Official Title: A Randomized, Double-Blind, Placebo-Controlled Study of the PI3Kδ Inhibitor Parsaclisib Plus Ruxolitinib in Participants With Myelofibrosis Who Have Suboptimal Response to Ruxolitinib

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Statistical Analysis Plan

INCB 50465-304

A Randomized, Double-Blind, Placebo-Controlled Study of the PI3Kδ Inhibitor Parsaclisib Plus Ruxolitinib in Participants With Myelofibrosis Who Have Suboptimal Response to Ruxolitinib

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SAP Author:	[redacted], **Biostatistics**
Date of Plan:	**11 SEP 2024**

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
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	Clinical Study Report
CT	computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DIPSS	Dynamic International Prognostic Scoring System
DMC	Data Monitoring Committee
ECG	electrocardiogram
[redacted]	[redacted]
eCRF	electronic case report form
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
HGB	hemoglobin
HR	hazard ratio
HSD	Hwang-Shih-DeCani
ITT	intent-to-treat
[redacted]	[redacted]
JAK	Janus kinase
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
[redacted]	[redacted]
MRI	magnetic resonance imaging
NCI	National Cancer Institute

Abbreviation	Term
OS	overall survival
PET-MF	post–essential thrombosis myelofibrosis
[redacted]	[redacted]
PI3K	phosphoinositide 3-kinase
PP	per-protocol
PPV-MF	post–polycythemia vera myelofibrosis
[redacted]	[redacted]
PT	preferred term
QD	once daily
QoL	quality of life
QTc	QT interval corrected
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
[redacted]	[redacted]
SAP	Statistical Analysis Plan
SOC	system organ class
TEAE	treatment-emergent adverse event
TSS	total symptom score
ULN	upper limit of normal
WHO	World Health Organization
[redacted]	[redacted]

1. INTRODUCTION

This is a Phase 3, randomized, double-blind study of the combination of the PI3Kδ inhibitor parsaclisib or matching placebo and the JAK1/2 inhibitor ruxolitinib in participants with PMF or secondary MF (PPV-MF or PET-MF) who have had suboptimal response while receiving ruxolitinib monotherapy. Participants will be randomized to 1 of 2 treatment groups, with stratification for baseline platelet count ($\geq 100 \times 10^9$/L vs 50 to $< 100 \times 10^9$/L inclusive) and DIPSS risk category (high vs intermediate-2 vs intermediate-1). If a participant's platelet count has decreased to $< 50 \times 10^9$/L at baseline, the platelet count at screening will be used for stratification/randomization. Section 2 of the Protocol provides a detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with parsaclisib.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the INCB 50465-304 Protocol. A total of 212 participants will be randomized 1:1 to parsaclisib plus ruxolitinib or placebo plus ruxolitinib groups using the stratification factors of platelet count and DIPSS risk category. Two nonbinding futility analyses are planned at the time when the first 30% of the participants reach Week 12 and Week 24 assessments of spleen volume and MFSAF TSS or discontinue from their respective treatment.

The primary endpoint of the proportion of participants with ≥ 25% reduction in spleen volume at Week 24 and the key secondary endpoints of the proportion of participants with ≥ 50% reduction in MFSAF TSS at Week 24 and OS will be tested following a fixed-sequence-testing procedure.

[redacted]

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 50465-304 Protocol Amendment 2 dated 20 OCT 2022 and CRFs approved 21 OCT 2022. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate and compare the efficacy of parsaclisib plus ruxolitinib versus placebo plus ruxolitinib on spleen volume at Week 24.[a]	Proportion of participants achieving ≥ 25% reduction in spleen volume from baseline to Week 24 as measured by MRI (or CT scan in applicable participants).
Secondary	
To evaluate and compare the effect of parsaclisib plus ruxolitinib versus placebo plus ruxolitinib on participant reports of MF symptoms.[b,c]	Proportion of participants who have a ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MFSAF v4.0 diary. Change in TSS from baseline to Week 24 as measured by the MFSAF v4.0 diary. Time to the first ≥ 50% reduction in TSS as measured by the MFSAF v4.0 diary.
To evaluate and compare the effect of parsaclisib plus ruxolitinib versus placebo plus ruxolitinib with respect to OS.[d]	OS determined from the date of randomization until death due to any cause.
To evaluate and compare the safety and tolerability of parsaclisib plus ruxolitinib versus placebo plus ruxolitinib.	Safety and tolerability will be assessed by monitoring the frequency and severity of AEs, performing physical examinations, and evaluating changes in vital signs, ECGs, and laboratory results.
To evaluate and compare the time to onset and duration of response in spleen volume of participants receiving parsaclisib plus ruxolitinib versus placebo plus ruxolitinib.[e]	Time to the first ≥ 25% reduction in spleen volume and duration of maintenance of a ≥ 25% reduction in spleen volume.

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory	
[redacted]	

Table 1: Objectives and Endpoints (Continued)

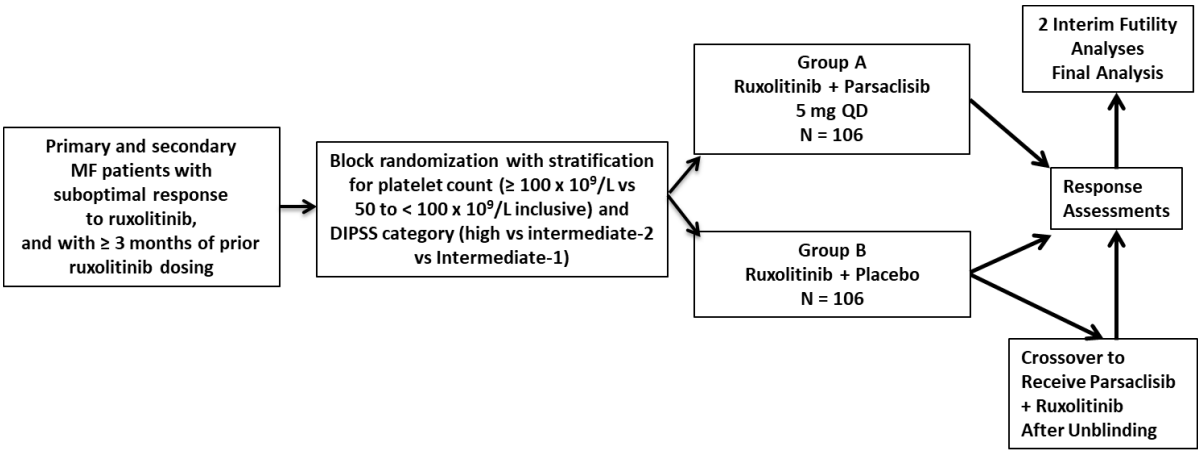
Objectives	Endpoints
Exploratory (continued)	
[redacted]	

[a] Hypothesis 1: Proportions of participants achieving ≥ 25% reduction in spleen volume from baseline to Week 24 in the 2 treatment groups are different.
[b] Hypothesis 2: Proportions of participants achieving ≥ 50% reduction in TSS from baseline to Week 24 as measured by the MFSAF v4.0 diary in the 2 treatment groups are different.
[c] Hypothesis 3: Time to the first ≥ 50% reduction in TSS as measured by the MFSAF v4.0 diary in the 2 treatment groups are different.
[d] Hypothesis 4: The OS in the 2 treatment groups are different.
[e] Hypothesis 5: Time to the first ≥ 25% reduction in spleen volume and/or duration of maintenance of ≥ 25% reduction in spleen volume for the 2 treatment groups are different.

3. STUDY DESIGN

This is a Phase 3, randomized, double-blind study of the combination of the PI3Kδ inhibitor parsaclisib or matching placebo and the JAK1/2 inhibitor ruxolitinib in participants with PMF or secondary MF (PPV-MF or PET-MF) who have had suboptimal response while receiving ruxolitinib monotherapy. Participants must meet Protocol-defined criteria for suboptimal response to ruxolitinib monotherapy. After participants have been determined to meet all criteria, they will be randomized to 1 of 2 treatment groups and will receive parsaclisib or matching placebo at a dose of 5 mg QD beginning on Day 1. Participants will also continue to receive the stable dose of ruxolitinib they were taking for the 8 weeks prior to Day 1. Both parsaclisib/matching placebo and ruxolitinib dosing will continue for the duration of participation in the study. Figure 1 presents the study design schema.

Figure 1: Study Design Schema



3.1. Randomization

Approximately 212 participants will be randomized 1:1 to parsaclisib plus ruxolitinib or placebo plus ruxolitinib with stratification for DIPSS risk category (intermediate-1 vs intermediate-2 vs high) and baseline platelet count ($\geq 100 \times 10^9$/L vs 50 to $< 100 \times 10^9$/L inclusive). Note that if a participant's platelet count is $< 50 \times 10^9$/L at baseline, the platelet count at screening will be used for stratification/randomization.

3.2. Control of Type I Error

This study defines a single primary endpoint with a single primary analysis. The study will be claimed to have achieved the primary efficacy objective when the primary endpoint shows a significant result at 2-sided alpha of 0.05 at final analysis. The key secondary efficacy endpoints will be alpha-controlled and will be analyzed only when the study has reached the efficacy objective in the primary endpoint. The key secondary efficacy variables will be tested following a fixed-sequence-testing procedure with each at the 2-sided alpha level of 0.05 in the order below. Overall survival will be tested only if MFSAF TSS is significant.

1. The proportion of participants who have a ≥ 50% reduction from baseline to Week 24 in the MFSAF TSS
2. OS

Descriptive statistics will be provided for other secondary [redacted] endpoints.

There will be 2 planned, nonbinding, futility analyses for this study based on the first 30% of participants enrolled in the study reaching Week 12 and Week 24 assessments of spleen volume and MFSAF TSS or discontinuing from treatment. As no formal decision for efficacy will be made based on these interim analyses, no overall alpha will be spent.

An independent DMC will be assembled to monitor safety data, efficacy data, and study conduct on a regular and ongoing basis during the study. See Section 10 for details regarding the alpha-spending plan and interim analyses conducted in this study.

3.3. Sample Size Considerations

The primary endpoint of this study is the proportion of participants with ≥ 25% spleen volume reduction from baseline to Week 24 as measured by MRI (or CT scan in applicable participants). The primary endpoint will be analyzed by the CMH test stratified by baseline (or screening, if applicable) platelet count (≥ 100×10^9/L vs 50 to < 100×10^9/L inclusive) and DIPSS risk category (high vs intermediate-2 vs intermediate-1) at randomization. Assuming a 25% response rate for ruxolitinib + parsaclisib versus 5% for ruxolitinib + placebo, to achieve a 95% power to detect a statistically significant difference with a 2-sided Type 1 error of 5%, a sample size of 212 participants is required to be randomized equally between treatment groups.

