CLINICAL TRIAL PROTOCOL

A Phase 3, Randomized, Double-Blind, Active-Control Study of Pelabresib (CPI-0610) and Ruxolitinib vs. Placebo and Ruxolitinib in JAKi Treatment Naive MF Patients

Clinical Trial Protocol No:	CPI 0610-04
Clinical Trial Protocol Name:	MANIFEST-2
Version:	CTP v. 6.0, 04-Oct-2023
Clinical Trial Phase:	3
Product Name:	Pelabresib (CPI-0610)
Sponsor:	Constellation Pharmaceuticals, Inc. (Constellation Pharmaceuticals, Inc. is a fully owned subsidiary of MorphoSys U.S. Inc.)
Sponsor's Address:	470 Atlantic Avenue, Suite 1401 Boston, MA 02210 United States
EU Trial Number:	2020-001989-10
IND No:	147351

Sponsor Signatory:

[redacted] **Date**

[redacted] **Date**

Medical Monitor Name and Contact Information: Refer to the Investigator Site File

PRINCIPAL INVESTIGATOR'S SIGNATURE

I agree to conduct the clinical trial in accordance with this clinical trial protocol, the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the principles which have their origin in the Declaration of Helsinki, and applicable local regulations, including the following:

- Personally, conduct or supervise the investigation
- Ensure that an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), that complies with the requirements of GCP and local regulations, will be responsible for the initial and continuing review and approval of the clinical trial.
- Promptly report to the IRB/IEC (directly or through the sponsor) changes in the research activity, and new information that may adversely affect the safety of the patients or the conduct of the trial.
- Not implement any deviation from, or changes to the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to patients
- Inform patients, that the investigational medicinal product is being used for investigational purposes and ensure that the requirements relating to obtaining informed consent, including IRB/IEC review and approval thereof, are met.
- Report adverse events to the sponsor.
- Read and understand the information in the investigator's brochure.
- Ensure that sub-investigator(s) and other staff assisting in the conduct of the clinical trial are informed about their obligations in meeting this commitment.
- Maintain adequate and accurate records, provide direct access to those records for monitoring, audits, and inspection, and allow any regulatory agency to inspect the trial site.

Signature: ---------- **Date:** _____

(DD Mmm YYYY)

Name: ----------

PROTOCOL HISTORY

Version	Date	Reason for Change
Amendment 5 (Version 6.0)	04 Oct 2023	Updated contraception language; study design modifications
Amendment 4 (Version 5.2)	11 Apr 2023	Canada Only
Amendment 4 (Version 5.1)	30 Mar 2023	Germany Only
Amendment 4 (Version 5.0)	10 Mar 2023	Study design change
Amendment 3 (Version 4.4)	14 Oct 2022	Romania only
Amendment 3 (Version 4.3)	19 Jul 2022	Germany only
Amendment 3 (Version 4.2)	13 Apr 2022	Czech Republic only
Amendment 3 (Version 4.1)	15 Dec 2021	Germany only
Amendment 3 (Version 4.0)	15 Nov 2021	Study design change
Amendment 2 (Version 3.1)	24 Sep 2021	Czech Republic only
Amendment 2 (Version 3):	26 Feb 2021	Study design change
Amendment 1 (Version 2.2):	02 Dec 2020	France only
Amendment 1 (Version 2.1):	20 Nov 2020	United Kingdom only
Amendment 1 (Version 2):	14 Sep 2020	Study design change
Original Protocol (Version 1):	17 April 2020	Not applicable

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1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Constellation Pharmaceuticals

Name of Investigational Product: Pelabresib (CPI-0610)

Protocol Number: CPI 0610-04

Title of Study: A Phase 3, Randomized, Double-blind, Active-Control Study of Pelabresib (CPI-0610) and Ruxolitinib vs. Placebo and Ruxolitinib in JAKi Treatment Naive MF Patients

Primary Study Period (years):	**Phase of Development:**
Actual date first patient enrolled: 23 April 2021 Estimated date last patient will complete Week 24: Q3 2023	Phase 3

Objectives and Endpoints:

Primary	
• To determine the efficacy of pelabresib + ruxolitinib compared with placebo + ruxolitinib	• Splenic response at Week 24
Key Secondary	
• To determine the effect of pelabresib + ruxolitinib on the absolute change in TSS at Week 24 vs Baseline compared with placebo + ruxolitinib	• Absolute change in TSS at Week 24 compared to baseline
• To determine the efficacy of pelabresib + ruxolitinib compared with placebo + ruxolitinib	• TSS50 response at Week 24
Secondary	
• To determine the effect of pelabresib + ruxolitinib on the percent change in TSS at Week 24 vs Baseline compared with placebo + ruxolitinib	• Percent change in TSS at Week 24 compared to baseline
• To characterize the effects of pelabresib + ruxolitinib compared with placebo + ruxolitinib in the bone marrow	• Improvement in bone marrow fibrosis by at least 1 grade at Week 24 compared to baseline
• To determine the effect of pelabresib + ruxolitinib on the durability of splenic	• Splenic response at Week 48

response compared with placebo + ruxolitinib	
• To determine the effect of pelabresib + ruxolitinib on the durability of TSS response compared with placebo + ruxolitinib	• TSS50 response at Week 48
• To determine the effect of pelabresib + ruxolitinib on the durability of absolute change in TSS at Week 48 vs Baseline compared with placebo + ruxolitinib	• Absolute change in TSS at Week 48 compared to baseline
• To determine the effect of pelabresib + ruxolitinib compared with placebo + ruxolitinib on the rate of RBC transfusion over the first 24 weeks of treatment	• Rate of RBC transfusion over the first 24 weeks of treatment
• To determine the effect of pelabresib + ruxolitinib compared with placebo + ruxolitinib on the conversion from RBC transfusion dependence to independence	• Conversion from RBC transfusion dependence at baseline to independence
• To evaluate the PGIC at Week 24	• Categorical change of PGIC at Week 24 compared to Baseline
• To evaluate PFS in patients treated with pelabresib + ruxolitinib compared with placebo + ruxolitinib	• PFS
• To evaluate OS in patients treated with pelabresib + ruxolitinib compared with placebo + ruxolitinib	• OS
• To evaluate AML conversion in patients treated with pelabresib + ruxolitinib compared with placebo + ruxolitinib	• Proportion of patients with transformation to blast phase (AML)
• To determine the safety and tolerability of pelabresib + ruxolitinib compared with placebo + ruxolitinib	• AEs of all grades and SAEs
• To characterize the PK of pelabresib	• Population PK assessment including determination of exposure metrics and secondary parameters (i.e., $AUC_{0\text{-}t}$, T_{max}, C_{max}, $T_{1/2}$, Vd/F, CL/F)

• To characterize the effects, if any, of pelabresib on the PK of ruxolitinib	• Descriptive assessment of ruxolitinib plasma concentrations in the presence or absence of pelabresib
• To determine the effect of pelabresib + ruxolitinib on the duration of splenic response compared with placebo + ruxolitinib	• Duration of the splenic response
• To determine the effect of pelabresib + ruxolitinib on the modified TSS compared with placebo + ruxolitinib	• Modified TSS response at Week 24 (TSS score without the fatigue sub-domain)
• To determine the effect of pelabresib + ruxolitinib on the duration of TSS response compared with placebo + ruxolitinib	• Duration of the TSS50 response
• **Exploratory**	
• To determine the efficacy of pelabresib + ruxolitinib compared with placebo + ruxolitinib on the percent change in splenic volume at Week 24	• Percent change in splenic volume at Week 24
• To determine the effect of pelabresib + ruxolitinib compared with placebo + ruxolitinib on RBC transfusion dependence rate	• RBC transfusion dependence at Week 24
• To determine the effect of pelabresib + ruxolitinib compared with placebo + ruxolitinib on hemoglobin response	• Hemoglobin response
[redacted]	

[redacted]	
• To characterize the PD effects of pelabresib + ruxolitinib compared with placebo + ruxolitinib in the blood	• Post-treatment changes from baseline in circulating concentrations of cytokines • Post-treatment changes from baseline in the ratio of mutant to wild type *JAK2*, [redacted]
[redacted]	
• To determine the effect of pelabresib + ruxolitinib on the time to splenic response compared with placebo + ruxolitinib	• Time to first SVR35 response
[redacted]	

AE = adverse event; AML = acute myeloid leukemia; AUC = area under the plasma concentration-time curve; BET = bromodomain and extra terminal; C_{max}= maximal concentration; ECG = electrocardiogram; HRQOL = health related quality of life; [redacted]; MF = myelofibrosis; OS = overall survival; PD = pharmacodynamic; PFS = progression-free survival; PGIC = Patient Global Impression of Change; PK = pharmacokinetics; RBC = red blood cell; SAE = serious adverse event; $T_{1/2}$ = half-life; T_{max} = time to maximal concentration; TSS = total symptom score.

Study Design: This is a Phase 3, global, multicenter, randomized, double-blind, active-controlled study of pelabresib + ruxolitinib vs placebo + ruxolitinib in JAK inhibitor treatment naïve patients with primary MF (PMF), post-polycythemia vera (PV) MF (PPV-MF) or post-essential thrombocythemia (ET) MF (PET-MF).

Following screening eligible patients will be randomized in a 1:1 ratio to one of two treatment groups: 1) pelabresib + ruxolitinib (experimental group) or 2) placebo + ruxolitinib (control group). Patients will be assessed for the primary and key secondary endpoints, splenic and total symptom score (TSS) response, respectively, at Week 24. After 24 weeks, patients in the control group who have progressive disease by radiological parameters (increase in splenomegaly) may be treated with pelabresib + ruxolitinib provided that they remain eligible for the study.

Patient randomization will be stratified by the following factors:

- Dynamic International Prognostic Scoring System (DIPSS) risk category: Intermediate-1 vs. Intermediate-2 vs. High
- Platelet count: $> 200 \times 10^9$/L vs. $100 – 200 \times 10^9$/L
- Spleen volume: ≥ 1800 cm^3 vs. < 1800 cm^3

Number of patients (planned): Approximately 400 patients (200 in the pelabresib + ruxolitinib group and 200 in the placebo + ruxolitinib group) will be enrolled in the study.

Diagnosis and study population (key eligibility criteria): Eligible patients are adults who have a confirmed diagnosis of MF (PMF or PPV-MF or PET-MF) in accordance with the 2016 World Health Organization (WHO) criteria, have never received a JAKi for treatment of a myeloproliferative neoplasm, and are DIPSS risk category Intermediate-1 or higher.

Investigational product, dosage, and mode of administration:

Double-blind treatment (pelabresib or matching placebo) will be administered once daily (QD) for 14 consecutive days followed by a 7-day break, which is considered 1 cycle of treatment (1 cycle = 21 days). Ruxolitinib will be administered twice daily (BID) for all 21 days within each cycle.

The MANDATORY starting dose for the treatment regimen at Cycle 1 Day 1 will be pelabresib/placebo at 125 mg QD for all patients and ruxolitinib at 10 mg BID (for patients with baseline platelet count $100 – 200 \times 10^9$/L) or 15 mg BID (for patients with baseline platelet count $> 200 \times 10^9$/L) (5 mg BID lower than the recommended dose in the applicable approved package insert).

It is MANDATORY to increase the ruxolitinib dose by 5 mg BID at Cycle 2 Day 1 if platelet count is $>125 \times 10^9$/L and ANC is $> 0.75 \times 10^9$/L at Cycle 2 Day 1 and the patient did not have ≥ Grade 3 non-hematological toxicity in Cycle 1 that required dose interruption or reduction (regardless of percent change in spleen size by palpation from pre-treatment baseline).

In the case of lack of spleen response, the ruxolitinib dose may be increased according to the applicable approved package insert and local clinical practice starting at Cycle 3 Day 1 provided patients meet criteria for doing so. If these criteria are met, the ruxolitinib dose should be increased in 5 mg BID increments, not more frequently than once every cycle, to up to 25 mg BID. Pelabresib/placebo dose increase is only allowed from Cycle 5 Day 1 or thereafter provided that patients meet criteria for doing so. If these criteria are met, the pelabresib/placebo dose can be increased in 25 mg QD increments, not more frequently than once every 2 cycles, to a maximum dose of 175 mg QD. Both ruxolitinib and pelabresib/placebo doses cannot be increased in the same cycle.

If a patient experiences a treatment-emergent adverse event (TEAE), the doses of ruxolitinib and/or pelabresib/placebo may be down-titrated. The doses may be re-escalated after resolution of toxicities provided patients meet criteria for doing so.

Duration of treatment: Patients may receive blinded treatment in the study until disease progression or discontinuation or withdrawal from treatment, whichever occurs first, and will subsequently be followed for progression-free survival or overall survival. Patients who have enrolled in the control group (i.e., treated with placebo + ruxolitinib) and have progressive disease after 24 weeks of treatment by radiological parameters may be crossed over to receive the experimental treatment of pelabresib + ruxolitinib.

Statistical Considerations:

Analysis populations:

- Modified Intent-to-Treat (mITT) Population: All randomized patients who were administered at least one dose of study drug. This is the population for some sensitivity analysis on efficacy endpoints. All analyses using this population will be based on the treatment assigned by the Interactive Response Technology (IRT) system.
- Intent-to-Treat (ITT) Population: All randomized patients. This is the primary population for all efficacy endpoints. All analyses using this population will be based on the treatment assigned by the Interactive Response Technology (IRT) system.
- Safety Population: A subset of the ITT population that includes all randomized patients who were administered at least one dose of study drug. This population will be used for the safety analyses. All analyses using this population will be based on the treatment actually received.
- Per Protocol (PP) Population: A subset of the ITT population that includes patients who have received adequate exposure to on-study therapy and do not have any protocol deviations that could confound the interpretation of the primary analyses conducted on the ITT population. All protocol deviations or conditions leading to exclusion from the PP population will be specified in the statistical analysis plan (SAP). All analyses using this population will be based on the treatment received.
- PK/pharmacodynamic (PD) Population: All randomized and treated patients who have at least 1 evaluable sample for PK/PD analysis.

Efficacy analysis:

To ensure family-wise error rate is controlled at 5% (two-sided) the following endpoints will be tested hierarchically in the following order:

1. Primary Endpoint: SVR35 at week 24 using CMH test
2. Key Secondary Endpoint: Absolute change in TSS at Week 24 compared to baseline using ANCOVA model
3. Key Secondary Endpoint: TSS50 at Week 24 using CMH test

The probability of a splenic response at Week 24 will be estimated by calculating the splenic response rate, or the percentage of patients with a splenic response, at Week 24 for each of the two treatment groups. The response rate between the two treatment groups will be compared using a Cochran-Mantel-Haenszel (CMH) test controlling for baseline DIPSS (Intermediate-1 vs. Intermediate-2 vs. High), platelet count (100-200 $\times 10^9$/L vs. > 200 $\times 10^9$/L), and spleen volume ($\geq$ 1800 cm^3 vs. < 1800 cm^3).

An ANCOVA (Analysis of Covariance) model will be used to analyze the absolute change from baseline in TSS at Week 24. The dependent variable is change from baseline in TSS at Week 24, with treatment group as independent variable, baseline DIPSS (Intermediate-1 vs. Intermediate-2 vs. High), baseline platelet count (100-200 $\times 10^9$/L vs. > 200 $\times 10^9$/L) and baseline spleen volume (< 1800 cm^3 vs. $\geq$ 1800 cm^3) and the baseline TSS as covariates.

Similar to SVR35, the difference in proportion of TSS50 responders between Experimental Group and Control Group will be obtained using the CMH test controlling for the same strata used in SVR35 analysis.

Safety analysis:

Safety will be evaluated by incidence of TEAEs and by changes from baseline in physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory values using the population evaluable for safety. Exposure to study drug and reasons for discontinuation will also be summarized.

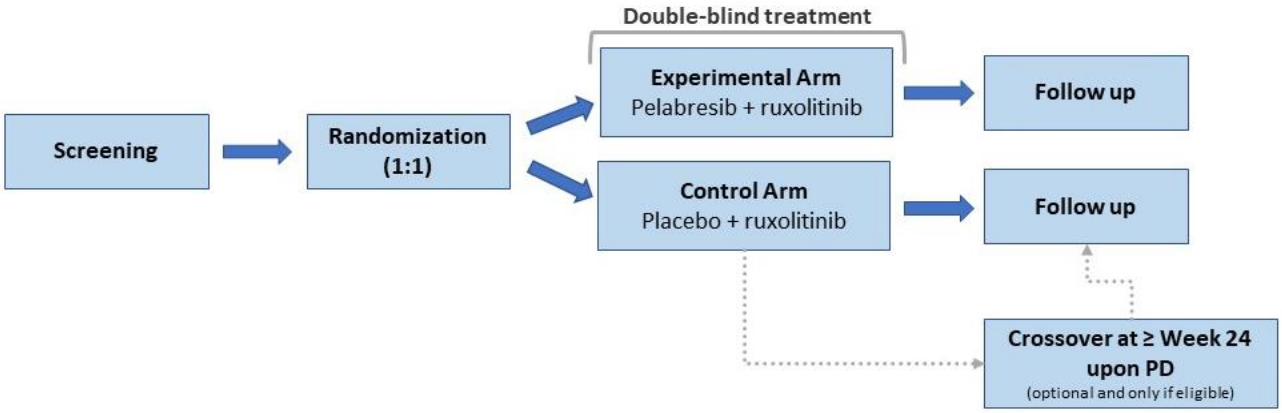
Sample size determination:

Assuming a splenic response rate of 62% in the experimental group and 29% in the control group, and assuming a TSS response rate of 57% in the experimental group, and 42.2% in the control group, a sample size of approximately 200 patients in each treatment group (approximately 400 patients in total) will provide > 99% power for testing the primary endpoint and 81% power for testing the key secondary endpoint TSS50 at the final analysis, using the 2-group continuity corrected χ^2 test with a 5% 2-sided significance level and accounting for 2% non-evaluable patients.

Data and Safety Monitoring Board (DSMB):

An independent DSMB will be used to review data to monitor patient safety in the study. Membership, roles, and responsibilities of the DSMB will be described in the DSMB charter.

