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

INCB 39110-209

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

IND Number:	[redacted]
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Protocol Version:	**Amendment 1 dated 14 AUG 2017**
CRF Approval Date:	**22 AUG 2017**
SAP Version:	**Original**
SAP Author:	[redacted]**PhD** [redacted]
Date of Plan:	**15 NOV 2017**

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

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
AUC	area under the concentration-time curve
[redacted]	[redacted]
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
CTEP	Cancer Therapy Evaluation Program
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELN	European LeukemiaNet
ET	essential thrombocythemia
FAS	Full Analysis Set
[redacted]	[redacted]
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MFSAF v2.0	Myelofibrosis Symptom Assessment Form version 2.0
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PGIC	Patient Global Impression of Change
PK	pharmacokinetic
PT	preferred term
PV	polycythemia vera
QD	once daily
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SI	International System of Units
SMQ	Standard MedDRA Query

Abbreviation	Term
SOC	system organ class
SVR	spleen volume reduction
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
T_{max}	time of occurrence of C_{max}
TSS	total symptom score
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

This is an open-label and sponsor-unblinded Phase 2 study with 2 cohorts.

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

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

The protocol provides a detailed description of the investigational products, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with itacitinib.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the Study INCB 39110-209 Protocol. The scope of this plan includes the interim and final analyses that are planned and will be executed by the Department of Biostatistics or designee. The analysis of PK [redacted] are not described in this SAP.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 39110-209 Protocol Amendment 1 dated 14 AUG 2017 and CRFs approved 22 AUG 2017. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and CRF versions.

2.2. Study Objectives and Endpoints

Study objectives and endpoints are presented in Table 1.

Table 1: Study Objectives and Endpoints

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

Table 1: Study Objectives and Endpoints (Continued)

3. STUDY DESIGN

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

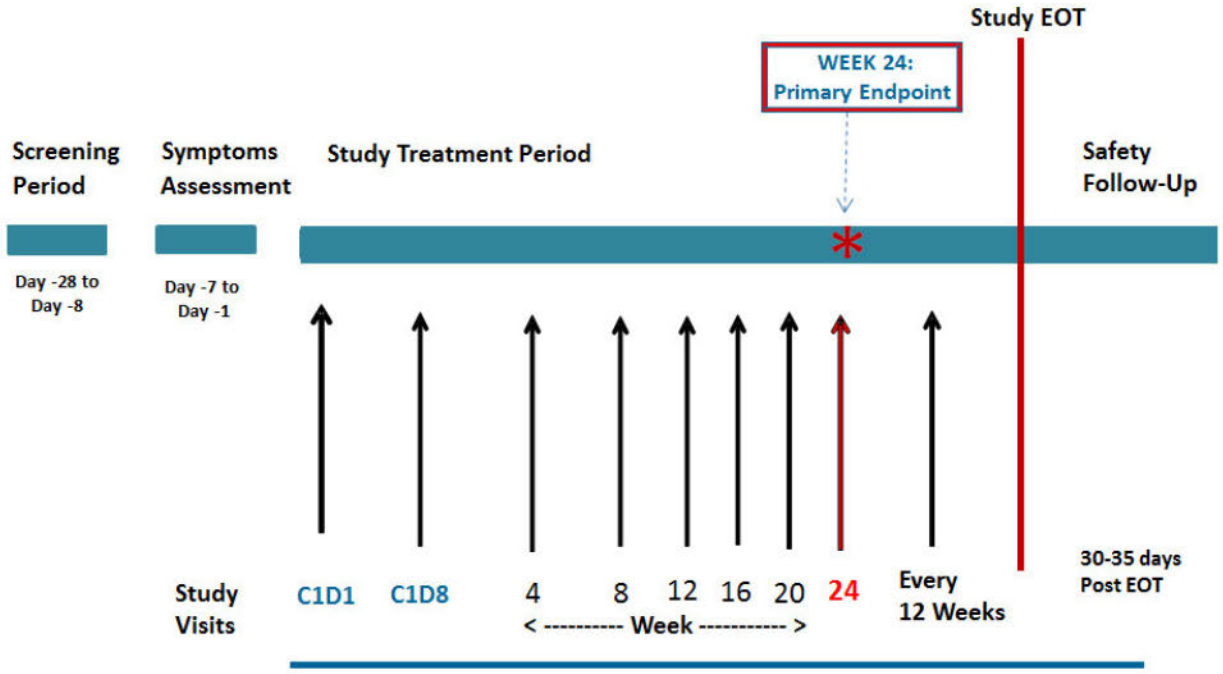
- **Cohort A**: MF subjects who are tolerating a ruxolitinib dose of less than 20 mg daily with no dose increase or no dose modification in the last 8 weeks before screening visit will receive a combination of the JAK1 inhibitor itacitinib at the dose of 200 mg QD and the JAK 1/2 inhibitor ruxolitinib.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

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

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

The overall study design is shown in Figure 1.