For the key secondary endpoint of MFSAF TSS, assuming a response rate of 35% (25%) with ruxolitinib + parsaclisib for participants with normal (low) platelet counts and a response rate of 15% (10%) with ruxolitinib + placebo for participants with normal (low) platelet counts, a sample size of 212 will provide 81.3% power using the CMH test given a 2-sided Type 1 error of 5%.

A test for OS will be performed when 84 deaths are observed or the last participant achieved Week 24 assessments of spleen volume and MFSAF TSS, whichever is later, using the log-rank test at a 2-sided Type 1 error level of 0.05. The log-rank test will provide 80% power to detect an HR of 0.54 with 84 deaths. Assuming a median survival time of 3.7 years for ruxolitinib + placebo and an enrollment duration of 1 year, the expected total study duration is 4 years.

3.4. Schedule of Assessments

Refer to Protocol INCB 50465-304 Amendment 2 dated 20 OCT 2022 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 parsaclisib/placebo is administered to the participants.

For randomized participants not treated with parsaclisib/placebo, Day 1 is defined as the date of randomization.

4.1.2. Day 1 of Crossover for Crossover Participants

For participants who cross over from placebo plus ruxolitinib to parsaclisib plus ruxolitinib, Day 1 of crossover is the date the first dose of open-label parsaclisib is administered to the participants.

4.1.3. Study Day

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

Day # = (visit/reporting date – Day 1 date + 1).

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

Day # = (visit/reporting date – Day 1 date).

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

4.1.4. Baseline Value

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

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

When scheduled assessments and unscheduled assessments occur on the same day and the 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 the 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 the baseline.

4.1.5. Handling of Missing and Incomplete Dates

In general, values for missing dates will not be handled unless methods for handling missing dates are specified in this section or relevant sections. The original reported dates collected on the eCRF should be used in all relevant listings. The following rules will be used for handling partial dates for analyses requiring dates.

When calculating the time since diagnosis of MF, a partial MF disease diagnosis date will be handled as follows in the calculation:

- If only the day is missing, then the first day of the month will be used.
- If both the month and day are missing, then 01 JAN of the year will be used.
- If the diagnosis date is completely missing, then the time since diagnosis will not be calculated.

When the date of the last dose is used in deriving variables such as duration of treatment or TEAE flag, a missing or partial date of the last dose will be handled as follows:

- If only the day is missing, then the earlier date of the last day of the month or the date that the participant discontinued treatment will be used.
- If both the month and day are missing, then the earlier date of 31 DEC of the year or the date that the participant discontinued treatment will be used.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

For relevant efficacy endpoints, a partial date of the death date will be handled as follows in the calculation:

- If mmyyyy for the last known alive date = mmyyyy for the death date, then the death date will be set to the day after the last known alive date.
- If mmyyyy for the last known alive date < mmyyyy for the death date, then the death date will be set to the first day of the death month.
- Otherwise, the partial death date will not be imputed.

4.2. Variable Definitions

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

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

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

4.2.2. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of parsaclisib/placebo.

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

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

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of parsaclisib/placebo. In the listing, it will be indicated whether a medication is only prior, only concomitant, 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; v9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include but not be limited to the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

Interim analyses are planned for this study as defined in Section 10.

5.2. Treatment Groups

This is a randomized, double-blind, parallel treatment group design. Participants will be summarized by treatment group. A participant randomized to the control group may make a crossover to the active treatment prior to Week 24 if the participant meets the criteria for an early crossover. Unless specified, efficacy and safety analyses for between-treatment comparisons (parsaclisib + ruxolitinib vs placebo + ruxolitinib) will be conducted using the data truncated at the time of treatment crossover for those participants who made an early treatment crossover prior to Week 24. Data collected after the treatment crossover will be summarized and tabulated separately without treatment comparisons.

5.3. Analysis Endpoints

The methods and populations for primary and secondary analyses are provided in Table 2.

Table 2: Primary and Secondary Analyses Methods and Populations

Endpoint	Statistical Method	Analysis Population	Preplanned (P) or Supportive (S)
Primary endpoint			
Proportion of participants achieving ≥ 25% reduction in spleen volume from baseline to Week 24 as measured by MRI (or CT scan in applicable participants)	CMH test stratified by baseline (or screening, if applicable) platelet count (≥ 100×10^9/L vs 50 to < 100×10^9/L inclusive) and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization	ITT	P
		PP	S
Secondary endpoints			
Proportion of participants who have a ≥ 50% reduction in total symptom score from baseline to Week 24 as measured by the MFSAF v4.0 diary	CMH test stratified by baseline (or screening, if applicable) platelet count (≥ 100×10^9/L vs 50 to < 100×10^9/L inclusive) and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization	ITT	P
		PP	S
OS determined from the date of randomization until death due to any cause	Inference: Log-rank test stratified by baseline (or screening, if applicable) platelet count (≥ 100×10^9/L vs 50 to < 100×10^9/L inclusive) and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization Estimation: Kaplan-Meier	ITT	P
		PP	S
	Inference: Cox regression model including treatment group, baseline (or screening, if applicable) platelet count (≥ 100×10^9/L vs 50 to < 100×10^9/L inclusive) at randomization, and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization	ITT	S

Table 2: Primary and Secondary Analyses Methods and Populations (Continued)

Endpoint	Statistical Method	Analysis Population	Preplanned (P) or Supportive (S)
OS adjusted for crossover using rank-preserving structural failure time	Inference: Cox regression model including treatment group, baseline (or screening, if applicable) platelet count ($\geq 100 \times 10^9$/L vs 50 to $< 100 \times 10^9$/L inclusive) and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization	ITT	S
Time to the first ≥ 25% reduction in spleen volume	Inference: Log-rank test with stratification of baseline (or screening, if applicable) platelet count ($\geq 100 \times 10^9$/L vs 50 to $< 100 \times 10^9$/L inclusive) and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization Estimation: Kaplan-Meier	ITT	P
Duration of maintenance of a ≥ 25% reduction in spleen volume	Estimation: Kaplan-Meier	ITT with spleen response	P
Time to the first ≥ 50% reduction in TSS as measured by the MFSAF v4.0 diary	Inference: Log-rank test with stratification of baseline (or screening, if applicable) platelet count ($\geq 100 \times 10^9$/L vs 50 to $< 100 \times 10^9$/L inclusive) and DIPSS (high vs intermediate-2 vs intermediate-1) at randomization Estimation: Kaplan-Meier	ITT	P

Due to the early termination of the study, only preplanned analyses will be performed. Supportive analyses will not be included. Time to event analyses with too few events observed at the time of study termination will not be conducted as well.

5.4. Analysis Populations

5.4.1. Intent-to-Treat Population

All participants who are randomized will constitute the ITT population. Treatment groups for this population will be defined according to the treatment assignment at the time of randomization regardless of the actual study drug the participant might take during his/her participation in the study.

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

Participants with missing baseline assessments will be excluded from the ITT population for the responder analyses.

5.4.2. Per-Protocol Population

Participants in the ITT population who are considered to be sufficiently compliant with the Protocol will compose the PP population.

The following procedures will be performed to identify those participants who are to be excluded from the PP population:

- Clinical review of protocol deviations, including but not limited to
  - Clinical review of concomitant medications as defined in Section 6.8 of the Protocol
  - Clinical review of the dose administration and drug accountability listing
  - Clinical review of inclusion/exclusion criteria

Participants with missing baseline assessments will be excluded from the PP population for the responder analyses.

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

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

Due to early termination of the study, analyses with PP population will not be performed.

5.4.3. Safety Population

The safety population will include all participants who received at least 1 dose of parsaclisib/placebo or ruxolitinib. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned study drug treatment.

All safety analyses will be conducted using the safety population.

6. BASELINE, EXPOSURE, AND DISPOSITION

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

6.1. Demographics, Baseline Characteristics, and Disease History

6.1.1. Demographics and Baseline Characteristics

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

6.1.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized for the ITT population by treatment group: ECOG performance status, neutrophils, platelets, hemoglobin, and leukocytes at baseline.

6.1.3. Myelofibrosis Disease History

The following MF disease history will be summarized for the ITT population by treatment group: the time since diagnosis to randomization, current MF disease, prognostic factors, risk level as defined by the DIPSS, whether a prior splenic irradiation was performed, if splenectomy was performed, and whether transfusions were received in the 12 weeks before randomization.

Time since diagnosis will be calculated as follows:

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

The MF screening symptom individual and total scores will be summarized for the ITT population by treatment group.

6.1.4. Prior Therapy

The number of prior systemic regimens for MF other than ruxolitinib will be summarized for all participants in the ITT population by treatment group. The component drugs of prior systemic therapy regimens will be coded using the WHO Drug Dictionary. The number and percentage of participants who received each drug will be summarized by WHO drug class and WHO drug PT. The regimen name, route, dose, frequency, start and stop dates, and reason for discontinuation will be listed.

The number of participants who received prior radiation for non–MF-related cancer treatment will be summarized for the ITT population by treatment group. The radiotherapy type, body site, start and stop dates, reason for regimen, total dose, number of fractions received, and best response will be listed.

The number of participants who had prior surgery or a surgical procedure for non–MF-related cancer treatment will be summarized for the ITT population by treatment group. The date and description of the surgery/procedure will be listed.

6.1.5. Medical History

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

6.1.6. Ruxolitinib History

The duration and total daily dose of ruxolitinib treatment prior to Day 1, as well as the duration and total daily dose of stable ruxolitinib treatment prior to Day 1 will be summarized for the ITT population by treatment group.

6.2. Disposition of Participant

The number and percentage of participants who were randomized, who were treated, who were ongoing with study treatment, who discontinued study treatment with a primary reason for discontinuation, who were still in the study, and who withdrew from the study with a primary reason for withdrawal will be summarized for the ITT population by treatment group. The number of participants randomized by country and/or site will also be provided by treatment group.

6.3. Protocol Deviations

Protocol deviations recorded in the clinical trial management system will be summarized and listed.