1.2. Schema


Double-blind treatment
Screening
Randomization (1:1)
Experimental Arm
Pelabresib + ruxolitinib
Control Arm
Placebo + ruxolitinib
Follow up
Follow up
Crossover at ≥ Week 24 upon PD
(optional and only if eligible)

1.3. Schedule of Activities (SoA)

Procedure	Section	Screening Period	Treatment Period (including crossover)						Follow-Up Period[b]		
		Screening (within 28 days of C1D1)	C1 or initiation of crossover treatment[a]		C2-8	C9 and all odd cycles after[f]	C10 and all even cycles after	EOT (within 7 days after last dose of pelabresib/ placebo)	Safety F/U (30 days [±3d] after last dose of pelabresib/ placebo)	PD F/U (every 3 months [±14d] after last MRI/ CT scan)	Survival F/U (every 3 months [±14d] after PD)
			D1	D14 (±1d)	D1 (±3d)	D1 (±3d)	D1 (±3d)				
Informed consent	10.1.3	X									
Inclusion and exclusion criteria	5.1, 5.2	X									
Demographics	8.1	X									
Medical history	8.1	X									
Full PE and VS	8.3.2	X	X								
Targeted PE and VS	8.3.2			X	X	X		X			
Height	8.3.2	X									
Weight	8.3.2	X	X	X	X	X		X			
MF risk category	10.5	X									
Transfusion history	8.1	X	X		X	X	X	X		X	
ECOG status	8.3.3	X	X		X			X			
IWG-MRT response evaluation	10.7	X	X			Cycle 9 only					

Procedure	Section	Screening Period	Treatment Period (including crossover)						Follow-Up Period[b]		
		Screening (within 28 days of C1D1)	C1 or initiation of crossover treatment[a]		C2-8	C9 and all odd cycles after[f]	C10 and all even cycles after	EOT (within 7 days after last dose of pelabresib/ placebo)	Safety F/U (30 days [±3d] after last dose of pelabresib/ placebo)	PD F/U (every 3 months [±14d] after last MRI/ CT scan)	Survival F/U (every 3 months [±14d] after PD)
			D1	D14 (±1d)	D1 (±3d)	D1 (±3d)	D1 (±3d)				
12-lead ECG[c]	8.3.4	X	X		X (C2, C3, C5, C7 only)	X		X			
Serum or urine pregnancy test (WOCBP only)[d]	8.3.5	X	X		X	X	X	X and monthly thereafter until 184 days after the last dose of study drug			
Hematology	8.3.5	X	X (within 72 hrs of C1D1)[e]	X	X	X		X		X	
Clinical chemistry	8.3.5	X	X (within 72 hrs of C1D1)[e]	X	X	X		X			
Coagulation parameters	8.3.5	X	C3 D1, and every odd cycle thereafter					X			
Iron studies	8.3.5	X	C5 D1, C9 D1, and every 4 cycles thereafter								

Procedure	Section	Screening Period	Treatment Period (including crossover)						Follow-Up Period[b]		
		Screening (within 28 days of C1D1)	C1 or initiation of crossover treatment[a]		C2-8	C9 and all odd cycles after[f]	C10 and all even cycles after	EOT (within 7 days after last dose of pelabresib/ placebo)	Safety F/U (30 days [±3d] after last dose of pelabresib/ placebo)	PD F/U (every 3 months [±14d] after last MRI/ CT scan)	Survival F/U (every 3 months [±14d] after PD)
			D1	D14 (±1d)	D1 (±3d)	D1 (±3d)	D1 (±3d)				
HbA1c and serum lipid panel	8.3.5	X	Every 6 months after screening (follow the local approved ruxolitinib labeling for the frequency of lipid monitoring if different)					X			
TB testing	8.3.5	X (per local regulations)									
Assess hepatitis B/C, HIV, and COVID-19 risk and test if indicated	5.2	X									
MRI (or CT) scan	8.2.1	X	Every 12 weeks from C1 D1 (window ±14 days) irrespective of any delay in cycle due to drug hold until PD or initiation of another anti-cancer therapy MRI is preferred method. Method of assessment used at screening should remain consistent throughout study. Repeated at EOT only if PD has not been previously documented (or in the absence of PD, if imaging has not been performed within the previous 6 weeks).								
Bone marrow biopsy	8.2.1, Table 6	X (only if not done within 12 weeks of C1 D1)	Every 24 weeks (window ±14 days) from C1 D1 to Week 72, then every 48 weeks thereafter (window ±28 days), irrespective of any delay in cycle due to drug hold, and at EOT (EOT sample does not need to be collected if performed within previous 12 weeks), until PD or initiation of another anti-cancer therapy								
MFSAF v4.0	8.2.2	X (daily for at least 5 of 7 days before randomization)	Once daily (completed around the same time each day) until 12 weeks after EOT								
PGIC	8.2.2		Once weekly (completed on the same day each week) until 12 weeks after EOT								

Procedure	Section	Screening Period	Treatment Period (including crossover)						Follow-Up Period[b]		
		Screening (within 28 days of C1D1)	C1 or initiation of crossover treatment[a]		C2-8	C9 and all odd cycles after[f]	C10 and all even cycles after	EOT (within 7 days after last dose of pelabresib/ placebo)	Safety F/U (30 days [±3d] after last dose of pelabresib/ placebo)	PD F/U (every 3 months [±14d] after last MRI/ CT scan)	Survival F/U (every 3 months [±14d] after PD)
			D1	D14 (±1d)	D1 (±3d)	D1 (±3d)	D1 (±3d)				
EQ-5D	8.2.2	X (once weekly)	Once weekly (completed on the same day each week) until 12 weeks after EOT								
PK	8.6, Table 5		X	X	C3D1 and C7D1	X (C9 only)					
Biomarker sampling	8.7, Table 6		X	X		X (C9, C17 only)					
Randomization	6.3	X									
Pelabresib or placebo administration	6.1		QD for first 14 days of each cycle If dose increases on even cycle, odd cycle activities should be followed.								
Ruxolitinib administration	6.1		BID for all 21 days of each cycle If dose increases on even cycle, odd cycle activities should be followed.								
AE review	8.4		Throughout								
Concomitant medication review	8.1		Throughout								
Subsequent anti-MF therapy review	7.1								Throughout		

AE = adverse event; BID = twice daily; C = cycle; CT = computerized tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; F/U = follow-up; MFSAF = Myelofibrosis Symptom Assessment Form; MRI = magnetic resonance imaging; PD = progressive disease; PE = physical exam; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; QD = once daily; QTcF = Fridericia-corrected QT interval; TB = tuberculosis; VS = vital signs; WOCBP = women of childbearing potential.

Note: Laboratory assessments and other safety assessments must be performed predose when a window is specified.
Note: Assessments performed at unscheduled visits due to safety reasons are at the discretion of the Investigator.
a Patients who cross over should be re-consented at the initiation of crossover treatment. Details on the crossover part of the study are provided in Section 6.6.
b Follow-up visits may be conducted via telephone when clinic visits are not required. Patients who discontinue treatment for reasons other than documented disease progression as defined in Section 7.1 should have follow-up visits every 12 weeks to document response by imaging, and transfusion requirements until initiation of another anti-cancer therapy, disease progression, death, or the end of the study, whichever comes first (PD F/U period). Continuing ruxolitinib monotherapy as standard of care treatment after the discontinuation of treatment on study is not considered the initiation of another anti-cancer medication/therapy. Patients who discontinue study treatment for documented disease progression or start another anti-cancer medication/therapy should have a follow-up visit/phone call every 12 weeks to document overall survival (Survival F/U). Information on subsequent anti-MF medication will be collected in both PD F/U and Survival F/U periods.
c QTcF (Fridericia) is to be used at screening to evaluate eligibility per Section 5.1 and throughout the study to maintain consistency.
d For WOCBP, pregnancy testing (serum preferred) at Screening and at C1D1 before study drug administration; thereafter pregnancy testing can be either highly sensitive urine or serum testing at D1 of every Cycle before study drug administration, at EOT and thereafter at monthly intervals during 184 days after last dose of study drug; urine pregnancy testing may be conducted at home when clinic visits are not required. The Investigator must be informed immediately about the results of home pregnancy tests, and the results are to be recorded by the Investigator.
e Laboratory assessments for C1D1 do not need to be repeated, and screening values may be used, if performed within 72 hours of C1D1 assessments.
f After C9D1 patients may come in every odd cycle if they meet criteria listed in Section 8.

2. INTRODUCTION

2.1. Background

MF is a clonal myeloproliferative disease. It shares many of the characteristics of the other myeloproliferative diseases (essential thrombocythemia and polycythemia vera) but is characterized by more exaggerated abnormalities in megakaryocytes and by a more aggressive disease course with complications from cytopenias and transformation to acute leukemia (Ciurea et al., 2007). The megakaryocytes of patients with MF are hyperplastic, and this hyperplasia accounts for the thrombocytosis that may be seen early in the natural history of the disease. The hyperplastic megakaryocytes are also functionally abnormal. In the bone marrow, they release abnormal amounts of TGF-β, which stimulates the proliferation of fibroblasts (Kuter et al., 2007). The fibroblasts deposit collagen in the bone marrow, leading to the fibrosis that is a hallmark of this disease and that impairs normal hematopoiesis. The hyperplastic megakaryocytes also release a diverse array of cytokines that account for many of the constitutional symptoms of the disease. Many cytokines signal through the JAK-STAT pathway, which explains why JAKi have activity in this disease. In addition, approximately 50% of patients with MF have activating mutations in *JAK2* (Pikman et al., 2006; Tefferi et al., 2011). Regardless of the *JAK2* mutational status of patients, it is thought that patients with MF have deregulated JAK-STAT signaling, which is why they respond to JAKi therapy regardless of their mutational status. Irrespective of the presence of mutations, the JAK/STAT pathway has been implicated in the inflammatory state of MF and other myeloproliferative diseases. More recently, the elevated pro-inflammatory cytokines present in MF have also been linked to the NF-κB pathway (Kleppe et al., 2018). The resultant inflammation in MF has several downstream ramifications, including bone marrow fibrosis, constitutional symptoms and EMH. The bone marrow fibrosis and EMH are some of the key factors leading to anemia, one of the signature features of MF (Naymagon & Mascarenhas, 2017). In fact, at the time of diagnosis, approximately 40% of patients have anemia (defined as hemoglobin <10g/dL), and about 25% of patients require RBC transfusions (Tefferi et al., 2012). As MF progresses, virtually all patients end up developing anemia.

The only potentially curative treatment for MF is allogeneic HSCT, but HSCT is associated with high mortality rates and cannot be used in patients who are elderly and/or have multiple comorbidities (Gerds, 2016; Tefferi & Barbui, 2019; Vannucchi, 2011). The current approved treatment options for MF are JAKi (e.g., ruxolitinib and fedratinib); however, these agents have limited effects on underlying disease modification and bone marrow fibrosis. Both of these agents were associated with treatment-emergent new or worsening ≥ Grade 3 anemia, worsening transfusion dependence, and Grade ≥3 thrombocytopenia (FDA JAKAFI™ [ruxolitinib] label; FDA INREBIC™ [fedratinib] label). The need for frequent transfusions significantly reduces patient's quality of life and imposes additional risks for complications (Newberry et al., 2017). In addition, fedratinib is associated with more frequent gastrointestinal toxicities (e.g., diarrhea, nausea, and vomiting) and has a box warning for serious and fatal encephalopathy including Wernicke's (FDA INREBIC™ label). Thus, there remains a major unmet medical need to improve treatment options for patients with advanced MF.

Therapeutic agents developed in recent years that target epigenetic mechanisms of disease have shown promise in hematological malignancies (Kleppe et al., 2018). Pelabresib is a potent, oral, and selective small molecule that is currently being developed in patients with MF. Pelabresib belongs to the class of BETi. BET proteins are transcriptional regulators that control key oncogenic pathways, including NF-κB and TGF-β signaling, important drivers of inflammation and fibrosis, respectively, in MF. Pelabresib can potentially improve constitutional symptoms and spleen volumes and may elicit an effect on the underlying disease through its inhibitory effects on: (I) megakaryocyte differentiation and proliferation; (II) inflammatory cytokine expression and release via the NF-κB signaling pathway; (III) targeting genes of TGF-ß signaling, especially secretion of collagen by fibroblasts, and (IV) bone marrow fibrosis through inhibition of pro-fibrotic pathways (Kleppe et al., 2018; Nicodeme et al., 2010).

Pelabresib has been evaluated in three Phase 1 clinical studies in patients with various hematologic malignancies (lymphoma [Study 0610-01]; AML, MDS, or MDS/MPN [Study 0610-02]; or multiple myeloma [Study 0610-03]). Pelabresib monotherapy showed antitumor activity in patients with lymphoma, including patients with follicular lymphoma, T cell histiocyte rich B cell lymphoma, and NF-κB-dependent activated B cell diffuse large B cell lymphoma. In addition, BET target engagement, demonstrated by downregulation of *IL8* mRNA, was also achieved at well-tolerated doses in these patients. Refer to the Investigator's Brochure (IB) for more detailed information.

Thrombocytopenia reported in the Phase 1 studies was dose-dependent in both incidence and severity, reversible, and non-cumulative. The consistency and predictability of this finding, along with the observation that thrombocytopenia was a common finding with other BET inhibitors, led to the investigation of the effects of pelabresib on megakaryocytes and subsequently the inclusion of patients with MF in the ongoing global, multicenter, open label Phase 2 expansion portion of Study 0610-02 (MANIFEST; NCT02158858).

A detailed description of the chemistry, pharmacology, safety, and efficacy of pelabresib is provided in the IB (see Sections 3.1-3.4 for chemistry, Section 5.2 for pharmacology, and Section 5.3 for safety and efficacy).

2.2. Study Rationale

Preclinical studies suggest that a combination of a BETi and JAKi can result in synergistic reduction of splenomegaly, bone marrow fibrosis, and mutant cell burden (Kleppe et al., 2018). These findings support the potential complementary activity of pelabresib and a JAKi for MF treatment (Mascarenhas et al., 2021).

Pelabresib is currently being investigated in the Phase 2 MANIFEST study as a monotherapy in patients with MF who are refractory/intolerant to ruxolitinib, as an add-on to ruxolitinib in patients who have suboptimal or lost response to ruxolitinib, or in combination with ruxolitinib in JAKi treatment naïve patients with MF. Due in part to the effects on SVR and TSS observed in the Phase 2 MANIFEST study, along with the potential for disease-modifying effects, the Sponsor is evaluating pelabresib in this Phase 3 study in patients with MF who have never been treated with a JAKi or BETi.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of pelabresib may be found in the pelabresib Investigator's Brochure.

2.3.1. Risk Assessment

The following events are potential anticipated AEs with pelabresib:

- **Thrombocytopenia:** Thrombocytopenia has been the most consistent and predictable toxicity of pelabresib in patients enrolled in the Phase 1 and Phase 2 studies of pelabresib. In the three Phase I dose escalation clinical studies, this thrombocytopenia was dose-dependent in both incidence and severity, reversible (sometimes requiring 14 days off treatment), and non-cumulative. This protocol includes directions for dose interruption for hematologic toxicities.
- **Anemia, neutropenia, and lymphopenia:** Although AEs of anemia, neutropenia, and decreased lymphocyte count have occurred in patients treated with pelabresib in the Phase 1 and Phase 2 studies; these cases have been infrequent and without apparent relationship to pelabresib dose. The frequency of opportunistic infections has been consistent with that expected in the patient populations treated. This protocol includes directions for dose interruption for hematopoietic cytopenias and infections. Support with antibiotics and transfusions should follow standard medical practice and institutional guidelines.
- **Gastrointestinal toxicity:** The clinical experience with pelabresib in the Phase 1 and Phase 2 studies to date demonstrates a GI toxicity profile. Nausea, vomiting, and diarrhea have been among the most frequently observed events. Patients with impaired GI function or GI diseases (including active IBD) that may alter the absorption of study drug are ineligible to participate in clinical studies of pelabresib. This protocol includes recommendations for managing GI toxicities during pelabresib treatment.
- **Hyperglycemia**: Mild to moderate increases in serum glucose were observed in the preclinical toxicology studies of pelabresib. In clinical experience, hyperglycemia related to pelabresib has been observed in approximately < 5% of patients treated with pelabresib in Phase 1 and Phase 2 studies, the majority of which at low grade only. Serum glucose will be monitored throughout this study.
- **Testicular toxicity:** Degeneration of the germinal epithelium with oligo/aspermia was observed in the preclinical toxicology studies of pelabresib. Interference with germ cell formation is expected with BET bromodomain inhibition, given the role of *MYC* in proliferating tissues and the expression of BRDT (as well as the other BET family members) in the testis.
- **Embryofetal toxicity:** Preclinical animal studies have demonstrated that pelabresib has teratogenic potential. Both male and female patients must agree to use highly effective contraception methods during treatment with study drug, as outlined in Section 6.9.

- **Genotoxicity:** In a rat bone marrow micronucleus study, pelabresib induced statistically significant increases in micronucleus formation in all test article treatment groups when compared with the vehicle control article group and was thus determined to be likely genotoxic. The clinical implication of the rat micronucleus study is uncertain, and these findings may not translate into an increased risk of second primary malignancies in human studies. Additional information about the risk of genotoxicity with pelabresib may be found in the pelabresib Investigator's Brochure.
- **Treatment withdrawal syndrome:** Respiratory distress was observed after treatment discontinuation in 2 patients treated in Arm 3 (combination treatment with pelabresib and ruxolitinib) of the MANIFEST study. Patients remained on study for 22 and 26 cycles, respectively, before a decision was made to discontinue treatment due to Grade 3 thrombocytopenia and in the setting of progressive disease. The event of acute respiratory distress syndrome (ARDS) was reported for both patients 5 days after last ruxolitinib dose and 12 days after last pelabresib dose. These 2 reported cases of ARDS have been considered by the treating Investigator to be part of a "ruxolitinib discontinuation syndrome" (RDS). Instances of severe adverse events occurring subsequent to ruxolitinib withdrawal have been reported in the literature. RDS includes clinical manifestations ranging from acute relapse of disease-related symptoms, rapid spleen volume enlargement, and worsening of cytopenias to more severe complications, such as acute respiratory distress, disseminated intravascular coagulation (DIC), splenic infarction, and tumor lysis-like syndrome (Palandri et al., 2021). Additional information about these cases, the risk of RDS, and guidance for the Investigator may be found in the pelabresib IB.

The effects of pelabresib on response to viral infections, including COVID-19, is not yet known. Physicians should use their clinical judgment and weigh the benefit/risk of study participation during the COVID-19 pandemic for each patient.

More detailed information about the known and expected risks of pelabresib may be found in the pelabresib IB.

The risks of ruxolitinib are outlined in the applicable approved package insert.

2.3.2. Benefit Assessment

There are several mechanisms by which pelabresib has the potential to improve constitutional symptoms and spleen enlargement, and may elicit an effect on the underlying disease through its inhibitory effects on: i) megakaryocyte differentiation and proliferation; ii) inflammatory cytokine expression and release via the NF-κB signaling pathway; iii) targeting genes of TGF-β signaling, especially secretion of collagen by fibroblasts; and iv) bone marrow fibrosis through inhibition of pro-fibrotic pathways. Support for these hypotheses is provided in the reduction of pro-inflammatory cytokines, platelet counts, spleen volume, mutant allele burden in peripheral blood, and fibrosis in mouse models of MF following BET inhibition (Kleppe et al., 2018). Importantly, some of these effects were of greater magnitude when BET inhibition was combined with ruxolitinib, supporting the potential for complementary activity of pelabresib and JAKi in the treatment of MF. The clinical data in patients with newly diagnosed or advanced

MF treated with pelabresib alone and in combination with ruxolitinib give credence to these nonclinical findings. Encouraging clinical activity has been observed with the combination of pelabresib and ruxolitinib in JAKi treatment naïve patients with MF in spleen volume reduction and symptom improvement (Harrison et al., 2019). Furthermore, patients with relapsed/refractory MF or sub-optimal response to ruxolitinib treated with pelabresib monotherapy or as add-on to ruxolitinib, respectively, have shown improvements in hemoglobin levels, conversions from transfusion dependence to independence, and improvement in bone marrow fibrosis, as well as improvement in symptoms and SVR (Mascarenhas et al., 2019).

More detailed information about the clinical activity observed with pelabresib is available in the pelabresib IB.

2.3.3. Overall Benefit-Risk Conclusion

The improvements in spleen volume, constitutional symptoms, hemoglobin levels, and bone marrow fibrosis in patients with MF, when combined with the generally acceptable and manageable safety profile of pelabresib and risk minimization measures, support its continued evaluation in patients with MF.

3. OBJECTIVES AND ENDPOINTS

The following are the objectives and endpoints to be evaluated in this study.

Further description of endpoints, including definitions used and applicable assessments, may be found in Section 9.3.

Objectives	Endpoints
Primary	
• To determine the efficacy of pelabresib + ruxolitinib compared with placebo + ruxolitinib	• Splenic response at Week 24
Key Secondary	
• To determine the effect of pelabresib + ruxolitinib on the absolute change in TSS at Week 24 vs Baseline compared with placebo + ruxolitinib	• Absolute change in TSS at Week 24 compared to baseline
• To determine the efficacy of pelabresib + ruxolitinib compared with placebo + ruxolitinib	• TSS50 response at Week 24
Secondary	

• To determine the effect of pelabresib + ruxolitinib on the percent change in TSS at Week 24 vs Baseline compared with placebo + ruxolitinib	• Percent change in TSS at Week 24 compared to baseline
• To characterize the effects of pelabresib + ruxolitinib compared with placebo + ruxolitinib in the bone marrow	• Improvement in bone marrow fibrosis by at least 1 grade at Week 24 compared to baseline
• To determine the effect of pelabresib + ruxolitinib on the durability of splenic response compared with placebo + ruxolitinib	• Splenic response at Week 48
• To determine the effect of pelabresib + ruxolitinib on the durability of TSS response compared with placebo + ruxolitinib	• TSS50 response at Week 48
• To determine the effect of pelabresib + ruxolitinib on the durability of absolute change in TSS at Week 48 vs Baseline compared with placebo + ruxolitinib	• Absolute change in TSS at Week 48 compared to baseline
• To determine the effect of pelabresib + ruxolitinib compared with placebo + ruxolitinib on the rate of RBC transfusion over the first 24 weeks of treatment	• Rate of RBC transfusion over the first 24 weeks of treatment
• To determine the effect of pelabresib + ruxolitinib compared with placebo + ruxolitinib on the conversion from RBC transfusion dependence to independence	• Conversion from RBC transfusion dependence at baseline to independence
• To evaluate the PGIC at Week 24	• Categorical change of PGIC at Week 24 compared to Baseline
• To evaluate PFS in patients treated with pelabresib + ruxolitinib compared with placebo + ruxolitinib	• PFS
• To evaluate OS in patients treated with pelabresib + ruxolitinib compared with placebo + ruxolitinib	• OS

• To evaluate AML conversion in patients treated with pelabresib + ruxolitinib compared with placebo + ruxolitinib	• Proportion of patients with transformation to blast phase (AML)
• To determine the safety and tolerability of pelabresib + ruxolitinib compared with placebo + ruxolitinib	• AEs of all grades and SAEs
• To characterize the PK of pelabresib	• Population PK assessment incl. determination of exposure metrics and secondary parameter (i.e., AUC_{0-t}, t_{max}, C_{max}, $T_{1/2}$, Vd/F, CL/F)
• To characterize the effects, if any, of pelabresib on the PK of ruxolitinib	• Descriptive assessment of ruxolitinib plasma concentrations in the presence or absence of pelabresib
• To determine the effect of pelabresib + ruxolitinib on the duration of splenic response compared with placebo + ruxolitinib	• Duration of the splenic response
• To determine the effect of pelabresib + ruxolitinib on the modified TSS compared with placebo + ruxolitinib	• Modified TSS response at Week 24 (TSS score without the fatigue sub-domain)
• To determine the effect of pelabresib + ruxolitinib on the duration of TSS response compared with placebo + ruxolitinib	• Duration of the TSS50 response
• **Exploratory**	
• To determine the efficacy of pelabresib + ruxolitinib compared with placebo + ruxolitinib on the percent change in splenic volume at Week 24	• Percent change in splenic volume at Week 24
• To determine the effect of pelabresib + ruxolitinib compared with placebo + ruxolitinib on RBC transfusion dependence rate	• RBC transfusion dependence at Week 24
• To determine the effect of pelabresib + ruxolitinib compared with placebo + ruxolitinib on hemoglobin response	• Hemoglobin response

[redacted]	
• To characterize the PD effects pelabresib + ruxolitinib compared with placebo + ruxolitinib in the blood	• Post-treatment changes from baseline in circulating concentrations of cytokines • Post-treatment changes from baseline in the ratio of mutant to wild type *JAK2*, [redacted]
[redacted]	
• To determine the effect of pelabresib + ruxolitinib on the time to splenic response compared with placebo + ruxolitinib	• Time to first SVR35 response
[redacted]	

AE = adverse event; AML = acute myeloid leukemia; AUC = area under the plasma concentration-time curve; BET = bromodomain and extra terminal; C_{max}= maximal concentration; ECG = electrocardiogram; HRQOL = health related quality of life; [redacted] MF = myelofibrosis; OS = overall survival; PD = pharmacodynamic; PFS = progression-free survival; PGIC = Patient Global Impression of Change; PK = pharmacokinetics; RBC = red blood cell; SAE = serious adverse event; $T_{1/2}$ = half-life; T_{max} = time to maximal concentration; TSS = total symptom score.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, global, multicenter, randomized, double-blind, active-controlled study of pelabresib + ruxolitinib vs placebo + ruxolitinib in JAKi-treatment naïve patients with PMF, PPV-MF, or PET-MF.