Figure 1: Study Design



3.1. Randomization

Not applicable.

3.2. Control of Type I Error

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

All other statistical analyses are exploratory in nature. Unless otherwise specified, all CIs provided will be at the 95% confidence level.

3.3. Sample Size Considerations

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

3.4. Schedule of Assessments

Refer to Protocol Amendment 1 dated 14 AUG 2017 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 itacitinib is administered to the subjects.

4.1.2. 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.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of itacitinib, unless otherwise defined.

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.

4.1.4. 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 subject discontinued treatment.
- Otherwise, the date that the subject 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

Subject 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, 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 itacitinib.

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

- Before the date of first administration of itacitinib 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 itacitinib and is ongoing or ends during the course of study drug.

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

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

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; Version 9 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 subjects in each category.

5.2. Treatment Groups

This is an open-label Phase 2 study with 2 cohorts. Subjects will be summarized overall and by cohort. Planned cohorts for this study are as follows:

- **Cohort A:** 200 mg QD itacitinib + ruxolitinib.
- **Cohort B:** 600 mg QD itacitinib monotherapy.

5.3. Analysis Populations

5.3.1. Full Analysis Set

The FAS includes all subjects enrolled in the study who received at least 1 dose of itacitinib.

The FAS will be used for the summary of demographics, baseline characteristics, subject disposition, and analyses of all efficacy data.

5.3.2. Extension Population

The extension population includes all subjects in the FAS population who continued into the extension period of the study and received at least 1 dose of itacitinib after entering the extension period.

5.3.3. Safety Population

The safety population includes all enrolled subjects who received at least 1 dose of itacitinib. Treatment cohorts for this population will be determined according to the actual treatment the subject received regardless of assigned study drug treatment.

All safety analyses will be conducted using the safety population.

5.3.4. Ruxolitinib-Treated Population

The ruxolitinib-treated population includes all subjects in the safety population who received at least 1 dose of ruxolitinib on or after Day 1 (ie, the first day of itacitinib administration).

5.3.5. Pharmacokinetic [redacted] Evaluable Population

The PK evaluable population will include all subjects who received at least 1 dose of itacitinib and provided at least 1 postdose plasma sample for PK. The study pharmacokineticist will

review data listings of study drug administration and sample records to identify subjects to be excluded from analyses of PK data.

[redacted]

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Appendix A provides a list of data displays. Shells for data displays are provided in a separate document.

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

6.1.1. Demographics

The following demographics will be summarized for the FAS population: age, sex, race, ethnicity, weight, and height.

6.1.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized for the FAS population: ECOG performance status.

6.1.3. Disease History

Time since diagnosis, MF disease type (primary MF, post-PV–MF, post-ET–MF), IWG-MRT Risk Category (Low, Intermediate-1, Intermediate-2, High-risk) at diagnosis and screening, MF grade at diagnosis and screening, [redacted] largest percentage reduction in spleen by palpation during ruxolitinib treatment, largest percentage volume reduction in spleen by CT or MRI during ruxolitinib treatment, prior transfusions for MF (Y/N), and transfusion dependency at baseline (Y/N) will be summarized for all subjects in the FAS population.

Time since diagnosis will be calculated as:

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

6.1.4. Prior Therapy

Subjects' ruxolitinib treatment history will be summarized, including the maximum daily dose of ruxolitinib (in mg) administered, total daily dose of ruxolitinib (in mg) prescribed at screening for subjects in Cohort A, and duration of ruxolitinib treatment.

Prior systemic MF therapy treatments will be summarized for all subjects in the FAS population. Component drugs, start and stop date, and reason for discontinuation will be listed.

Number of subjects who received prior splenic radiation or prior hematopoietic stem cell transplant will be summarized for the FAS population.