6.4. Exposure

For participants in the safety population, exposure to parsaclisib/placebo and ruxolitinib will be summarized descriptively as the following:

- **Duration of treatment with ruxolitinib (days):** date of last dose of ruxolitinib – date of first dose of ruxolitinib + 1.
- **Duration of treatment with parsaclisib/placebo (days):** date of last dose of parsaclisib/placebo – date of first dose of parsaclisib/placebo + 1.
- **Average daily dose of ruxolitinib (mg/day):** total actual ruxolitinib dose taken (mg) / duration of treatment with ruxolitinib (days).
- **Average daily dose of parsaclisib/placebo (mg/day):** total actual parsaclisib/placebo dose taken (mg) / duration of treatment with parsaclisib/placebo (days).

  Total actual dose taken will be calculated based on the information entered on the Drug Exposure eCRF.
- **Total dose administered for ruxolitinib (mg):** sum of ruxolitinib administered (mg) during treatment.
- **Total dose administered for parsaclisib/placebo (mg):** sum of parsaclisib/placebo administered (mg) during treatment.

6.5. Study Drug Compliance

For participants in the safety population, overall compliance (%) for parsaclisib/placebo will be calculated for all participants as follows:

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 eCRF. If there are dispensed drugs that have not been returned yet, the actual dose taken starting from the dispense date of the unreturned drugs will be imputed by the dose taken as reported on the Dosing eCRF.

6.6. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. The number and percentage of participants in the ITT population for each prior and concomitant medication will be summarized by WHO drug class and WHO drug PT for each treatment group.

7. EFFICACY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

7.1. General Considerations

Unless otherwise stated, the strata identified in the randomization process will be used in all efficacy analyses. Within a platelet category, in the event that the study fails to enroll a sufficient number of participants in a particular DIPSS stratification level, at the time of final analysis for database lock, that stratification will be combined with the nearest adjacent DIPSS level (eg, intermediate-1 vs intermediate-2 vs high). For example, if either intermediate-1 or high-risk is too small (eg, fewer than 10 participants), it will be merged with intermediate-2. If intermediate-2 has too few participants (eg, fewer than 10 participants), then it will be merged with the smaller of the 2 adjacent strata. At the time of interim analyses, all DIPSS stratification levels will be combined if too few participants (eg, fewer than 10 participants) are enrolled in 1 DIPSS stratification level.

The ITT population will be used for all efficacy analyses unless otherwise stated.

7.2. Efficacy Hypotheses

The primary hypothesis is that the percentage of participants achieving ≥ 25% reduction in spleen volume from baseline to Week 24 in the parsaclisib plus ruxolitinib treatment group will not be the same as the percentage of participants achieving ≥ 25% reduction in spleen volume from baseline to Week 24 in the placebo plus ruxolitinib treatment group as measured by the odds ratio. The hypotheses of the study are as follows:

- H_0 (null hypothesis): $\theta_{PAR} = \theta_{PLB}$
- H_A (alternative hypothesis): $\theta_{PAR} \neq \theta_{PLB}$

7.3. Analysis of the Primary Efficacy Endpoint

7.3.1. Primary Efficacy Analysis

The primary endpoint of this study is the proportion of participants with ≥ 25% spleen volume reduction from baseline to Week 24 as measured by MRI (or CT scan in applicable participants). The primary endpoint will be analyzed by the CMH test stratified by DIPSS risk category (intermediate-1 vs intermediate-2 vs high) and baseline (or screening, if applicable) platelet count (≥ 100×10^9/L vs 50 to < 100×10^9/L inclusive).

The baseline spleen volume will be measured during the baseline visit (Days −7 to 1); the last value will be used if there are multiple values measured during the baseline visit.

The Week 24 spleen volume will be measured during the Week 24 visit; the last value will be used if there are multiple values measured during the Week 24 visit. Missing values will not be imputed.

The percentage change from baseline to Week 24 will be calculated using the following formula:

> % change = 100 × [Week 24 spleen volume – baseline spleen volume] / baseline spleen volume.

A participant will be considered as having achieved ≥ 25% reduction of spleen volume from baseline to Week 24 if the participant had both baseline and Week 24 spleen volume measurements, the participant did not make an early crossover to receive parsaclisib plus ruxolitinib prior to the Week 24 visit, and the percentage change from baseline reduction was ≥ 25%.

A participant who has a missing Week 24 spleen volume, discontinues treatment before Week 24, or makes an early crossover to receive parsaclisib plus ruxolitinib prior to the Week 24 visit will be considered as a nonresponder for the endpoint of ≥ 25% reduction of spleen volume.

A participant who has a missing baseline assessment will be considered as nonevaluable.

At the time of interim analysis, a participant who is still on treatment, but has not followed up for the timepoint assessment and has no timepoint assessment, will also be considered as nonevaluable.

7.3.2. Subgroup Analyses for Primary Endpoint

Subgroups will be formed based on the following participant characteristics and baseline variables for those participants whose data are available. If the number of participants is too small (eg, 10 participants) in a subgroup, then the analysis will not be conducted in that subgroup.

- Baseline platelet count: $\geq 100 \times 10^9$/L versus 50 to $< 100 \times 10^9$/L inclusive. Note that if a participant's platelet count is $< 50 \times 10^9$/L at baseline, the platelet count at screening will be used for stratification/randomization.
- DIPSS risk category: high versus intermediate-2 versus intermediate-1
- Sex: male versus female
- Age group: ≤ 65 years or > 65 years
- MF type: PMF, PPV-MF, or PET-MF
- Ruxolitinib average total daily dose during the 8 weeks before randomization: < 20 mg, 20 to 30 mg inclusive, or > 30 mg
- Overall duration of treatment with ruxolitinib before randomization: $\leq$ median or $>$ median
- Presence/absence of V617F mutation at baseline
- Presence/absence of HMR mutations at baseline
- Baseline spleen volume group: $\leq$ median or $>$ median
- Baseline spleen palpation size group: ≤ 10 cm or > 10 cm
- Race: White/Caucasian, Black/African-American, Asian, American-Indian/Alaska Native, Native Hawaiian/Pacific Islander, or other
- Ethnicity: Hispanic/Latino, not Hispanic/Latino, or other

A forest plot with odds ratio and 95% CI for the primary endpoint subgroup analyses will be provided.

7.3.3. Sensitivity and Supportive Analyses for Primary Endpoint

The primary endpoint will be analyzed using the PP population as a supportive analysis to the ITT population.

The participants who make an early crossover and later turn into responders will be considered as responders and analyzed in the placebo group as a supportive analysis.

In the event that 2 DIPSS stratification levels are combined, a sensitivity analysis for the primary endpoint without combining levels will be conducted.

Due to early study termination, sensitivity and supportive analyses will not be performed.

7.4. Analysis of the Secondary Efficacy Parameters

7.4.1. Spleen Volume Reduction

7.4.1.1. Time to the First ≥ 25% Reduction in Spleen Volume

The time to the first ≥ 25% reduction in spleen volume is defined as the time from randomization to the first time participants have a ≥ 25% reduction in spleen volume. Participants with baseline and postbaseline MRI or CT scan who do not have a ≥ 25% reduction in spleen volume at the time of analysis will be censored at the time of the last MRI or CT scan. If the participants have no baseline or postbaseline MRI or CT scan, they will be censored at the date of randomization.

The stratified log-rank test will be used to compare the time to the first ≥ 25% reduction in spleen volume between the 2 treatment groups in the ITT population at a 1-sided 2.5% significance level, stratified for baseline (or screening, if applicable) platelet count and DIPSS category. The strata identified in the randomization process will be used for the analysis.

Kaplan-Meier curves for the time to the first ≥ 25% reduction in spleen volume will be presented by treatment group. The KM estimate of median time to the first ≥ 25% reduction in spleen volume will be presented with its 95% CI. The 95% CI will be calculated using the generalization of method of Brookmeyer and Crowley (1982) with log-log transformation (Klein and Moeschberger 1997).

Since only a limited number of ≥ 25% reduction in spleen volume response was observed at the time of study termination, time to the first 25% reduction in spleen volume will not be performed.

7.4.1.2. Duration of Maintenance of a ≥ 25% Reduction in Spleen Volume

The duration of a ≥ 25% reduction from baseline in spleen volume is defined as the interval between the first spleen volume measurement that is ≥ 25% reduction from baseline and the date of the first measurement that is no longer a ≥ 25% reduction from baseline. If the end date is not observed before the database cutoff, the duration will be censored at the last assessment.

The endpoint will be derived for participants who were randomized and who had at least 1 measurement of ≥ 25% reduction from baseline.

Kaplan-Meier estimates of median duration with 95% CIs will be provided.

The ITT population with spleen volume response will be used.

A supportive analysis for the duration of a ≥ 25% reduction from baseline in spleen volume defined as the interval between the first spleen volume measurement that is ≥ 25% reduction from baseline and the date of the first measurement that is no longer a ≥ 25% reduction from baseline that is also a > 25% increase from nadir will be provided.

At the time of study termination, only a limited number of ≥ 25% reduction in spleen volume response was observed; therefore, duration of a 25% reduction in spleen volume will not be performed.

7.4.2. Myelofibrosis Symptom Assessment Form Total Symptom Score v4.0

The MFSAF v4.0 is composed of 7 individual symptom scores (fatigue, night sweats, itchiness, abdominal discomfort, pain under left ribs, early satiety, and bone pain), each collected daily with a 0- to 10-point scale.

The daily MFSAF TSS is the sum of the 7 individual symptom scores collected on the same day. The MFSAF TSS will be missing if there are any missing individual scores. Observations with missing dates will be excluded from the analysis.

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

The Week 12 total score will be the average of daily total scores from the first 7 consecutive days starting on Day 78; the Week 12 total score will be missing if there are ≥ 4 missing out of the 7 daily total scores.

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

The percentage change from baseline to Week 12/Week 24 will be calculated using the following formula:

% change = 100 × [Week 12/Week 24 MFSAF TSS – baseline MFSAF TSS] / baseline MFSAF TSS.

7.4.2.1. Windowing of Myelofibrosis Symptom Assessment Form v4.0 Total Symptom Score

7.4.2.1.1. Myelofibrosis Symptom Assessment Form v4.0 Total Symptom Score for Non–Time-to-Event Endpoints

The MFSAF v4.0 TSS for baseline, Week 12, and Week 24 will be determined by averaging the daily MFSAF v4.0 TSS for the days between the start and end of windows as described in Table 3. By-question summaries for the 7 individual symptom scores that compose the MFSAF TSS at baseline, Week 12, and Week 24 will use the same windowing algorithm as used for the daily TSS.