The study design schematic is shown in Section 1.2.

The 28-day screening period begins on the day the patient signs the Informed Consent Form (ICF). Patients deemed eligible for enrollment will be randomized in a 1:1 ratio to 1 of 2 treatment groups: 1) pelabresib + ruxolitinib (experimental group), or 2) placebo + ruxolitinib (control group). Dosing should begin as soon as possible following randomization and both randomization and dosing (C1D1) must occur within 28 days from the beginning of screening. Patients who have not been randomized during the screening period can be rescreened if they fulfill the criteria outlined in Section 4.5.1 (Screen failures). Patients who have been randomized, but not dosed within 28 days since the start of Screening cannot be rescreened and will be terminated from the study.

Patients will be assessed for the primary and key secondary endpoints, splenic and TSS response, respectively, at Week 24. After 24 weeks, patients in the control group who have progressive disease by radiological parameters as defined in Section 7.1 (increase in splenomegaly) may be crossed over and treated with pelabresib + ruxolitinib provided that they remain eligible for the study (Section 6.6).

Double-blind treatment (pelabresib or matching placebo) will be administered QD for 14 consecutive days followed by a 7-day break, which is considered 1 cycle of treatment (1 cycle = 21 days). Ruxolitinib will be administered BID for all 21 days within each cycle.

Patient randomization will be stratified by DIPSS, platelet count, and spleen volume (Section 6.3).

Approximately 400 patients (approximately 200 per treatment arm) will be enrolled in the study (Section 9.4).

4.2. Scientific Rationale for Study Design

Since its global approvals, ruxolitinib is currently the standard of care for patients with MF (NCCN, 2019). Ruxolitinib has been proven to primarily reduce spleen volume and to provide symptomatic relief in patients (≥35% reduction from baseline spleen size [SVR35 response] = 29–42% and ≥50% reduction in total symptom score [TSS response] = 42–46% at Week 24 (Verstovsek et al., 2012). Patients receiving ruxolitinib may achieve suboptimal responses or can develop treatment-emergent anemia and worsening transfusion dependence (Harrison et al., 2017a; Mesa et al., 2017). Synergistic therapeutic agents are needed, including agents with a

novel mechanism of action with potential for disease-modifying effects leading to overall improvement in the prognosis of MF. BET proteins are transcriptional regulators that control key oncogenic pathways, including NFκB, and TGF-β signaling, important drivers of inflammation and fibrosis, respectively, in MF. Preclinical studies suggest that inhibition of both BET and JAK pathways can result in synergistic reduction of splenomegaly, bone marrow fibrosis and mutant cell burden (Kleppe et al., 2018). Pelabresib is a selective and potent oral small molecule BETi with effects on megakaryocyte differentiation and cytokine expression in preclinical studies (see pelabresib IB), as well as clinical studies (Mertz et al., 2018), and has shown antitumor activity and a wide therapeutic window in a Phase 1 lymphoma study (Blum et al., 2018).

This combination of pelabresib and ruxolitinib has the potential to improve upon the clinical activity of ruxolitinib alone, as evidenced by the preliminary clinical data from the ongoing Phase 2 MANIFEST study of this combination in JAKi naïve patients with MF (Harrison et al., 2019). This Phase 3 study is intended to confirm the splenic and TSS responses observed in Phase 2 while also evaluating disease-modifying effects of pelabresib, such as improvement in bone marrow fibrosis and other clinically relevant endpoints.

4.3. Justification for Dose

After a review of the safety data on pelabresib across three Phase 1 studies in hematologic malignancies, 225 mg QD was considered to be the recommended Phase 2 dose of pelabresib as monotherapy. However, a lower starting dose of pelabresib (125 mg QD) was chosen for the Phase 2 MANIFEST study based on the Phase 1 experience in which target engagement was near maximal at 125 mg QD with acceptable reversible and low-grade thrombocytopenia, which was the most consistent and predictable toxicity of pelabresib. In the Phase 2 MANIFEST study, patients with MF have been treated with pelabresib up to 225 mg QD doses both as monotherapy (Arm 1) and in combination with ruxolitinib (Arms 2 and 3). Because of the known risk of thrombocytopenia with ruxolitinib and pelabresib, in the Phase 2 MANIFEST study, the SRC reviewed data from the first six patients enrolled in Arm 3 of the ongoing Phase 2 MANIFEST study in June 2019. The SRC recommended a starting ruxolitinib dose of 5 mg BID lower than the recommended starting dose in the label, with dose increases to be made as needed in combination with pelabresib 125 mg QD.

Approximately 70% of patients in the Phase 3 COMFORT-1 study of ruxolitinib had dose reductions of ruxolitinib and the onset of thrombocytopenia was found to be typically within 4 weeks of initiation of treatment (FDA Medical Review of Ruxolitinib, 2011). Thus, the potential lower starting dose is consistent with that recommended in the approved product labeling (Jakafi®, US Prescribing Information, 2017; Jakavi®, Summary of Product Characteristics, 2019).

This dose modification paradigm was used in the Phase 2 MANIFEST study in which benefit for patients treated with pelabresib has been demonstrated with a manageable AE profile.

Based on the mechanism of action of ruxolitinib and the expected synergistic effects of pelabresib and ruxolitinib, there is a possibility that this combination may cause increased thrombocytopenia. Therefore, a conservative approach to initial ruxolitinib dosing (the same used in the Phase 2 MANIFEST study) will be used. This study also utilizes a lower starting

dose of ruxolitinib in Cycle 1 (5 mg BID below the recommended dose in the local approved product labeling) in order to enhance safety and tolerability for the first cycle. The ruxolitinib dose will be increased at Cycle 2 Day 1 (i.e., after 3 weeks) to the target dose levels per approved product labeling as long as prespecified criteria are met. This approach is aligned with clinical practice (Talpaz et al., 2018).

4.4. DSMB

An independent DSMB will be used to review data to monitor patient safety in the study. The DSMB will review safety data at regular intervals. The DSMB will also be provided with enrollment updates.

The DSMB may provide recommendations based on their review of the data, including whether to halt the study due to safety issues.

The DSMB will consist of at least 2 independent hematologists/oncologists and at least 1 biostatistician.

Further details about the membership, meeting frequency, and operational aspects of the DSMB can be found in its charter.

4.5. Study Participation

4.5.1. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study or randomly assigned to study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Patients who are considered screen failures only based on Inclusion Criterion #7 (Section 5.1) may be rescreened only after a 6-week period. Rescreened patients should not be assigned the same patient number as for the initial screening. If a patient is a screen failure and later becomes eligible for the study, the screening MRI or CT scan may not need to be repeated if obtained within 4 weeks of Cycle 1 Day 1 and the screening bone marrow biopsy may not need to be repeated if obtained within 12 weeks of Cycle 1 Day 1.

4.5.2. Duration of Treatment and Study Participation

Patients may receive treatment in the study until disease progression or discontinuation or withdrawal from treatment (Section 7.1), whichever occurs first, and will subsequently be followed for disease progression and overall survival.

4.5.3. Patient Follow-Up

Patients who discontinue treatment in the absence of disease progression will enter the progression-free survival (PFS) follow-up period until disease progression (central radiology assessment confirmation is required for splenic progression) or until initiation of another

systemic anti-cancer therapy. All patients with documented disease progression or initiation of another systemic anti-cancer therapy will continue to be followed for overall survival (Section 1.3). A patient is considered to have completed the study (EOS) if all parts of the study were completed, including the EOT visit, safety follow-up, and the visits in the PFS/survival follow-up period to assess disease progression and overall survival.

4.5.4. End of Study

The sponsor may end the study when the availability of an early access program or roll-over protocol exists into which patients remaining on study may enter and continue to receive access to drug if they are deriving clinical benefit and/or being monitored for long-term follow-up. Such a protocol would be written for pelabresib if pelabresib is not yet commercially available. A patient who is still on study without disease progression and deriving clinical benefit may be consented to an extension/roll-over protocol or compassionate use protocol or transition to commercial supply if available at the time. The date of the end of the study (study completion) is defined as the date of the last visit of the last patient in the study before transitioning to a roll-over or compassionate use program or commercial supply (if available).

5. STUDY POPULATION

Prospective approval of protocol deviations to eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

Age

1. ≥ 18 years of age at the time of signing the informed consent

Type of Patient and Disease Characteristics

2. Have a confirmed diagnosis of MF (PMF or PPV-MF or PET-MF) in accordance with the 2016 WHO criteria (Section 10.4)
3. Require therapy for MF in the opinion of the Investigator and are eligible for treatment with ruxolitinib
4. Have DIPSS risk category Intermediate-1 or higher (Section 10.5)
5. Have spleen volume of ≥ 450 cm^3 by MRI or CT scan (either local or central read)
6. Have completed the MFSAF v4.0 (Section 10.6) at least 5 of 7 days prior to randomization
7. Have at least 2 symptoms with an average score ≥ 3 over the 7-day period prior to randomization or an average total score of ≥ 10 over the 7-day period prior to randomization using the MFSAF v4.0 (Section 10.6)
8. Have acceptable laboratory assessments obtained within 28 days prior to the first dose of study medication:
    - ANC ≥ 1×10^9/L in the absence of growth factors or transfusions for the previous 4 weeks

- Platelet count ≥ 100 × 10^9/L in the absence of growth factors or transfusions for the previous 4 weeks
- Peripheral blood blast count < 5%
- Isolated elevation of AST and/or ALT ≤ 2.5 × ULN of the local reference interval (≤ 5 × if the elevation can be ascribed to liver involvement, e.g., presence of hepatomegaly)
- Isolated elevation of serum direct bilirubin < 2.0 × ULN of the local reference interval
- Calculated or measured CrCl of ≥ 45 mL/min*

9. ECOG performance status of ≤ 2
10. Life expectancy > 24 weeks per Investigator assessment
11. Have fully recovered from major surgery, intervention, and from the residual Grade 1 toxicity from prior MF-specific therapy (grade 1 peripheral neuropathy and alopecia are allowed).
12. Both male and female patients and partners of patients, with reproductive potential, must agree to use at least one highly effective contraceptive method (preferably low user dependency contraception methods, as in Section 6.9, in particular when contraception is introduced as a result of participation in a clinical study) while on study therapy and for 94 days after the last dose of study drug for male patients and male partners of female patients, and for 184 days after the last dose of study drug for female patients and female partners of male patients. Patients of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. NOTE: Patients may consider seeking information from the study investigator regarding donation and cryopreservation of germ cells prior to treatment. Male patients should be informed of the risk of testicular toxicity and provided with adequate advice regarding sperm preservation.

*Equation used for calculating the estimated creatinine clearance will be captured in the eCRF.

Informed Consent

13. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

5.2. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Had splenic irradiation within 6 months of starting study drug.
2. Had prior splenectomy.
3. Are a candidate for, and willing to undergo allogeneic HSCT, and, in the opinion of the Investigator, the benefit of proceeding to an allogeneic HSCT prior to treatment with a JAK2 inhibitor outweighs its risks.

4. Have current known active or chronic infection with HIV, hepatitis B, or hepatitis C. Screening of patients with serologic testing for these viruses is not required. However, patients who have a past history of viral hepatitis or in whom there is a current suspicion of viral hepatitis should have serologic testing for hepatitis B and hepatitis C performed to determine whether there is any current evidence for ongoing infection with these viruses. Patients considered to be at risk for HIV infection should have HIV testing performed.
5. Have an active infection. Patients will not be eligible for enrollment until recovery to ≤ Grade 1 for at least 2 weeks prior to the first dose of study drug. Testing for COVID-19 is not mandatory during the screening for this study. However, based on the local epidemiologic situation and each patient's individual COVID-19 exposure risk and/or vaccination status, investigators should consider testing and in the case of COVID-19 positivity consider delaying the start of the study treatment until the infection is resolved.
6. Have impaired gastrointestinal function or gastrointestinal disease, including active IBD, that could significantly alter the absorption of study drug, including any unresolved nausea, vomiting, or diarrhea > Grade 1.
7. Have known hypersensitivity to the investigational agent or ruxolitinib, or its metabolites or formulation excipients.
8. Have a history of progressive multifocal leukoencephalopathy.
9. Have impaired cardiac function or clinically significant cardiac diseases, including any of the following:
    - Acute myocardial infarction or unstable angina pectoris ≤ 6 months prior to starting study drug
    - QTcF > 500 msec on the screening ECG (QTcF interval is not relevant in patients with pacemaker-controlled arrythmia)
    - New York Heart Association Class III or IV congestive heart failure
    - Uncontrolled clinically significant cardiac arrhythmia (patients with rate-controlled arrhythmias are not excluded)

    Note that patients with a history of coronary artery disease and revascularization are not excluded.
10. Have ongoing uncontrolled hypertension (resting systolic blood pressure >160 mmHg and resting diastolic blood pressure >100 mmHg) despite maximal treatment with at least 2 anti-hypertensive agents.
11. Have ongoing uncontrolled blood glucose increase/uncontrolled diabetes (HbA1c ≥9%) despite maximal treatment with oral and/or injectable anti-hyperglycemic agents.
12. Have a history of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year prior to randomization, adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 3 years.

13. Have any other concurrent severe and/or uncontrolled concomitant medical condition that in the opinion of the Investigator could compromise participation in the study or analysis of study data. This includes but is not limited to clinically significant pulmonary disease or neurological disorders.

Prior/Concomitant Therapy

14. Had prior treatment with any JAKi or BET inhibitor for treatment of a myeloproliferative neoplasm.
15. Had systemic anti-cancer treatment, with the exception of hormonal therapy, less than 2 weeks (or 5 half-lives, whichever is longer) before the first dose of study drug. **NOTE:** Hydroxyurea and anagrelide are permitted up to 24 hours prior to start of study drug. Consult the Medical Monitor with questions if needed.
16. Had any investigational agent (whether as cancer treatment or not) less than 2 weeks (or 5 half-lives, whichever is longer) before the first dose of study drug.
17. Had hematopoietic growth factor (granulocyte growth factor, erythropoiesis stimulating agent, thrombopoietin mimetic) or androgenic steroids less than 4 weeks before the first dose of study drug.
18. Had a strong CYP3A4 inhibitor or inducer within 2 weeks prior to the first dose of study drug (Section 10.8), including St. John's wort. Initiation of treatment or concomitant use of a strong CYP3A4 inhibitor or inducer during study treatment is prohibited.
19. Require systemic corticosteroids of >10 mg QD prednisolone or equivalent 4 weeks before the first dose of study drug. Patients who received topical, nasal, intra-articular, inhaled, and other forms of corticosteroids without systemic activity are eligible.
20. Had a live vaccination within 30 days prior to the first dose of study drug (Czech Republic only).

Other Exclusions

21. Females who are breastfeeding or pregnant (as documented by a highly sensitive urine or serum β-hCG pregnancy test consistent with pregnancy, obtained within 72 hours prior to the first dose of study drug) or expecting to conceive or males expecting to father children within the projected duration of the trial, starting with the screening visit through 184 days after the last dose of study drug. Female patients of non-child bearing potential (post-menopausal for more than 1 year; underwent a hysterectomy, bilateral salpingectomy, and bilateral oophorectomy) do not require a serum pregnancy test.
22. Are unwilling or unable to comply with this study protocol or study requirements.

6. STUDY DRUG

Study drug is defined as any investigational intervention, marketed product, or placebo intended to be administered to a study patient for evaluation of safety and efficacy according to the study protocol.

Study treatment is defined as the combination of pelabresib + ruxolitinib or placebo + ruxolitinib.

Pelabresib (CPI-0610) tablets, 25 mg and 100 mg contain the active pharmaceutical ingredient (pelabresib monohydrate) and the following inactive excipients: microcrystalline cellulose, lactose monohydrate, hydroxypropyl cellulose, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, magnesium stearate, poly vinyl alcohol, titanium dioxide, polyethylene glycol and talc. Both tablet strengths (25 mg and 100 mg) are supplied in HDPE bottles with heat induction sealed caps. Each bottle contains 15 count, film-coated, plain-faced white tablets. Matching placebo contains all above excipients (no active pharmaceutical ingredient) and is visibly identical to experimental drug in size, shape, and packaging.

6.1. Study Drugs Administered

The study drugs outlined in Table 1 will be administered.

Table 1: Study Drugs to be Administered

Arm Name	Experimental Group (pelabresib + ruxolitinib)	Control Group (placebo + ruxolitinib)
Treatment	Pelabresib monohydrate tablets + ruxolitinib phosphate tablets	Matching placebo tablets + ruxolitinib phosphate tablets
Starting Dosage Levels and Administration	Pelabresib 125 mg PO QD + ruxolitinib 10 or 15 mg PO BID for 14 consecutive days followed by ruxolitinib 10 or 15 mg PO BID for 7 days in a 21-day cycle	Matching placebo PO QD + ruxolitinib 10 or 15 mg PO BID for 14 consecutive days followed by ruxolitinib 10 or 15 mg PO BID for 7 days in a 21-day cycle
Use	Experimental	Placebo/active comparator
Definition	Pelabresib: IMP Ruxolitinib: NIMP (SOC)	Placebo: IMP Ruxolitinib: NIMP (SOC)
Sourcing	Pelabresib provided centrally by the Sponsor; ruxolitinib sourcing varies by country and site.	Blinded placebo provided centrally by the Sponsor; ruxolitinib sourcing varies by country and site.
Packaging and Labeling	Pelabresib will be provided in HDPE bottles with heat induction sealed caps. Each bottle will be labeled as required per country requirement.	Matching placebo will be provided in HDPE bottles with heat induction sealed caps. Each bottle will be labeled as required per country requirement

BID = twice daily; HDPE = high density polyethylene; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; PO = by mouth; QD = once daily, SOC = standard of care.

Patients should be instructed to take their daily dose of pelabresib or placebo at approximately the same time each day. Pelabresib or placebo should be taken in the morning unless otherwise instructed (see supportive care guidelines for nausea and vomiting in Section 6.7.1). Each daily dose of pelabresib or placebo should be taken with a glass of water and consumed over as short a time as possible (e.g., all tablets within 5 minutes). Patients should be instructed to swallow tablets whole and to not chew them.

Ruxolitinib is a standard of care and should be taken according to the local approved package insert unless otherwise defined in this protocol, including if discontinuation of ruxolitinib is required.

No food should be consumed for 2 hours prior to and 1 hour after their daily dose of study drugs unless otherwise instructed (see supportive care guidelines for nausea and vomiting in Section 6.7.1). The tablets should be swallowed whole, with water, at home first thing in the morning except for days that study drug will be administered in the study center under the observation of the study personnel.

On days when PK and/or pharmacodynamic samples need to be collected prior to taking study drug, the patient should take that day's pelabresib/placebo and/or ruxolitinib dose in the clinic.

If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose.

If the patient forgets to take his/her daily dose of pelabresib, then he/she should take their daily dose within 10 hours after the missed dose. If more than 10 hours have passed, then that day's dose should be omitted, and the patient should resume treatment with the next scheduled dose.

If the daily morning dose of ruxolitinib is missed, then the patient should take their daily dose within 10 hours after the missed dose. If more than 10 hours have passed, then that morning's dose should be omitted, and the patient should resume treatment with the next scheduled dose in the evening. If the daily evening dose of ruxolitinib is missed, then the dose should be omitted and the patient should resume treatment with the next scheduled dose the following morning.

6.2. Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.

Only patients enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

Pelabresib/placebo tablets should remain in the bottle provided, even after being dispensed to patients. The bottles should be stored at the investigational site at controlled room temperature (15-30°C). Containers should be kept closed during storage.