6.1.5. Medical History

For subjects in the FAS population, medical history will be summarized by assigned treatment cohort. This summation will include the number and percentage of subjects with significant medical history for each body system/organ class as documented on the CRF.

6.2. Disposition of Subjects

The number and percentage of subjects who were treated, completed study treatment through Week 24, discontinued study treatment prior to Week 24 with a primary reason for discontinuation, continued into the extension period, discontinued study treatment during the extension period with a primary reason for discontinuation, and discontinued from the study with a primary reason for withdrawal will be summarized for the FAS population. The number of subjects enrolled by site will also be provided by treatment cohort.

6.3. Protocol Deviations and Violations

Protocol deviations and violations recorded on the CRF will be presented in the subject data listings.

6.4. Exposure

For subjects in the safety population, exposure to itacitinib and ruxolitinib will be summarized descriptively as the following:

- **Duration of treatment with itacitinib (days)**: date of last dose of itacitinib – date of first dose of itacitinib + 1. For subjects who are continuing to receive itacitinib at the time of the analysis, the date of the last visit will be used.

  Average daily dose of itacitinib (mg/day): total actual itacitinib dose taken (mg) / duration of treatment with itacitinib (days). Total actual dose of itacitinib will be calculated based on the information entered on the drug accountability CRF.

- **Itacitinib dose modifications:** Number of subjects who had itacitinib dose reductions or interruptions will be summarized.

- **Duration of treatment with ruxolitinib (days):** date of last dose of ruxolitinib – date of first dose of on-study ruxolitinib + 1. For subjects who are continuing to receive ruxolitinib at the time of the analysis, the date of the last visit will be used.

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

- **Ruxolitinib dose modifications:** Number of subjects who had ruxolitinib dose reductions or interruptions on-study will be summarized.

6.5. Study Drug Compliance

For subjects in the safety population, overall compliance (%) for itacitinib will be calculated for all subjects 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 has 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.

Compliance for ruxolitinib will not be calculated.

6.6. Prior and Concomitant Medication

For subjects in the safety population, 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 subjects with prior and concomitant medications by PT and WHO drug class.

7. EFFICACY

Appendix A provides a list of data displays. Shells for data displays will be provided in a separate document.

7.1. General Considerations

7.2. Efficacy Hypotheses

The primary hypothesis is that itacitinib, in combination with low-dose ruxolitinib or as monotherapy for subjects who progressed after initial spleen reduction (either volume by MRI/CT or length by palpation) on ruxolitinib, will achieve a median percentage SVR of > 0% at Week 24 in either Cohort A or Cohort B.

7.3. Analysis of the Primary Efficacy Parameter

7.3.1. Primary Efficacy Analysis

The primary endpoint of change and percentage change of SVR (as measured by MRI or CT) at Week 24 will be summarized by cohort. Within each cohort, the sign test will be used to evaluate whether the median percentage of SVR is > 0%. For purposes of this test, subjects with missing Week 24 evaluations who discontinued prior to the planned Week 24 visit will be considered as not having achieved SVR. If 21 subjects are enrolled in a cohort, the null hypothesis of ≤ 0% median SVR will be rejected if 15 or more out of 21 subjects observe a > 0% SVR at Week 24.

The baseline spleen volume will be assessed between Study Day -7 and Day 1 (inclusive) with the last value in the assessment window used if there are multiple values measured during this period. Subjects with missing baseline spleen volume will not be evaluable for this analysis. The Week 24 spleen volume will be assessed during Week 24 (Day 168 ± 7), and the last value in the assessment window will be used if there are multiple values measured during the Week 24 visit.

7.3.2. Subgroup Analyses for Primary Endpoint

Subgroups will be formed based on the following subject characteristics and baseline variables for those subjects whose data are available. Note that all subgroup analyses are descriptive in nature.

- IWG Risk Category at screening (Low, Intermediate-1, Intermediate-2, High-risk)
- MF grade at screening (MF-0, MF-1, MF-2, MF-3)
- Transfusion-dependent at screening (Y/N)
- MF Disease Type (Primary MF, Post-PV–MF, Post-ET–MF)
- Sex (M/F)
- Race (Caucasian, Black, Asian, All Others, Unspecified)
- ECOG status at baseline (0, 1, 2)

7.4. Analysis of the Secondary Efficacy Parameters

7.4.1. Other Spleen Volume Reduction Analyses

Week 12 spleen volume, along with change and percentage change in SVR, will be assessed during Week 12 (Day 84 ± 7) using approaches outlined in Section 7.3.1.

