Official Title: A Phase 2 Study of the Safety, Tolerability, and Efficacy of INCB050465 in Combination With Ruxolitinib in Subjects With Myelofibrosis

NCT Number: NCT02718300

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Clinical Study Protocol

INCB 50465-201

A Phase 2 Study of the Safety, Tolerability, and Efficacy of INCB050465 in Combination With Ruxolitinib in Subjects With Myelofibrosis

Product:	**INCB050465**
IND Number:	[redacted]
Phase of Study:	**2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol:	**16 FEB 2016**
Amendment (Version) 1:	**13 APR 2016**
Amendment (Version) 2:	**18 MAY 2016**
Amendment (Version) 3:	**22 NOV 2016**
Amendment (Version) 4:	**06 JUN 2017**
Amendment (Version) 5:	**23 MAR 2018**
Amendment (Version) 6:	**11 OCT 2018**

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

INVESTIGATOR'S AGREEMENT

I have read the INCB 50465-201 Protocol Amendment 6 (Version 6 dated 11 OCT 2018) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: INCB050465	
Title of Study: A Phase 2 Study of the Safety, Tolerability, and Efficacy of INCB050465 in Combination With Ruxolitinib in Subjects With Myelofibrosis	
Protocol Number: INCB 50465-201	**Study Phase:** 2
Indication: Primary and secondary myelofibrosis (MF) with suboptimal response to ruxolitinib	

Primary Objectives:

- Part 1: To evaluate the safety and tolerability of INCB050465 in combination with ruxolitinib in subjects with MF (primary myelofibrosis [PMF], post–polycythemia vera myelofibrosis [PPV-MF] or post–essential thrombocythemia myelofibrosis [PET-MF]) and select a dose for further evaluation.
- Parts 2, 3 and 4: To evaluate the efficacy of INCB050465 in combination with ruxolitinib on spleen volume reduction in subjects with PMF, PPV-MF, or PET-MF.

Secondary Objectives:

- To evaluate the efficacy of INCB050465 in combination with ruxolitinib on subject reports of MF symptoms.
- To evaluate the efficacy of INCB050465 in combination with ruxolitinib on response using International Working Group (IWG)–Myeloproliferative Neoplasms Research and Treatment criteria.
- To assess the pharmacokinetics (PK) of INCB050465 and ruxolitinib alone and when given in combination in subjects with MF.
- To evaluate the safety and tolerability of INCB050465 when combined with ruxolitinib in subjects with MF.

[redacted]

Primary Endpoints:

- Part 1: Determination of doses of INCB050465 that are safe and tolerable in combination with ruxolitinib.
- Parts 2, 3 and 4: Change and percentage change in spleen volume from baseline through Week 12 as measured by magnetic resonance imaging (MRI; or computed tomography [CT] scan in applicable subjects).

Secondary Endpoints:

- Change and percentage change in spleen volume from baseline through Week 24 as measured by MRI (or CT scan in applicable subjects).
- Change and percentage change in total symptom score from baseline through Week 12 or Week 24 as measured by the Myelofibrosis Symptom Assessment Form version 3.0 (MFSAF v3.0) symptom diary and by the Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF).

- Number of subjects with responses according to the 2013 IWG consensus criteria for treatment response in PMF, PPV-MF, and PET-MF.
- Patient Global Impression of Change score at each visit where the variable is measured.
- Population PK parameters of INCB050465 and ruxolitinib alone and in combination (eg, AUC, C_{max}) will be summarized.
- Safety and tolerability of the treatment regimens through assessment of adverse events (AEs) and changes in safety assessments including laboratory parameters.

[redacted]

Overall Study Design:

This is a Phase 2 study of the combination of the PI3Kδ inhibitor INCB050465 and the JAK 1/2 inhibitor ruxolitinib in subjects with PMF or secondary MF (PPV-MF or PET-MF) who have suboptimal response while receiving ruxolitinib monotherapy. Suboptimal response is based on assessment of suboptimal reductions in spleen size or symptoms and is defined in the inclusion criteria. At least 6 months of prior ruxolitinib therapy is required, including ruxolitinib administration at a stable dose for at least 8 weeks before randomization. The study is composed of 4 parts:

Part 1 was an open-label safety run-in portion designed to assess the safety and tolerability of the combination of INCB050465 with ruxolitinib and to select appropriate doses of INCB050465 for Part 2 in this patient population. Part 1 has been completed.

Part 2 was planned to be a block-randomized open-label study with 2 treatment groups: TG10 and TG20. Both treatment groups use daily doses for the first 8 weeks, then weekly doses at the same strength through end of treatment (EOT). Enrollment in Part 2 was suspended with implementation of Amendment 5.

Part 3 was planned to be an open-label study to compare daily versus weekly long-term doses. All subjects would begin with INCB050465 20 mg once daily (QD). After 8 weeks, subjects in TG5 would continue receiving INCB050465 at 5 mg QD, and subjects in TG20 would continue receiving INCB050465 at 20 mg once weekly. Enrollment in Part 3 will be suspended with implementation of Amendment 6.

With Amendment 6, Part 4 is added to directly compare different daily dosing regimens and the impact of an initial higher dose of INCB050465 on long-term response. Subjects in Part 4 will be randomized to 1 of 2 groups: TG5D will begin on Day 1 with a daily dose of 5 mg, and subjects will continue receiving 5 mg QD indefinitely or until discontinuation criteria are met; TG5I/M will begin on Day 1 with a daily dose of 20 mg (the induction dose), and after 8 weeks subjects will switch to 5 mg QD (the maintenance dose). Treatment for subjects randomized to TG5I/M will continue indefinitely or until discontinuation criteria are met.

Randomization:

During Part 2, subjects were randomized 1:1 to the 2 treatment groups using block randomization, stratified by Eastern Cooperative Oncology Group (ECOG) performance status at screening (ECOG 0-1 vs ECOG 2).

During Part 3, subjects were randomized on a 3:2 ratio between TG5 and TG20. Stratification was by ECOG status as in Part 2.

During Part 4, subjects will be randomized on a 3:2 ratio between TG5D and TG5I/M until 25 total subjects have been randomized, with subsequent randomization on a 1:1 ratio until approximately 30 subjects have been enrolled in each group. Stratification will be by ECOG status as in Part 3.

Part 1: Safety Run-In Portion

The safety run-in portion was designed to test up to 3 doses of INCB050465 in combination with ruxolitinib for a 28-day assessment (4 weeks). Initially, 3 subjects were to be enrolled in Cohort 1 to receive INCB050465 10 mg together with ruxolitinib, at the dose ongoing at the time of enrollment. After 28 days, subjects who took at least 22 of 28 daily doses of INCB050465 AND ruxolitinib OR had a dose-limiting toxicity (DLT) during the first 28 days were to be included in the evaluation cohort. Additional subjects would have been enrolled into Cohort 1 if discontinuations resulted in fewer than 3 evaluable subjects. After evaluation, the following actions were planned to occur:

Cohort	No. of Subjects	Regimen	DLTs Observed	Action Taken
1	3	INCB050465 10 mg QD for 8 weeks followed by 10 mg once weekly plus ruxolitinib 5 mg BID to 25 mg BID*	0	Proceed to Cohort 2.
			1	Enroll 3 additional subjects, and evaluate the total of 6 subjects after 28 days. If < 2 subjects have a DLT, then proceed to Cohort 2. If ≥ 2 subjects have a DLT, then proceed to Cohort 3.
			> 1	Proceed to Cohort 3.
2	3 + 3	INCB050465 20 mg QD for 8 weeks followed by 20 mg once weekly plus ruxolitinib at 5 mg BID to 25 mg BID*	0 or 1	Enroll 3 additional subjects, and evaluate the total of 6 subjects after 28 days. If < 2 subjects have a DLT, then proceed to Part 2 using doses of 10 mg and 20 mg INCB050465.
			≥ 2	Proceed to Cohort 3.
3	6	INCB050465 5 mg QD for 8 weeks followed by 5 mg once weekly plus ruxolitinib at 5 mg BID to 25 mg BID*	0 or 1	If < 2 subjects have a DLT and if Cohort 1 exceeded the DLT allowance, then proceed to Part 2 as a single-group study of 5 mg INCB050465. If Cohort 1 did not exceed the DLT allowance, proceed to Part 2 with doses of 5 mg and 10 mg INCB050465.
			≥ 2	Terminate study. Alternatively, sponsor may elect to assess doses lower than 5 mg. If Cohort 1 did not exceed the DLT allowance, but Cohort 3 showed DLTs, additional Cohort expansion might be conducted to assess these and other doses of INCB050465, pending sponsor review and discussion of available data.

QD = once daily.

*The dose of ruxolitinib will be that which the subjects had been taking for at least 8 weeks before the first dose of INCB050465. The maximum dose of ruxolitinib allowed for subjects with baseline platelet count ≥ 100×10^9/L is 25 mg BID, and the maximum dose of ruxolitinib for subjects with baseline platelet count of ≥ 50×10^9/L to < 100×10^9/L is 10 mg BID.

Subjects receiving dose reductions (but not meeting DLT criteria) during the first 28 days who had not received at least 22 days of the prescribed dose of INCB050465 and ruxolitinib for that cohort were not considered evaluable for the purposes of determining the maximum tolerated dose (MTD) and were replaced.

The MTD of INCB050465 was planned to be the highest dose level tested that was considered tolerated on the basis of fewer than 2 DLTs in a cohort of 6 subjects. Individual subject dose reductions were made based on events observed at any time during treatment with INCB050465; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD of INCB050465, decisions were made based on events that were observed from the first day of study drug administration through and including Day 28. A lower MTD may have subsequently been determined based on relevant toxicities that became evident after Day 28.

After the 28-day safety evaluation period, safety run-in subjects received additional combination therapy of INCB050465 as a daily dose for a total of 8 weeks after first dose, followed by once-weekly dosing plus ruxolitinib as long as adequately tolerated with study visits each month and additional laboratory assessments biweekly. Measurements and procedures followed those described for the randomized portion. Dose modifications after the 28-day safety evaluation period in the safety run-in cohort followed the dose modification rules described in the body of the Protocol.

A DLT was defined as the occurrence of any of the toxicities shown below occurring up to and including Day 28, except those with a clear alternative explanation (eg, disease progression, other medications) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. All DLTs were assessed by the investigator using CTCAE v4.03 criteria. Subjects who received at least 22 of 28 doses of INCB050465 and ruxolitinib at the level assigned or had a DLT were considered evaluable for determining tolerability of the dose.

Dose-Limiting Toxicities

Nonhematologic

Nonhematologic DLT is defined as any clinically significant nonhematologic AE or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medication that occurs during the first 28 days of therapy, is assessed as being at least possibly related to study drugs, and meets any of the following criteria:

- CTCAE Grade 3 AST or alanine aminotransferase (ALT) for > 7 days.
- CTCAE Grade 4 AST or ALT of any duration.
- Grade 3 nausea/vomiting, dehydration, or diarrhea lasting more than 3 days in the setting of optimal supportive medications.
- Grade 3 fatigue lasting more than 5 days in the setting of optimal supportive medications
- Grade 3 biochemical abnormalities (eg, lipase elevation or bilirubin elevation) will only be considered a DLT if accompanied by clinical consequences. Grade 3 electrolyte abnormalities will only be considered DLTs if related to study drugs and not corrected by optimal replacement therapy or if persisting after 7 days of optimal replacement therapy.
- All Grade 4 nonhematologic toxicities of any duration.
- All other clinically significant nonhematologic AEs that are Grade 3 according to CTCAE 4.03.

Hematologic

Myelosuppression and cytopenias are expected outcomes of MF disease processes and MF treatments and per se will not constitute DLTs except as follows:

- Grade 4 thrombocytopenia with bleeding.
- Grade 4 neutropenia with fever that does not clinically resolve within 7 days in the setting of optimal interventions.

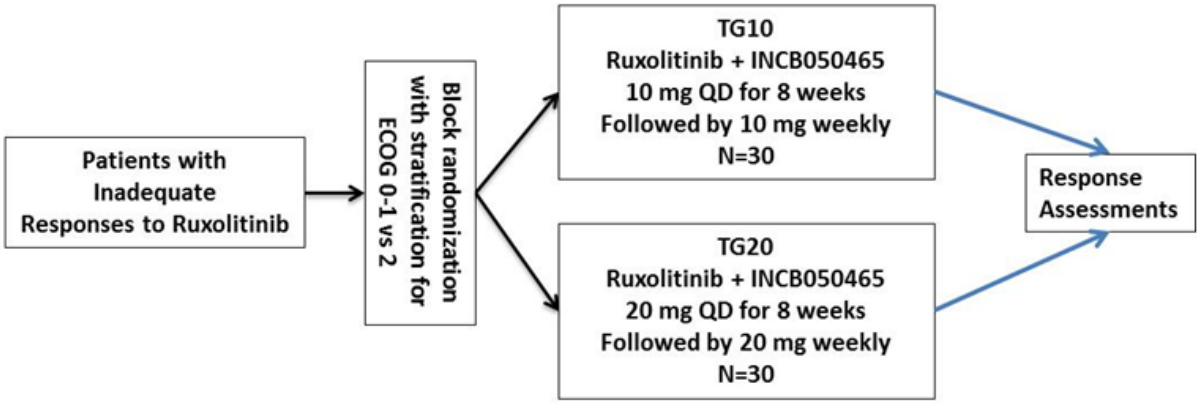
Anemia will not be considered in the definition of DLT.

Part 1 was conducted at selected clinical study sites. Enrollment was controlled by distribution of enrollment slots to the clinical sites by the sponsor or its designee. The sponsor conducted approximately weekly safety teleconferences with the investigators participating in Part 1 to review subject status and safety findings to ensure safe, appropriate administration.

Part 1 has been completed. No DLTs were observed. The treatment groups for Part 2 were determined to be TG10 and TG20.

Part 2: Randomized Portion

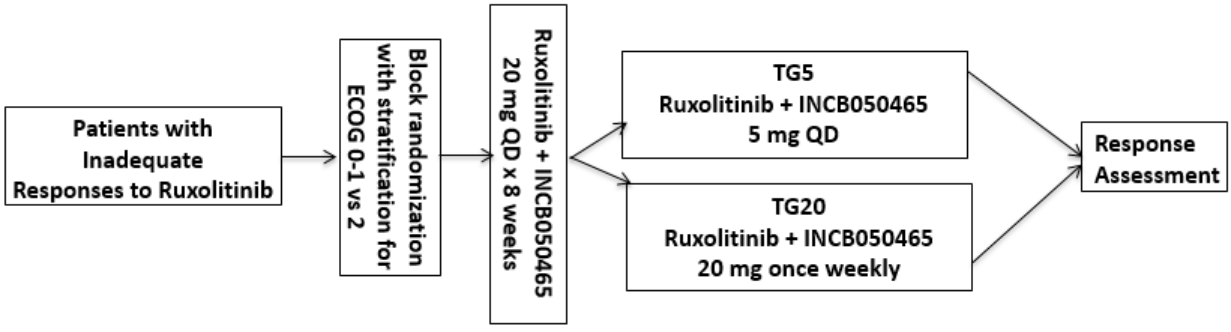
Part 2 was to be enrolled and conducted provided a tolerable dose could be established for INCB050465 in combination with ruxolitinib in Part 1 of the study. Part 2 was planned to enroll approximately 60 subjects randomized 1:1 by block randomization into 2 treatment groups:



Enrollment into Part 2 at a given study site is terminated effective with site-specific IRB approval of Protocol Amendment 5.

Part 3: Randomized Portion

In Part 3, all subjects will initially receive INCB050465 at 20 mg QD for 8 weeks in combination with ruxolitinib. After Week 8, subjects will be assigned to 1 of 2 dose groups based on block randomization at the time of entry into the study (using a randomization of 3:2 for TG5 versus TG20 for the first 40 subjects, followed by 1:1 randomization for additional subjects, up to a total of approximately 52 subjects):



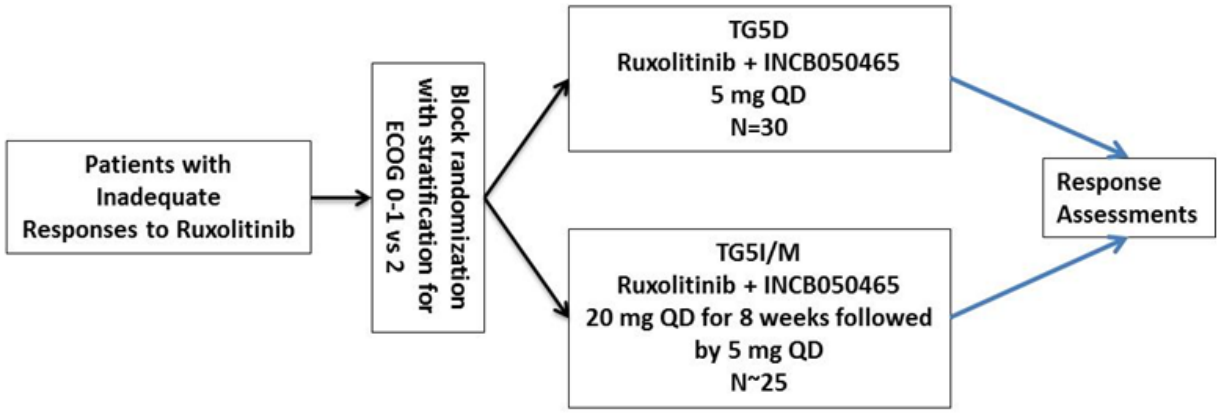
Subjects who were randomized into Part 2 before Amendment 5 and are currently receiving 10 mg QD will be allowed to cross over to the 20 mg QD dose if they are within the first 8 weeks of treatment, or to the 5 mg QD dose if they are beyond Week 8 of treatment, provided they demonstrate inadequate response to the current dose regimen; an adequate bone marrow reserve; and no evidence of uncontrolled renal, hapatic, cardiovascular, or gastrointestinal disease. A list of requirements for crossover is provided in the body of the Protocol.

As of site-specific approval of Amendment 6, there will be no further enrollment into Part 3 at the given site. Subjects already enrolled into TG5 in Part 3 will continue to receive INCB050465 according to the original randomization for Part 3 and may continue in the study indefinitely unless criteria for discontinuation are met. Subjects already enrolled into TG20 in Part 3 will have the opportunity to cross over to receive 5 mg QD of INCB050465 once they reach Week 8 provided they demonstrate inadequate response to the current dose regimen; an adequate bone marrow reserve; and no evidence of uncontrolled renal, hepatic, cardiovascular, or gastrointestinal disease. A list of requirements for crossover is provided in the body of the Protocol.

The TG20 group will be deemed full with enrollment of the 15th subject to that group considering all sites; all further enrollment to Part 3 will be to TG5 at a given site until Amendment 6 has been approved.

Part 4: Randomized Portion

Part 4 of the study is designed to compare different daily dosing regimens and to address the impact of an initial higher dose of INCB050465 on overall response. Subjects will be randomized to one of 2 groups: TG5D will receive INCB050465 5 mg QD from Day 1 until EOT. TG5I/M will receive INCB050465 20 mg QD for 8 weeks (induction phase) followed by 5 mg QD (maintenance phase) until EOT. Study drug administration will continue per the randomized group assignment indefinitely or until discontinuation criteria are met. Note that TG5I/M is identical to TG5 from Part 3; subjects from these 2 groups will be combined in the final analysis.



Study Population:

Male or female subjects aged 18 years or older who have been diagnosed with PMF or secondary MF (PPV-MF or PET-MF) and who have a suboptimal response while receiving ruxolitinib monotherapy for a period of at least 6 months, with a stable ruxolitinib dose for at least the last 8 weeks before the first dose of INCB050465.

Inclusion Criteria:

- Men and women aged 18 years or older.
- Diagnosis of PMF, PPV-MF, or PET-MF.
- Treated with ruxolitinib for ≥ 6 months with stable dose for ≥ 8 weeks (acceptable doses are 5 mg BID to 25 mg BID)
- Evidence of inadequate response to ruxolitinib:
  - Palpable spleen of > 10 cm below the left subcostal margin on physical examination at the screening visit OR
  - Palpable splenomegaly of 5 to 10 cm below left subcostal margin on physical exam AND active symptoms of MF at the screening visit as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form.

- Subjects with an ECOG performance status of 0, 1, or 2.
- Screening bone marrow biopsy specimen available or willingness to undergo a bone marrow biopsy at screening/baseline; willingness to undergo bone marrow biopsy at Week 24.
- Life expectancy of at least 24 weeks.
- Willingness to avoid pregnancy or fathering children based on the criteria below:
  - Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 50 years of age).
  - Woman of childbearing potential who has a negative serum pregnancy test at screening and before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.
  - Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 93 days after treatment with INCB050465. Permitted methods that are at least 99% effective in preventing pregnancy should be communicated to the subject and their understanding confirmed.

Exclusion Criteria:

- Use of experimental drug therapy for MF, or any other standard drug (eg, danazol, hydroxyurea, etc) with the exception of ruxolitinib within 6 months of starting study (combination) therapy and/or lack of recovery from all toxicities from previous therapy (except ruxolitinib) to Grade 1 or better.
- Inability to swallow food or any condition of the upper gastrointestinal tract that precludes administration of oral medications.
- Unwillingness to be transfused with blood components.
- Recent history of inadequate bone marrow reserve as demonstrated by the following:
  - Platelet count < 50×10^9/L in the 4 weeks before screening or platelet transfusion(s) within 8 weeks before screening.
  - Absolute neutrophil count levels < 0.5×10^9/L in the 4 weeks before screening.
  - Subjects with peripheral blood blast count of > 10% at the screening or baseline hematology assessments.
  - Subjects who are not willing to receive RBC transfusions to treat low hemoglobin levels.
- Inadequate liver function at screening visit as demonstrated by the following:
  - Direct bilirubin ≥ 2.0 × the upper limit of laboratory normal (ULN). (NOTE: direct bilirubin will only be determined if total bilirubin is ≥ 2.0 × ULN).
  - ALT or AST > 2.5 × ULN.
- Inadequate renal function at screening visit as demonstrated by creatinine clearance < 50 mL/min measured or calculated by Cockroft-Gault equation, or glomerular filtration rate < 50 mL/min/1.73 m^2 as calculated using the Modification of Diet in Renal Disease formula.
- Active bacterial, fungal, parasitic, or viral infection that requires therapy. Subjects with acute infections requiring treatment should delay screening/enrollment until the course of therapy has been completed and the event is considered resolved. Prophylactic antibiotics will be permitted.
- Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection that requires treatment or at risk for HBV reactivation. Hepatitis B virus DNA and HCV RNA must be undetectable upon testing. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti–hepatitis B core antibody positive. Cytomegalovirus must be undetectable by polymerase chain reaction.
- Known human immunodeficiency virus infection.
- Uncontrolled, severe, or unstable cardiac disease that in the investigator's opinion may jeopardize the safety of the subject or the compliance with the Protocol.

- Active invasive malignancy over the previous 2 years except treated basal or squamous carcinomas of the skin, completely resected intraepithelial carcinoma of the cervix, and completely resected papillary thyroid and follicular thyroid cancers. Subjects with malignancies with indolent behavior such as prostate cancer treated with radiation or surgery may be enrolled as long as they have a reasonable expectation to have been cured with the treatment modality received.
- Splenic irradiation within 6 months before receiving the first dose of INCB050465.
- Concurrent use of any prohibited medications.
- Active alcohol or drug addiction that would interfere with their ability to comply with the study requirements.
- Prior therapy with any drug that inhibits PI3K (examples of drugs targeting this pathway include but are not limited to INCB040093, idelalisib, duvelisib, and TGR-1202).
- Use of any potent cytochrome P450 3A4 inhibitors or inducers within 14 days or 5 half-lives (whichever is longer) before the first dose of INCB050465 or anticipated during the study.
- Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
- Currently breastfeeding or pregnant.
- Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
- Inability to comprehend or unwilling to sign the informed consent form.
- History of Grade 3 or 4 immune-related AEs from prior immunotherapy.
  - Any immune-related AEs of Grade 1 or 2 must be resolved before receiving the first dose of INCB050465.
- History of immune-related ocular AEs of any toxicity grade.
- Receipt of any live vaccine within 30 days of first dose of INCB050465.