The TSS and the 7 individual scores at Weeks 4, 8, 16, and 20 will be derived in a similar fashion using the first nonmissing daily TSS available between

Day (7 × Week X – 6) and Day (7 × Week X)

as the start of the window.

Table 3: Window for Deriving Myelofibrosis Symptom Assessment Form v4.0 Total Symptom Score for Baseline, Week 12, and Week 24

Period	Start of Window	End of Window	Missing
Baseline	7 days before end of window	Last day that a daily TSS was collected between Day −7 and Day −1 (inclusive)	4 or more missing of the 7 daily TSSs in the window
Week 12	First day a daily TSS was collected between Day 78 and Day 84 (inclusive)	7 days after start of window	4 or more missing of the 7 daily TSSs in the window
Week 24	7 days before end of window	The day before the Week 24 visit	4 or more missing of the 7 daily TSSs in the window

7.4.2.1.2. Myelofibrosis Symptom Assessment Form v4.0 Total Symptom Score for Time-To-Event Endpoints

The MFSAF v4.0 TSS for baseline will be derived the same way as in Section 7.4.2.1.1. The daily postbaseline TSS will be calculated from Day 7 to the day before the Week 24 visit. The Day X TSS is the average TSS between Day X − 6 and Day X. For example, the TSS on Day 7 is the average of the TSS from Day 1 to Day 7. The missing individual score and the missing daily TSS will follow the rule defined in Section 7.4.2.

7.4.2.2. Proportion of Participants With a ≥ 50% Reduction in Myelofibrosis Symptom Assessment Form v4.0 Total Symptom Score

The difference between the parsaclisib plus ruxolitinib group and the placebo plus ruxolitinib group in the proportion of participants who have a ≥ 50% reduction in TSS from baseline to Week 24 evaluated by MFSAF v4.0 will be assessed using the CMH test stratified by baseline (or screening, if applicable) platelet count and DIPSS category at randomization for the ITT population as primary analysis and the PP population as sensitivity analysis. In the case that there is an insufficient number of participants enrolled in any DIPSS level within a platelet category, the collapsing rule specified in Section 7.1 will be applied. Missing values will not be imputed.

The percentage change from baseline to Week 24 will be calculated using the following formula:

$$\% \text{ change} = 100 \times (\text{Week 24 total score} - \text{baseline total score}) / \text{baseline total score}.$$

A participant will be considered as having achieved ≥ 50% reduction of the TSS from baseline to Week 24 if the participant had both baseline and Week 24 TSSs, the participant did not make an early crossover to receive parsaclisib plus ruxolitinib prior to the Week 24 visit, and the percentage change from baseline was not missing and was less than or equal to −50%.

A participant who has a missing Week 24 TSS, discontinues treatment before Week 24, is unblinded prior to Week 24 for early crossover to parsaclisib plus ruxolitinib, or has a baseline value of 0 will be considered as having not achieved the ≥ 50% reduction.

A participant who has a missing TSS baseline assessment will be considered as nonevaluable.

At the time of interim analysis, a participant who is still on treatment but has no timepoint assessment for TSS will also be considered as nonevaluable.

7.4.2.3. Mean Change and Percentage Change in Myelofibrosis Symptom Assessment Form v4.0 Total Symptom Score

The mean change and percentage change from baseline to Week X will be calculated using the following formula:

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

The mean change and percentage change in TSS, the 7 individual scores, and the total score of the 3 spleen-related symptoms (including abdominal discomfort, pain under left ribs, and early satiety) from baseline to Week X will be summarized descriptively by treatment group and every 4 weeks using the ITT population. Missing values will not be imputed.

A plot of percentage change from baseline in MFSAF TSS at each visit will be provided.

7.4.2.4. Time to the First ≥ 50% Reduction in Myelofibrosis Symptom Assessment Form v4.0 Total Symptom Score

The time to the first ≥ 50% reduction in TSS is defined as the time from randomization to the first time participants have a ≥ 50% reduction in TSS. The daily TSS will be calculated according to the algorithm defined in Section 7.4.2.1.2. Participants with valid, calculated baseline TSS and at least 1 postbaseline TSS who do not have ≥ 50% reduction in TSS at the time of analysis will be censored at the time of the last valid calculated TSS. If the participants have no valid, calculated baseline or postbaseline TSS, they will be censored at the date of randomization.

The stratified log-rank test will be used to compare time to the first ≥ 50% reduction in TSS between the 2 treatment groups in the ITT population at a 1-sided 2.5% significance level, stratified for baseline (or screening, if applicable) platelet count and DIPSS category. The strata identified in the randomization process will be used for the analysis.

Kaplan-Meier curves for the time to the first ≥ 50% reduction in TSS will be presented by treatment group. The KM estimate of median time to the first ≥ 50% reduction in TSS will be presented with its 95% CI. The 95% CI will be calculated using the generalization of method of Brookmeyer and Crowley (1982) with log-log transformation (Klein and Moeschberger 1997).

7.4.3. Overall Survival

Overall survival is defined as the interval between the randomization date and the date of death due to any cause. Date of death will be determined using the Death Report, the Survival Follow-Up, and the Participant Status eCRFs. Participants who are lost-to-follow-up or still alive at the time of analysis will be right-censored at the earlier of the date the participant was last known alive and the clinical data cutoff date for the analysis. The last known alive date is defined as the later of the last study visit and the date the participant was last known alive from the Survival Follow-Up and Participant Status eCRFs. Partial death dates will be handled using the rules described in Section 4.1.5.

The treatment difference in survival for parsaclisib plus ruxolitinib and placebo plus ruxolitinib will be assessed by a log-rank test on the ITT population and PP population stratified for baseline (or screening, if applicable) platelet count and DIPSS category. The strata identified in the randomization process will be used for the analysis. In the event that stratification level combinations have limited numbers of participants, 2 or more of the strata may be combined to better facilitate estimation of the overall HR.

The HR estimate and CIs will be estimated based on a stratified Cox proportional hazards model using the same stratification factors as for the log-rank test with Efron's method (1977) accounting for ties in death days.

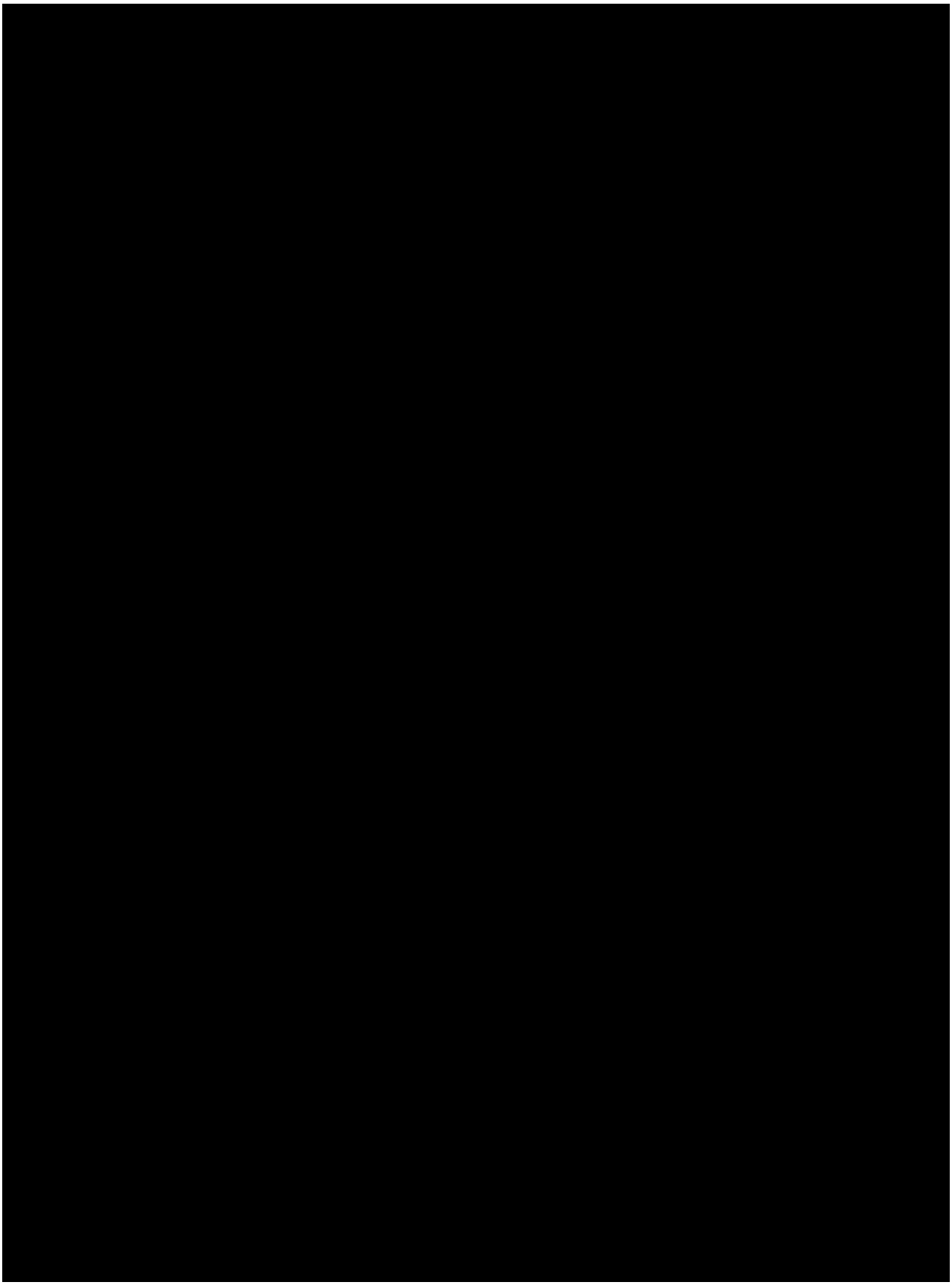
Kaplan-Meier time-to-event curves will be presented by treatment group. Median survival will be estimated using the KM method. Confidence intervals for median survival time will be calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).