For all scheduled spleen volume assessments (ie, Weeks 12, 24, 36, 48, etc), median percentage SVR will be calculated by cohort with associated 2-sided 90% exact binomial CI estimated.

7.4.2. Change and Percentage Change From Baseline in Spleen Length

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

7.4.3. MFSAF v2.0 and Total Symptom Score

The daily TSS for MFSAF v2.0 is determined on a study day basis and is the sum of the 6 individual symptom scores as measured by the daily symptom diary excluding the score for degree of inactivity. Included items are itching, night sweats, abdominal discomfort/bloating, early satiety, pain under the ribs on left side and bone/muscle pain. If any of the 6 components of the score are missing, then the daily TSS is missing on that day. Observations with missing dates will be excluded from the analysis.

The TSS for baseline, Week 12, and Week 24 will be determined by averaging the daily TSS for the days between the start and end of windows as described in Table 2. The TSS for Weeks 4, 8, 16, and 20 will be derived in a similar fashion using the first nonmissing daily TSS available between

Day ($7 \times week$)

and

Day ($7 \times week$) + 7

as the end of the window.

Table 2: Windows for Deriving Total Symptom Score for Baseline, Week 12, and Week 24

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

The percentage change at Week 4, 8, 12, 16, 20, and 24 will be calculated using the formula

% change = 100 × (Week xx total score – baseline total score) / baseline total score

and will be summarized with descriptive statistics (mean, standard deviation, etc).

[redacted]

Summaries for the 7 individual scores will be provided using the same windows used for the TSS.

7.4.4. MPN-SAF and Total Symptom Score

The TSS for the MPN-SAF is determined at visits where the Myeloproliferative Neoplasms Symptom Assessment Form is administered. When all items are completed for a visit, the TSS is the sum of the numeric values of the 10 questions (each scored on a 0-10 scale), which includes

fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. If only 6 to 9 items are completed, the TSS for the visit is the average completed TSS item score multiplied by 10. If 5 or fewer items are completed on the MPN-SAF, the TSS is missing for that visit (Emanuel et al 2012).

The percentage change at Week 4, 8, 12, 16, 20, and 24 will be calculated using the formula

% change = 100 × (Week xx total score – baseline total score) / baseline total score

and will be summarized with descriptive statistics (mean, standard deviation, etc).

[redacted]

Summaries for the 10 individual scores will be provided using the same windows and formula used for the TSS.

7.4.5. Patient Global Impression of Change

Patient Global Impression of Change is a 1-question patient-reported evaluation of the degree of symptom improvement received since the start of the study ranging from 1 (very much improved) to 7 (very much worse). The PGIC score will be tabulated and summarized descriptively (mean, standard deviation, etc) by visit.

[redacted]

8. PHARMACOKINETIC ANALYSES

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

[redacted]

10. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays. Shells for data displays are provided in a separate document.

10.1. 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 subjects.

10.2. Adverse Events

10.2.1. 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 CTEP 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 also 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.

10.2.2. Adverse Events of Special Interest or Adverse Events of Clinical Interest

Adverse events of special interest include Grade 4 thrombocytopenia, Grade 2 or higher anemia, and Grade 2 or higher hemorrhagic events as measured by CTCAE v4.03. Hemorrhagic events will be defined by the SMQ for Haemorrhage using the narrow definition (excluding laboratory terms). Anemia will be defined by the SMQ for haematopoietic erythropenia using the broad

definition. Thrombocytopenia will be defined by the SMQ for haematopoietic thrombocytopenia using the narrow definition. In addition, laboratory shift tables will be generated based on CTCAE v4.03 criteria for low platelet counts and hemoglobin.