INCB050465 Dosage, and Mode of Administration:

INCB050465 will be administered orally QD in the morning at doses of 20 mg for 8 weeks, followed by once-weekly dosing at 20 mg or QD dosing at 5 mg, or at 5 mg QD beginning on Day 1.

Reference Therapy, Dosage, and Mode of Administration:

Ruxolitinib will be administered orally, twice daily, approximately 12 hours apart using the stable dosing established before entering the study. Doses will be 5 mg BID to 25 mg BID.

Study Schedule/Procedures:

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

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

Subjects will have laboratory-only visits to collect hematology lab samples at Week 6, Week 10, Week 14, Week 18, and Week 22 and, if continuing beyond Week 24, every 4 weeks beginning with Week 26. Subjects participating in Part 1 will have additional laboratory assessments performed at Week 1 (ie, Day 8) and Week 3 (ie, Day 22). Subjects in Parts 2, 3, and 4 may visit a local laboratory for the interim hematology assessments provided that the laboratory data and corresponding normal ranges

can be scanned and emailed to the investigative site; interim laboratory visits at the study site laboratory are preferred. Additional laboratory assessments may be performed at investigator discretion, including following changes in dose, or if laboratory parameters are at Grade 3 or Grade 4 levels based on the CTCAE v4.03.

Subjects will have an MRI of the upper and lower abdomen and pelvis to determine the spleen volume at baseline, at Week 12 and Week 24, and every 12 weeks thereafter through Week 108. Computed tomography scan will be substituted for subjects who are not candidates for MRI or when MRI is not readily available. Patients Global Impression of Change questionnaire will be completed at each study visit. Determination of spleen length below the left costal margin will be measured by palpation at each study visit using a flexible ruler.

Subjects will complete an electronic symptom diary (MFSAF v3.0) daily from baseline through the Week 24 visit (total of 25 weeks).

Subjects will complete the MPN-SAF at baseline; at Weeks 4, 8, 12, 16, 20, and 24; and every 12 weeks thereafter.

Subjects receiving combination therapy with INCB050465 and ruxolitinib must receive prophylaxis against pneumocystis pneumonia from the start of study treatment through 2 to 6 months after the last dose of study drug (INCB050465).

Estimated Duration of Participation:

Screening: Up to 28 days.

Baseline: 7 days before first dose of INCB050465.

Treatment: Begins with the first dose of INCB050465 (Day 1). Treatment will continue as long as the regimen is tolerated and the subject does not meet discontinuation criteria. Subjects who discontinue study treatment will be followed for subsequent MF treatments and survival.

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

Survival follow-up: Until subject dies.

It is estimated that an individual subject will participate for approximately 24 months.

Principal Coordinating Investigator: [redacted], MD, MD Anderson Cancer Center, Houston, TX

Statistical Methods:

The primary endpoint of change from baseline in spleen volume at Week 12 will be compared between subjects randomized to TG5D and TG5I/M + TG5 in Parts 3 and 4 of the study using a van Elteren test to account for stratification by ECOG performance status at screening (ECOG 0-1 vs 2). If either of the 2 ECOG-based stratum in Part 4 fail to enroll a sufficient number of subjects, the primary endpoint will be assessed using a 2-sample Wilcoxon rank sum test with a normal approximation to the test statistic.

Results for subjects enrolled to TG10 and TG20 will be summarized descriptively with no formal statistical comparisons performed. The MTD was determined during the Part 1 safety run-in portion of the study based on the proportions of subjects experiencing DLTs. Adverse events will be tabulated for all parts of the study.

According to the Wilcoxon rank sum test, the primary efficacy endpoint has a 90% probability to reject the null hypothesis if the 2 treatment groups differ in percentage change in spleen volume from baseline at Week 12 by 11.4 percentage points with 30 subjects per treatment group, assuming both treatment groups are normally distributed with standard deviation of 14.5.

Secondary efficacy analyses will be conducted for the intent-to-treat population. Change and percentage change from baseline in quantitative variables will be summarized using descriptive statistics. Results for subjects enrolled to TG10 and TG20 will be compared descriptively to those of the other treatment groups, but no direct statistical comparisons are planned.

A difference between TG5D and TG5I/M + TG5 in total symptom score evaluated by the MFSAF v3.0 symptom diary and the MPN-SAF will be assessed separately using a van Elteren test to account for stratification by ECOG performance status. If TG5D or TG5I/M + TG5 in the randomized portion of the study fail to enroll a sufficient number of subjects in a particular stratum, then the difference in the 2 treatment groups for these endpoints will be assessed separately using a 2-sample Wilcoxon rank sum test with a normal approximation applied to the test statistic.

All other efficacy endpoints are exploratory in nature and will be tabulated by summary statistics.

There will be 1 planned interim analysis conducted for futility for this study. The interim analysis will be conducted during the randomized portion of the study once TG5D and TG5I/M + TG5 enroll 15 subjects and have been evaluated for spleen volume at Week 12. Further enrollment in a treatment group will be terminated if fewer than 4 subjects in the treatment group have spleen stability or a reduction from baseline in spleen volume (ie, percentage change from baseline $\leq 0\%$) as measured by MRI (or CT scan in applicable subjects) at Week 12. Subjects remaining in any terminated group may have their dose adjusted to reflect the ongoing group with sponsor approval.

If either TG5D or TG5I/M is terminated, then Part 4 will continue as a single-group study, and the primary endpoint will be analyzed. If both TG5D and TG5I/M are terminated, then the study will be terminated. The probabilities of stopping a treatment group for futility for various probabilities of a subject achieving $\geq 0\%$ decrease from baseline in spleen volume at Week 12 are provided in the full body of the Protocol.

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LIST OF ABBREVIATIONS

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

Abbreviation	Definition
AE	adverse event
AKT	protein kinase B
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BTK	Bruton's tyrosine kinase
CALR	calreticulin
CFR	Code of Federal Regulations
CI	clinical improvement
CMR	complete metabolic response
CMV	cytomegalovirus
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DIPSS	Dynamic International Prognostic Scoring System
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMH	extramedullary hematopoiesis
EOS	end of study
EOT	end of treatment
ET	essential thrombocythemia
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPAA	Health Insurance Portability and Accountability Act of 1996

Abbreviation	Definition
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL	interleukin
IN	Investigator Notification
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board
ITT	intent-to-treat
IXRS	interactive voice/web response system (use appropriate option and change to IVRS or IWRS throughout document)
IWG	International Working Group
JAK	Janus kinase
LDL	low-density lipoprotein
LCM	left costal margin
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
MPN-SAF	Myeloproliferative Neoplasms Symptom Assessment Form
MPN-SAF TSS	Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score
MRI	magnetic resonance imaging
MRT	Myeloproliferative Neoplasms Research and Treatment
MTD	maximum tolerated dose
NHL	non-Hodgkin lymphoma
PD	pharmacodynamic
PET-MF	post–essential thrombocythemia myelofibrosis
PGIC	Patient Global Impression of Change
P-gp	P-glycoprotein
PI3K	phosphatidylinositol 3-kinase
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetic
PMF	primary myelofibrosis
PPV-MF	post–polycythemia vera myelofibrosis
PR	partial response
PRBC	packed red blood cell

Abbreviation	Definition
PT	prothrombin time
PTT	partial thromboplastin time
PV	polycythemia vera
Q3W	every 3 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
Q24W	every 24 weeks
QD	once daily
QW	once weekly
RBC	red blood cell
R-ICE	rituximab, ifosfamide, carboplatin, and etoposide
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
STAT	signal transduction and activator of transduction
TEAE	treatment-emergent adverse event
TG5	Treatment Group 5 mg (20 mg once daily × 8 weeks followed by 5 mg once daily)
TG5D	Treatment Group 5 mg daily from Day 1 to end of treatment
TG5I/M	Treatment Group 20 mg once daily × 8 weeks followed by 5 mg once daily until end of treatment . Note this Part 4 dose group is identical to TG5 in Part 3.
TG10	Treatment Group 10 mg (10 mg once daily × 8 weeks followed by 10 mg once weekly)
TG20	Treatment Group 20 mg (20 mg once daily × 8 weeks followed by 20 mg once weekly)
TEN	toxic epidermal necrolysis
[redacted]	[redacted]
ULN	upper limit of laboratory normal
UNL	upper normal limit
WBC	white blood cell

1. INTRODUCTION

INCB050465 represents a novel, potent, and selective inhibitor of the Class IA phosphatidylinositol 3-kinase (PI3K) enzymes, with selectivity for the δ isoform, which is proposed for development for treatment of hematological malignancies. For a thorough discussion of the pharmacology of INCB054065, refer to the INCB054065 Investigator's Brochure (IB). Ruxolitinib, a potent and selective inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases, JAK1 and JAK2, is approved in multiple jurisdictions for myelofibrosis (MF), with variations on the specific indication language, and is currently in development for the treatment of myeloproliferative neoplasms, hematologic malignancies, and solid tumors. For a thorough discussion of the pharmacology of ruxolitinib (INCB018424), refer to the ruxolitinib IB.

1.1. Overview of Myelofibrosis

The classic myeloproliferative neoplasms (MPNs) include chronic myelogenous leukemia, polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Myelofibrosis can present as a *de novo* disorder (PMF) or evolve secondarily from previous PV or ET (post–polycythemia vera myelofibrosis [PPV-MF] or post–essential thrombocythemia myelofibrosis [PET-MF]). Regardless of whether MF is a primary or secondary disorder, it is characterized by a clonal stem cell proliferation associated with production of elevated serum levels of multiple inflammatory and proangiogenic cytokines, a characteristic bone marrow stromal pattern that includes varying degrees of collagen fibrosis, osteosclerosis and angiogenesis, and a peripheral blood smear showing a leukoerythroblastic pattern with varying degrees of circulating progenitor cells. Clinically, MF is characterized by progressive anemia, leukopenia or leukocytosis, thrombocytopenia or thrombocythemia, and multiorgan extramedullary hematopoiesis most prominently involving the liver and spleen. Patients may experience debilitating symptoms (Mesa et al 2013a, Mesa et al 2013b), sequelae of massive splenomegaly (pain, limitations of movement, early satiety and shortness of breath, hepatic obstruction, and splenic infarction), a hypermetabolic state with cachexia, progressive hematopoietic failure, progression to leukemia, and premature death.

The median age at diagnosis of MF is approximately 60 to 65 years, and the incidence of PMF has been estimated at 4 to 6 cases per 100,000 people in the US (Stein et al 2015). Survival in MF varies with the presence or absence of specific risk factors. Analysis of risk factors over the last 20 years has resulted in a number of prognostic scoring systems (for a review, refer to Bose and Verstovsek 2015). A prognostic scoring system based on a time-dependent risk evaluation has been developed: the Dynamic International Prognostic Scoring System (DIPSS) for PMF (Passamonti et al 2010). Age of greater than 65 years, presence of constitutional symptoms, anemia (hemoglobin less than 100 g/L), leukocytosis (white blood cell [WBC] count $> 25 \times 10^9$/L), and a circulating blast percentage of 1% or higher were assessed for their impact on survival when analyzed as time-dependent covariates in a multivariate Cox proportional hazard model. The approach showed that acquisition of anemia over time affects survival with a hazard ratio roughly double that of other parameters, and therefore anemia was assigned a score of 2, while the other 4 factors were assigned scores of 1. Four risk categories with nonoverlapping survival curves have been described in Table 1.

Table 1: Risk Categories for Myelofibrosis

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

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

For the subset of patients who are younger (generally < 65 years), are otherwise healthy, and have a histocompatible donor, allogeneic stem cell transplantation may provide a curative option, although with substantial risks of mortality (10%-20%; Deeg et al 2003). Drug therapies used in MF, including hydroxyurea, busulfan, 6-mercaptopurine, anagrelide, thalidomide, lenalidomide, interferon, corticosteroids, and erythropoiesis-stimulating agents or growth factors, have not been shown to improve survival. Some can increase the risk of leukemic transformation and can be poorly tolerated, and all have limited effectiveness in improving splenomegaly and constitutional symptoms. Splenectomy, performed in approximately 10% of the patient cohort reported by Cervantes et al (2009), is associated with significant morbidity and mortality. Splenic irradiation is also employed to reduce symptoms secondary to splenomegaly, but symptomatic improvement is variable and short-lived; moreover, transient and life-threatening pancytopenia and an approximate 20% treatment-related mortality have been noted.

1.2. Role of Janus Kinase Pathway in Myelofibrosis

Within the recent years it was discovered that approximately 95% of patients with PV and approximately 50% of patients with PMF and ET have a somatic gain-of-function mutation in the JAK2 gene resulting in substitution of phenylalanine for valine at position 617 (JAK2 V617F) within the pseudokinase domain of the encoded protein. Janus kinase 2 is 1 of 4 members of the JAK family, along with JAK1, JAK3, and TYK2. The JAKs are responsible for transduction of cell signaling from Type I and II cytokine receptors families, because these receptors do not possess intrinsic kinase activity to activate downstream signal transduction. Under physiologic conditions, the JAKs associate with the intracellular domain of the cytokine receptors in response to cytokine binding. They then undergo autophosphorylation, resulting in conformational changes that enable them to transduce intracellular signaling by phosphorylating and activating transcription factors called signal transduction and activator of transduction (STAT) proteins. The activated STATs translocate to the nucleus where they regulate transcription of a number of genes involved in cellular activation, proliferation, and survival. JAKs associate with the intracellular domain of the Type I and II cytokine receptors in pairs,

which may be homodimers (eg, 2 JAK2s) or heterodimers (eg, a JAK1 and a JAK2). Erythropoietin, which is responsible for stimulating erythropoiesis and thrombopoietin, which is responsible for stimulating thrombopoiesis, have been shown to signal only through receptors that utilize JAK2 homodimers. A large number of inflammatory mediators, such as interleukin (IL)-6, interferon -γ, and IL-17, are known to signal primarily through receptors that utilize JAK heterodimers.

It is also apparent that MF, as well as ET and even PV, occur in the absence of the JAK2 V617F mutation. In a minority of patients, other mutations in the JAK-STAT pathway have been identified, but in many patients, the mutations have not been identified yet or may not exist. Regardless, it appears that the majority of patients with MF have overactivation of the JAK-STAT pathway. In MF, excessive cytokine signaling through both JAK1 and JAK2 have been observed both in patients harboring the JAK2V617F mutation and in patients without known mutations. Therefore, JAK inhibitors have the potential to treat some or all of the manifestations of MF, despite the potential for mechanism-based myelosuppression.

Ruxolitinib, a potent and selective inhibitor of JAKs 1 and 2, is approved for use in patients with intermediate- or high-risk MF, including PMF, PPV-MF, and PET-MF. Registration studies showed improvement in spleen size, symptom burden, and overall survival with ruxolitinib use in this patient population (Harrison et al 2012, Cervantes et al 2013, Mesa et al 2013a, Mesa et al 2013b, Verstovsek et al 2012, Verstovsek et al 2015, Vannucchi et al 2015).

1.3. Role of PI3K/Protein Kinase B–Signaling Pathway in Myelofibrosis

Recent evidence suggests other regulatory pathways in addition to the JAK-STAT pathway are dysregulated in myeloproliferative neoplasms. The PI3K/protein kinase B (AKT) pathway is a signal transduction pathway that promotes survival and growth of cells in response to extracellular signals. There are multiple isoforms of PI3K; activated AKT, which results from interaction with activated PI3K, phosphorylates as many as 100 different substrates, leading to a wide range of growth and survival effects on the cell. Meadows et al (2013) reported that the primary isoform of PI3K expressed in CD34+ cells obtained from ruxolitinib-treated or -naive patients with MF was PI3Kδ. Khan et al (2013) described studies using cell lines and patient samples to show that inhibition of the PI3K/AKT pathway signaling with a selective AKT inhibitor induced proliferative arrest and apoptosis. Interestingly, both myeloid and erythroid colony formation by cells derived from PMF patient samples were more sensitive to inhibition by AKT inhibitor than their normal counterparts. A combination of AKT inhibitor plus ruxolitinib when added to SET2 cells, which harbor the JAK V617F mutation, suppressed cell growth; the combination was synergistic at all doses tested, suggesting that combining the 2 agents may provide efficacy at lower doses of ruxolitinib. The authors concluded that inhibition of the PI3K/AKT pathway represents an additional therapeutic target for treatment of MPNs.

1.4. Study Rationale

Despite statistically significant improvements in signs and symptoms of MF and overall survival rates, compared with either placebo or best available therapy demonstrated in the registration studies, ruxolitinib therapy fails to provide adequate and/or sustained response for some patients. A subgroup analysis of the Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment I

study did not identify subgroups (age, MF subtype, International Prognostic Scoring System risk group, baseline Eastern Cooperative Oncology Group (ECOG) score, baseline platelet or hemoglobin level, baseline spleen volume quartile, baseline symptom burden quartile, or presence/absence of V617F mutation) that did not benefit from ruxolitinib therapy (Verstovsek et al 2013); however, additional systemic and genetic factors may influence the response magnitude and duration in an individual patient. It is possible that for some patients, declining hemoglobin or platelet counts associated with ruxolitinib use preclude maintenance at optimal ruxolitinib dosages. Alternatively, some patients may have increases in inflammatory pathway signaling that is not JAK-mediated as a primary driver for their disease.

The persistent activation of the PI3K/AKT pathway in patients chronically treated with ruxolitinib suggests that the PI3K/AKT pathway may be a major driver of disease in patients who have a less than ideal response to JAK inhibitor therapy. These data suggest that concurrent PI3Kδ inhibition may envisage an efficacious and well-tolerated approach in patients with MF who have evidence of residual MF symptoms on chronic ruxolitinib therapy. INCB054065 is a novel, potent small molecule inhibitor of PI3K-delta with approximately 20,000-fold selectivity for the other PI3K family members. The present study will explore the combination of INCB050465 with ruxolitinib in subjects with MF with residual disease-related signs and symptoms while on chronic ruxolitinib therapy.

1.5. Overview of INCB050465

1.5.1. Pharmacology Summary

INCB050465 potently inhibits the human PI3Kδ kinase enzyme (IC_{50} = 1.1 ± 0.5 nM), with approximately 20,000-fold selectivity for the other PI3K family member enzymes and > 300-fold selectivity against a broad panel of 192 other kinases. Moreover, INCB050465 is potent (IC_{50} values of ≤ 10 nM) in cell-based assays relevant to the pathogenesis of B-cell malignancies, such as PI3Kδ-mediated signaling and growth of malignant human B-cell lines. This effect is not due to general cytotoxicity, because 10 μM INCB050465 had no significant effect on the growth of nonlymphoid cell lines. Compared with inhibition of B-cell proliferation, INCB050465 is similarly potent in blocking T-helper cell differentiation but is > 100 times less potent in assays that measure effects on human T-cell and natural killer-cell proliferation or monocyte function. These data suggest that the impact of INCB050465 on the human immune system will largely be restricted to B cells and T-cell differentiation.

In vivo, the effects of oral INCB050465 were evaluated in mice in the Pfeiffer human tumor xenograft model of B-cell malignancy. In the Pfeiffer model of non-Hodgkin lymphoma (NHL), INCB050465 inhibited PI3Kδ signaling and tumor growth as a single agent in a dose-dependent manner.

In summary, pharmacological data obtained in both *in vitro* and *in vivo* model systems support the potential utility of orally administered INCB050465 in the treatment of hematological malignancies and solid tumors. For a complete summary of the pharmacology of INCB050465, refer to the INCB050465 IB.

1.5.2. Nonclinical Toxicology Summary

Oral administration studies were conducted in rats and dogs to assess the potential systemic toxicity of INCB050465. Doses evaluated in repeat-dose studies were selected based on tolerability in earlier studies and projected margins over human exposure.

The most prominent findings following repeat-dose exposure to INCB050465 in both rats and dogs were lymphoid depletion (most notably B-cell regions) of multiple lymphoid organs, including lymph nodes, spleen, thymus, and gut-associated lymphoid tissue, at all doses and at high doses constituting the dose-limiting toxicity (DLT). The frequency and severity of these findings were dose-related. Effects secondary to immunosuppression led to euthanasia of 1 female rat administered a dose of 100 mg/kg per day (primary cause of deteriorating condition was necrotizing pancreatitis) and 1 female dog administered a dose of 3 mg/kg per day (primary cause of deteriorating condition was severe gastrointestinal inflammation) and to the death of 1 male dog administered 15 mg/kg per day (primary cause of death was severe pulmonary inflammation). Depletion of the bone marrow was observed in 2 female rats administered a dose of 100 mg/kg per day (including the female that was euthanized in extremis); in addition, 1 of these 2 animals showed bone marrow fibrosis. No changes in bone marrow were observed at lower doses or at the end of the recovery period. There were no bone marrow lesions in dogs at any dose. Plasma exposures (unbound AUC) in female rats administered 100 mg/kg were > 190-fold higher than projected clinical exposure at 10 mg once daily (QD). Pharmacokinetics (PK) and safety data will be evaluated in all subjects at each dose level before proceeding to the next dose. Effects on the lymphoid system are an expected result of immunomodulatory effects of PI3Kδ inhibition (Pillai and Cariappa 2009, Marone et al 2008). Reversibility of the effects on the lymphoid system was clearly demonstrated and would be expected to occur in a clinical setting.

There was no evidence of toxicity unrelated to the pharmacological activity (ie, "off-target" effects) of INCB050465 in dogs. In male rats, minimal to mild hypospermatogenesis was observed in the 28-day study at doses ≥ 30 mg/kg per day. Exposures (unbound AUC) associated with these findings are approximately 4-fold higher than projected human exposures at a dose of 30 mg QD. In 8- and 9-day exploratory non-GLP studies in rats, evidence of hepatotoxicity was observed at ≥ 100 mg/kg per day, although these findings were not reproduced in the 28-day GLP study at 100 mg/kg per day. Plasma exposures (unbound AUC) in rats administered ≥ 100 mg/kg were > 13-fold higher than projected clinical exposure at 30 mg QD.

Three-month studies with INCB050465 in rats and dogs demonstrated similar pharmacological effects and did not reveal any "off-target" toxicities.

INCB050465 was not mutagenic in a bacterial mutagenicity assay. INCB050465 was not clastogenic in the absence of S9 metabolic activation in an *in vitro* chromosome aberration assay in human lymphocytes, although results in the presence of metabolic activation were considered inconclusive. No increase in micronuclei were observed in the bone marrow of rats administered INCB050465 at up to the maximally tolerated dose in an *in vivo* micronucleus assay in rats. Therefore, based on the collective evidence, INCB050465 is not expected to present a genotoxic risk to humans.

The potential risk associated with INCB050465 clinical administration is expected to be low based on animal studies with adequate exposure margins, the demonstrated lack of findings in recovery animals following drug withdrawal, and comprehensive evaluation of safety and PK before each dose escalation in Study INCB 50465-101. For a complete summary of the nonclinical toxicology of INCB050465, refer to the INCB050465 IB.

For a complete summary of the pharmacology of INCB050465, refer to the INCB050465 IB.

1.5.3. Nonclinical Drug Metabolism and Pharmacokinetics

The absorption, distribution, metabolism, and excretion of INCB050465 have been studied in rats, dogs, and monkeys. Following intravenous (IV) administration, INCB050465 displayed low systemic clearance, representing 26%, 2%, and 5% of the hepatic blood flow in rats, dogs, and monkeys, respectively. The steady-state volume of distribution was moderate in rats (1.5 L/kg) and monkeys (0.7 L/kg) but low in dogs (0.3 L/kg), indicating species differences in distribution. The terminal elimination half-life values were favorable, ranging from 4.0 hours (rat) to 7.3 hours (monkey). The renal excretion of intact INCB050465 was minimal (< 2% across species). INCB050465 has limited penetration across the rat blood-brain barrier. Following oral administration, INCB050465 was rapidly absorbed, with T_{max} values of 0.3 hours (rat) to 2.5 hours (monkey). The bioavailability of INCB050465 was complete in dogs (100%), and high in monkeys (79%) and rats (74%). Based on preclinical data, the terminal elimination half-life of INCB050465 in human is projected to be approximately 12 hours, and the oral bioavailability is projected to be 70%.