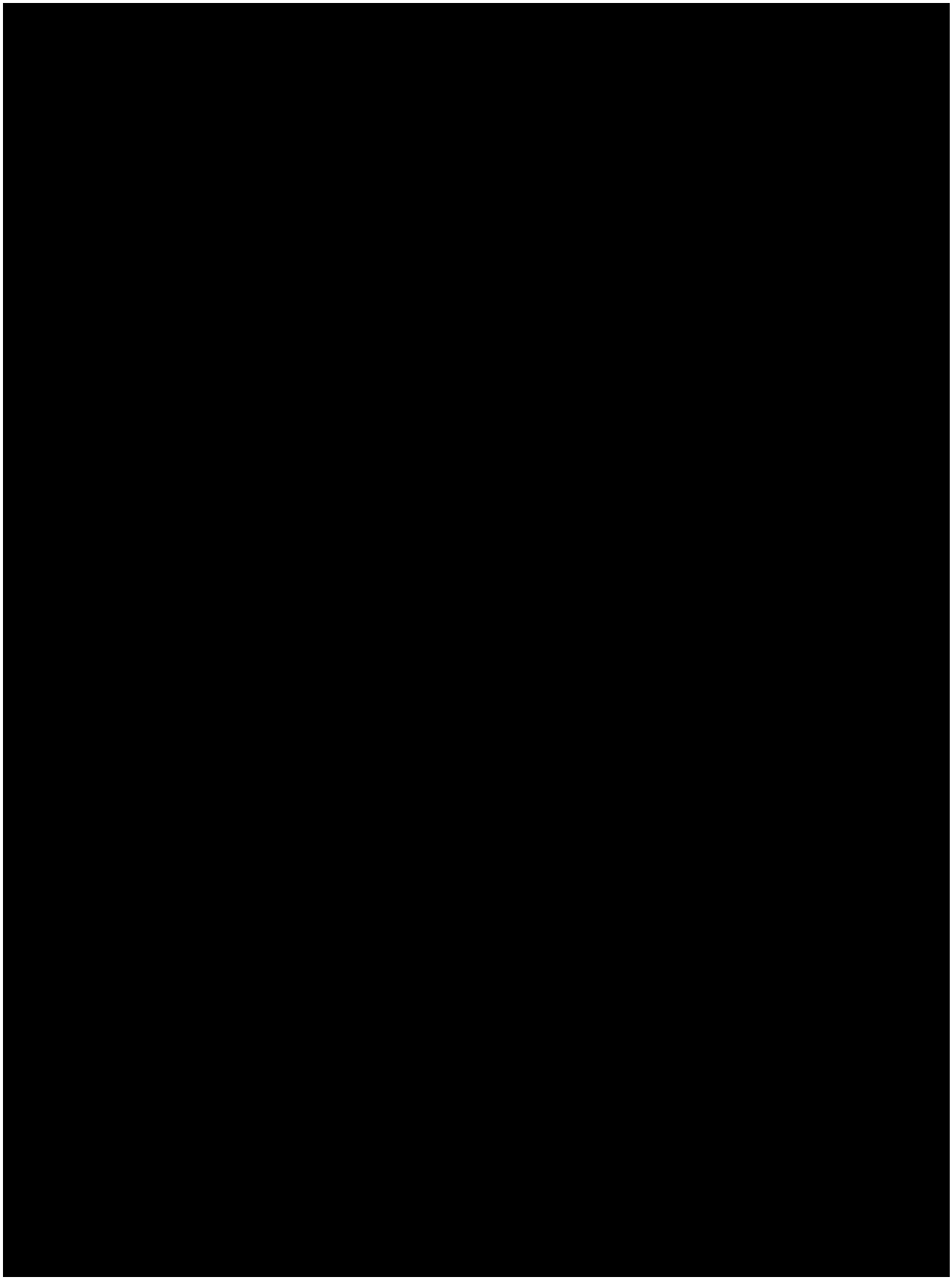
The ITT population will be used for the analysis of OS.

A sensitivity analysis of OS using PP population will be provided. The sensitivity analysis of OS will be analyzed using the rank-preserving structural failure time method to adjust the bias in OS due to crossover.

Due to the early study termination, the number of deaths observed was limited; therefore, the OS analyses will not be performed. A listing of deaths will be provided instead.

[redacted]





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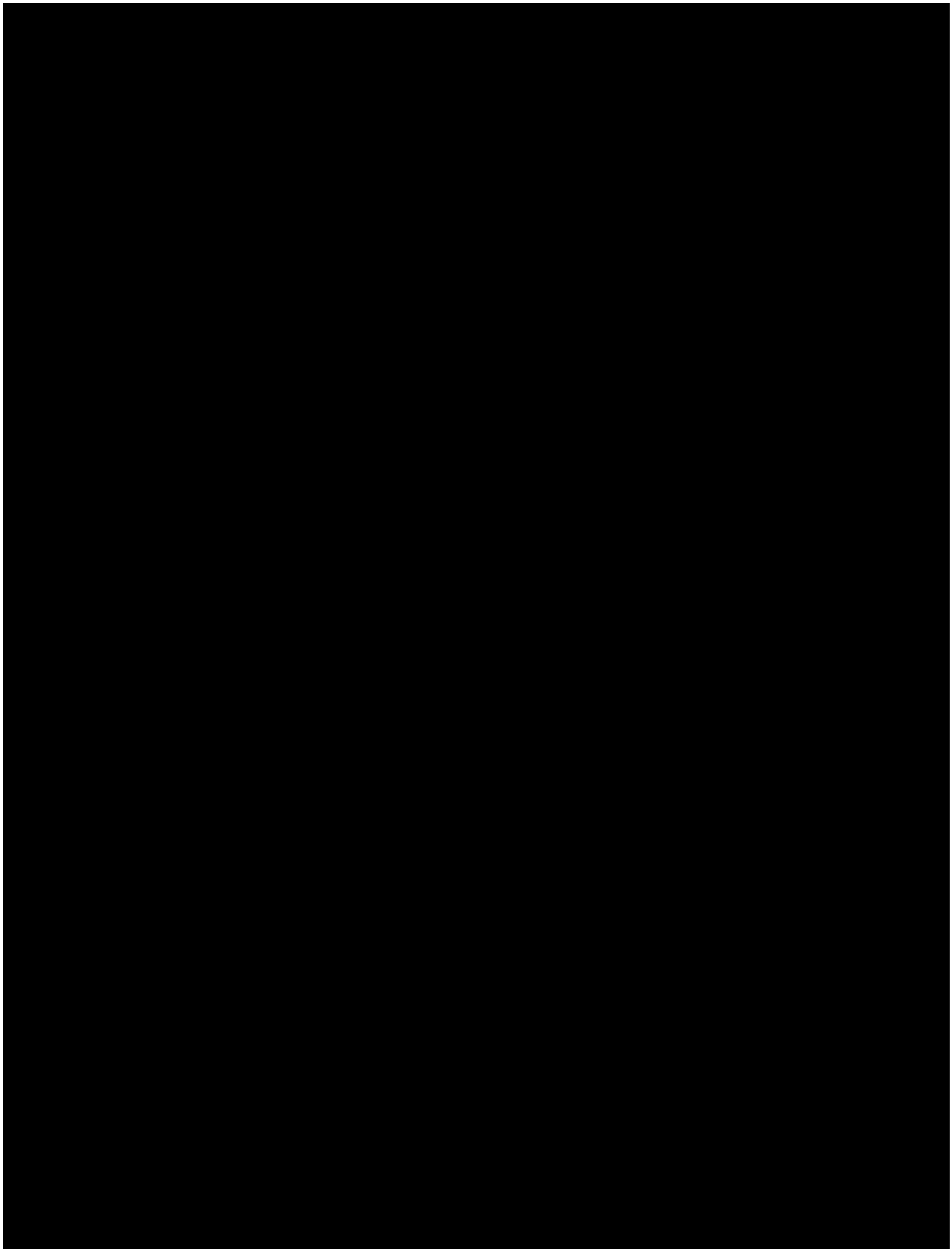
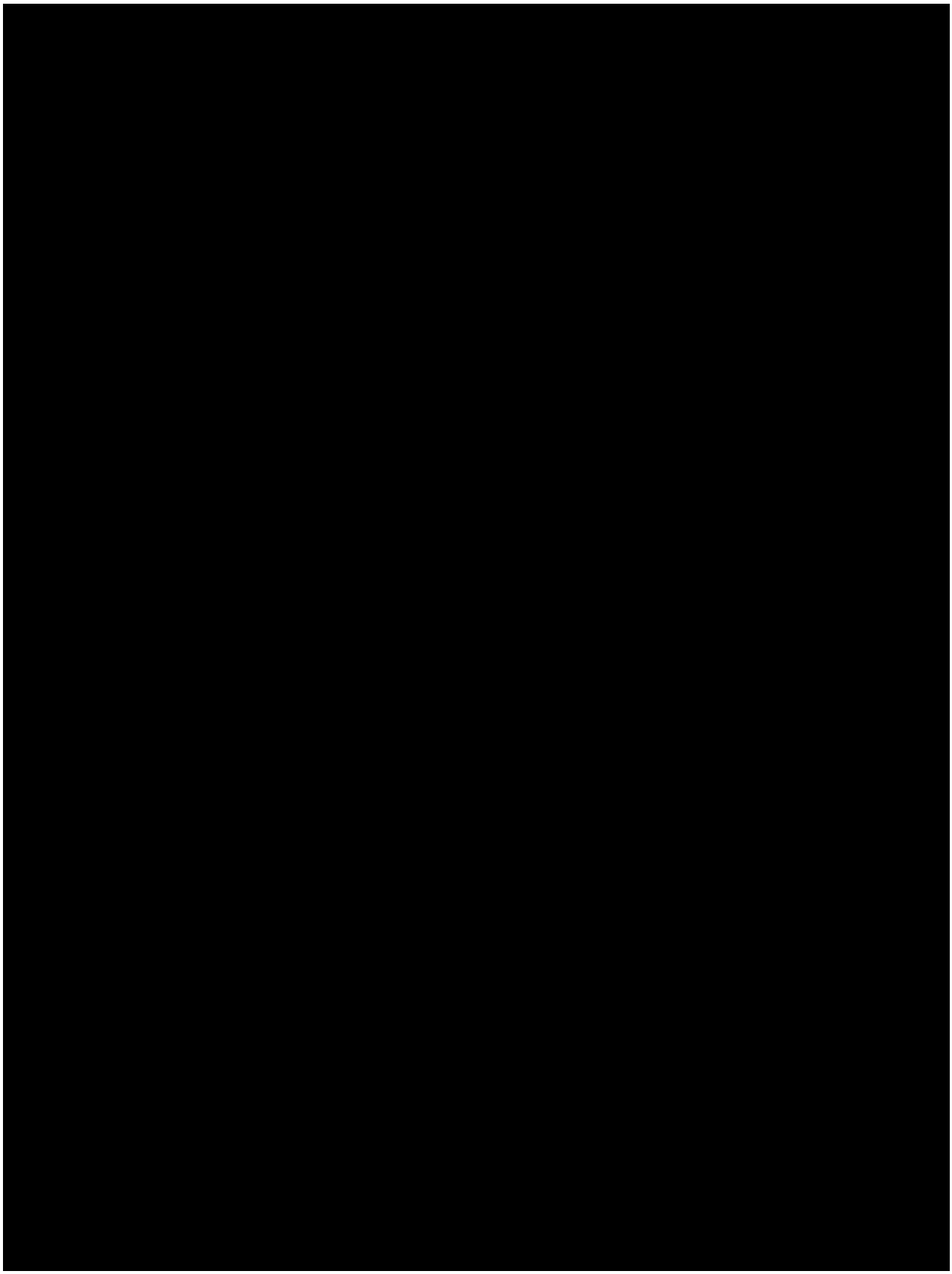




9. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

9.1. General Considerations

The safety analyses, including frequency and severity of AEs and SAEs and mean change and percentage change in vital signs, ECGs, and lab parameters, will be summarized by treatment group in 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 PTs reported on relatively few participants.