10.2.3. Adverse Event Summaries

An overall summary of AEs by cohort will include:

- Number (%) of subjects reporting any TEAEs
- Number (%) of subjects reporting any SAEs
- Number (%) of subjects reporting any Grade 3 or higher TEAEs
- Number (%) of subjects reporting any TEAEs related to itacitinib
- Number (%) of subjects reporting any TEAEs related to ruxolitinib
- Number (%) of subjects who temporarily interrupted itacitinib because of TEAEs
- Number (%) of subjects who temporarily interrupted ruxolitinib because of TEAEs
- Number (%) of subjects who permanently discontinued itacitinib because of TEAEs
- Number (%) of subjects who permanently discontinued ruxolitinib because of TEAEs
- Number (%) of subjects with itacitinib dose reductions because of TEAEs
- Number (%) of subjects with ruxolitinib dose reductions because of TEAEs
- Number (%) of subjects who had a fatal TEAE
- Number (%) of subjects who withdrew from study because of a TEAE

The following summaries will be produced by MedDRA term:

- 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 higher TEAEs by SOC and PT
- Summary of itacitinib treatment-related AEs by SOC and PT
- Summary of Grade 3 or higher itacitinib treatment-related AEs by SOC and PT
- Summary of itacitinib treatment-related AEs by SOC, PT, and maximum severity
- Summary of ruxolitinib treatment-related AEs by SOC and PT
- Summary of Grade 3 or higher ruxolitinib treatment-related AEs by SOC and PT
- Summary of ruxolitinib treatment-related AEs by SOC, PT, and maximum severity
- Summary of TEAEs with a fatal outcome 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 itacitinib treatment-related SAEs by SOC and PT
- Summary of ruxolitinib treatment-related SAEs by SOC and PT
- Summary of TEAEs leading to itacitinib dose reduction by SOC and PT
- Summary of TEAEs leading to ruxolitinib dose reduction by SOC and PT
- Summary of TEAEs leading to itacitinib 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 itacitinib by SOC and PT
- Summary of TEAEs leading to discontinuation of ruxolitinib by SOC and PT
- Summary of TEAEs leading to withdrawal from the study by SOC and PT
- Summary of treatment-emergent non-SAE by SOC and PT

10.3. Clinical Laboratory Tests

10.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit. Baseline will be determined according to Section 4.1.3. 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 or similar criteria where clinical intervention is required for CTCAE grading. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

10.3.2. 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, a set of standard normal ranges based on documented reference ranges will be applied to facilitate reporting the test results.

When there are multiple laboratory nonmissing values for a subject's particular test within a visit window, the convention described in Table 3 will be used to determine the record used for by-visit tabulations and summaries.

Table 3: Identification of Records for Postbaseline By-Visit Summaries

Priority	Laboratory Visit	Proximity to Visit Window	Tiebreaker
1	Scheduled	In-window	Use smallest laboratory sequence number
2	Unscheduled	In-window	
3	Scheduled	Out-of-window	

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 hemoglobin, platelet counts, WBC, and neutrophils.

Shift tables based on worst postbaseline value recorded will use all postbaseline values occurring within 30 days of stopping study treatment. Shift summaries will be produced for each test for the safety population. The denominator for the percentage calculation will use the number of subjects 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 subjects in the baseline category.

10.4. Vital Signs

Values at each scheduled visit, change, and percent change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, and body temperature will be summarized descriptively. In addition, body weight and change from baseline in body weight at scheduled assessment times will be summarized.

Criteria for clinically notable vital sign abnormalities are defined in Table 4. The abnormal values for subjects exhibiting clinically notable vital sign abnormalities will be listed along with their assigned treatment cohort. Alert vital signs are defined as an absolute value outside the defined range and percentage change greater than 25%. The abnormal values for subjects exhibiting alert vital sign abnormalities will be listed.

Table 4: Criteria for Clinically Notable Vital Sign Abnormalities

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

10.5. Electrocardiograms

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

11. INTERIM ANALYSES

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

12. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 5.

Table 5: Statistical Analysis Plan Versions

SAP Version	Date
Original	15 NOV 2017

12.1. Changes to Protocol-Defined Analyses

Not applicable.

12.2. Changes to the Statistical Analysis Plan

Not applicable.

13. REFERENCES

Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol 2012;30:4098-4103.