INCB050465 is a P-glycoprotein (P-gp) substrate, and the efflux transport is saturated at concentrations above 100 µM. Though INCB050465 is an inhibitor of P-gp (IC_{50} at 18.1 µM), a clinical drug interaction potential with a P-gp substrate is low based on FDA Guidance for Industry – Drug Interaction Studies (FDA 2012). INCB050465 is primarily metabolized by cytochrome P450 (CYP) 3A4 and is not an inhibitor of the major CYPs evaluated nor is it an inducer of CYP3A4. Thus, the drug-drug interaction potential via P450 is low. The metabolism profile of INCB050465 in rat, dog, and human *in vitro* preparations was quantitatively similar, and no human-specific *in vitro* metabolite was identified. The primary phase I metabolites identified from *in vitro* preparations were oxidative. From the drug safety perspective, no glutathione adducts were detected upon incubation of INCB050465 in the presence of glutathione, suggesting that INCB050465 should not present a risk for immune-mediated toxicity due to reactive metabolites formation. Metabolites in plasma and urine samples from the rat and dog 28-day toxicokinetic studies were similar to that observed *in vitro*. Only 1 oxidation metabolite was detected in rat and dog plasma at abundance greater than 10% of parent or drug related material.

For additional details, refer to the INCB050465 IB.

1.5.4. Clinical Summary

As of 30 MAR 2018, INCB050465 is being evaluated in 8 ongoing clinical studies for oncology indications: Studies INCB 50465-101, INCB 50465-202, INCB 50465-204, and INCB 50465-205 as monotherapy; Study INCB 50465-102 in combination with bendamustine and obinutuzumab; Study INCB 50465-201 in combination with ruxolitinib (JAK 1/2 inhibitor); Studies INCB 50465-101 and INCB 39110-106 in combination with itacitinib (JAK 1 inhibitor);

and Study INCB 39110-107 in combination with pembrolizumab (an anti–PD-1 monoclonal antibody). The combination of INCB050465 and R-ICE is also being assessed in Study INCB 50465-101.

As of the data cutoff, 351 unique participants have been exposed to INCB050465 as monotherapy (139 participants) or in combination with R-ICE (5 participants), bendamustine and obinutuzumab (6 participants), itacitinib (11 participants with B-cell malignancies and 73 participants with advanced solid tumors), ruxolitinib (28 participants), or pembrolizumab (89 participants).

For the 342 participants included in the safety analysis (Studies INCB 50465-101,INCB 50465-102, INCB 50465-201, INCB 50465-202, INCB 39110-106, and INCB 39110-107), 312 participants (91.2%) had at least 1 TEAE. The most frequently reported TEAEs overall were fatigue (31.0%), nausea (29.5%), diarrhea (25.1%), and pyrexia (20.8%).

The most frequently reported TEAEs for participants who received INCB050465 monotherapy and combination therapy are as follows:

- INCB050465 monotherapy (n = 130): nausea (26.9%), diarrhea (24.6%), and fatigue (21.5%).
- INCB050465 and pembrolizumab combination therapy (n = 89): fatigue (43.8%), nausea (37.1%), diarrhea (31.5%), and pyrexia (29.2%).
- INCB050465 and itacitinib combination therapy (n = 84): fatigue (39.3%), nausea (31.0%), decreased appetite (28.6%), vomiting (25.0%), and diarrhea and pyrexia (21.4% each).
- INCB050465 and ruxolitinib combination therapy (n = 28): cough, epistaxis, nausea, and thrombocytopenia (17.9% each)
- INCB050465 and bendamustine + obinutuzumab combination therapy (n = 6): diarrhea (66.7%).
- INCB050465 and R-ICE combination therapy (n = 5): anemia (100.0%)

Refer to the INCB050465 IB for further details.

1.5.4.1. Study INCB 50465-101

Study INCB 50465-101 is an open-label dose-escalation study in participants previously diagnosed with and treated for B-cell malignancies. As of the data cutoff date of 30 MAR 2018, INCB050465 was administered in doses from 5 mg QD to 45 mg QD. A regimen of 20 mg QD for 9 weeks followed by 20 mg QW was also administered. Of the 72 participants who were administered INCB050465 monotherapy, the median duration of treatment was 124.5 days (range, 7-914 days). Treatment-emergent AEs occurred in 68 participants (94.4%), with the most frequent TEAE being nausea and diarrhea in 26 participants (36.1%) each.

Two participants in the monotherapy group (2.8%) had a TEAE leading to death (sepsis and respiratory failure). Serious AEs were observed in all dose cohorts. Thirty-one participants (43.1%) who received monotherapy had a SAE. The most frequent SAE reported was diarrhea (8.3%). Fourteen participants (19.4%) discontinued INCB050465 treatment because of a TEAE. None of the events that led to study drug discontinuation occurred during the QW dosing period.

The most frequent TEAEs that led to discontinuation of INCB050465 were diarrhea (3 participants [4.2%]) and colitis and dermatitis exfoliative (2 participants [2.8%] each). No DLTs occurred during the DLT assessment period.

Final efficacy results for Study INCB 50465-101 are as follows (data cutoff 18 AUG 2017). A total of 88 participants were treated with INCB050465 monotherapy (n = 72), INCB050465 and itacitinib combination therapy (n = 11), or INCB050465 and R-ICE combination therapy (n = 5). Objective responses occurred at all doses, except 5 mg QD, with 28 of 30 responses observed at first assessment. For the 11 participants who received INCB050465 and itacitinib combination therapy, a best overall response of CR/CMR was observed in 1 participant with CLL and FL, each. A best overall response of PR/PMR was observed for 1 participant with MCL and 1 participant with classical Hodgkin lymphoma. For the 5 participants who received INCB050465 and R-ICE combination therapy, a best overall response of CMR was observed in 3 participants with DLBCL.

Refer to the INCB050465 IB for further details.

1.5.4.2. Study INCB 39110-106

Study INCB 39110-106 is an open-label study in participants with advanced or metastatic solid tumors. As of the data cutoff date (30 MAR 2018), 73 participants enrolled in the study and were assigned to INCB050465 (0.3 mg to 10 mg QD) in combination with itacitinib (100 or 300 mg QD). Of the 73 participants who were administered combination therapy of INCB050465 + itacitinib, the median duration of treatment was 61.0 days. Generally, the combination of INCB050465 + itacitinib has been well-tolerated. Sixty-five participants (89.0%) had at least 1 TEAE. Thirty participants (41.1%) receiving INCB050465 + itacitinib had an SAE. The most frequent SAEs reported were acute kidney injury, disease progression, and vomiting (5.5% each) and abdominal pain, dehydration, malignant neoplasm progression, and nausea (4.1% each). Other SAEs occurring in more than 1 participant included hyponatremia, lung infection, peripheral edema, pulmonary embolism, and tumor pain (2.7% each). Fourteen participants (19.2%) were discontinued from INCB050465 because of a TEAE. Treatment-emergent AEs that led to discontinuation of INCB050465 and occurred in more than 1 participant included fatigue (4.1%) and anemia, dyspnea, and tumor pain (2.7% each). Refer to the INCB050465 IB for further details.

Ten participants had fatal TEAEs. Six participants who received INCB050465 10 mg QD + itacitinib 300 mg QD had fatal TEAEs of death (n = 1); disease progression (n = 1); gastritis, lung infection, and sepsis (n = 1); and malignant neoplasm progression (n = 3). One participant who received INCB050465 0.3 mg QD + itacitinib 100 mg QD and 1 participant who received INCB050465 0.3 mg QD + itacitinib 300 mg QD had fatal TEAEs of disease progression. One participant who received INCB050465 1 mg + itacitinib 100 mg had fatal TEAEs of colon cancer and metastases to the liver. One participant who received INCB050465 5 mg QD + itacitinib 300 mg QD had a fatal TEAE of TEN. The event of TEN was considered a suspected unexpected serious adverse reaction. On Study Day 3, [redacted] started on PJP prophylaxis with dapsone. On Study Day 12, the participant was hospitalized with high-grade fever and rash. Subsequently, the participant developed diffuse skin sloughing and fatal multi-organ failure on study Day 19. The case was also confounded by Grade 1 rash at baseline, which occurred while receiving previous treatment with an investigational checkpoint inhibitor and evidence of bullous

vaginal mucosal lesions before receiving study treatment. Dapsone is known to cause hypersensitivity reactions that are potentially fatal, and serious cutaneous reactions, including TEN, are listed in the United States product insert. While the sponsor and the investigator believed that dapsone was the most likely cause of TEN in this participant, a contributory role of INCB050465 and/or itacitinib could not be excluded.

1.5.4.3. Study INCB 39110-107

Study INCB 39110-107 is an open-label study in participants with advanced solid tumors. As of the data cutoff date (30 MAR 2018), 89 participants received combination therapy with INCB050465 (0.3-30 mg QD) and pembrolizumab (200 mg every 3 weeks). INCB050465 in Study INCB 39110-107 has been generally well-tolerated in participants with INCB050465 doses up to 30 mg in combination with pembrolizumab. Of the 89 participants who were administered combination therapy of INCB050465 + pembrolizumab, the median duration of treatment was 80.0 days. Treatment-emergent AEs occurred in all 89 participants (100.0%), with the most frequent TEAE being fatigue (43.8%).

Fifty-one participants (57.3%) receiving INCB050465 + pembrolizumab had an SAE in Study INCB 39110-107. The most frequently reported SAEs were pneumonia and sepsis (7.9% each), disease progression (6.7%), and urinary tract infection (4.5%). Twenty-one participants (23.6%) were discontinued from INCB050465 because of a TEAE. All TEAEs leading to discontinuation of INCB050465 occurred in 1 participant each, with the exception of depressed level of consciousness and increased aspartate aminotransferase (2 participants, 2.2% each). Refer to the INCB050465 IB for further details.

Twenty participants receiving INCB050465 + pembrolizumab had fatal TEAEs: disease progression (n = 6), malignant lung neoplasm and respiratory failure (n = 2 each), and cardiac failure congestion, multiorgan failure, metastases to central nervous system, cerebrovascular accident, completed suicide, malignant neoplasm progression, oliguria, PJP, sepsis, and transitional cell carcinoma (n = 1 each). The fatal event of PJP was reported in a [redacted]-year-old participant receiving INCB050465 20 mg with 200 mg of pembrolizumab. The onset of the PJP started on Day 60 of the study. On Day 63, INCB050465 treatment was held. On Day 64, the participant reported to the clinic with Grade 3 fatigue, dyspnea with minimal exertion, and a continuing nonproductive cough. On the same day, the participant was hospitalized, and despite intensive treatment for the PJP, the participant's condition continued to deteriorate. On Study Day 72, the participant had a ventricular tachycardia, which led to cardiac arrest and death. The event of PJP was considered possibly related to INCB050465 (see Section 5.7.1 for information regarding PJP prophylaxis).

1.5.4.4. Study INCB 50465-202

Study INCB 50465-202 is an ongoing, open-label efficacy study of INCB050465 monotherapy in participants with relapsed or refractory DLBCL who were either BTK-inhibitor naïve (Group A) or BTK-inhibitor experienced (Group B). As of the data cutoff date of 30 MAR 2018, INCB050465 has been generally well-tolerated in participants administered 20 mg QD for 8 weeks followed by 20 mg QW. Of the 58 participants who were administered INCB050465 monotherapy (Group A, n = 54; Group B, n = 4) the median duration of treatment was 57.5 days (range, 11-234 days).

Treatment-emergent AEs occurred in 49 participants (84.5%) with the most frequent TEAEs being nausea and pyrexia in 9 participants (15.5%) each. Four participants (6.9%) had TEAEs leading to death (abdominal pain and pyrexia, general physical health deterioration, multiple organ dysfunction syndrome, and acute respiratory failure), all of which were considered related to disease progression. Serious AEs were observed in both treatment groups. Thirty-five participants (60.3%) had an SAE. The most frequent SAE reported was pyrexia (8.6%). Eleven participants (19.0%) discontinued INCB050465 treatment because of a TEAE. The most frequent TEAE that led to discontinuation of INCB050465 was hypercalcemia (3 participants [5.2%]). Refer to the INCB050465 IB for further details.

1.5.4.5. Current Study: INCB 50465-201

Study INCB 50465-201 is the current, ongoing study to assess the safety, tolerability, and efficacy of the combination of INCB050465 and the JAK 1/2 inhibitor ruxolitinib in subjects with primary MF or secondary MF who had a suboptimal response while receiving ruxolitinib monotherapy. Subjects are required to have been on ruxolitinib for at least 6 months, and at a stable dose for at least the 8 weeks before study entry. Suboptimal response is defined based on spleen size and presence of symptoms.

Before Amendment 6, the study had 3 parts. Part 1 was a safety run-in part to establish tolerable doses. The dosing regimen for the 2 dose groups in Part 2 was INCB050465 10 and 20 mg QD, respectively, for 8 weeks followed by weekly dosing at the same dose. Part 3 explored different long-term dosing strategies by comparing INCB050465 5 mg QD versus 20 mg QW in subjects who first received 20 mg QD for 8 weeks. As of the cutoff date (30 MAR 2018), 28 participants received combination therapy with INCB050465 (10 and 20 mg QD) and ruxolitinib in Parts 1 and 2. The median duration of treatment was 122.0 days. Twenty-one subjects (75.0%) had a TEAE. The most frequently reported TEAEs were cough, epistaxis, nausea, and thrombocytopenia (17.9% each) and fatigue, headache, stomatitis, and vomiting (14.3% each). Serious TEAEs were reported for 3 participants: hematoma, influenza, nausea, and pyrexia in 1 participant, fall in 1 participant, and blood bilirubin increased in 1 participant. Subsequent to the elevation in bilirubin in the latter participant, a diagnosis of acute myeloid leukemia was made; this event was fatal. No TEAEs led to INCB050465 discontinuation. Refer to the INCB050465 IB for further details. No data are available for subjects in Part 3.

1.6. Overview of Ruxolitinib

1.6.1. Clinical Safety Summary

1.6.1.1. Healthy Subject Studies

Ruxolitinib has been administered in Novartis or Incyte sponsored clinical studies to approximately 385 healthy volunteers as single, repeat single, or multiple doses for up to 10 days' duration, 32 subjects with various degrees of renal impairment, and 24 subjects with various degrees of hepatic impairment. In healthy volunteer studies, a transient, reversible decrease in neutrophil count has been seen after doses of 25 to 50 mg, which reverses 12 to 24 hours after stopping drug. These neutropenia events were generally of Grade 1 or Grade 2 severity, with a single instance of severe Grade 4 neutropenia that led to study drug

discontinuation in 1 subject receiving 50 mg ruxolitinib twice daily (BID; highest dose). The MTD in healthy volunteers was determined to be 25 mg BID or 100 mg QD.

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

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

1.6.1.2. Phase 3 Studies in Subjects With Myelofibrosis

Up to 22 FEB 2018, ruxolitinib has been administered to more than 8738 subjects in Novartis- and Incyte-sponsored interventional clinical trials. Two pivotal Phase 3 studies (COMFORT-I and COMFORT-II) enrolled subjects with MF, and together they support the efficacy and safety of ruxolitinib for the treatment of patients with PMF, PPV-MF, or PET- MF. COMFORT-I, conducted in the United States, Canada, and Australia, was a double-blind, placebo-controlled study that enrolled 309 subjects, and COMFORT-II was an open-label study conducted in Europe that compared ruxolitinib with best available therapy in 219 patients.

In the randomized period of the 2 pivotal studies in MF, COMFORT-I and COMFORT-II (cutoff: 01 MAR 2011, median duration of exposure = 10.8 months) discontinuation due to AEs, regardless of causality, was observed in 11.3% of subjects. The most frequently reported adverse drug reactions were thrombocytopenia and anemia. Hematologic adverse reactions (any CTCAE grade) included anemia (82.4%), thrombocytopenia (69.8%) and neutropenia (16.6%). Anemia, thrombocytopenia, and neutropenia are dose-related effects. The 3 most frequent nonhematologic adverse reactions were bruising (21.6%), dizziness (15.3%), and headache (14.0%). The 3 most frequent nonhematologic laboratory abnormalities were raised ALT (27.2%), raised AST (18.6%), and hypercholesterolemia (16.9%).

Long-term treatment and follow-up in subjects with MF (including 615 subjects treated with ruxolitinib during the controlled and extension phases of studies INCB 18424-251: cutoff, 01 OCT 2012; COMFORT-I: 15 OCT 2015; COMFORT-II: 20 APR 2015) has shown that as expected, the numbers and proportions of AEs and SAEs has increased. However, no new safety signals have emerged (median duration of exposure for this population is 28.78 months, with 1578.45 patient-years of exposure).

1.6.1.3. Other Ongoing Studies

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

1.7. Justification of Study Treatment Regimen

In clinical studies to date, DLTs have not been observed at doses of INCB050465 up to 20 mg, and target inhibition as assessed by phosphorylated protein kinase B levels in peripheral blood showed > 80% inhibition at trough in subjects receiving 5 mg, 10 mg, 15 mg, or 20 mg of INCB050465. Exploration of doses of 5, 10, 20, or 30 mg in the present study is therefore clinically reasonable. Indeed, doses of 10 or 20 mg given daily for 8 weeks followed by weekly have been well tolerated, and no DLTs were observed.

Previously, Part 3 was implemented to explore daily doses beyond Week 8. The 8-week higher dose was retained, and subjects in Part 3 either switched to weekly dosing or remained on daily doses but at a lower dose. Part 4 will use all daily dose regimens and will directly examine the

role a higher initial dose might play in overall response and duration of response. From the subject's perspective, taking the same dose every day from start to finish would be the simplest regimen to follow. However, the initial use of a higher dose might be critical to achieve significant decreases in spleen size and/or symptom scores more quickly in this refractory population. Part 4 of the study will compare a group of subjects who begin receiving INCB050465 at 20 mg QD, then decrease to 5 mg QD after 8 weeks (dose group TG5I/M) with a group who begin at and remain on doses of 5 mg QD (dose group TG5D).

All parts of the study require that subjects be on a stable dose of ruxolitinib for at least 8 weeks before the screening visit; doses of ruxolitinib may not exceed 25 mg BID for subjects with platelet counts $\geq 100 \times 10^9$/L and may not exceed 10 mg BID for subjects with platelet count $\geq 50 \times 10^9$/L but $< 100 \times 10^9$/L, which mirrors the recommendations for treatment doses in the ruxolitinib complete prescribing information. The requirement for a stable dose before study entry further implies adequate tolerability for the dose of ruxolitinib in a given subject.

1.8. Potential Risks and Benefits of the Treatment Regimen

1.8.1. Potential Risks of INCB050465 Based on Preclinical Safety

Potential risks with administration of INCB050465 based on preclinical findings include lymphoid depletion (refer to the INCB050465 IB). This may result in infections, fever, or cytokine release resulting in fever, chills, hypotension, wheezing, and/or rash.

In both rats and dogs, immunosuppression (evident as minimal to marked depletion of lymphoid tissues, including thymus, lymph nodes, spleen, and gut-associated lymphoid tissue) was observed at all doses and considered to be consistent with the pharmacologic activity of INCB050465. The incidence and severity of these findings increased with dose.

1.8.2. Potential Risks of INCB050465 Based on Prior Clinical Studies

INCB050465 has effects on the immune system. Therefore, subjects must be monitored closely for evidence of infections or new cancers, and administration should be discontinued if there is evidence of clinically significant infection or new cancer.

For studies combining INCB050465 with a JAK inhibitor (eg, INCB039110, INCB052793, or ruxolitinib), all immune-related AEs must be completely resolved to baseline for 2 weeks before starting study medications, and subjects with history of Grade 3 or 4 immune-related AEs from prior immunotherapy will be excluded. Subjects with a history of immune-related ocular AEs will also be excluded.

One case of PJP has been reported with the use of INCB050465 in combination with pembrolizumab. The subject had not received PJP prophylaxis before the event. All subjects who receive INCB050465 (as monotherapy or combination therapy) will also receive PJP prophylaxis. Subjects allergic to or at risk for standard PJP prophylaxis with sulfonamide antibiotics will receive either inhaled pentamidine or atovaquone (Mepron®) for prophylaxis; dapsone should not be used in such subjects. Prophylaxis should be given while subjects are receiving study treatment and continued for 2 to 6 months after the last dose of study drug.

1.8.3. Potential Benefits of INCB050465 Based on Prior and Ongoing Clinical Studies

Based on emerging efficacy and safety data from the ongoing Study INCB 50465-101 (see Section 1.5.4.1), the treatment regimen for Study INCB 50465-201 Part 1 was selected to be 10 mg QD (Cohort 1) or 20 mg QD (Cohort 2) given for 8 weeks, followed by 10 mg (Cohort 1) or 20 mg (Cohort 2) given once weekly. Doses of 10 mg or 20 mg QD provide trough concentrations exceeding the IC_{90} (based on an *in vitro* whole-blood assay). Furthermore, 20 mg QD has demonstrated efficacy in DLBCL and in other types of NHLs. However, 24% of all subjects in study INCB 50465-101 discontinued study treatment due to an AE. Consequently, after administration of daily INCB050465 for 8 weeks in the present study, the dosing regimen was reduced to once-weekly dosing for Part 1 and Part 2.

Pharmacodynamic data from INCB 50465-101 showed that a single dose of 20 mg exhibited maximal inhibition of AKT in an *ex vivo* pharmacodynamic assay, and PK modeling suggests that 20 mg once weekly will 1) achieve maximal inhibition equivalent to approximately 10 × IC_{90}, 2) exceed the IC_{90} for approximately 36 hours, and 3) have minimal to no inhibition for approximately half the dosing interval. This once-weekly regimen is similar to that of another PI3K inhibitor (copanlisib), which is administered IV on Days 1, 8, and 15 of a 28-day cycle, and which achieved 7 objective responses in 9 subjects with NHL (Patnaik et al 2016). Among the 51 subjects who received study drug, 4 discontinued treatment due to an AE. There were 2 events of Grade 3 noninfectious pneumonitis, 1 event of Grade 3 diarrhea, and no events of colitis.

This once-weekly regimen was proposed to maintain response while providing time off from pathway inhibition, which may reduce the frequency of AEs. This was the dosing frequency used for both Part 1 (now completed) and Part 2. As of MAR 2018, with approximately 28 total subjects treated with this dosing frequency in Parts 1 and 2, no DLTs had been observed, and no trends for late-onset toxicity had been noted using available nonverified data. There did not appear to be a meaningful difference between the 10 mg and 20 mg dose groups for safety or efficacy. Part 3 was initiated to compare long-term weekly dosing with long-term, low-dose daily dosing: INCB050465 20 mg QD for 8 weeks followed by 20 mg once weekly (TG20) versus INCB050465 20 mg QD for 8 weeks followed by 5 mg QD (TG5).

As of SEP 2018, the safety profile continues to be similar between dose groups. Part 4 of the study will explore and compare 2 all daily dose regimens: subjects in group TG5D will receive 5 mg QD from study start until EOT; subjects in group TG5I/M will receive 20 mg QD for the first 8 weeks and then transition to 5 mg QD. Part 4 thus directly assesses the impact of an initial higher dose on overall response in this refractory population.