The Investigator is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

All non-dispensed, and dispensed but unused, study drug will be retained at the site until it is inventoried by the monitor. All non-dispensed, dispensed but unused, or expired study drug should be destroyed by sites per their own internal destruction procedures. If a site's procedures do not allow for destruction, unused/expired/damaged study drug should be returned to the supplying depot for subsequent destruction. All material containing study drug will be treated and disposed of as hazardous waste in accordance with governing regulations.

Further guidance and information for the final disposition of unused study drug are provided in supplemental study materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

This study has a double-blind design in which patients and investigators are blinded to study drug; study drugs will be packaged identically (Section 6.1).

All patients will be randomly assigned to either treatment group in a 1:1 ratio using a centralized IVRS/IWRS. Before the study is initiated, operational logistics for the IVRS will be provided to each site in an IRT manual. Note: dosing should begin as soon as possible following randomization, and no later than 28 days from start of the screening period (Section 4.1).

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the responsibility for determining if unblinding of a patient's intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor or the CRO medical monitor prior to unblinding a patient's intervention assignment unless this could delay emergency treatment of the patient. If a patient's intervention assignment is unblinded, the Sponsor must be notified within 24 hours that emergency unblinding was performed. It is important that the Sponsor remains blinded and the patient's intervention assignment is not to be shared with the study team until primary analysis takes place. The date that the blind was broken must be recorded in the source documentation and IVRS/IWRS, as applicable.

Each patient in the study is identified by a unique patient number. The procedures for patient numbering and coordination between the study sites will be provided in a separate document prior to study start. The unique patient number is a combination of his/her study center number and a second number reflecting the sequence of patient enrollment. The study center number is assigned by the Sponsor to each investigative site. Upon signing the ICF, the patient is assigned a patient number. Once assigned to a patient, a patient number will not be reused.

To ensure balance between treatment arms, patient randomization will be stratified by the following factors:

- DIPSS risk category: Intermediate-1 vs. Intermediate-2 vs. High
- Platelet count: $> 200 \times 10^9$/L vs. $100 – 200 \times 10^9$/L
- Spleen volume: ≥ 1800 cm^3 vs. < 1800 cm^3

6.4. Study Drug Compliance

When patients are dosed at the site, they will receive study drug directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study drug and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug.

Study drug administration should be recorded on the patient dosing diary, and compliance will be assessed at each visit. Compliance will also be assessed by counting tablets during the site visits and documented in the source documents and eCRF/IRT. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of study drug tablets dispensed to and taken by each patient must be maintained and reconciled with study drug and compliance records. Intervention start and stop dates, including dates for drug delays and/or dose reductions will also be recorded in the eCRF.

6.5. Ruxolitinib and Pelabresib/Placebo Starting Doses and Dose Modification Guidelines

Topic	Ruxolitinib	Pelabresib /Placebo
Starting dose	Section 6.5.1	Section 6.5.1
Dose increase for lack of spleen response	Section 6.5.2.1	Section 6.5.2.2
Dose modification and restarting rules for toxicities	Section 6.5.3, Table 3 and Table 4	Section 6.5.3, Table 3 and Table 4
Dose re-escalation following reduction for toxicity	Section 6.5.4.1	Section 6.5.4.2

6.5.1. Starting Doses of Pelabresib/Placebo and Ruxolitinib

The starting doses for ruxolitinib and pelabresib/placebo at Cycle 1 Day 1 and the subsequent ruxolitinib dose increase at Cycle 2 Day 1 are detailed in Table 2.

- The MANDATORY starting dose for the treatment regimen at Cycle 1 Day 1 will be pelabresib/placebo at 125 mg QD for all patients.
- Ruxolitinib is started at 10 mg BID (for patients with baseline platelet count 100 – 200 × 10^9/L) or 15 mg BID (for patients with baseline platelet count > 200 × 10^9/L) (i.e., 5 mg BID lower than the recommended dose in the applicable approved package insert).

It is MANDATORY to increase the ruxolitinib dose by 5 mg BID at Cycle 2 Day 1 if:

- Platelet count is >125 × 10^9/L and
- ANC is > 0.75 × 10^9/L at Cycle 2 Day 1 and
- The patient did not have ≥ Grade 3 non-hematological toxicity in Cycle 1 that required dose interruption or reduction (regardless of percent change in spleen size by palpation from pre-treatment baseline).

Table 2: Starting Doses of Pelabresib/Placebo and Ruxolitinib and Dose Increase at Cycle 2 Day 1

Treatment Cycle/Day	Ruxolitinib (mg BID)	Pelabresib/placebo (mg QD)	Treatment Cycle
C1D1 (starting dose)	10 (if PLT 100-200 × 10^9/L) OR 15 (if PLT >200 × 10^9/L)	125	MANDATORY to start ruxolitinib at 10 or 15 mg BID (5 mg BID below the recommended dose per PLT count at baseline as described in the ruxolitinib local approved product labeling) (regardless of hemoglobin or transfusion status at C1D1)
C2D1	10 to 15 OR 15 to 20	125	MANDATORY to increase ruxolitinib dose by 5 mg BID if: • PLT ≥125 × 10^9/L and ANC >0.75× 10^9/L • No ≥ G3 non-hematological toxicity in C1 requiring dose interruption or reduction (regardless of % change in spleen size by palpation from pretreatment baseline)

BID = twice daily; C = cycle; D = day; G= grade; PLT = platelet; QD = once daily.

6.5.2. Criteria and Process to Increase Doses of Ruxolitinib and Pelabresib/Placebo

6.5.2.1. Ruxolitinib Dose Increases for Lack of Spleen Response

Following the mandatory dose increase on Cycle 2 Day 1 described above in Section 6.5.1 and Table 2, the ruxolitinib dose may be increased by 5 mg BID increments from Cycle 3 Day 1 or thereafter if all the criteria outlined below are met. If these criteria are met, the ruxolitinib dose may be increased in 5 mg BID increments, not more frequently than once every cycle, to a maximum of 25 mg BID.

The following criteria must be met for ruxolitinib dose increase from Cycle 3 Day 1 and thereafter:

- Failure to achieve a reduction from pretreatment baseline in either palpable spleen length by 50% or by MRI or CT scan by 35%
- Platelet count ≥125 × 10^9/L over the course of the prior one cycle
- ANC >0.75 × 10^9/L
- No AE requiring any dose interruption and/or reduction in the previous cycle

NOTE: both ruxolitinib and pelabresib/placebo doses cannot be increased in the same cycle.

6.5.2.2. Pelabresib/Placebo Dose Uptitration Rules for Lack of Spleen Response

Pelabresib/placebo dose increase is only allowed from Cycle 5 Day 1 or thereafter based on the criteria outlined below. Patients who have not had a dose reduction or hold because of an AE in previous cycles may increase the pelabresib/placebo dose from Cycle 5 Day 1 or thereafter only if all the following criteria are met. If these criteria are met, the pelabresib/placebo dose can be

increased in 25 mg QD increments, not more frequently than once every 2 cycles, to a maximum dose of 175 mg QD.

The following criteria must be met for a pelabresib/placebo dose increase from Cycle 5 Day 1 and thereafter:

- The ruxolitinib dose is at least 20 mg BID for the previous 1 cycle.
- Failure to achieve a spleen response by MRI/CT scan at Week 12 (i.e., has not achieved ≥35% reduction in spleen volume). Note: spleen response by palpation will not be considered for response evaluation.
- Platelet count ≥125 × 10^9/L over the course of the prior one cycle
- ANC >0.75 × 10^9/L
- No AE requiring any dose interruption and/or reduction in the previous cycles

Note: both ruxolitinib and pelabresib/placebo doses cannot be increased in the same cycle.

6.5.3. Ruxolitinib and Pelabresib/Placebo Dose Modification and Restarting Rules for Platelet Count Decrease and Other Toxicities

Guidance for dose modification of ruxolitinib is outlined below.

If a patient experiences a TEAE (e.g., platelet count decrease or other toxicities as specified in Table 3 and Table 4, respectively), follow the actions required as outlined in the tables below. In general, for a ruxolitinib dose reduction, the dose will be decreased by at least 5 mg BID per day (minimum dose level 5 mg QD). For a pelabresib/placebo dose reduction, the dose will be titrated downwards at least by 25 mg QD per day (minimum dose level 50 mg QD).

During the course of treatment, if ruxolitinib must be held for >28 days and/or if a ruxolitinib dose lower than 5 mg QD is required due to toxicity, ruxolitinib must be discontinued. If pelabresib/placebo must be held for >35 days due to toxicity, pelabresib/placebo must be permanently discontinued and the patient must come off study treatment, unless the investigator has provided the sponsor medical team with a benefit-risk assessment that supports the patient's continuation on study treatment. Assessment of clinical benefit vs. risk to justify continuation on study treatment may include, but is not limited to, reviewing changes in spleen volume, safety labs, adverse events, and other factors that could be impacting study drug hold.

Cycles are defined throughout the study as every 3 weeks or 21 days. In the event that treatment with pelabresib/placebo (and/or ruxolitinib) is interrupted, the duration of cycle/treatment will not be extended and missed doses will not be made up. This means, for example, if a patient misses Days 8-14 of a cycle, the patient will remain off pelabresib for Days 15-21 (the prescribed 7-day off period per regimen schedule). Patients should have a minimum of 7 days off pelabresib/placebo in between cycles.

Guidance for dose modifications, including reduction and/or hold of ruxolitinib and/or pelabresib/placebo, due to platelet count decrease are provided in Table 3 and Figure 1, and due to other toxicities are provided in Table 4. Dose reductions should be considered if the platelet counts decrease as outlined in Table 3 with the goal of avoiding dose interruptions for thrombocytopenia. Note: these dose modifications do not apply to starting dose in Cycle 1.

Directions for possible re-escalation after dose reduction for toxicity are provided in Section 6.5.4.1 for ruxolitinib and in Section 6.5.4.2 for pelabresib/placebo.

In case a patient becomes infected with COVID-19 during the study, the Investigator should use their clinical judgment about study drug interruption, depending on the patient's symptoms, disease status, comorbidities, and concomitant medications. Per Table 4, pelabresib/placebo should be held for ≥ Grade 3 infection. In cases of Grade 1-2 COVID-19 infection and/or COVID-19-related medical conditions, study drug may also be held per investigator clinical judgment and according to local and institutional standards of care.

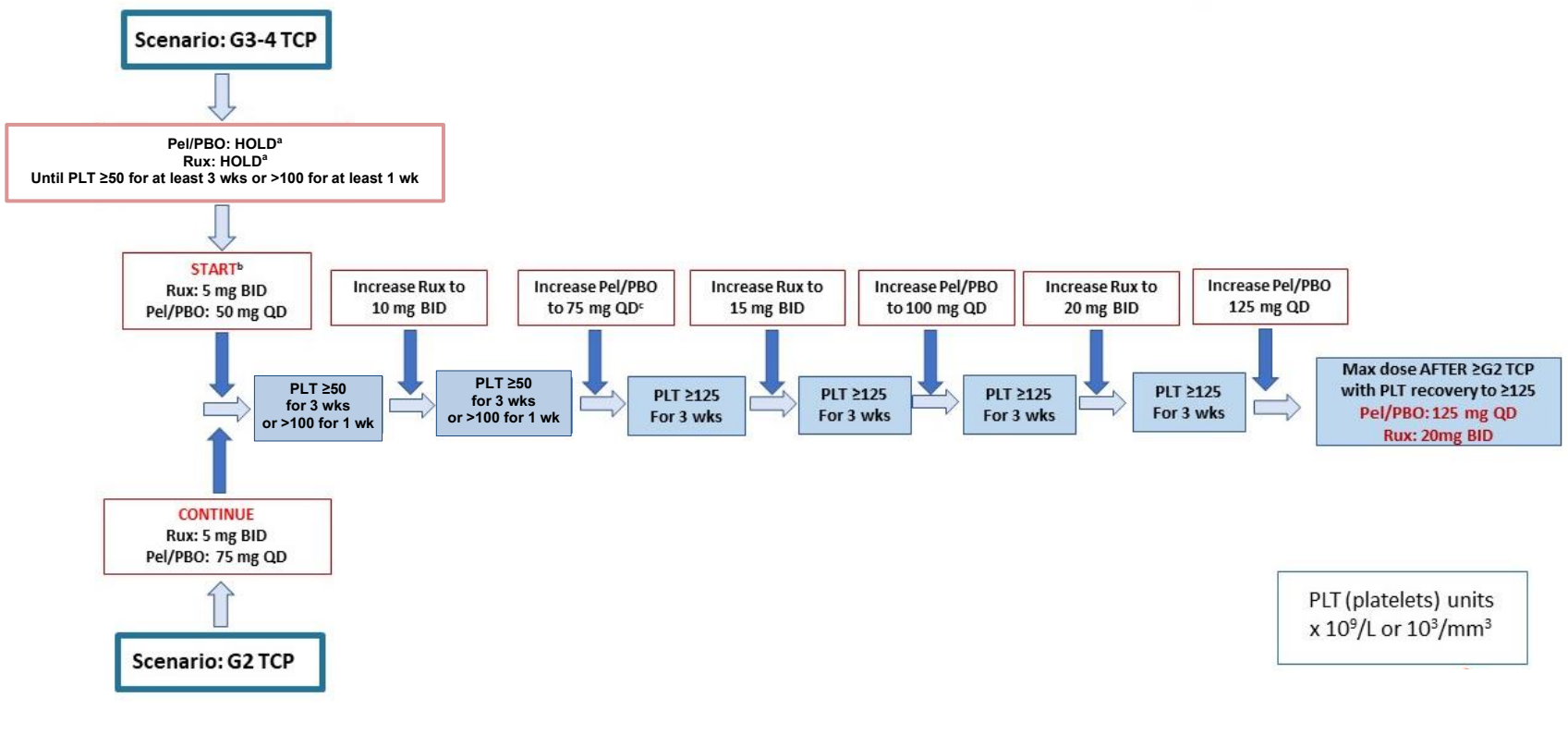
Table 3: Ruxolitinib and Pelabresib/Placebo Dose Modification Guidance for Platelet Count Decrease after Initial Dosing on Cycle 1 Day 1

PLT Count after C1D1	Dose at the Time of PLT Decline					
	Ruxolitinib Dose[a]					Pelabresib/Placebo Dose[a]
	25 mg BID	20 mg BID	15 mg BID	10 mg BID	5 mg BID	75 – 125 mg QD
100 - <125 × 10^9/L	20 mg BID	15 mg BID	No Change	No Change	No Change	No Change
75 - <100 × 10^9/L	10 mg BID	10 mg BID	10 mg BID	No Change	No Change	75 mg QD
50 - <75 × 10^9/L (G2)	• Ruxolitinib 5 mg BID and pelabresib/placebo 75 mg QD • If PLT ≥ 50 × 10^9/L for at least 3 weeks or ≥100 × 10^9/L for at least one week, may increase ruxolitinib to 10 mg BID and maintain dose of pelabresib/placebo at 75 mg QD • Maintain the above dose regimen until PLT recovers to ≥ 125 × 10^9/L and follow Figure 1 for further dose escalation					
<50 × 10^9/L (G3 – 4)	• HOLD both ruxolitinib and pelabresib/placebo until PLT recovery to ≥ 50 × 10^9/L. NOTE: if a patient is considered to be at high risk for ruxolitinib discontinuation syndrome (RDS, see Section 6.7.4), HOLD pelabresib and consider tapering ruxolitinib instead of an abrupt stop. The risk of thrombocytopenia vs risk of developing RDS has to be considered by the treating physician, and if a taper is implemented, platelets need to be followed closely per treating physician judgment. 1. If PLT recovers to ≥ 50 × 10^9/L for at least 3 weeks or ≥100 × 10^9/L for at least one week, restart ruxolitinib 5 mg BID and pelabresib/placebo at 50 mg QD 2. If PLT ≥ 50 × 10^9/L for another 3 weeks or ≥100 × 10^9/L for at least one week, increase ruxolitinib to 10 mg BID and maintain pelabresib/placebo at 50 mg QD 3. If PLT ≥ 50 × 10^9/L for another 3 weeks or ≥100 × 10^9/L for at least one week, maintain ruxolitinib 10 mg BID and increase pelabresib/placebo to 75 mg QD • Maintain the above dose regimen until PLT recovers to ≥ 125 × 10^9/L and follow Figure 1 for further dose escalation • If G3 PLT recurs after restarting the start of treatment, HOLD both ruxolitinib and pelabresib/placebo until PLT recovers to ≥ 50 × 10^9/L and follow Steps 1 – 3 above. • If ruxolitinib is held for >28 days, DISCONTINUE treatment.					

	• If pelabresib/placebo is held for >35 days, DISCONTINUE treatment unless the benefit-risk assessment supports the continuation on study treatment (e.g., safety and signs of efficacy) after discussion with the Sponsor's medical team.

BID = twice daily; C = cycle; D = day; G = grade; PLT = platelet; QD = once daily.
a. Both ruxolitinib and pelabresib/placebo cannot be increased in the same cycle.
NOTE: These dose modifications do not apply to starting dose in Cycle 1.

Figure 1: Guidance for Dose Modification After Prior Dose Reduction/Hold for Thrombocytopenia



BID = twice daily; pel = pelabresib (CPI-0610); PLT = platelet; QD = once daily; rux = ruxolitinib; TCP = thrombocytopenia; wks = weeks.
Note: PLT (platelets) units × 10^9/L or 10^3/mm^3
Note: both ruxolitinib and pelabresib/placebo doses cannot be increased in the same cycle.
a. If pelabresib dosing is held for >35 days AND/OR ruxolitinib dosing is held for >28 days, DISCONTINUE study treatment.
b. If G4 recurs after starting ruxolitinib 5 mg BID and pelabresib 50mg QD, DISCONTINUE study treatment.
c. If pelabresib/placebo is already at 75 mg QD, wait until PLT ≥125 × 10^9/L for further dose escalation.

Estimated maximum dose re-escalation PLT ≥50 × 10^9/L: ruxolitinib 10 mg BID and pelabresib/placebo 75 mg QD
Estimated maximum dose re-escalation for PLT ≥125 × 10^9/L: ruxolitinib ≥20 mg BID and pelabresib/placebo 125 mg QD

Table 4: Ruxolitinib and Pelabresib/Placebo Dose Modifications for Other Toxicities

Toxicity	Actions Required
Hematology	

G4 neutropenia (ANC < 0.5 × 10^9/L)	• HOLD ruxolitinib for up to 28 days and pelabresib/placebo for up to 35 days. NOTE: if a patient is considered to be at high risk for ruxolitinib discontinuation syndrome (RDS, see Section 6.7.4), HOLD pelabresib and consider tapering ruxolitinib instead of an abrupt stop. The risk of neutropenia vs risk of developing RDS has to be considered by the treating physician, and if a taper is implemented, neutrophils need to be followed closely per treating physician judgment.
	• Repeat CBC at least weekly until resolution to > 0.75 × 10^9/L
	• Once resolved to > 0.75 × 10^9/L, restart:
	  ○ Ruxolitinib reduced by 5 mg per dose
	  ○ Pelabresib/placebo reduced by 25 mg/day
	• In the case of febrile neutropenia, administer GCSF according to institutional guidelines.

