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

Document Date: Statistical Analysis Plan Version 3: 21-May-2021

STATISTICAL ANALYSIS PLAN

INCB 50465-201

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

IND Number:	[redacted]
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Protocol Version:	**Protocol Amendment 6 dated 11 OCT 2018**
CRF Approval Date:	**06 MAY 2020**
SAP Version:	**Amendment 3**
SAP Author:	[redacted]**, PhD** [redacted]**, Biostatistics**
Date of Plan:	**21 MAY 2021**

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{(0-\infty)}$	AUC from time 0 (predose) extrapolated to infinite time
$AUC_{(0-\tau)}$	AUC from time 0 (predose) to time of last observed quantifiable concentration within a participant across all treatments
BID	twice daily
BP	blood pressure
CI	confidence interval
C_{max}	maximum observed concentration
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
Hgb	hemoglobin
[redacted]	[redacted]
IWG-MRT RD	International Working Group – Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
K	potassium
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MFSAF v3.0	Myelofibrosis Symptom Assessment Form version 3.0
MPN-SAF	Myeloproliferative Neoplasms Symptom Assessment Form
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
PD	pharmacodynamic
PET-MF	post–essential thrombocythemia myelofibrosis
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic

Abbreviation	Term
PMF	primary myelofibrosis
PPV-MF	post–polycythemia vera myelofibrosis
PT	preferred term
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SOC	system organ class
SR	sustained release
t	time of last observed quantifiable concentration
$t_{½}$	terminal phase half-life
TBL	total bilirubin level
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
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 (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)
T_{max}	time of occurrence of C_{max}
[redacted]	[redacted]
[redacted]	[redacted]
TSS	total symptom score
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

This is a Phase 2 randomized, open-label study in participants who have been diagnosed with primary or secondary myelofibrosis or PET-MF and have suboptimal response while receiving ruxolitinib monotherapy for a period of at least 6 months. Part 1 was a 3 + 3 design to determine the MTD of the PI3Kδ inhibitor INCB050465 in combination with the JAK 1/2 inhibitor ruxolitinib and selected 2 dose levels of INCB050465 to be evaluated in the randomized portion (Part 2) of the study. In Part 2 of the study, approximately 60 participants were planned to be enrolled and randomized 1:1 between the 2 selected doses of INCB050465 + ruxolitinib from Part 1. Randomization was stratified by ECOG performance status (0 or 1 vs 2). With Amendment 5, Part 3 was planned to be an open-label study where all participants will begin with INCB050465 20 mg QD. After 8 weeks, participants in TG5 would continue receiving INCB050465 at 5 mg QD, and participants in TG20 would continue receiving INCB050465 at 20 mg once weekly. The enrollment in Part 3 was suspended with implementation of Protocol Amendment 6. With IRB approval of Protocol Amendment 6 at a given site, participants randomized to TG20 at that site may cross over to 5 mg QD once Week 8 has been reached. With Amendment 6, Part 4 is added to compare different daily dosing regimens and the impact of an initial higher dose of INCB050465 on long-term response. Participants 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 participants 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 participants will switch to 5 mg QD (the maintenance dose). Section 1 of the Protocol provides a detailed description of the investigational product including targeted patient population, the rationale for doses to be examined, and the potential risks and benefits from combined INCB050465 and ruxolitinib treatment.

The purpose of the SAP is to provide details of the statistical analyses that have been outlined in the Study INCB 50465-201 Protocol. The scope of this plan includes the final analyses that are planned and will be executed by the Department of Biostatistics or designee.

Population PK analysis will be conducted by the Incyte pharmacokineticist, and the details of the analysis methodology and results will appear in a separate report.

[redacted]

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 50465-201 Protocol Amendment 6 dated 11 OCT 2018 and CRFs approved 06 MAY 2020. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and CRF versions.

2.2. Study Objectives

2.2.1. Primary Objectives

- Part 1: To evaluate the safety and tolerability of INCB050465 in combination with ruxolitinib in participants 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 participants with PMF, PPV-MF, or PET-MF.

2.2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy of INCB050465 in combination with ruxolitinib on participant reports of MF symptoms.
- To evaluate the efficacy of INCB050465 in combination with ruxolitinib on response using IWG-MRT criteria.
- To assess the PK of INCB050465 and ruxolitinib alone and when given in combination in participants with MF.
- To evaluate the safety and tolerability of INCB050465 when combined with ruxolitinib in participants with MF.

[redacted]

2.3. Study Endpoints

2.3.1. 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 MRI (or CT scan in applicable participants).

2.3.2. Secondary Endpoints

- Change and percentage change in spleen volume from baseline through Week 24 as measured by MRI (or CT scan in applicable participants).
- Change and percentage change in TSS from baseline through Week 12 or Week 24 as measured by the MFSAF v3.0 symptom diary and by the MPN-SAF.
- Number of participants 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]

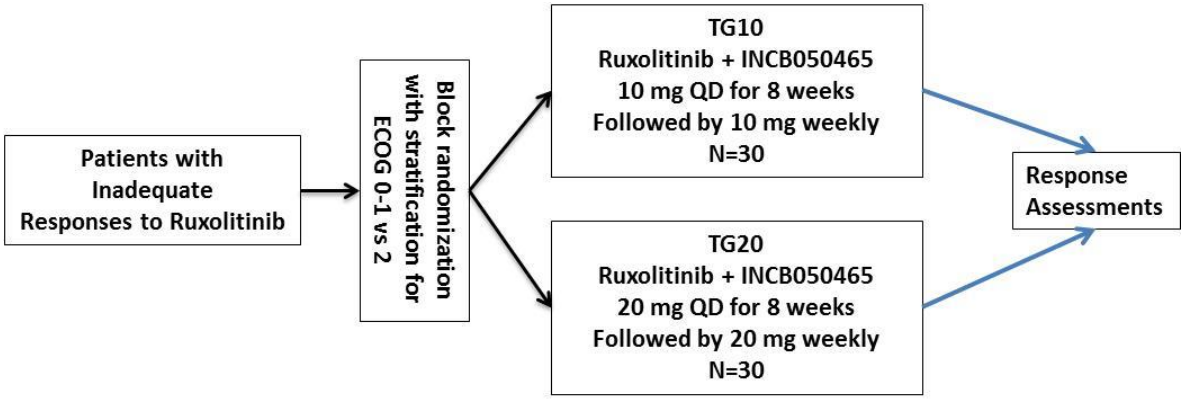
3. STUDY DESIGN

This is an open-label, Phase 2 study in participants who have been diagnosed with primary or secondary MF (PPV-MF or PET-MF) and who have had suboptimal response while receiving ruxolitinib monotherapy for a period of at least 6 months. The study consists of an open-label, safety run-in portion (Part 1) evaluating the combination of the PI3Kδ inhibitor INCB050465 and the JAK 1/2 inhibitor ruxolitinib and an open-label, randomized portion (Part 2) evaluating the 2 dose levels determined in Part 1. With Amendment 5, another open-label, randomized portion (Part 3) was added to the study to evaluate a new dose level in comparison with the one dose level chosen from Part 1. With Amendment 6, there will be no further enrollment into Part 3 at the given site. Another randomized portion (Part 4) is designed to compare different daily dosing regimens and to address the impact of an initial higher dose of INCB050465 on overall response.

The safety run-in portion of the study was to examine up to 3 cohorts to confirm the safety and tolerability of INCB050465 in combination with ruxolitinib and to select 2 dose levels of INCB050465 to be evaluated in the randomized portion (Part 2) of the study. The cohorts were to be tested sequentially beginning with Cohort 1 (ruxolitinib + INCB050465 10 mg QD) and then Cohort 2 (ruxolitinib + INCB050465 20 mg QD). If Cohort 2 failed, Cohort 3 (ruxolitinib + INCB050465 5 mg QD) would be examined. If ≥ 2 participants in any cohort experienced a DLT, this dose level would be considered as not tolerated. More details of the safety run-in portion are provided in Section 3.1.

Part 2 was planned to be a randomized open-label study with 2 treatment groups: TG10 and TG20. Randomization occurred centrally, using an interactive response technology. Block randomization was used with the strata for each participant determined by the participant's ECOG performance status (0 or 1 vs 2) at time of screening. Participants with ECOG performance status of 3 or greater were not eligible for participation in this study. The study design for Part 2 is shown in Figure 1.