1.8.4. Potential Risks of PI3Kδ Inhibition Based on Other Agents in Class

Idelalisib was approved by the FDA in July 2014 for treatment of relapsed/refractory follicular lymphoma and relapsed small lymphocytic lymphoma and for treatment of chronic lymphocytic leukemia in combination with rituximab. Severe toxicities seen with the use of this agent include hepatotoxicity (fatal or serious occurring in 14%), fatal and/or serious diarrhea or colitis (14%), intestinal perforation, and infections including pneumonitis and cytomegalovirus (CMV) reactivation. Subjects will be monitored closely for the development of these conditions and will have treatment interrupted and dose reduced as appropriate. Subjects will receive prophylaxis for PJP and will be monitored for CMV viremia during the study.

Based on experience with idelalisib, hepatotoxicity is a risk with this class of agents. Preclinically, hepatotoxicity with INCB050465 was only seen at plasma exposures > 65-fold higher than the projected clinical exposure at 10 mg QD. The pharmacophore of INCB050465 is different from idelalisib. Other PI3Kδ inhibitors with a different pharmacophore have not shown hepatotoxicity in early studies (Savona et al 2013).

1.8.5. Potential Risks of Ruxolitinib

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

The primary clinical risks with ruxolitinib treatment are the potential sequelae of decreased hematopoietic proliferation attributable to the inhibition of growth factor pathways associated with JAK inhibition. Dose-dependent, reversible thrombocytopenia has been observed in studies of subjects with MF. Anemia and, less frequently, neutropenia have also been observed in studies in subjects with MF. Increased rates of infection and anemia are potential risks of myelosuppression, and there are multiple sequelae of anemia, including the burden and risks of transfusion. In healthy volunteers, rheumatoid arthritis subjects, and hormone-refractory prostate cancer subjects with greater bone marrow reserve, the effects on hematopoietic proliferation appear to be less pronounced (ruxolitinib IB).

1.8.6. Potential Risks of the Combination of INCB050465 and Ruxolitinib

The principle toxicity of inhibiting both PI3Kδ and JAK pathways is expected to be reversible effects on immune function. Combined inhibition may adversely affect both B-cell and T-cell immune function with resultant increased risk of a variety of infections. Subjects should be closely monitored for bacterial infections and opportunistic infections, and treatment will be interrupted for infections that can be easily managed with antibiotic therapy and discontinued for infections that are serious or require prolonged antibiotic therapy. Subjects should be monitored for varicella-zoster virus and herpes simplex virus infections and treatment started promptly. Subjects will be assessed for CMV viremia periodically during the study, and treatment started promptly if there is evidence of CMV reactivation.

Ongoing Study INCB 40093-102 combines another PI3Kδ inhibitor INCB040093 with the experimental JAK1 inhibitor INCB039110 in subjects with previously treated B-cell malignancies. As of December 2015, 67 subjects have been enrolled. Five cases of PJP have been reported by subjects receiving this combination therapy (7.5% incidence); PJP is a rare but serious complication observed in lymphoma patients undergoing treatment. Because of the increased risk of PJP in subjects receiving INCB03911 in combination with INCB040093, a standard prophylaxis regimen is now required for all subjects; no additional cases of PJP have been observed. In the present study, a standard PJP prophylaxis regimen will be required for all subjects receiving combination treatment with INCB050465. Subjects who are allergic to sulfonamide antibiotics should be treated with either inhaled pentamidine or atovaquone for PJP prophylaxis. Dapsone should not be used in such subjects.

Effects on WBC, red blood cell (RBC), and platelet counts could result from JAK inhibition and result in infections, anemia, or thrombocytopenia requiring transfusions. Subjects will be

monitored closely for hematology parameters with weekly blood draws for subjects in Part 1 and twice monthly blood draws for hematology for subjects in Part 2, Part 3, and Part 4.

Combined inhibition is not expected to increase the risk of hepatic toxicity, and liver function testing will be monitored regularly. Any hepatic toxicity is expected to be reversible. These potential risks are considered acceptable in a population with MF that is at least partially refractory to ongoing ruxolitinib treatment.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

- Part 1: To evaluate the safety and tolerability of INCB050465 in combination with ruxolitinib in subjects with MF (PMF, PPV-MF, or PET-MF) and select a dose for further evaluation.
- Parts 2, 3, and 4: To evaluate the efficacy of INCB050465 in combination with ruxolitinib on spleen volume reduction in subjects with PMF, PPV-MF, or PET-MF.

2.1.2. Secondary Objectives

- To evaluate the efficacy of INCB050465 in combination with ruxolitinib on subject reports of MF symptoms.
- To evaluate the efficacy of INCB050465 in combination with ruxolitinib on response using International Working Group (IWG)–Myeloproliferative Neoplasms Research and Treatment (MRT) criteria.
- To assess the PK of INCB050465 and ruxolitinib alone and when given in combination in subjects with MF.
- To evaluate the safety and tolerability of INCB050465 when combined with ruxolitinib in subjects with MF.

[redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoints

- Part 1: Determination of the doses of INCB050465 that are safe and tolerable in combination with ruxolitinib.
- Parts 2, 3, and 4: Change and percentage change in spleen volume from baseline through Week 12 as measured by magnetic resonance imaging (MRI; or computed tomography [CT] scan in applicable subjects).

2.2.2. Secondary Endpoints

- Change and percentage change in spleen volume from baseline through Week 24 as measured by MRI (or CT scan in applicable subjects).
- Change and percentage change in total symptom score from baseline through Week 12 or Week 24 as measured by the Myelofibrosis Symptom Assessment Form version 3.0 (MFSAF v3.0) symptom diary and by the Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF).
- Number of subjects with responses according to the 2013 IWG consensus criteria for treatment response in PMF, PPV-MF, and PET-MF.
- Patient Global Impression of Change score at each visit where the variable is measured.
- Population PK parameters of INCB050465 and ruxolitinib alone and in combination (eg, AUC, C_{max}) will be summarized.
- Safety and tolerability of the treatment regimens through assessment of AEs and changes in safety assessments including laboratory parameters.

[redacted]

3. SUBJECT ELIGIBILITY

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

3.1. Study Population

Male or female individuals subjects aged 18 years or older who have been diagnosed with PMF or secondary MF (PPV-MF or PET-MF) and who have a suboptimal response while receiving ruxolitinib monotherapy for a period of at least 6 months, with a stable ruxolitinib dose regimen for at least 8 weeks before the first administration of INCB050465.

3.2. Subject Inclusion Criteria

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

1. Men and women aged 18 years or older.
2. Diagnosis of PMF, PPV-MF, or PET-MF.
3. Treated with ruxolitinib for ≥ 6 months with a stable dose for ≥ 8 weeks (acceptable doses are 5 mg BID to 25 mg BID).
4. Evidence of inadequate response to ruxolitinib:
    a. Palpable spleen of > 10 cm below the left subcostal margin on physical examination at the screening visit OR
    b. Palpable splenomegaly of 5 to 10 cm below left subcostal margin on physical exam AND active symptoms of MF at the screening visit as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form (Appendix D).
5. Subjects with an ECOG performance status of 0, 1, or 2 (see Appendix G).
6. Screening bone marrow biopsy specimen available or willingness to undergo a bone marrow biopsy at screening/baseline; willingness to undergo bone marrow biopsy at Week 24.
7. Life expectancy of at least 24 weeks.
8. Willingness to avoid pregnancy or fathering children based on the criteria below:
    a. Woman of nonchildbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 50 years of age).
    b. Woman of childbearing potential who has a negative serum pregnancy test at screening and before the first dose on Day 1 and who agrees to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through safety follow-up. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.

c. Man who agrees to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 93 days after treatment with INCB050465. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the subject and their understanding confirmed.

3.3. Subject Exclusion Criteria

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

1. Use of experimental drug therapy for MF or any other standard drug (eg, danazol, hydroxyurea, etc.), with the exception of ruxolitinib within 6 months of starting study (combination) therapy and/or lack of recovery from all toxicities from previous therapy (except ruxolitinib) to Grade 1 or better.
2. Inability to swallow food or any condition of the upper gastrointestinal tract that precludes administration of oral medications.
3. Unwillingness to be transfused with blood components.
4. Recent history of inadequate bone marrow reserve as demonstrated by the following:
   a. Platelet count $< 50 \times 10^9$/L in the 4 weeks before screening or platelet transfusion(s) within 8 weeks before screening.
   b. Absolute neutrophil count (ANC) levels $< 0.5 \times 10^9$/L in the 4 weeks before screening.
   c. Subjects with peripheral blood blast count of > 10% at the screening or baseline hematology assessments.
   d. Subjects who are not willing to receive RBC transfusions to treat low hemoglobin levels.
5. Inadequate liver function at screening visit as demonstrated by the following:
   a. Direct bilirubin $\geq 2.0 \times$ the upper limit of laboratory normal (ULN). (NOTE: direct bilirubin will only be determined if total bilirubin is $\geq 2.0 \times$ ULN).
   b. ALT or AST $> 2.5 \times$ ULN.
6. Inadequate renal function at screening visit as demonstrated by creatinine clearance < 50 mL/min measured or calculated by Cockroft-Gault equation, or glomerular filtration rate < 50 mL/min/1.73 m^2 as calculated using the Modification of Diet in Renal Disease formula.
7. Active bacterial, fungal, parasitic, or viral infection that requires therapy. Subjects with acute infections requiring treatment should delay screening/enrollment until the course of therapy has been completed and the event is considered resolved. Prophylactic antibiotics will be permitted.
8. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection that requires treatment or at risk for HBV reactivation. Hepatitis B virus DNA and HCV RNA must be undetectable upon testing. At risk for HBV reactivation is defined as hepatitis B surface antigen positive or anti–hepatitis B core antibody positive. Cytomegalovirus must be undetectable by polymerase chain reaction.

9. Known human immunodeficiency virus (HIV) infection.
10. Uncontrolled, severe, or unstable cardiac disease that in the investigator's opinion may jeopardize the safety of the subject or the compliance with the Protocol.
11. Active invasive malignancy over the previous 2 years except treated basal or squamous carcinomas of the skin, completely resected intraepithelial carcinoma of the cervix, and completely resected papillary thyroid and follicular thyroid cancers. Subjects with malignancies with indolent behavior such as prostate cancer treated with radiation or surgery may be enrolled as long as they have a reasonable expectation to have been cured with the treatment modality received.
12. Splenic irradiation within 6 months before receiving the first dose of INCB050465.
13. Concurrent use of any prohibited medications (see Section 5.7.4 for specific prohibited medications and the associated timeframe over which they are prohibited).
14. Active alcohol or drug addiction that would interfere with their ability to comply with the study requirements.
15. Prior therapy with any drug that inhibits PI3K (examples of drugs targeting this pathway include but are not limited to INCB040093, idelalisib, duvelisib, and TGR-1202).
16. Use of any potent CYP3A4 inhibitors or inducers (Appendix B) within 14 days or 5 half-lives (whichever is longer) before the first dose of INCB050465 or anticipated during the study.
17. Inadequate recovery from toxicity and/or complications from a major surgery before starting therapy.
18. Currently breastfeeding or pregnant.
19. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
20. Inability to comprehend or unwilling to sign the informed consent form (ICF).
21. History of Grade 3 or 4 immune-related AEs from prior immunotherapy.
    a. Any immune-related AEs of Grade 1 or 2 must be resolved before receiving the first dose of INCB050465.
22. History of immune-related ocular AEs of any toxicity grade.
23. Receipt of any live vaccine within 30 days of first dose of INCB050465.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is a Phase 2 study of the combination of the PI3Kδ inhibitor INCB050465 and the JAK 1/2 inhibitor ruxolitinib in subjects with PMF or secondary MF (PPV-MF or PET-MF) who have suboptimal response while receiving ruxolitinib monotherapy. Suboptimal response is based on assessment of suboptimal reductions in spleen size or symptoms and is defined in the inclusion criteria (Section 3.2). At least 6 months of prior ruxolitinib therapy is required, including ruxolitinib administration at a stable dose for at least 8 weeks before randomization. The study is composed of 4 parts:

Part 1 was an open-label safety run-in portion designed to assess the safety and tolerability of the combination of INCB050465 with ruxolitinib and to select appropriate doses of INCB050465 for Part 2 in this patient population. Part 1 has been completed.

Part 2 was planned to be a block-randomized open-label study with 2 treatment groups: TG10 and TG20. Both treatment groups use daily doses for the first 8 weeks, then weekly doses at the same strength through EOT. Enrollment in Part 2 was suspended with implementation of Amendment 5.

Part 3 was planned to be an open-label study to compare daily versus weekly long-term doses. All subjects would begin with INCB050465 20 mg QD. After 8 weeks, subjects in TG5 would continue receiving INCB050465 at 5 mg QD, and subjects in TG20 would continue receiving INCB050465 at 20 mg once weekly. Enrollment in Part 3 will be suspended with implementation of Amendment 6.

With Amendment 6, Part 4 is added to directly compare different daily dosing regimens and the impact of an initial higher dose of INCB050465 on long-term response. Subjects in Part 4 will be randomized to 1 of 2 groups: TG5D will begin on Day 1 with a daily dose of 5 mg, and subjects will continue receiving 5 mg QD indefinitely or until discontinuation criteria are met; TG5I/M will begin on Day 1 with a daily dose of 20 mg (the induction dose), and after 8 weeks subjects will switch to 5 mg QD (the maintenance dose). Treatment for subjects randomized to TG5I/M will continue indefinitely or until discontinuation criteria are met.

Randomization:

During Part 2, subjects were randomized 1:1 to the 2 treatment groups using block randomization, stratified by Eastern Cooperative Oncology Group (ECOG) performance status at screening (ECOG 0-1 vs ECOG 2).

During Part 3, subjects were randomized on a 3:2 ratio between TG5 and TG20. Stratification was by ECOG status as in Part 2.

During Part 4, subjects will be randomized on a 3:2 ratio between TG5D and TG5I/M until 25 total subjects have been randomized, with subsequent randomization on a 1:1 ratio until approximately 30 subjects have been enrolled in each group. Stratification will be by ECOG status as in Part 3.

4.1.1. Part 1: Safety Run-In Portion

The safety run-in portion was to test up to 3 doses of INCB050465 in combination with ruxolitinib for a 28-day assessment (4 weeks). Initially, 3 subjects were enrolled in Cohort 1 to receive INCB050465 10 mg together with ruxolitinib, at the dose ongoing at the time of enrollment. After 28 days, subjects who took at least 22 of 28 daily doses of INCB050465 AND ruxolitinib OR had a DLT during the first 28 days (see Table 3) were included in the evaluation cohort. Additional subjects were to be enrolled into Cohort 1 if discontinuations resulted in fewer than 3 evaluable subjects. After evaluation, the actions listed in Table 2 were to occur.

Table 2: Safety Run-In Cohorts

Cohort	No. of Subjects	Regimen	DLTs Observed	Action Taken
1	3	INCB050465 10 mg QD for 8 weeks followed by 10 mg once weekly plus ruxolitinib 5 mg BID to 25 mg BID[a]	0	Proceed to Cohort 2.
			1	Enroll 3 additional subjects, and evaluate the total of 6 subjects after 28 days. If < 2 subjects have a DLT, then proceed to Cohort 2. If ≥ 2 subjects have a DLT, then proceed to Cohort 3.
			> 1	Proceed to Cohort 3.
2	3 + 3	INCB050465 20 mg QD for 8 weeks followed by 20 mg once weekly plus ruxolitinib 5 mg BID to 25 mg BID[a]	0 or 1	Enroll 3 additional subjects, and evaluate the total of 6 subjects after 28 days. If < 2 subjects have a DLT, then proceed to Part 2 using doses of 10 mg and 20 mg INCB050465.
			≥ 2	Proceed to Cohort 3.
3	6	INCB050465 5 mg QD for 8 weeks followed by 5 mg once weekly plus ruxolitinib 5 mg BID to 25 mg BID[a]	0 or 1	If < 2 subjects have a DLT and if Cohort 1 exceeded the DLT allowance, then proceed to Part 2 as a single-group study of 5 mg INCB050465. If Cohort 1 did not exceed DLT allowance, proceed to Part 2 with doses of 5 mg and 10 mg INCB050465.
			≥ 2	Terminate study. Alternatively, sponsor may elect to assess doses lower than 5 mg. If Cohort 1 did not exceed the DLT allowance, but Cohort 3 showed DLTs, additional cohort expansion might be conducted to assess these and other doses of INCB050465, pending sponsor review and discussion of available data.

[a] The dose of ruxolitinib will be that which the subjects had been taking for at least 8 weeks before the first dose of INCB050465. The maximum dose of ruxolitinib allowed for subjects with baseline platelet count ≥ 100×10^9/L is 25 mg BID, and the maximum dose of ruxolitinib for subjects with baseline platelet count of ≥ 50×10^9/L to < 100×10^9/L is 10 mg BID.

Subjects receiving dose reductions (but not meeting DLT criteria) during the first 28 days who had not received at least 22 days of the prescribed dose of INCB050465 and ruxolitinib for that cohort were not considered evaluable for the purposes of determining the MTD and were replaced.

The MTD of INCB050465 was planned to be the highest dose level tested that was considered tolerated on the basis of fewer than 2 DLTs in a cohort of 6 subjects. Individual subject dose reductions were made based on events observed at any time during treatment with INCB050465; however, for the purposes of dose cohort escalation/de-escalation, expanding a dose cohort, and determining the MTD of INCB050465, decisions were made based on events that were observed from the first day of study drug administration through and including Day 28. A lower MTD

may have subsequently been determined based on relevant toxicities that became evident after Day 28.

After the 28-day safety evaluation period, safety run-in subjects received additional combination therapy of INCB050465 plus ruxolitinib as long as adequately tolerated with study visits each month and additional laboratory assessments biweekly. INCB050465 administration was QD for total of 8 weeks after the first dose, followed by once-weekly administration at the cohort-specified dose. Measurements and procedures followed those described for the randomized portion. Dose modifications after the 28-day safety evaluation period in the safety run-in cohort followed the dose modification rules in Section 5.5.1.

A DLT was defined as the occurrence of any of the toxicities shown in Table 3 occurring up to and including Day 28, except those with a clear alternative explanation (eg, disease progression, other medications) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. All DLTs were assessed by the investigator using CTCAE v4.03 criteria. Subjects who received at least 22 of 28 doses of INCB050465 and ruxolitinib at the level assigned or had a DLT were considered evaluable for determining tolerability of the dose.

Table 3: Dose-Limiting Toxicities for Part 1

Dose-Limiting Toxicities
Nonhematologic
Nonhematologic DLT is defined as any clinically significant nonhematologic AE or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medication that occurs during the first 28 days of therapy, is assessed as being at least possibly related to study drugs, and meets any of the following criteria: • CTCAE Grade 3 AST or ALT for > 7 days. • CTCAE Grade 4 AST or ALT of any duration. • Grade 3 nausea/vomiting, dehydration, or diarrhea lasting more than 3 days in the setting of optimal supportive medications. • Grade 3 fatigue lasting more than 5 days in the setting of optimal supportive medications. • Grade 3 biochemical abnormalities (eg, lipase elevation or bilirubin elevation) will only be considered a DLT if accompanied by clinical consequences. Grade 3 electrolyte abnormalities will only be considered DLTs if related to study drugs and not corrected by optimal replacement therapy or if persisting after 7 days of optimal replacement therapy. • All Grade 4 nonhematologic toxicities of any duration. • All other clinically significant nonhematologic AEs that are Grade 3 according to CTCAE v4.03.
Hematologic
Myelosuppression and cytopenias are expected outcomes of MF disease processes and MF treatments and per se will not constitute DLTs except as follows: • Grade 4 thrombocytopenia with bleeding. • Grade 4 neutropenia with fever that does not clinically resolve within 7 days in the setting of optimal interventions. Anemia will not be considered in the definition of DLT.

Part 1 was conducted at selected clinical study sites (in the United States only). Enrollment was controlled by distribution of enrollment slots to the clinical sites by the sponsor or its designee. The sponsor conducted approximately weekly safety teleconferences with the investigators

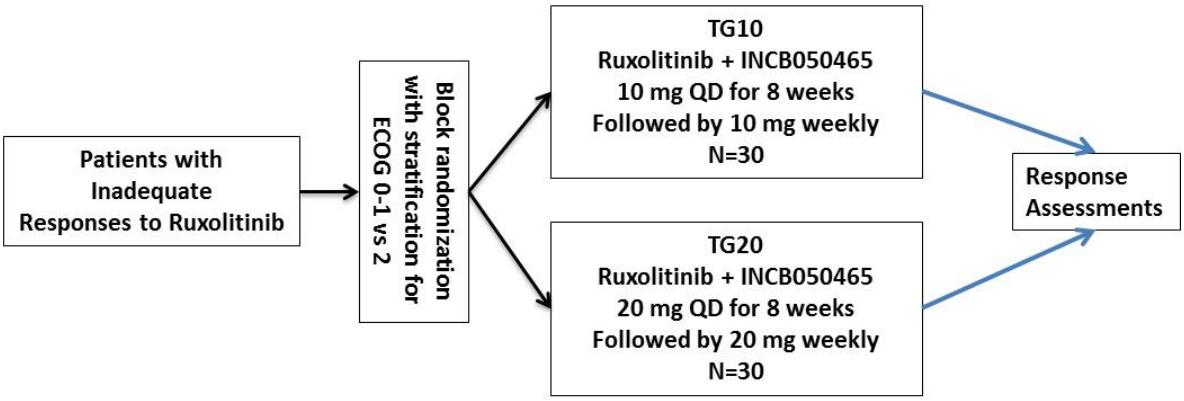
participating in Part 1 to review subject status and safety findings to ensure safe, appropriate administration. Part 1 has been completed. No DLTs were observed. The treatment groups for Part 2 were determined to be TG10 and TG20.

4.1.2. Part 2: Randomized Portion

Part 2 was to be enrolled and conducted provided that a tolerable dose could be established for INCB050465 in combination with ruxolitinib in Part 1 of the study. Part 2 was planned to enroll approximately 60 subjects randomized 1:1 by block randomization into 2 treatment groups, TG10 and TG20.

Figure 1 shows the study design for Part 2.

Figure 1: Part 2 Study Design

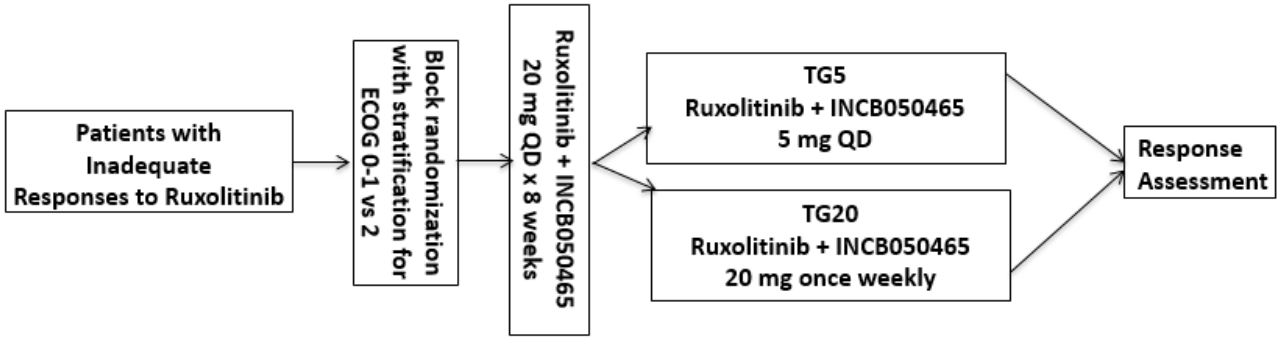


Enrollment into Part 2 at a given study site is terminated effective with site-specific IRB approval of Protocol Amendment 5.

4.1.3. Part 3 Randomized Portion

In Part 3, all subjects will initially receive INCB050465 at 20 mg QD for 8 weeks in combination with ruxolitinib. After Week 8, subjects will be assigned to 1 of 2 dose groups based on block randomization at the time of entry into the study (using a randomization of 3:2 for TG5 vs TG20 for the first 40 subjects, followed by 1:1 randomization for additional subjects, up to a total of approximately 52 subjects) as shown in Figure 2.