Anemia	• Blood transfusion should be considered for severe (Hgb <8.0 g/dL) and/or symptomatic anemia • No pelabresib/placebo dose reduction or interruption is needed for anemia, dose increase is allowed if other criteria in Section 6.5.4.2 are met
Reduction in platelet count	• Repeat CBC as clinically indicated and at least once weekly until resolution to ≤ G1 • Refer to Table 3 and Section 6.5.4.1 for ruxolitinib dose modification and re-escalation rules • Refer to Table 3 and Section 6.5.4.2 for pelabresib/placebo dose modification and re-escalation rules
Hepatic	
≥ Direct bilirubin >3 × ULN	• HOLD pelabresib/placebo for up to 35 days • Repeat direct bilirubin at least weekly until resolution to ≤ G1 or baseline • Once resolves to ≤ G1, restart pelabresib/placebo reduced by 25 mg/day • If ≥ G3 recurs despite pelabresib/placebo reduction, continue pelabresib/placebo at the reduced dose and HOLD ruxolitinib for up to 28 days • Repeat direct bilirubin at least weekly until resolution to ≤ G1 or baseline • Once resolves to ≤ G1, restart ruxolitinib reduced by 5 mg per dose
≥ G3 ALT (>5 × ULN) in patients who enroll with ≤ G1 ALT **OR** Tripling of ALT in patients who enroll with G2 ALT	• HOLD pelabresib/placebo for up to 35 days • Repeat serum transaminases at least weekly until resolved to ≤ G1/baseline • Once resolves to ≤ G1, restart pelabresib/placebo reduced by 25 mg/day • If ≥ Gr 3 recurs despite pelabresib/placebo reduction, continue pelabresib/placebo at the reduced dose and HOLD ruxolitinib for up to 28 days. • Repeat serum transaminases at least weekly until resolved to ≤ G1/baseline • Once resolves to ≤ G1, restart ruxolitinib reduced by 5 mg per dose

Toxicity	Actions Required
≥ Direct bilirubin >1.5 × ULN **AND** ≥ G2 ALT (>3 × ULN) in patients who enroll with ≤ G1 ALT **OR** ≥ Direct bilirubin >1.5 × ULN **AND** tripling of ALT in patients who enroll with G2 ALT	• HOLD ruxolitinib for up to 28 days and pelabresib/placebo for up to 35 days • Once resolved to ≤ G1/baseline, if another cause is identified, restart pelabresib/placebo and ruxolitinib at same dose • Permanently discontinue pelabresib/placebo in the absence of biliary obstruction or other potential causes deemed responsible for the concurrent elevation of direct bilirubin and ALT • Investigator may restart ruxolitinib off protocol at his/her discretion.
Gastrointestinal	
G3 nausea, or ≥ G3 vomiting, or ≥ G3 diarrhea	• Treat with optimal supportive care as per guidelines provided in Section 6.7.1.2 until resolution to ≤ G1 • HOLD pelabresib/placebo up to 35 days • Patient should be contacted by the Investigator or study nurse daily until resolution to ≤ G1 or increase support (e.g., hospitalization) • Resume pelabresib/placebo in the presence of symptomatic prophylaxis at same dose if duration is ≤ 72 hours, or resume with dose reduced by 25 mg/day if the duration is >72 hours or if hospitalization is required despite optimal supportive care • If ≥ G3 persists >72 hours despite holding pelabresib/placebo dose, then also HOLD ruxolitinib for up to 28 days. NOTE: if a patient is considered to be at high risk for RDS (see Section 6.7.4), consider tapering ruxolitinib instead of an abrupt stop. • Resume ruxolitinib at same dose once recovers to ≤ G1 and resume pelabresib/placebo in the presence of symptomatic prophylaxis at same dose if duration is ≤ 72 hours, or resume with dose reduced by 25 mg/day if the duration is >72 hours or if hospitalization is required despite optimal supportive care **NOTE:** If toxicity recurs, and a hold of ruxolitinib was previously required because the duration was >72 hours, HOLD pelabresib/placebo for up to 35 days and ruxolitinib for up to 28 days. **NOTE:** In some instances, separation of pelabresib and ruxolitinib intake by a few hours or pelabresib intake in the evening prior to bedtime has mitigated gastrointestinal AEs.
Rash	
≤ G2	• Provide supportive care (Section 6.7.3)
G3	• Provide supportive care (Section 6.7.3) • If resolution to ≤ G1 takes >72 hours, continue ruxolitinib and HOLD pelabresib/placebo until resolution to ≤ G1 or for a maximum of 35 days, whichever occurs first • Resume pelabresib/placebo with dose reduced by 25 mg/day
G4	• Provide supportive care (Section 6.7.3) • Permanently discontinue pelabresib treatment
Infection*	
≤ G2	• Provide active treatment and supportive care, as needed • Continue ruxolitinib and pelabresib/placebo at the same dose

Toxicity	Actions Required
≥ G3	• Provide active treatment and supportive care, as needed • HOLD pelabresib/placebo until resolution to ≤ G1 or for up to 35 days, whichever occurs first, continue ruxolitinib • HOLD pelabresib/placebo and ruxolitinib for G4 until resolution to ≤ G1, or for up to 28 days for ruxolitinib and up to 35 days for pelabresib/placebo • Resume pelabresib/placebo with dose reduced by 25 mg/day following hold • Resume ruxolitinib with dose reduced by 5 mg per dose following hold
Other non-specified, including Renal and Electrolytes*	
≥ G2 that, in the opinion of the Investigator, requires dose reduction	• For G2, consider dose reduction of pelabresib/placebo by 25 mg daily: for G3, HOLD offending agent(s) up to 28 days for ruxolitinib and up to 35 days for pelabresib/placebo • Evaluate at least once weekly until toxicity resolves to ≤ G1 or stabilizes • Resume with dose of offending agent(s) reduced by 1 level (i.e., reduce 25 mg/day for pelabresib/placebo or 5 mg per dose for ruxolitinib).
Any toxicity that requires >35 days hold of pelabresib/placebo	• Discontinue pelabresib/placebo unless there is clear evidence of clinical benefit and after a discussion with the Sponsor's medical team
Any toxicity that requires >28 day hold of ruxolitinib	• Discontinue ruxolitinib

Note: Pseudo hyperkalemia is a common finding in myeloproliferative disorders that may lead to inappropriate management of patients. These elevations of plasma potassium in the majority of MF patients may be due to in vitro hemolysis. ≥ Grade 2 plasma potassium increase requires specific laboratory assessments (Section 10.2) and ≥ Grade 3 plasma potassium increase require an ECG (Section 8.3.4). If dose modification is required, follow the relevant instructions in the "Other non-specified" area of the table above.

Note: Any AE that causes a drug hold of >28 days for ruxolitinib or >35 days for pelabresib/placebo, regardless of relationship, will cause the patient to discontinue treatment and enter the follow-up phase, as per protocol Section 6.5.3.

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; CBC = complete blood count; D = day; G = grade; GCSF = granulocyte colony stimulating factors; Hgb = hemoglobin; PLT = platelet; QD = once daily; ULN = upper limit of normal.

*Please refer to ruxolitinib package insert for guidance on dose adjustment/hold for disseminated herpes simplex virus

6.5.4. Re-escalation Criteria and Process

6.5.4.1. Re-escalation of Ruxolitinib after Dose Reduction for Toxicity

If a dose of ruxolitinib has been reduced for a given patient, the dose may be increased on Day 1 of the next cycle. Doses may be increased in 5 mg BID increments and should not be increased more frequently than once every cycle (3 weeks).

When considering re-escalation of ruxolitinib, the goal should be to keep increasing the dose regardless of spleen response until it reaches the dose level at the time of reduction. Further escalation may be considered for failure to achieve a reduction from pretreatment baseline in either palpable spleen length of ≥50% or a ≥35% reduction in spleen volume as measured by MRI or CT scan at Week 12.

The following criteria must be met for the dose of ruxolitinib to be considered for re-escalation:

- If the dose has been reduced due to thrombocytopenia, a dose increase can be instituted based on platelet count, as indicated in Table 3 and Figure 1.
- If the dose has been reduced due to neutropenia, a dose increase cannot be instituted until the ANC is > 0.75×10^9/L for at least 1 cycle.
- There are no safety concerns requiring pelabresib/placebo dose interruption or reduction on the day the ruxolitinib dose increase is under consideration.

- If the dose has been reduced for a non-hematologic toxicity, a dose increase cannot be instituted until the toxicity has resolved to ≤ Grade 1 for at least 1 cycle. If the same toxicity recurs after dose re-escalation, further dose increases are prohibited.
- If the dose has been reduced due to Grade 4 non-hematologic toxicity, a subsequent dose increase is prohibited.

If the above criteria are met, a ruxolitinib dose increase can be considered. After the dose level prior to dose reduction is reached, subsequent dose increase of ruxolitinib is allowed provided that the criteria described in Section 6.5.2.1 are met.

NOTE: both ruxolitinib and pelabresib/placebo dose cannot be increased in the same cycle.

6.5.4.2. Re-escalation of Pelabresib/Placebo after Dose Reduction for Toxicity

Patients who have had a dose reduction or dose hold of ruxolitinib or pelabresib/placebo because of an AE may increase the dose of pelabresib/placebo only if all of the following criteria are met:

- The ruxolitinib dose has reached at least 10 mg BID for the previous 1 cycle (see exceptions in Table 3 and Figure 1).
- If dose has been reduced due to thrombocytopenia, a dose increase can be instituted based on platelet count, as indicated in Table 3 and Figure 1.
- If dose reduced due to neutropenia, a dose increase cannot be instituted until the ANC is > 0.75×10^9/L for at least 1 cycle.
- There are no safety concerns requiring ruxolitinib dose interruption or reduction on the day the pelabresib/placebo dose increase is under consideration.
- If dose has been reduced for a non-hematologic toxicity, a dose increase cannot be instituted until the toxicity has resolved to ≤ Grade 1 for at least 1 cycle. If the same toxicity recurs after dose re-escalation, further dose increases are prohibited.
- If the dose is reduced due to Grade 4 non-hematologic toxicity, a subsequent dose increase is prohibited.

If these criteria are met, the pelabresib/placebo dose can be increased in 25 mg QD increments, not more frequently than once every 2 cycles, to a maximum dose of 125 mg QD.

NOTE: both ruxolitinib and pelabresib/placebo dose cannot be increased in the same cycle.

6.6. Crossover Period

Patients who have enrolled in the control group (i.e., treated with placebo + ruxolitinib) and have progressive disease after 24 weeks of treatment by radiological parameters may be crossed over to receive the experimental treatment of pelabresib + ruxolitinib. The following sections detail the design, operational, and statistical aspects of the crossover part of the study.

6.6.1. Crossover Design

All patients who have progressive disease at any time will be required to discontinue the double-blind- study treatment. Patients in the control group who have progressive disease due to

splenomegaly (i.e., defined as enlargement of spleen volume by MRI or CT scan of ≥25% compared to the baseline value, as confirmed by the central review; not due to leukemic transformation or an increase in peripheral blood blast percentage of ≥20% associated with an absolute blast count of ≥1 × 10^9/L that persists for at least 2 weeks; see Section 7.1) at or after Week 24 may have the option to cross over to receive the experimental treatment of ruxolitinib + pelabresib in an open label fashion. Patients in the control group who have to discontinue study treatment due progressive disease due to splenomegaly prior to Week 24 will not have the option to cross over. In addition, patients in the experimental group who have progressive disease due to splenomegaly at any time will not have the option to cross over. Data collected as part of the crossover period will be analyzed descriptively.

6.6.2. Operational Considerations for Crossover

At the time of crossover consideration, patients will be fully informed of the crossover treatment option within the study, as well as all available treatment options, including approved and investigational, outside of the study as part of re-consenting (Section 10.1.3). Patients who opt in for the crossover treatment must also be re-evaluated against applicable entry criteria (Section 6.6.3) to determine if they are still eligible for study participation. While awaiting determination of eligibility for crossover, patients will continue receiving treatment with ruxolitinib without dose increases. Patients who discontinue the double-blind study treatment without crossing over and those who cross over and subsequently discontinue the open label study treatment will remain on study for survival follow-up (Section 4.5.3). Unblinding will only occur after it is confirmed by the unblinded medical monitor that the patient met eligibility criteria for crossover.

Since patients will have to be unblinded before a crossover decision can be made, selected data collected up to the point when a patient is being considered for a possible crossover will be cleaned and locked prior to the revelation of treatment assignment. In the event that any of the locked data change after unblinding, such a change will be treated as an unlocking of a locked patient variable and documented in full detail.

The goal prior to unblinding is to minimize any potential for bias in measures that could have impact due to their subjectivity. The following are variables that would be locked prior to unblinding at a patient level for a potential crossover:

- Spleen volume (Section 8.2.1)
- MFSAF (Section 8.2.2)
- Bone marrow fibrosis scoring (Section 8.2.1)
- Transfusion data (Section 8.1)
- Hematology values (Section 8.3.5)
- PGIC (Section 8.2.2)
- EQ-5D (Section 8.2.2)
- AE components, including relatedness, seriousness, and intensity (Section 8.4)

6.6.3. Clinical Considerations for Crossover

Eligibility

Patients must meet the following inclusion criteria at the time of crossover being considered:

- Splenic progression (≥25% increase from baseline) assessed by central review within 28 days of initiating crossover
- Have acceptable laboratory assessments obtained within the 28-day crossover screening interval:
  - ANC ≥ 1×10^9/L in the absence of growth factors for the previous 4 weeks
  - Platelet count ≥ 75×10^9/L in the absence of growth factors or platelet transfusions for the previous 4 weeks
  - Peripheral blood blast count < 5%
  - AST and/or ALT ≤ 2.5 × ULN of the local reference interval (≤ 5 × if the elevation can be ascribed to hepatic MF involvement, e.g., presence of hepatomegaly)
  - Serum direct bilirubin < 2.0 × ULN of the local reference interval
  - Calculated or measured CrCl of ≥ 45 mL/min
- ECOG performance status of ≤ 2
- Life expectancy > 24 weeks per Investigator assessment
- Have fully recovered from major surgery and interventions
- Both male and female patients and partners of patients, with reproductive potential, must agree to use at least one highly effective contraceptive method per Inclusion Criteria 12 (Section 5.1)
- Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol
- Receiving ruxolitinib for ≥24 weeks and on a stable dose of ruxolitinib for ≥8 weeks
- Has not received another systemic anti-cancer treatment, except for hormonal therapy and ruxolitinib, during the crossover screening interval.

Patients who have progressive disease based on leukemic transformation or who are unable to continue on ruxolitinib due to AEs will not be eligible for crossover.

Starting Doses and Uptitration Criteria

The ruxolitinib dose should remain the same as at the time of crossover and for at least 2 crossover cycles unless a dose modification is required for toxicity.

The starting dose of pelabresib in the crossover will be 125 mg QD, the same as used in the experimental group at Cycle 1 Day 1. Dose increase up to 175 mg QD is allowed if the criteria defined below are met:

- Platelet count $\geq 125 \times 10^9$/L over the course of the previous cycle
- ANC $>0.75 \times 10^9$/L
- No AE requiring any dose interruption and/or reduction in the previous crossover cycles

NOTE: if the above criteria are met, the pelabresib dose can be increased in 25 mg QD increments and not more frequently than once every 2 cycles, to a maximum dose of 175 mg QD.

Dose Modifications

Follow the guidelines specified in Section 6.5.3.

Assessments and Procedures

Patients who cross over will follow the same SoA as in the double-blind treatment period (Section 1.3). However, patients will restart the crossover treatment at Cycle 1 Day 1 assessments (i.e., Cycle 1 Day 1 of the crossover treatment is the day on which the patient receives the first dose of the open-label experimental treatment).

Patients who discontinue crossover study treatment will still continue on study for survival follow-up according to the time points in the SoA.

6.6.4. Statistical Considerations for Crossover

The crossover design will have no impact on the analysis of the primary (splenic response at Week 24) and key secondary (TSS response at Week 24) endpoints, as the crossover will only occur after the Week 24 assessments. Since spleen volume will be independently assessed in a blinded fashion, and since the MFSAF questionnaire cannot be altered for any reason, these endpoints will not be affected by unblinding.

The efficacy data collected during the crossover treatment period will be summarized in a descriptive manner. For safety analysis, an AE that occurs after the administration of the first dose of open-label experimental treatment will be considered treatment-emergent for the crossover treatment period. However, a TEAE for the crossover treatment period that occurs within 30 days after the last dose of double-blind treatment will be considered treatment-emergent for the double-blind treatment period as well.

6.7. Supportive Care

6.7.1. Nausea and/or Vomiting

6.7.1.1. Prophylaxis for Nausea and/or Vomiting

It is strongly recommended that patients receive oral nausea/vomiting prophylaxis for the first 2 cycles prior to doses of pelabresib/placebo. To this end, patients are recommended to receive ondansetron 4 to 8 mg QD PO (or a comparable antiemetic) 30 minutes before each pelabresib/placebo dose from Cycle 1 Day 1 through the first 6 weeks of treatment or other anti-emetic therapy as per the Investigator's clinical judgment with regards to potential drug-drug interaction.

6.7.1.2. Management of Nausea and/or Vomiting

If a patient still experiences ≥ Grade 3 nausea/vomiting despite prophylaxis, consider following the NCCN guidelines or local applicable guidelines for the treatment of nausea/vomiting.

From the Phase 2 experience, separation of pelabresib/placebo and ruxolitinib intake by a few hours or pelabresib/placebo intake in the evening prior to bedtime may mitigate gastrointestinal AEs (i.e., nausea and vomiting). Evening administration of pelabresib/placebo should be avoided on days prior to PK assessments (time points noted in the SoA [Section 1.3]).

In addition to using prophylactic/supportive medications for these gastrointestinal AEs, it is important to guide patients to drink plenty of non-caffeinated fluids to replace the body fluid lost and follow a proper diet. The Sponsor also recommends close monitoring of renal function for early identification of any potential abnormality secondary to dehydration and/or other comorbidities.

Refer to Table 4 for ruxolitinib and pelabresib/placebo dose hold and restarting criteria and dose for nausea and vomiting.

6.7.2. Management of Diarrhea

Patients who develop diarrhea should be treated with anti-diarrhea medication, such as loperamide, as per standards of care and/or institutional guidelines. Fluid intake should be maintained to avoid dehydration.

Patients who develop significant new or worsening diarrhea during study treatment must be contacted by the Investigator or study nurse daily until it is clear that the problem has resolved or requires additional support (e.g., hospitalization). Subsequently, the prophylactic use of anti-diarrheal medication is allowed for those patients as needed.

From the Phase 2 experience, separation of pelabresib/placebo and ruxolitinib intake by a few hours or pelabresib/placebo intake in the evening prior to bedtime may mitigate gastrointestinal AEs, including diarrhea.

Refer to Table 4 for ruxolitinib and pelabresib/placebo dose hold and restarting criteria and dose for diarrhea.

6.7.3. Management of Rash

Patients who develop rash should be treated with supportive care as follows: for Grade 1, provide an oral antihistamine (e.g., hydroxyzine) as needed and a topical corticosteroid cream as needed. For ≥ Grade 2, begin a course of oral prednisone 10 mg once daily for 1 week, followed by 5 mg once daily until rash resolves to ≤ Grade 1. For subsequent doses, premedication may be administered at the discretion of the Investigator. In cases of Grade 4 rash, pelabresib/placebo must be discontinued.

Refer to Table 4 for ruxolitinib and pelabresib/placebo dose hold and restarting criteria and dose for rash.

6.7.4. Management of Ruxolitinib Discontinuation Syndrome (RDS)

Instances of severe adverse events occurring subsequent to ruxolitinib withdrawal have been reported in the literature. RDS includes clinical manifestations ranging from acute relapse of disease-related symptoms, rapid spleen volume enlargement, and worsening of cytopenias to more severe complications, such as acute respiratory distress, DIC, splenic infarction, and tumor lysis-like syndrome.

The incidence of RDS has been reported in approximately 15% of patients after discontinuation of ruxolitinib, with severe cases (defined as requiring IV medication, hospitalization, splenectomy, or HSCT delay) occurring in 1-11% of cases (Palandri et al., 2021; Shanavas et al., 2016; Tefferi et al., 2011). The risk of RDS was significantly higher in patients with a greater burden of the disease with massive splenomegaly; patients with low platelet count were also at an increased risk (Palandri et al., 2021). RDS is mainly a diagnosis of exclusion. There are no specific clinical features, laboratory or histopathology findings that are diagnostic, and the syndrome can be suspected based on the temporal relationship between drug withdrawal and onset of clinical manifestations that can appear from less than 24 hours up to 3 weeks after discontinuation, with median time of onset of 7 days after the last ruxolitinib dose, with severe cases typically occurring earlier (Palandri et al., 2021).

Based on the literature, the following steps are reasonable measures to mitigate this risk once a decision about treatment discontinuation or interruption is made:

- A ruxolitinib taper instead of abrupt discontinuation is recommended where appropriate:
  - Example of commonly used tapering strategy: decrease ruxolitinib dose by 5 mg BID every 2 weeks, consider additional lowest dose of 5 mg daily dose before stopping
- For high-risk patients (high disease burden, low platelets), consideration may be given to a planned bridge to alternative MF therapy to start immediately after ruxolitinib discontinuation
- For patients developing symptoms of RDS, consider urgent resumption of treatment with ruxolitinib, steroids, and supportive care (Palandri et al., 2021; Tefferi et al., 2011)

- Provide patient education about the symptoms of RDS and the importance of prompt reporting and the need to be evaluated in person for signs and symptoms of RDS if needed during the window when RDS may be expected (up to 3 weeks after ruxolitinib discontinuation)

6.8. Concomitant Therapy

The following concomitant medications are prohibited during study treatment (and some require a washout period, as noted below):

- Systemic anti-neoplastic medications, including hydroxyurea and anagrelide. Patients should discontinue hydroxyurea or anagrelide 24 hours prior to the first dose of study drug. If alternative anti-MF therapy is required for treatment of the patient's disease, the patient should be discontinued from study drug and the reason for removal recorded in the eCRF.
- Myeloid, erythroid or thrombopoietin growth factor or androgenic steroids. Patients should discontinue use of any of these growth factors or androgenic steroids 4 weeks prior to the first dose of study drug.
- Strong CYP3A4 inhibitors or inducers, including St. John's wort (Section 10.8)
- Immunosuppressive agents with systemic activity (topical agents without systemic activity like eye drops with calcineurin inhibitors such as cyclosporine A or tacrolimus are allowed)
- Live vaccinations. Live vaccination within 30 days prior to the first dose of study drug, during study treatment, and for 90 days after the last dose of study drug, is prohibited except for COVID-19 vaccination (see below).
  - The potential effects of pelabresib on COVID-19 vaccine efficacy or safety is not known at this time. Vaccination with synthetic or inactivated anti-COVID-19 vaccines is not prohibited during the study; however, whenever feasible, it is recommended to complete vaccination against COVID-19 before the start of study treatment. Potential of vaccination with live anti-COVID vaccines or with any anti-COVID vaccines which use live viral vector as a platform of delivery should be discussed with the Sponsor's Medical Monitor and applied on a case-by-case basis with regards to existing clinical safety and efficacy data, risk/benefit analysis, and patient status as per investigator's clinical judgment, local and institutional regulations, and standards of care.
- Pelabresib inhibits CYP2C19 in vitro. Therefore, concomitant medications with a narrow therapeutic window metabolized through CYP2C19 should be monitored for adverse reactions. Alternative treatment to clopidogrel should be considered if indicated. If warfarin is indicated, it is recommended to monitor international normalized ratio (INR) more closely when treatment with pelabresib is initiated.
- Pelabresib showed potential to inhibit CYP2C8 and to induce CYP2C8 and CYP3A in vitro. Narrow therapeutic index substrates of CYP2C8 and CYP3A should be used with caution and monitored for drug-related adverse events and loss of efficacy. In

addition, concomitant use of pelabresib with hormonal contraceptives should be avoided. If concomitant use cannot be avoided, an alternative contraceptive that is not affected by enzyme inducers (e.g., intrauterine system) or additional non-hormonal contraception (e.g., condoms) should be recommended since pelabresib has the potential to reduce the exposure, and possibly the efficacy of the hormonal contraceptives.