Safety analyses for treatment comparisons will exclude data collected after treatment crossover. Data post-treatment crossover will be analyzed separately and descriptively without any treatment comparisons. Day 1 of crossover will be used for the crossover participants in the crossover phase.

9.2. Adverse Events

9.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after the first dose of study drug until 30 to 35 days after the last 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. For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE v5. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

The subset of AEs considered by the investigator to be related to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study

drug, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, serious TEAEs will also be tabulated.

To summarize TEAEs using the life-table method, the time to first occurrence of a TEAE is defined as the interval between the date of first dose of study drug and the date of the first occurrence of a TEAE. Participants who have not experienced a TEAE at the time of analysis will be right-censored at the earlier of 30 to 35 days after the last dose of study drug and the date of last study visit through the end of safety follow-up. The effective sample size is defined as the number of participants at the beginning of interval minus half the participants censored in the interval. The conditional proportion is calculated as the number of first events divided by the effective sample size in the interval. If participants have missing or partial last dose dates of study drug, the partial or missing dates will be handled using the rules explained in Section 4.1.5. Any missing onset date of a TEAE will be handled according the following rules:

- If completely missing, then Day 1 will be used.
- If only the day is missing, then the first day of the month or Day 1, whichever is later, will be used.
- If both the month and day are missing, then 01 JAN of the year or Day 1, whichever is later, will be used.

9.2.2. Adverse Events of Special Interest

The following TEAEs, regardless of seriousness, will be tabulated by MedDRA PT for the safety population for each treatment group.

- Colitis
- Diarrhea of Grade 2 or higher
- Rash of Grade 2 or higher
- Pneumonitis
- Dermatitis exfoliative
- Intestinal perforation
- Cytomegalovirus infection
- Herpes simplex infection, including oral herpes and genital herpes as AE terms
- Herpes (varicella) zoster virus infection, including herpes zoster, shingles, and VZV as AE terms
- Pneumocystis jirovecii infection
- ALT increased $\geq 5 \times$ ULN
- AST increased $\geq 5 \times$ ULN

Adverse events of special interest should be captured in the eCRF.

The time to onset of the first occurrence of each AESI will be analyzed using the KM method. Median time to onset of the first occurrence of each AESI will be estimated by the KM method. Participants with no AESI at the time of analysis will be censored at the time of analysis.

The longest duration of AESI will be analyzed using the KM method for participants in the safety population with at least 1 occurrence of the AESI. The median longest duration of each AESI will be estimated by the KM method. Participants whose AESI was not resolved at the time of analysis will be censored at the time of the analysis. Participants with nonserious TEAEs not resolved by 35 days after the end-of-treatment visit will be censored at 35 days after the end-of-treatment visit.

Two consecutive AESIs with different toxicity grades but with the start date of the later AESI overlapped with the end date of the previous AESI are considered as 1 AESI in calculating the duration of AESI.

9.2.3. Adverse Event Summaries

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

- Number (%) of participants who had any TEAEs
- Number (%) of participants who had any serious TEAEs
- Number (%) of participants who had any Grade 3 or higher TEAEs
- Number (%) of participants who had any TEAEs related to parsaclisib
- Number (%) of participants who had any TEAEs related to ruxolitinib
- Number (%) of participants who had any TEAEs related to parsaclisib or ruxolitinib
- Number (%) of participants who temporarily interrupted parsaclisib because of TEAEs
- Number (%) of participants who temporarily interrupted ruxolitinib because of TEAEs
- Number (%) of participants who permanently discontinued parsaclisib because of TEAEs
- Number (%) of participants who permanently discontinued ruxolitinib because of TEAEs
- Number (%) of participants who had parsaclisib dose reductions because of TEAEs
- Number (%) of participants who had ruxolitinib dose reductions because of TEAEs
- Number (%) of participants who had any fatal TEAEs

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

- Summary of TEAEs by MedDRA SOC and PT
- Summary of TEAEs by MedDRA PT in decreasing order of frequency
- Summary of TEAEs by MedDRA SOC, PT, and CTCAE grade category
- Summary of Grade 3 or higher TEAEs by MedDRA SOC and PT
- Summary of Grade 3 or higher TEAEs by MedDRA PT in decreasing order of frequency
- Summary of serious TEAEs by MedDRA SOC and PT
- Summary of serious TEAEs by MedDRA PT in decreasing order of frequency
- Summary of parsaclisib/placebo treatment-related TEAEs by MedDRA SOC and PT
- Summary of ruxolitinib treatment-related TEAEs by MedDRA SOC and PT
- Summary of parsaclisib/placebo/ruxolitinib treatment-related TEAEs by MedDRA SOC and PT
- Summary of parsaclisib/placebo treatment-related TEAEs by MedDRA PT in decreasing order of frequency
- Summary of ruxolitinib treatment-related TEAEs by MedDRA PT in decreasing order of frequency
- Summary of parsaclisib/placebo treatment-related TEAEs by MedDRA SOC, PT, and CTCAE grade category
- Summary of ruxolitinib treatment-related TEAEs by MedDRA SOC, PT, and CTCAE grade category
- Summary of Grade 3 or higher parsaclisib/placebo treatment-related TEAEs by MedDRA SOC and PT
- Summary of Grade 3 or higher ruxolitinib treatment-related TEAEs by MedDRA SOC and PT
- Summary of parsaclisib/placebo treatment-related serious TEAEs by MedDRA SOC and PT
- Summary of ruxolitinib treatment-related serious TEAEs by MedDRA SOC and PT
- Summary of TEAEs with a fatal outcome by MedDRA SOC and PT
- Summary of TEAEs leading to parsaclisib/placebo dose reduction by MedDRA SOC and PT
- Summary of TEAEs leading to ruxolitinib dose reduction by MedDRA SOC and PT
- Summary of TEAEs leading to parsaclisib/placebo dose interruption by MedDRA SOC and PT

- Summary of TEAEs leading to ruxolitinib dose interruption by MedDRA SOC and PT
- Summary of TEAEs leading to discontinuation of parsaclisib/placebo by MedDRA SOC and PT
- Summary of TEAEs leading to discontinuation of ruxolitinib by MedDRA SOC and PT
- Summary of TEAEs by MedDRA PT: life-table method
- Summary of TEAEs by MedDRA SOC and PT: life-table method
- Summary of treatment-emergent AESIs by MedDRA PT
- Median time to the first onset of treatment-emergent AESIs by MedDRA PT
- Median longest duration of treatment-emergent AESIs by MedDRA PT

9.3. Clinical Laboratory Tests

9.3.1. Laboratory Value Definitions

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

Laboratory test values will be assessed for severity based on the numerical component of CTCAE v5.

9.3.2. Laboratory Value Summaries

All test results and associated normal ranges from central laboratories will be reported in SI units. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units.

When there are multiple nonmissing laboratory values for a participant's particular test at a scheduled visit, central laboratory values have higher priority over local laboratory values. If a tie still exists, the laboratory value with the smallest laboratory sequence number will be used in by-visit summaries.

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

A table for the number of participants with abnormal ALT, AST, bilirubin, and creatinine will be tabulated by treatment group.

For test results that will be summarized with available normal ranges, the number and percentage of participants with laboratory values being low (but never high), normal, high (but never low), and both low and high will be calculated for each test.

Severity grades will be assigned to laboratory test values based on the numerical component of CTCAE v5. Shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of participants in the baseline category. The number of participants who experienced worsening of laboratory abnormalities will be summarized by maximum severity.

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

9.3.3. Potential Hy's Law Events

Participants with elevated ALT or AST > 3 × ULN range and alkaline phosphatase < 2 × ULN range accompanied by total bilirubin > 2 × ULN range at the same visit will be listed by treatment group.

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, temperature, respiratory rate, and weight will be summarized descriptively.

Normal ranges for vital signs are defined in Table 5. For participants exhibiting vital sign abnormalities, the abnormal values will be listed along with their assigned treatment group. Alert vital signs are defined as an absolute value outside the defined normal range and percentage change greater than 25%. Note that the definition of alert vital signs does not apply for body temperature and weight. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 5: Normal Ranges for Vital Sign Values

Parameter	High Threshold	Low Threshold
Systolic blood pressure	≤ 155 mmHg	≥ 85 mmHg
Diastolic blood pressure	≤ 100 mmHg	≥ 40 mmHg
Pulse	≤ 100 bpm	≥ 45 bpm
Temperature	≤ 38°C	≥ 35.5°C
Respiratory rate	≤ 24 breaths/min	≥ 8 breaths/min

9.5. Electrocardiograms

Twelve-lead ECGs including PR, QT, QRS, RR, QTc, QTcB, and QTcF intervals will be obtained for each participant during the study. Values at each scheduled visit, change, and percentage change from baseline will be summarized for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of parsaclisib, placebo, or ruxolitinib.

Normal ranges for ECG values are defined in Table 6. Electrocardiogram values will also be considered abnormal if the absolute percentage change from baseline is more than 25% (30% for QRS interval). Participants exhibiting ECG abnormalities will be listed with study visit and assigned treatment group. Abnormal values for participants with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed. Outliers of QT and QTc values, defined as absolute values > 500 milliseconds, ≥ 480 milliseconds, and > 450 milliseconds for each parameter or change from baseline > 30 milliseconds and > 60 milliseconds for each parameter, will be summarized.