Figure 2: Part 3 Study Design

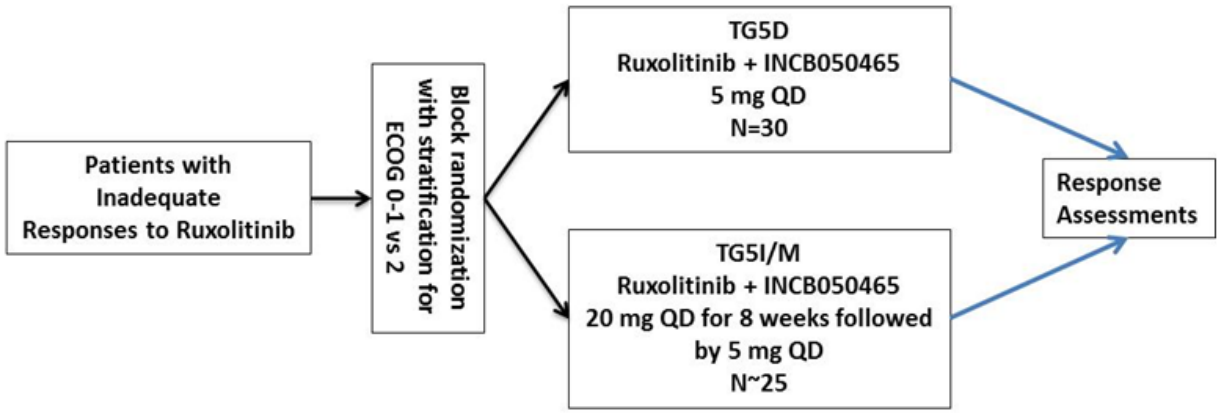


As of site-specific approval of Amendment 6, there will be no further enrollment into Part 3 at the given site. Subjects already enrolled into TG5 in Part 3 will continue to receive INCB050465 according to the original randomization for Part 3 and may continue in the study indefinitely unless criteria for discontinuation are met. Subjects already enrolled into TG20 in Part 3 will have the opportunity to cross over to receive 5 mg QD of INCB050465 once they reach Week 8 provided they demonstrate inadequate response to the current dose regimen; an adequate bone marrow reserve; and no evidence of uncontrolled renal, hepatic, cardiovascular, or gastrointestinal disease. A list of requirements for crossover is provided in Section 5.2.3. The TG20 group will be deemed full with enrollment of the 15th subject to that group considering all sites; all further enrollment to Part 3 will be to TG5 at a given site until Amendment 6 has been approved.

4.1.4. Part 4 Randomized Portion

Part 4 of the study is designed to compare different daily dosing regimens and to address the impact of an initial higher dose of INCB050465 on overall response. Subjects will be randomized to one of 2 groups: TG5D will receive 5 mg daily doses of INCB050465 from Day 1 until EOT visit. TG5I/M will receive doses of 20 mg daily for 8 weeks (induction phase), followed by 5 mg daily dosing (maintenance phase). Dosing will continue per the randomized group assignment indefinitely or until discontinuation criteria are met. Note that TG5I/M is identical to TG5 from Part 3; subjects from these 2 groups will be combined in the final analysis. Figure 3 shows the study design for Part 4.

Figure 3: Study Design for Part 4



4.2. Measures Taken to Avoid Bias

This is an open-label comparison of 2 dose regimens of INCB050465. Subjects will be randomized by block randomization. Measurements of safety and efficacy are objective measurements.

4.3. Number of Subjects

4.3.1. Planned Number of Subjects

Part 1 was expected to enroll 9 to 18 subjects (10 were enrolled), Part 2 was planned to enroll a total of 60 subjects before termination; because Part 3 was added, only 20 subjects were enrolled. Part 3 was expected to enroll approximately 52 subjects; approximately 5 subjects may be enrolled. Part 4 will enroll approximately 55 subjects. Twenty or more clinical sites will participate.

4.3.2. Replacement of Subjects

As noted in Section 4.1, a minimum of 3 subjects must be deemed evaluable for each cohort of Part 1 that is enrolled. If a subject becomes nonevaluable either because of dose compliance < 80% (correct administration of INCB050465 for 22 of 28 days in the safety evaluation period) or withdraws because of an AE that does not meet the criteria for a DLT, then an additional subject will be enrolled to ensure the minimum evaluable cohort is achieved.

4.4. Duration of Treatment and Subject Participation

Screening: Up to 28 days.

Baseline: 7 days before first dose of INCB050465

Treatment: Begins with the first dose of INCB050465 (Day 1). Treatment will continue as long as the regimen is tolerated and the subject does not meet discontinuation criteria. Subjects will receive daily doses of INCB050465 throughout the study, or daily doses for 8 weeks, followed by once-weekly administration or QD administration (determined by the study part to which subjects were enrolled). Subjects who discontinue study treatment will be followed for subsequent MF treatments and survival.

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

Survival follow-up: Until subject dies.

It is estimated that an individual subject will participate for approximately 24 months.

4.5. Overall Study Duration

The study begins when the first subject signs the ICF. The end of the study will occur when all subjects have completed the follow-up visit or discontinued study.

4.6. Study Termination

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

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

5. TREATMENT

5.1. Treatment Assignment

5.1.1. Subject Numbering and Treatment Assignment

Each subject will be identified in the study by a unique subject ID number, which is a combination of the site ID and subject number. Site staff will work through the interactive web response system (IRT/IWRS) to obtain subject number.

Enrollment for Part 1 will be controlled by distribution of enrollment slots to the clinical sites by the sponsor or its designee.

Enrollment for Part 2, Part 3, and Part 4 will be controlled by the IRT/IWRS.

Subjects who are screen failures and are not enrolled in the study will still have data entered into the case report form (CRF). Consult the CRF instructions to determine which CRF pages must be completed for screen failures.

5.1.2. Randomization

For Part 2, Part 3, and Part 4, randomization will occur centrally by IRT/IWRS. Full details will be provided in the INCB 50465-201 Study Manual.

5.2. Cohorts and Treatment Groups

5.2.1. Part 1: Safety Run-In Portion

Up to 3 doses of INCB050465 were to be explored in successive cohorts (see Table 4). All subjects would also receive the same ruxolitinib dose regimen that individual subjects were taking at the time of the screening visit.

Table 4: Part 1 Treatment Groups

Cohort	Dose Regimen
Cohort 1	INCB050465 10 mg QD for 8 weeks followed by once-weekly dosing at 10 mg.
Cohort 2	INCB050465 20 mg QD for 8 weeks followed by once-weekly dosing at 20 mg
Cohort 3	INCB050465 5 mg QD for 8 weeks followed by once-weekly dosing at 5 mg

After the 28-day safety evaluation period, safety run-in subjects may receive additional combination therapy of INCB050465 plus ruxolitinib long as adequately tolerated and if no

discontinuation criteria are met. Cohorts 1 and 2 were completed. No DLTs were observed. Part 1 is complete.

5.2.2. Part 2, Part 3, and Part 4 Treatment Groups: Randomized Portion

TG10: Ruxolitinib at stable dose plus INCB050465 at 10 mg QD for 8 weeks followed by 10 mg once weekly.

TG20: Ruxolitinib at stable dose plus INCB050465 at 20 mg QD for 8 weeks followed by 20 mg once weekly. Note that enrollment in Part 2 was suspended with implementation of Amendment 5.

TG5: Ruxolitinib at stable dose plus INCB050465 at 20 mg QD for 8 weeks followed by 5 mg QD. Note that enrollment in Part 3 will be suspended with implementation of Amendment 6.

TG5I/M: Ruxolitinib at stable dose plus INCB050465 at 20 mg QD for 8 weeks followed by 5 mg QD. Note this Part 4 dose group is identical to TG5 group in Part 3.

TG5D: Ruxolitinib at stable dose plus INCB050465 at 5 mg QD.

5.2.3. Crossover of Part 2 or Part 3 Subjects

It is anticipated that approximately 15 to 20 subjects will have been enrolled into Part 2. With IRB approval of Protocol Amendment 5 at a given site, subjects randomized to TG10 at that site may cross over to either 20 mg QD followed by 5 mg QD after Week 8 (if subject is within the first 8 weeks of treatment at the time of crossover), or to 5 mg QD (if subject is beyond 8 weeks of treatment and receiving 10 mg once weekly at the time of crossover). With IRB approval of Protocol Amendment 6 at a given site, subjects randomized to TG20 at that site may cross over to 5 mg QD once Week 8 has been reached. All potential crossover subjects must meet <u>all of the following criteria</u>:

1. Spleen size by palpation at most recent visit has decreased by < 25% from baseline while on study.
2. Has recent history of adequate bone marrow reserve as demonstrated by the following:
   a. Platelet count $\geq 50 \times 10^9$/L in the 4 weeks before crossover.
   b. ANC levels $\geq 0.5 \times 10^9$/L in the 4 weeks before crossover.
3. Has adequate liver function at most recent study visit as demonstrated by the following:
   a. Direct bilirubin < 2.0 × the ULN. (NOTE: direct bilirubin will only be determined if total bilirubin is ≥ 2.0 × ULN).
   b. ALT or AST < 2.5 × ULN.
4. Has adequate renal function at most recent visit as demonstrated by creatinine clearance > 50 mL/min measured or calculated by Cockroft-Gault equation.
5. Subject has been at least 85% compliant with study drug administration per drug accountability assessments at visits to date.
6. Subject has not developed a cardiovascular or gastrointestinal condition since Day 1 that would have excluded him/her from study entry.

Subjects who do not meet these criteria, or subjects who do meet the criteria but do not wish to cross over, may continue on the originally assigned regimen, and may crossover at any time provided the criteria for crossover are met and crossover is determined by subject and investigator to represent the best option.

5.3. Study Drugs

5.3.1. INCB050465

5.3.1.1. Description and Administration

<table>
<tr><td>Compound name</td><td colspan="2">INCB050465</td></tr>
<tr><td>Dosage strengths</td><td colspan="2">1 mg, 2.5 mg, 5 mg, and 20 mg</td></tr>
<tr><td>Form</td><td colspan="2">Tablet</td></tr>
<tr><td>Active compound</td><td colspan="2">INCB050465</td></tr>
<tr><td>Route of administration</td><td colspan="2">Oral</td></tr>
<tr><td>Dose and regimen for Part 3</td><td colspan="2">20 mg QD for 8 weeks followed by randomization to either 5 mg QD or 20 mg once weekly</td></tr>
<tr><td>Dose and regimen for Part 4</td><td colspan="2">TG5I/M: 20 mg QD for 8 weeks followed by 5 mg QD until EOT
TG5D: 5 mg QD from Day 1 until EOT</td></tr>
<tr><td>Instructions</td><td colspan="2">INCB050465 will be taken orally with water in a fasted state except on mornings of monthly study visits (see Table 9) where they must arrive for their study visit in the fasted state for study drug administration at the visit. Subjects should refrain from food consumption for at least 1 hour after administration of INCB050465.
For Part 3 subjects only: Once 8 weeks of daily dosing have been completed, subject will switch to either 5 mg QD or 20 mg once weekly, beginning the next weekday after the last daily dose:</td></tr>
<tr><td></td><td>Last daily dose</td><td>First weekly dose</td></tr>
<tr><td></td><td>Monday</td><td>Tuesday, then every Tuesday</td></tr>
<tr><td></td><td>Tuesday</td><td>Wednesday, then every Wednesday</td></tr>
<tr><td></td><td>Wednesday</td><td>Thursday, then every Thursday</td></tr>
<tr><td></td><td>Thursday</td><td>Friday, then every Friday</td></tr>
<tr><td></td><td>Friday</td><td>Friday (the following week, then every subsequent Friday)</td></tr>
</table>

Note that subjects must be instructed to withhold the morning dose of INCB050465 and to arrive in the fasted state until reaching the clinic for each study visit where administration will occur (first 24 weeks of therapy only). The dose must be reduced or interrupted for declining platelet count or ANC as described in Section 5.5 and will be increased or restarted with recovery of hematologic parameters.

5.3.1.2. Supply, Packaging, and Labeling

INCB050465 tablets are packaged in high-density polyethylene bottles, no preparation is required.

All Incyte investigational product labels will be in the local language and will comply with the legal requirements of each country and will state "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

5.3.1.3. Storage

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

5.3.2. Ruxolitinib

5.3.2.1. Description and Administration

Ruxolitinib will be self-administered as a BID oral treatment using the dose designated as the stable dose at the time of the screening visit for each subject. Acceptable doses are 5 mg BID to 25 mg BID.

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

Note that subjects must be instructed to withhold the morning dose or ruxolitinib until reaching the clinic for each study visit where administration will occur. The dose may need to be reduced or interrupted for declining platelet count or ANC as described in Section 5.5 and will be increased or restarted with recovery of hematologic parameters.

5.3.2.2. Supply, Packaging, and Labeling

Subjects will continue to take the commercial supplies of ruxolitinib that have been prescribed for them.

5.3.2.3. Storage

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

5.3.3. Instruction to Subjects for Handling INCB050465 and Ruxolitinib

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

- To store at room temperature.
- To only remove the number of tablets needed from the bottle of INCB050465 at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses of INCB050465 and ruxolitinib on schedule.
- To report any missed doses at the next study visit.
- Not to take another dose if vomiting occurs taking study drug(s).
- To keep all study medications out of reach of children.
- To bring all used and unused study drug kits to the site at each visit.
- To skip a dose of study drug if it is missed by more than 4 hours and to take the next scheduled dose at the usual time.

5.4. Treatment Compliance

Compliance with all study-related treatments should be emphasized to the subject by the site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with INCB050465 administration will be calculated by the sponsor based on the drug accountability documented by the site staff and monitored by the sponsor/designee (tablet counts). Subjects will be instructed to bring all used and unused bottles of INCB050465 with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability. The drug accountability documentation will be used by the sponsor to calculate treatment compliance.

Although commercial supplies of ruxolitinib will be utilized, compliance with ruxolitinib will also be documented in the medical record and monitored by the sponsor or its designee. Subjects will record the doses of ruxolitinib taken on a paper diary issued by the site and collected at each visit.

5.5. Treatment Interruptions and Adjustments

5.5.1. Dose Modifications

Selections and modifications to the study drug regimen are planned for dose-escalation cohorts. Dose interruptions and modifications also may occur for individual study subjects. The identification of DLTs will define the doses used in planned cohorts (see Table 3 and Section 4.1). Further, the occurrence of DLTs and other toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual subjects.

5.5.2. Dose Limiting Toxicities

See Table 3 and Section 4.1 for definition of DLTs.

5.5.3. Management of Dose-Limiting Toxicities or Other Urgent Situations

In all cases, investigators may employ any measures or concomitant medications, after discussion with the sponsor (whenever possible), necessary to optimally treat the subject.

5.5.4. Follow-Up of Dose-Limiting Toxicities

Any DLT should be followed until it resolves to baseline or appears to have stabilized for a minimum of 2 weeks. During follow-up, subjects should be seen as often as medically indicated to assure safety.

5.5.5. Procedures for Cohort Review and Dose Escalation

Telephone conferences will be scheduled by the sponsor with study investigators in order to review cohort-specific data and overall safety data, agree on dose escalation, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions.

5.5.6. Criteria and Procedures for Dose Interruptions and Adjustments of INCB050465

Treatment with INCB050465 may be delayed up to 2 weeks (14 days) to allow for resolution of toxicity. Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact the sponsor to discuss the case of any subject whose treatment has been delayed for more than 14 days before restarting treatment with INCB050465.

Table 5 shows dose reduction and interruptions for INCB050465. Because subjects may enter the study with extensive pretreatment and/or severe bone marrow infiltration by the primary disease, these dose reduction rules are provided as guidelines (see Table 5 and Table 6). **Individual decisions regarding dose reduction should be made using investigator clinical judgment and in consultation with the sponsor's medical monitor in those cases where the guidelines will not be followed, taking into account relatedness of the AE to the study drug and the subject's underlying condition**. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules.

Table 5: Guidelines for Interruption and Restarting of INCB050465

ADVERSE EVENT	ACTION TAKEN
Chemistry	
• AST and/or ALT are > 5.0 × ULN. Note: In subjects with bone metastasis-related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor. **Step 2:** Restart study drug at same dose. If assessed as related to study drug, restart study drug at next lower dose (or at 25% reduction, rounded down to the nearest pill strength); monitor as clinically indicated.
Hematology	
• ANC ≤ 1.0 × 10^9/L unless because of underlying disease. Applies only if this represents a worsening grade from baseline. • Platelet count ≥ 50 × 10^9/L and < 75 × 10^9/L unless because of underlying disease. Applies only if this represents a worsening grade from baseline.	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 or pretherapy baseline. **Step 2:** Restart study drug at same dose and monitor as clinically indicated.
• Grade 4 ANC (< 0.5 × 10^9/L) regardless of baseline grade. • ≥ Grade 3 ANC with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection regardless of baseline grade. • Platelet count is < 50 × 10^9/L, regardless of baseline grade.	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 or pretherapy baseline. **Step 2:** Restart study drug at same dose. If assessed as related to study drug, restart study drug at next lower dose; monitor as clinically indicated.

Table 5: Guidelines for Interruption and Restarting of INCB050465 (Continued)

ADVERSE EVENT	ACTION TAKEN
Nonhematologic toxicities	
• Diarrhea/colitis (Grade 1)	**Step 1:** Treat with antimotility agents (eg, 4 mg loperamide followed by 2 mg every 4 hours or after every unformed stool) and initiate supportive care (see Section 5.5.6.1). If not improved after 48 hours, treat per guidance for Grade ≥ 2.
• Diarrhea/colitis (≥ Grade 2)	**Step1:** Interrupt INCB050465. Perform work-up for infection (including CMV, *C. difficile*, etc). Initiate or continue supportive care (see Section 5.5.6.1). Consider colonoscopy with biopsy for Grade ≥ 3. **Step 2:** If infection is ruled out, start oral steroids, or consider IV steroids if subject is being given IV fluids. If no improvement with oral steroids, switch to IV steroids. When diarrhea resolves to Grade ≤ 1, continue supportive care and taper steroids over 4 weeks. When taper is complete and diarrhea is Grade ≤ 1, restart INCB050465 at next lower dose with approval of the medical monitor. If Grade ≥ 2 diarrhea reoccurs, permanently discontinue INCB050465.
• Pneumonitis (Grade 1)	**Step 1:** Interrupt INCB050465 until the toxicity has resolved. **Step 2:** Restart INCB050465 at next lower dose. Monitor as clinically indicated.
• Pneumonitis (≥ Grade 2)	Permanently discontinue INCB050465.
• Skin toxicity (eg, rash, pruritus, etc, unless otherwise specified) (Grade 2-3)	**Step 1:** Interrupt INCB050465 until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart INCB050465 at same dose. If assessed as related to INCB050465, restart at next lower dose.
• Exfoliative dermatitis (Grade 1)	**Step 1:** Interrupt INCB050465 until the toxicity has resolved. **Step 2:** Restart INCB050465 at next lower dose. Monitor as clinically indicated.
• Exfoliative dermatitis (≥ Grade 2)	Permanently discontinue INCB050465.
• Intestinal perforation (any grade)	Permanently discontinue INCB050465.
• *Pneumocystis jirovecii* pneumonia infection	Interrupt INCB050465. Permanently discontinue INCB050465 if *Pneumocystis jirovecii* pneumonia infection is confirmed.
• CMV infection	Subjects with CMV viremia without associated clinical signs of CMV infection should be carefully monitored. Consider interrupting INCB050465 for subjects with CMV viremia and clinical signs of infection until the infection has resolved. Restart INCB050465 reduced by 1 dose level if approved by the medical monitor.
• Varicella zoster infection	Interrupt INCB050465. Restart INCB050465 only by approval of the medical monitor.

Table 5: Guidelines for Interruption and Restarting of INCB050465 (Continued)

ADVERSE EVENT	ACTION TAKEN
• Any Grade 1 or Grade 2 toxicity unless otherwise specified.	Continue study drug treatment and treat the toxicity; monitor as clinically indicated.
• Any Grade 3 toxicity, if clinically significant and not manageable by supportive care unless otherwise specified.	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until toxicity resolves to ≤ Grade 1. **Step 2:** Restart INCB050465 at same dose. If assessed as related to INCB050465, restart at next lower dose. If interrupted for > 14 days, contact the medical monitor for approval to restart INCB050465. Monitor as clinically indicated.
• Any recurrent Grade 3 toxicity after 2 dose reductions.	Discontinue study drug administration and follow-up per Protocol. (Exceptions require approval of sponsor.)
• Any other Grade 4 toxicity.	Discontinue study drug administration and follow-up per Protocol. Exceptions require approval of sponsor.

Table 6: Dose Levels for INCB050465

Starting Dose Level	First Dose Reduction	Second Dose Reduction
20 mg daily	10 mg daily	5 mg daily
20 mg weekly	10 mg weekly	5 mg weekly
5 mg daily	2.5 mg daily	1 mg daily

5.5.6.1. Supportive Care Guidelines for Diarrhea/Colitis

Subjects should be informed to immediately report to the investigator any event of diarrhea. Subjects should receive appropriate supportive care measures as deemed necessary by the investigator. For any ≥ Grade 1 diarrhea, subjects should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. Subjects should try to eat 5 to 6 small meals per day; low-fat, high-protein foods; and cooked instead of raw vegetables. Subjects may supplement their diet with bananas, rice, applesauce, and toast to reduce the number of bowel movements, and may also try crackers, gelatin, noodles, or oatmeal. Subjects should avoid fried, fatty, greasy, or spicy foods; milk, milk products, and acidic drinks; high-fiber foods and foods that cause gas; and alcohol, caffeine, and herbal supplements (Coutré et al 2015).

For each occurrence, attempts should be made to rule out other causes, such as metastatic disease or bacterial or viral infection (including CMV), which might require additional supportive care.

It may be necessary to perform conditional procedures such as colonoscopy with biopsy as part of evaluation of the event. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain or cramping, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

5.5.6.2. Definition for Immune-Related Adverse Events

Adverse events of a potential immunologic etiology, or immune-related AEs (irAEs), may be defined as an AE consistent with an immune phenomenon associated with study drug exposure after all other etiologies have been eliminated. Immune-related AEs may be expected based on previous experience with INCB050465 and other drugs (eg, idelalisib) that inhibit PI3Kδ. Special attention should be paid to AEs that may be suggestive of potential irAEs. Based on emerging data from the ongoing Study INCB 50465-101, most irAEs occur after the first 9 weeks of study drug administration. However, an irAE could occur at any time. Suspected irAEs should be discussed with the medical monitor when possible.

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of drug-related AEs with potential immunologic etiology are outlined in Table 5 and Section 5.5.6.1. For each AE, attempts should be made to rule out other causes, including but not limited to metastatic disease or bacterial or viral infection, which might require specific supportive care.

5.5.7. Criteria for Permanent Discontinuation of INCB050465

The occurrence of unacceptable toxicity not caused by the underlying disease will be presumed to be related to study drug treatment and will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- Occurrence of an AE that is related to treatment with the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- An AE requiring more than 2 dose reductions (exception requires sponsor approval).
- Persistent AE requiring a delay of therapy for more than 2 weeks (14 days), unless a greater delay has been approved by the sponsor.

5.5.8. Criteria and Procedures for Dose Interruptions or Adjustments for Ruxolitinib

Dose modifications of ruxolitinib because of toxicity are not required unless INCB050465 modifications/interruptions have been first implemented for 14 days with no improvement in toxicity grade. In such a case, a brief interruption or dose decrease may be needed. Dose interruptions and modifications for ruxolitinib because of hematologic toxicity that continues after interruption of INCB050465 are shown in Table 7.