Pelabresib has demonstrated no potential to prolong the QT interval during its preclinical evaluation, including a study in telemeterized dogs. To date, there has been no clinically relevant prolongation of QTc noted on ECGs in any of the three Phase 1 studies of pelabresib. Despite this, it is recommended that treatment with medications that are known to prolong the QT interval be used with caution.

Acceptable concomitant medications include:

- Topical, nasal intra-articular, and inhaled corticosteroids, and daily doses of ≤ 10 mg QD oral prednisone or equivalent (pelabresib/placebo dose hold not required). Daily doses up to 20 mg oral prednisone or equivalent may be allowed for ≤7 days if indicated, after consultation with the Sponsor or its designee. A pelabresib/placebo dose hold is required and can be resumed at least 1 week after completion of the higher dose (≥10 mg) steroid treatment.
- Supportive care measures, as detailed in Section 6.7

6.9. Contraception

Instructions on the use of effective contraceptive measures during and after study treatment follow the current recommendations of the HMA/CTFG and EMA.

6.9.1. Female Patients

Female patients of childbearing potential (WOCBP) are required to use at least one highly effective method of contraception (preferably low user dependency contraception methods, in particular when contraception is introduced as a result of participation in a clinical study) while receiving study drug and for 184 days after the last dose of study drug.

Women will be considered of childbearing potential after the onset of their first menstrual period. Women who are documented as being of nonchildbearing potential (postmenopausal or having undergone surgical sterilization) are exempt from this requirement. Women will be considered postmenopausal if they have had 12 months of consecutive spontaneous amenorrhea or less than 12 months of consecutive spontaneous amenorrhea and a serum FSH level > 40 mIU/mL at Screening. Women will be considered surgically sterile if they are post-hysterectomy, 6 months post-surgical bilateral oophorectomy, or 6 months post-surgical salpingectomy.

In accordance to CTFG guidelines, highly effective contraceptive methods for WOCBP are:

- Combined (estrogen and progestogen containing) hormonal birth control associated with inhibition of ovulation[#]
  - Oral[*]

  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[#]
  - Oral[*]
  - Injectable
  - Implantable[**]
- Intrauterine device (IUD)[**]
- Intrauterine hormone-releasing system (IUS)[**,#]
- Bilateral tubal occlusion[**]
- Vasectomised partner[**, +]
- Sexual abstinence if the preferred and usual lifestyle of the male and female subjects, and partners of subjects

[#] *Concomitant use of pelabresib with hormonal contraceptives should be avoided. If concomitant use cannot be avoided an alternative contraceptive that is not affected by enzyme inducers (e.g., intrauterine system) or additional non-hormonal contraception (e.g., condoms) should be used, since pelabresib has the potential to reduce the exposure, and possibly the efficacy, of hormonal contraceptives.*

***** *If patients have been experiencing vomiting or diarrhea, the investigator should consider avoiding oral hormonal contraceptives as highly effective contraceptive methods and should consider other contraceptive methods listed above.*** *Contraception methods that are considered to have low user dependency.*

[+] *Azoospermia must be documented in repeated examinations of the ejaculate before the first dose of study drug (Day 1) and/or demonstration of the absence of the vas deferens on ultrasound before the first dose of study drug (Day 1).*

It is highly recommended for male partners of female patients of childbearing potential to use additional highly effective contraception methods in combination.

6.9.2. Male Patients

Due to the potential risk of genotoxicity based on pre-clinical data, male patients regardless of fertility must use a condom during sexual intercourse while receiving study drug and for 94 days after the last dose of study drug.

6.9.3. Female Partners (WOCBP, Non-pregnant) of Male Patients

It is highly recommended for female (WOCBP, non-pregnant) partners of male patients to use additional highly effective contraception methods (listed above) in combination with male condom.

6.9.4. Oocyte and Sperm Donation

Donation of oocytes by the female patients during the study and for 184 days after the last dose of study drug is not allowed. Donation of sperm by the male patients during the study and for 94 days after the last dose of study drug is not allowed.

7. DISCONTINUATION OF STUDY DRUG AND PATIENT WITHDRAWAL FROM THE STUDY

7.1. Discontinuation of Study Drug

Study treatment is to be permanently discontinued for patients meeting any of the following criteria:

- Patients who were randomized, but not able to start treatment within 28 days of the start of screening. Study treatment is defined as the combination of pelabresib + ruxolitinib or placebo + ruxolitinib.
- Unacceptable toxicity
- Disease progression (as defined below), with the exception of patients in the control group who cross over to receive the experimental treatment (Section 6.6)
- Patients undergoing splenectomy
- Patients proceeding to stem cell transplantation (permitted for eligible patients who have completed at least 24 weeks of study treatment)
- Need for intervention or therapy (determined by the Investigator to be medically necessary) that is precluded by study participation according to the protocol.
- Patient noncompliance with study treatment/procedures or voluntary withdrawal of consent
- Female patient who becomes pregnant or suspects pregnancy

Progressive disease is defined by meeting 1 of the following criteria:

- Progressive splenomegaly, defined as enlargement of spleen volume by MRI or CT scan of ≥25% compared to the baseline value, as confirmed by the central radiology review
- Leukemic transformation, confirmed by a bone marrow blast count of ≥20%
- A peripheral blood blast percentage of ≥20% associated with an absolute blast count of $\geq 1 \times 10^9$/L that persists for at least 2 weeks

For patients progressing via imaging (MRI or CT scan), confirmation of progression by central radiology review is required. Study drug should only be discontinued while waiting for confirmation of progression if the patient is experiencing toxicities. Central review of imaging and confirmation of disease progression is not required for the other two clinical criteria for progression, i.e., leukemic transformation of bone marrow and increase in peripheral blood blast percentage. Patients who are determined by the central read of the scans not to have progressive

disease will continue on study treatment unless there is progression by clinical criteria. Patients who have progressed may either be discontinued from treatment (if in the experimental group) or crossed over to the treatment group (if in the control group; Section 6.6).

EOT and follow-up visits for progression and survival are required for all patients according to the timing detailed in the SoA (Section 1.3). The safety follow-up visit may be conducted by telephone. All patients will be followed for AEs and SAEs for 30 days following the last dose of pelabresib/placebo or the start of alternative (off-study) treatment for MF, whichever occurs first, at the time points noted in the SoA. Patients who discontinue study treatment and refuse to return for the EOT visit will be contacted for safety evaluations during the 30 days following the last dose of pelabresib/placebo. Patients who discontinue treatment for reasons other than documented disease progression should have follow-up visits every 12 weeks to document response by imaging, and transfusion requirements until initiation of another anti-cancer therapy, progression, death, or the end of the study, whichever comes first. Continuing ruxolitinib monotherapy as standard-of-care treatment after the discontinuation of treatment on study is not considered the initiation of another anti-cancer medication/therapy. Imaging collected during the progression-free survival follow-up will be sent to central review for analysis. Patients who discontinue study treatment for documented disease progression or start another anti-cancer medication/therapy should have a follow-up visit/phone call every 12 weeks to document overall survival. Information on subsequent anti-MF therapy will be collected in both follow-up periods.

7.2. Patient Withdrawal from the Study Treatment/Study

A patient may withdraw from the study treatment/study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

Patients have the option to withdraw from study treatment and stay in the follow-up or to withdraw from the study entirely. At the time of withdrawing from study treatment, if possible, an EOT visit should be conducted, as shown in the SoA (Section 1.3). The patient will be permanently discontinued from study treatment and enter the appropriate follow-up period. Patient's may withdraw from the follow-up phase at the same time as study treatment or later.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3. Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in

the study. These contact attempts should be documented in the patient's medical record.

- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study (Section 7.2).

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.11.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3).

Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed to confirm that potential patients meet all eligibility criteria.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA. If an AE or SAE occurs that causes a drug hold, directions in Section 6.5 should be followed regarding study visits and dose holds. If a visit is delayed for reasons other than an AE/SAE, e.g., a winter storm delays the visit by 3 days, Day 1 of the cycle and dosing should be delayed until the patient is able to come to the clinic. If a visit occurs early due to any reason, no dosing should occur until the patient has completed the mandatory 7-day break between cycles.

As detailed in the SoA, patients should be seen in the clinic by the Investigator or designee during screening, and on Days 1 and 14 of Cycle 1. Subsequently, patients should be seen in the clinic by the Investigator or designee on Day 1 of all cycles through Cycle 9 Day 1 to assess wellbeing and compliance with the study. After the Cycle 9 Day 1 visit, the frequency of study visits may be reduced such that patients are only seen in the clinic by the Investigator or designee every odd cycle (Cycle 11, Cycle 13, etc.) provided that the patient is tolerating the study treatment and the doses of pelabresib/placebo and ruxolitinib have remained stable for at least 6 weeks.

8.1. Demographics and Medical History Assessments

Patient demographics will be documented during screening and will include patient's year of birth, gender, ethnicity, and race.

The patient will have a complete medical history taken to include all past and ongoing medical conditions. The medical history will also include details on the MF diagnosis with a description of all related prior therapies, including treatment dates, dosage, response on therapy including symptom, spleen and transfusion responses, and reasons for treatment discontinuation.

Additionally, concomitant medications will be listed and will include all medications being taken at the time points included in the SoA (Section 1.3).

8.2. Efficacy Assessments

8.2.1. Disease Status Assessments

The patient's disease status will be evaluated by measurement of peripheral blood counts, history/documentation of transfusion requirements, MF-associated symptoms, spleen size by palpation and by MRI/CT, and grading of bone marrow fibrosis as assessed by bone marrow biopsy. Disease status assessment should be performed at the end of double-blind treatment and at the end of progressive disease follow-up.

A complete transfusion history for the 16 weeks prior to Cycle 1 Day 1 and throughout the study will be taken at the time points noted in the SoA (Section 1.3) to include the date, type (e.g., whole blood, platelets, packed cells), number of units of the transfusion, as well as the hemoglobin and platelet values prior to the transfusion.

MRI is preferred method of imaging for spleen volume measurement. An MRI (or CT scan) will be done at the time points noted in the SoA (Section 1.3). The imaging method should remain consistent throughout the study (i.e., if MRI was used at screening, MRI should also be used for all subsequent visits). An MRI or CT scan should be repeated at the EOT visit only if progressive disease has not been previously documented or, in the absence of documented progressive disease, imaging has not been performed within the previous 6 weeks. Local practices for spleen volume assessment should be used. Imaging data for spleen volume measurement (imaging studies, derived assessments, and reports) must be available for central radiology review for all imaging time points noted in the SoA, including screening. Details on the central radiology review will be provided in a charter, provided as a document separate from the protocol.

Bone marrow biopsy samples will be collected as specified in the SoA (Section 1.3) and assessed by a local hematopathologist for grading of bone marrow fibrosis following the European classification (Thiele et al., 2005) for a timepoint IWG-MRT response evaluation (Tefferi et al., 2013) (Section 10.7). Three stained slides [one slide of each: H&E, reticulin, and trichrome] that were used for local review and 6-10 unstained slides should be sent to the central lab for storage prior to analysis for central pathology review and exploratory assessment. If stained slides are unable to be sent for central review per institution policy or due to any other reason, 10 unstained slides should be sent to the central lab for central pathology review and exploratory assessment. Refer to the laboratory manual and flow chart for details on the collection, handling, storage, and/or shipping of bone marrow samples.

The bone marrow biopsy sample at screening does not need to be repeated if obtained within 12 weeks of Cycle 1 Day 1. The EOT bone marrow biopsy does not need to be collected if a biopsy has been performed within the previous 12 weeks.

Bone marrow biopsy samples may also be used for exploratory assessment of changes in hematopoietic cell populations and transcriptomic analyses.

8.2.2. Patient-Reported Outcomes

The MFSAF assessment (version 4.0) should be completed electronically every day irrespective of any cycle delays starting from at least 7 days prior to randomization until 12 weeks after the end of treatment. The MFSAF asks patients to rate the severity of each of seven symptoms (fatigue, night sweats, pruritus, abdominal discomfort, pain under the ribs on the left side, early satiety, and bone pain) at its worst during the past 24 hours using a 0 (absent) to 10 (worst imaginable) numeric rating scale. See Section 10.6 for more information about the MFSAF.

Patients are requested to complete the PGIC assessment electronically on a weekly basis after the start of study treatment irrespective of any delay in cycle due to drug hold. Patients should complete the PGIC on the same day each week until 12 weeks after the end of treatment. The PGIC is a single question to assess the patient's impression of change in their MF symptoms since the start of study treatment. The PGIC has been widely used to evaluate a patient's overall sense of whether a treatment has been beneficial. The patient will answer the following question: "Since the start of the treatment you've received in this study, your myelofibrosis symptoms are (1) Very much improved, (2) Much improved, (3) Minimally improved, (4) No change, (5) Minimally worse, (6) Much worse, (7) Very much worse."

Patients are requested to complete the EQ-5D assessment electronically on a weekly basis during both the screening and treatment periods irrespective of any delay in cycle due to drug hold. Patients should complete the EQ-5D on the same day each week until 12 weeks after the end of treatment. The EQ-5D measures a patient's health-related quality of life across 5 different domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

8.3. Safety Assessments

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the SoA (Section 1.3). Toxicity will be assessed according to the NCI CTCAE, v5.0. The Investigator should carefully assess all treatment-associated toxicities and, whenever possible, determine if they can be attributed to ruxolitinib alone, pelabresib/placebo alone, or to the combination of ruxolitinib + pelabresib/placebo.

8.3.1. Concomitant Medications

Any other permitted medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

8.3.2. Physical Examinations, Including Spleen Examination, and Vital Signs

A complete physical examination will be performed at the time points noted in the SoA (Section 1.3) and will include general appearance, HEENT, neck, cardiovascular, thorax/lungs, breasts, abdomen, genitourinary, musculoskeletal, lymph nodes, skin, neurological and mental

status examination. Abdominal examination will include splenomegaly and hepatomegaly. The edge of the spleen shall be determined by palpation, and measured in centimeters, using a soft ruler from the costal margin to the point of greatest splenic protrusion. Targeted physical exams may be focused on areas of known disease and potential areas of MF involvement. A targeted physical examination must include weight and examination of the abdomen to assess the spleen length by palpation.

Height and weight will be assessed at the time points noted in the SoA (Section 1.3). BMI will be calculated using these assessments.

The physical examination performed during screening does not need to be repeated on Cycle 1 Day 1 if it is conducted within 72 hours of the first dose of study drug.

Vital signs (temperature, pulse rate, respiratory rate, and blood pressure) will be assessed at the time points noted in the SoA. Vital signs should be conducted ≤ 72 hours before the start of each scheduled cycle. Blood pressure and pulse measurements should be assessed in the same position at each time point and should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions.

The Investigator will evaluate the clinical significance of any abnormal findings on physical examinations or vital sign assessments. Pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not AEs, but are recorded as medical history. If any clinically significant abnormal findings are reported after informed consent or if any pre-existing conditions worsen during the study, these must be recorded as AEs.

8.3.3. ECOG Performance Status

ECOG performance status will be assessed at the time points noted in the SoA (Section 1.3). ECOG assessment should be conducted ≤ 72 hours before the start of each scheduled cycle.

8.3.4. Electrocardiograms

A single 12-lead ECG will be obtained at the time points noted in the SoA (Section 1.3) at least 1 hour after dosing of study drug. Additional unscheduled ECGs should be performed per investigator judgment (e.g., in the event of ≥ Grade 3 plasma potassium increase [see Section 10.2] or hyperkalemia).

The Investigator will evaluate the clinical significance of the ECGs. Clinically significant abnormal findings will be reported as AEs.

Approximately 200 patients will have ECGs from screening to Week 24 assessed both locally for safety and centrally for QT/QTcF effects of patients taking ruxolitinib and pelabresib in comparison to patients taking ruxolitinib and placebo. ECGs will be collected and sent to the vendor to be centrally read in real time or may be centrally read retrospectively. Patient selection for ECG analysis will be based on time of enrollment into study. Approximately the last half of patients enrolled will be sent to central review for analysis.

8.3.5. Clinical Safety Laboratory Assessments

The laboratory assessments to be collected during the study at the time points noted in the SoA (Section 1.3) are detailed in Section 10.2. These assessments include hematology, clinical chemistry, coagulation parameters, serum lipids, HbA1c, and pregnancy testing (only in female patients of childbearing potential).

Laboratory assessments should be completed at a local lab whenever possible.

Laboratory assessments performed during screening do not need to be repeated on Cycle 1 Day 1 if they are conducted within 72 hours of the first dose of study drug.

The Investigator will review the laboratory results and evaluate and record whether the results are normal or abnormal and whether abnormal results are non-clinically significant or clinically significant. Pre-existing clinically significant conditions diagnosed as a result of the screening procedures must be recorded as medical history. If any clinically significant abnormal findings are discovered after signing the ICF or any pre-existing conditions worsen during the trial, these must be recorded as AEs. The laboratory report will be signed and dated by the Investigator.

8.4. AEs and SAEs

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE throughout the study and remain responsible for following up AEs that are considered at least possibly related to the study drug or study procedures, or that caused the patient to discontinue study drug or withdraw from the study (Section 7), and all SAEs until event resolution, stabilization, the event is otherwise explained, or the patient is lost to follow up (Section 7.3).

8.4.1. AE and SAE Definitions

An AE is any untoward medical occurrence in a patient administered a study drug that does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not it is considered to be related to the study drug. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

A clinical laboratory AE is any laboratory value that is considered clinically significant by the Investigator and has caused a medical intervention, dose hold, dose reduction or schedule change. Laboratory abnormalities that have not required medical intervention should not be recorded as AEs and will be captured and reported in the clinical study report.

An SAE is any untoward medical occurrence that at any dose:

- Results in **death**
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the event as it occurred (i.e., it does not include an event that hypothetically might have caused death had it occurred in a more severe form).
- Requires in-patient **hospitalization or prolongation of existing hospitalization** (see clarification below on planned hospitalizations). Hospitalization means that the

patient was admitted to the hospital as an in-patient for a period of at least 24 hours. Over-night stays for observation, stays at an emergency department, or treatment on an out-patient basis do not constitute hospitalizations. However, medical judgment must always be exercised and when in doubt the case should be considered serious (i.e., if case fulfills the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute an SAE.

- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a **congenital anomaly/birth defect**
- Is an **important medical event**. An important medical event is an event that may not immediately result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or may require medical or surgical intervention to prevent 1 of the outcomes listed in the definition above for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of drug dependency or drug abuse.

Intensity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

8.4.2. Time Period and Frequency for Collecting AE and SAE Information

All AEs, both non-serious and serious, and deaths will be collected and recorded on the eCRF from the signing of the ICF through 30 (±3) days after administration of the last dose of pelabresib/placebo or the start of alternative (off-study) treatment for MF, whichever occurs first, at the time points noted in the SoA.

All SAEs, including deaths that occur during the course of the study and designated safety follow-up period, must be recorded, and reported by the Investigator to the safety contract research organization following instructions provided in supplemental study materials within 24 hours from the point in time when the Investigator becomes aware of the SAE.

Any SAE, including deaths, that occurs at any time after 30 days after the last dose of pelabresib/placebo and that the Investigator considers to be related to pelabresib/placebo must be recorded and reported to the Safety CRO within 24 hours of the site's knowledge of the event.

See Section 10.3 for more information about reporting SAEs.

In addition to the above, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor or its designee in the same timeframe as SAEs to meet certain local requirements:

- Is a secondary malignancy that is not a condition of this study
- Is associated with an overdose (Section 8.4.8)

Each case of COVID-19 infection, including asymptomatic infections and/or COVID-19-related medical conditions, should be recorded as an AE in the clinical database and appropriately

assessed for intensity/severity and for seriousness. If available, Investigators should provide additional information on the confirmatory test, COVID-19 vaccination status, treatment received for COVID-19 infection, and actions taken with study drugs due to COVID-19 infection events.

8.4.3. Method of Detecting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded in the appropriate section of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

If a patient suffers from the same AE more than once and the patient recovers in between the events, the AEs should be recorded separately. If an AE changes in intensity, a worst-case approach should be used when recording the event, i.e., the highest intensity and the longest duration of the event.

