the study medication in accordance with the Schedule of Observations.

For Part 3, PK samples will be obtained pre-dose and 2 hours after administration of the morning dose of the study medication in accordance with the Schedule of Observations. The exact date and time of the PK blood draws will be recorded along with the date and time of the last dose of study medication preceding the blood draw.

See Appendix IV for specific information regarding the procedures for PK blood sample collection, processing and shipment.

8.7.2 Bioanalytical Methodology

The plasma samples will be analyzed for INCB018424 by a validated LC/MS/MS assay, carried out by Incyte Corporation (Wilmington, DE) or Incyte's designee.

8.7.3 Pharmacokinetic Parameter Assessment

The following parameters will be calculated using non-compartmental PK methods:

C_{max} Maximum observed plasma concentration

T_{max} Time to maximum plasma concentration

C_{min} Minimum (trough) observed plasma concentration

$t_{½}$ Apparent elimination half-life

AUC_{0-t} Area under the steady-state plasma concentration-time curve from time zero to the time of the last sample obtained

Pharmacokinetic calculations will be performed using commercial software such as WinNonlin (Pharsight Corporation, Version 5.0.1 or greater). Nominal times will be used in all cases, except when the difference between the actual time and nominal time is greater than 15 minutes for samples collected up to 4 hours after administration and greater than 30 minutes for samples collected more than 4 hours after administration; in these cases actual time will be used for the PK analysis.

8.7.4 Population Pharmacokinetic Analysis

If there is a sufficient amount of plasma concentration data from this study, the data will be analyzed by standard population PK methods, using appropriate software (eg, WinNonLin). If there is only a limited amount of plasma concentration data from this study, then the data may be pooled with the results of a Phase 1 study in healthy volunteers to perform the population PK analysis. If there is sufficient demographic diversity in the population, an attempt will be made to evaluate the effect of demographic characteristics and baseline characteristics (eg, age, weight, sex, race, renal function, smoking history) on the population PK profile.

8.8 Pharmacodynamics Method

8.8.1 Blood Collection for PD Assay

For Part 1, venous whole blood samples will be obtained on Cycle 1 Days 1 and 15 at pre-dose, 2, 6 and 9 hours following administration of the morning dose of study medication and pre-dose on Cycle 2 Day 1, Cycle 3 Day 1, pre-dose at each subsequent visit and at End of Study in accordance with the Schedule of Observations Chart.

For Part 2 Schedules A, B, C, venous whole blood samples will be obtained pre-dose on Cycle 1 Day 1, at pre-dose, 2 and 6 hours post-dose on Cycle 1 Day 15, predose on Cycle 2 Day 1, Cycle 3 Day 1 and at each subsequent visit and at End of Study per the respective Schedule of Observations Flow Chart. The exact date and time of the blood draws will be recorded along with the date and time of the last dose of study medication preceding the blood draw. Additional pharmacodynamic markers may be evaluated at the discretion of the Sponsor utilizing excess PK samples.

In Part 3, plasma samples will be collected at Screening, Cycle 1 Day 1 predose and then at each clinic visit and at the End-of Study visit for analysis of plasma PD markers. Additional pharmacodynamic markers may be evaluated at the discretion of the Sponsor utilizing excess PK samples. See Appendix V for specific information regarding the procedures for PD blood sample collection, processing and shipment.

8.8.2 Pharmacodynamic Analysis

The whole blood samples will be evaluated both unstimulated and following stimulation with a cytokine (eg, IL-6, GM-CSF) to activate the JAK/STAT pathways and then analyzed for both basal and activated levels of JAKs and STATs, including phosphorylated STAT3 and STAT5. Phosphorylated STAT3 and STAT5 will be measured using phospho-specific STAT3 and STAT5 ELISAs. For each patient, the percent inhibition of phosphorylated STAT3 and/or STAT5 will be calculated on Day 1 by comparing predose values with values obtained at different times after dose.

Additional PD markers (eg, other kinases, cytokine levels, chemokine levels or other non-genomic protein markers that can measured by Western blot or ELISA) may be evaluated at the discretion of the Sponsor utilizing excess PD or PK samples. These analyses will be carried out by Incyte Corporation (Wilmington, DE) or Incyte's designee. Analysis of plasma samples for changes in levels of cytokines (eg, IL-6), chemokines (eg, MCP-1), growth factors (eg, erythropoietin), soluble receptors (eg, TNFRII) and acute phase proteins (eg, C-reactive protein) will be conducted using multiplexed immunoassays and/or ELISAs. For each patient, the percent change will be calculated by comparing predose values on Day 1 with values obtained at different times after dose

8.9 Bone Marrow Aspiration, Biopsy and Cytogenetics

Bone marrow aspiration and biopsy will be taken pre-dose during the screening phase and at Day 1 ± 7 days of Cycle 4, Day 1 of Cycle 7 ± 7 days and thereafter on Day 1 ± 7 days of each sixth subsequent cycle for patients enrolled in Part 1, Part 2 and Part 3. This includes staining for fibrosis and determination of cytogenetics if abnormal prior to therapy. Collection, processing of bone marrow aspirations and biopsy samples will be done in accordance with standard procedures at the investigative site.

8.9.1 Bone Marrow Biopsy and Aspirate Assessment

The bone marrow biopsy and aspirate should be assessed by an experienced hematopathologist using his/her standard examination. Bone marrow evaluation will include staining for fibrosis, cytogenetics if abnormal prior to therapy and JAK2 mutation analysis if present prior to therapy. Bone marrow fibrosis should be graded using the European consensus grading system (Barosi et al, 1999; Tefferi et al, 2006). During or following the study conduct, at the Sponsor's discretion, a central review of any or all of the bone marrow studies may be conducted by external expert(s) in hematopathology.

8.9.2 Cytogenetics

Cytogenetic studies will be repeated only in patients with abnormalities at baseline. This will be generally done on the bone marrow samples provided at the defined time points

but may also be done on peripheral blood collected at these time points in the event bone marrow aspirate could not be obtained.

8.9.3 Quantitative JAK2 Mutation Assay

JAK2 mutation (V617F) will be determined using a validated available assay on bone marrow as well as peripheral blood.

8.10 Clinical Safety Assessments

8.10.1 Electrocardiograms (ECGs)

12-lead ECGs will be obtained for each patient during the study as per the Schedule of Observations. Baseline ECGs will be obtained at Screening. All 12-lead ECGs obtained at subsequent time points during the study will be compared with the baseline 12-lead ECGs as follows:

- For ECG morphology, all postdose ECG recordings will be compared to Day 1 predose ECG.
- For the calculation of changes in cardiac intervals (QT interval), the intervals from the Screening and Day 1 pre-dose ECGs will be computed and averaged, and used as the baseline for comparison of all post-dose intervals.

12-lead ECGs will be acquired using an ECG analysis system with analysis and printing capabilities, as well as digital transmission capabilities to a central capture module at the central ECG laboratory. The Investigator and research staff will receive adequate training by a qualified person on the use and operation of the analysis system. The successful digital submission of a 12-lead ECG, meeting quality standards, to the central ECG laboratory by the site must be ensured prior to enrollment of the first patient.

The study manual for procedures that must be followed for the recording and transmission of ECGs and the operator's manual with instructions for operating the digital capture module will be shipped to the site along with the device.

8.10.2 ECG Analysis and Reporting

The Investigator or another appropriately trained individual will perform the initial ECG analysis of the data collected for each patient. ECG data will be sent to the central ECG laboratory for their review. ECGs transmitted to the central laboratory will be analyzed by a cardiologist and reported back to the sites via FAX. The original ECG reports will be sent by a traceable carrier to the Sponsor on a monthly basis. All ECGs will be analyzed according to ECG Abnormality Criteria defined in cooperation with the Sponsor and taking into account the protocol requirements.

The overall ECG interpretation will be indicated by a flagging system which will help distinguish between a normal ECG, ECG abnormalities where no further investigation is required, and ECG abnormalities where trial exclusion, further cardiovascular investigation, and/or prompt action may be necessary depending on the clinical context. A suitable flag will be included in the "Overall ECG Interpretation" section of the report when an ECG is considered to be technically unacceptable or un-interpretable. If several different abnormalities exist corresponding to different levels of flagging, the label will reflect the most severe level.

The decision to include/exclude a patient or discontinue a patient's participation in the study that has an ECG flagged as "Abnormal, Significant" is the responsibility of the Investigator, in consultation with the Sponsor, as appropriate. Flagging by the central expert cardiologist of these significant abnormalities should only be regarded as a suggestion. This service is intended to assist the Investigator in his/her interpretation of the ECG and decision-making. It is not intended to replace the Investigator's expert judgment and knowledge of the patient's medical condition.

Twelve-lead ECGs that are identified by the Investigator as "Abnormal, Significant" will also be sent to the Sponsor for review. The following individual will receive a fax copy:

Edward Bradley, MD.
Vice President, Oncology Drug Development
Incyte Corporation
Route 141 and Henry Clay Road
Wilmington, DE 19880
(302) 498-6994 (Office Telephone)
(302) 498 6847 (24 hour coverage)
(302) 425-2766 (FAX)
ebradley@incyte.com (E-Mail)

9.0 SELECTION AND WITHDRAWAL OF PATIENTS

9.1 Selection and Enrollment of Patients

Once written informed consent has been obtained and a patient has met all inclusion criteria and none of the exclusion criteria, the patient may be enrolled in the study.

