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

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Statistical Analysis Plan

INCB 18424-272

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

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SAP Author:	[redacted]
Date of Plan:	**24 SEP 2019**

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	Definition
AE	adverse event
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
CMH	Cochran-Mantel-Haenszel
CR	complete remission
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELN	European LeukemiaNet
ET	essential thrombocythemia
[redacted]	[redacted]
HU	hydroxyurea
IB	Investigator's Brochure
IMQ	Incyte MedDRA Query
ITT	intent-to-treat
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MPN-SAF TSS	Myeloproliferative Neoplasm–Symptom Assessment Form Total Symptom Score
[redacted]	[redacted]
[redacted]	[redacted]
PP	per protocol
PR	partial remission
PV	polycythemia vera
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan

Abbreviation	Definition
SMQ	Standardized MedDRA Query
TEAE	treatment-emergent adverse event
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

Ruxolitinib (INCB018424) is a potent and selective inhibitor of Janus kinase (JAK) 1 and JAK2 with selectivity against tyrosine kinase 2 and JAK3. Ruxolitinib has been granted marketing authorisation approval for the treatment of myelofibrosis (MF) and polycythemia vera and is currently in development for the treatment of myeloproliferative neoplasms, essential thrombocythemia (ET), and other hematologic malignancies. For a thorough discussion of the pharmacology of ruxolitinib, refer to the Investigator's Brochure (IB).

INCB 18424-272 is a double-blind, double-dummy Phase 2 randomized study to evaluate the efficacy and safety of ruxolitinib versus anagrelide in subjects with ET who are resistant to or intolerant of hydroxyurea (HU). Section 1 of the Protocol provides a detailed description of the investigational product, target patient population, the rationale for doses to be examined, and the potential risks and benefits from ruxolitinib treatment. The purpose of this document is to provide a detailed Statistical Analysis Plan (SAP).

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 18424-272 Protocol Amendment 2 dated 28 SEP 2018 and case report forms (CRFs) approved 14 APR 2017. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and electronic case report form (eCRF) versions.

2.2. Study Objectives

2.2.1. Primary Objective

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

2.2.2. Secondary Objectives

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

2.3. Study Endpoints

2.3.1. Primary Endpoint

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

2.3.2. Secondary Endpoints

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

3. STUDY DESIGN

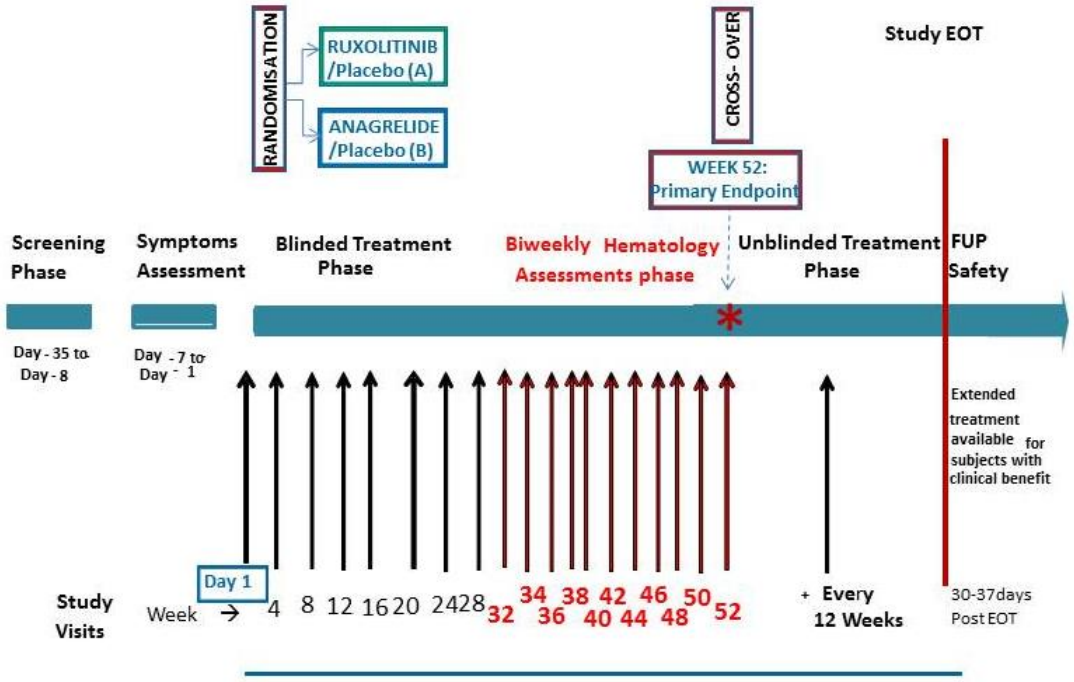
Study INCB 18424-272 is a Phase 2, randomized, double-blind, double-dummy study in subjects with ET who are resistant to or intolerant of HU (modified ELN criteria) with a screening platelet count $\geq 650 \times 10^9$/L and WBC $\geq 11.0 \times 10^9$/L. Approximately 120 subjects will be enrolled and randomized to the following treatment groups:

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

Subjects will receive blinded study treatment for 52 weeks. Subjects originally randomized to ruxolitinib with anagrelide placebo (Group A) who are receiving benefit from therapy can 1) continue receiving open-label ruxolitinib until the study is concluded or they meet discontinuation criteria, or 2) choose to discontinue therapy. Subjects originally randomized to receive anagrelide plus ruxolitinib placebo (Group B) have 3 options: 1) they may cross over to begin receiving ruxolitinib if they meet eligibility criteria after consultation with the sponsor and may then continue until the study is concluded or they meet discontinuation criteria; 2) they may continue receiving anagrelide until the study is concluded or they meet discontinuation criteria; or 3) they can choose to discontinue therapy. Note that subjects originally randomized to Group B may cross over to receive ruxolitinib at any time during the open-label part of the study.

All subjects will be followed for safety (eg, reporting of AEs and serious adverse events [SAEs]) 30 to 37 days after last dose of blinded study treatment or open-label ruxolitinib. The overall study design is shown in Figure 1.

Figure 1: Study Design



3.1. Randomization

This study will enroll approximately 120 subjects stratified by JAK2V617F mutation status (positive vs negative), platelet count ($\geq 1000 \times 10^9$/L or $< 1000 \times 10^9$/L), and prior anagrelide use (yes vs no) at screening. Subjects will be randomized 1:1 to the following 2 treatment groups:

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

3.2. Control of Type I Error

The level of significance for the primary endpoint is 2-sided 0.05. The family wise alpha level will be controlled at 0.05 and will be controlled using a fixed sequential testing procedure. The proportion of subjects who achieve CR or PR at Week 32, as defined by ELN 2013 response criteria, will only be formally tested if the hypothesis for the primary endpoint is rejected. No other efficacy endpoints will be included in the alpha control.

3.3. Sample Size Considerations

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

3.4. Schedule of Assessments

Refer to Protocol Amendment 2 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 is administered to the subject. For subjects who are randomized and not treated with any study drug, Day 1 is defined as the day of randomization.

4.1.2. Study Day

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

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

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

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

4.1.3. Baseline Value

Baseline is defined as the last nonmissing measurement obtained on or before the first administration of study drug. When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or time of first dose is not available, the following convention will be used 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.

For subjects who were originally assigned to anagrelide and crossed over to ruxolitinib, the corresponding new baseline will be defined, when appropriate, as the last available assessment on or before the date of first administration of ruxolitinib.

4.1.4. Analysis Window

For analyses of efficacy parameters, scheduled assessments will be used. If no scheduled assessment is available, then the unscheduled assessment closest to the visit target day within the analysis window will be used. An analysis window based on the assessment date is described in the relevant section if the analysis window is applied; otherwise only the nominal visit as recorded on the eCRF will be used.