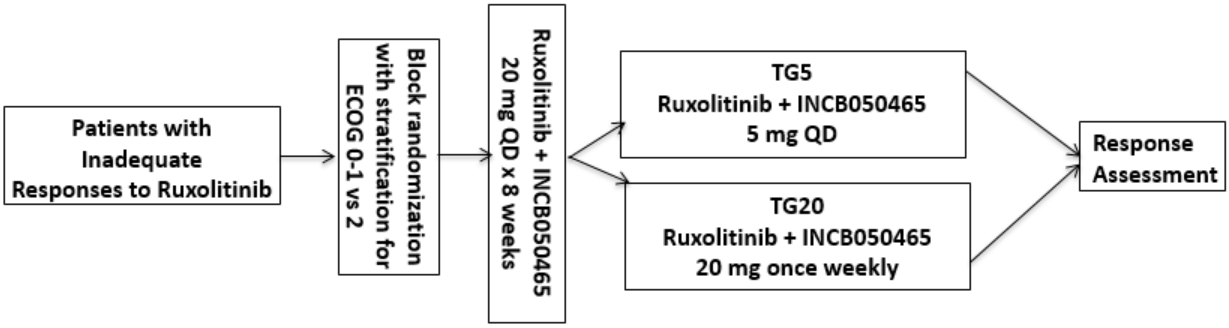
Figure 1: Part 2 Study Design



With Amendment 5, Part 3 was added to be an open-label block-randomized study where all participants will begin with INCB050465 20 mg QD. After 8 weeks, participants in TG5 will continue receiving INCB050465 at 5 mg QD, and participants in TG20 will continue receiving INCB050465 at 20 mg once weekly. Part 3 will use the same stratification as that in Part 2. The study design for Part 3 is shown in Figure 2. Note that enrollment in Part 3 was suspended with

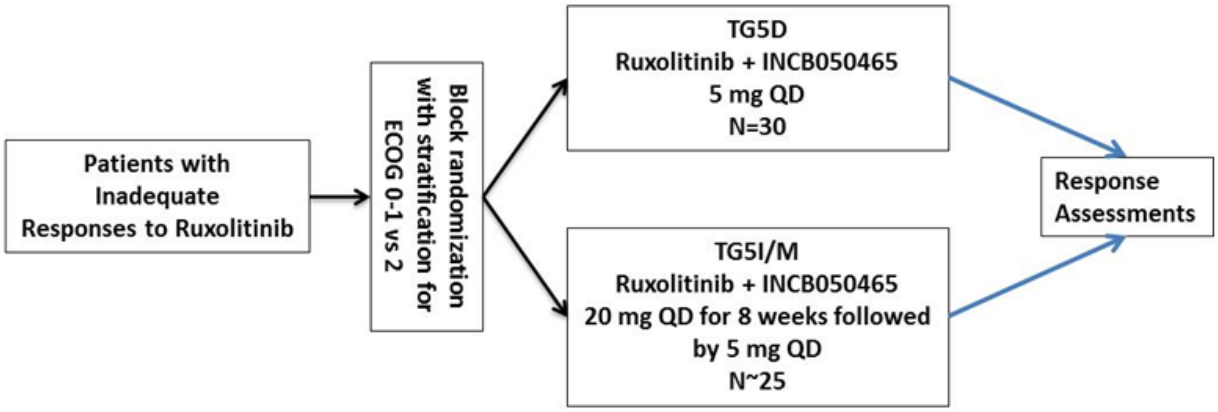
implementation of Protocol Amendment 6. Participants randomized to TG20 at that site may cross over to 5 mg QD once Week 8 has been reached.

Figure 2: Part 3 Study Design



With Amendment 6, Part 4 is added to be an open-label, block-randomized study. Participants 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, followed by 5 mg daily dosing. Dosing will continue per the randomized group assignment indefinitely or until discontinuation criteria are met. Figure 3 shows the study design for Part 4.

Figure 3: Part 4 Study Design



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 participant. Acceptable doses of ruxolitinib are 5 mg BID to 25 mg BID. INCB050465 will be self-administered QD. Participants who discontinue treatment with the study drug will be followed for subsequent treatment regimens and survival.

3.1. 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 participants 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, participants who took at least 22 of 28 daily doses of INCB050465 AND ruxolitinib OR had a DLT during the first 28 days (refer to Table 3 of the Protocol) were to

be included in the evaluation cohort. Additional participants were to be enrolled into Cohort 1 if discontinuations result in fewer than 3 evaluable participants. After evaluation, the actions listed in Table 1 would occur.

Table 1: Safety Run-In Cohorts

Cohort	No. of Participants	Regimen	DLTs Observed	Action Taken
1	3	INCB050465 10 mg QD for 8 weeks, followed by 10 mg once weekly plus ruxolitinib at 5 mg BID to 25 mg BID[a]	0	Proceed to Cohort 2.
			1	Enroll 3 additional participants, and evaluate the total of 6 participants after 28 days. If < 2 participants have a DLT, then proceed to Cohort 2. If ≥ 2 participants have a DLT, proceed to Cohort 3.
			> 1	Proceed to Cohort 3.
2	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 participants, and evaluate the total of 6 participants after 28 days. If < 2 participants have a DLT, then proceed to Part 2 using doses of 10 mg and 20 mg of 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 participants have a DLT and if Cohorts 1 and 2 exceeded DLT allowance, then proceed to Part 2 as a single arm study of 5 mg of 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.

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

3.2. Part 2 Randomized Portion

The open-label randomized portion of the study was planned to enroll approximately 60 participants randomized 1:1 by block randomization into 2 treatment groups, TG10 and TG20.

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

3.3. Part 3 Randomized Portion

In Part 3, all participants were planned to initially receive INCB050465 at 20 mg QD for 8 weeks in combination with ruxolitinib. After Week 8, participants were to 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 participants, followed by 1:1 randomization for additional participants, up to a total of approximately 52 participants).

Enrollment in Part 3 was suspended with implementation of Amendment 6. Participants already enrolled into TG5 in Part 3 would 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. Participants already enrolled into TG20 in Part 3 would have the opportunity to cross over to receive INCB050465 5 mg QD once they reach Week 8 provided they demonstrate inadequate response to the current dose regimen.

3.4. Part 4 Randomized Portion

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

3.5. Crossover Portion

With IRB approval of Protocol Amendment 5 at a given site, participants randomized to TG10 in Part 2 at that site may cross over to either 20 mg QD followed by 5 mg QD after Week 8 (if participant is within the first 8 weeks of treatment at the time of crossover), or to 5 mg QD (if participant 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, participants randomized to TG20 at that site may cross over to 5 mg QD once Week 8 has been reached. All potential crossover participants must meet the criteria listed in Protocol Amendment 6, Section 5.2.3.

Participants who do not meet these criteria, or participants 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 participant and investigator to represent the best option.

The crossover portion starts when the participants are assigned to and receive their first dose of a different treatment. The original portion of the study for crossover participants ends the day before crossover.

3.6. Control of Type I Error

For the primary endpoint in Parts 2, 3, and 4, the overall 2-sided Type I error is 0.10 for detecting a difference between TG5D and TG5 (TG5I/M). This means that there is a 10% risk of observing a significant location shift in percentage change of spleen volume from baseline between TG5D and TG5 (TG5I/M) even when there is none.

3.7. Sample Size Considerations

3.7.1. Cohort Size in Safety Run-In Portion

For the safety run-in portion, the decision to de-escalate the dose was driven by the number of observed toxicities and could be calculated based on the binomial distribution. During the safety run-in portion of the study, dose escalation between Cohorts 1 and 2 was to follow a 3 + 3 design algorithm. Doses were to 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 2. In the table, a cohort is considered toxic if 2 or more of the first 6 participants experienced a DLT. A cohort is considered safe if fewer than 2 of the first 6 participants experienced a DLT with the exception that Cohort 1 will also be considered safe for escalating to Cohort 2 if 0 of the first 3 participants experience a DLT. There was alternative allowance to assess additional doses if Cohort 3 was determined to be above the MTD.

Table 2: 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 arm 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

During Part 1, the probabilities of declaring a dose to be tolerable for the 3 cohorts at various DLT rates are provided in Table 3.

Table 3: Probability of Declaring a Dose to be Tolerable

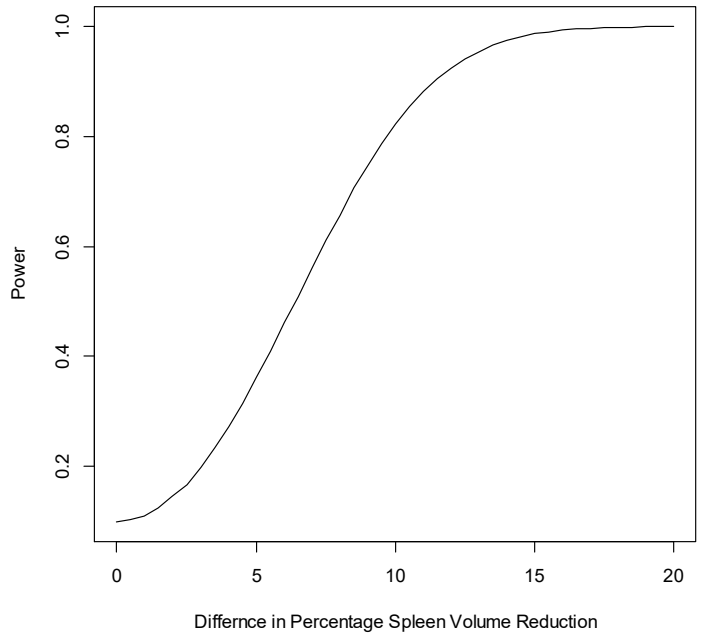
True DLT Rate	Probability of Declaring the Dose to be Tolerable	
	In Cohort 1	In Cohorts 2 and 3
20%	70.8%	65.7%
30%	49.4%	42.0%
40%	30.9%	23.3%
50%	17.2%	10.9%
60%	8.02%	4.01%

3.7.2. Sample Size in Randomized Portion

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. The data from Study INCB 18424-351 (COMFORT-1) suggested a mean reduction of 8.44 in percentage change from baseline of spleen volume with a standard deviation of 14.5 from baseline to Week 12 for the active group in that study. For a 2-sided Type I error of 0.10 and Type II error of 0.10 with 30 participants 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.

In the event that only 1 dose was selected during the Part 1 safety-run in portion of the study or the event that 1 of the treatment groups was terminated for futility at the interim analysis during the randomized portion, the median spleen volume reduction would be estimated and a CI constructed based on the exact binomial CI. Figure 4 plots the power of the design with 30 participants per treatment group at various percentage point location shifts between the 2 groups in spleen volume reduction.