9.2 Withdrawal Criteria and Procedures

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

A patient may be discontinued from the study, if in the Investigator's medical judgment, the patient is non-compliant with the study requirements, or in the Investigator's medical judgment, further participation would be injurious to the patient's health or well-being. When a decision is made to discontinue the therapy, it is recommended that tapering of the INCB018424 be considered based on the investigator's clinical judgment. If a decision has been made to discontinue the patient without a taper and anxiety, insomnia, weakness or other untoward symptoms occur which are determined by the investigator to be possibly related to the study drug withdrawal and can be best managed by re-introduction of study drug, then INCB018424 may be restarted up to 2 weeks later in order to institute a tapering strategy to minimize these symptoms (See Sections 5.2.4 Patient Discontinuation and 5.3.4 Dose Tapering Strategy).

When a patient discontinues treatment early, every effort will be made to conduct a post-treatment Follow-Up Visit within 30 to 35 days after the last dose of study medication or prior to the initiation of new treatment. This post-treatment evaluation may be conducted over the phone if the patient is unable to return to the clinic. The reason(s) for withdrawal must be recorded. Criteria for terminating participation in the study are listed below.

The Investigator MUST discontinue a patient from this study if the following occurs:

- The patient becomes pregnant.
- The patient is judged by the Investigator to be at significant risk.
- Progressive disease.
- Unacceptable toxicity.
- Patient withdrawal of consent.
- Investigator's discretion that it is in the best interest of the patient to withdraw.
- Intercurrent illness: a condition, injury, or disease unrelated to MPD, that renders continuing treatment unsafe or regular follow-up impossible.
- Platelet count or ANC levels that continue to remain below the levels required for dose reinitiation after dose holding for 2 months.
- General or specific changes in the patient's condition that renders the patient ineligible for further treatment.
- Noncompliance with study medication or protocol-required evaluations and Follow-Up Visits.
- Termination of the clinical trial by the Sponsor.

In the event that any patient discontinues the study prior to completion, regardless of reason, reasonable efforts should be made to have the patient return for an Early Termination Visit and perform all of the study termination assessments. Due diligence

will be exercised for the patient to return for the Follow-Up Visit. If the patient is not able to return for the visit, then an attempt will be made to review any AEs via a telephone contact.

In the case that a patient becomes pregnant while participating in the study, the patient will be withdrawn from the study, and will be followed to determine the outcome of the pregnancy (see Section 11.1.3).

If a patient is withdrawn from the study:

- The study monitor (Sponsor) must be notified.
- The reason(s) for withdrawal must be documented in the patient's medical record and CRF.
- An Early Termination Visit is to be performed.
- All patients must be followed for safety until the time of the Follow-Up evaluation or until study medication related toxicities resolve, whichever is longer.

9.3 Replacement Patients

There will be no replacement for patients who have experienced a DLT. Patients who terminate the study within the first 28 days (1-cycle) in Part 1 or Part 2, Schedule A without experiencing a DLT, or without receiving the study drug, may be replaced. Patients who discontinue the study may be replaced at the Sponsor's discretion to ensure that at least 3 to 6 evaluable patients per cohort complete the first 28-day (Cycle 1) of the Part 1 or Part 2, Schedule A of the study. Patients, who terminate the study in Part 2, Schedules B within first 12-weeks and C within first 8-weeks of enrollment without experiencing a DLT, or without receiving the study drug, may be replaced at Sponsor's discretion. Patient replacement is not allowed during Part 3.

9.4 Protocol Deviations

Any relevant deviation from the protocol or Statistical Analysis Plan will be documented (including rationale) and summarized in the final Clinical Study Report.

10.0 TREATMENT OF PATIENTS

10.1 Investigational Product(s) Description

The characteristics of INCB018424 phosphate tablets are provided in Section 3.2 of this protocol.

10.1.1 Dosage and Dose Regimen

INCB018424 tablets will be administered as an oral dose with water in an outpatient setting in accordance with specified dosing schedules. The dosage strength is 5 and 25 mg/tablet INCB018424 phosphate (free base equivalent). Administration instructions will be provided at Study Visits. The administration instructions will state that medication is "For Investigational Use Only".

10.1.2 Packaging and Labeling

INCB018424 5 and 25 mg tablets are packaged as 35 count in HDPE bottles. The bottles will include labeling "New Drug - Limited by Federal (USA) Law to Investigational Use Only".

10.1.3 Storage

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

10.1.4 Drug Accountability

Responsibility for drug accountability at the study site rests with the Investigator; however, the Investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be readily

available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

The Investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study medication until the end of the study. The Investigator or designee must maintain records that document investigational product delivery to the study site, the inventory at the site, use by each patient from each supply dispensed based on tablet count, and the return to the Investigator or designee. These records should include dates, quantities, batch/serial numbers (if available), retest dates (as required), and any unique code numbers assigned to patients participating in the study.

The Investigator must ensure that the investigational product is used only in accordance with the protocol. The Investigator will also maintain records adequately documenting that the patients were provided the study medication specified and reconciling all investigational products that were received.

In order to determine study medication use by patients, tablets will be counted on Day 1 of each cycle or on Day 1 of every scheduled subsequent visit during the treatment phase of the trial.

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 medication back to the Sponsor or Sponsor's designee for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from Incyte.

10.2 Preparation of Study Medication(s)

No preparation of study medication(s) is necessary.

10.3 Administration of Study Medication(s)

Patients will self-administer the study medication. On days when PK and PD blood samples are to be collected, patients' medication will be administered at the site in the morning to allow a pre-dose blood draw. All other dosing will be in an outpatient setting.

10.4 Dose Interruption of Study Medication

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse experiences that may have an unclear relationship to study medication. Study medication may be held by the Investigator at any time if there is concern about patient safety. When a decision is made to interrupt the therapy, it is recommended that tapering of the INCB018424 be considered based on patient's condition and the investigator's clinical judgment (See Section 5.2.4 Patient Discontinuation and 5.3.4 Dose Tapering Strategy).

Dosing must be interrupted immediately if either of the following occur:

- Platelet counts fall below 50 K/μL
- ANC levels fall below 500/μL

Dosing may be reinstated following dose holding using the re-start schema detailed in Section 5.3, Dose Adjustments. In order to provide sufficient data to make the dose adjustment decisions, it is recommended that CBCs be obtained at least weekly for platelet count $<100 \times 10^9$/L or ANC $< 1.0 \times 10^9$/L and at least two times weekly for platelet count $< 50 \times 10^9$/L or ANC $< 0.5 \times 10^9$/L.

Drug may be held up to 2 months for platelet or ANC abnormalities but if counts do not return to the level for reinstituting drug by that time, the patient will be discontinued from the study. Similarly, if drug is held for a non-hematologic toxicity for greater than two months, then the patient must be discontinued from the study. Erythropoietin is not allowed during the study. Granulocyte growth factors are not allowed while study medication is being administered but may be used for severe neutropenia at the

Investigator's discretion while study medication is being held. In emergency situations, the investigator may use any treatment to manage life-threatening events including events which may be secondary to discontinuation, interruption or reduction of administration of INCB018424.

10.5 Duration of Treatment

Study medication will be administered in 28-day cycles. Treatment will continue indefinitely unless one or more withdrawal criteria is met or at the Investigator's discretion.

10.6 Concomitant Medications / Measures

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

10.7 Prohibited or Restricted Medications

The following medications are prohibited during the study:

- Granulocyte growth factors are not allowed while study medication is being administered but may be used for severe neutropenia at the Investigator's discretion while study medication is being held.
- Anagrelide and hydroxyurea are not allowed.
- Steroid doses greater than the equivalent of 10 mg prednisone per day, unless part of a dose tapering regimen for a discontinuing subject. During study participation, if a patient requires steroids for a comorbid condition, then continuation in the study will be considered on an individual basis by the Sponsor and the Investigator.
- Erythropoietin is not allowed during the study.

- Any investigational medication other than the study medications. Use of such medications within 14 days or 6 half-lives, whichever is longer, prior to the first dose of study medication and during the study through the Follow-up Visit is prohibited.
- In emergency situations, the investigator may use any treatment to manage life-threatening events including events which may be secondary to discontinuation, interruption or reduction of administration of INCB018424.

The following medications are restricted during the study:

- Drugs that are classified as CYP3A4 and CYP1A2 inhibitors and/or inducers are restricted (Appendix VII). Use of CYP inducers or inhibitors should be avoided but may be permitted if the Investigator and the Sponsor agree. Use of potent CYP inhibitors will require that BID doses of INCB018424 be used on a QD basis (eg, a dose of 20 mg BID will be 20 mg QD) for the duration of concomitant use. Use of CYP inhibitors (including grapefruit juice) will require no dose adjustment.

10.8 Compliance

Study medication compliance will be ascertained by tablet count of study medication at each protocol required clinic visit.

11.0 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event

An adverse event (AE) is any unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the clinical study. Clinically relevant abnormal laboratory findings (eg, requiring unscheduled diagnostic procedures or treatment measures, or resulting in withdrawal from study) are considered to be adverse events. Worsening of a sign or symptom of the condition under treatment

will normally be measured by efficacy parameters. However, if the outcome fulfills the definition of "serious adverse event," it must be recorded as such.

An adverse event may be:

- A new illness
- Worsening of a concomitant illness
- An effect of the study medication, including comparator
- A combination of two or more of these factors.

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term "adverse event."

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of the study treatment. In the latter case, the condition should be reported as medical history.

Worsening of a pre-existing illness other than the disease under study will be assessed as an AE. Worsening of signs or symptoms of the disease under treatment will normally be measured by efficacy parameters. Those that fall within the limits of expected changes for the disease under treatment and that are not assessed as worsening of the disease should not be reported as AEs. However, any change assessed as clinically significant worsening of the disease from baseline must be documented as an AE. In addition, if an AE meets the definition of an SAE, it must be recorded as such.