Table 7: Dose Reductions/Interruptions and Restarts for Hematologic Toxicities That Persist for > 14 Days After Interruption of INCB050465

ANC ($\times 10^9$/L)			Platelet Count ($\times 10^9$/L)		
Value	**CTCAE Grade**		**Value**	**CTCAE Grade**	**Dose of Study Drug (Ruxolitinib)**
0.5 to < 1.0	3	or	25 to < 50	3	In case of hematological toxicity, INCB050465 will be the first drug to be interrupted, as this is the newly added agent. If the Grade 3 cytopenia persists > 14 days after interrupting INCB050465 or if the primary investigator deems that earlier ruxolitinib interruption is necessary, then ruxolitinib will be interrupted until the toxicity is resolved to ≤ Grade 1 or pretherapy baseline and then restarted at the current dose. If a Grade 3 event recurs and persists > 14 days after interrupting INCB050465 or if the primary investigator deems that earlier ruxolitinib interruption is necessary, then ruxolitinib will be interrupted, and the restart dose (after recovery to ≤ Grade 1 or pretherapy baseline) of ruxolitinib will be 1 dose level (5 mg BID less) lower than the dose that resulted in the cytopenia.
< 0.5	4	or	< 25	4	In case of hematological toxicity, INCB050465 will be the first drug to be interrupted as this is the newly added agent. If Grade 4 neutropenia occurs and persists > 14 days after interrupting INCB050465 or if the primary investigator deems that earlier ruxolitinib interruption is necessary, then ruxolitinib will be interrupted until the toxicity resolved to ≤ Grade 1 or pretherapy baseline, and the restart dose will be 1 dose level (5 mg BID less) lower than the dose that resulted in the cytopenia. If Grade 4 thrombocytopenia occurs and persists > 14 days after interrupting INCB050465 or if the primary investigator deems that earlier ruxolitinib interruption is necessary, then the ruxolitinib will be interrupted until toxicity is resolved to ≤ Grade 1 or pretherapy baseline, and the restart dose will be 1 dose level (5 mg BID less) lower than the dose that resulted in the cytopenia.
Neutropenic fever					INCB050465 will be the first drug to be interrupted as this is the newly added agent. If the neutropenia (ANC < 1.0) persists > 14 days after interrupting INCB050465 or if the primary investigator deems that earlier ruxolitinib interruption is necessary, then the ruxolitinib will be interrupted until recovery of ANC to ≥ 1.0×10^9/L, and the restart dose will be 1 dose level (5 mg BID less) lower than the dose that resulted in the cytopenia.

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

Except for the hematologic criteria specified above, interruption of ruxolitinib for safety reasons is at the discretion of the investigator with approval from the medical monitor. In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse

experiences that may have an unclear relationship to study drug or thought to be more likely attributable to the ruxolitinib. Except for cases specified in Table 5, restart of study drug administration should occur at the original dose. If the same AE recurs after restart of study drug, the investigator should consider reducing the study drug dose for any subsequent restart after recovery.

5.6. Withdrawal of Subjects From Study Treatment

5.6.1. Withdrawal Criteria

A subject **must** be withdrawn from study treatment (INCB050465 and ruxolitinib) for the following reasons:

- The subject has had an unacceptable toxicity or a toxicity that does not recover within 14 days of drug interruptions. Investigators who wish to continue treatment after a delay of > 14 days must consult with the sponsor's medical monitor for approval to continue/restart study treatment.
- The subject becomes pregnant.
- Consent is withdrawn. NOTE: Consent withdrawn means that the subject will no longer be followed. Subjects may choose to discontinue study treatment but remain on study to be followed for survival.
- Further participation would be injurious to the health or well-being, in the investigator's medical judgment.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

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

- If a subject is noncompliant with study procedures or study drug administration in the investigator's opinion, then the sponsor should be consulted for instruction on handling the subject.

5.6.2. Withdrawal Procedures

The decision to discontinue study treatment (eg, INCB050465 and ruxolitinib) will <u>not</u> constitute study withdrawal or study completion. In the event that the decision is made to discontinue study treatment, the treatment portion will be considered complete and the follow-up portion will begin. Subjects who discontinue treatment with the study drug will be followed for subsequent MF treatment regimens and survival.

Upon discontinuation of study treatment, the EOT visit should be completed as outlined in the schedules of assessments (Table 8 and Table 9). The date of the last dose of study drug will be recorded in the CRF, and the reason for subject withdrawal will be recorded. After discontinuation of study treatment, the subject will remain in the follow-up portion of the study, and site staff will conduct phone calls at approximately 12-week intervals to the study subject to collect data on subsequent MF treatment regimens and survival.

If a subject is withdrawn from the study:

- The study monitor or sponsor must be notified.
- The reason(s) for withdrawal must be documented in the subject's medical record and in the CRF.
- The EOT visit should be performed.
- The EOT data will be reported to IXRS.
- Subjects must be followed for safety until the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

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

5.7. Concomitant Medications

5.7.1. Pneumocystis Pneumonia Prophylaxis

All subjects receiving combination study treatment with INCB050465 and ruxolitinib are required to receive a standard PJP prophylaxis regimen determined by the investigator. Examples of standard PJP prophylaxis therapies for this population include trimethoprim-sulfamethoxazole, atovaquone, dapsone with or without pyrimethamine, and pentamidine (NCCN 2016). Subjects with sulfonamide allergy should be treated with either inhaled pentamidine or atovaquone for PJP prophylaxis; dapsone should not be used in such subjects. Prophylaxis should be given while subjects are receiving INCB050465 and continue for 2 to 6 months after the last dose of INCB050465.

5.7.2. Permitted Medications

All concomitant medications and treatments must be recorded in the CRF.

5.7.3. Restricted Medications

- Aspirin in doses exceeding 125 mg/day is not permitted. Low-dose aspirin (≤ 125 mg/day) is permitted.
- Caution should be used when administering ibuprofen or other nonsteroidal anti-inflammatory drugs with long elimination half-lives; subjects should be monitored closely for toxicity, especially for myelosuppression and renal and gastrointestinal toxicity.
- Inducers of CYP3A4 (Appendix B) may be used with caution, and investigators should seek other options if available.

- Moderate CYP3A4 inhibitors (Appendix B) may be used with caution. Differences in individual sensitivity and variation in potency of inhibition of various CYP enzymes may result in the need for a reduced dose of ruxolitinib during a period of concomitant medication use. If required for safety, then the ruxolitinib dose may be reduced from BID to QD in these circumstances; this should be clearly documented in the treating physician notes. The sponsor's medical monitor may be consulted for advice when using these agents.
- If concomitant administration of an anticoagulant/antiplatelet medication is indicated, then caution and enhanced monitoring is required. History of thrombocytopenia and any concurrent ruxolitinib-related thrombocytopenia should be a factor in the choice of anticoagulant and dose.

5.7.4. Prohibited Medications

The following medications are prohibited during the treatment and maintenance portions of the study:

- Any concurrent MF therapy other than that specified in the Protocol.
- Any investigational medication within 28 days or 5 half-lives, whichever is longer, before the first dose of study drug and at any time before complete withdrawal from the study.
- Use of potent inhibitors of CYP3A4 (eg, ketoconazole, clarithromycin, itraconazole, nefazodone or telithromycin, voriconazole or posaconazole; see Appendix B). Ketoconazole may be used with caution if other options are not available. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole in the study.
- Any live vaccine beginning 30 days before the first dose of study medication through the safety follow-up visit.

6. STUDY ASSESSMENTS

All study assessments will be performed as indicated in the schedule of assessments (Table 8), and all laboratory assessments will be performed as indicated in Table 9. Table 10 presents a summary of clinical laboratory analytes to be assessed. Table 11 provides the PK analysis sample collection plan. The order of assessments is suggested by the order of mention within the schedule. See Section 7 for instructions on each assessment. Further details of study procedures and assessments can be found in the study reference manual.

Table 8: Schedule of Assessments – Part 1, Part 2, Part 3, and Part 4

Visit Day (Range)	Screening Day -35 to Day -8	Baseline Day -7 to Day -1	Day 1	End of Week 2	End of Weeks 4, 8 ± 5 Days	End of Week 12 ± 5 Days	End of Weeks 16, 20 ± 5 Days	End of Week 24 ± 5 Days	Extension Visits (Q12W After Week 24) ± 7 Days	EOT or Early Termination Visit ± 5 Days	Follow-Up 30-35 Days After Last Dose of INCB050465	Survival Follow-Up Every 12 Weeks
Informed consent	X											
Contact IXRS	X		X		X	X	X	X	X	X		
Inclusion/exclusion criteria	X	X										
Prior medical & medication history	X	X										
Concomitant medication review		X	X		X	X	X	X	X	X	X	
Transfusion history/status	X	X	X		X	X	X	X	X	X	X	
Screening Symptom Form	X											
Record AEs	X	X	X	X	X	X	X	X	X	X	X	
Comprehensive physical examination	X							X			X	
Targeted physical examination					X	X	X		X	X		
Spleen palpation	X	X			X	X	X	X	X	X	X	
Vital signs	X	X			X	X	X	X	X	X	X	
12-lead ECG	X							X		X		
Bone marrow biopsy[a]	X	X						X	X[a]			
MRI/CT of the upper and lower abdomen and pelvis		X				X		X	X			
Dispense and/or bring MFSAF v3.0 diary to visit		X	X		X	X	X	X				
ECOG status	X							X			X	
PGIC[b]					X	X	X	X	X	X		
IWG-MRT assessment[c]								X	X			
Modified MFSAF v3.0 diary (Appendix E)		Completed every evening from baseline through Week 24										
MPN-SAF (Appendix F)		X			X	X	X	X	X	X		
Laboratory assessments[d]	X	X	X	X	X	X	X	X	X	X	X	
Dispense reminder card		X	X		X	X	X	X	X			
Administer study drug during visit			X	X	X	X	X	X				
Dispense study drug			X		X	X	X	X	X			
Drug accountability assessment					X	X	X	X	X	X		
Survival follow-up data collection[e]												X

ECG = electrocardiogram; PGIC = Patient Global Impression of Change.

[a] Bone marrow biopsy must be completed at screening or baseline visit, unless biopsy and data from previous 2 months are available. Additional biopsies will be performed at Week 24, Week 48, and every 24 weeks.

[b] Patient Global Impression of Change (Appendix H).

[c] International Working Group response will be assessed at Week 24 and every 24 weeks thereafter.
[d] See Table 9 and Table 10.
[e] After discontinuation of INCB050465, the subject will remain in the follow-up phase of the study, and site staff will conduct phone calls at approximately 12-week intervals to collect data on subsequent MF therapy and survival.

Table 9: Schedule of Laboratory Assessments – Part 1, Part 2, Part 3, and Part 4

	Screening	Baseline	Day 1	Weeks 1, 3 (Day 8, 22) Part 1 ONLY	End of Weeks 2, 6, 10, 14, 18, 22, then Q4W	End of Weeks 4, 8, 12, 16, 20, 24, then Q12W	EOT or Early Termination Visit	Follow-Up 30-37 Days After Last Dose of INCB050465	Notes
Window				**The window for laboratory visits is ± 3 days**					
Local Laboratory Assessments									
Serum chemistries	X	X*	X*	X		X	X	X	*Should be taken as close as possible to Day 1 but may be drawn up to 3 days before first dose. Only 1 sample for baseline/Day 1 is required.
Hematology	X	X*	X*	X	X	X	X	X	*Should be taken as close as possible to Day 1 but may be drawn up to 3 days before first dose. Only 1 sample for baseline/Day 1 is required.
Coagulation panel	X					X*	X	X	*Required Weeks 12 and 24 and Q12W.
Urine pregnancy test		X				X*	X*		All female subjects of childbearing potential. *Pregnancy tests should be repeated if required by local regulations.
Bone marrow biopsy, aspirate, and analysis	X*					X**			*Predose biopsy/aspirate is not required if biopsy has occurred in previous 2 months as long as biopsy/aspirate and data are available for review by investigator and/or sponsor. **Week 24 and Q24W. Samples of biopsy and unstained slides will be sent to a central vendor.
Central Laboratory Samples*									*The central laboratory is the sponsor or sponsor's designee.
Lipid panel (requires overnight fast)	X					X*	X		*Required Weeks 12 and 24 and Q12W.
Serology - hepatitis and HIV	X								HBV, HCV, HIV
Serology - CMV	X					X*			* CMV measured at Weeks 4, 8, 12, then Q12 weeks.
Urinalysis	X					X*		X	*Required Weeks 12 and 24 and Q12W.
Serum pregnancy	X							X	All female subjects of childbearing potential.
FSH	X								To document hormonal menopause.
PK samples			X		X*	X*			*PK sampling will occur on Day 1, Week 2, and Week 4 only. See Table 8.

Table 9: Schedule of Laboratory Assessments – Part 1, Part 2, Part 3, and Part 4 (Continued)

	Screening	Baseline	Day 1	Weeks 1, 3 (Day 8, 22) Part 1 ONLY	End of Weeks 2, 6, 10, 14, 18, 22, then Q4W	End of Weeks 4, 8, 12, 16, 20, 24, then Q12W	EOT or Early Termination Visit	Follow-Up 30-37 Days After Last Dose of INCB050465	Notes
Window				**The window for laboratory visits is ± 3 days**					
[redacted]									

FSH = follicle-stimulating hormone; [redacted]; Q4W = every 4 weeks; Q12W = every 12 weeks; Q24W = every 24 weeks.

Table 10: Laboratory Tests: Required Analytes

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

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

Table 11: Schedule of Pharmacokinetic Sampling for Part 1, Part 2, Part 3, and Part 4

Study Day 1	Week 2	Week 4
Subject arrives having withheld both INCB050465 and ruxolitinib[a] Predose sample = Time 0 sample Administer ruxolitinib Timed samples[b]: 1 hour postdose 2 hour postdose[c] 4 hour postdose Administer INCB050465	Subject arrives having withheld both INCB050465 and ruxolitinib[a] Predose sample = Time 0 sample Administer INCB050465 Timed samples[b]: 1 hour postdose 2 hour postdose[c] 4 hour postdose Administer ruxolitinib	Subject arrives having withheld both INCB050465 and ruxolitinib[a] Predose sample = Time 0 sample Administer INCB050465 plus ruxolitinib Timed samples[b]: 1 hour postdose 2 hour postdose[c] 4 hour postdose

[a] Subjects are also to arrive at the study visits in the fasted state.
[b] Window for 1-, 2-, and 4-hour collections is ± 15 minutes.
[c] Subjects may eat after the 2-hour timepoint sample has been drawn.

6.1. Screening

Screening is the interval between signing the ICF and the beginning of the 7-day baseline period (ie, Day -35 to Day -8). Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

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

Procedures conducted as part of the subject's routine clinical management (eg, blood count, serum chemistry) and obtained before signing of informed consent may be used for screening provided that the procedure meets the Protocol-defined criteria and has been performed in the timeframe of the study (ie, up to 28 days before Day 1). All information associated with eligibility requirements must be entered into the appropriate CRF pages. Eastern Cooperative Oncology Group assessment will be used to stratify subjects for Parts 2, 3, and 4 and must be reported via IXRS at the time.

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

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before enrollment/randomization or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available

result before randomization/treatment assignment will be used to determine subject eligibility. Treatment should start as soon as possible, but within 3 days after the date of enrollment/randomization. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status (eg, after recovery from an infection). In this case, a new subject number must be assigned via IXRS.

6.2. Baseline

Subjects who have signed the ICF and meet all the entry criteria (see Section 3) may be enrolled in the study and will be contacted by clinical site staff to schedule the baseline visit. The baseline interval corresponds to the 7 days before initiating treatment with INCB050465 and during which the baseline MRI (or CT scan in applicable subjects) and symptom diary will be initiated.

- The modified MFSAF v3.0 diary (Appendix E) should be distributed. Subjects will be issued a hand-held device and will complete the diary questions each night beginning on Day -7 up to the Week 24 visit. Subjects will be instructed to place the device on the docking station (also provided) for automatic data transmittal each night after completing the questions. Subjects will be instructed to leave the device in the docking station when not answering the questions so that the unit remains fully charged. Subjects will receive training on the device by study site staff before leaving the site. Subjects will bring the device with them to study visits on Day 1, Week 4, Week 8, Week 12, Week 16, and Week 20 so that the device charging can be verified and to download accumulated data. The device will then be returned to the subject at these same visits for continued use each night. Subjects will return the device and the docking station for the final time at the Week 24 Visit, so that all data can be archived.
- The MRI (or CT scan in applicable subjects) should be conducted on the first or second day of the baseline interval to allow ample time for the laboratory to verify scan quality.
- Blood samples for hematology and serum chemistry analyses should be taken as close as possible to Day 1 but may be drawn up to 3 days before first dose of INCB050465. This blood sample will serve as the pre-INCB050465 baseline sample; a Day 1 sample is not required provided the baseline sample is within 3 days of the first dose of INCB050465.

6.3. Treatment

The treatment period begins with the first dose of INCB050465 (Day 1) through the point at which the investigator determines the subject will be permanently discontinued from study drug.

There will be study visits and laboratory-only visits in the study. Table 8, Table 9, and Table 10 provide the scheduled assessments for each study visit and laboratory-only visit.

Subjects will have a regularly scheduled study visit at screening, baseline, Day 1, and after 4, 8, 12, 16, 20, and 24 weeks of treatment (ie, visits designated Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24) and then every 12 weeks thereafter if continuing on treatment, where blood samples, spleen measurements, and other assessments will be obtained. There is also a

study visit at the end of 2 weeks treatment (designated visit Week 2) for PK sampling, AE assessment and hematology blood draws. The visit window is ± 5 days for visits through Week 24 and ± 7 days for visits in the extension portion. The timing for study visits will be based on the date of the Day 1 visit when treatment with INCB050465 is initiated.

All serology, lipid profile, and urinalysis laboratory assessments collected at the visits in Table 9 will be analyzed by a central laboratory. Serum chemistry, hematology, and coagulation parameters will be assessed using local laboratories. Where needed, urine pregnancy will be assessed by local lab. Bone marrow biopsy samples will be assessed for MF characteristics by local lab; subsequent studies using remaining material will be conducted by sponsor or its designee. [redacted] PK samples will be collected and analyzed by the sponsor or sponsor's designee. Subjects will arrive for all study visits (including Week 2, not at laboratory-only visits) having withheld the morning dose of ruxolitinib and INCB050465 and in the fasted state; administration will occur in the clinic (first 24 weeks only). Subjects should be told to bring a snack or small meal to the study visits, as they will arrive for the visits in the fasted state.

Subjects will have laboratory-only visits to collect hematology lab samples as noted in Table 10. Subjects participating in Part 1 will have additional laboratory assessments performed at Week 1 (ie, Day 8) and Week 3 (ie, Day 22). The window for laboratory visits is ± 3 days. Subjects in Parts 2, 3, and 4 may visit a local laboratory for the interim hematology assessments provided that the laboratory data and corresponding normal ranges can be scanned and emailed to the investigative site; interim laboratory visits at the study site laboratory are preferred. Additional laboratory assessments may be performed at the investigator's discretion, including following changes in dose, or if laboratory parameters are at Grade 3 or Grade 4 levels based on the CTCAE v4.03.

Subjects will have an MRI of the upper and lower abdomen and pelvis to determine the spleen volume at baseline, at Week 12 and Week 24, and every 12 weeks thereafter through Week 108. Computed tomography scan will be substituted for subjects who are not candidates for MRI or when MRI is not readily available. Patients Global Impression of Change questionnaire (Appendix H) will be completed at each study visit. Determination of spleen length below the left costal margin will be measured by palpation at each study visit.

Subjects will complete an electronic symptom diary (MFSAF v3.0) daily from baseline through the Week 24 visit (total of 25 weeks; Appendix E).

Subjects will complete the MPN-SAF (Appendix F) at visits noted in Table 8.

6.4. End of Treatment

There is no predefined EOT. When the subject permanently discontinues INCB050465, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, then the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the CRF. The subject should be encouraged to return for the follow-up visit.

6.5. Follow-Up

6.5.1. Safety Follow-Up

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

Subjects are required to remain on PJP prophylaxis for at least 2 to 6 months after the last dose of study drug (see Section 5.7.1) and should be reminded of this at the safety follow-up visit. Sites should follow up with subjects to confirm that they have been compliant with the prophylactic treatment for the duration of this period.

6.5.2. Survival Follow-Up

Once a subject has received the last dose of study drug, the subject moves into the survival follow-up period and should be contacted by telephone, email, or visit at least every 12 weeks to assess for subsequent MF treatments and survival status until death, withdrawal of consent, or end of study (EOS), whichever occurs first.

6.6. End of Study

The EOS will occur when the last enrolled/randomized subject has completed the follow-up visit.

6.7. Unscheduled Visits

Unscheduled visits may be held at any time at the investigator's discretion, and appropriate clinical and laboratory measurements may be performed based on AEs or other findings.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures using an ICF approved by the local IRB/IEC that contains all elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; the original signed ICF must be retained by the investigator, and a copy of the signed ICF must be provided to the study subject. The informed consent process for each subject must be documented in writing within the subject source documentation.

7.2. Interactive Web Response System Procedure

The IWRS will be accessed to obtain a subject ID number when a subject enters the screening portion. Upon determining that the subject is eligible for study entry, and using the screening ECOG score, the IWRS will be contacted to obtain treatment group and study drug assignment. Additionally, the IWRS will be contacted at each regular study visit to update the study drug supply. Full details will be provided in the IWRS manual.

7.3. Demography and Medical History

7.3.1. Demographics and General Medical History

Demographic data will be collected at screening, including age, sex, race, and ethnicity. A complete medical history will be obtained.

7.3.2. Disease Characteristics and Treatment History

A disease-targeted medical and medication history will be collected at screening. Date of MF diagnosis and prior bone marrow biopsy data as to fibrosis stage will be recorded. All treatments for MF, including a complete history of ruxolitinib usage, will be recorded.

7.3.3. Transfusion History Status

All transfusions of RBC products or platelets from at least 16 weeks before the screening visit will be recorded. The product(s) delivered, date of transfusion, and units delivered will be recorded on the CRF.

7.3.4. Screening Symptom Form

In order to satisfy inclusion Criterion 4, active symptoms of MF at the screening visit as demonstrated by presence of 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 using the Screening Symptom Form (Appendix D) will be recorded on the CRF.

7.4. Prior and Concomitant Medications and Procedures

Prior and concomitant medications and procedures will be reviewed to determine subject eligibility. All concomitant medications and measures must be recorded in the CRF, and any medication received or procedure performed within 30 days before the first dose of INCB050465 and up to the end of study will be recorded in the CRF. The medication record will be maintained after signing the ICF to document concomitant medications, including any changes to the dose or regimen. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study will also be recorded in the CRF.

7.5. Safety Assessments

7.5.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and CRFs regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.5.2. Physical Examinations

Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

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

Clinically notable abnormalities that are considered clinically significant in the judgment of the investigator are to be reported as AEs.

7.5.2.1. Comprehensive Physical Examination

The comprehensive physical examination will include height (at screening) and body weight and assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination. The comprehensive physical examination should also include an assessment of body fluid abnormalities including ascites and edema.

7.5.2.2. Targeted Physical Examination

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

7.5.3. Vital Signs

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

7.5.4. Electrocardiograms

All 12-lead ECGs will be performed with the subject in a recumbent or semi recumbent position after 5 minutes of rest. Electrocardiograms will be performed at the screening visit, Week 24 and the EOT visits, or as clinically indicated at investigator discretion.

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

7.6. Efficacy Assessments

7.6.1. Bone Marrow Biopsy

Bone marrow biopsy (and additional aspirate collection) will be collected at screening, at Week 24, and every 24 weeks thereafter. Subjects without circulating blasts at the screening hematology assessment may use a historical biopsy obtained within the 2 months before screening, and all data and reports are available for investigator's review. The previous data will need to be entered into the CRF for this study, with explanation as to the origin of the data (date of biopsy/aspirate). Subjects without a previous biopsy report as indicated above must have a biopsy at screening or baseline or they will not be able to enroll in the study. Collection, processing, and staining of bone marrow samples will be performed in accordance with standard procedures at the investigative sites. The bone marrow biopsy and optional aspirate should be assessed by an experienced hematopathologist using his/her standard examination. Samples of bone marrow biopsy and aspirate will be sent to Incyte or its designee for additional immune and molecular profiling.