4.1.5. 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 disease 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.

4.2. Variable Definitions

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

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. Body Mass Index

Body mass index (BMI) will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m)]^2

4.2.3. Prior and Concomitant Medication

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

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

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

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of study drug. 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.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; version 9.1 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. [redacted]

5.2. Treatment Groups

This is a randomized, double-blind, and parallel treatment group design. Subjects will be summarized by treatment groups. For subjects who crossed over to ruxolitinib from anagrelide, applicable efficacy and safety will be summarized separately.

5.3. Analysis Populations

5.3.1. Intent-to-Treat Population

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

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

5.3.2. Per Protocol Population

The per protocol (PP) population will include those ITT subjects who are considered to be sufficiently compliant with the Protocol.

The following procedures will be performed to identify those subjects who are to be excluded from the PP population before the database freeze:

- Clinical review of Protocol deviations/violations.
- Clinical review of concomitant medications as defined in Section 5.6 of the Protocol.
- Clinical review of the dose administration and drug accountability listing.

Subjects who do not meet the criteria for ET diagnosis or hydroxyurea resistance/intolerance (inclusion criteria 2 and 3; refer to Section 3 of the Protocol) and subjects who are < 80% compliant during the primary endpoint assessment period (Weeks 32-52) as determined by drug accountability assessment will be excluded from per protocol population.

The determination of subjects being considered for exclusion from the PP population by the clinical team will be prepared and signed before database freeze.

The PP population will be used in the supportive sensitivity analyses for efficacy endpoints.

5.3.3. Safety Population

The safety population includes all randomized subjects who received at least 1 dose of study drug. All safety analyses will be conducted using the safety population.

[redacted]

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Appendix F provides a list of data displays.

6.1. Demographics and Baseline Characteristics, and Disease History

6.1.1. Demographics

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

6.1.2. Baseline Characteristics

The following baseline disease characteristics will be summarized for the ITT population: baseline platelet counts, baseline WBC counts, baseline hematocrit, [redacted], JAK2V617F mutation status (positive vs negative), prior anagrelide use (yes vs no), MPL mutation status, CALR mutation status, triple-negative status, [redacted], and ECOG status (Appendix B).

6.1.3. Disease History

Time since initial diagnosis, number of prior systemic therapies, prior thrombosis, and prior hemorrhage and cardiovascular (CV) risk factors including smoking, hypertension, hypercholesterolemia, and diabetes will be summarized for all the subjects in the ITT population.

Time since diagnosis will be calculated as follows:

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

6.1.4. Prior Therapy

Number of subjects who received prior systemic therapy for ET will be summarized for the ITT population. Drug name, start and stop dates, best response, and reason for discontinuation will be listed.

6.1.5. Medical History

For subjects in the ITT population, medical history will be summarized by system organ class and preferred term and will be listed.

6.2. Disposition of Subjects

The number and percentage of subjects who were randomized, were treated, discontinued the randomized treatment before and after unblinding with a primary reason for discontinuation, crossed over to ruxolitinib from anagrelide, discontinued ruxolitinib after crossing over with a primary reason for discontinuation, and withdrew from the study before and after unblinding with a primary reason for withdrawal will be summarized for the ITT population.

6.3. Protocol Deviations

Protocol deviations collected on eCRF will be presented in the subject data listings.

6.4. Exposure

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

- **Duration of treatment with ruxolitinib/anagrelide**:

  Duration of treatment (weeks) = [date of last dose of ruxolitinib/anagrelide – date of first dose of ruxolitinib/anagrelide + 1]/7

- **Average daily dose of ruxolitinib/anagrelide**:

  Average daily dose of ruxolitinib/anagrelide (mg/day) = total actual ruxolitinib/anagrelide dose taken (mg) / duration of treatment with ruxolitinib/anagrelide

- **Dose modifications**:

  Number of subjects who had ruxolitinib/anagrelide dose reduction, escalation, and interruption will be summarized.

Exposure to ruxolitinib for subjects who crossed over to ruxolitinib from anagrelide will be summarized separately.

6.5. Study Drug Compliance

For subjects in the safety population, overall compliance (%) for ruxolitinib/anagrelide will be calculated for all subjects as follows:

> Overall compliance (%) = 100 × [total dose actually taken (mg)] / [total prescribed dose (mg)]

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 eCRF. 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 eCRF.

Compliance of ruxolitinib will be summarized descriptively and listed.

6.6. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. For subjects in the safety population, the number and percentage of subjects with prior and concomitant medications will be summarized by WHO drug class and WHO drug term. In the data listing, each medication will be recorded as prior, concomitant, or both prior and concomitant.

[redacted]

7. EFFICACY

Appendix F provides a list of data displays.

7.1. Efficacy Hypotheses

The primary hypothesis is that ruxolitinib will improve the responder rate compared with anagrelide in subjects with ET who are resistant or intolerant to HU. Cochran-Mantel-Haenszel (CMH) method will be used to test the primary hypothesis at 2-sided of alpha level 0.05.

- H_0 (null hypothesis): $\pi_{ruxolitinib} = \pi_{anagrelide}$
- H_A(alternative hypothesis): $\pi_{ruxolitinib} \neq \pi_{anagrelide}$

Where $\pi_{ruxolitinib}$ and $\pi_{anagrelide}$ are the responder rates in the ruxolitinib and anagrelide groups, respectively.

7.2. Analysis of the Primary Efficacy Parameter

7.2.1. Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects who achieve a simultaneous reduction of platelet counts to $< 600 \times 10^9$/L and of WBC counts to $< 10 \times 10^9$/L for at least 80% (6 out of 7 consecutive visits) of biweekly assessments for 12 consecutive weeks between Week 32 and Week 52. This analysis will be based on the ITT population according to the treatment assigned at randomization. The proportion of subjects who meet the response criteria will be estimated with 95% confidence interval. The CMH test stratified by JAK2V617F mutation status (positive or negative), screening platelet count ($\geq 1000 \times 10^9$/L or $< 1000 \times 10^9$/L), and prior anagrelide use (yes vs no) will be applied to compare the 2 treatment groups. The test will be 2-sided at 5% significant level. The overall stratum-adjusted odds ratio, along with its 95% confidence interval, will be presented.

In the analysis of the primary efficacy endpoint, the evaluable scheduled assessments will be used. If no scheduled assessment is available, then the unscheduled assessment closest to the visit target day within the analysis window will be used. If there are 2 unscheduled assessments at the same distance to the target day, then the second one will be used for the evaluation. A window of the target day ± 7 days will be applied for all unscheduled visits. For example, the target day for Week 32 is at Day 225 (= 32 × 7 + 1).

Missing platelet counts or WBC counts at a visit (with no scheduled visit and no unscheduled visit within window of target day) in the range of at least 12 consecutive weeks of assessment of the primary endpoint will be considered as not achieving platelet control and WBC control during that visit. Subjects who discontinue study treatment without meeting the response criteria will be considered as nonresponders. Subjects who meet the primary endpoint criteria of a response but discontinue study drug before Week 52 will be considered as responders.

7.2.2. Subgroup Analyses for the Primary Endpoint

Subgroups will be formed based on the following subject characteristics and baseline variables for those subjects whose data are available:

- JAK2V617F mutation status at baseline: positive versus negative.
- Prior anagrelide use at baseline: yes versus no.
- MPL mutation status at baseline: positive versus negative.
- CALR mutation status at baseline: positive versus negative.
- Triple-negative status at baseline: yes versus no.
- Platelet count at baseline: $\geq 1000 \times 10^9$/L versus $< 1000 \times 10^9$/L.
- Sex: male versus female.
- Age: ≤ 65 years versus > 65 years.
- Prior thrombosis or hemorrhage: yes versus no.
- CV risk factors at baseline: yes versus no.