The intensity of an AE will be graded according to the protocol-defined toxicity criteria based on the NCI-CTCAE v3.0. If the AE term is not included in the CTCAE, the intensity will be graded on a 4-point scale:

- **Mild (Grade 1)**: Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
- **Moderate (Grade 2)**: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.
- **Severe (Grade 3)**: Marked limitation in activity, some assistance usually required; medical intervention/therapy required; hospitalizations possible.
- **Life-threatening (Grade 4)**: Extreme limitation in activity; significant assistance required; significant medical intervention/therapy required; hospitalization or hospice care probable.

The relationship of an AE to treatment will be assessed as follows:

- **Unrelated:** There is not a temporal relationship to the study drug administration or the adverse event is clearly and incontrovertibly due only to progress of the underlying disease, or to extraneous causes.
- **Possible:** The association of the adverse event with the study treatment is unknown; however, the adverse event is not reasonably attributed to any other condition.
- **Probable:** There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge. Rechallenge not required.
- **Definite:** There is a reasonable causal relationship between the study drug and the AE, when the event responds to withdrawal of the study drug (dechallenge), and recurs with rechallenge by administration of the study drug.

For reporting purposes, Incyte also considers the occurrence of overdose (regardless of adverse outcome) as an event that must be reported as important medical events. Adverse events classified as serious must be recorded on the appropriate CRF page and

require expeditious handling and reporting to Incyte or their designee to comply with regulatory requirements.

11.1.2 Serious Adverse Event

A serious adverse event (SAE) is any medical occurrence that:

- Results in death.
- Is life-threatening at the time of the event.
- Requires inpatient hospitalization or prolongation of an existing hospitalization.
- Results in persistent or significant disability/incapacity defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event that, when based upon appropriate medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition for a serious adverse event. (Examples of such events include allergic bronchospasm requiring intensive treatment at an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

"Life threatening" means that the patient was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

11.1.3 Pregnancy

Pregnancy, in and of itself, is not regarded as an adverse event, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive

medication or method. The procedures that will be followed based on whether a pregnancy is confirmed by a positive serum or urine test result are listed below:

Pregnancy Confirmed by a Positive Serum Test Result

- Investigator and patient must notify each other immediately
- Investigator must notify the Sponsor or the Sponsor's designee immediately
- Discontinue study medication immediately
- Withdraw the patient from the study
- Perform the required End-of-Treatment Visit study evaluations
- Investigator must complete and submit the initial and follow-up Pregnancy Report Form to the Sponsor or Sponsor's designee

Pregnancy Confirmed by a Positive Urine Test Result

- Investigator and patient must notify each other immediately
- Investigator must notify the Sponsor or Sponsor's designee immediately
- Study medication must be discontinued immediately
- A serum pregnancy test must be performed to confirm the urine test result. (The serum test should be performed at the investigative site to ensure the test will be performed promptly and the result available immediately for review.)

If a positive serum test confirms the urine test result, then:

- Withdraw the patient from the study
- Perform the required End-of-Treatment Visit study evaluations
- Investigator must complete and submit the required initial and follow-up Pregnancy Report Form to the Sponsor or Sponsor's designee

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

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

Any pregnancy diagnosed during the study, or that occurs within 30 days after stopping study medication, must be reported immediately to the Investigator. The Investigator will notify the Sponsor or Sponsor's designee. The outcome of all such pregnancies (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be documented and followed-up on a Pregnancy Report Form that will be provided by the Sponsor or Sponsor's designee. The pregnancy will be followed to term and the outcome, including any premature termination, must be reported to the Sponsor or Sponsor's designee. All live births must be followed for a minimum of 30 days or to the first well-baby visit. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE for this study. Elective abortion procedures, without complications, should not be considered as adverse events.

11.2 Reporting and Classification

11.2.1 Adverse Event Recording

All identified adverse events must be recorded and described on the appropriate non-serious or serious adverse event page of the CRF. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all adverse events: name of the reporter, an identifiable patient, study product(s), the event name, date of onset and resolution, severity of the event, seriousness of the event and the criteria met if the event is considered serious, Investigator's opinion of the relationship to investigational product, action and treatment required for the adverse event, cause of the event (if known), and information regarding resolution/outcome.

Adverse events fall into the categories of "nonserious" and "serious." All adverse events must be recorded in the CRF, regardless of apparent causality from use of the study treatment. To avoid colloquial expressions, the adverse event should be reported in standard medical terminology and will be coded according to MedDRA. Whenever possible, the adverse event should be evaluated and reported as a diagnosis rather than as individual signs or symptoms. If a definitive diagnosis is not possible, the individual symptoms and signs should be recorded.

Any laboratory abnormalities deemed clinically significant by the Investigator should be reported on the adverse event screen of the CRF. A clinically significant abnormality is a confirmed abnormality (by repeat test) that is changed sufficiently from Baseline so that in the judgment of the Investigator a change in management or care is warranted. This alteration may include: monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment. Whenever possible, the etiology of the abnormal findings will be documented on the CRF. Repeated additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

Any clinically significant laboratory abnormalities that are either unexplained or considered treatment-related should be promptly reported to the Sponsor or Sponsor's designee. Any additional relevant laboratory results obtained by the Investigator during the course of this study will be supplied to the Sponsor or Sponsor's designee and recorded on the CRF.

The intensity of an adverse event will be graded according to the scale below to estimate the grade of intensity. For details see Section 11.1.1 on Adverse Events.

When the intensity of an adverse event changes over time for a reporting period (eg, between visits), each change in intensity will be reported as an adverse event until the event resolves. For example, two separate adverse events will be reported if a patient

experiences Grade 1 diarrhea for 3 days, meeting the definition of an adverse event, and then after 3 days the event increases to a Grade 3 intensity that lasts for 2 days and then resolves. The Grade 1 event will be reported as an adverse event with a start date equal to the day the event met the adverse event definition and a stop date equal to the day that the event increased in intensity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an adverse event with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date on the day that the event changed intensity again or resolved. For analysis purposes, this will be considered one adverse event for this patient and the maximum intensity will be recorded.

The relationship or association of the adverse event to a study treatment will be characterized as unrelated, possible, probable or definite as defined in Section 11.1.1.

Grade 4 toxicity (DLT), as defined by CTCAEv3 criteria, does not automatically imply occurrence of an SAE unless classified as such by the Investigator.

11.2.2 Serious Adverse Events Reporting

Any serious adverse events, including death due to any cause, that occur during the study from the time of the first dose of study medication to within 30 days following discontinuation of study treatment, regardless of relationship to the study treatment, must be reported immediately by telephone or FAX to the global safety and pharmacovigilance representative.

Medical Affairs/Pharmacovigilance
PPD, Inc
SAE Hotline: (800) 201-8725
SAE Fax line: (888) 488-9697

The required SAE information should also be completed on CRFs. A copy of the submitted SAE form must be retained on file by the Investigator. If required, the Investigator must submit copies of the SAE forms to the appropriate Institutional Review Board (IRB)/Ethics Review Committee (ERC) and retain documentation of these submissions in the site study file.

All patients who have adverse events, whether considered associated with the use of the investigational product or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found, or the Investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied when and if available.

11.2.3 Period of Observation

The period of observation for collection of adverse events extends from the time the patient takes the first dose of study medication up to 30 days after the last dose of study medication is taken.

If the Investigator detects a serious adverse event in a study patient after the end of the period of observation, and considers the event possibly related to prior study treatment, he or she should contact the medical monitor to determine how the event should be documented and reported.

11.3 Emergency Procedures

In emergency situations, the Investigator should contact the Sponsor's medical representatives at the number(s) listed below:

Edward Bradley, M.D.
Vice President, Oncology Drug Development
Incyte Corporation
Route 141 and Henry Clay Road
Wilmington, DE 19880
(302) 498-6994 (Office Telephone)
(302) 498-6847 (24 hour coverage)
(302) 425-2766 (FAX)
ebradley@incyte.com (E-Mail)

12.0 STATISTICS

12.1 Study Population

All patients who received at least one dose of study medication will be included in the safety analyses.

All patients who received at one dose of study medication with at least one follow up assessment for safety and efficacy will be included in the efficacy analyses.

12.2 Efficacy Variables

The efficacy variables include:

- Clinical response.
- Spleen and liver volumes.
- Duration of maintenance of spleen volume reduction as measured by MRI.
- Reduction in bone marrow fibrosis.
- Cytogenetic response.
- Quantitative evaluation of percentage of cells with the mutated JAK2 allele (%V617F).
- Patient reported QOL using the EORTC QLQ-C30 and Modified Myelofibrosis Symptom Assessment Form for Part 3 patients.
- Distance (in meters) walked in six minutes for Part 3 Group II and III patients.
- Total steps taken per day and average steps per minute as measured by accelerometer Part 3 Group II and III patients.
- Hand grip strength in lbs. at Part 3 Group II and III patients.
- Total body water and extracellular water (in liters) Part 3 Group II and III patients.
- Calculated estimate of lean body mass Part 3 Group II and III patients.
- Cross-sectional area of the left quadriceps muscle.
- ECOG scores.

12.3 PK/PD Variables

The PK and PD variables will include:

- Determination of the PK of INCB018424 by measuring plasma concentration time profiles.
- Determination of PD markers including % inhibition of STAT3/5 protein phosphorylation.

12.4 Efficacy Analysis

Efficacy analyses will be exploratory in nature. All efficacy measures will be estimated with 95% confidence intervals by study part and/or dose schedule/group. Exploratory analyses to explore treatment effects between different dose levels and different demographic groups may also be carried out when the data become available.