Any laboratory abnormality, vital sign finding, or finding from physical examination that is assessed as clinically significant by the Investigator will be considered as an AE (pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not AEs, but are recorded as medical history).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study or before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned).

NOTE: A procedure is not an AE; the reason for conducting the procedure is. Hospitalization is not an AE; the reason for hospitalization is. Death is not an AE; the cause of death is (an exception is sudden death of unknown cause, which is an AE).

The Investigator must report all SAEs, whether or not considered to be causally related to the study drug, that occurred from the signing of the ICF through 30 days (± 3 days) after administration of the last dose of pelabresib/placebo or the start of alternative (off-study) treatment for study indication, whichever occurs first, and all SAEs considered related to pelabresib/placebo that occurs after 30 days of the last dose of pelabresib/placebo, to the Safety CRO as noted in Section 8.4.2. The information collected will include a minimum of the following: patient identification number, a narrative description of the event, and an assessment by the Investigator as to the intensity of the event and relatedness to study intervention. A sample of the SAE Form may be found in the supplemental study materials. Follow-up information on the SAE may be requested by the Sponsor or the Safety CRO.

When recording a death on an eCRF or SAE paper report form, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept.

Further details on recording and follow-up of AEs and SAEs can be found in Section 10.3.

Intensity for each AE and SAE, including any laboratory abnormality, will be determined by using the NCI CTCAE, Version 5.0 (Section 10.3).

For both non-serious AEs and SAEs, relationship to study intervention administration will be determined by the Investigator according to best medical judgment by selecting one of the options of definitely related, probably related, possibly related, unlikely related and not related. Further details are provided in Section 10.3.

8.4.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs considered at least possibly related to study drug and all SAEs that occur during the reporting period (during the course of the study and designated safety follow-up period) will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor or its designee (Safety CRO) of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor or Safety CRO will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators. SAEs will be considered reportable regardless of whether or not the study intervention was used in accordance with the provisions in the protocol and the Investigator's Brochure. In addition, all AEs resulting from study drug overdose (Section 8.5) and all secondary malignancies, even if not meeting any seriousness criterion, should be reported as if they were SAEs (Section 8.4.2).

Investigator safety reports must be prepared by the Sponsor and/or Safety CRO for SUSAR according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor and/or Safety CRO will review and then file it along with the current version of the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.6. Pregnancy

A positive urine pregnancy test requires immediate interruption of study drug until serum HCG is performed and found to be negative. If a female patient or a female partner of a male patient becomes pregnant or suspects pregnancy while participating in this study and during the follow-up contraception period (184 days after the last dose of study drug), the Investigator must be informed immediately. If a female patient becomes pregnant or suspects pregnancy, they must permanently discontinue study drug (if applicable). The pregnancy must be reported to the Safety CRO within 24 hours of the site's knowledge of the pregnancy in accordance with the instructions provided in the supplemental study materials. The pregnancy must be followed through the final pregnancy outcome and one month after the expected due date. Abnormal

pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. Any outcome which the Investigator and/or the Sponsor considers to be related to the study intervention will be treated as an expedited report.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes

The FDA guidance on safety reporting directs Sponsors to specify AEs that may be common in the study population and as such may not meet the guidance criteria for expedited reporting. Per the guidance, a limited number of occurrences of an AE in a study population in which occurrences of the event are anticipated independent of drug exposure, do not constitute an adequate basis to conclude that the event is a "suspected adverse reaction." An individual occurrence of one of these SAEs is uninformative as a single case, and therefore it will not be considered as a "suspected adverse reaction."

Patients with advanced hematological malignancies, the patient population to be enrolled in this study, are at risk for many AEs as a result of their disease and the consequences of prior therapy. Expected events due to MF or to the treatment of MF are listed below and will not be subject to expedited reporting to the Health Authorities as an ICSR unless they are thought to be related to study drug; however, if any of the below meet the definition of serious during the study reporting period, they should be reported to the Safety CRO as noted in Section 8.4.2:

- AEs related to myelosuppression and bone marrow activity
  - Anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia, leukocytosis
- Electrolyte abnormalities (sodium, potassium, bicarbonate, magnesium)
- Chemistry abnormalities (LDH, phosphate, calcium, protein, albumin, uric acid, glucose)
- Liver function test abnormalities (ALT, AST, direct and total bilirubin, alkaline phosphatase)
- Renal function test abnormalities (creatinine, BUN/urea)
- Coagulation abnormalities
- Bone, joint, or muscle pain
- Renal failure related to tumor lysis syndrome

When reporting an event of progression of the disease under investigation, specific manifestations, or signs/symptoms of the progression (e.g., "malignant pleural effusion," "lymphadenopathy from underlying cancer") should be reported, rather than the general term "disease progression." If a death is attributed to progression of disease, where the specific manifestations of the progression cannot be identified, record "disease progression" as the SAE term on the SAE paper report form.

The occurrence of these AEs will be monitored by the Sponsor and an expedited report will be submitted if an aggregate analysis indicates that the events are occurring more frequently or at greater intensity or for longer duration than in historical control groups.

8.4.8. Adverse Events of Special Interest (AESIs)

Selected non-serious and serious adverse events are also known as AESIs and must be reported within 24 hours to the Safety CRO. For the time period beginning when the ICF is signed through 30 days after administration of the last dose of pelabresib/placebo or the start of alternative (off-study) treatment for MF, whichever is earlier, any AESI, or follow up to an AESI, whether related to study drug or not, must be reported within 24 hours to the Safety CRO.

AESIs for this trial include:

1. Treatment discontinuation syndrome: exacerbation of MF symptoms following interruption or discontinuation of study treatment, fever, respiratory distress, hypotension, DIC, or multi-organ failure
2. Acute respiratory distress syndrome (ARDS)

8.5. Treatment of Overdose

For this study, any dose of study drug greater than the recommended Phase 2 dose of pelabresib (225 mg QD; Section 4.3) per day or greater than 50 mg (25 mg BID) of ruxolitinib per day will be considered an overdose. The Sponsor does not recommend specific treatment for an overdose. In the event of an overdose, the Investigator should contact the Sponsor's Medical Monitor or its designee immediately and the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. Overdoses should be reported according to Section 8.4.2.

8.6. Pharmacokinetics

Blood samples (approximately 4 mL per sample) will be collected for the determination of pelabresib and its metabolites M542/M544 as well as ruxolitinib concentrations in plasma. The specific collection timepoints are listed in Table 5. When PK sampling coincides with 12-lead ECGs, blood draws for PK should be taken within 5 minutes after ECG assessment.

Actual collection date and time of each PK sample will be recorded on the eCRF. On days when PK and/or pharmacodynamic samples need to be collected prior to taking study drug, the patient should take that day's pelabresib/placebo and/or ruxolitinib dose in the clinic.

Additional details regarding the collection, handling and shipping of samples are provided in the laboratory manual and flow chart.

Table 5: Pharmacokinetic Collection Time Points

Dosing Day	Collection Timepoint and Windows
C1 D1, C1 D14, C9 D1	Predose 30 m to 1 h postdose 3 to 4.5 h postdose
C3 D1, C7 D1	Predose 5 m post ECG assessment

C = cycle; D = day; h = hour; m = minute.

8.7. Pharmacodynamics

The following biomarker assessments will be completed in all patients. Table 6 outlines the pharmacodynamic sampling schedule.

Additional details regarding the collection, handling and shipping of samples are provided in the laboratory manual.

All blood and bone marrow samples collected as detailed in the SoA (Section 1.3) may be used for additional exploratory analysis of predictive biomarkers of response and to further understand the mechanism of action of pelabresib. Since biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. Any results from exploratory biomarkers analyses may be reported separately from the CSR.

Bone marrow biopsy evaluation

Bone marrow biopsy samples will be collected for grading of bone marrow fibrosis and for exploratory assessment of hematopoietic cell populations and read centrally, as described in Section 8.2.1. Samples will be collected according to the time points in the SoA (Section 1.3).

Circulating analytes evaluation

Peripheral blood samples (approximately 10 mL of whole blood at each time point) will be collected for the measurement of circulating concentrations of cytokines and other analytes. Samples will be collected prior to the administration of study drug at the time points in the SoA (Section 1.3).

Mutant allele burden evaluation

Peripheral blood samples (approximately 10 mL of whole blood at each time point) will be collected for the measurement of mutant allele burden of selected genes (e.g., *JAK2*, *CALR*) using a focused NGS assay. Samples will be collected according to the time points in the SoA (Section 1.3). Correlation of mutation profile and response to pelabresib in combination with ruxolitinib will be used to identify predictive biomarkers. Additionally, changes in allelic burden of specific mutations in patients may identify increase in activity of certain mutational contexts to pelabresib.

Table 6: Biomarker Assessment Collection Time Points

Sample Collected	Dosing Day	Time Point
Bone marrow biopsy	See time points in SoA (Section 1.3)	Anytime up to 2 years after study treatment until PD
Mutant allele burden	C1 D1, C17 D1	Pre-dose
Circulating analytes	C1 D1, C1 D14, C9 D1, C17 D1	Pre-dose (+matched to mutant allele burden sampling, when applicable)

9. STATISTICAL CONSIDERATIONS

A more technical and detailed description of the statistical methods will be provided in the SAP.

9.1. Study Endpoints

9.1.1. Primary Endpoint

The primary endpoint of the study is splenic response, defined as a ≥ 35% reduction from baseline in spleen volume as measured by MRI or CT and assessed by central radiology read, at Week 24.

9.1.2. Key Secondary Endpoints

The key secondary endpoints of the study are the absolute change in TSS at Week 24 compared to baseline and TSS response, defined as a ≥ 50% decrease from baseline in TSS as measured by the MFSAF v4.0, at Week 24.

Baseline TSS is calculated as the average of non-missing daily total symptom scores over the 7-day period prior to day of randomization. The TSS for a treatment week is the average of non-missing daily total symptom scores over that week. However, the weekly TSS will be considered missing if there are less than 4 daily total symptom scores available for that week. A window of +/- 3 weeks will be applied for patients with missing TSS at Week 24.

9.1.3. Secondary Endpoints

The following secondary endpoints will be calculated and summarized for each treatment group:

- Percent change in TSS at Week 24 compared to baseline
- Improvement in bone marrow fibrosis by at least 1 grade at Week 24 compared to baseline
- Splenic response at Week 48, defined as a ≥35% reduction from baseline in spleen volume as measured by MRI or CT and assessed by central radiology read, at Week 48
- TSS response at Week 48, defined as a ≥50% decrease from baseline in TSS as measured by the MFSAF v4.0, at Week 48
- TSS response at Week 48, defined as the absolute change in TSS as measured by the MFSAF v4.0 at Week 48
- Rate of RBC transfusions, defined as the average number of units of RBC transfusion per month (4 weeks), over the first 24 weeks of treatment
- Conversion from RBC transfusion dependence (≥6 units of RBC transfusion during the 12-week baseline period prior to dosing) to independence (no RBC transfusions during any 12-week period post baseline)
- Categorical change of PGIC at Week 24 compared to Baseline

- PFS, defined as the time from randomization until documented progression (see definition of progression in Section 7.1), or until death from any cause for patients without documented progression
- OS, defined as the time from randomization until death from any cause
- Proportion of patients with transformation to blast phase (AML)
- AEs of all grades and SAEs
- Population PK assessment including determination of exposure metrics and secondary parameter (i.e., AUC_{0-t}, t_{max}, C_{max}, $T_{1/2}$, Vd/F, CL/F)
- Descriptive assessment of ruxolitinib plasma concentrations in the presence or absence of pelabresib
- Duration of splenic response, defined as the time from onset of splenic response until the time at which the patient has a <35% decrease from baseline in spleen volume and a >25% increase from nadir, as confirmed by the central review) or death, whichever comes first
- Modified TSS50 response at Week 24 (TSS score without the fatigue sub-domain).
- Duration of TSS response, defined as the time from onset of TSS50 response until the time at which the patient has a <50% reduction in TSS from baseline and an increase of ≥25% from nadir

9.1.4. Exploratory Endpoints

The following exploratory endpoints may be calculated and summarized for each treatment group:

- Percent change in splenic volume at Week 24
- RBC transfusion dependence, defined as ≥ 6 units of RBC transfusion during the prior 12 weeks, at Week 24
- Hemoglobin response, defined as a ≥ 1.5 g/dL increase in hemoglobin from baseline in the absence of transfusion during the previous 12 weeks
- [redacted]

[redacted]

[redacted]

[redacted]

- Post-treatment changes from baseline in circulating concentrations of cytokines

- Post-treatment changes from baseline in the ratio of mutant to wild type *JAK2*, [redacted]

[redacted]

- Time to first SVR35 response
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.2. Analysis Populations

The analysis populations for this study are defined in Table 7.

Table 7: Analysis Populations

Population	Description
mITT	All randomized patients who were administered at least one dose of study drug. This is the population for some sensitivity analysis on efficacy endpoints. All analyses using this population will be based on the treatment assigned by the Interactive Response Technology (IRT) system.
ITT	All randomized patients. This is the primary population for all efficacy endpoints. All analyses using this population will be based on the treatment assigned by the Interactive Response Technology (IRT) system.
Safety	A subset of the ITT population that includes all randomized patients who were administered at least one dose of study drug. This population will be used for the safety analyses. All analyses using this population will be based on the treatment actually received.
Per Protocol	A subset of the ITT population that includes patients who have received adequate exposure to on-study therapy and do not have any protocol deviations that could confound the interpretation of the primary analyses conducted on the ITT population. All protocol deviations or conditions leading to exclusion from the PP population will be specified in the statistical analysis plan (SAP). All analyses using this population will be based on the treatment received.
PK/PD	All randomized and treated patients who have at least 1 evaluable sample for PK or PD analysis.

9.3. Statistical Analyses

9.3.1. General Considerations

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage (n, %) of patients within each classification. Two-sided 95% confidence intervals will also be presented as appropriate.

If Cycle 1 Day 1 (baseline) visit assessment is not available, screening visit value will be used for statistical analysis purposes.

9.3.2. Demographic and Baseline Characteristics

Patient demographics (e.g., age, sex, race, ethnicity) and physical characteristics (e.g., height, weight, BMI) will be summarized by treatment group. Baseline disease characteristics (e.g., MF subtype, risk status, mutational profile, ECOG performance score, RBC transfusion status, total symptom score, spleen volume) will also be summarized by treatment group.

9.3.3. Efficacy Analyses

9.3.3.1. Analysis of Primary and Key Secondary Endpoints

The primary analysis will take place after all randomized patients have either completed their Week 24 visit or been prematurely discontinued. By this time, it is expected that at least 50% of

the randomized patients will have completed their Week 36 visit. Until the primary analysis takes place, patients, investigators, and the Sponsor will remain blinded to patient allocation to study arms, except for those patients who were enrolled into the crossover portion of the study at or after Week 24 and therefore had to be unblinded.

The continuous key secondary efficacy endpoint of this study is defined as absolute change in TSS at Week 24 compared to baseline. Descriptive summary statistics including the number of patients (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum of TSS values at Baseline and Week 24, and the absolute change from baseline at Week 24 will be present.

An ANCOVA (Analysis of Covariance) model will be used to analyze the absolute change from baseline in TSS at Week 24. The dependent variable is change from baseline in TSS at Week 24, with treatment group, baseline DIPSS (Intermediate-1 vs. Intermediate-2 vs. High), baseline platelet count (100-200 × 109/L vs. > 200 × 109/L) and baseline spleen volume (< 1800 cm3 vs. ≥ 1800 cm3) as fixed effects and the baseline TSS as a covariate.

For the binary primary endpoint, the null hypothesis that the probability of a splenic response at Week 24 for patients treated with pelabresib + ruxolitinib is equal to the probability for patients treated with placebo + ruxolitinib will be tested against the alternative hypothesis that the probability of a splenic response at Week 24 for patients treated with pelabresib + ruxolitinib is not equal to the probability for patients treated with placebo + ruxolitinib. Likewise, for the binary key secondary endpoint TSS50, the null hypothesis that the probability of a TSS response at Week 24 for patients treated with pelabresib + ruxolitinib is equal to the probability for patients treated with placebo + ruxolitinib will be tested against the alternative hypothesis that the probability of a TSS response at Week 24 for patients treated with pelabresib + ruxolitinib is not equal to the probability for patients treated with placebo + ruxolitinib.

The probability of a splenic response at Week 24 will be estimated by calculating the splenic response rate, or the percentage of patients with a splenic response, at Week 24 for each of the two treatment groups. Likewise, the probability of a TSS response at Week 24 will be estimated by calculating the TSS response rate, or the percentage of patients with a TSS50 response, at Week 24 for each of the two treatment groups. The response rate between the two treatment groups will be compared using a CMH test controlling for baseline DIPSS (Intermediate-1 vs. Intermediate-2 vs. High), platelet count (100-200 × 10^9/L vs. > 200 × 10^9/L), and spleen volume (< 1800 cm^3 vs. ≥ 1800 cm^3). Pooling of stratum will be performed in the case of insufficient information in any stratum. Details will be provided in SAP, which will be finalized prior to unbinding of data for primary analysis.

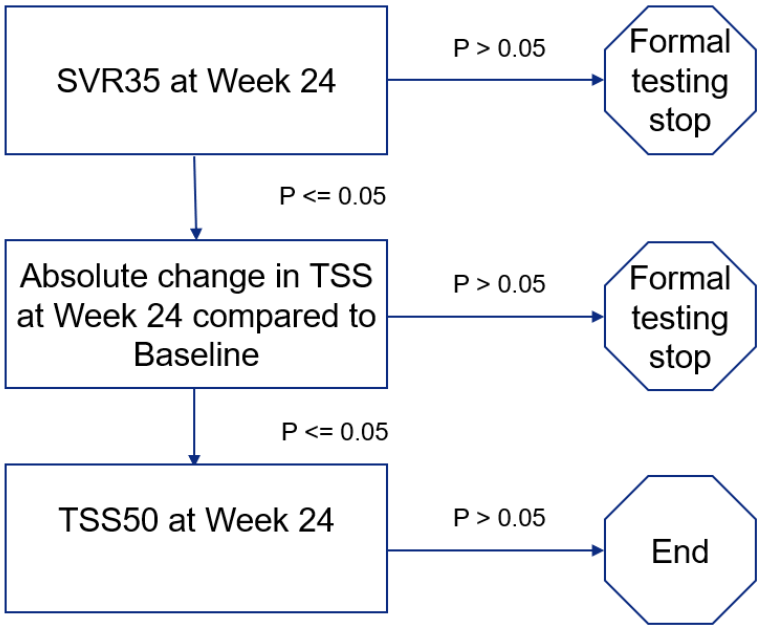
Multiplicity and Type I Error Control

To ensure family-wise error rate is controlled at 5% (two-sided) the following endpoints will be tested hierarchically in the following order:

1. Primary Endpoint: SVR35 at week 24 using CMH test
2. Key Secondary Endpoint: Absolute change in TSS at Week 24 compared to baseline using ANCOVA model
3. Key Secondary Endpoint: TSS50 at Week 24 using CMH test

If for a given endpoint p-value >0.05 (two-sided) at any stage of the hierarchy, the remaining endpoints will not be tested for statistical significance. However, p-values might be reported for descriptive purposes.

Figure 2: Sequential Testing of Pre-Specified Endpoints



The main analysis will be performed on ITT population.

Handling of Missing Data

For the main analysis of the primary and key secondary endpoints, all ITT patients will be included in the calculation and analysis of response rates. Patients without the Week 24 assessment will be considered non-responders.

In addition, the following sensitivity analyses will be conducted to assess the impact of missing data:

- Multiple imputation with SAS PROC MI: missing Week 24 spleen volume/TSS will be imputed using a parametric regression model with the assumption of multivariate normality and a monotone missing data pattern. If there are patients with a non-monotone missing data pattern, datasets with only monotone missing data patterns will be created first by imputing the intermediate missing values using the Markov Chain Monte Carlo method.
- LOCF: missing Week 24 spleen volume/TSS will be imputed using the last non-missing value

Additional details of missing data imputation will be included in the SAP

9.3.3.2. Analysis of Other Efficacy Endpoints

Details of the analyses of other secondary endpoints and exploratory endpoints will be provided in the SAP.

9.3.4. Safety Analyses

All safety analyses will be conducted using the Safety Population.

Safety will be evaluated by incidence of TEAEs and by changes from baseline vital signs, ECGs, and clinical laboratory values. Exposure to study drug and reasons for discontinuation will also be summarized.

Treatment-emergent AEs are those that first occur or worsen in severity after the administration of first dose of study drug. Treatment-emergent AEs will be tabulated according to the MedDRA by system organ class and preferred term and will include the following categories:

- TEAEs
- TEAEs related to study drug
- TEAEs of Grade 3 or higher
- TEAEs related to study drug that are Grade 3 or higher in severity
- TEAEs resulting in study drug discontinuation
- Treatment-emergent SAEs
- Treatment-emergent SAEs related to study drug
- Treatment-emergent SAEs resulting in study drug discontinuation
- Treatment-emergent SAEs resulting in death

The most commonly reported treatment-emergent AEs (i.e., those events reported by ≥10% of all patients) will be summarized by MedDRA System Organ Class and Preferred Term.

Adverse event of interest including, but not limited to, treatment discontinuation syndrome and ARDS will be summarized separately.