Cardiovascular risk factors including smoking, hypertension, hypercholesterolemia, and diabetes.

For each subgroup, the proportion of subjects who meet the primary response criteria will be estimated with 95% confidence interval; Fisher exact test will be performed to compare the 2 treatment groups, and odds ratio and its 95% confidence interval will be presented.

7.2.3. Sensitivity and Supportive Analyses for Primary Endpoint

The primary endpoint will be analyzed using the PP population as a sensitivity analysis to the ITT population. If the JAK2V617F mutation status at randomization is not consistent with the JAK2V617F mutation status collected on the eCRF, additional sensitivity analysis of the primary endpoint will be performed by stratifying the JAK2V617F mutation status collected on the eCRF, screening platelet count, and prior anagrelide use (yes vs no).

7.2.3.1 Additional Sensitivity Analyses for Primary Endpoint

Excess missing data will affect the validity of the study. All efforts will be made to minimize missing data. In addition, sensitivity analysis will be conducted to assess the impact of the missing data if > 10% of subjects with primary endpoint status missing.

7.2.3.1.1. Primary Endpoint Status Determination

The primary efficacy endpoint is the proportion of subjects who achieve a simultaneous reduction of platelet counts to $< 600 \times 10^9$/L and of WBC counts to $< 10 \times 10^9$/L for at least 80% (6 out of 7 consecutive visits) of biweekly assessments for 12 consecutive weeks between Week 32 and Week 52. There are 5 consecutive 12-week periods: Weeks 32 to 44, Weeks 34 to 46, Weeks 36 to 48, Weeks 38 to 50 and Weeks 40 to 52.

For each of the 5 consecutive 12-week periods, 7 scheduled biweekly visits are planned. A subject will be flagged as "Responder," "Nonresponder," or :"Nondeterminable" as the following at each period:

- If a subject has ≥ 6 visits with platelet counts $< 600 \times 10^9$/L and WBC counts $< 10 \times 10^9$/L, then this subject is flagged as Responder at this period.
- If a subject has ≥ 2 visits with platelet count $\geq 600 \times 10^9$/L or WBC counts $\geq 10 \times 10^9$/L, then this subject is flagged as Nonresponder at this period.
- If the above 2 conditions are not met for a subject, then this subject is flagged as nondeterminable at this period.
- If a subject discontinued from the study treatment between Weeks 32 and 52, the response status for the periods after the treatment discontinuation will not be assessed.

The primary endpoint status for a subject can be determined as the following:

- If any period is deemed as Responder for a subject, then the primary endpoint status of this subject is Responder.
- If "Nonresponder" is flagged in all assessed periods for a subject, then the primary endpoint status of this subject is Nonresponder.
- Otherwise, the primary endpoint status for a subject cannot be determined and the value will be missing.

If a subject discontinued from the study treatment before Week 32, then the primary endpoint status of this subject is missing.

7.2.3.1.2. Missing Data Display

For subjects discontinued before Week 32, the primary endpoint status will be missing. The number and percentage of subjects discontinued before Week 32 as well as the primary reasons for treatment discontinuation will be tabulated by treatment group.

For subjects in the study on or after Week 32 but with primary endpoint status missing as described in Section 7.2.3.1.1, the number of visits with nonmissing assessments of platelet counts and WBC counts between Weeks 32 and 52, as well as the number of visits where platelet counts are $< 600 \times 10^9$/L and WBC counts are $< 10 \times 10^9$/L will be tabulated by treatment group.

7.2.3.1.3. Covariates

Based on the clinical judgment (Daly 2011, Carel and Eviatar 1985), the following covariates that may be related to the primary endpoint status will be considered:

- JAK2V617F mutation status at baseline: positive versus negative.
- Prior anagrelide use at baseline: yes versus no.
- Platelet count at baseline: $\geq 1000 \times 10^9$/L versus $< 1000 \times 10^9$/L.
- Last nonmissing assessment of platelet counts.
- Last nonmissing assessment of WBC counts.
- Last nonmissing assessment of hemoglobin.
- Any infection: yes versus no.
  - For subjects discontinued from the treatment before Week 32, any infection in the study period is considered; for subjects still in the study after Week 32, any infection after Week 32 is considered.
- Any trauma or surgery: yes versus no.
  - For subjects discontinued from the treatment before Week 32, any trauma or surgery in the study period is considered; for subjects still in the study after Week 32, any trauma or surgery after Week 32 is considered.

The covariates will be assessed based on data availability.

7.2.3.1.4. Multiple Imputation

For each missing value of the primary endpoint status, a list of m (m = 5) imputed values will be generated through multiple imputation method and replaced for the missing value. The primary endpoint status is a dichotomous variable with values of responder and nonresponder; thus, logistic regression imputation method will be used to impute missing values of the primary endpoint status. In the logistic regression imputation method, a logistic regression model is fitted for the primary endpoint status variable with a set of covariates constructed from the effects, where the set of covariates is listed in Section 7.2.3.1.3 plus treatment group. The sample SAS code for multiple imputation is included in Appendix E.

After multiple imputation, m imputed complete datasets will be generated. For each of m imputed datasets, the proportion of subjects who achieve primary endpoint will be summarized by treatment group. The combined results from m imputed data on proportion of subjects who achieve the primary endpoint will also be summarized, where the combined proportion is the average of the estimated proportion from each of m imputed datasets.

For each of m imputed datasets, a logistic regression model will be fitted for the primary endpoint status variable with treatment group, JAK2V617F mutation status, screening platelet count ($\geq 1000 \times 10^9$/L or $< 1000 \times 10^9$/L), and prior anagrelide use (yes vs no) as covariates.

Additional multiple imputation methods may be explored to assist assessing the robustness of the primary endpoint due to missing value.

7.3. Analysis of the Secondary Efficacy Parameter

Secondary efficacy analyses will be conducted for the ITT population.

7.3.1. European LeukemiaNet Response

Response status assessed by investigation based on the European LeukemiaNet (ELN) 2013 response criteria (Appendix A) will be collected on the eCRF.

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

The proportion of subjects with CR at Week 32 and the proportion of subjects with PR at Week 32 will be analyzed in a similar fashion to that above.

If no scheduled response status assessment at Week 32 is available, then assessment within a window of the target day (Day 225) ± 14 days will be used. Subjects with missing ELN response status at Week 32 will be considered as nonresponders.

If the JAK2V617F mutation status at randomization is not consistent with the JAK2V617F mutation status collected on the eCRF, an additional sensitivity analysis will be performed by stratifying the JAK2V617F mutation status collected on the eCRF, screening platelet count, and prior anagrelide use (yes vs no).

7.3.2. Duration of Response

For subjects who achieve primary response as defined in Section 7.2.1, duration of response will be assessed using Kaplan-Meier method.

Duration of response is defined as the time from the start of response until the end of response. The start of a response will be the first visit where both platelet control (defined as a reduction to $< 600 \times 10^9$/L) and WBC control (defined as a reduction to $< 10 \times 10^9$/L) are achieved, provided that the platelet and WBC control are ongoing at the time of Week 32 if the start of the response is before Week 32. Loss of response will be defined as 2 consecutive visits where either platelet count is $\geq 600 \times 10^9$/L or WBC is $\geq 10 \times 10^9$/L. The earlier of the 2 consecutive visits will be used as the end of response time. Subjects who are still maintaining both platelet control and WBC control at the time of database freeze or discontinuation of study drug will be censored at the date of the last assessment (platelet and WBC). The duration of response should include the 12 consecutive weeks between Week 32 and Week 52 when the primary response defined in Section 7.2.1 is achieved.