Table 6: Normal Ranges for Electrocardiogram Intervals

Parameter	High Threshold	Low Threshold
PR	≤ 220 ms	≥ 75 ms
QT	≤ 500 ms	≥ 300 ms
QRS	≤ 120 ms	≥ 50 ms
QTc	≤ 450 ms	≥ 295 ms
RR	≤ 1330 ms	≥ 600 ms

10. INTERIM ANALYSES

10.1. Overview of Interim Analyses

There will be 2 planned, nonbinding, interim analyses conducted for futility for this study, based on the first 30% of participants enrolled in the study. The first interim analysis will be conducted when the first 30% of the planned randomized participants (approximate 32 in each treatment group) reach Week 12 assessments of spleen volume and MFSAF TSS or discontinue from treatment. Based on the results of this interim analysis, the DMC may recommend to terminate the study, continue the study with no changes to enrollment, or continue the study with no further enrollment permitted until review of the second interim analysis.

The second interim analysis will be initiated when the first 30% of the planned randomized participants reach their Week 24 assessments of spleen volume and MFSAF TSS or have discontinued from treatment. The DMC may recommend to either terminate the study for futility or continue the study, based on the results of this analysis.

At the interim analyses for Week 12 and Week 24 data, MFSAF TSS will be tested for futility only if spleen volume does not cross the futility boundary.

10.2. Data Cutoff for Interim Analysis

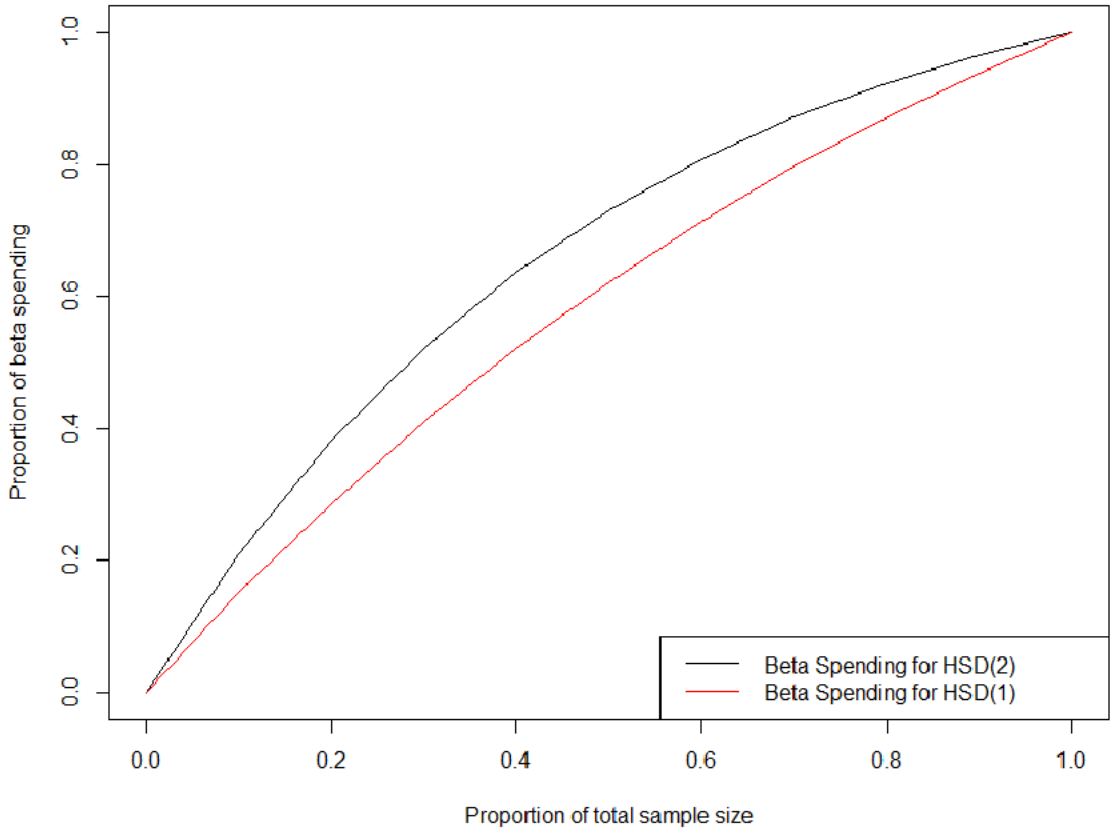
For analyses of spleen volume reduction and MFSAF TSS, a cutoff for clinical data used in the first interim analysis will be based on the date when the first 30% of the planned randomized participants (approximate 32 in each treatment group) reach Week 12 assessments of spleen volume and MFSAF TSS or discontinue from treatment. At the second interim analysis, the clinical cutoff date will be the date when the first 30% of the planned randomized participants reach Week 24 assessments of spleen volume and MFSAF TSS or discontinue from treatment.

10.3. Derivations and Calculations for Interim Analyses

For the second analysis of futility, an HSD spending function (Hwang et al 1990) with $\gamma = 2$ and an HSD spending function with $\gamma = 1$ will be used to allocate beta spending for spleen volume and MFSAF TSS, respectively. Figure 2 shows that the beta spending functions allocate minimal beta for the second interim analysis.

The first analysis of futility will use the same futility boundary as the second futility analysis, but no beta will be spent.

Figure 2: Beta Spending



10.4. Guidelines for Decision Rules

Table 7 and Table 8 provide the projected stopping rules if the interim analyses are conducted at the projected number of participants.

Table 7: Interim Analysis for Spleen Volume With HSD(2)

Number of Participants	Second Interim Analysis		Final Analysis	
	64		212	
Decision Outcome	**Stop for Futility**	**Continue to Test MFSAF TSS**	**Do Not Reject Null Hypothesis**	**Reject Null Hypothesis**
Z-statistic	≤ 0.16	> 0.16	≤ 1.96	> 1.96
One-sided p-value	≥ 0.436	< 0.436	≥ 0.025	< 0.025
Parsaclisib + ruxolitinib response rate[a]	≤ 5.9%	> 5.9%	≤ 12.7%	> 12.7%

[a] Assumes spleen volume response rate is 5% in ruxolitinib + placebo.

Table 8: Interim Analysis for MFSAF TSS With HSD(1)

Number of Participants	Second Interim Analysis		Final Analysis	
	64		212	
Decision Outcome	**Stop for Futility**	**Continue**	**Do Not Reject Null Hypothesis**	**Reject Null Hypothesis**
Z-statistic	≤ 0.22	> 0.22	≤ 1.96	> 1.96
One-sided p-value	≥ 0.413	< 0.413	≥ 0.025	< 0.025
Parsaclisib + ruxolitinib odds ratio (RR for 50 × to < 100 × 10^9/L, ≥ 100 × 10^9/L PLT)[a]	≤ 1.08 (11%, 16%)	> 1.08 (11%, 16%)	≤ 2.37 (21%, 29%)	> 2.37 (21%, 29%)

[a] Assumes TSS response rate for 50 × to < 100 × 10^9/L inclusive and ≥ 100 × 10^9/L platelet is 10% and 15% in ruxolitinib + placebo group.

Preplanned analyses of safety and efficacy will be provided to an independent DMC as specified in the DMC charter. The process by which the DMC will review data and make recommendations and decisions will be documented in the DMC charter.

11. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 9.

Table 9: Statistical Analysis Plan Versions

SAP Version	Date
Original	08 JAN 2021
Amendment 1	25 APR 2022
Amendment 2	11 SEP 2024

11.1. Changes to Protocol-Defined Analyses

In Section 9.5, QTcB and QTcF were collected by the sites and added to the analyses. In Appendix A, listings were added for both QTcB and QTcF.

11.2. Changes to the Statistical Analysis Plan

11.2.1. Amendment 1

- Section 5.4.1 was updated to clarify that participants with missing baseline assessments will be excluded from the ITT population for the responder analyses.
- In Section 7.1, the combination of DIPSS stratification levels at the time of interim analyses were added.
- In Section 7.3.1 and Section 7.4.2.2, the nonevaluable definitions for the primary endpoint analysis of spleen volume and secondary endpoint analysis of MFSAF TSS, respectively, were added.
- In Section 7.4.2, the window for deriving MFSAF TSS at Week 24 was modified to capture the assessments from the last week before participants return the device.
- Incorporation of administrative changes. Other minor, administrative changes and changes according to the Protocol Amendment 1 were incorporated throughout the SAP.

11.2.2. Amendment 2

- In Section 5, Section 7.3.3, Section 7.4, and Section 7.5, language was added to indicate that supportive, sensitivity analyses as well as some efficacy analyses with immature data will not be performed due to due to the early study termination.
- In Section 9, box-and-whisker plot was replaced by line plot for HGB, platelet counts, leukocytes, and neutrophils for readability.
- In Appendix A, numbers of the tables, figures, and listings were updated to keep them consistent with the numbering in the latest table, figure, and listing standard shells, and to align with updated data analysis based on the termination of the study. A shift table for bone marrow fibrosis was added to explore the treatment effect on the bone marrow fibrosis.
- Other, minor, administrative changes have been incorporated throughout the SAP.

12. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

Efron B. The efficiency of Cox's likelihood function for censored data. J Am Stat Assoc 1977;72:557-565.

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Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of Type I error probability spending functions. Stat Med 1990;9:1439-1445.

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Thiele J, Kvasnicka HM, Facchetti F, Franco V, van der Walt J, Orazi A. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica 2005;90:1128-1132.

APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures, and listings for the CSR. Shells are provided in a separate document for tables that are not in the Standard Safety Tables v1.9.