Figure 4: Plot of Power at Various Differences Between Treatment Groups



3.8. Schedule of Assessments

Refer to Protocol Amendment 6 dated 11 OCT 2018 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of study drug INCB050465 is administered to the participants. For randomized participants not treated with any study drug, Day 1 is defined as the day of randomization.

4.1.2. Day 1 of Crossover for Crossover Participants

For participants who cross over from TG10/TG20 to TG5D, Day 1 of crossover is the date that the participants are assigned to TG5D based on the assigned dose in the exposure CRF.

4.1.3. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (Visit/Reporting Date – Day 1 date).

A study day of -1 indicates 1 day before Day 1.

4.1.4. Baseline Value

Baseline is the last nonmissing measurement obtained within the baseline window before the first administration of INCB050465, unless otherwise defined.

For randomized participants not treated with any study drug, baseline is defined as the last nonmissing assessment before randomization for all parameters.

When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.5. Last Available Value

The last available value is the last nonmissing measurement obtained after starting INCB050465 and within 30 days after the last dose of INCB050465.

4.1.6. Handling of Missing and Incomplete Data

In general, values for missing data will not be imputed unless methods for handling missing data are specified in this section or relevant sections.

Partial MF diagnosis date will be handled as follows:

- If only the day is missing, then the imputed day will be the first of the month.
- If both the month and day are missing, then the imputed day and month will be 01 JAN.
- No imputation will be done if the date is completely missing.

Missing or partial date of last dose will be handled as follows:

- If only the day is missing, then the imputed date of the last dose will be the earlier date of the first day of the month or the date that the participant discontinued treatment.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

4.2. Variable Definitions

The following variables will only be calculated if not reported on the CRF.

4.2.1. Age

Participant age will be calculated as the integer part of the number of years from date of birth to the date of signing the informed consent form (ICF), using the following formula:

Age = integer part of (date of informed consent – date of birth + 1) / 365.25

4.2.2. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of INCB050465.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of INCB050465 and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of INCB050465 and is ongoing or ends during the course of study drug.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of INCB050465. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant medication.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

All participants receiving combination study treatment with INCB050465 and ruxolitinib are required to receive a standard PCP prophylaxis regimen determined by the investigator. A summary will be provided for PCP prophylaxis regimen.

4.2.3. Prior Ruxolitinib

A complete history of ruxolitinib usage before screening will be recorded on the CRF and produced as a listing by participant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

5.2. Treatment Groups

As the study was terminated early, participants from all parts will be combined. Data will be summarized overall and by treatment group based on the dose regimen initially assigned in the initial portion:

- TG10: Ruxolitinib at stable dose plus INCB050465 10 mg QD for 8 weeks followed by 10 mg once weekly.
- TG20: Ruxolitinib at stable dose plus INCB050465 20 mg QD for 8 weeks followed by 20 mg once weekly.
- TG5, TG5I/M: Ruxolitinib at stable dose plus INCB050465 20 mg QD for 8 weeks followed by 5 mg QD.
- TG5D: Ruxolitinib at stable dose plus INCB050465 5 mg QD from Day 1 until EOT visit.

Note that TG5I/M in Part 4 is identical to TG5 from Part 3; participants from these 2 groups will be combined in the final analysis.

The crossover participants will be summarized in the initial portion from the date of randomization to the date before crossover.

In the crossover portion, the crossover participants will be summarized in TG5D from the date of crossover to the end of study. Only the crossover participants will be summarized in the crossover portion. Participants in TG5 (TG5I/M) and TG5D and the participants in TG10 or TG20 who do not meet the crossover criteria will remain in the treatment group initially assigned in the initial portion.

5.3. Analysis Populations

5.3.1. Safety Population

The safety population includes all participants in Parts 1, 2, 3, and 4 who received at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned study drug treatment. The safety population will be used for all analyses.

The participants in TG5D and TG5 (TG5I/M) will be summarized under TG5D and TG5 (TG5I/M), respectively, in the initial portion. The participants crossed over from TG10/TG20 to TG5D will be summarized under TG10/TG20 in the initial portion before crossover and under a separate crossover group after crossover.

5.3.2. Spleen Volume Evaluable Population at Week XX

The spleen volume evaluable population includes all participants enrolled in the study who received at least 1 dose of study drug (INCB050465 or ruxolitinib), completed a spleen volume baseline assessment, and met at least 1 of the following criteria:

- The participant has Week XX spleen volume assessment.
- The participant has been on study for a minimum of (7 × XX + 7) days of follow-up.
- The participant has discontinued from treatment on or before Week XX.

5.3.3. Crossover Population

The crossover population includes all participants enrolled in TG10/TG20 who receive at least 1 dose of study drug and later crossover to TG5D.

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

The lists of tables, figures, and listings are provided in Appendix A. Sample data displays are provided in a separate document. The lists and the shells are to be used as a guideline. Modifications of the lists or shells that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

Data will be summarized overall and by treatment group based on the dose regimen initially assigned for the safety population.

6.1.1. Demographics

The following demographics will be summarized for the safety population by treatment group: age, sex, race, ethnicity, weight (kg), and height.

6.1.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized for the safety population by treatment group: disease subtype (PMF, PPV-MF, or PET-MF), baseline TSS, and ECOG performance status reported to IWRS.

6.1.3. Disease History

Date of MF diagnosis and prior bone marrow biopsy data as to fibrosis grade, cellularity, and transfusion history in the prior 12 weeks to enrollment; prior splenic irradiation; and MF prognostic factors including: age > 65 years, presence of constitutional symptoms (weight loss > 10% of the baseline value in the year preceding MF diagnosis, unexplained fever, or excessive night sweats persisting for more than 1 month), marked anemia (Hgb < 10g/dL) at screening, WBC > 25×10^9/L at screening, circulating blasts ≥ 1% at screening, and risk level as defined by IWG (Passamonti et al 2010) will be recorded and summarized for the safety population by treatment group.

Time since diagnosis will be calculated as:

Time since diagnosis (years) = (date of Day 1 – date of diagnosis + 1) / 365.25

6.1.4. Prior Therapy

Number of prior systemic cancer therapy regimens will be summarized for all participants in the safety population by treatment group. Regimen name, component drugs, start and stop date, purpose of the regimen, best response, reason for discontinuation, and date of relapse/progression will be listed.

Number of participants who received prior radiation will be summarized for safety population by treatment group. Radiotherapy type, body site, start and stop date, total dose, and best response will be listed.

Number of participants who had prior surgery or surgical procedure for the malignancies under study will be summarized for the safety population by treatment group. Date and description of the surgery/procedure will be listed.

All treatments for MF, including a complete history of ruxolitinib usage, will be summarized for all participants in the safety population by treatment group.

6.2. Disposition of Participants

The number and percentage of participants who were enrolled, randomized, treated, completed the study, discontinued study treatment with a primary reason for discontinuation, and discontinued from the study with a primary reason for withdrawal will be summarized for all participants in the safety population by treatment group. The number of participants randomized/enrolled by site will also be provided for the safety population by treatment group.

6.3. Protocol Deviations

Protocol deviations recorded on the CRF will be presented in the participant data listings.

6.4. Exposure

For participants in the safety population, exposure to INCB050465 and ruxolitinib will be summarized descriptively by treatment group for initial portion and crossover portion separately as the following:

- **Duration of treatment with study drug** (INCB050465)**:** Date of last dose of INCB050465– date of first dose of INCB050465 + 1
- **Duration of treatment with study drug** (ruxolitinib)**:** Date of last dose of ruxolitinib – date of first dose of ruxolitinib + 1
- **Dose intensity for INCB050465:** Let *S* be the earliest study day after permanent discontinuation from study, last study visit, or participant death; let $D_1, D_2, \ldots, D_K$, be the *K* daily doses (mg) of INCB050465 prescribed to the participant accounting for dose increases on study days $S_1, S_2, \ldots, S_K$,. Dose intensity for INCB050465 is defined as

  dose intensity (%) = 100 × [total dose (mg)] / [assigned dose (mg)],

  where a participant's assigned dose of INCB050465 is defined as the sum of the doses prescribed had the participant not experienced dose delays or reductions on each of the *S* study days. Formally expressed,

  assigned dose = $\sum_{i=1}^{K} D_i(t_{i+1} - t_i)$ where $t_1 = 1$ and $t_{K+1} = S$

  For example, suppose a participant is assigned INCB050465 10 mg QD, dose escalates per investigator decision to 20 mg QD on Day 19, and discontinues on Day 31. The assigned dose of INCB050465 for the participant in question is

  assigned dose = $(19 - 1) \times 10 + (31 - 19) \times 20 = 420$ mg.

- **Dose intensity for ruxolitinib:** Let *S* be the earliest study day after permanent discontinuation from study, last study visit, or participant death; let $D_1, D_2, \ldots, D_K$, be the *K* daily doses (mg) of ruxolitinib prescribed to the participant accounting for dose increases on study days $S_1, S_2, \ldots, S_K$,. Dose intensity for ruxolitinib is defined as

  dose intensity (%) = 100 × [total dose(mg)]/[assigned dose (mg)],

  where a participant's assigned dose of ruxolitinib is defined as the sum of the doses prescribed had the participant not experienced dose delays or reductions on each of the *S* study days. Formally expressed,

  assigned dose = $\sum_{i=1}^{K} D_i(t_{i+1} - t_i)$ where $t_1 = 1$ and $t_{K+1} = S$

  For example, suppose a participant is assigned ruxolitinib 10 mg BID, dose de-escalates per investigator decision to 5 mg BID on Day 19, and discontinues on Day 31. The assigned dose of ruxolitinib for the participant in question is

  assigned dose = $(19 - 1) \times 20 + (31 - 19) \times 10 = 480$ mg.