For the calculation of duration of response, the evaluable scheduled assessments will be used. If no scheduled assessment is available, then the unscheduled assessment closest to the visit target day within the analysis window will be used. The following windows will be applied to the target day:

- On or before Week 52: +/- 7 days
- Week 56 and after: +/- 14 days

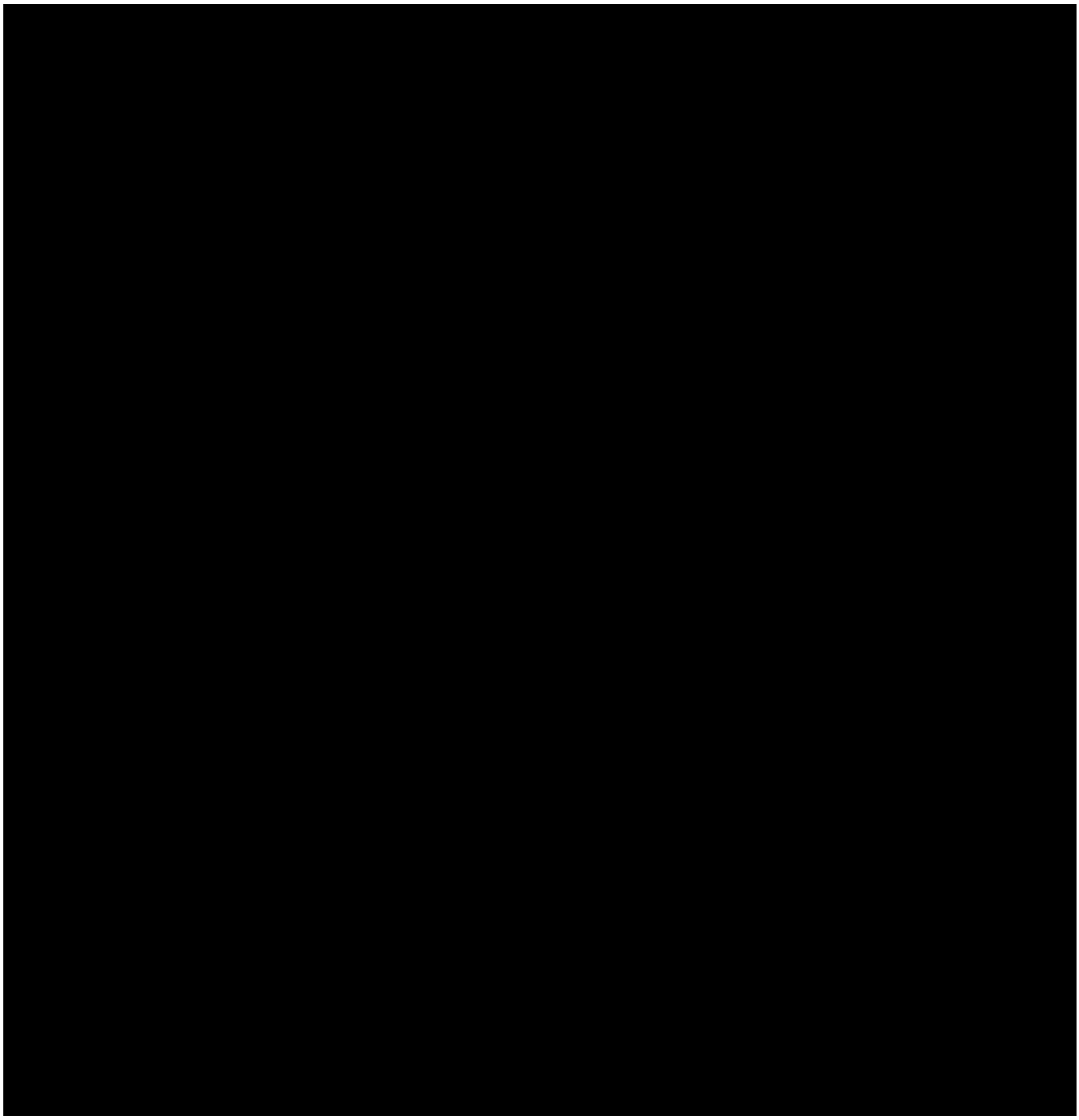
Missing platelet counts or WBC at a visit (with no scheduled visit and no unscheduled visit within window of target day) will be considered as not achieving platelet control and WBC control during that visit.

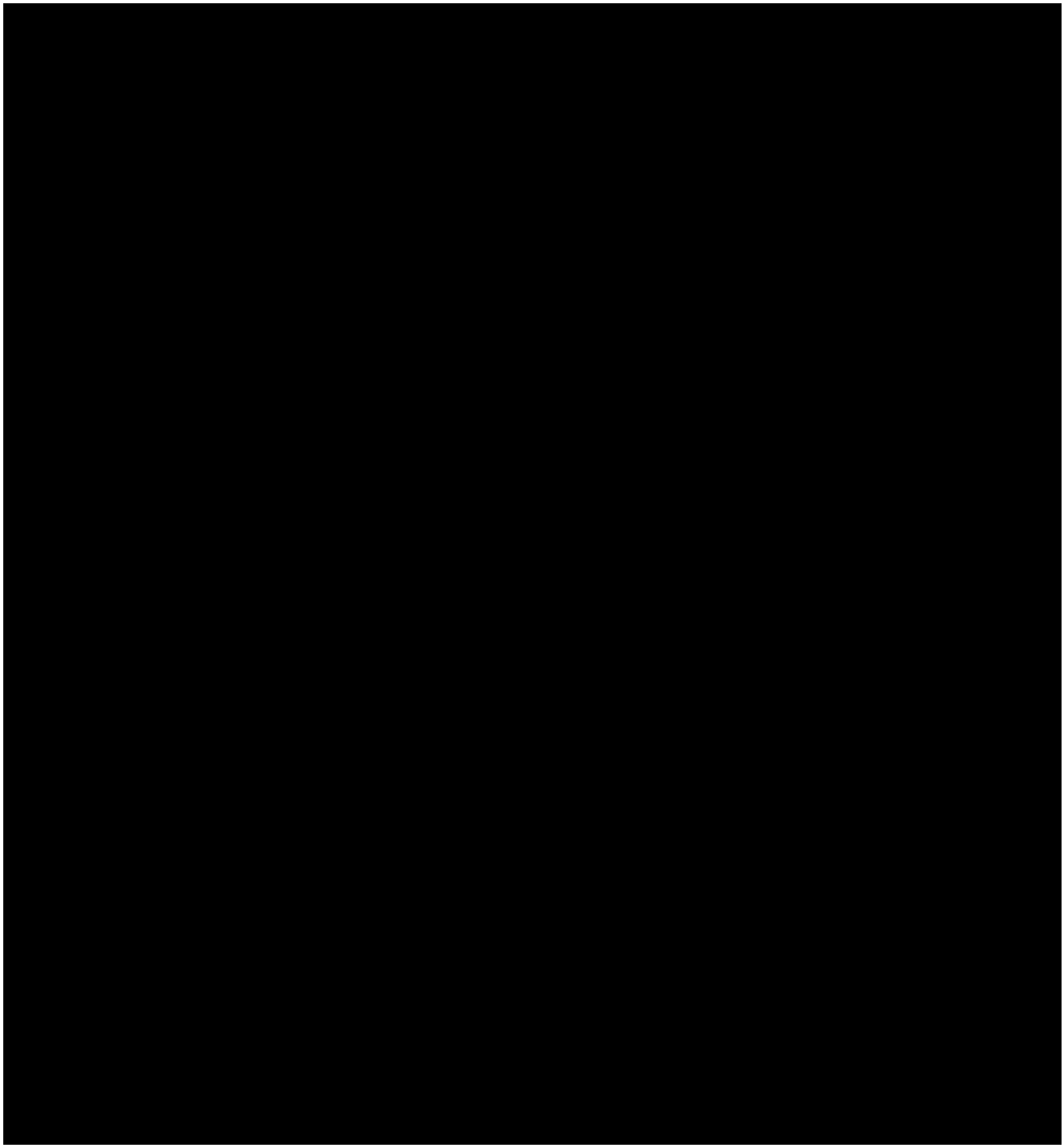
7.3.3. Individual Components of the Primary Endpoint

The proportion of subjects who achieve a reduction of platelet counts to $< 600 \times 10^9$/L for at least 80% of biweekly assessments for a consecutive 12-week period between Weeks 32 and 52 will be summarized along with their 95% confidence interval.