7.6.2. Spleen Palpation

Spleen length will be assessed by manual palpation at every study visit (laboratory-only visits not included) and will be used for routine subject management. Investigators will be provided with a soft centimeter ruler so that palpable spleen length is measured in centimeters and not in finger breadths. The edge of the spleen shall be determined by palpation and measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion. Spleen length must be recorded on the CRF.

7.6.3. Imaging

The primary measure of spleen size will be by MRI (or CT scan in applicable subjects). An MRI of the upper and lower abdomen and pelvis will be performed at baseline, Week 12 and Week 24, and every 12 weeks thereafter through Week 108. An MRI will be performed with a body coil because the objective is to measure organ volume, not to find very small lesions. The MRIs will be read initially by local radiologists who will assess the scan for quality and send all scans (MRI or CT) to the central imaging laboratory the same day, if at all possible. The scans from an individual subject will be read by a central reader. Spleen and liver volume will be obtained by outlining the circumference of the organ and determining the volume using the validated technique of least squares. The MRI will not determine spleen length below the costal margin, as there are no validated approaches for determining this measurement. Procedure-specific training for scanning and image capture will be provided by the vendor.

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

7.6.4. Symptom Diary

Symptoms of MF will be assessed using a symptom diary (modified MFSAF v3.0 diary; Appendix E). Subjects will be issued a hand-held device on which to record answers to queries regarding MF symptoms. Symptoms assessed will include filling up quickly/early satiety, abdominal discomfort, abdominal pain, inactivity, night sweats, itching, and bone/muscle pain. The modified MFSAF v3.0 diary will be completed by subjects each night beginning at Day -7 (first day of baseline) and continuing to the Week 24 visit (25 weeks total). Subjects will bring the device to the study site at study visits on Day 1 and Weeks 4, 8, 12, 16, and 20, so that the device charging can be verified and the accumulated data can be downloaded. NOTE: Subjects who will have overnight stays associated with their study visit must also bring their docking station so that their device can be fully charged at all times and so that they can complete the evening diary entries. The device will then be returned to the subject at these same visits for continued use each night. The subject will return the device and the docking station for the final time at the Week 24 visit so that the data can be archived. Detailed directions for the administration of the modified MFSAF v3.0 diary will be provided in a reference manual. French and Spanish translations of the modified MFSAF v3.0 diary will be available.

7.6.5. Myeloproliferative Neoplasms Symptom Assessment Form

The MPN-SAF (Emanuel et al 2012; Appendix F) will be completed by subjects at the study visits noted in Table 8.

7.6.6. Eastern Cooperative Oncology Group Status

Eastern Cooperative Oncology Group performance scores (see Appendix G) will be required at screening to evaluate eligibility and stratification category and will be assessed at other study visits noted in Table 8.

7.6.7. Patient Global Impression of Change

The PGIC will be administered at each visit beginning with Week 4 and consists of a single question to which the subject answers on a scale of 1 to 7. See Appendix H.

7.6.8. IWG-MRT Assessment

Overall response assessment will be graded according to the IWG consensus criteria for treatment response in PMF, PPV-MF, and PET-MF (Tefferi et al 2013). International Working Group–MRT assessment will be performed at Week 24 and every 24 weeks thereafter as per Table 8. Recently published response criteria developed by the IWG on MF will be utilized in this study (Tefferi et al 2013) and are defined as described in Appendix I.

7.7. Laboratory Assessments

Refer to Table 9 and Table 10 for the schedule of laboratory assessments and the laboratory tests that will be performed. All blood draws for laboratory assessments will be performed before administration of INCB050465 or morning ruxolitinib dose.

7.7.1. Chemistry

Serum chemistries will be performed by the local laboratory using institutional best practices. Results and normal reference ranges will be entered onto the CRF.

7.7.2. Hematology

Hematology assessments including complete blood count with differential will be performed at the local laboratory using institutional best practices. Results and normal reference ranges will be entered onto the CRF.

7.7.3. Urinalysis

Urinalysis will be performed by a central laboratory.

7.7.4. Coagulation

Coagulation parameters will be determined at the local laboratory using institutional best practices. Results and normal reference ranges will be entered onto the CRF.

7.7.5. Lipid Panel

Lipid panel will be performed on samples collected at screening, at Weeks 12 and 24, and every 12 weeks thereafter. Subjects must arrive for this blood collection after an overnight fast of at least 12 hours. These assessments will be performed by the central laboratory.

7.7.6. Pregnancy Testing

A serum pregnancy test will be required for all women of childbearing potential during screening) and at the end of treatment visit. This assessment will be performed by the central laboratory. Urine pregnancy tests will be conducted as outlined in Table 9, as medically indicated or per country-specific requirement. Urine pregnancy tests will be performed locally. If a urine pregnancy test is positive, then the results should be confirmed with a serum pregnancy test.

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

Follicle-stimulating hormone levels will be determined only at screening to verify hormonal menopause in relevant subjects.

7.7.7. Serology

Serology will be performed by the central laboratory. Serology will include HBV DNA and HCV RNA measurement, hepatitis B surface antigen, anti–hepatitis B core antibody, CMV DNA, and HIV testing.

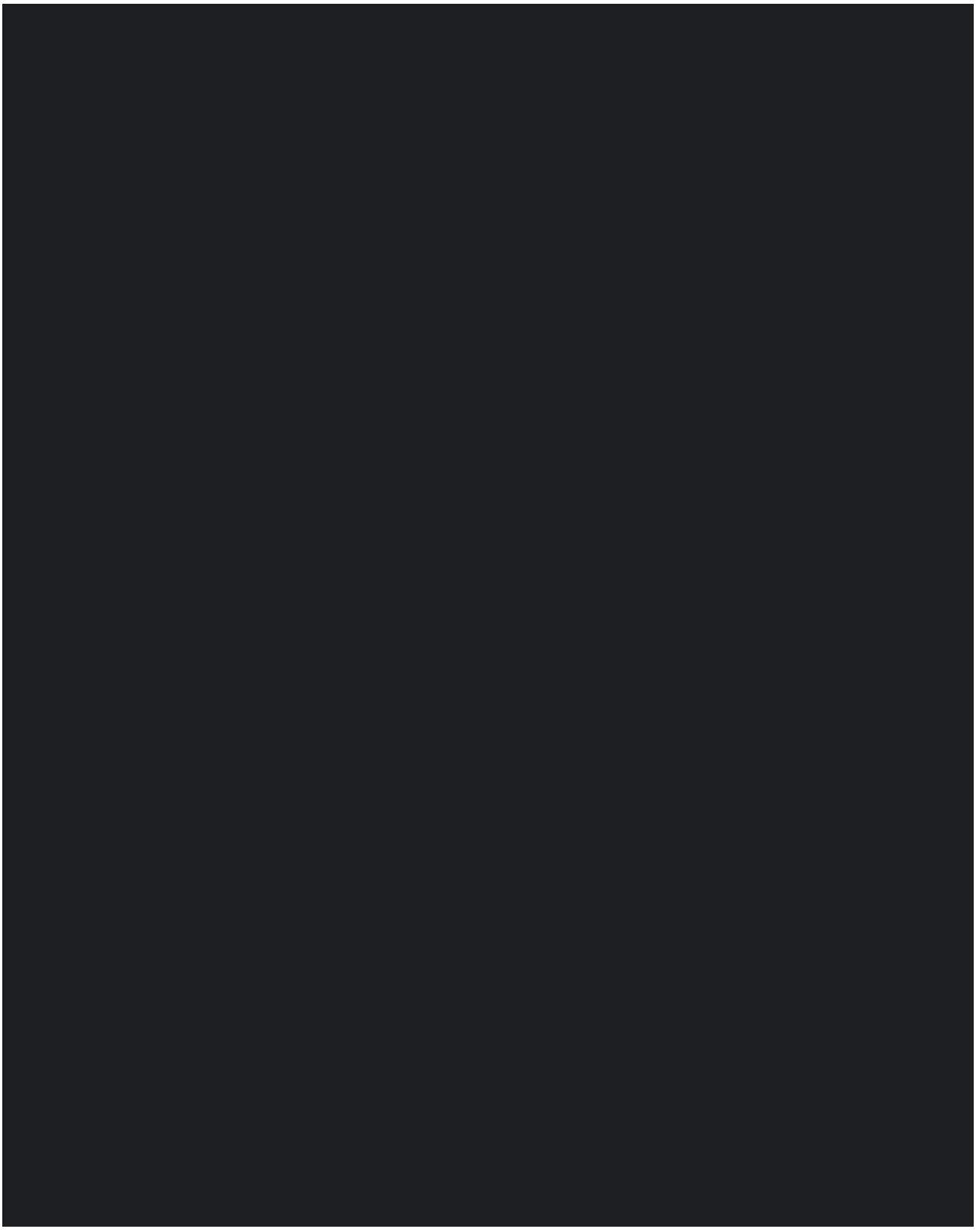
7.8. Pharmacokinetic Assessments

7.8.1. Blood Sample Collection

Pharmacokinetic sampling will occur on 3 separate days in Part 1, Part 2, Part 3, and Part 4 of the study (see Table 11 for timing of PK samples). The Laboratory Manual will describe sample collection and shipping to the central laboratory, where samples will be held until processing.

7.8.2. Bioanalytical Methodology and Analysis

The plasma samples will be analyzed for INCB050465 and/or ruxolitinib using validated liquid chromatography tandem-mass spectrometry methods. Day 1 samples will be analyzed for INCB050465 only; Week 2 samples will be analyzed for ruxolitinib only; Week 4 samples will be analyzed for both INCB050465 and ruxolitinib. The plasma samples may also be used for incurred sample reanalysis to ensure data quality. [redacted]



7.10. Other Study Procedures

7.10.1. Distribution of Subject Reminder Cards

Subjects will be provided with a reminder card at each visit. The subject reminder card will indicate the date and time of the next visit, remind subjects to hold their morning dose of both INCB050465 and ruxolitinib on the day of the visit (all study visits including Week 2, not laboratory-only visits), and remind subjects that overnight fast of at least 12 hours is required for all study visits (including Week 2, not laboratory-only visits). Space will be provided on reminder cards for the Week 2 and Week 4 visit to record the time of the evening dose of ruxolitinib for the day before these visits.

7.10.2. Data Collection for Survival Follow-Up

For subjects having entered the survival follow-up period of the study, the site will use continuing subject records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), and overall survival in the CRF. For subjects who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, subject records, and public records/databases at intervals of no longer than 12 weeks.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions

For the purposes of this Protocol, an AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related, that occurs after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

8.1.2. Reporting

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

The term "disease progression" should be recorded as an AE/SAE only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms.

When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (eg, resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s) as described in Section 8.3.2. In both cases (ie, AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the Adverse Events form of the CRF.

The severity of AEs will be assessed using CTCAE v4.03 Grades 1 through 4. The CTCAE v4.03 severity of Grade 5 will not be used; AEs resulting in death will be graded accordingly using Grades 1 through 4 and have the outcome noted as fatal. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity:

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

The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. To the extent possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 4).
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no).
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug.
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per SAE definition provided in Section 8.3.1.

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

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

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

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

8.2. Laboratory Test Abnormalities

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

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) AE does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1. A dose modification for the laboratory abnormality may be required (see Section 5.5) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

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

- Is fatal or life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - A routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - An elective surgery or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.

- A treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission.
- Any social reasons and respite care, in the absence of any deterioration in the subject's general condition.

- Results in persistent or significant disability, incapacity, or a substantial disruption of a person's ability to conduct normal life functions.
- Constitutes a congenital anomaly or birth defect.
- Is considered to be an important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above.

8.3.2. Reporting

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

Information about all SAEs is collected and recorded on the Adverse Event form of the CRF. The investigator must assess and record the causal relationship of each SAE to the study treatments (INCB050465 and ruxolitinib).

The investigator must also complete the Incyte Serious Adverse Event Report Form, in English, and send the completed and signed form to the sponsor or designee within 24 hours of becoming aware of the SAE. The investigator must provide a causality assessment, that is, assess whether there is at least a reasonable possibility that the SAE is related to the study treatment: suspected (yes) or not suspected (no). Causality must be assessed for INCB050465, for ruxolitinib and for the combination. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form.

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

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

recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

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

- The study drug must be discontinued immediately (female subjects only; see Section 5.5.8 for the maximum permitted duration of study drug interruption).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

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

8.6. Warnings and Precautions

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

8.7. Product Complaints

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

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

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

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

9. STATISTICS

9.1. Study Populations

The intent-to-treat (ITT) population includes all randomized subjects.

The per protocol population includes all randomized subjects who were sufficiently compliant with the Protocol. Specific criteria for this population will be defined in the Statistical Analysis Plan (SAP).

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

The safety run-in population includes all subjects enrolled in the safety run-in portion of the study (Part 1) taking at least 1 dose of study drug.

The PK [redacted] evaluable population includes all subjects who received at least 1 dose of study drug and provided at least 1 sample for PK [redacted]

9.2. Selection of Sample Size

The sample size and power calculations for the randomized portion of the study are based on a 2-sample Wilcoxon rank sum test with a normal approximation applied to the test statistic. For a 2-sided Type I error of 0.10 and Type II error of 0.10 with 30 subjects per treatment group, the

test is powered to detect an 11.4 percentage point location shift between the 2 groups in regards to percentage change in spleen volume. The 2 populations are assumed to be normally distributed with a common standard deviation of 14.5.

9.3. Level of Significance

The level of significance for detecting a difference between TG5D and TG5I/M + TG5 for the primary endpoint is 10% (2-sided). In other words, there is a 10% risk of declaring a difference in the percentage change in spleen volume between the 2 groups when it is not so.

9.4. Statistical Analyses

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

9.4.1. Efficacy Analyses

9.4.1.1. Primary Efficacy Analyses

The primary endpoint is change in percentage spleen volume from baseline at 12 weeks as measured by MRI (or CT scan in applicable subjects). Statistical comparisons between treatment groups for the primary endpoint will only be performed between subjects randomized to TG5D and TG5I/M + TG5 in Parts 3 and 4 of the study.

A location shift in percentage change in spleen volume between TG5D and TG5I/M accounting for stratification by ECOG performance status at screening (ECOG 0-1 vs 2) will be assessed using a van Elteren test (van Elteren 1960).

Within each stratum, subjects who discontinue from the study or who have missing values for the Week 12 spleen volume will be imputed as having the largest possible increase in percentage spleen volume and given the lowest rank in the stratum. The subject with the largest percentage reduction in spleen volume in a stratum will be given the highest rank within the stratum. In the case of ties, average ranks will be assigned.

If the randomized portion of the study fails to enroll a sufficient number of subjects in a particular stratum, then the primary endpoint will be assessed using a 2-sample Wilcoxon rank sum test with a normal approximation applied to the test statistic, for purposes of calculation stability. Ranking will be carried out using the same approach but without stratification.

Results for subjects enrolled to TG10 and TG20 will be summarized descriptively with no formal statistical comparisons performed.

9.4.1.2. Secondary Efficacy Analyses

Secondary efficacy analyses will be conducted for the ITT population. Change and percentage change from baseline in quantitative variables will be summarized using descriptive statistics. Results for subjects enrolled to TG10 and TG20 will be compared descriptively to those of the other treatment groups, but no direct statistical comparisons are planned. A location shift in percentage change in total symptom score evaluated by the MFSAF v3.0 symptom diary and the MPN-SAF between TG5D and TG5I/M + TG5 in Parts 3 and 4 of the study accounting for stratification by ECOG performance status will be assessed separately using a van Elteren test with the same approach applied for the primary endpoint. If the randomized portion of the study

fails to enroll a sufficient number of subjects in a particular stratum, then the location shift in percentage change in total symptom score evaluated by the MFSAF v3.0 symptom diary, and the MPN-SAF between the 2 treatment groups will be assessed separately using a 2-sample Wilcoxon rank sum test with a normal approximation applied to the test statistic. The number of subjects with responses according to the 2013 IWG consensus criteria will be tabulated. Patient Global Impression of Change scores will be tabulated at scheduled assessments.

9.4.1.3. Other Efficacy Analyses

All other analyses will be conducted for the ITT population, with summary statistics provided for both treatment groups.

9.4.1.4. Statistical Methods for a Single-Group Study

In the event that only 1 dose is selected during the Part 1 safety-run in portion of the study or if either TG5D or TG5I/M is terminated, the median spleen volume reduction will be estimated and a confidence interval constructed based on the exact binomial confidence interval.

9.4.2. Safety Analyses

9.4.2.1.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug. Analysis of AEs will be limited to TEAEs, but data listings will include all AEs regardless of their timing to study drug administration. Adverse events will be tabulated by the MedDRA preferred term and system organ class. Severity of AEs will be based on the National Cancer Institute CTCAE v4.03 using Grades 1 through 4.

The subset of AEs considered by the investigator to have a relationship to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, then the AE will be considered treatment-related. The incidence of AEs and treatment-related AEs will be tabulated.

9.4.2.2. Clinical Laboratory Tests

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

Laboratory data will be classified into Grades 1 through 4 using CTCAE v4.03. The following summaries will be produced for the laboratory data:

- Number and percentage of subjects with worst postbaseline CTCAE grade (regardless of baseline value). Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables from baseline to the worst postbaseline value using CTCAE grade.
- For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value using the low/normal/high classifications based on laboratory reference ranges.

9.4.2.3. Vital Signs

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

Table 12: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38ºC	< 35.5ºC
Respiratory rate	> 24/min	< 8/min

9.4.2.4. Electrocardiograms

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 (Table 13). Subjects exhibiting clinically notable ECG abnormalities will be listed.

Table 13: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 460 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec
RR	> 1330 msec	< 600 msec

QTcF = Fridericia correction.

9.4.2.5. Adverse Events of Special Interest

The principle toxicity of inhibiting both PI3Kδ and JAK pathways is expected to be reversible effects on immune function. Combined inhibition may adversely affect both B-cell and T-cell immune function with resultant increased risk of a variety of infections or other immune-related events. Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported per the SAE reporting timelines (see Section 8.3.2).

- ALT ≥ 5 × ULN
- AST ≥ 5 × ULN
- Colitis
- Diarrhea ≥ Grade 2

- Rash ≥ Grade 2
- Intestinal perforation
- Pneumonitis
- *Pneumocystis jirovecii* infection
- CMV infection
- Herpes simplex virus infection
- Varicella zoster virus infection
- Exfoliative dermatitis

9.4.3. Pharmacokinetic Analysis

The PK parameters of C_{max}, T_{max}, C_{min}, $AUC_{0\text{-}t}$, and Cl/F will be calculated from the blood plasma concentrations of INCB050465 and ruxolitinib using standard noncompartmental (model-independent) PK methods. The dose-dependent PK parameters (C_{max} and AUC) for INCB050465 and ruxolitinib will be summarized alone and in combination by mean, median, standard deviation, minimum, and maximum. Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin®. 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 PK analysis. Refer to Appendix C for a detailed list and description of the PK parameters. The PK parameters will be summarized by part and dose regimen.

[redacted]

9.5. Interim Analysis

9.5.1. Interim Safety Analysis

The Part 1 safety run-in portion of the study will test up to 3 doses of INCB50465 in combination with ruxolitinib for a 28-day assessment. During the safety-run in portion of the study, dose escalation between Cohorts 1 and 2 will follow a 3 + 3 design algorithm. Doses will be selected for Part 2 based on the safety outcomes in the Part 1 safety run-in portion of the study according to the rules outlined in Table 14. In the table, a cohort is considered toxic if 2 or more of the first 6 subjects experience a DLT. A cohort is considered safe if fewer than 2 of the first 6 subjects experience a DLT (see Table 2 and Section 4.1.1), with the exception that Cohort 1 will also be considered for escalating to Cohort 2 if 0 of the first 3 subjects experience a DLT. There will be alternative allowance to assess additional doses if Cohort 3 is determined to be above the MTD.

Table 14: Matrix of Part 2 Dose Selection Based on Part 1 Safety Outcomes by Dose Cohort

Cohort 1 10 mg QD	Cohort 2 20 mg QD	Cohort 3 5 mg QD	Decision for Part 2
Toxic	Toxic	Safe	Single group or explore dose < 5 mg QD
Safe	Toxic	Safe	Randomized between 5 mg QD and 10 mg QD
Safe	Safe		Randomized between 10 mg and 20 mg QD
Toxic	Toxic	Toxic	Terminate or explore doses < 5 mg

The probabilities of declaring a dose to be tolerable for the 3 cohorts at various DLT rates are provided in Table 15.

Table 15: Probability of Declaring a Dose to be Tolerable

True DLT Rate	Probability of Declaring the Dose to be Tolerable	
	In Cohort 1	In Cohorts 2 and 3
20%	70.8%	65.7%
30%	49.4%	42.0%
40%	30.9%	23.3%
50%	17.2%	10.9%
60%	8.02%	4.01%

For example, if the true DLT rate is 50% for a cohort, then there is a 17.2% chance that the dose in Cohort 1 will be considered tolerable and selected for treatment in Part 2 and a 10.9% chance that the dose in Cohorts 2 and 3 would be declared tolerable for treatment in Part 2. Further, if the true DLT rate is 20%, then there is a 70.8% chance that the dose in Cohort 1 would be declared to be tolerable for treatment in Part 2 and a 65.7 % chance that the dose in Cohorts 2 and 3 would be declared tolerable for treatment in Part 2.

9.5.2. Interim Efficacy Analysis

There will be 1 planned interim analysis conducted for futility for this study. The interim analysis will be conducted during the randomized portion of the study once TG5D and TG5I/M + TG5 enroll 15 subjects and have been evaluated for spleen volume at Week 12. Further enrollment in a treatment group will be terminated if fewer than 4 subjects in the treatment group have spleen stability or a reduction from baseline in spleen volume (ie, percentage change from baseline ≤ 0%) as measured by MRI (or CT scan in applicable subjects) at Week 12. Subjects remaining in any terminated group may have their dose adjusted to reflect the ongoing group with sponsor approval.

If either TG5D or TG5I/M is terminated, then Part 4 will continue as a single-group study, and the primary endpoint will be analyzed as described in Section 9.4.1.4. If both of the treatment groups are terminated, then the study will be terminated. The probabilities of stopping a treatment group for futility for various probabilities of a subject achieving ≥ 0% decrease in spleen volume at Week 12 are provided in Table 16.

Table 16: Probability of Stopping a Treatment Group for Futility

Probability of Subject Having ≥ 0% Decrease in Spleen Volume at Week 12 in a Treatment Group	Probability of Stopping a Treatment Group for Futility
5%	99.5%
10%	94.4%
20%	64.8%
25%	46.1%
30%	29.7%
40%	9.1%
50%	1.8%

10. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

10.1. Investigator Responsibilities

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

The investigator will be responsible for:

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

- Obtaining approval from the IRB/IEC before the start of the study and for any changes to the clinical study Protocol, important Protocol deviations, routine updates, and safety information in accordance with institutional requirements and local law.
  - The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by the IRB/IEC.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling subjects who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws, but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
  - All 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.

10.2. Accountability, Handling, and Disposal of Study Drug

The investigator is responsible for drug accountability at the study site; however, some of the drug accountability duties may be assigned to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Subject use of the study drug including pill or unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study subjects.

Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate on-site destruction of investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

10.3. Data Management

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

The investigator will be provided with access to an EDC system so that a CRF can be completed for each subject. Entries made in the CRF must be verifiable against source documents; if updates to the database are not possible, any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and CRF entries, and will sign and date the designated forms in each subject's CRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all query responses.

Protocol deviations will be identified and recorded in the Protocol Deviation form of the CRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

10.4. Data Privacy and Confidentiality of Study Records

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

Subject names will not be supplied to the sponsor or its designee, if applicable. Only the subject number and subject's initials (subject's initials will only be recorded if allowable by local regulations) will be recorded in the CRF, where permitted; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of

the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

10.5. Financial Disclosure

Not applicable.