12.4.1 Clinical response

The clinical responses are defined as complete remission (CR), partial remission (PR) or clinical improvement (CI) by the International Working Group (IWG) Response Criteria for PMF and Post-PV/ET MF (IWG-MRT).

Percent of patients with different responses at baseline and each consequent assessment will be tabulated with summary statistics.

12.4.2 Spleen and liver volumes

Spleen and liver volumes at baseline and each consequent visit will be tabulated with summary statistics. Change from baseline of Spleen and liver volumes will be assessed with Wilcoxon Sign Rank test. The percent of subjects who have ≥ 35% reduction in spleen volume based on MRI measurement, at each visit where the variable is measured, will be estimated with 95% confidence intervals.

The duration of ≥ 35% reduction from baseline in spleen volume is defined as the longest duration of consecutive measurements of ≥ 35% reduction observed prior to the time of

database freeze for subjects who have at least one measured ≥ 35% reduction, and who either had at least one subsequent measurement or, who subsequently dropped out prior to another assessment. Specifically:

1) If the first MRI showing ≥ 35% reduction from baseline in spleen volume is the last MRI performed on a patient who is continuing in the study but the patient has not had a subsequent MRI prior to database freeze, the subject will be excluded from the analysis of duration of ≥ 35% reduction in spleen volume.

2) Alternatively, if a subject discontinues from the study after the first MRI showing ≥ 35% reduction in spleen volume then the duration of maintenance will be considered censored with a duration of at least one day.

3) If the last observed spleen volume value still represents ≥ 35% reduction from Baseline at the time of database freeze and this measure belongs to the longest duration, the duration will be considered as censored with a duration of at least the observed duration plus one day.

The median duration of ≥ 35% spleen volume reduction will be estimated using Kaplan-Meier method. If the median is not observed, an exponential distribution will be used to estimate the median.

12.4.3 Bone Marrow, Cytogenetics and ECOG

Reduction in bone marrow fibrosis will be measured in grades (see Appendix VIII). Cytogenetic responses are measured in percent of total metaphases that are abnormal.

Reduction in bone marrow fibrosis, Cytogenetic response, Quantitative evaluation of percentage of cells with the mutated JAK2 allele (%V617F) and ECOG scores at each visit will be tabulated with summary statistics.

12.4.4 Symptom and Quality of Life Assessment

Modified Myelofibrosis Symptom Assessment at each visit will be tabulated with 95% confidence intervals.

The EORTC QLQ-C30 QOL will be scored according to the EORTC QLQ-C30 scoring manual and the resulting scores and the changes from baseline will be estimated at each visit with 95% confidence intervals.

12.4.5 Six Minute Walk Test

Change from baseline of 6MWT to each follow up visit in distance walked will be tabulated with summary statistics, including median, 25th, and 75th percentile, as well as mean, standard deviation, and 95% confidence intervals. Median change from baseline will be tested using Wilcoxon signed rank test. For patients who dropped out due to lack of efficacy (for example, disease deterioration, needing of other treatment), distance walked in the subsequent visits will be considered as zero. For patients who were lost to follow up, or have missing data due to reasons not related to lack of efficacy, last observation carrying forward (LOCF) algorithm will be used to impute the missing values. The higher of the two pre-dose (baseline) 6MWT results will be used as the baseline for these comparisons.

Other exploratory analyses may also be carried out to explore relationships between the distance walked in six minutes and other endpoints, as well as potential covariates. The analyses will also be repeated using the average of the two pre-study 6MWT results as the baseline.

12.4.6 Activity Monitoring via Accelerometer

Total daily steps and steps per minutes will be calculated by averaging the data over a seven day span (Days 1 and 2 of the 9-day data collection period will be censored as this will be the time when patient's may be traveling back to their homes and therefore do not represent normal activity periods). Change from baseline of total daily steps and steps per minute to each follow up visit will be tabulated with summary statistics, including median, 25th, and 75th percentile, as well as mean, standard deviation, and 95% confidence intervals. Median change from baseline will be tested using Wilcoxon signed rank test. For patients who dropped out due to lack of efficacy (for example, disease

deterioration, needing of other treatment), the outcomes in the subsequent visits will be considered as zero. For patients who were lost to follow up, or have missing data due to reasons not related to lack of efficacy, last observation carrying forward (LOCF) algorithm will be used to impute the missing values.

12.4.7 Grip Strength and Quadriceps Area

Hand grip strength and the cross-sectional area of the left quadriceps measured at baseline and each visit indicated on the Schedule of Observations will be tabulated with summary statistics, including median, 25^{th} and 75^{th} percentile, as well as mean, standard deviation and 95% confidence intervals. Median change from baseline will be tested using Wilcoxon signed rank test. For patients who dropped out due to lack of efficacy (for example, disease deterioration, needing of other treatments), hand grip strength in the subsequent visits will be considered as zero. For patients who were lost to follow up, or have missing data due to reasons not related to lack of efficacy, last observation carried forward (LOCF) algorithm will be used to impute the missing values. For cross-sectional area of the left quadriceps, LOCF algorithm will be used to impute missing values.

12.4.8 Body Composition Measurements

Total body water and extracellular water will be determined for each patient. Values will be expressed in liters (L). From these values, intracellular water (TBW-ECW) will be calculated. Along with a precise body weight, these values will be used to derive estimates of the patient's body cell mass and lean body mass, using established formulas. Change from baseline of total body water, extracellular water, as well as body cell mass and lean body mess to each subsequent visit will be tested using Wilcoxon Sign Rank test. Missing values will be imputed using LOCF.

12.5 PK/PD Analysis

Efficacy analyses will be exploratory in nature. All efficacy measures will be estimated with 95% confidence intervals at the dose used in the expanded cohort. The clinical response, the hematological response, and the of percentage of cells with the mutated

JAK2 allele (%V617F) will be estimated with 95% confidence intervals at each time point. The response rates over time may be analyzed graphically or using a statistical model. If there are adequate data at each dose level, dose response curves will be explored graphically or with a statistical model.

The PK parameters of INB018424 will be summarized for each dose group using descriptive statistics, and the log-transformed INCB018424 PK parameters will be compared among the dose groups using a 1-factor analysis of variance. If the PK data are sufficiently robust, the dose-proportionality of INCB018424 C_{max} and AUC may be evaluated using a power function regression model (eg, $C_{max} = \alpha \cdot Dose^{\beta}$). The mean values of the PK parameters may be compared to historical data in healthy volunteers to determine if the INCB018424 PK profile is different between patients with PMF and Post-PV/ET MF and healthy patients.

The percent change from Baseline of stimulated and unstimulated STAT3/5 and IL-6 blood concentrations and other plasma PD biomarkers at Baseline and during treatment cycles will be estimated with a 95% confidence interval. For each patient who has taken study medication, the PD parameters will be calculated to explore preliminary evidence of PD activity by assessing the effect of INCB018424 on pre- and post-dose. If the p-STAT3/5 signaling data are sufficiently robust, an exploratory PK/PD analysis will be performed.

12.6 Safety Analysis

The clinical safety data (vital signs, ECGs, routine laboratory tests and adverse events) will be analyzed using summary statistics (eg, mean, frequency) and no formal statistical comparisons among the treatment groups are planned.

12.6.1 Adverse Events

Adverse events will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA®) preferred term and by system organ class. Severity of adverse events will

be based on the NCI–CTCAE v3.0 (NCI Common Terminology Criteria for Adverse Events, Publ. Aug 9, 2006).

The subset of adverse events that are considered by the Investigator to have a possible or probable relationship to study medication will be considered to be treatment-related adverse events. If the Investigator does not specify the relationship of the adverse event to study medication, the adverse event will be considered to be treatment-related. The incidence of adverse events and treatment-related adverse events will be tabulated.

12.6.2 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.

12.6.3 Vital Signs

Descriptive statistics and mean change from Baseline will be determined for vital signs (blood pressure, heart rate, respiratory rate and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities and patients exhibiting clinically notable vital sign abnormalities will be listed.

12.6.4 Electrocardiograms (ECGs)

Descriptive statistics and mean change from Baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria. Patients exhibiting clinically notable ECG abnormalities will be listed. Adverse events will be reported for clinically notable abnormalities that are considered clinically significant in the judgment of the Investigator.

12.7 Selection of Sample Size

The dose escalation part of the study is a standard 3 + 3 cohort design. For Part 1 with approximately 26 patients at the recommended therapeutic dose and the expanded cohort

of the study (approximately 6 in the dose escalation cohort and 20 in the expanded cohort), there will be a greater than 90% chance to see at least one event of an AE with a 10% underlining prevalence rate. Similarly, if the response rate is at least 10%, the probability of seeing at least one response is greater than 90%. Parts 2 and 3 are more exploratory and their sample size is chosen for practical reasons and to gain more experience with various treatment regimens

13.0 STUDY ADMINISTRATION

13.1 Access to Source Documents

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

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

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

The study monitor will regularly inspect the various records of the study (CRFs, patient medical and laboratory records, and other pertinent data) provided that patient confidentiality is maintained in accordance with local institution, state, country, and

federal requirements. The study monitor will verify the CRF data against 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.

The study monitor will visit the site shortly after the first patient is enrolled in the study and then as agreed upon by Sponsor and CRO thereafter. Depending on the rate of patient accrual or quality issues, the frequency of monitoring visits may be modified. Medication dispensing and clinical drug supply records will be 100% verified at the study site by the study monitor. The study monitor will generate queries as required using the CRF system. Queries will be tracked via a central reporting tool until satisfactory resolution is achieved.