The proportion of subjects who achieve a reduction of WBC counts to $<10 \times 10^9$/L for at least 80% of biweekly assessments for a consecutive 12-week period between Weeks 32 and 52 will be summarized along with their 95% confidence interval.

[redacted]





[redacted]

9. SAFETY AND TOLERABILITY

Appendix F provides a list of data displays.

9.1. General Considerations

The analyses for this section will be provided for the safety population. 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 preferred terms reported on relatively few subjects.

For vital sign and laboratory test values, a primary set of the safety analyses will be based on the safety population, and all safety data will be summarized by visit and by treatment group. Separate analyses will be conducted for crossover subjects, and only the assessments that occurred after the crossover will be summarized.

For safety events, a primary set of the analyses will be based on the safety population, and results will be summarized by treatment group up to the end of the randomization period. The end of the randomization period is defined as the earliest of discontinuation or the individual unblinding date. Separate analyses of safety events will be conducted for all subjects, including those who cross over to ruxolitinib from anagrelide and those who continue on ruxolitinib after unblinding. For crossover subjects, only safety events and assessments that occurred in the crossover period will be counted. For subjects originally taking ruxolitinib, safety events and assessments that occurred in both the randomization and open-label treatment periods will be counted. Results will be shown by treatment group (ruxolitinib and ruxolitinib after crossover).

9.2. Adverse Events

9.2.1. Adverse Event Definitions

A treatment-emergent adverse event (TEAE) is any AE either reported for the first time or worsening of a pre-existing event after the 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.

An AE will be attributed to the crossover phase if the onset of the newly emerged or worsened AE is on or after the start date on ruxolitinib. If an end date of the event is after the start date for ruxolitinib, but the onset is registered before the crossover, this event will be attributed to the treatment actually received in the randomized treatment phase.

Adverse events will be tabulated by MedDRA preferred term and system organ class. Severity of AEs will be described and graded using the National Cancer Institute (NCI) CTCAE version 4.03 (NCI 2010). The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

A grading (severity) scale is provided for each AE term. If the toxicity is not included in the CTCAE v4.03 criteria, then it will be rated on a scale of 1 to 5 as follows: 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, and 5 = death due to AE. All toxicities will be graded based on the worst level reached, not the level that they may have reached if they had not been treated. When the intensity of an AE changes over time for a reporting period (eg, between visits), then each change in intensity will be reported as an AE until the event resolves.

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, then the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. Serious AEs will also be tabulated.

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

- An unsolved missing causality will be considered treatment-related.
- An unsolved 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.

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

[redacted] The naming of SMQs/IMQs and grouping of preferred terms into corresponding SMQs/IMQs will be based on the MedDRA version at the time of analyses.

9.2.3. Adverse Event Summaries

An overall summary of AEs by treatment group will include the following:

- 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 treatment-related TEAEs
- Number (%) of subjects with TEAEs leading to temporary dose interruption
- Number (%) of subjects with TEAEs leading to dose reductions
- Number (%) of subjects with TEAEs leading to permanent discontinuation of study drug
- Number (%) of subjects with TEAEs leading to withdrawal from the study
- Number (%) of subjects who had a fatal TEAE

The following summaries will be produced by MedDRA term (if ≤ 10 subjects appear in a table, then a listing may be appropriate):

- Summary of TEAEs by system organ class and preferred term
- Summary of TEAEs by preferred term in decreasing order of frequency
- Summary of TEAEs by system organ class, preferred term, and worst CTCAE grade
- Summary of Grade 3 or higher TEAEs by system organ class and preferred term
- Summary of treatment-related AEs by system organ class and preferred term
- Summary of treatment-related AEs by system organ class, preferred term, and worst CTCAE grade
- Summary of TEAEs leading to death by system organ class and preferred term
- Summary of treatment-emergent SAEs by system organ class and preferred term
- Summary of treatment-emergent SAEs by preferred term in decreasing order of frequency
- Summary of treatment-related SAEs by system organ class and preferred term
- Summary of TEAEs leading to dose interruption by system organ class and preferred term
- Summary of TEAEs leading to dose reduction by system organ class and preferred term

- Summary of TEAEs leading to discontinuation of study drug by system organ class and preferred term
- Summary of TEAEs leading to withdrawal from the study by system organ class and preferred term
- Summary of treatment-emergent nonserious AEs by system organ class and preferred term

9.3. Clinical Laboratory Tests

9.3.1. Laboratory Value Definitions

For numeric laboratory results, the change and percentage change from baseline will be calculated. Baseline will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, then the central value has priority over the local value. Thereafter, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline. For crossover subjects, the corresponding new baseline will be defined, when appropriate, as the last available assessment on or before the date of the first nonzero dose of ruxolitinib. This applies to all laboratory assessments.

Laboratory test values outside of the normal range will be assessed for severity based on CTCAE grade or similar criteria where clinical intervention is required for CTCAE grading.

9.3.2. 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 numeric laboratory values, baseline value, postbaseline value, change from baseline, and percentage change from baseline will be summarized by visit. In addition, mean change from baseline will be plotted over time for selected laboratory parameters including WBC, platelet count, hemoglobin, absolute neutrophil count, alanine aminotransferase, aspartate aminotransferase (AST), bilirubin, blood urea nitrogen, and creatinine.

For the laboratory parameters that have CTCAE grading, shift tables will also be presented by treatment group showing change in CTCAE severity grade from baseline to worst grade postbaseline up to the end of randomization period. Separate analyses of laboratory CTCAE grading will be conducted for all subjects, including those who cross over to ruxolitinib from anagrelide and those who continue on ruxolitinib after unblinding. The denominator for the percentage calculation will be the number of subjects in the baseline category.

Categorical laboratory data will be tabulated by visit at baseline and postbaseline visits where appropriate.

9.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, respiration rate, and body temperature will be summarized descriptively.

Criteria for clinically notable vital sign abnormalities are defined in Table 1. The abnormal values for subjects exhibiting clinically notable vital sign abnormalities will be listed. Alert vital signs are defined as an absolute value outside of the defined range and percentage change from baseline > 25%. The abnormal values for subjects exhibiting alert vital sign abnormalities will also be listed.

Table 1: Criteria for Clinically Notable Vital Sign Abnormalities

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

10. INTERIM ANALYSES

No interim analysis for efficacy and futility will be conducted in this study.

11. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 2.

Table 2: Statistical Analysis Plan Versions

SAP Version	Date
Original	25 JUL 2016
Amendment 1	21 DEC 2016
Amendment 2	24 SEP 2019

11.1. Changes to Protocol-Defined Analyses

Not applicable.