- **Average daily dose of INCB050465 (mg/day):** total actual INCB050465 dose taken (mg) / duration of treatment with INCB050465 (days).
- **Average daily dose of ruxolitinib (mg/day):** total actual ruxolitinib dose taken (mg) / duration of treatment with ruxolitinib (days).

  Total actual dose taken will be calculated based on the information entered on the drug accountability CRF.
- **INCB050465 dose modifications:** Number of participants who had INCB050465 dose reduction, escalation, and interruption will be summarized.
- **Ruxolitinib dose modifications:** Number of participants who had ruxolitinib dose reduction, escalation, and interruption will be summarized.
- **Starting dose of ruxolitinib:** The starting dose of ruxolitinib at the time of the first dose of INCB050465 will be summarized.

6.5. Study Drug Compliance

The participants in the safety population by treatment group for the initial portion and crossover portion separately, overall compliance (%) for INCB050465 will be calculated as

compliance (%) = 100 × [total dose actually taken] / [total prescribed dose].

The total prescribed dose is defined as the sum of the doses prescribed by the investigator accounting for dose modifications.

The total actual dose taken will be calculated based on information entered on the drug accountability CRF. If there is dispensed drug that have not been returned yet, the actual dose taken starting from the dispense date of the unreturned drug will be imputed by the dose taken as reported on the dosing CRF.

Ruxolitinib will be commercially supplied, and the compliance of ruxolitinib will not be calculated.

6.6. Prior and Concomitant Medication

For participants in the safety population by treatment group, prior medications and concomitant medications will be coded using the WHO Drug Dictionary and summarized by WHO drug class and WHO drug term. Results will be summarized as number and percentage of participants with prior and concomitant medications by PT and WHO drug class for the safety population by treatment group.

Prior medication information will also be used to identify medications for MF received by participants before enrollment into the study. Prior MF medication data will be summarized and presented for participants in the safety population by treatment group, as well as provided in a listing.

7. EFFICACY

The lists of tables, figures, and listings are provided in Appendix A. Sample data displays are provided in a separate document. The lists and the shells are to be used as a guideline. Modifications of the lists or shells that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

7.1. General Considerations

Unless otherwise stated, the strata identified in the randomization process will be used in all efficacy analyses.

7.2. Efficacy Hypotheses

7.2.1. Primary Endpoint

The primary hypothesis is that there will be a location shift in the percentage change from baseline at 12 weeks in spleen volume between TG5D and TG5I/M.

7.3. Analysis of the Primary Efficacy Parameter

7.3.1. Primary Efficacy Analysis

The primary endpoint is change and percentage change in spleen volume from baseline at 12 weeks as measured by MRI (or CT scan in applicable participants). A location shift in percentage change in spleen volume between TG5D and TG5I/M for stratification by ECOG performance status at screening (0 or 1 vs 2) will be assessed using a van Elteren test (van Elteren 1960).

The baseline spleen volume will be measured by MRI (or by CT for applicable participants) during the baseline visit (Days -7 to 1); the last value will be used if there are multiple values measured during the baseline visit.

The Week 12 spleen volume will be measured by MRI (or by CT for applicable participants) during the Week 12 visit (Day 84 ± 7 days); the last value will be used if there are multiple values measured during the Week 12 visit.

Within each stratum, participants who discontinue from the study or who have missing values for the Week 12 spleen volume will be imputed as having the largest possible percentage increase in spleen volume and given the lowest rank in the stratum. The participant 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 study fails to enroll a sufficient number of participants in a particular stratum, a sensitivity analysis using a 2-sample Wilcoxon rank sum test with a normal approximation applied to the test statistic, for purposes of calculation stability, will be conducted. Ranking will be carried out using the same approach but without stratification.

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

Statistical comparison will be conducted for TG5D versus TG5 (TG5I/M). To explore the difference in daily dosing and daily/weekly dosing, the statistical comparison will also be performed for daily dosing (TG5D + TG5I/M) versus daily/weekly dosing (TG10 + TG20).

In the event of a single-arm trial, a 95% CI for median percentage change in spleen volume from baseline at Week 12 will be calculated from the exact binomial distribution.

The percentage change from baseline at Week 12 will be calculated using the formula:

% change = 100 × [Week 12 spleen volume – baseline spleen volume] / baseline spleen volume

The number of participants with spleen volume reductions from baseline to every 12 weeks will be summarized categorically. The number of participants with < 0% reduction (increase), 0% to < 10% reduction, ≥ 10% to < 35% reduction, and ≥ 35% reductions will be summarized by treatment group. For the analysis of spleen volume reduction response rate, the Cochran-Mantel-Haenszel test will be applied to these categories and stratified by ECOG performance status (0 or 1 vs 2) at screening, and a 95% CI will be reported using the row mean scores differ option under SAS PROC FREQ. This option accounts for the ordinal nature of the response categories.

7.3.2. Subgroup Analyses for Primary Endpoint

Subgroups will be formed based on the following participant characteristics and baseline variables for those participants whose data are available: disease subtype and baseline spleen volume by tertile.

7.4. Analysis of the Secondary Efficacy Parameter

7.4.1. Change and Percent Change in Spleen Volume at Week 24

Baseline spleen volume is defined in Section 7.3.1 and percent change in spleen volume from baseline at 24 weeks takes the same definition given in Section 7.3.1 for percentage change in spleen volume from baseline at 12 weeks. Change and percentage change in spleen volume from baseline at 24 weeks as measured by MRI (or CT scan in applicable participants) will be analyzed as described in Section 7.3.1. Results for participants enrolled to TG10 or TG20 will

be compared descriptively with those of the other treatment groups, but no direct statistical comparisons are planned.

Statistical comparison will be conducted for TG5D versus TG5 (TG5I/M) and for daily dosing (TG5D + TG5I/M) versus daily/weekly dosing (TG10 + TG20).

7.4.2. Total Symptom Score and Total Symptom Score – Fatigue

The difference between TG5D and TG5 (TG5I/M) in change and percentage change in TSS from baseline to Week 12 and baseline to Week 24 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 the study fails to enroll a sufficient number of participants in a particular stratum, 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 as a sensitivity analysis. The difference between TG5D and TG5 (TG5I/M) in change and percentage change in TSS – Fatigue from baseline to Week 12 and baseline to Week 24 evaluated by the MFSAF v3.0 will use the same rule as regular TSS.

The difference in TSS between daily dosing (TG5D + TG5I/M) and daily/weekly dosing (TG10 + TG20) will be assessed in the same way.

7.4.2.1. MFSAF v3.0

The MFSAF v3.0 is comprised of 19 individual symptom scores (night sweats, fatigue, itchiness, low energy, abdominal discomfort, exhaustion, pain under left ribs, physical weakness, early satiety, bone/muscle pain, heavy limbs, tiredness, confusion, forgetfulness, interference with physical activity, interference with daily activities, frustration, inactivity, sleepiness), each collected daily with a 0 to 10 point scale.

The daily TSS is composed of 6 of these individual symptom scores (nights sweats, itchiness, abdominal discomfort, pain under left ribs, early satiety, bone/muscle pain) collected on the same day. The TSS – Fatigue is composed of 13 individual symptom scores that are related to fatigue (fatigue, low energy, exhaustion, physical weakness, heavy limbs, tiredness, confusion, forgetfulness, interference with physical activity, interference with daily activities, frustration, inactivity, sleepiness).

Regular TSS and TSS – Fatigue will be missing if there are any missing individual scores. Observations with missing dates will be excluded from the analysis.

The baseline total score is defined as the average of daily total scores from the last 7 days before the first dose of INCB050465; the baseline total score will be missing if there are ≥ 4 missing out of the 7 daily total scores.

The Week 12 total score will be the average of daily total scores from the last 7 consecutive days before the Week 12 visit; the Week 12 total score will be missing if there are ≥ 4 missing out of the 7 daily total scores, or the 28 days are completed outside the window for Week 12 visit (Day 84 ± 7).

The Week 24 total score will be the average of daily total scores from the last 7 consecutive days before the Week 24 visit; the Week 24 total score will be missing if there are ≥ 4 missing out of

the 7 daily total scores or if the 7 days are completed outside the window for the Week 24 visit (Day 168 ± 7).

The percentage change from baseline to Week 12 and baseline to Week 24 will be calculated using the formulas:

% change = 100 × (Week 12 total score – Baseline total score) / Baseline total score

% change = 100 × (Week 24 total score – Baseline total score) / Baseline total score

7.4.2.1.1. Windowing of MFSAF v3.0 Total Symptom Score

The MFSAF v3.0 TSS for baseline, Week 12, and Week 24 will be determined by averaging the daily MFSAF v3.0 TSS for the days between the start and end of windows as described in Table 4. By-question summaries for the 6 individual symptom scores that compose the TSS at baseline, Week 12, and Week 24 will use the same windowing algorithm as used for the daily TSS. By-question summaries will also be provided for all 19 individual symptom scores included in the MFSAF v3.0 at baseline, Week 12, and Week 24 using the same windowing algorithm used for the daily TSS.

The TSS and the 19 individual scores at Weeks 4, 8, 16, and 20 will be derived in a similar fashion using the first nonmissing daily TSS available between

Day (7 × week)

and

Day (7 × week) + 7

as the end of the window.