Descriptive statistics for the actual values of clinical laboratory parameters and changes from baseline in clinical laboratory parameters will be presented over time. Mean laboratory values over time will be plotted for key laboratory parameters. Clinically significant hematologic and non-hematologic laboratory abnormalities will be listed and summarized according to the NCI CTCAE (version 5.0).

Descriptive statistics for the actual values and the changes from baseline vital signs, and weight over time will be tabulated by scheduled time point.

All concomitant medications collected from screening through the study period will be classified according to the WHO drug dictionary.

Additional safety analyses may be determined to further define the safety profile of pelabresib + ruxolitinib.

9.3.5. PK/PD Analyses

PK data evaluation will be performed using an integrated population PK approach. PK/PD data evaluation will be provided in a separate document.

9.4. Sample Size Determination

Assuming a splenic response rate of 62% in the experimental group and 29% in the control group, and assuming a TSS response rate of 57% in the experimental group and 42.2% in the control group (Mascarenhas et al., 2019; Mesa et al., 2017), if the sequential testing of the primary (splenic response) and key secondary (TSS response) endpoints is conducted at a 2-sided significance level of 0.05 at the final analysis, a sample size of approximately 200 patients in each treatment group (approximately 400 patients in total) will provide > 99% power for testing the primary endpoint and 81% power for testing the key secondary endpoint at the final analysis, using the 2-group continuity corrected χ^2 test with a 5% two-sided significance level and accounting for 2% non-evaluable patients. This sample size will also provide more than 90% power to reject the null hypothesis of equal means when mean absolute TSS change from baseline difference between two arms is 4 points with a standard deviation for both groups of 12 using the two-sample t-test with a 5% two-sided significance level. The assumption of absolute change difference of 4 points is based on the median percentage change difference observed from Mesa et al., 2017 and Mascarenhas et al., 2019.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

The study will be conducted in accordance with the ICH GCP and the appropriate regulatory requirement(s). The clinical study can only begin once approval from all required authorities has been received. The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and wellbeing of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator or the Sponsor, as allowable by local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH GCP and all applicable regulatory requirement(s) and will be subject to approval by the Sponsor or its designee.

Patients who are rescreened or who are crossed over to receive experimental treatment with pelabresib (Section 6.6) are required to sign a new ICF.

10.1.4. Data Protection

In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports and communications will identify the patient by the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the patient's original medical records for verification of data collected on the eCRFs and to audit the data collection process. The patient's confidentiality will be maintained in accordance with all applicable laws and regulations.

The Sponsor or its designees will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for which they are responsible.

eCRFs will be completed for each study patient. It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, other observations, and patient status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected. An explanation should be provided for all missing data.

The audit trail entry will show the user's identification information, and the date and time of the correction. The Investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he is responsible.

The Sponsor or its designees will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc or other electronic media will be placed in the Investigator's study file.

10.1.5. Use of Information

All information regarding pelabresib supplied by or on behalf of the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical trial will be used towards the development of pelabresib and potentially other product candidates and may be disclosed to

regulatory authority(ies), other Investigators, existing or potential corporate or financing partners, or consultants.

10.1.6. Dissemination of Clinical Study Data

Upon completion of the clinical trial and evaluation of results by the Sponsor, hospital or institution and/or Investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

Study information and tabular study results will be available on publicly accessible sites, such as the US National Institute of Health's website http://www.clinicaltrials.gov.

10.1.7. Data Quality Assurance

The Sponsor or its designated representative will conduct a study site visit to verify the qualifications of each Investigator, inspect trial site facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated web-based EDC application. The Sponsor will have read-only access to all data upon entry in the EDC application.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability (including verification of IRT entries), and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Study monitors will discuss instances of missing or uninterpretable data with the Investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

10.1.8. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9. Study Monitoring

Monitoring and auditing procedures developed or approved by the Sponsor will be followed, in order to comply with GCP guidelines. On-site and remote review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor or its designee (site monitor) who will review the eCRFs and source documents. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, e-mail, and fax).

All non-dispensed, dispensed but unused, or expired study drug should be destroyed by sites per their own internal destruction procedures. If a site's procedures do not allow for destruction, unused/expired/damaged study drug should be returned to the supplying depot for subsequent destruction.

10.1.10. Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the study site is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol.

Where allowed, the Investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to the Sponsor (or disposal of the drug, if approved by the Sponsor) will be maintained by the clinical site. These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from the Sponsor. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. The Sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

10.1.11. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of patients.

Recruitment and enrollment strategies for this study may include recruitment from the Investigators' local practices or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the IRB or IEC. Any other arrangements will be described in the study manual.

The Sponsor may also terminate the study at any time for any reason (eg, SAEs, an unfavorable change to risk-benefit ratio, recommendations of the DSMB) at the discretion of the Sponsor. The Sponsor or its designee also reserves the right to close study sites. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines

- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.12. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission and to comply with the applicable provisions of any clinical trial agreement. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor and site will comply with the requirements for publication of study results as defined in the clinical trial agreement. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the table below will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of patients are detailed in Section 5 of the protocol.
- The results of each test must be entered into the eCRF. Investigators must document their review of each laboratory safety report.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- If a particular laboratory test is not available locally, an equivalent test assessing the same parameter may be used instead

Laboratory Assessments	Parameters
Hematology	Platelet count, RBC count, hemoglobin, hematocrit, RBC indices: MCV (optional), MCH, % reticulocytes (optional), WBC count with differential (percentages and/or absolute values): neutrophils, lymphocytes, monocytes, eosinophils, basophils, % blasts Note: Automated CBC analyzers should be used whenever possible.

Clinical chemistry	Sodium, potassium*, carbon dioxide (bicarbonate), serum glucose, serum creatinine, total and direct bilirubin, alkaline phosphatase, AST/SGOT, ALT/SGPT, LDH, uric acid, calcium, phosphorus/phosphate, EPO (optional – only if feasible at local institution), CRP, iron**, total iron binding capacity (TIBC)**, ferritin**, transferrin**, transferrin saturation**, HbA1c*** * if ≥ Grade 2 plasma potassium increase is observed, consider repeating plasma potassium using Li-Heparin or Na-Heparin tubes for confirmation if appropriate according to institutional standards of care ** Iron, TIBC, ferritin, transferrin, and transferrin saturation are required at Screening, after 12 weeks of treatment (Cycle 5 Day 1), after 24 weeks of treatment (Cycle 9 Day 1), every 12 weeks (4 cycles) thereafter. Note that TIBC, serum transferrin, and transferrin saturation values are related to each other and can be calculated if necessary. If all of the above tests are not available on the testing menu, measuring serum iron and transferrin OR serum iron and TIBC OR serum iron and transferrin saturation is sufficient. *** HbA1C is required at Screening, every 6 months throughout the study, and at EOT.
Coagulation parameters	PT and/or INR, aPTT
Serum lipids	Serum lipid panel including total cholesterol, cholesterol LDL, cholesterol HDL, triglycerides Note: Investigators are advised to follow the local approved ruxolitinib labeling for the frequency of lipid monitoring if different from the SoA. Serum lipid levels can be measured in either fasting or non-fasting state.
Pregnancy test	Highly sensitive urine/serum β-hCG pregnancy test in female patients of childbearing potential
TB test	Per local regulations

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta human chorionic gonadotropin; CBC = complete blood count; CRP = C-reactive protein; EPO = erythropoietin; HDL = high density lipoprotein; INR = International Normalized Ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; LDH = lactate dehydrogenase; LDL = low density lipoprotein; PT = prothrombin time; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; SoA = Schedule of Activities; TB = tuberculosis; WBC = white blood cell;

10.3. Appendix 3: Procedures for Recording, Evaluating, and Follow-up of AEs

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all available documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the appropriate AE eCRF and/or SAE paper report form. • It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to the Safety CRO in lieu of completion of the appropriate AE eCRF and/or SAE paper report form. • There may be instances when copies of medical records for certain cases are requested by the Safety CRO or the Sponsor or another designee of the Sponsor. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study using the NCI CTCAE, Version 5.0. In the case that an intensity grade is not able to be made using NCI CTCAE, the Investigator will make an assessment of severity using the WHO grading system (mild, moderate, severe, life threatening and death).
Assessment of Seriousness
The Investigator will make an assessment of seriousness for each AE reported during the study using the ICH E2A Guidelines on the seriousness assessment of AEs or reactions as noted in Section 8.4.1.
Assessment of Causality

• For both AEs and SAEs, the Investigator must determine the relationship of the event to each study drug. The causal relationship to study drugs will be determined by the Investigator according to best medical judgment, as follows:
  ○ Definitely related: This category applies when, after careful medical consideration, there is almost no consideration of other causation.
  ○ Probably related: There is a clinically plausible time sequence between onset of the AE and administration of study drugs. The AE is unlikely to be caused by a concurrent and/or underlying illness, other drugs, or procedures. If applicable, the AE follows a clinically consistent resolution pattern upon withdrawal of study drugs.

  - Possibly related: There is a clinically plausible time sequence between onset of the AE and administration of study drugs, but the AE could also have been caused by the concurrent/underlying illness, other drugs, or procedures. Information regarding withdrawal of study drugs may be lacking or unclear. "Possible" should be used when study drug administration is 1 of several biologically plausible causes of the AE.
  - Unlikely related: The AE is most likely due to a non-study drug-related cause. However, association with study drugs cannot be completely ruled out.
  - Not related: Another cause of the AE is most plausible, and a clinically plausible temporal sequence is inconsistent with the onset of the AE and administration of study drugs and/or a causal relationship is considered biologically implausible.
- The Investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data via the SAE paper report form.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Safety CRO or the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Safety CRO within 24 hours of receipt of the information via the SAE paper report form.

10.4. Appendix 4: WHO Diagnostic Criteria for MF

WHO criteria for overt PMF

Major Criteria

1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3*
2. Not meeting WHO criteria for ET, PV, *BCR-ABL1*$^{+}$ CML, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,† or absence of reactive MF‡

Minor Criteria

Presence of at least 1 of the following, confirmed in 2 consecutive determinations:

a. Anemia not attributed to a comorbid condition
b. Leukocytosis ≥11 × 10^9/L
c. Palpable splenomegaly
d. LDH increased to above ULN of institutional reference range
e. Leukoerythroblastosis

Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion

Source: (Arber et al., 2016)
CML = chronic myeloid leukemia; LDH = lactate dehydrogenase; MF = myelofibrosis; ULN = upper limit of normal; WHO = World Health Organization.
* Refer to Table 8 of (Arber et al, 2016)
** Refer to Table 6 of (Arber et al, 2016) for WHO criteria for prePMF
† In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (e.g., *ASXL1*, *EXH2*, *TET2*, *IDH1*/*IDH2*, *SRSF2*, *SF3B1*) are of help in determining the clonal nature of the disease.
‡ Bone marrow fibrosis secondary to infection, autoimmune disorder, or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

For classification criteria for PPV-MF and PET-MF refer to (Barosi et al, 2008)

10.5. Appendix 5: DIPSS

The DIPSS score is calculated based on the following 5 variables:

a. Age >65: 1 point
b. Leukocyte count >25 × 10^9/L: 1 point
c. Hemoglobin <10 g/dL: 2 points
d. Circulating blast cells ≥1%: 1 point
e. Constitutional symptoms*: 1 point

* Weight loss >10% of the baseline value in the year preceding MF diagnosis, and/or unexplained fever or excessive sweats persisting for more than one month.

The resulting DIPSS score is interpreted as follows:

- 0 points: low risk
- 1-2 points: intermediate-1 risk
- 3-4 points: intermediate-2 risk
- 5-6 points: high risk

10.6. Appendix 6: MFSAF, Version 4

The response scale for the questions below: 0 (Absent) to 10 (Worst Imaginable).

- During the past 24 hours how severe was your worst fatigue (weariness, tiredness)?
- During the past 24 hours how severe was your worst night sweats (or feeling hot or flushed)?
- During the past 24 hours how severe was your worst itching?
- During the past 24 hours how severe was your worst abdominal discomfort (feeling pressure or bloating)?
- During the past 24 hours how severe was the worst pain under your ribs on the left side?
- During the past 24 hours what was the worst feeling of fullness you had after beginning to eat?
- During the past 24 hours how severe was your worst bone pain (not joint or arthritis pain)?

10.7. Appendix 7: IWG-MRT Response Criteria

Category	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)
CR	Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤ Grade 1 MF† and Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥ 1 × 10^9/L and <UNL; Platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
PR	Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤ Grade 1 MF†, and peripheral blood: Hemoglobin ≥85 but <100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥50, but <100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
CI	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia§
SD	Belonging to none of the above listed response categories
PD	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or Leukemic transformation confirmed by a bone marrow blast count of ≥20% or A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 × 10^9/L that lasts for at least 2 weeks
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or Loss of anemia response persisting for at least 1 month or Loss of spleen response persisting for at least 1 month

Source: (Tefferi et al., 2013).
CI = clinical improvement; CR = complete remission; EMH = extramedullary hematopoiesis; LCM = left costal margin; MF = myelofibrosis; PD = progressive disease; PR = partial remission; SD = stable disease; UNL = upper normal limit.
* Baseline and posttreatment bone marrow slides are to be interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.
† Grading of MF is according to the European classification (Thiele et al., 2005). It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.
‡ Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, <5% immature myeloid cells is allowed.
§ See above for definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the CTCAE version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥25,000 × 10^9/L and ANC of ≥0.5 × 10^9/L.

10.8. Appendix 8: Strong CYP3A4 Inducers or Inhibitors

The following lists were compiled from these resources and is not considered an all-inclusive list:

- FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. See: https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.
- Indiana University Department of Medicine Clinical Pharmacology Drug Interaction Tables. See: http://medicine.iupui.edu/CLINPHARM/DDIS
- Bloomer J, Derimanov G, Dumont E et al. Optimizing the in vitro and clinical assessment of drug interaction risk by understanding co-medications in patient populations. Expert Opin. Drug Metab. Toxicol. 2013;9(6):737-751.

Strong CYP3A4 Inhibitors	Strong CYP3A4 Inducers
amprenavir	carbamazepine
atazanavir	efavirenz
boceprevir	enzalutamide
clarithromycin	etravirine
cobicistat	mitotane
conivaptan	phenobarbital
diltiazem	phenytoin
fosamprenavir	rifabutin
grapefruit (fruit or juice)[a]	rifampin
idelalisib	rifapentine
indinavir	St. John's wort[b]
itraconazole	
ketoconazole	
lopinavir	
nefazodone	
nelfinavir	
posaconazole	
ritonavir	
saquinavir	
starfruit (fruit or juice)	
suboxone	
telaprevir	
telithromycin	
troleandomycin	
voriconazole	

a. The effect of grapefruit juices varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A4 inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A4 inhibitor" when another preparation was used (e.g., low does, single strength).
b. The effect of St. John's wort varies widely and is preparation-dependent.

10.9. Appendix 9: Study Conduct in Unforeseen Circumstances

Summary:

This appendix may be utilized by clinical trial sites during unforeseen circumstances that would result in increased risk associated with completion of the protocol conduct for study patients, such as during natural disasters (floods, tornadoes, earthquakes, hurricanes) or acts of people (e.g., acts of terrorism, riots, strikes, wars), and pandemics (e.g., COVID-19). These measures may be implemented if allowed by applicable country laws and regulations. These optional measures are put in place to preserve the risk-benefit for study participation. Measures should be documented by the site and reported by the Sponsor in the CSR.

This appendix describes possible adaptations to:

1. Consent Process
2. IMP Shipment
3. Patient Visits
4. Trial Assessments
5. Sample Collection
6. Adverse Event Reporting
7. Protocol Deviations

Topic Requiring Adaptation	Section	Description
Consent Process	5.1 Inclusion Criteria 5.2 Exclusion Criteria	Original consent to enter the study must be performed in person at the clinical site.
	10.1.3 Informed Consent	If original consent to enter the study has been obtained, subsequent remote consent is allowable for patients unwilling or unable to come to study site. Alternative consents, in line with local/institutional guidelines, such as usage of electronic signatures, faxing the signed consent forms, online consenting, oral consenting if the consent is obtained through audio/video communication through different

		telecommunication applications. The specific consent process and the patient's consent should be documented in the patient's chart. The patient should re-sign the consent once able to visit the clinic.
Study Drug Shipment *All safety assessments must be carried out at the clinical trial site prior to the first treatment cycle and study drug being dispensed to the patient for the first time*	6.1 Study Drugs Administered 6.2 Preparation/ Handling/Storage/ Accountability	If patients are unable to pick up drug, Sites may ship study drug directly to patients per local procedures and using the below guidelines. Constellation (the Sponsor) cannot ship drug directly to the patient. The chain of custody must be documented at each step below: • Prior to shipping, confirm the patient's address. Also, confirm availability to receive drug. • Investigator Pharmacy can ship directly or may sign out to appropriate study team members. Whoever signs out the drug is requested to package and ship the drug • Ship the same day or overnight (Monday-Thursday only), signed receipt is required, and tracking number recorded in the appropriate pharmacy records/systems, as well as provided to the study coordinator for filing in the patient's chart for reconciliation by the Study Monitor. Temperature Controlled Device is not required. • Confirm receipt (email or phone) and document the reception in the patient records.

		• Invoice the Sponsor for pass-through costs associated with the study drug shipments (Privacy rules prevent us from using our account for shipping as we would get the patients' address on the form). Up to 2 cycles of drug may be dispensed to patients as needed.
Patient Visits *Screening and Day 1 of Cycle 1 must be conducted in person at the clinical trial site*	1.3 Schedule of Activities 8 Study Assessments and Procedures	If the investigator believes that travel to the study site for a study assessment would place the study patient at increased risk relative to the benefit of the in-person assessment, the assessment can be conducted remotely through telemedicine (phone, video call, etc.) by a trained clinician on the study team. These can be billed as a visit while conducting standard assessments and to identify adverse events and ensure continuous medical care and oversight for the MANIFEST-2 trial. Visit changes will be considered a Protocol Deviation related to the unforeseen circumstances, such as COVID-19, and should be documented by study standard procedures.

Study Assessments (including imaging and laboratory assessments) *All safety assessments must be carried out at the clinical trial site prior to the first treatment cycle and study drug being dispensed to the patient for the first time*	1.3 Schedule of Activities 8 Study Assessments and Procedures	Laboratory assessment can be completed locally and sent to the study site, taking into consideration study drug may get sent for more than 1 cycle worth, that safety labs must be reviewed by an investigator to verify if the patient is fit for treatment continuation. Communication pathway should be agreed to with local office, including when to expect results, prior to completion of the assessment. • Patient-Reported Outcome Assessments: Please remember to remind patients about the importance of ePRO assessments. • Imaging assessment and protocol-mandate bone marrow biopsies should be conducted as soon as they are considered safe and feasible; out of window assessments are preferable to a missed assessment. Visit changes will be considered a Protocol Deviation related to the unforeseen circumstances, such as COVID-19, and should be documented by study standard procedures. Performing an out of window imaging assessment is preferable to missing the assessment entirely.
Sample Collection		In the event that a research laboratory is not accepting samples, the site should hold the samples at the requested shipping temperature per the Laboratory Manual.

AE Reporting	8.4.2 Time Period and Frequency for Collecting AE and SAE Information 8.4.5 Regulatory Reporting Requirements for SAEs 10.3 Procedures for Recording, Evaluation, and Follow-Up of AEs and SAEs	If physical visits are reduced or postponed, the investigators will continue collecting AEs from the patient through alternative means, e.g., by phone calls or telemedicine visits, as appropriate.
Protocol Deviations		Protocol deviations (e.g., out of visit windows, etc.) should be captured per the usual study/institutional requirements.

10.10. Appendix 10: Abbreviations

AE	adverse event
ALT	aspartate aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	alanine aminotransferase
AUC	area under the plasma concentration-time curve
BET	bromodomain and extraterminal
BETi	bromodomain and extraterminal inhibitor
BID	twice daily
BMI	body mass index
BUN	blood urea nitrogen
C_{max}	maximal concentration
CMH	Cochran-Mantel-Haenszel
CrCl	creatinine clearance
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DIPSS	Dynamic International Prognostic Scoring System
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EMH	extramedullary hematopoiesis
EOT	end of treatment
GCP	Good Clinical Practice
HDPE	high density polyethylene
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
HSCT	hematopoietic stem cell transplant

IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation
ICSR	individual case safety report
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine system
IVRS/IWRS	interactive voice response system/interactive web response system
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
JAKi	Janus kinase inhibitor
LDH	lactate dehydrogenase
LOCF	last observation carried forward
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
mITT	modified intent-to-treat
MPN	myeloproliferative neoplasms
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NIMP	Non-investigational medicinal product
OS	overall survival

PD	pharmacodynamic
PET-MF	post essential thrombocythemia myelofibrosis
PFS	progression-free survival
PK	pharmacokinetic
PMF	primary myelofibrosis
PO	per os (by mouth)
PPV-MF	post-polycythemia vera myelofibrosis
QD	once daily
QTcF	Fridericia-corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	spleen volume response
$T_{1/2}$	half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximal concentration
TSS	total symptom score
ULN	upper limit of normal
WHO	World Health Organization

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