11.2. Changes to the Statistical Analysis Plan

11.2.1. Amendment 1

The original SAP has been updated to incorporate the Protocol Amendment 1 updates as well as FDA reviewer comments. Specific changes are outlined below:

- [redacted]
- [redacted].
- The study design has been updated to allow crossover from anagrelide to ruxolitinib after Week 52; analyses related to crossover have been added.
- Sensitivity analyses for the primary and key secondary efficacy endpoints will be performed if JAK2V617 mutation status changes after the randomization.
- Sensitivity analysis planned for the missing data on the primary endpoint has been added.
- Subgroup analyses based on the presence of JAK2V617 mutation, MPL mutation, CALR mutation, and triple-negative status have been added.

11.2.2. Amendment 2

Statistical Analysis Plan Amendment 1 has been updated to incorporate the Protocol Amendment 2 updates as well as FDA reviewer comments. Specific changes are outlined below:

- The study design was updated to align the inclusion criteria values for platelet and WBC count and to reflect the options for the open-label treatment phase.
- The per protocol population analyses were updated to exclude subjects with major protocol violations, including those who do not meet the criteria for ET diagnosis or hydroxyurea resistance/intolerance (inclusion criteria 2 and 3) and those who are < 80% compliant during the primary endpoint assessment period (Weeks 32-52)as determined by drug accountability assessment.
- Analyses for the proportion of subjects with CR at Week 32 and the proportion of subjects with PR at Week 32 based on ELN 2013 response criteria were added.
- The grading scale for toxicities not included in CTCAE v4.03 was updated to include Grade 5, death due to AE.
- Prior anagrelide use (yes vs no) was added as one of the stratification factors for randomization and efficacy analyses to address potential bias introduced by enrolling subjects with prior anagrelide use.
- Other minor, administrative changes have been incorporated throughout the Statistical Analysis Plan and are noted in the redline version of the amendment.

12. REFERENCES

Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood 2013;121:4778-4781.

Carel RS, Eviatar J. Factors affecting leukocyte count in healthy adults. Prev Med 1985;14:607-619.

Daly ME. Determinants of platelet count in humans. Haematologica 2011;96:10-13.

INC424 (INCB018424) Ruxolitinib Investigator's Brochure (IB). Basel, Switzerland: Novartis.

National Cancer Institute (NCI). Common Terminology Criteria for Adverse Events version 4.0. 2010. http://ctep.cancer.gov/reporting/ctc.html. Accessed July 15, 2016.

Oken MM, Creech RH, Tormey DC. Toxicity and response criteria of the Eastern Cooperative Oncology Group. J Clin Oncol 1982;5:649-655.

APPENDIX A. RESPONSE CRITERIA FOR ESSENTIAL THROMBOCYTHEMIA

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

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

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

[a] Lasting at least 12 weeks.

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

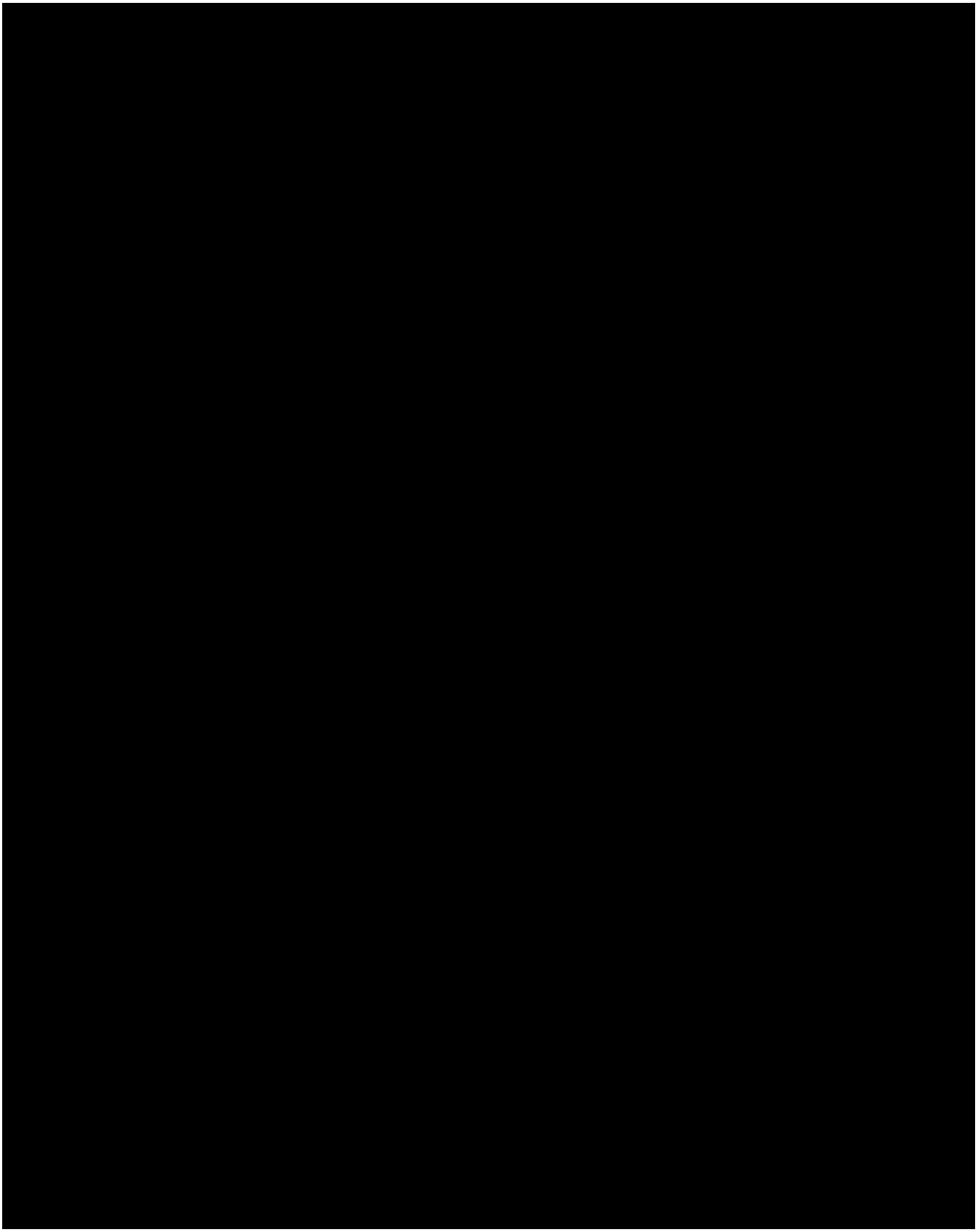
[c] For the diagnosis of PV, refer to the WHO 2016 criteria 13; for the diagnosis of post-ET myelofibrosis, refer to the IWG-MRT criteria 12; for the diagnosis of myelodysplastic syndrome and acute leukemia, refer to the WHO criteria.