Change and percentage change from baseline for the 19 individual scores and change and percentage change from baseline for the TSS will be summarized by week.

The number of participants with reductions in MFSAF v3.0 TSS from baseline at Weeks 12 and 24 will also be summarized categorically. The number of participants with < 0% reduction (increase), 0% to 25% reduction, 25 to < 50% reduction, and ≥ 50% reductions will be summarized by treatment group. For the analysis of MFSAF v3.0 TSS reduction rate, the Cochran-Mantel-Haenszel test will be applied to these categories and stratified by ECOG performance status (0 or 1 vs 2) at screening, and a 95% CI will be reported using the row mean scores differ option under SAS PROC FREQ. This option accounts for the ordinal nature of the response categories.

Table 4: Window for Deriving MFSAF v3.0 Total Symptom Score for Baseline, Week 12, and Week 24

Period	Start of Window	End of Window	Missing
Baseline	7 days on or before end of window	Last day that a daily TSS was collected between Day -7 and Day -1 (inclusive)	4 or more missing of the 7 daily TSSs in the window, or no measurement between Day -7 and Day -1
Week 12	First day a daily TSS was collected between Day 78 and Day 84 (inclusive)	7 days on or after start of window	4 or more missing of the 7 daily TSSs in the window, or no measurement between Day 84 and Day 90
Week 24	First day a daily TSS was collected between Day 162 and Day 168 (inclusive)	7 days on or after start of window	4 or more missing of the 7 daily TSSs in the window, or no measurement between Day 168 and Day 174

7.4.2.2. MPN-SAF

The MPN-SAF weekly total score is defined as the sum of 10 individual symptom scores (fatigue, nights sweats, itchiness, bone pain, fever, unintentional weight loss last 6 months, early satiety, abdominal discomfort, inactivity, problems with concentration, each with a 0 to 10 point scale) collected at the same visit; the score will be missing if there are any missing individual scores.

The number of participants with reductions in MPN-SAF TSS from baseline to every 4 weeks will be summarized categorically, and a Cochran-Mantel-Haenszel test will be applied as described in Section 7.4.2.1.1.

7.4.3. Analysis of IWG-MRT Consensus Criteria

IWG-MRT criteria provides criteria for response to treatment in MF. Recently published response criteria developed by the IWG on MF will be used in this study (Tefferi et al 2013). Overall response assessment will be graded according to the IWG-MRT consensus criteria for treatment response in PMF, PPV-MF, and PET-MF. The criteria for response assessment according to IWG-MRT is provided in Appendix B.

The IWG-MRT assessment will be performed at baseline, Week 24, and every 24 weeks thereafter. The number of participants with responses according to investigator-reported IWG-MRT consensus criteria will be summarized by treatment group. Best overall response under the IWG-MRT consensus criteria will also be summarized. Best overall response is defined as the highest overall response achieved postbaseline prior to and including the first confirmed progressive disease in the order of complete response, partial response, clinical improvement, stable disease, partial disease, and relapse. A listing of the clinical data used by Incyte to derive the IWG-MRT responses will be provided.

7.4.4. Analysis of Patient Global Impression of Change Score

The Patient Global Impression of Change questionnaire consists of question with 7 possible answers. The Patient Global Impression of Change questionnaire will be completed at each study visit. The PGIC score will be tabulated and summarized descriptively (mean, standard deviation, etc) by treatment group and by daily and daily/weekly dosing for the safety population in the initial portion at each visit.

8. SAFETY AND TOLERABILITY

The lists of tables, figures, and appendices are provided in Appendix A. Sample data displays are provided in a separate document. The lists and the shells are to be used as a guideline. Modifications of the list or shells that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

8.1. General Considerations

Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few participants.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

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 (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE. The CTCAE version 4.03 is used for this study. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

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

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment emergent.

8.2.2. Dose-Limiting Toxicities

A DLT or dose limiting toxicity will be defined as the occurrence of a toxicity, with the exception of events clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity; the list of toxicities that will be designated as DLTs are provided in Table 3 of the Protocol.

The number of participants with DLTs and the type of DLT will be listed by treatment group.

8.2.3. Maximum Tolerated Dose

The MTD of INCB050465 is the highest treatment group tested that is considered tolerated on the basis of fewer than 2 DLTs in a cohort of 6 participants.

8.2.4. 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. Infections and inflammation reactions will be monitored and comprise AEs of special interest as indicated in Table 5.

Liver chemistry tests as assessed by ALT, AST, total bilirubin, alkaline phosphatase tests are also considered as events of special interest and will be summarized for the safety population by dose group for initial portion and crossover portion separately. Participants with elevations in liver chemistry tests will be summarized, and a listing for participants with ALT ≥ 5 × ULN or AST ≥ 5 × ULN will be provided.

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities. The number and proportion of participants experiencing the events listed in Table 5 (regardless of seriousness) will be summarized by treatment group. The AESIs will be summarized for the safety population by dose group for the initial portion and crossover portion separately.

Table 5: Adverse Events of Special Interest

Category of AEs	Specific AEs in Category
Liver Chemistry Tests	ALT/AST elevations equal to or above 5 × ULN
Inflammation/reactions	Colitis, diarrhea ≥ Grade 2, rash ≥ Grade 2, pneumonitis, exfoliative dermatitis, intestinal perforation
Infections	CMV infection, herpes simplex virus infection, varicella zoster virus infection, *Pneumocystis jirovecii* infection

8.2.5. Adverse Event Summaries

An overall summary of AEs by treatment group will include:

- Number (%) of participants reporting any TEAEs
- Number (%) of participants reporting any DLTs
- Number (%) of participants reporting any SAEs
- Number (%) of participants reporting any Grade 3 or 4 TEAEs
- Number (%) of participants reporting any TEAEs related to INCB050465
- Number (%) of participants reporting any TEAEs related to ruxolitinib
- Number (%) of participants who temporarily interrupted INCB050465 because of TEAEs

- Number (%) of participants who temporarily interrupted ruxolitinib because of TEAEs
- Number (%) of participants who permanently discontinued INCB050465 because of TEAEs
- Number (%) of participants who permanently discontinued ruxolitinib because of TEAEs
- Number (%) of participants with INCB050465 dose reductions because of TEAEs
- Number (%) of participants with ruxolitinib dose reductions because of TEAEs
- Number (%) of participants who had a fatal TEAE
- Number (%) of participants who withdrew from study because of an TEAE
- Number (%) of participants reporting any treatment-emergent AESIs

The following summaries will be produced by MedDRA term (if 10 or fewer participants appear in a table, a listing may be appropriate):

- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of TEAEs by SOC, PT, and maximum severity
- Summary of Grade 3 or 4 TEAEs by SOC and PT
- Summary of INCB050465 treatment-related AEs by SOC and PT
- Summary of Grade 3 or 4 INCB050465 treatment-related AEs by SOC and PT
- Summary of INCB050465 treatment-related AEs by SOC, PT, and maximum severity
- Summary of ruxolitinib treatment-related AEs by SOC and PT
- Summary of Grade 3 or 4 ruxolitinib treatment-related AEs by SOC and PT
- Summary of ruxolitinib treatment-related AEs by SOC, PT, and maximum severity
- Summary of TEAEs leading to death by SOC and PT
- Summary of treatment-emergent SAEs by SOC and PT
- Summary of treatment-emergent SAEs by PT in descending order of frequency
- Summary of INCB050465 treatment-related SAEs by SOC and PT
- Summary of ruxolitinib treatment-related SAEs by SOC and PT
- Summary of TEAEs leading to INCB050465 dose reduction by SOC and PT
- Summary of TEAEs leading to ruxolitinib dose reduction by SOC and PT
- Summary of TEAEs leading to INCB050465 dose interruption by SOC and PT
- Summary of TEAEs leading to ruxolitinib dose interruption by SOC and PT

- Summary of TEAEs leading to discontinuation of INCB050465 by SOC and PT
- Summary of TEAEs leading to discontinuation of ruxolitinib by SOC and PT
- Summary of TEAEs by SOC and PT: life-table method
- Summary of treatment-emergent AESIs

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. Baseline will be determined according to Section 4.1.4. If there are multiple values that meet the criteria for baseline, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Laboratory test values outside the normal range will be assessed for severity based on CTCAE grade where clinical intervention is required for CTCAE grading. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

8.3.2. Laboratory Value Summaries

All test results and associated normal ranges from central laboratories will be reported in SI units. All tests with numeric values will have a unique unit per test. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units. For the limited number of cases where the associated normal ranges from a local laboratory cannot be obtained despite due diligence, if query is unsuccessful at resolving the issues and analysis is mandatory, then the clinical scientist and medical monitor can provide a suitable normal range to be used in determining CTC grading and flags for above and below normal.

When there are multiple laboratory nonmissing values for a participant's particular test within a visit window, the convention described in Table 6 will be used to determine the record used for by-visit tabulations and summaries.

Table 6: Identification of Records for Postbaseline By-Visit Summaries

Priority	Laboratory Visit	Central or Local Laboratory	Proximity to Visit Window	Tiebreaker
1	Scheduled	Central	In-window	Use smallest laboratory sequence number
2	Scheduled	Local	In-window	
3	Unscheduled	Central	In-window	
4	Unscheduled	Local	In-window	
5	Scheduled	Central	Out-of-window	
6	Scheduled	Local	Out-of-window	

Shift tables based on worst postbaseline value recorded will use all postbaseline values occurring within 30 days of stopping study treatment.