10.6. Publication Policy

By signing the study Protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

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

Such methods include:

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

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

Source: CTFG 2014.

APPENDIX B. CYTOCHROME P450 INHIBITORS AND INDUCERS

CYP 3A4 Inhibitors

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

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

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

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

CYP 3A4 Inducers

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

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

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

APPENDIX C. PHARMACOKINETIC ANALYTICAL PARAMETERS

C_{ave}	Average steady-state plasma concentration (AUC_{0-12h}/12h or AUC_{0-24h}/24h)
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration during the dosing interval
T_{max}	Time to maximum plasma concentration
AUC_{0-t}	Area under the single-dose plasma concentration-time curve from Hour 0 to the last quantifiable measurable plasma concentration, calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
$AUC_{0-\tau}$ (ie, AUC_{0-12h} or AUC_{0-24h})	Area under the steady-state plasma concentration-time curve over 1 dosing interval (ie, from Hour 0 to 12 for BID administration or from Hour 0 to 24 for QD administration), calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
λ_z	Apparent terminal phase disposition rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{½}$	Apparent plasma terminal phase disposition half-life (whenever possible), where $t_{½} = (\ln 2) / \lambda_z$
Cl/F	Oral dose clearance
V_z/F	Apparent oral dose volume of distribution
Fluctuation	Steady-state fluctuation ($[C_{max} – C_{min}]/C_{ave}$)

APPENDIX D. SCREENING SYMPTOM FORM

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

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

Investigators/Site Staff:

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

ELIGIBILITY CRITERION	CONFIRMATION
A symptom score of at least 5 on at least1 of the symptoms	□ Yes □ No
A symptom score of 3 or greater on at least 2 of the symptoms	□ Yes □ No

APPENDIX E. MODIFIED MYELOFIBROSIS SYMPTOM ASSESSMENT FORM VERSION 3.0

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

1. During the past 24 hours, how severe were your worst night sweats (or feeling hot or flushed) due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
2. During the past 24 hours, how severe was your worst fatigue due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
3. During the past 24 hours, how severe was your worst itchiness due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
4. During the past 24 hours, how severe was your worst feeling of low energy due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
5. During the past 24 hours, how severe was your worst abdominal discomfort (feel uncomfortable, pressure of bloating) due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
6. During the past 24 hours, how severe was your worst exhaustion due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
7. During the past 24 hours, how severe was your worst pain under the ribs on the left side due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
8. During the past 24 hours, how severe was your worst feeling of physical weakness due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
9. During the past 24 hours, what was your worst feeling of fullness (early satiety) you had after beginning to eat, due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
10. During the past 24 hours, how severe was your worst feeling bone or muscle pain due to MF (diffuse not joint or arthritis pain)?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
11. During the past 24 hours, how severe was your worst feeling of heavy limbs due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

12. During the past 24 hours, what was the worst tiredness due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
13. During the past 24 hours, what was your worst feeling of confusion due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
14. During the past 24 hours, what was your worst feeling of forgetfulness due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
15. In the past 24 hours, how much did MF interfere with your physical activity?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
16. In the past 24 hours, how much did MF interfere with your daily activities?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
17. In the past 24 hours, what was your worst level of frustration due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
18. During the past 24 hours, what was your worst degree of inactivity (including work and social activities) you had due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
When answering the following question, please think about the time since you woke up today	
19. Since waking up today, how severe was your worst feeling of sleepiness due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

APPENDIX F. MYELOPROLIFERATIVE NEOPLASMS SYMPTOM ASSESSMENT FORM

Subject Number _____ _____

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

APPENDIX G. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS (ECOG)

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

Source: Oken et al 1982.

APPENDIX H. PATIENT GLOBAL IMPRESSION OF CHANGE

Instructions: circle the answer that is most appropriate.

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

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

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

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

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

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

[a] Baseline and post-treatment bone marrow slides are to be interpreted at 1 sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

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

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

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

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

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

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

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

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

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

APPENDIX J. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	13 APR 2016
Amendment (Version) 2:	18 MAY 2016
Amendment (Version) 3:	22 NOV 2016
Amendment (Version) 4:	06 JUN 2017
Amendment (Version) 5:	23 MAR 2018
Amendment (Version) 6:	11 OCT 2018

Amendment 6 (11 OCT 2018)

Overall Rationale for the Amendment:

The purpose of this amendment is to add Part 4 to the study. Part 4 will examine the role an initial higher dose may play in overall efficacy and safety. There are 2 groups in Part 4:

- TG5I/M: 20 mg QD for 8 weeks followed by 5 mg QD until EOT
- TG5D: 5 mg QD from Day 1 until EOT

1. **Synopsis; Section 1.7, Justification of Study Treatment Regimen; 1.8.3, Potential Benefits of INCB050465 Based on Prior and Ongoing Clinical Studies; Section 2, Study Objectives and Endpoints; Section 4.1, Overall Study Design; Section 4.3.1, Planned Number of Subjects; Section 5, Treatment**

   Description of change: Added Part 4, which will compare a group of subjects who receive an initial higher dose of INCB050465 20 mg QD for 8 weeks followed by 5 mg QD with a group who will receive 5 mg QD from Day 1. Further enrollment into Part 3 is suspended effective with site-specific IRB approval of Amendment 6.

   Rationale for change: To examine the role an initial higher INCB050465 dose may play in overall efficacy and safety.

2. **Synopsis; Section 4.1, Overall Study Design; Section 5.2.2, Part 2, Part 3, and Part 4 Treatment Groups: Randomized Portion**

   Description of change: Simplified the description of the 4 parts of the study and indicated that Parts 2 and 3 are no longer enrolling subjects.

   Rationale for change: To simplify and remove redundant language and to clarify that Parts 2 and 3 are no longer enrolling.

3. **Synopsis; Section 5.2.3, Crossover of Part 2 and Part 3 Subjects**

   Description of change: Described how subjects randomized to TG20 in Part 3 may cross over to receive INCB050465 5 mg QD once they have reached Week 8.

   Rationale for change: To provide criteria for Part 3 subjects to cross over.

4. **Synopsis; Section 9.4.1, Efficacy Analysis**

   Description of change: Changed treatment group comparisons from all ITT subjects in TG5 and TG20 groups in Parts 2 and 3 to TG5D and TG5I/M + TG5 groups in Parts 3 and 4.

   Rationale for change: Updated analysis for new treatment groups.

5. **Synopsis; Section 9.5.2, Interim Efficacy Analysis**

   Description of change: Updated to include subjects in TG5I/M and TG5D in Part 4. Note that TG5 subjects from Part 3 will also be included in the TG5I/M group.

   Rationale for change: Updated analysis for new treatment groups.

6. **Section 1.5.4, Clinical Summary**

   Description of change: Updated clinical information for INCB050465.

   Rationale for change: To provide updated information and alignment with the current Investigator's Brochure.

7. **Section 1.6, Overview of Ruxolitinib**

   Description of change: Updated information on ruxolitinib safety data in healthy volunteers and MF patients.

   Rationale for change: To simplify and provide updated information consistent with the current Investigator's Brochure.

8. **Section 1.8.2, Potential Risks of INCB050465 Based on Prior Clinical Studies**

   Description of change: Deleted information regarding potential phototoxicity.

   Rationale for change: Phototoxicity studies have been conducted and did not show any phototoxocitity.

9. **Appendix B, Cytochrome P450 Inhibitors and Inducers**

   Description of change: Replaced old table of inducers and inhibitors with a new one.

   Rationale for change: To provide updated information for investigators.

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

Amendment 5 (23 MAR 2018)

Overall Rationale for the Amendment:

The purpose of this amendment is to add Part 3 to the study in order to compare INCB050465 20 mg QD for 8 weeks followed by 20 mg once weekly versus INCB050465 20 mg QD for 8 weeks followed by 5 mg QD. As of March 2018, with approximately 25 total subjects treated with the once-weekly dosing frequency in Parts 1 and 2, no DLTs have been observed, and no trends for late onset toxicity have been noted using available nonverified data. There does not appear to be a meaningful difference between the 10 mg and 20 mg dose groups for safety or efficacy. Therefore, it is reasonable to simplify the dosing regimen so that all patients begin receiving INCB050465 at 20 mg QD with comparison between different long-term dose strategies.

1. **Synopsis; Section 1.7.2, Potential Risks of INCB050465 Based on Prior Clinical Studies; Section 2, Study Objectives and Endpoints; Section 4.1, Overall Study Design; Section 5, Treatment**

   Description of change: Added Part 3, which compares dose regimens for long-term administration of INCB050465. Further enrollment into Part 2 is suspended effective with site-specific IRB approval of Amendment 5.

   Rationale for change: Part 3 will explore 2 dose options beyond 8 weeks.

2. **Synopsis; Section 1.7.2, Potential Risks of INCB050465 Based on Prior Clinical Studies; Section 4, Investigational Plan; Section 5, Treatment; Section 9, Statistics**

   Description of change: Added designations for dose groups: TG10 (10 mg QD × 8 weeks followed by 10 mg once weekly), TG20 (20 mg QD × 8 weeks followed by 20 mg once weekly), and TG5 (20 mg QD × 8 weeks followed by 5 mg QD).

   Rationale for change: To simplify the Protocol sections discussing dose groups.

3. **Synopsis; Section 4.1, Overall Study Design; Section 5.2.1, Part 1: Safety Run-In Portion**

   Description of change: Add wording to indicate Part 1 has been completed. Change tense for enhanced readability.

   Rationale for change: Part 1 was completed.

4. **Synopsis; Section 5.2.3, Crossover of Part 2 Subjects to Part 3**

   Description of change: Described how subjects randomized to 10 mg in Part 2 may cross over to Part 3 doses.

   Rationale for change: To provides criteria for Part 2 subjects to cross over to Part 3.

5. **Synopsis; Section 4.4, Duration of Treatment and Subject Participation; Section 6, Study Assessments (Table 8, Schedule of Assessments); Section 6.1, Screening**

   Description of change: Change screening windows from Day -28 to Day -8 to Day -35 to Day -8 (increases period from 21 days to 28 days)

   Rationale for change: A 28-day screening period is consistent with other protocols.

6. **Section 6, Study Assessments (Table 11, Schedule of Pharmacokinetic Sampling for Part 1, Part 2, and Part 3)**

   Description of change: Added footnotes.

   Rationale for change: To provide windows for sample collection and fasting details.

7. **Synopsis; Section 9.4.1, Efficacy Analysis**

   Description of change: Changed treatment group comparisons from all ITT subjects in Part 2 to TG5 and TG20 subjects in both Parts 2 and 3.

   Rationale for change: Updated analysis for new treatment groups.

8. **Synopsis; Section 9.5.2, Interim Efficacy Analysis**

   Description of change: Updated to include subjects in TG5 and TG20 in Parts 2 and 3.

   Rationale for change: Updated analysis for new treatment groups.

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

Amendment 4 (06 JUN 2017)

The primary purpose of this amendment is to update the clinical safety and efficacy information for the study drug INCB050465, to clarify visit scheduling and cohort enrollment, and to add 1 additional exclusion criteria.

This amendment includes the changes to the Protocol INCB 50465-201 Amendment 3 (dated 22 NOV 2016) summarized below. A redline version of the amendment depicting the updated and previous text is also provided.

1. **Synopsis; Section 4.1.1, Part 1: Safety Run-In Portion (Table 2, Safety Run-In Cohorts; Table 3, Dose-Limiting Toxicities for Part 1); Section 4.3.1, Planned Number of Subjects**

   Description of change: The language describing how many subjects are enrolled in each cohort and what the action taken will be has been clarified. The description of ruxolitinib-related neutrophil margination has been removed.

   Rationale for change: The wording caused some confusion regarding the total number of subjects enrolled in Cohort 2 and the outcome if 10 mg QD doses are not tolerated. Because new onset neutropenia will be handled by discontinuing INCB050465, the ruxolitinib wording is not needed.

2. **Synopsis; Section 3.2, Subject Inclusion Criteria**

   Description of change: The inclusion criteria regarding willingness to avoid fathering a child has been modified to provide for continued precautions from screening through 93 days after treatment with INCB050465.

   Rationale for change: For consistency with other protocols using INCB050465.

3. **Synopsis; Section 3.3, Subject Exclusion Criteria; Section 5.7.4, Prohibited Medications**

   Description of change: Exclusion criteria regarding liver and renal function tests modified to specify that the screening test, rather than both screening and baseline tests, will be used for inclusion/exclusion. Exclusion criterion added to prohibit receipt of live vaccines within 30 days before the first dose of INCB050465, and live vaccines added to prohibited medications list.

   Rationale for change: Consistency with other INCB050465 protocols and clarification.

4. **Section 5.3.1.1, Description and Administration**

   Description of change: Added descriptive wording to indicate how to schedule weekly doses following the 8 weeks of daily dose administration of INCB050465.

   Rationale for change: Provide clarification for study site personnel.

5. **Section 5.5.6, Criteria and Procedures for Dose Interruptions and Adjustments of INCB050465 (Table 6, Dose Levels for INCB050465)**

   Description of change: Added descriptive wording to indicate that medical monitor should be consulted for dose modifications below 5 mg QD or once weekly.

Rationale for change: Provide clarification for study site personnel.

6. **Synopsis; Section 6, Study Assessments (Table 8, Schedule of Assessments; Table 9, Schedule of Laboratory Assessments); Section 6.3, Treatment**

   Description of change: Clarification of visit scheduling to indicate that study visits occur at the end of indicated weeks (eg, Week 4 is after 4 weeks of treatment).

   Rationale for change: To clarify visit scheduling.

7. **Synopsis; Section 1.7.2, Potential Risks of INCB050465 Based on Prior Clinical Studies; Section 5.7.1, Pneumocystis Pneumonia Prophylaxis; Section 6.5.1, Safety Follow-Up**

   Description of change: Extended *Pneumocystis jirovecii* prophylaxis to 2 to 6 months after the last dose of INCB050465.

   Rationale for change: To provide updated information consistent with new Investigator's Brochure (IB).

8. **Section 6, Study Assessments (Table 8, Schedule of Assessments); Section 7.6.8, IWG-MRT Assessment**

   Description of change: Removal of IWG-MRT assessment at baseline.

   Rationale for change: Typographical error in original protocol.

9. **Section 1.5, Overview of INCB050465**

   Description of change: Language for Section 1.5.1 (Pharmacology Summary), Section 1.5.2 (Nonclinical Toxicology Summary), Section 1.5.3 (Nonclinical Drug Metabolism and Pharmacokinetics), and Section 1.5.4 (Clinical Summary) updated to reflect new IB.

   Rationale for change: To provide updated information consistent with new IB.

10. **Section 1.7, Potential Risks and Benefits of the Treatment Regimen**

    Description of change: Language for Section 1.7.1 (Potential Risks of INCB050465 Based on Preclinical Safety) and Section 1.7.2 (Potential Risks of INCB050465 Based on Prior Clinical Studies) updated to reflect new IB.

    Rationale for change: To provide updated information consistent with new IB.

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

Amendment 3 (22 NOV 2016)

The primary purpose of this amendment is to update the clinical safety and efficacy information for the study drug INCB050465, and to modify the dosing regimen for both Part 1 and Part 2.

1. **Synopsis; Section 4.1.1, Part 1: Safety Run-In Portion; Section 4.4, Duration of Treatment and Subject Participation; Section 5.2, Cohorts and Treatment Groups; Section 5.3.1.1, Description and Administration**

   Description of change: The doses and administration schedule for Part 1 have been changed. Cohorts 1, 2, and 3 will test doses of 10 mg, 20 mg, and 5 mg, respectively. Doses will be given once daily for 8 weeks, followed by once weekly at the same dose.

   Rationale for change: As of 02 SEP 2016, among all subjects (n = 46) in study INCB 50465-101, 11 (24%) have discontinued study drug due to an adverse event (AE). Among the subjects with an objective response (n = 20), 7 (35%) discontinued study treatment due to an AE. The dose has been change to potentially reduce the frequency of AEs that lead to study drug discontinuation.

2. **Synopsis; Section 4.1.1, Safety Run-In Cohorts (Table 2); Section 9.5.1, Interim Safety Analysis**

   Description of change: Information regarding subject enrollment and dose-limiting toxicity evaluation in the safety run-in cohorts has been updated. Interim safety analysis information was updated accordingly.

   Rationale for change: To provide updated cohort descriptions and decisions based on safety observations.

3. **Section 1.5.3, Clinical Summary**

   Description of change: Safety and efficacy data for study INCB 50465-101 have been updated based on a data cut of 02 SEP 2016.

   Rationale for change: To provide investigators with up-to-date information and support the rationale for the new dose schedule.

4. **Section 1.7.1, Potential Risks of INCB050465 Based on Preclinical Safety**

   Description of change: Reworded for clarity.

   Rationale for change: To clarify risks based on preclinical safety studies.

5. **Section 1.7.2, Potential Risks of INCB050465 Based on Clinical Studies**

   Description of change: The potential risks and benefits of the treatment regimen were updated based on the 02 SEP 2016 data cut of study INCB 50465-101.

   Rationale for change: To provide current interpretation of risks based on the most recent data.

6. **Section 5.5.6, Criteria and Procedures for Dose Interruptions and Adjustments of INCB050465**

   Description of change: Table 5 (Guidelines for Interruption and Restarting of INCB050465) was updated, Table 6 (Dose Level for INCB050465) was added, and

supportive care guidelines for diarrhea/colitis and definition of the term "immune-related adverse event" were added.

Rationale for change: New guidance was provided for AEs that have caused treatment discontinuation in Study INCB 5-465-101 to assist physicians managing these AEs.

7. **Section 9.4.2.5 Adverse Events of Special Interest**

   Description of change: The list of adverse events of special interest was expanded to match other sponsored studies with INCB050465.

   Rationale for change: The list of AEs reflects risks of inhibition of immune function in general, and includes AEs that have led to treatment discontinuation in study INCB 50465-101.

8. **Appendix F, Myeloproliferative Neoplasms Symptom Assessment Form for Use in IWG-MRT Response Criteria**

   Description of change: The MPN-SAF questionnaire was modified to 10 items. The full MPN-SAF contains 18 questions or items; only 10 of the items will be analyzed in the study as part of the IWG-MRT response.

   Rationale for change: To simplify the administration of the questionnaire for both subject and site staff, the MPN-SAF for the present study will present only the 10 questions of interest.

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

Amendment 2 (18 MAY 2016)

The primary purpose of this amendment is to update the clinical safety and efficacy information for the study drug INCB050465, and to include additional exclusion criteria related to subject history of immune-related adverse events.

1. **Synopsis; Section 3.3, Subject Exclusion Criteria**

   Description of change: Two new exclusion criteria were added (#21 and 22):

   21. History of Grade 3 or 4 immune-related AEs from prior immunotherapy.
       - Any immune-related AEs of Grade 1 or 2 must be resolved before receiving the first dose of INCB050465.
   22. History of immune-related ocular AEs of any toxicity grade.

   Rationale for change: A serious immune-related adverse event occurred when INCB050465 was combined with a JAK 1 inhibitor (not ruxolitinib). Although the role INCB050465 may have played in the event is unclear, subjects with a history of such events will be excluded from the study.

2. **Section 1.5.3, Clinical Summary**

   Description of change: Updated data as of 30 MAR 2016 have been added for studies INCB 50465-101, INCB 39110-106, and INCB 39110-107.

   Rationale for change: To provide investigators with up-to-date information.

3. **Section 1.7.2, Potential Risks of INCB050465 Based on Prior Clinical Studies**

   Description of change: Background information added on the potential risk of the infection or new cancer and immune-related adverse events, based on prior clinical studies with INCB050465.

   Rationale for change: To provide investigators with up-to-date information.

4. **Section 1.7.5, Potential Risks of the Combination of INCB050465 and Ruxolitinib; Section 5.7.1, Pneumocystis Pneumonia Prophylaxis**

   Description of change: Revised to indicate that subjects who are allergic to sulfonamide antibiotics should be treated with either inhaled pentamidine or atovaquonone for *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis, and dapsone should not be used in such subjects.

   Rationale for change: To provide instructions for PCP prophylaxis for subjects with sulfa allergies.

5. **Section 6, Study Assessments**

   Description of change: Table 7 (Schedule of Assessments – Part 1 and Part 2 Subjects) was updated to include the survival follow-up phase. After discontinuation of INCB050465, the subject will remain in the follow-up phase of the study, and site staff will conduct phone calls at approximately 12-week intervals to collect data on subsequent MF therapy and survival.

Rationale for change: To provide consistency with study processes described in subsequent Protocol sections.

6. **Section 6.2, Baseline**

   Description of change: Sentence indicating that blood samples for hematology and serum chemistry should be taken as close as possible to Day 1, but may be drawn up to 3 days before the anticipated date of the first dose of INCB050465, has been deleted.

   Rationale for change: Sentence was a duplicate of subsequent sentence.

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

Amendment 1 (13 APR 2016)

The primary purpose of this amendment is to:

- Add language regarding mandatory prophylaxis for pneumocystis pneumonia. Delete Serum (1,3)-β-D-glucan testing as it is unnecessary with prophylaxis.
- Add language indicating that subjects must be monitored for CMV reactivation.
- Clarify the need for overnight fasting before each study visit.
- Clarify that a Day 1 blood sample for serum chemistry/hematology is not required provided the baseline blood samples were drawn within 3 days before first dose of study drug.
- Provide language regarding dose adjustments in the case of a group being terminated as the result of interim analysis.

Additional revisions were also made to provide internal consistency within the Protocol.

1. **Synopsis; Section 1.7, Potential Risks and Benefits of the Treatment Regimen; Section 3.3, Subject Exclusion Criteria; Section 5.7.1, Pneumocystis Pneumonia Prophylaxis; Section 6, Study Assessments (Table 8: Schedule of Laboratory Assessments; Table 9: Laboratory Tests: Required Analytes); Section 6.5.1, Safety Follow-Up; Section 7.7.8, Serum (1,3)-β-D glucan; Section 9.4.2.5, Adverse Events of Special Interest**

   Description of change: Added mandatory prophylaxis for pneumocystis pneumonia and deleted serum (1,3)-β-D-glucan testing.

   Rationale for change: To provide additional patient safety for the combination of PI3Kδ inhibitor plus JAK inhibitor. B-D-glucan testing was deleted as it is unnecessary with prophylaxis.

2. **Synopsis; Section 1.7, Potential Risks and Benefits of the Treatment Regimen; Section 3.3, Subject Exclusion Criteria; Section 7.7.7, Serology; Section 6, Study Assessments (Table 8: Schedule of Laboratory Assessments; Table 9: Laboratory Tests: Required Analytes); Section 9.4.2.5, Adverse Events of Special Interest**

   Description of change: Added serology test for cytomegalovirus (CMV) viremia at screening. Require periodic determination of CMV viremia during study, as well as varicella-zoster virus and herpes simplex virus infections.

   Rationale for change: To provide additional patient safety for the combination of PI3Kδ inhibitor plus JAK inhibitor.

3. **Section 6, Study Assessments (Table 7: Schedule of Assessments); Section 6.3, Treatment; Section 7.10.1, Distribution of Subject Reminder Cards**

   Description of change: Provided clarification that subjects will arrive for all study visits, including Week 2, in the fasted state and having held morning drug doses.

   Rationale for change: Previous wording was unclear.

4. **Section 6, Study Assessments (Table 8: Schedule of Laboratory Assessments); Section 6.2 Baseline**

   Description of change: Clarified that a Day1 blood sample for serum chemistry and hematology need not be drawn if the baseline blood draw was within the 3 days before the first dose of study drug.

   Rationale for change: Simplify procedures for sites.

5. **Synopsis; Section 9.5.2, Interim Efficacy Analysis**

   Description of change: Added language regarding possible dose adjustments in the case that a Part 2 group is terminated because of the interim analysis.

   Rationale for change: To clarify that there is possibility for dose adjustments for subjects continuing in the study in a terminated group.

6. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment, to provide consistency within the Protocol.