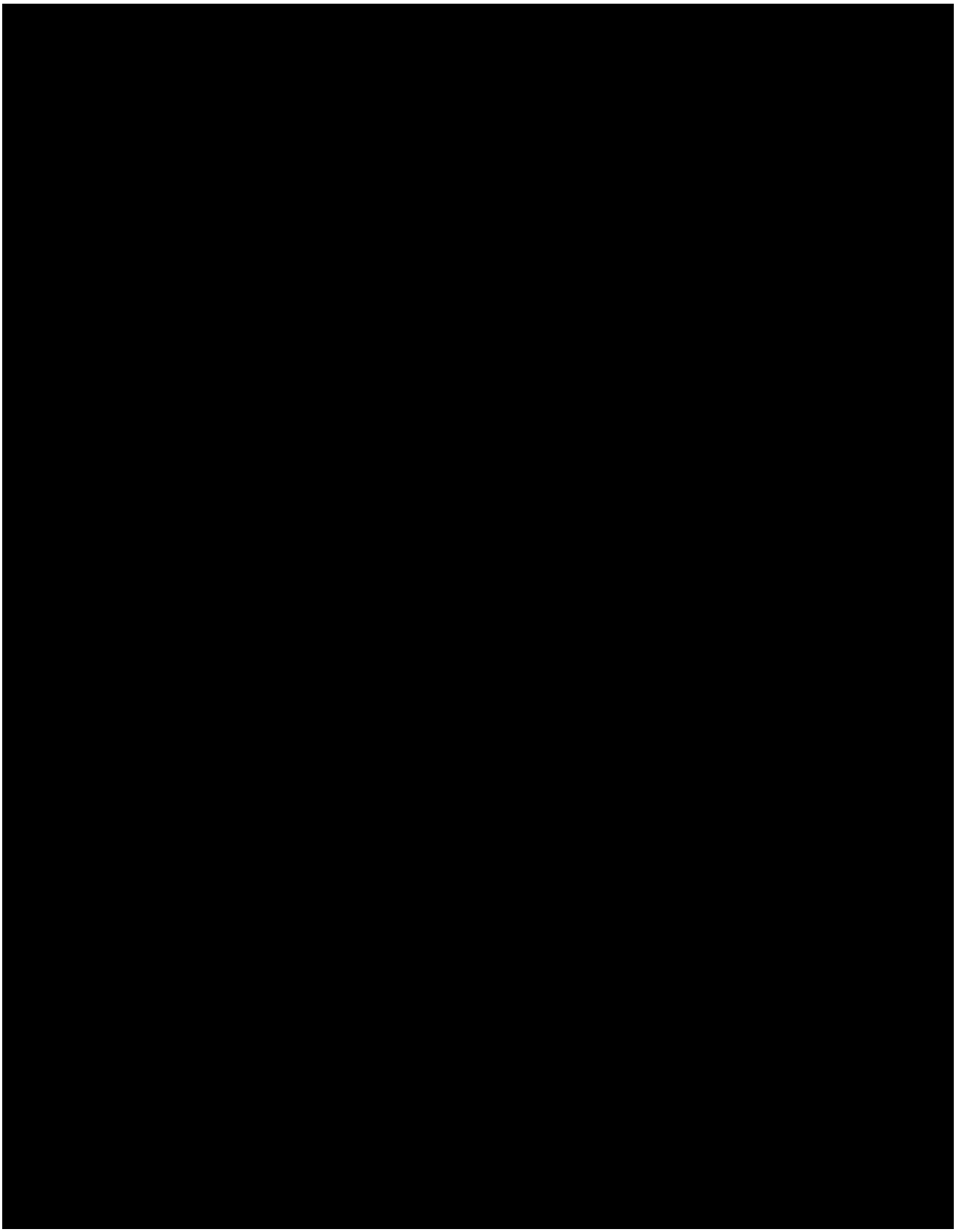
Source: Barosi et al 2013.

APPENDIX B. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

Source: Oken et al 1982.





APPENDIX E. SAMPLE SAS CODE

Below is the sample SAS code for multiple imputation of the primary endpoint status.

```
PROC MI DATA=ANAL NIMPUTE=5 SEED=8554633463 OUT=ANAL_MI;
      CLASS Resp Treat JAK2V617F Plat_BS Infection Trauma Anagre_use;
      MONOTONE  LOGISTIC(Resp = Treat JAK2V617F Plat_BS Infection
                     Trauma PLAT WBC Hemoglobin Anagre_use/ details);
      VAR Treat JAK2V617F Plat_BS Infection Trauma PLAT WBC Hemoglobin
          Anagre_use;
      RUN;
```

Below is the sample SAS code to analyze the multiple imputed datasets:

```
PROC LOGISTIC DATA=ANAL_MI;
      CLASS Resp Treat JAK2V617F  plat_screen Anagre_use;
      MODEL Respo = Treat JAK2V617F  plat_screen Anagre_use;
      By _Imputation_;
      ODS OUTPUT ParameterEstimates=lgsparms;
      RUN;

PROC MIANALYZE PARMS=LGSPARMS;
      MODELEFFECTS Treat JAK2V617F plat_screen Anagre_use;
      RUN;
```

APPENDIX F. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures, and listings for the Clinical Study Report. Standard tables will follow the conventions in the Standard Safety Tables initial version.

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				
1.1.1	Analysis Populations	All enrolled	X	X
1.1.2	Summary of Subject Disposition	ITT	X	X
1.2.1	Summary of Demographics and Baseline Characteristics	ITT	X	X
1.2.2	Summary of Disease History	ITT	X	X
1.2.3	Summary of Prior Therapy for ET	ITT	X	X
1.3	Summary of Medical History	ITT	X	
1.4.1	Summary of Prior Medications	ITT	X	
1.4.2	Summary of Concomitant Medications	ITT	X	
[redacted]	[redacted]	[redacted]		
Efficacy				
2.1.1	Proportion of Subjects Achieving the Primary Response	ITT		X
2.1.2	Proportion of Subjects Achieving the Primary Response	PP		X
2.1.3	Proportion of Subjects Achieving Individual Components of the Primary Response	ITT		X
2.1.4	Proportion of Subjects Achieving the Primary Response by Baseline JAKV617F Mutation Status	ITT		
2.1.5	Proportion of Subjects Achieving the Primary Response by Baseline MPL Mutation Status	ITT		
2.1.6	Proportion of Subjects Achieving the Primary Response by Baseline CALR Mutation Status	ITT		
2.1.7	Proportion of Subjects Achieving the Primary Response by Baseline Triple-Negative Status	ITT		
2.1.8	Proportion of Subjects Achieving the Primary Response by Baseline Platelet Count	ITT		
2.1.9	Proportion of Subjects Achieving the Primary Response by Sex	ITT		
2.1.10	Proportion of Subjects Achieving the Primary Response by Age Group	ITT		
2.1.11	Proportion of Subjects Achieving the Primary Response by Prior Thrombosis or Hemorrhage	ITT		
2.1.12	Proportion of Subjects Achieving the Primary Response by CV Risk Factors at Baseline	ITT		

Table No.	Title	Population	Standard	In-Text
2.1.13	Sensitivity Analysis of Proportion of Subjects Achieving the Primary Response – JAKV617F Mutation Change	ITT		
2.1.14	Sensitivity Analysis of Proportion of Subjects Achieving the Primary Response – Multiple Imputation	ITT		
2.2	Summary of Duration of Response	ITT		X
2.3.1	Proportion of Subjects Achieving ELN Response at Week 32	ITT		X
2.3.2	Sensitivity Analysis of Proportion of Subjects Achieving ELN Response at Week 32 – JAKV617F Mutation Change	ITT		
2.3.3	Proportion of Subjects Achieving ELN Complete Response at Week 32	ITT		
2.3.4	Proportion of Subjects Achieving ELN Partial Response at Week 32	ITT		
[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]		
Safety				
3.1.1	Summary of Study Drug Exposure and Compliance in Randomized Phase	Safety	X	X
3.1.2	Summary of Study Drug Exposure in All Ruxolitinib Treated Phase			
3.2.1	Overall Summary of Treatment-Emergent Adverse Events in Randomized Phase	Safety	X	X
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in Randomized Phase	Safety	X	
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in Randomized Phase	Safety	X	X
3.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Worst CTCAE Grade in Randomized Phase	Safety	X	
3.2.5	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in Randomized Phase	Safety	X	X
3.2.6	Summary of Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term in Randomized Phase	Safety	X	