Numeric laboratory values will be summarized descriptively in SI units, and non-numeric test values will be tabulated when necessary. In addition, line graphs and box-and-whisker plots will be provided for Hgb, platelet counts, WBC, and neutrophils.

For test results that will be summarized with available normal ranges, the number and percentage of participants with the laboratory values being low (but never high), normal, high (but never low), and both low and high will be calculated for each test. This shift summary will be produced for each test for the safety population. The denominator for the percentage calculation will use the number of participants in the baseline category (ie, low, high, normal, missing) as the denominator for the percentage in each of the categories during the treatment period.

Shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of participants in the baseline category.

In cases where differentials of hematology parameters are obtained without corresponding absolute count data, efforts will be made to investigate if the conversion to an absolute value will lead to additional abnormalities. This will be discussed with the clinical team regarding appropriate documentation and action.

Participants with the following elevations in liver chemistry tests will be summarized by treatment group for the safety population:

- ALT > 5 × ULN
- AST > 5 × ULN
- ALT or AST > 5 × ULN
- TBL > 2 × ULN
- ALT or AST > 5 × ULN and TBL > 2 × ULN and ALP < 2 × ULN

8.4. Vital Signs

Values at each scheduled visit, change, and percent change from baseline for vital signs, including weight, height, SBP, DBP, pulse, respiration rate, and body temperature will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 7. The abnormal values for participants exhibiting clinically notable vital sign abnormalities will be listed along with their assigned treatment group. Alert vital signs are defined as an absolute value outside the defined range and percentage change greater than 25%. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 7: 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

8.5. Electrocardiograms

Twelve-lead ECGs will be obtained for each participant during the study. Electrocardiogram abnormalities, both at baseline and postbaseline visits, will be tabulated by treatment group for the initial portion and crossover portion separately. Incidences of abnormalities will be listed with study visit, assigned treatment group, and a description of the abnormality.

9. INTERIM ANALYSES

There will be no planned, formal interim analyses for the Part 1 dose escalation portion of the study. The review of accrued clinical data will be conducted by Incyte and provided to study investigators via teleconferences at the end of Part 1 of the study. Based on review of the most current safety data, the sponsor (in consultation with the study investigators and using the dose-escalation/de-escalation rules) will determine if and at what dose additional participants should be treated in the study.

For TG5D and TG5 (TG5I/M) in the safety population, a formal interim analysis for futility is planned after 15 participants are enrolled into each treatment group and have discontinued or had their Week 12 visit. If 4 or fewer participants in a given dose 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 participants), then the dose in question will be terminated.

If either TG5D or TG5 (TG5I/M) is terminated, then Part 4 will continue as a single-arm study, and the primary endpoint will be analyzed as described in Section 3.6. If both of the treatment groups are terminated, the study will be terminated. The probabilities of stopping a treatment group for futility for various probabilities of a participant achieving ≥ 0% decrease in spleen volume at Week 12 are provided in Table 8. Additional operational details of the interim analyses, including TFLs provided to the DMC, will be provided in the DMC Charter.

Table 8: Probability of Stopping a Treatment Group for Futility

Probability of Participant 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. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 9.

Table 9: Statistical Analysis Plan Versions

SAP Version	Date
Original	27 JAN 2017
Amendment 1	17 MAY 2017
Amendment 2	30 APR 2019
Amendment 3	21 MAY 2021

10.1. Changes to Protocol-Defined Analyses

Not applicable.

10.2. Changes to the Statistical Analysis Plan

10.2.1. Original to Amendment 1

Additional summaries for the primary and secondary endpoints were incorporated into the SAP. The number of participants with spleen volume reductions from baseline, changes in MFSAF v3.0 TSS from baseline, and changes in MPN-SAF TSS from baseline will be summarized categorically. Two-sided Cochran-Mantel-Haenszel tests will be performed for spleen volume reduction rate, MFSAF v3.0 TSS reduction rate, and MPN-SAF TSS reduction rate stratified by ECOG performance status (0 or 1 vs 2) at screening. The Cochran-Mantel-Haenszel tests will incorporate the ordinality of the response categories. Best overall response for investigator-reported IWG-MRT response assessments will also be summarized. These changes led to updates in Sections 7.3 and 7.4, including descriptions of the response categories for spleen volume reductions, MFSAF v3.0 TSS reductions, and MPN-SAF TSS reductions, as well as a description of how best overall response is determined under the IWG-MRT consensus criteria.

Other minor updates include the following:

Appendix A was modified with additional summaries added to reflect the additional analyses. Additional minor edits and renumbering of tables were included in this section for internal consistency.

10.2.2. Amendment 1 to Amendment 2

- The analyses of Part 4 were added to the study in order to compare INCB050465 5 mg QD from Day 1 to EOT versus INCB050465 20 mg QD for 8 weeks followed by 5 mg QD. How participants enrolled in Part 2 TG10 and Part 3 TG20 may cross over to TG5 was described, and the handling of analyses population for crossover participants regarding the efficacy and safety analyses was defined.
- The window of MFSAF TSS was revised from the last 28 consecutive days to last 7 consecutive days before the assessment visit. The total score will be missing if there are ≥ 4 missing out of the 7 daily total scores.
- The analyses of MFSAF TSS – Fatigue were added.
- Analyses for the AESIs including a summary of treatment-emergent AESIs and summary of participants with elevations in liver chemistry tests were added. A summary of TEAE life table by SOC and PT was added to summarize the frequencies of TEAEs separately for ≤ 8 weeks, > 8 weeks and ≤ 16 weeks, > 16 weeks and ≤ 24 weeks, and > 24 weeks.
- Table shells were moved to a separate document from the SAP.
- Incorporation of administrative changes. Other minor, administrative changes have been incorporated throughout the SAP.

10.2.3. Amendment 2 to Amendment 3

The primary purpose of this amendment is to update the statistical analyses as enrollment has been terminated early.

- Intent-to-treat population, per-protocol population, and safety run-in population were removed. All analyses will be conducted using the safety population.
- In addition to the comparison between TG5D and TG5I/M, the comparison between daily dosing (TG5D + TG5I/M) and daily/weekly dosing (TG10 + TG20) in the endpoints of interest were added.
- The algorithm of the window for deriving MFSAF v3.0 total symptom score for baseline, Week 12, and Week 24 in Table 4 was updated to fix the issue when the participants have missing values in the end of window.
- Elevations in liver chemistry tests were added.
- Incorporation of administrative changes. Other minor, administrative changes have been incorporated throughout the SAP.

11. REFERENCES

Passamonti F, Cervantes F, Vannucchi AM, et al. Adynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood 2010;115:1703-1708.

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

Thiele J, Kvasnicka HM, Facchetti F, et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica 2005;90:1128-1132.

van Elteren PH. On the combination of independent two sample tests of Wilcoxon. Bulletin de l'Institut International de Statistique 1960;37:351-361.

APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned TFLs for the CSR. Standard tables will follow the conventions in the Standard Safety Tables initial version. Shells are provided for nonstandard tables. In-text tables are identical in structure and content as appendix tables but follow a Rich Text Format.

The list of TFLs and the shells are to be used as guideline. Modifications of the list or shells that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population	Standard
Baseline and Demographic Characteristics			
1.1 Disposition			
1.1.1	Analysis Populations	All Participants	X
1.1.2.1	Summary of Participant Disposition	Safety	X
1.1.2.2	Summary of Participant Disposition – Daily vs Daily/Weekly	Safety	X
1.1.3.1	Summary of Number of Participants Enrolled by Site	Safety	X
1.2 Demography			
1.2.1.1	Summary of Demographics	Safety	X
1.2.1.2	Summary of Demographics – Daily vs Daily/Weekly	Safety	X
1.3 Baseline Characteristics			
1.3.1.1	Summary of Baseline Disease Characteristics	Safety	
1.3.1.2	Summary of Baseline Disease Characteristics – Daily vs Daily/Weekly	Safety	
1.3.2.1	Summary of Disease History	Safety	
1.3.2.2	Summary of Disease History – Daily vs Daily/Weekly	Safety	
1.3.3.1	Summary of Prior Cancer Therapy	Safety	
1.4 Prior Medication and Concomitant Medication			
1.4.1.1	Summary of Prior Medications	Safety	X
1.4.2.1	Summary of Concomitant Medications	Safety	X
1.4.3.1	Summary of Prior Ruxolitinib History	Safety	
1.4.3.2	Summary of Prior Ruxolitinib History – Daily vs Daily/Weekly	Safety	
1.5+ Others			
1.5.1.1	Summary of General Medical History	Safety	X
Efficacy			
2.1 Primary Efficacy			
2.1.1.1	Summary of Percent Change in Spleen Volume by Visit	Safety Initial Portion	
2.1.1.2	Summary of Percent Change in Spleen Volume by Visit	Safety Crossover Portion	
2.1.1.3	Summary of Percent Change in Spleen Volume by Visit – Daily vs Daily/Weekly	Safety Initial Portion	
2.1.2.1	Van Elteren Test of Percent Change in Spleen Volume for TG5 (TG5I/M) and TG5D	Safety Initial Portion	
2.1.2.2	Van Elteren Test of Percent Change in Spleen Volume for Daily and Daily/Weekly Dosing	Safety Initial Portion	