The Investigator or designee must maintain adequate and accurate records of the amounts and dates for clinical supplies received from the Sponsor, dispensed during the study, and unused clinical supplies that were returned or destroyed. All clinical supplies must be accounted for at the termination of the study and a written explanation provided for discrepancies. All unused clinical supplies must be returned to the Sponsor/designee, or, if authorized in writing by the Sponsor, properly destroyed at the study site (except for retained samples in the case of bioavailability/bioequivalence studies).

13.2 Protocol Adherence

Each Investigator must adhere to the protocol as described in this document (Appendix I) and agree that deviations to the protocol, with the exception of medical emergencies, must be discussed and approved by the Sponsor prior to seeking approval from the IRB/ERC. Each Investigator is responsible for enrolling patients who have met the

protocol inclusion and exclusion criteria or must have obtained prior documented approval from the Sponsor prior to enrollment in the study. The IRB/ERC that granted original approval, or the IRB/ERC 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 patient, and/or that may adversely affect the rights of the patient or validity of the investigation. The Investigator must send a copy of the approval letter from the IRB/ERC to the CRO and retain the original in the site study regulatory file.

13.3 Study Termination

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

13.4 Financial Disclosure

All clinical Investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators are required prior to study initiation to submit a completed Clinical Investigator Financial Certification/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 sub-Investigator who is directly involved in the treatment or evaluation of research patients, including the spouse and any dependent child of the Investigator, but not that of any sub-Investigators. 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. At the conclusion of the covered clinical study, the Investigators will be reminded of their obligation to report to the Sponsor/designee any changes to the financial disclosure information previously reported. The clinical Investigators will also be

reminded that they must report any changes in their financial information regarding significant equity interests and significant payments for a period of 1 year after completion of their participation in the covered clinical study.

13.5 Quality Control and Assurance

13.5.1 Sponsor Audits

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

13.5.2 Inspection by Regulatory Authorities

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

14.0 ETHICS

14.1 Institutional Review Board or Ethics Review Committee

It is the responsibility of the Investigator to assure that all aspects of the ethics review are conducted in accordance with the current Declaration of Helsinki (Appendix II) as described in the International Conference on Harmonisation (ICH) E6(R1): Guideline for

Good Clinical Practice (GCP), and/or local laws, whichever provides the greatest level of protection for the study participants. The protocol and any information supplied to the patient to obtain informed consent, including written informed consent form(s), patient recruitment procedures (eg, advertisements), and written information to be provided to patients (information leaflets), must be reviewed and approved by a qualified IRB/ERC prior to enrollment of participants in the study. Prior to initiation of the study, the Sponsor must receive documentation of the IRB/ERC approval, which specifically identifies the study/protocol, and a list of the committee members.

Amendments to the protocol and revisions to the informed consent must also be submitted to and, if required, approved by the IRB/ERC.

At intervals required by the IRB/ERC, but not less than annually, the Investigator must submit to the IRB/ERC a progress report with a request for re-evaluation and re-approval of the study. A copy of the progress report and re-approval of the study must be sent to the Sponsor.

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

After completion or termination of the study, the Investigator must submit a final report to the IRB/ERC and to the Sponsor. This report should include: deviations from the protocol, the number and types of participants evaluated, the number of participants who discontinued (with reasons), results of the study, if known, and significant adverse events, including deaths that occurred during the conduct of the study.

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

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

14.2 Informed Consent

Before being enrolled in the clinical study, patients must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them.

An informed consent document that includes both information about the study and the consent form will be prepared and given to the patient. This document will include all elements required by the ICH, GCP, and applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form must also include a statement that the Sponsor or designee and regulatory authorities have direct access to patient records. Prior to the beginning of the study, the Investigator must have the IRB/ERC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the patients.

The document must be in a language understandable to the patient and must specify who informed the patient. Where required by local law, the person who informs the patient must be a physician.

After reading the informed consent document, the patient must give consent in writing. The patient's consent must be confirmed at the time of consent by the personally dated signature of the patient and by the personally dated signature of the person conducting the informed consent discussions.

If the patient is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to patients must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the

personally dated signature of the patient or by a local legally recognized alternative (eg, the patient's thumbprint or mark). The witness and the person conducting the informed consent discussions must also sign and personally date the consent document.

A copy of the signed consent document must be given to the patient. The original signed consent document will be retained by the Investigator.

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

The Investigator must inform the patient's primary physician about the patient's participation in the trial if the patient has a primary physician and if the patient agrees to the primary physician being informed.

The informed consent and any other information provided to patients or the patient's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the patient's consent, and should receive IRB/ERC approval/favorable opinion prior to use. The Investigator, or a person designated by the Investigator should fully inform the patient or the patient's legally acceptable representative of all pertinent aspects of the study and of any new information relevant to the patient's willingness to continue participation in the study. This communication should be documented. During a patient's participation in the trial, any updates to the consent form and any updates to the written information will be provided to the patient.

15.0 DATA MANAGEMENT

15.1 Data Collection

Site personnel will collect study data using CRFs. Data will be collected on the CRFs (verbatim) such as adverse events, medical history, and prior therapy. These data will be coded using MedDRA. Prior and concomitant medications and prior therapies will be coded using WHO DRUG Dictionary.

15.2 Documentation of Study Findings

Data reflecting the patient's participation in the study and experiences with the study treatment must be reported by the Investigator to the Sponsor. These data must be recorded on CRFs or other media approved by the Sponsor. For rules regarding completion and correction of CRFs, see the CRF instructions that accompany the CRFs. The final released CRFs must be signed and dated by the Investigator or sub-Investigator and must be submitted in a timely manner to the Sponsor.

16.0 RECORD KEEPING / RETENTION OF RECORDS

16.1 Term of Retention

The Investigator must ensure that all records pertaining to the conduct of the clinical study, informed consent forms, drug accountability records, source documents, and other study documentation are adequately maintained for a period of 2 years following the date of marketing application approval for the drug indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

16.2 Destruction of 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.

16.3 Study Documentation

Study documentation includes all CRFs and audit trails, safety reports received from the Sponsor, SAE reports sent to the Sponsor, data correction forms, source documents, monitoring logs, Sponsor-Investigator correspondence, protocols and amendments, clinical supplies receipt, dispensing and final disposition records, IRB correspondence and approvals, signed consent forms, and Statement of Investigator forms.

Source documents include all original records of observations, results, and activities necessary to reconstruct and evaluate the study. Source documents include, but are not limited to, laboratory reports, ECG tracings, X-ray films, ultrasound photographs, patient progress notes, hospital charts, appointment books, radiology reports or pharmacy records, and any other records or reports of procedures performed during the study. Source documents may also include copies of the CRF or Sponsor-supplied worksheets when original information is recorded directly onto these forms.

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

All CRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The Sponsor will retain the original CRF data and audit trail.

16.4 Confidentiality

Patient names will not be supplied to the Sponsor. Only the patient number and patient initials will be recorded in the CRF, and if the patient 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 patients will be informed that representatives of the Sponsor, IRB/ERC, 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.

17.0 USE OF STUDY RESULTS

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

In recognition of the importance of disseminating information relating to any novel or important observations or results from the work to be performed under the protocol, but recognizing the Sponsor's (Incyte) right to protect its confidential information, the Investigators shall have the right to publish or publicly present the results of the study in accordance with the following terms:

- Investigators and their institutions agree that they will submit to Incyte all proposed publications, papers, abstracts, slides, and/or other written materials related to the study at least 30 days before the submission of the contemplated publication. During such 30-day period, Incyte shall have the opportunity to review and comment upon the contents of the publication with regard to Incyte's confidential and proprietary information. Investigators agree to discuss in good faith any Incyte request for modification of a proposed publication and agree to remove any confidential information Incyte requests.
- In the event Incyte determines that an enabling description of patentable patient matter is contained in such written material or outline, it shall notify the Investigator and institution within the 30-day period and the publication or disclosure will be withheld for a reasonable period of time, not to exceed 120 days from the date the Investigator first submits to Incyte the materials proposed for submission for publication, to permit appropriate patent application(s) to be prepared and filed by Incyte, if it so elects.
- Investigators and their institutions agree not to publish or publicly present any interim results of studies without the prior written consent of Incyte.

To the extent that participation in the protocol is part of a multicenter study, all parties agree to initially publish or publicly present their results only together with the other study sites, unless specific written permission is obtained in advance from Incyte to disclose separately such results; provided, however, if there has been no multicenter publication within 12 months of the completion of the multicenter studies by all sites, then Investigators and their institution shall be entitled to publish separately its study results after complying with the other terms of this section. Incyte shall serve as the coordinator of multicenter study disclosures and, in the event of a disagreement among the Investigators in a multicenter study, the lead Investigator and a representative of Incyte shall serve as coarbiters of such dispute. Any publication(s) resulting from the study shall give appropriate credit to the scientific contributions made by Incyte personnel. All clinical Investigators contributing at least one evaluable patient to the study will be considered as coauthors for the principal study manuscript(s). For such manuscript(s), masthead roles for clinical Investigators will be determined based primarily on scientific contribution to the protocol and data interpretation and secondarily on patient enrollment.

18.0 REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality of life instrument for use in international clinical trials in oncology. *J. Natl. Cancer Inst.* 1993;85:365-376.

American Thoracic Society. ATS Statement: Guidelines for the Six-Minute walk Test. *Am. J. Respir Crit Care Med.* 2002;166:111-117.

Barosi G, et al. The Italian Consensus Conference on diagnostic criteria for myelofibrosis with myeloid metaplasia. *BR. J. Haematol.* 1999;104:730-737.

Dupriez B, Morel P, Demory JL, et al. Prognostic Factors in Agnogenic Myeloid Metaplasia: A Report on 195 Cases with a New Scoring System. *Blood.* 1996;88:1013-1018.

Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers; CDER July 2005.

Incyte Corporation. Investigator's Brochure INCB018424 Phosphate Capsules/Tablets.

Kim J, et al. Extracellular Water : Sodium Bromide Dilution Estimates Compared with Other Markers in Patients with Acquired Immunodeficiency Syndrome *J. Parenteral and Enteral Nutr.* 1999;23(2):61-66.

Mesa RA, Pardanani A, Vertovsek S, Kantarjian H, Tefferi A. The Myelofibrosis Symptom Assessment Form (MFSAF): An Evidence-based Brief Inventory to Measure Quality of Life and Symptomatic Response to treatment in Myelofibrosis. Personal communication. Submitted for publication to Leukemia Research.

Mesa RA, Verstovsek S, Cervantes F, et al.: Primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (post-PV MF), post essential thrombocythemia myelofibrosis (post-ET MF), blast phase PMF (PMF-BP): Consensus on terminology by the international working group for myelofibrosis research and treatment (IWG-MRT). *Leuk Res.* 2007); published in advance on line.

Moore F.D, Olesen, KH, McMurray, JD, Parker, HV, Ball, MR, and Boyden, CM The body cell mass and its supporting environment : Body composition in Health and Disease 1963 Philadelphia: Saunders.

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE) online at the NCI website, Published August 9, 2006: http://ctep.cancer.gov/reporting/ctc.html

Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of The Eastern Cooperative Oncology Group. *Am. J. Clin. Oncol.* 1982;5:649-55.

Peolsson A, Hedlund R, Oberg B. Intra- and inter-tester reliability and reference values for hand strength. *J Rehabil Med.* 2001;33 :36-41.

Pierson RN, Wang J, Thornton JC, Heymsfield SB. The Quality of the Body Cell Mass—1996: Are We Ready to Measure It? *Appl. Radiat. Isot.* 1998:49:429-435.

Pikman Y, Lee BH, Mercher T, et al. *MPLW515L* Is a Novel Somatic Activating Mutation in Myelofibrosis with Myeloid Metaplasia. *PLoS Med.* 2006;3(7):1140-51.

Richards L, Palmiter-Thomas P. Grip strength measurement: A critical review of tools, methods, and clinical utility. C*ritical Reviews in Physical and Rehabilitation Medicine.* 1996;8:87-109.

Scott LM, Tong W, Levine RL, et al. JAK2 Exon 12 Mutations in Polycythemia Vera and Idiopathic Erythrocytosis. *N Engl J Med.* 2007;356:459-68.

Tefferi A, Barosi G, Mesa RA, et al. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). *Blood.* 2006;108:1497-1503.

Trussell J. Contraceptive failure in the United States. *Contraception.* 2004;70:89–96.

Valentino L, Pierre J. JAK/STAT signal transduction: regulators and implication in hematological malignancies. *Biochem Pharmacol.* 2006;71:713-21.

Westaway MD, Stratford PW, Binkley JM. The patient specific functional scale: validation of its use in persons with neck dysfunction. *J Orthrop Sports Phys Ther.* 1998;27(5):331-338.

19.0 INVESTIGATOR'S SIGNATURE PAGE

Protocol INCB 18424-251 Amendment 7

Protocol Dated 17 June 2009

I have read, understand, and agree to follow the attached version, cited above, of Protocol INCB 18424-251 Amendment 7.

_____ _____

(Investigator Signature) (Date)

_____

(Printed Name)

20.0 SPONSOR'S SIGNATURE PAGE

Protocol INCB 18424-251 Amendment 7

Protocol Dated 17 June 2009

I have read, understand, and agree to follow the attached version, cited above, of Protocol INCB 18424-251 Amendment 7.

Date: _____ Signature: _____

Edward C Bradley, MD
Vice President, Oncology Drug Development
Incyte Corporation

21.0 APPENDICES

APPENDIX I - RESPONSIBILITIES OF THE INVESTIGATOR

Incyte Corporation and the Investigator agree to conduct this clinical trial according to all applicable laws and regulations, and the guidelines for good clinical practice. As this study is being conducted under an Investigational New Drug Application (IND), all of the regulations stipulated in the Code of Federal Regulations (CFR) Title 21 CFR, Parts 50, 56 & 312 must be satisfied. The Investigator must sign a "Statement of Investigator" form, Form FDA 1572, which commits the principal Investigator to adhere to these IND regulations:

The Investigator will conduct the study in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights or welfare of subjects.

The Investigator agrees to personally conduct or supervise the described investigation(s).

The Investigator agrees to inform any subject, or any persons used as controls, that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

The Investigator agrees to report to the Sponsor adverse experiences that occur in the course of the Investigation(s) in accordance with 21 CFR 312.64.

The Investigator must read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the drug.

The Investigator agrees to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

The Investigator agrees to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

The Investigator will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. The Investigator also agrees to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, the Investigator will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

The Investigator agrees to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

APPENDIX II - DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975,

35th WMA General Assembly, Venice, Italy, October 1983,

41st WMA General Assembly, Hong Kong, September 1989,

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the

subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic, and therapeutic procedures, and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic, and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research, and for those for whom the research is combined with care.

Research Investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal, or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

9. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

10. Appropriate caution must be exercised in the conduct of research which may affect the environment; and the welfare of animals used for research must be respected.

11. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed Ethical Review Committee, which must be independent of the Investigator, the Sponsor, or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, Sponsors, institutional affiliations, other potential conflicts of interest, and incentives for subjects.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

13. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

14. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

15. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

16. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

17. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

18. The subjects must be volunteers and informed participants in the research project.

19. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

20. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study, and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

21. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case, the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

22. For a research subject who is legally incompetent, physically or mentally incapable of giving consent, or is a legally incompetent minor, the Investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

23. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the Investigator must obtain that assent in addition to the consent of the legally authorized representative.

24. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that

renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

25. Both authors and publishers have ethical obligations. In publication of the results of research, the Investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations, and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

26. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic, or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

27. The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists. See footnote.

28. At the conclusion of the study, every subject entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study. See footnote.

29. The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

30. In the treatment of a subject, where proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic, and therapeutic measures, if in the physician’s judgment it offers hope of saving life, re-establishing health, or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all

cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

Where for compelling and scientifically sound methodological reasons, its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic, or therapeutic method; or

Where a prophylactic, diagnostic, or therapeutic method is being investigated for a minor condition and the subjects who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic, and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the Ethical Review Committee may consider such arrangements during its review.

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association, the global representative body for physicians. It was first adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

APPENDIX III - CLINICAL LABORATORY TESTS

Serum Chemistry	**Hematology:**	**Other Tests:**
Albumin Alkaline Phosphatase	Complete Blood Count (CBC), Differential, Platelets and Reticulocyte count.	Hepatitis A virus antibody (IgM)
ALT		Hepatitis B surface antigen
AST		Hepatitis B surface antigen antibody
Bicarbonate		Hepatitis B core antibody
BUN		Hepatitis C virus antibody
Calcium		HIV Antibody
Chloride Cholesterol Creatinine Gamma glutamyl transferase Glucose		*Pregnancy Test - female patients of childbearing potential only; serum test at Screening. Urine test at subsequent visits per the schedule of observations.
Iron Lactate dehydrogenase Phosphorus	**Coagulation:**	FSH (postmenopausal female patients only)
Potassium Sodium	PT (INR) PTT	NOTE: hepatitis tests at Screening for subjects enrolled under Amendment 7 should be conducted for subjects with evidence of active hepatitis infection.
Total Bilirubin		
Total Protein		
Triglycerides		
Uric acid		
Urinalysis:		
Color and appearance		
pH and Specific Gravity	Immunology	
Bilirubin	CD34+	
Glucose		
Ketones		
Leukocytes		
Nitrite		
Occult blood		
Protein		
Urobilinogen		
Note: If laboratory tests are within 4 days of Cycle 1 Day 1, clinical laboratory testing may not be repeated at Investigator's discretion on Cycle 1 Day 1.		

APPENDIX IV - PHARMACOKINETIC SAMPLE COLLECTION AND SHIPMENT

PK Blood Processing, Storage, and Shipment

For Study Center:

1. Collect PK blood samples to analyze INCB018424 plasma concentrations using 4 mL lavender-top (K_2EDTA) Vacutainer® collection tubes at the time points indicated in the Schedule of Observations.

2. After obtaining the PK blood sample, gently mix by slowly inverting the collection tube no less than 5 times to activate clotting agent.

3. Place the collection tube in an ice/water bath.

4. Within 45 minutes of collection, process collection tubes in a refrigerated centrifuge set at approximately 2000*g* for 15 minutes at approximately 5°C.

5. Transfer plasma into two aliquots of approximately equal volume, using standard laboratory technique, into 2 appropriately-labeled storage tubes.

6. Secure labels to each storage tube, affixing the label lengthwise along the tube for barcode reading, and wrapping clear tape around the tube to secure. Labels will include the following information: protocol number, patient number, Study Day and time of collection, aliquot/matrix (eg, Plasma Aliquot A or Plasma Aliquot B). Additional information regarding labels will be provided with the Laboratory Manual for the study.

7. Package Plasma Aliquot A samples as instructed in laboratory manual and ship samples to laboratory on the day of collection. Plasma Aliquot B samples will be shipped separately from the Plasma Aliquot A samples. Plasma Aliquot B samples will be shipped at the direction of the Sponsor. Store plasma aliquots in a freezer set to maintain a temperature of - 20 to - 80°C until ready for shipment.