Table No.	Title	Population	Standard	In-Text
3.2.7	Summary of Treatment-Related Adverse Events by MedDRA System Organ Class, Preferred Term, and Worst CTCAE Grade in Randomized Phase	Safety	X	
3.2.8	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term in Randomized Phase	Safety	X	X
3.2.9	Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term in Randomized Phase	Safety	X	X
3.2.10	Summary of Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in Randomized Phase	Safety	X	X
3.2.11	Summary of Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term in Randomized Phase	Safety	X	
3.2.12	Summary of Treatment-Emergent Adverse Events Leading to Dose Interruption by MedDRA System Organ Class and Preferred Term in Randomized Phase	Safety	X	
3.2.13	Summary of Treatment-Emergent Adverse Events Leading to Dose Reduction by MedDRA System Organ Class and Preferred Term in Randomized Phase	Safety	X	
3.2.14	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term in Randomized Phase	Safety	X	X
3.2.15	Summary of Treatment-Emergent Adverse Events Leading to Withdrawal From the Study by MedDRA System Organ Class and Preferred Term in Randomized Phase	Safety	X	
3.2.16	Summary of Treatment-Emergent Non-Serious Adverse Events by MedDRA System Organ Class and Preferred Term in Randomized Phase	Safety	X	
3.2.17	Summary of Treatment-Emergent Adverse Events of Special Interest in Randomized Phase	Safety	X	
3.2.18	Overall Summary of Treatment-Emergent Adverse Events in All Ruxolitinib Treated Phase	Safety	X	
3.2.19	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in All Ruxolitinib Treated Phase	Safety	X	
3.2.20	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in All Ruxolitinib Treated Phase	Safety	X	
3.2.21	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Worst CTCAE Grade in All Ruxolitinib Treated Phase	Safety	X	
3.2.22	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term in All Ruxolitinib Treated Phase	Safety	X	
3.2.23	Summary of Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term in All Ruxolitinib Treated Phase	Safety	X	

Table No.	Title	Population	Standard	In-Text
3.2.24	Summary of Treatment-Related Adverse Events by MedDRA System Organ Class, Preferred Term, and Worst CTCAE Grade in All Ruxolitinib Treated Phase	Safety	X	
3.2.25	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term in All Ruxolitinib Treated Phase	Safety	X	
3.2.26	Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term in All Ruxolitinib Treated Phase	Safety	X	
3.2.27	Summary of Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency in All Ruxolitinib Treated Phase	Safety	X	
3.2.28	Summary of Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term in All Ruxolitinib Treated Phase	Safety	X	
3.2.29	Summary of Treatment-Emergent Adverse Events Leading to Dose Interruption by MedDRA System Organ Class and Preferred Term in All Ruxolitinib Treated Phase	Safety	X	
3.2.30	Summary of Treatment-Emergent Adverse Events Leading to Dose Reduction by MedDRA System Organ Class and Preferred Term in All Ruxolitinib Treated Phase	Safety	X	
3.2.31	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug by MedDRA System Organ Class and Preferred Term in All Ruxolitinib Treated Phase	Safety	X	
3.2.32	Summary of Treatment-Emergent Adverse Events Leading to Withdrawal From the Study by MedDRA System Organ Class and Preferred Term in All Ruxolitinib Treated Phase	Safety	X	
3.2.33	Summary of Treatment-Emergent Non-Serious Adverse Events by MedDRA System Organ Class and Preferred Term in All Ruxolitinib Treated Phase	Safety	X	
3.2.34	Summary of Treatment-Emergent Adverse Events of Special Interest in All Ruxolitinib Treated Phase	Safety	X	
Laboratory Assessments				
3.3.1	Summary of Laboratory Values - Hematology	Safety	X	
3.3.2	Summary of Laboratory Values - Hematology for Crossover Subjects	Safety	X	
3.3.3	Shift Summary of Hematology Values in CTC Grade - To the Worst Abnormal Value in Randomized Phase	Safety	X	
3.3.4	Shift Summary of Hematology Values in CTC Grade - To the Worst Abnormal Value in All Ruxolitinib Treated Phase	Safety	X	
3.3.5	Summary of Laboratory Values - Chemistry	Safety	X	
3.3.6	Summary of Laboratory Values - Chemistry for Crossover Subjects	Safety	X	
3.3.7	Shift Summary of Chemistry Values in CTC Grade - To the Worst Abnormal Value in Randomized Phase	Safety	X	
3.3.8	Shift Summary of Chemistry Values in CTC Grade - To the Worst Abnormal Value in All Ruxolitinib Treated Phase	Safety	X	
3.3.9	Summary of Laboratory Values - Urinalysis	Safety	X	

Table No.	Title	Population	Standard	In-Text
3.3.10	Summary of Laboratory Values - Urinalysis for Crossover Subjects	Safety	X	
Vital Signs				
3.4.1	Summary of Systolic Blood Pressure	Safety	X	
3.4.2	Summary of Systolic Blood Pressure for Crossover Subjects	Safety	X	
3.4.3	Summary of Diastolic Blood Pressure	Safety	X	
3.4.4	Summary of Diastolic Blood Pressure for Crossover Subjects	Safety	X	
3.4.5	Summary of Heart Rate	Safety	X	
3.4.6	Summary of Heart Rate for Crossover Subjects	Safety	X	
3.4.7	Summary of Body Temperature	Safety	X	
3.4.8	Summary of Body Temperature for Crossover Subjects	Safety	X	
3.4.9	Summary of Respiration Rate	Safety	X	
3.4.10	Summary of Respiration Rate for Crossover Subjects	Safety	X	
3.4.11	Summary of Weight	Safety	X	
3.4.12	Summary of Weight for Crossover Subjects	Safety	X	

Figures

Figure No.	Title
4.2.1	Plot of Odds Ratios by Subgroups
4.2.2	Kaplan-Meier Estimates of Duration of Response (ITT)
4.2.3	Kaplan-Meier Estimates of Time to Treatment Discontinuation (ITT)
[redacted]	[redacted]
[redacted]	[redacted]
4.2.6	Line Graph of Mean Change From Baseline for Selected Laboratory Values (Safety)

Listings

Listing No.	Title
2.1.1	Analysis Population
2.1.2	Subject Enrollment and Disposition Status
2.1.3	Subject Inclusion and Exclusion Criteria
2.2	Protocol Deviations
2.4.1	Demographic and Baseline Characteristics
2.4.2	Disease History
2.4.3	Medical History
2.4.4	Prior and Concomitant Drug Treatments
2.6.1	Primary Response
2.6.2	Duration of Primary Response
2.6.3	ELN Response Status
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
2.6.7	Bone Marrow Biopsy
2.6.8	ECOG Status
2.7.1	Study Drug Administration and Compliance

Listing No.	Title
2.7.2	Adverse Events
2.7.3	Treatment-Related Adverse Events
2.7.4	Serious Adverse Events
2.7.5	Adverse Events Leading to Death
2.7.6	Adverse Events Leading to Discontinuation of Study Drug
2.7.7	Adverse Events Leading to Withdrawal From Study
2.8.1	Clinical Laboratory Values - Hematology
2.8.2	Clinical Laboratory Values - Chemistry
2.8.3	Abnormal Clinical Laboratory Values - Hematology
2.8.4	Abnormal Clinical Laboratory Values - Chemistry
[redacted]	[redacted]
2.8.6	Bone Marrow Biopsy
2.9.1	Vital Signs
2.9.2	Abnormal Vital Sign Values
2.9.3	Alert Vital Sign Values
2.10.1	Clinically Notable ECG Abnormalities
2.11.1	Physical Examinations