Table No.	Title	Population	Standard
2.1.3.1	Summary of Response Categories for Spleen Volume Reduction for TG5 (TG5I/M) and TG5D	Safety Initial Portion	
2.1.3.2	Summary of Response Categories for Spleen Volume Reduction for Daily and Daily/Weekly Dosing	Safety Initial Portion	
2.2 Secondary Efficacy			
2.2.1.1	Summary of MFSAF v3.0 Total Symptom Score Using 7-Day Window by Visit	Safety Initial Portion	
2.2.1.2	Summary of MFSAF v3.0 Total Symptom Score Using 7-Day Window by Visit	Safety Crossover Portion	
2.2.1.3	Summary of MFSAF v3.0 Total Symptom Score Using 7-Day Window by Visit – Daily vs Daily/Weekly	Safety Initial Portion	
2.2.1.4	Summary of MFSAF v3.0 Total Symptom Score - Fatigue Using 7-Day Window by Visit	Safety Initial Portion	
2.2.1.5	Summary of MFSAF v3.0 Total Symptom Score - Fatigue Using 7-Day Window by Visit	Safety Crossover Portion	
2.2.2.1	Summary of Percent Change in MFSAF v3.0 Total Symptom Score Using 7-Day Window at Weeks 12 and 24	Safety Initial Portion	
2.2.2.2	Summary of Percent Change in MFSAF v3.0 Total Symptom Score Using 7-Day Window at Weeks 12 and 24	Safety Crossover Portion	
2.2.2.3	Summary of Percent Change in MFSAF v3.0 Total Symptom Score Using 7-Day Window at Weeks 12 and 24 – Daily vs Daily/Weekly	Safety Initial Portion	
2.2.2.4	Summary of Percent Change in MFSAF v3.0 Total Symptom Score - Fatigue Using 7-Day Window at Weeks 12 and 24	Safety Initial Portion	
2.2.2.5	Summary of Percent Change in MFSAF v3.0 Total Symptom Score - Fatigue Using 7-Day Window at Weeks 12 and 24	Safety Crossover Portion	
2.2.3.1	Van Elteren Test of MFSAF v3.0 Total Symptom Score for TG5 (TG5I/M) and TG5D	Safety Initial Portion	
2.2.3.2	Van Elteren Test of MFSAF v3.0 Total Symptom Score for Daily vs Daily/Weekly Dosing	Safety Initial Portion	
2.2.3.3	Van Elteren Test of MFSAF v3.0 Total Symptom Score - Fatigue for TG5 (TG5I/M) and TG5D	Safety Initial Portion	
2.2.3.4	Van Elteren Test of MFSAF v3.0 Total Symptom Score - Fatigue for Daily vs Daily/Weekly Dosing	Safety Initial Portion	
2.2.4.1	Summary of Response Categories for MFSAF v3.0 Total Symptom Score by Visit for TG5 (TG5I/M) and TG5D	Safety Initial Portion	
2.2.4.2	Summary of Response Categories for MFSAF v3.0 Total Symptom Score by Visit for Daily vs Daily/Weekly	Safety Initial Portion	
2.2.4.3	Summary of Response Categories for MFSAF v3.0 Total Symptom Score - Fatigue by Visit for TG5 (TG5I/M) and TG5D	Safety Initial Portion	
2.2.4.4	Summary of Response Categories for MFSAF v3.0 Total Symptom Score - Fatigue by Visit for Daily vs Daily/Weekly	Safety Initial Portion	
2.2.5.1	Summary of MPN-SAF Total Symptom Score by Visit	Safety Initial Portion	
2.2.5.2	Summary of MPN-SAF Total Symptom Score by Visit	Safety Crossover Portion	
2.2.5.3	Summary of MPN-SAF Total Symptom Score by Visit - Daily vs Daily/Weekly	Safety Initial Portion	
2.2.6.1	Summary of Percent Change in MPN-SAF Total Symptom Score at Weeks 12 and 24	Safety Initial Portion	

Table No.	Title	Population	Standard
2.2.6.2	Summary of Percent Change in MPN-SAF Total Symptom Score at Weeks 12 and 24 - Daily vs Daily/Weekly	Safety Initial Portion	
2.2.7.1	Van Elteren Test of MPN-SAF Total Symptom Score for TG5 (TG5I/M) and TG5D	Safety Initial Portion	
2.2.7.2	Van Elteren Test of MPN-SAF Total Symptom Score for Daily vs Daily/Weekly Dosing	Safety Initial Portion	
2.2.8.1	Summary of Response Categories for MPN-SAF Total Symptom Score for TG5 (TG5I/M) and TG5D	Safety Initial Portion	
2.2.8.2	Summary of Response Categories for MPN-SAF Total Symptom Score for Daily vs Daily/Weekly Dosing	Safety Initial Portion	
2.2.9.1	Summary of Patient Global Impression of Change (PGIC) Score	Safety Initial Portion	
2.2.9.2	Summary of Patient Global Impression of Change (PGIC) Score	Safety Crossover Portion	
2.2.9.3	Summary of Patient Global Impression of Change (PGIC) Score - Daily vs Daily/Weekly	Safety Initial Portion	
2.2.10.1	Summary of Investigator-Reported IWG-MRT Response Assessment for TG5 (TG5I/M) and TG5D	Safety Initial Portion	
2.2.11.1	Summary of Best Overall Response for Investigator-Reported IWG-MRT Response Assessment for TG5 (TG5I/M) and TG5D	Safety Initial Portion	
2.2.12.1.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Night Sweats	Safety Initial Portion	
2.2.12.1.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Night Sweats	Safety Crossover Portion	
2.2.12.2.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Itchiness	Safety Initial Portion	
2.2.12.2.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Itchiness	Safety Crossover Portion	
2.2.12.3.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Abdominal Discomfort	Safety Initial Portion	
2.2.12.3.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Abdominal Discomfort	Safety Crossover Portion	
2.2.12.4.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Pain Under Left Ribs	Safety Initial Portion	
2.2.12.4.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Pain Under Left Ribs	Safety Crossover Portion	
2.2.12.5.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Early Satiety	Safety Initial Portion	
2.2.12.5.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Early Satiety	Safety Crossover Portion	
2.2.12.6.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Bone/Muscle Pain	Safety Initial Portion	
2.2.12.6.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Bone/Muscle Pain	Safety Crossover Portion	
2.2.12.7.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Fatigue	Safety Initial Portion	

Table No.	Title	Population	Standard
2.2.12.7.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Fatigue	Safety Crossover Portion	
2.2.12.8.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Low Energy	Safety Initial Portion	
2.2.12.8.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Low Energy	Safety Crossover Portion	
2.2.12.9.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Exhaustion	Safety Initial Portion	
2.2.12.9.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Exhaustion	Safety Crossover Portion	
2.2.12.10.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Physical Weakness	Safety Initial Portion	
2.2.12.10.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Physical Weakness	Safety Crossover Portion	
2.2.12.11.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Heavy Limbs	Safety Initial Portion	
2.2.12.11.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Heavy Limbs	Safety Crossover Portion	
2.2.12.12.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Tiredness	Safety Initial Portion	
2.2.12.12.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Tiredness	Safety Crossover Portion	
2.2.12.13.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Confusion	Safety Initial Portion	
2.2.12.13.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Confusion	Safety Crossover Portion	
2.2.12.14.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Forgetfulness	Safety Initial Portion	
2.2.12.14.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Forgetfulness	Safety Crossover Portion	
2.2.12.15.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Interference With Physical Activity	Safety Initial Portion	
2.2.12.15.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Interference With Physical Activity	Safety Crossover Portion	
2.2.12.16.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Interference With Daily Activities	Safety Initial Portion	
2.2.12.16.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Interference With Daily Activities	Safety Crossover Portion	
2.2.12.17.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Frustration	Safety Initial Portion	
2.2.12.17.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Frustration	Safety Crossover Portion	
2.2.12.18.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Inactivity	Safety Initial Portion	
2.2.12.18.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Inactivity	Safety Crossover Portion	
2.2.12.19.1	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Sleepiness	Safety Initial Portion	

Table No.	Title	Population	Standard
2.2.12.19.2	Summary of MFSAF v3.0 Individual Symptom Scores by Visit, Sleepiness	Safety Crossover Portion	
2.2.13.1	Summary of Progression-Free Survival for TG5 (TG5I/M) and TG5D	Safety Initial Portion	
2.2.13.2	Summary of Progression-Free Survival for Daily and Daily/Weekly Dosing	Safety Initial Portion	
2.2.14.1	Summary of Overall Survival for TG5 (TG5I/M) and TG5D	Safety Initial Portion	
2.2.14.2	Summary of Overall Survival for Daily and Daily/Weekly Dosing	Safety Initial Portion	
[redacted]			
Safety			
3.1 Dose Exposure			
3.1.1.1	Summary of Study Drug Exposure and Compliance to INCB050465	Safety Initial Portion	X
3.1.1.2	Summary of Study Drug Exposure and Compliance to INCB050465	Safety Crossover Portion	X
3.1.2.1	Summary of Study Drug Exposure and Compliance to Ruxolitinib	Safety Initial Portion	X
3.1.2.2	Summary of Study Drug Exposure and Compliance to Ruxolitinib	Safety Crossover Portion	X
3.2 Adverse Events			
3.2.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety Initial Portion	X
3.2.1.2	Overall Summary of Treatment-Emergent Adverse Events	Safety Crossover Portion	X
3.2.2.1	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.3.1	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety Initial Portion	X
3.2.3.2	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety Crossover Portion	X
3.2.4.1	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety Initial Portion	X
3.2.4.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety Crossover Portion	X
3.2.5.1	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.5.2	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.6.1	Summary of INCB050465 Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.6.2	Summary of INCB050465 Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X