The lists of tables, figures, and listings are to be used as guidelines. Modifications of the lists that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population	Standard
Baseline and Demographic Characteristics			
1.1 Disposition			
1.1.1	Analysis Populations	ITT	X
1.1.2	Summary of Participant Disposition	ITT	X
1.1.3	Summary of Number of Participants Enrolled by Country and Site	ITT	X
1.1.4	Summary of Protocol Deviations	ITT	X
1.2 Demography and Baseline Characteristics			
1.2.1	Summary of Demographics and Baseline Characteristics	ITT	X
1.3 Baseline Disease Characteristics			
1.3.1	Summary of Baseline Disease Characteristics	ITT	
1.3.2	Summary of Myelofibrosis History	ITT	
1.3.3	Summary of Myelofibrosis Screening Symptom Score	ITT	
1.3.4	Summary of Prior Systemic Cancer Therapy by WHO Drug Class and Preferred Term	ITT	X
1.4 Prior Medication and Concomitant Medication			
1.4.1	Summary of Prior Medications	ITT	X
1.4.2	Summary of Concomitant Medications	ITT	X
1.4.3	Summary of Prior Ruxolitinib History	ITT	
1.5+ Others			
1.5.1	Summary of General Medical History	ITT	X
Efficacy			
2.1 Primary Efficacy			
2.1.1.1	Cochran-Mantel-Haenszel Test of Proportion of Participants With ≥ 25% Reduction in Spleen Volume at Week 12 and Week 24	ITT	
2.2 Secondary Efficacy			
2.2.1.4	Summary of Spleen Volume by Visit	ITT	
2.2.2.1	Cochran-Mantel-Haenszel Test of Proportion of Participants With ≥ 50% Reduction in MFSAF v4.0 Total Symptom Score at Week 12 and Week 24	ITT	
2.2.2.3	Time to the First ≥ 50% Reduction in MFSAF v4.0 Total Symptom Score	ITT	
2.2.2.4	Summary of MFSAF v4.0 Total Symptom Score Using 7-Day Window by Visit	ITT	
2.2.2.5.1	Summary of MFSAF v4.0 Individual Symptom Scores by Visit – Fatigue	ITT	
2.2.2.5.2	Summary of MFSAF v4.0 Individual Symptom Scores by Visit – Night Sweats	ITT	
2.2.2.5.3	Summary of MFSAF v4.0 Individual Symptom Scores by Visit – Itchiness	ITT	
2.2.2.5.4	Summary of MFSAF v4.0 Individual Symptom Scores by Visit – Abdominal Discomfort	ITT	
2.2.2.5.5	Summary of MFSAF v4.0 Individual Symptom Scores by Visit – Pain Under Left Ribs	ITT	
2.2.2.5.6	Summary of MFSAF v4.0 Individual Symptom Scores by Visit – Early Satiety	ITT	
2.2.2.5.7	Summary of MFSAF v4.0 Individual Symptom Scores by Visit – Bone Pain	ITT	
2.2.2.6	Summary of MFSAF v4.0 Spleen-Related Symptom Scores by Visit	ITT	

Table No.	Title	Population	Standard
2.2.3.1	Summary of Proportion of Participants With ≥ 25% Reduction in Spleen Volume	ITT	
2.2.3.2	Summary of Response Categories for MFSAF v4.0 Total Symptom Score by Visit	ITT	
[redacted]			
Safety			
3.1 Dose Exposure			
3.1.1	Summary of Exposure and Duration of Exposure to Parsaclisib/Placebo	Safety	X
3.1.2	Summary of Exposure and Duration of Exposure to Ruxolitinib	Safety	X
3.1.3	Summary of Parsaclisib Compliance	Safety	X
3.2 Adverse Events			
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	Safety	X
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.5	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and CTCAE Grade Category	Safety	X

Table No.	Title	Population	Standard
3.2.6	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.7	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.8	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.9	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.10.1	Summary of Parsaclisib/Placebo Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.10.2	Summary of Ruxolitinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.10.3	Summary of Parsaclisib/Placebo/Ruxolitinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.11.1	Summary of Parsaclisib/Placebo Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.11.2	Summary of Ruxolitinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety	X
3.2.13.1	Summary of Parsaclisib/Placebo Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and CTCAE Grade Category	Safety	X
3.2.13.2	Summary of Ruxolitinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and CTCAE Grade Category	Safety	X
3.2.14.1	Summary of Grade 3 or Higher Parsaclisib/Placebo Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.14.2	Summary of Grade 3 or Higher Ruxolitinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.15.1	Summary of Parsaclisib/Placebo Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.15.2	Summary of Ruxolitinib Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.16	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.18.1	Summary of Treatment-Emergent Adverse Events Leading to Parsaclisib/Placebo Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.18.2	Summary of Treatment-Emergent Adverse Events Leading to Ruxolitinib Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.19.1	Summary of Treatment-Emergent Adverse Events Leading to Parsaclisib/Placebo Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.19.2	Summary of Treatment-Emergent Adverse Events Leading to Ruxolitinib Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.20.1	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Parsaclisib/Placebo by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.20.2	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Ruxolitinib by MedDRA System Organ Class and Preferred Term	Safety	X
3.2.22	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term: Life-Table Method	Safety	X

Table No.	Title	Population	Standard
3.2.23	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term: Life-Table Method	Safety	X
3.2.24.1	Summary of Treatment-Emergent Adverse Events of Special Interest by MedDRA Preferred Term	Safety	X
3.2.24.2	Kaplan-Meier Estimates of Time to the First Onset of Treatment-Emergent Adverse Events of Special Interest by MedDRA Preferred Term	Safety	X
3.2.24.3	Kaplan-Meier Estimates of Longest Duration of Treatment-Emergent Adverse Events of Special Interest by MedDRA Preferred Term	Safety	X
3.3 Laboratory			
3.3.1.1	Summary of Laboratory Values - Hematology	Safety	X
3.3.1.2	Summary of Laboratory Values - Chemistry	Safety	X
3.3.1.3	Summary of Laboratory Values - Coagulation	Safety	X
3.3.3.1	Shift Summary of Hematology Laboratory Values in CTC Grade - to the Worst Abnormal Value	Safety	X
3.3.3.2	Shift Summary of Chemistry Laboratory Values in CTC Grade - to the Worst Abnormal Value	Safety	X
3.3.3.3	Shift Summary of Coagulation Laboratory Values in CTC Grade - to the Worst Abnormal Value	Safety	X
3.3.3.4	Treatment-Emergent Worsening of Laboratory Abnormalities - Hematology	Safety	X
3.3.3.5	Treatment-Emergent Worsening of Laboratory Abnormalities - Chemistry	Safety	X
3.3.3.6	Treatment-Emergent Worsening of Laboratory Abnormalities - Coagulation	Safety	X
3.3.4.1	Summary of Participants With Elevations in Liver Chemistry Tests	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 Weight	Safety	X
3.5 ECG			
3.5.1	Summary of PR Interval (ms) From 12-Lead ECG	Safety	X
3.5.2	Summary of QRS Interval (ms) From 12-Lead ECG	Safety	X
3.5.3	Summary of QT Interval (ms) From 12-Lead ECG	Safety	X
3.5.4	Summary of QTcB Interval (ms) From 12-Lead ECG	Safety	X
3.5.4.1	Summary of QTc Interval (ms) From 12-Lead ECG	Safety	X
3.5.5	Summary of QTcF Interval (ms) From 12-Lead ECG	Safety	X
3.5.6	Summary of RR Interval (ms) From 12-Lead ECG	Safety	X
3.5.8	Summary of Outliers of QT and QTc Interval Values (ms) From 12-Lead ECG	Safety	X
3.5.9	Summary of Clinically Significant ECG Abnormalities	Safety	X

Figures

Figure No.	Title
4.1 Primary Efficacy	
4.1.2	Forest Plot for Spleen Volume Reduction of ≥ 25% at Week 24 by Subgroup
4.2 Secondary Efficacy	
4.2.2	Kaplan-Meier Estimates of Time to the First ≥ 50% Reduction in MFSAF v4.0 Total Symptom Score
4.2.5	Plot of Percentage Change From Baseline in MFSAF v4.0 Total Symptom Score at Each Visit
[redacted]	

Figure No.	Title
4.3 Adverse Events	
4.3.1	Kaplan-Meier Estimates of Time to the First Onset of Treatment-Emergent Adverse Events of Special Interest by MedDRA Preferred Term
4.3.2	Kaplan-Meier Estimates of Duration of Treatment-Emergent Adverse Events of Special Interest by MedDRA Preferred Term
4.6 Laboratory Data	
4.6.1	Line Plot of Selected Laboratory Values by Study Visit

Listings

Listing No.	Title
2.1 Discontinued Participants (Participant Disposition)	
2.1.1	Participant Enrollment and Disposition Status
2.1.3	Participant Inclusion and Exclusion Criteria Violations
2.2 Protocol Deviations	
2.2.1	Protocol Deviations
2.3 Data Excluded From [redacted] Efficacy, and/or Safety Analyses	
2.3.1	Analysis Population
2.3.2	Crossover Participants
2.4 Demographic and Baseline Characteristics (Including Prior and Concomitant Medications)	
2.4.1	Demographic and Baseline Characteristics
2.4.2.1	Disease History
2.4.2.2	Prior Radiation Treatment
2.4.2.3	Prior Systemic Therapy for MF Other Than Ruxolitinib
2.4.2.4	Prior Surgery or Surgical Procedure
2.4.3	Medical History
2.4.4	Prior and Concomitant Medication
2.5 Drug Compliance	
2.5.1	Study Drug Compliance of Parsaclisib
2.5.2	Study Drug Administration of Parsaclisib/Placebo
2.5.4	Study Drug Administration of Ruxolitinib
2.6 Efficacy	
2.6.1	Spleen Volume
2.6.2	MFSAF v4.0 Total Symptom Score
2.6.3	Death
[redacted]	
2.7 Adverse Events	
2.7.1	Adverse Events
2.7.2	Serious Adverse Events
2.7.3	Grade 3 or Higher Adverse Events

Listing No.	Title
2.7.4	Fatal Adverse Events
2.7.5	Parsaclisib/Placebo Treatment-Related Adverse Events
2.7.6	Adverse Events Leading to Interruption, Reduction, or Discontinuation of Parsaclisib or Ruxolitinib
2.8 Laboratory, ECG, and Vital Signs Data	
2.8.1.1	Clinical Laboratory Values – Hematology
2.8.1.1.1	Abnormal Clinical Laboratory Values – Hematology
2.8.1.2	Clinical Laboratory Values – Chemistry
2.8.1.2.1	Abnormal Clinical Laboratory Values – Chemistry
2.8.1.4	Clinical Laboratory Values – Coagulation
2.8.1.4.1	Abnormal Clinical Laboratory Values – Coagulation
2.8.1.7	Potential Hy's Law Events
2.8.2.1	Vital Signs
2.8.2.2	Abnormal Vital Sign Values
2.8.2.3	Alert Vital Sign Values
2.8.3.1	12-Lead ECG Values
2.8.3.2	Abnormal 12-Lead ECG Values
2.8.3.3	Alert 12-Lead ECG Values
2.11 Physical Examination	
2.11.1	Physical Examinations