For the Site Laboratory Only:

8. At times specified by the Sponsor, ship Plasma Aliquot A samples for PK analysis of INCB018424with a 2-day supply of dry ice to:

   Thomas Emm
   Incyte Corporation
   Route 141 & Henry Clay Road
   Building 400- 3431
   Wilmington, DE 19880
   (302) 498-6775 (Office Telephone)
   (302) 425-2759 (Office Fax)
   temm@incyte.com (E-mail)

9. At times specified by the Sponsor, ship Plasma Aliquot B samples, along with a 2-day supply of dry ice to the above address.

10. On the day of any shipment, the site staff will notify by email the Sponsor and analytical laboratory of the pending shipment, including tracking information: temm@incyte.com

APPENDIX V – PHARMACODYNAMIC SAMPLE COLLECTION AND SHIPMENT

PART 1 AND 2: WHOLE BLOOD PHARMACODYNAMIC SAMPLE COLLECTION AND SHIPMENT (STAT3/5)

1. Collect PD blood samples using 4 mL green-top (sodium heparin) Vacutainer® evacuated collection tubes at the time points indicated in Section 7.1 and 7.2, Schedule of Observations.

2. After obtaining the PD blood sample, gently mix evacuated-collection tube thoroughly by slowly inverting the collection tube several times.

3. Secure labels to each storage tube using a strip of tape wrapped completely around the tube. Labels will include the following information: protocol and study number; patient number (eg, 01); time of sample collection (eg, 4 hours post-dose); study treatment (eg, Study Treatment A).

4. Store blood samples at room temperature until shipment. On each day of collection, samples collected at time 0, 2 hours, 6 and 9 hours post-dose should be sent together as the first shipment. Samples collected at 9 hours post-dose may be sent as the second shipment.

5. Within 12 hours of collection, ship blood samples at room temperature in an insulated container, preferably with a temperature tracking device for priority (next morning) overnight delivery to Peggy Scherle or designee. Week-end shipments will be handled individually in consultation with the Sponsor.

   Peggy Scherle
   Senior Director, In Vitro Biology
   Incyte Corporation
   Route 141 and Henry Clay Road
   Building 400
   Wilmington, DE 19880

6. On the day of shipment, the study center's staff will notify by email the Sponsor (pscherle@incyte.com and smalhotra@incyte.com) of the pending shipment, including tracking information

   (302) 498-6793 (Office Telephone)
   (302) 425-2760 (Office FAX)
   pscherle@incyte.com (E-mail)

PART 3 ONLY:

PLASMA PHARMACODYNAMIC SAMPLE COLLECTION AND SHIPMENT FOR PD MARKERS:

1. Draw 4 mL of blood in a 4-mL heparinized tube (Becton Dickinson Vacutainer sterile disposable needles and Becton Dickinson Vacutainer green capped tube with sodium heparin) at the times noted in the Schedule of Observations (Section 7.3).

2. Immediately invert 3 times gently to mix.

3. Within 1 hour, centrifuge at 1200 rpm (400*g*) for 10 minutes to separate cells and plasma.

4. Transfer plasma into two aliquots of approximately equal volume, using standard laboratory technique, into 2 appropriately labeled storage tubes.

5. Secure labels to each storage tube and wrapping clear tape around the tube to secure. Labels will include the following information: protocol number, patient number, Study Day and time of collection, aliquot (eg, Plasma Aliquot A or Plasma Aliquot B). Additional information regarding labels will be provided with the laboratory manual for the study.

6. Freeze on dry ice or at -20ºC to -70ºC immediately.

7. At times specified by the Sponsor, ship Plasma Aliquot A samples for PD analysis of INCB018424 with a 2-day supply of dry ice to:

   Peggy Scherle, Sr. Director
   Incyte Corporation
   Route 141 and Henry Clay Road
   Building 400
   Wilmington, DE 19880.

   The samples may be shipped along with PK samples at frequency as specified by the sponsor

8. On the day of shipment, the study center's staff will notify by email the Sponsor (pscherle@incyte.com) of the pending shipment, including tracking information.

   (302)-498-6793 (Office Telephone)
   (302)-425-2760 (Office Fax)
   pscherle@incyte.com (E-mail)

APPENDIX VI - EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

[a] Oken et al,1982.

APPENDIX VII - CYP3A4 AND CYP1A2 INHIBITORS AND INDUCERS

Reference: http://medicine.iupui.edu/flockhart/table.htm Last Updated: 10/17/2006 14:13:48

CYP1A2 Inhibitors	CYP3A4 Inhibitors	CYP1A2 Inducers	CYP3A4 Inducers
amiodarone cimetidine ciprofloxacin fluoroquinolones fluvoxamine furafylline interferon methoxsalen mibefradil	HIV Antivirals delaviridine **indinavir** **nelfinavir** **ritonavir** amiodarone aprepitant NOT azithromycin chloramphenicol cimetidine **clarithromycin** diethyl-dithiocarbamate diltiazem erythromycin fluconazole fluvoxamine gestodene grapefruit juice imatinib **itraconazole** **ketoconazole** mifepristone **nefazodone** norfloxacin norfluoxetine mibefradil star fruit **telithromycin** verapamil voriconazole	insulin methyl - cholanthrene modafinil nafcillin beta-naphthoflavone omeprazole tobacco	HIV Antivirals efavirenz nevirapine barbiturates carbamazepine efavirenz glucocorticoids modafinil nevirapine phenobarbital phenytoin **rifampin** **St. John's wort** troglitazone oxcarbazepine pioglitazone rifabutin

Potent inducers and inhibitors are shown in red, underline and **BOLDED** text.

APPENDIX VIII - CONSENSUS ON GRADING BONE MARROW FIBROSIS

FIBROSIS DENSITY SHOULD BE ASSESSED IN HEMATAPOIETIC AREAS

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

Tefferi et al; International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for IWG for Myelofibrosis Research and Treatment (IWG-MRT) *Blood*. 2006;108:1497-1503.

APPENDIX IX - INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

The following methods have been determined to be more than 99% effective (failure rate less than 1% per year, when used consistently and correctly) (Trussell 2004).

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

Ref: Trussell J. Contraceptive Failure in the United States. *Contraception*. 2004;70:89–96.

APPENDIX X -COLLECTION, PROCESSING, STORAGE AND SHIPMENT OF JAK2V617F MUTATION BLOOD SAMPLE

- The PAXgene Blood DNA Tube (Qiagen Cat. No. 761115) should be the last tube drawn. Ensure that the PAXgene Blood DNA Tube is at room temperature (18-25°C).
- Collect 8.5 mL of blood in a PaxGene tube for JAK2V617F genotyping at the time points indicated in Section 7, Schedule of Observations. *Ensure that the blood has stopped flowing into the tube before removing the tube from the holder.*
- After obtaining the JAK2V617F genotyping blood sample, gently mix collection tube thoroughly by slowly inverting the collection tube ten times.
- Secure labels to each tube using a strip of tape wrapped completely around the tube. Labels will include the following information: Protocol and Study Number; Patient Number (eg, 01); Patient Initials; Visit Number (eg, Prescreening, Cycle 2 Day 1, Cycle 3 Day 1…); Date of sample collection (eg, May 14, 2007); INCB018424 Dose (eg, 50 mg).
- Store blood samples upright in a 4°C refrigerator until shipment.
- Within 12 hours of collection, package tubes in bubble wrap and sealed envelopes and place in an insulated container containing ice packs from a -20^{o}C freezer. Do not place unwrapped tubes directly on ice packs. Ship with a temperature tracking device using priority (next morning) overnight delivery to:

  Tim Burn
  Incyte Corporation
  Route 141 and Henry Clay Road
  Building E336-237B
  Wilmington, DE 19880
  tburn@incyte.com (E-mail)

Note: Weekend and holiday sample shipment may be delayed in consultation with the Sponsor.

- On the day of shipment, the study center's staff will notify by email the Sponsor (tburn@incyte.com and smalhotra@incyte.com) of the pending shipment, including tracking information

  (302) 498-6787 (Office Telephone)
  (302) 425-2721 (Office FAX)

APPENDIX XI – EORTC QLQ-C30 (VERSION 3)

EORTC QLQ-C30 version 3 is a validated quality of life questionnaire (QLQ) for assessing the health-related quality of life (QOL) of cancer patients participating in clinical trials (Aaronson et al, 1993) . *The QLQ-C30 is a set of core questionnaire that includes a range of physical, emotional, and social health issues commonly experienced by cancer patients. The QLQ comprises distinct scales, each of which represents a different aspect of QOL. The response to questionnaire is assessed by using scoring procedures provided in the EORTC QLQ-C30 user manual. Version 3 is currently the standard version of the QLQ-C30*

- Patients enrolled in Part 3 will be asked to use EORTC QLQ-C30v3 questionnaires to answer some health related questions on Cycle 1 Days 1 and 15, and then on Day 1 of each clinic visit, at End-of-Study and at Follow-up visits in accordance with Part 3 Schedule of Observations.

- EORTC QLQ-C30 must be administered and completed by the patient, preferably prior to any study specific procedure. The completed, signed and dated EORTC QLQ-C30 must be placed in a sealed envelope before MFSAF is administered to the patient for completion.

- In all instances, the EORTC QLQ-C30 questionnaire is completed and sealed prior to the patient's appointment with the Investigator.

- The questionnaire asks patients to rate the level of activity or symptom experienced during the preceding 7 days.

- The questionnaire comprises of both multi-item scales and single–item measures. EORTC QLQ-C30v3 has four-point rating scale of 1 to 4 for the first 28 questions and four response categories ranging from 1 = Not at all, 2 = A Little, 3 = Quite a bit and 4 = very much. Last two questions relating to overall health and quality of life provide have 7 categories for response ranging from 1= Poor to 7 = Excellent.