APPENDIX A. PLANNED TABLES AND FIGURES

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

The list of tables, figures, listings, 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	In-Text
Baseline and Demographic Characteristics				
1.1 Disposition				
1.1.1	Analysis Populations	FAS	X	X
1.1.2	Summary of Subject Disposition	FAS	X	X
1.1.3	Summary of Number of Subjects Enrolled by Site	FAS	X	
1.2 Demography				
1.2.1	Summary of Demographics	FAS	X	X
1.3 Baseline Characteristics				
1.3.1	Summary of Baseline Disease Characteristics	FAS		X
1.3.2	Summary of Prior Therapy for Myelofibrosis	FAS	X	
1.4 Prior Medication and Concomitant Medication				
1.4.1	Summary of Prior Medications	FAS	X	
1.4.2	Summary of Concomitant Medications	FAS	X	
1.5+ Others				
1.5.1	Summary of General Medical History	FAS	X	
1.90.# AD HOC or Additional Analyses				
Efficacy				
2.1 Primary Efficacy				
2.1.1	Number of Subjects With SVR at Week 24	FAS		X
2.1.2	Summary of Spleen Volume by Visit	FAS		X
2.1.3	Summary of Spleen Volume by Visit and HMR Gene Mutation Status	FAS		X
2.2 Secondary Efficacy				
2.2.1	Summary of Spleen Length Measured by Palpation by Visit	FAS		X
2.2.2.1	Summary of Total Symptom Score Using MFSAF Version 2.0 by Visit	FAS		X
2.2.2.2	Summary of Percentage Change in Total Symptom Score Using MFSAF Version 2.0 by Visit	FAS		X
2.2.2.3	Summary of Total Symptom Score Using MFSAF Version 2.0 by Visit and HMR Gene Mutation Status	FAS		X
2.2.2.4	Summary of Percentage Change in Total Symptom Score Using MFSAF Version 2.0 by Visit and HMR Gene Mutation Status	FAS		X

Table No.	Title	Population	Standard	In-Text
2.2.2.5	Summary of MFSAF Version 2.0 Components by Visit	FAS		X
2.2.3.1	Summary of Total Symptom Score Using MPN-SAF by Visit	FAS		X
2.2.3.2	Summary of Percentage Change in Total Symptom Score Using MPN-SAF by Visit	FAS		X
2.2.3.3	Summary of Total Symptom Score Using MPN-SAF by Visit and HMR Gene Mutation Status	FAS		X
2.2.3.4	Summary of Percentage Change in Total Symptom Score Using MPN-SAF by Visit and HMR Gene Mutation Status	FAS		X
2.2.3.5	Summary of MPN-SAF Components by Visit	FAS		X
2.2.4.1	Summary of PGIC by Visit	FAS		X
[redacted]				
2.90.# AD HOC or Additional Analyses				
Safety				
3.1 Dose Exposure				
3.1.1.1	Summary of Exposure to Itacitinib	Safety		X
3.1.1.2	Summary of Exposure to Itacitinib by Study Period	Safety		X
3.1.1.3	Summary of Compliance With Itacitinib	Safety		
3.1.2.1	Summary of Exposure to Ruxolitinib	Ruxolitinib Treated		X
3.1.2.2	Summary of Exposure to Ruxolitinib by Study Period	Ruxolitinib Treated		X
3.2 Adverse Events				
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	Safety	X	X
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X	X
3.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety	X	
3.2.5	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events By MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.6	Summary of Itacitinib Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.7	Summary of Grade 3 or Higher Itacitinib Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	

Table No.	Title	Population	Standard	In-Text
3.2.8	Summary of Itacitinib Treatment-Related Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety	X	
3.2.9	Summary of Ruxolitinib Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Ruxolitinib Treated	X	
3.2.10	Summary of Grade 3 or Higher Ruxolitinib Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Ruxolitinib Treated	X	
3.2.11	Summary of Ruxolitinib Treatment-Related Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Ruxolitinib Treated	X	
3.2.12	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.13	Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.14	Summary of Treatment-Emergent Serious Adverse Events by Preferred Term in Decreasing Order of Frequency	Safety	X	X
3.2.15	Summary of Itacitinib Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.16	Summary of Ruxolitinib Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Ruxolitinib Treated	X	X
3.2.17	Summary of Treatment-Emergent Adverse Events Leading to Itacitinib Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.18	Summary of Treatment-Emergent Adverse Events Leading to Ruxolitinib Dose Reduction by MedDRA System Organ Class and Preferred Term	Ruxolitinib Treated	X	
3.2.19	Summary of Treatment-Emergent Adverse Events Leading to Itacitinib Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.20	Summary of Treatment-Emergent Adverse Events Leading to Ruxolitinib Dose Interruption by MedDRA System Organ Class and Preferred Term	Ruxolitinib Treated	X	
3.2.21	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Itacitinib by MedDRA System Organ Class and Preferred Term	Safety	X	X
3.2.22	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Ruxolitinib by MedDRA System Organ Class and Preferred Term	Ruxolitinib Treated	X	
3.2.23	Summary of Treatment-Emergent Adverse Events Leading to Withdrawal from the Study by MedDRA System Organ Class and Preferred Term	Safety	X	
3.2.24[a]	Summary of Non-Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X	
3.3 Laboratory				
3.3.1.1	Summary of Laboratory Values – Hematology	Safety	X	
3.3.1.2	Shift Summary of Hematology Laboratory Values in CTC Grade – To the Worst Abnormal Value	Safety	X	X
3.3.2.1	Summary of Laboratory Values – Chemistry	Safety	X	