Table No.	Title	Population	Standard
3.2.7.1	Summary of Grade 3 or 4 INCB050465 Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.7.2	Summary of Grade 3 or 4 INCB050465 Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.8.1	Summary of Grade 3 or 4 INCB050465 Treatment-Related Adverse Events by MedDRA Preferred Term in Order of Decreasing Frequency	Safety Initial Portion	X
3.2.8.2	Summary of Grade 3 or 4 INCB050465 Treatment-Related Adverse Events by MedDRA Preferred Term in Order of Decreasing Frequency	Safety Crossover Portion	X
3.2.9.1	Summary of Ruxolitinib Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.9.2	Summary of Ruxolitinib Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.10.1	Summary of Grade 3 or 4 Ruxolitinib Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.10.2	Summary of Grade 3 or 4 Ruxolitinib Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.11.1	Summary of Ruxolitinib Treatment-Related Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety Initial Portion	X
3.2.11.2	Summary of Ruxolitinib Treatment-Related Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety Crossover Portion	X
3.2.12.1	Summary of Serious Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.12.2	Summary of Serious Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.13.1	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.13.2	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.14.1	Summary of Serious Treatment-Emergent Adverse Events by Preferred Term in Decreasing Order of Frequency	Safety Initial Portion	X
3.2.14.2	Summary of Serious Treatment-Emergent Adverse Events by Preferred Term in Decreasing Order of Frequency	Safety Crossover Portion	X
3.2.15.1	Summary of Non-Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.15.2	Summary of Non-Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.16.1	Summary of INCB050465Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X

Table No.	Title	Population	Standard
3.2.16.2	Summary of INCB050465Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.17.1	Summary of Ruxolitinib Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.17.2	Summary of Ruxolitinib Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.18.1	Summary of Treatment-Emergent Adverse Events Leading to INCB050465 Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.18.2	Summary of Treatment-Emergent Adverse Events Leading to INCB050465 Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.19.1	Summary of Treatment-Emergent Adverse Events Leading to Ruxolitinib Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.19.2	Summary of Treatment-Emergent Adverse Events Leading to Ruxolitinib Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.20.1	Summary of Treatment-Emergent Adverse Events Leading to INCB050465 Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.20.2	Summary of Treatment-Emergent Adverse Events Leading to INCB050465 Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.21.1	Summary of Treatment-Emergent Adverse Events Leading to Ruxolitinib Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.21.2	Summary of Treatment-Emergent Adverse Events Leading to Ruxolitinib Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.22.1	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of INCB050465 by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.22.2	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of INCB050465 by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.23.1	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Ruxolitinib by MedDRA System Organ Class and Preferred Term	Safety Initial Portion	X
3.2.23.2	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Ruxolitinib by MedDRA System Organ Class and Preferred Term	Safety Crossover Portion	X
3.2.24.1	Summary of Treatment-Emergent Adverse Events of Special Interest	Safety Initial Portion	X
3.2.24.2	Summary of Treatment-Emergent Adverse Events of Special Interest	Safety Crossover Portion	X
3.2.25.1	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: Life Table Method	Safety Initial Phase	X

Table No.	Title	Population	Standard
3.2.25.2	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: Life Table Method	Safety Crossover Portion	X
3.3 Laboratory			
3.3.1.1	Summary of Laboratory Values – Hematology	Safety Initial Portion	X
3.3.1.2	Summary of Laboratory Values – Hematology	Safety Crossover Portion	X
3.3.2.1	Shift Summary of Hematology Laboratory Values in CTC Grade – To the Worst Abnormal Value	Safety Initial Portion	X
3.3.2.2	Shift Summary of Hematology Laboratory Values in CTC Grade – To the Worst Abnormal Value	Safety Crossover Portion	X
3.3.3.1	Summary of Laboratory Values – Chemistry	Safety Initial Portion	X
3.3.3.2	Summary of Laboratory Values – Chemistry	Safety Crossover Portion	X
3.3.4.1	Shift Summary of Chemistry Laboratory Values in CTC Grade – To the Worst Abnormal Value	Safety Initial Portion	X
3.3.4.2	Shift Summary of Chemistry Laboratory Values in CTC Grade – To the Worst Abnormal Value	Safety Crossover Portion	X
3.3.5.1	Summary of Laboratory Values – Coagulation	Safety Initial Portion	X
3.3.5.2	Summary of Laboratory Values – Coagulation	Safety Crossover Portion	X
3.3.6.1	Shift Summary of Coagulation Values in CTC Grade – To the Worst Abnormal Value	Safety Initial Portion	X
3.3.6.2	Shift Summary of Coagulation Values in CTC Grade – To the Worst Abnormal Value	Safety Crossover Portion	X
3.3.7.1	Summary of Participants With Elevations in Liver Chemistry Tests	Safety Initial Portion	X
3.3.7.2	Summary of Participants With Elevations in Liver Chemistry Tests	Safety Crossover Portion	X
3.4 Vital Signs			
3.4.1.1	Summary of Systolic Blood Pressure (mmHg)	Safety Initial Portion	X
3.4.1.2	Summary of Systolic Blood Pressure (mmHg)	Safety Crossover Portion	X
3.4.2.1	Summary of Diastolic Blood Pressure (mmHg)	Safety Initial Portion	X
3.4.2.2	Summary of Diastolic Blood Pressure (mmHg)	Safety Crossover Portion	X
3.4.3.1	Summary of Heart Rate (bpm)	Safety Initial Portion	X
3.4.3.2	Summary of Heart Rate (bpm)	Safety Crossover Portion	X
3.4.4.1	Summary of Respiration Rate (bpm)	Safety Initial Portion	X
3.4.4.2	Summary of Respiration Rate (bpm)	Safety Crossover Portion	X
3.4.5.1	Summary of Body Temperature (°C)	Safety Initial Portion	X
3.4.5.2	Summary of Body Temperature (°C)	Safety Crossover Portion	X
3.4.6.1	Summary of Weight (kg)	Safety Initial Portion	X
3.4.6.2	Summary of Weight (kg)	Safety Crossover Portion	X
3.5 ECG			
3.5.1.1	Summary of Treatment Emergent, Clinically Significant ECG Abnormality From Baseline	Safety Initial Portion	
3.5.1.2	Summary of Treatment Emergent, Clinically Significant ECG Abnormality From Baseline	Safety Crossover Portion	

Figures

Figure No.	Title
4.1 Primary Efficacy	
4.1.1	Kaplan-Meier Estimates of Overall Survival
4.2 Secondary Efficacy	
4.2.1	Kaplan-Meier Estimates of Progression-Free Survival
4.90.# AD HOC or Additional Analyses of Other Safety Data	
4.90.1	Line Graph of Selected Laboratory Values by Study Visit
4.90.2	Box-and-Whisker Plot of Selected Laboratory Values by Study Visit

Listings

Listing No.	Title
2.1 Discontinued Participants (Participant Disposition)	
2.1.1	Participant Enrollment and Disposition Status
2.1.2	Participant Inclusion and Exclusion Criteria Deviations
2.2 Protocol Deviation	
2.2.1	Protocol Deviations
2.3 Data Excluded From PK, Efficacy, and/or Safety Analyses	
2.3.1	Analysis Population
2.4 Demography and Baseline (including Prior and Concomitant Medications)	
2.4.1	Demographic and Baseline Disease Characteristics
2.4.2	Disease History
2.4.3	Prior Radiation Treatment
2.4.4	Prior Systemic Therapy
2.4.5	Prior Surgery or Surgical Procedure
2.4.6	Prior Stem Cell Transplant
2.4.7	Medical History
2.4.8	Prior and Concomitant Medication
2.4.9	Prior Ruxolitinib History
2.5 Drug Compliance	
2.5.1	Study Drug Compliance
2.6 Efficacy (and/or PK Data)	
2.6.1	Deaths
2.6.2	Progression-Free Survival
2.6.3	Incyte-Derived IWG-MRT Response
2.6.4	ECOG Status
[redacted]	
2.7 Adverse Events (and Exposure)	
2.7.1	Study Drug Administration
2.7.2	Adverse Events
2.7.3	Dose-Limiting Toxicities
2.7.4	Serious Adverse Events
2.7.5	Grade 3 or 4 Adverse Events
2.7.6	Fatal Adverse Events

Listing No.	Title
2.7.7	Treatment-Related Adverse Events
2.7.8	Adverse Events Leading to Interruption, Reduction, or Discontinuation of INCB050465 or Ruxolitinib
2.8 Laboratory Data	
2.8.1	Clinical Laboratory Values – Hematology
2.8.2	Clinical Laboratory Values – Chemistry
2.8.3	Clinical Laboratory Values – Coagulation
2.8.4	Clinical Laboratory Values – Serology
2.8.5	Abnormal Clinical Laboratory Values
2.8.6	Participants With AST ≥ 5 × ULN or ALT ≥ 5 × ULN
2.9 Vital Signs	
2.9.1	Vital Signs
2.9.2	Abnormal Vital Sign Values
2.9.3	Alert Vital Sign Values
2.10 ECG	
2.10.1	12-Lead ECG Values
2.10.2	Abnormal 12-Lead ECG Values
2.10.3	Alert 12-Lead ECG Values
2.11 Physical Examination	
2.11.1	Physical Examinations
2.11.2	Body Weight

APPENDIX B. IWG-MRT CRITERIA FOR TREATMENT RESPONSE

IWG-MRT Criteria for Treatment Response

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]

IWG-MRT Criteria for Treatment Response (Continued)

Response Categories	Required Criteria (for All Response Categories, Benefit Must Last for ≥ 12 Weeks to Qualify as a Response)
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
	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.