- Questionnaire should be administered to patients consistent with guideline from European Organisation for Research and Treatment of Cancer, also referred to as EORTC QLQ-C30 or standard guideline for QOL questionnaires.

- Patients must complete the questionnaire without assistance from any study staff by circling the number that best applies to them. Patients must be asked to respond to all questions.

- Study Staff should be available to provide clarification but must not take an active role (verbal or written) in completion of the forms

- Patients must be notified that there is no right or wrong answer. Additionally, it should be emphasized that the patient **is required to respond to all questions in the EORTC QLQ-C30 questionnaire** and that the information provided by them will stay confidential.

- EORTC QLQ-C30 serves as the source documents and original form must be completed and dated by the patient.

- The questionnaires must be completed by each patient enrolled in Part 3 on Cycle 1 Day 1 visit unless screening visit is within -3 to -1 days of Cycle 1 Day 1. Study staff must ensure that the patient knows that that their response is required to all questions.

- Completed questionnaire must be placed in a sealed envelope prior to administration of MFSAF symptom assessment form. The original form must remain sealed until data entry and will be retained in the patient file after data entry.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX XII – MODIFIED MYELOFIBROSIS SYMPTOM ASSESSMENT FORM (MFSAF)

This is a newly developed tool for assessment of symptoms experienced by patients with myelofibrosis (Mesa et al, personal communication). The modified form is designed to capture patient's assessment of symptoms on a scale of 1 to 10.

Note: Study staff must enter patient ID before giving the form to patient for completion. **This questionnaire is administered to the patient after the EORTC QLQ-C30 questionnaire has been completed and has been placed in a sealed envelope.**

For Completion by Patient:

- Patients enrolled in Part 3 will be asked to use MFSAF questionnaires (see attached sample form) to answer some health related questions on Cycle 1 Day 1 and Day 15 and then on Day 1 of each clinic visit, at End-of-Study and at Follow-up visits in accordance with Part 3 Schedule of Observations.

- MFSAF questionnaire asks the patients to rate the symptoms they are experiencing at the time or day of the visit.

- The questionnaire asks patients to rank the symptom on scale of 1 to 10 with "0" being "Not Present" and "1" being most favorable and "10" being the "Worst" or least favorable. Use NA when "Not applicable" and UNK when "Unknown"

- The questionnaire comprises fifteen common signs or symptoms experienced by patients with Myelofibrosis.

- Questionnaire should be administered to patients consistent with standard guideline for administration of QOL questionnaires.

- Patients must complete the questionnaire without assistance from any study staff by ranking the sign or symptom on a scale of 1 to10 or 0 that best applies to them. Rating of number 1 is most favorable and 10 being least favorable. Patients must be asked to respond to all questions.

- Study Staff should be available to provide clarification but must not take an active role (verbal or written) in completion of the forms

- Patients must be notified that there is no right or wrong answer and that the information provided by them will stay confidential.

- The questionnaires must be completed by each patient enrolled in Part 3 on Cycle 1 Day 1 visit unless screening visit is within -3 to -1 days of Cycle 1 Day 1. Study staff must ensure that patient knows that they are required to respond to all questions.

- MFSAF serves as the source document and original form for patient's reported experience must be completed, and dated by the patient.
- Patient's completed questionnaire is placed in a sealed envelope and must not be shared with the Investigator.
- Patient completed MFSAF form remains in the sealed envelope in the patient file until data entry. The original form is a source document and must be retained in the patient file after data entry.

Patient ID ⊥⊥⊥⊥⊥⊥⊥
Visit Day **Cycle 1 Day 1**

Modified Myelofibrosis Symptom Assessment Form (MFSAF)

The form is to be completed **by the patient** according to standard instructions on clinic visit days per Schedule of Observations *(refer to publication Tefferi et al).*
Patient's assessments must be done independent of the Investigator assessments.

Pease fill in your initials: ⊥⊥⊥⊥
Your date of birth (Day-Month-Year): ⊥⊥⊥-⊥⊥⊥⊥-⊥⊥⊥⊥⊥
Today's date: (Day-Month-Year): ⊥⊥⊥-⊥⊥⊥⊥-⊥⊥⊥⊥⊥

Symptom	**1 to 10 (0 if absent) ranking* 1 is most favorable and 10 least favorable**
General fatigue	
Night Sweats	
Itching	
Muscle or bone Pain	
Fever or uncomfortable feeling of warmth	
Cough	
Ability to move and walk around including exercise	
Swelling of extremities (arms and legs)	
Ability to bend down including to tie shoes	
Abdominal discomfort/bloating/pain	
Altered bowel movement and/or difficult or painful urination	
Appetite (include weight gained or lost)	
Difficulty sleeping	
Body image and hindrance to perform daily activities	
Patient's perception on overall quality of life	

*As reported by patient
**National Cancer Institute Common Terminology Criteria for Adverse Events
Use NA when "Not applicable" and UNK when "Unknown"

APPENDIX XIII – MEASUREMENT OF TBW (DEUTERIUM OXIDE METHOD) AND ECW (SODIUM BROMIDE METHOD)

Overview

Patients should be fasting prior to start of TBW and ECW measurements. The assay will begin by administering small amount (1/2 ounce) of salty tasting water containing deuterium and sodium bromide (cocktail). The patient will drink this cocktail and then wash it down (swish and swallow) with fresh water immediately afterward.

Two blood specimens of 4 mL each are required—1 obtained before drinking the cocktail and one obtained 3 hours after cocktail. No food intake is allowed during the three hour assay period.

Procedure

1. When the patient is ready for the test, take one of the Body Composition Study Packages from the refrigerator, and place it on a table with a clean and smooth surface. The package contains:

    a. Dose vial containing cocktail of deuterium and sodium bromide doses. Each vial will be serially numbered.

    b. Administration cup to drink cocktail

    c. 2 green top tubes for blood draw

    d. 2 transfer pipettes (for transferring plasma)

    e. 4 cryogenic storage vials (transfer plasma to these vials)

    f. Test Information Form for the sites to fill out prior to returning samples

2. Record the site number, name of investigator and prescribed day at the top of the test information form. Enter the subject's initials, baseline and allocation #, study site number, the sample collection date and time, serial number of the vial administered (containing cocktail) and subject body weight and gender on the form with a water resistant marker.

3. Draw 4 mL of blood sample in a green top tube labeled for predose blood. Centrifuge the blood immediately at 3000 rpm for 10 minutes and aliquot the plasma in approximately equal volumes into two cryovial storage tubes labeled 'Aliquot A' and 'Aliquot B' for predose plasma. Store the plasma at ≤ -20°C until shipment. The 2 green-top test tubes can be discarded after the blood is centrifuged and transferred to the cryovial storage tubes.

4. Place the dose vial on the table with the cap in the "up" position. Slowly remove the twist-off cap by turning counter-clockwise, and place the cap (with inner side up) next to the dose vial.

5. Use one hand to hold the empty cup, and use the other to pour the cocktail into the empty cup slowly, avoiding splashing and spilling. Then hold the dose vial bottom up over the cup and

tap the rim of the vial on the cup lightly at least 5 times to empty the dose vial as completely as possible.

6. Place the dose vial bottom down on the table. To rinse the dose vial, pour about 10 mL of tap water (to fill the dose vial less than one half) into the dose vial. Cover the vial well with the vial cap, shake the vial several times, and then repeat steps 5 and 6.

7. Hold the dose cup, and ask the patient to drink the "cocktail" as quickly and completely as possible.

8. Immediately, pour about 10 to 20 mL of tap water into the dose cup (as marked), and ask the patient to drink it again, as quickly as possible, to rinse down any remaining dose.

9. Repeat step 9 at least 1 more time, and a maximum of 3 times for a total of no more than 80 mL, until the dose cup appears to be thoroughly rinsed.

10. Record the time when step 10 is completed on the Test Information Form as the dosing time and write down the time for taking the post-blood sample—3 hours after dosing time.

11. **Remind the patient that no food or beverage intake is allowed during the 3-hour period**.

    Make sure to observe and to record on the Information Form if there is any dose loss due to splashing, spilling, incomplete drinking down, or vomiting. If there is any loss of dose, unless the exact amount that is administered to the patient can be determined, the test should be stopped, and may not be repeated for one week. Contact the SPONSOR immediately if such an event occurs.

12. At the expected final sample time (3 hours after dosing time), draw another 4 mL of blood sample in the green-top tube labeled for postdose blood. Centrifuge the blood immediately at 3000 rpm for 10 minutes and aliquot the plasma in approximately equal volumes into two cryovial storage tubes labeled 'Aliquot A' and 'Aliquot B' labeled for postdose plasma, and store it as described in step 3. Record the accurate time of collection of the postdose plasma on the Test Information Form. The 2 green-top test tubes can be discarded after the blood is centrifuged and transferred to the cryovial storage tubes.

13. Place all specimen cryovials containing plasma into provided boxes, in which the 'A' and 'B' aliquots will be stored separately. Store the samples at ≤ -20°C until shipment. Save the Test information Form as instructed by the Sponsor.

14. When instructed ship the specimens with dry ice on the same day by FedEx overnight priority to the address provided by the Sponsor. Aliquots marked 'A' will be shipped first, and 'B' aliquots will be shipped separately at a later time.

APPENDIX XIV – NEW YORK HEART ASSOCIATION CRITERIA

NYHA CLASS

I	No symptoms and no limitation in ordinary physical activity. eg, Shortness of breath when walking, stair climbing, etc.
II	Mild symptoms (mild shortness of breath and/or angina pain) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity (eg walking short distances, ~ >20 - 100m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest, mostly bed bound patients