Table No.	Title	Population	Standard	In-Text
3.3.2.2	Shift Summary of Chemistry Laboratory Values in CTC Grade – To the Worst Abnormal Value	Safety	X	X
3.3.3.1	Summary of Laboratory Values – Coagulation	Safety	X	
3.3.3.2	Shift Summary of Coagulation Values – To the Worst Abnormal Value	Safety	X	
3.4 Vital Signs				
3.4.1	Summary of Systolic Blood Pressure	Safety	X	
3.4.2	Summary of Diastolic Blood Pressure	Safety	X	
3.4.3	Summary of Pulse	Safety	X	
3.4.4	Summary of Respiratory Rate	Safety	X	
3.4.5	Summary of Body Temperature	Safety	X	
3.4.6	Summary of Body Weight	Safety	X	
3.5 ECG				
3.5.1	Summary of Abnormalities From 12-Lead ECG	Safety	X	X
3.6 Physical Examination				
3.7+ Other Safety				
3.90.# AD HOC or Additional Other Safety Analyses				

[a] Non-SAE table will be generated for the study for the express purpose of clinical trial results posting.

Figures

Figure No.	Title
4.1 Primary Efficacy	
4.1.1	Forest Plot of Proportions of SVR Responders at Week 24; FAS Population
4.2 Secondary Efficacy	
[redacted]	
4.4 AD HOC or Additional Efficacy Analyses	
4.5 Adverse Events	
4.5.90.# AD HOC or Additional AE Analyses	
4.6 Laboratory Data	
4.6.90.# AD HOC or Additional Laboratory Analyses	
4.7 Vital Signs	
4.8 ECG	
4.9+ Other Data	
4.90.# AD HOC or Additional Analyses of Other Safety Data	
4.90.x.1	Line Graph of Selected Laboratory Values by Study Visit
4.90.x.2	Box-and-Whisker Plot of Selected Laboratory Values by Study Visit

Listings

Listing No.	Title
2.1 Discontinued Subjects (Subject Disposition)	
2.1.1	Subject Enrollment and Disposition Status
2.1.2	Subject Inclusion and Exclusion Criteria Violations
2.2 Protocol Deviation	
2.2.1	Protocol Deviations and Violations
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	Myelofibrosis History
2.4.3	Prior Systemic Therapy
2.4.4	Prior Surgery or Surgical Procedure for Myelofibrosis
2.4.5	Prior Hematopoietic Stem Cell Transplant
2.4.6	General Medical History
2.4.7	Prior and Concomitant Medication
2.5 Drug Compliance	
2.5.1	Study Drug Compliance for Itacitinib
2.6 Efficacy (and/or PK Data)	
2.6.1	Spleen Volume Measurements
2.6.2	Spleen Length by Palpation
2.6.3	MFSAF v2 by Study Day
2.6.4	IWG-MRT Response Assessment by Visit
2.6.5	Bone Marrow Testing
[redacted]	
2.6.7	ECOG Status
2.6.8	PRBC/Platelet Transfusion
2.7 Adverse Events (and Exposure)	
2.7.1.1	Itacitinib Administration
2.7.1.2	Ruxolitinib Administration
2.7.2	Adverse Events
2.7.3	Serious Adverse Events
2.7.4	Grade 3 and Higher Adverse Events
2.7.5	Fatal Adverse Events
2.7.6	Itacitinib or Ruxolitinib Treatment-Related Adverse Events
2.7.7	Adverse Events Leading to Interruption, Reduction, or Discontinuation of Itacitinib or Ruxolitinib
2.7.8	Adverse Events Leading to Withdrawal From Study
2.7.9	Death Report
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 – Urinalysis
2.8.5	Abnormal Clinical Laboratory Values

Listing No.	Title
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	Abnormal 12-Lead ECG Values
2.11 Physical Examination	
2.11.1	Body Weight