CLINICAL TRIAL PROTOCOL

A Phase 1/2 Study of CPI-0610, a Small Molecule Inhibitor of BET Proteins: Phase 1 (Dose Escalation of CPI-0610 in Patients with Hematological Malignancies) and Phase 2 (Dose Expansion of CPI-0610 with and without Ruxolitinib in Patients with Myeloproliferative Neoplasms)

Clinical Trial Protocol No:	0610-02 / NCT02158858
Clinical Trial Protocol:	MANIFEST
Version:	CTP v. 14, 23 Feb 2024
Clinical Trial Phase:	1/2
Product Name:	Pelabresib (CPI-0610)
Sponsor:	Constellation Pharmaceuticals, Inc. (Constellation Pharmaceuticals, Inc. is a fully owned subsidiary of MorphoSys US Inc.)
Sponsor's Address:	470 Atlantic Avenue, Ste. 1401 Boston, MA 02210 United States
Indications:	Phase 1: Acute Leukemia, Myelodysplastic Syndrome, and Myelodysplastic/Myeloproliferative Neoplasms, and Phase 2: Myeloproliferative Neoplasms (Myelofibrosis and Essential Thrombocythemia)
EU Trial Number:	2018-000579-34
IND Number:	147351

Sponsor Signatory:

PPD

Global Clinical Program Head

Date

PPD

Program Statistician

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

Amendment Number	Date	Reason for Change
Original Protocol (Version 1):	13 September 2013	Not applicable
Amendment 1 (Version 2):	16 April 2014	Study design change
Amendment 2 (Version 3):	22 September 2014	Study design change
Amendment 3 (Version 4):	02 November 2015	Study design change
Amendment 4 (Version 5):	11 December 2015	Study design change
Amendment 5 (Version 6):	03 August 2016	Study design change
Amendment 6 (Version 7):	04 January 2018	Study design change
Amendment 6 (Version 7.1):	14 March 2018	European administrative changes
Amendment 6 (Version 7.2):	30 April 2018	UK administrative changes
Amendment 6 (Version 7.3):	21 June 2018	Logistical administrative changes
Amendment 7 (Version 8):	07 September 2018	Study design change
Amendment 7 (Version 8.1):	05 November 2018	Canada only
Amendment 7 (Version 8.2):	19 November 2018	France and Germany administrative change
Amendment 7 (Version 8.3):	10 December 2018	Belgium only
Amendment 7 (Version 8.4):	18 December 2018	Germany only
Amendment 7 (Version 8.5):	24 January 2019	France only
Amendment 8 (Version 9)	23 September 2019	Study design change
Amendment 8 (Version 9.1)	30 September 2019	Germany and France only
Amendment 8 (Version 9.2)	26 November 2019	Germany only
Amendment 9 (Version 10.0)	14 April 2020	Study design change

Amendment Number	Date	Reason for Change
Amendment 9 (Version 10.1)	14 April 2020	France only
Amendment 9 (Version 10.2)	14 April 2020	Germany only
Amendment 9 (Version 10.3)	28 May 2020	Canada only
Amendment 9 (Version 10.4)	22 July 2020	Germany only
Amendment 9 (Version 10.5)	25 February 2021	United States only
Amendment 10 (Version 11.0)	25 September 2020	Study design change
Amendment 10 (Version 11.1)	25 September 2020	France and Germany only
Amendment 10 (Version 11.2)	23 November 2020	Canada only
Amendment 10 (Version 11.3)	01 December 2020	Rest of world only
Amendment 10 (Version 11.4)	25 February 2021	Rest of world only
Amendment 10 (Version 11.5)	25 February 2021	France and Germany only
Amendment 10 (Version 11.6)	25 February 2021	Canada only
Amendment 10 (Version 11.7)	13 October 2021	Belgium only
Amendment 11 (Version 12.0)	16 September 2022	Study design change
Amendment 11 (Version 12.1)	16 May 2023	Canada only
Amendment 12 (Version 13.0)	27 November 2023	Global
Amendment 13 (Version 14.0)	23 February 2024	Global

SYNOPSIS

NOTE: As of Amendment 6, Phase 1 is complete and all new patients will be enrolled in Phase 2. See Amendment 6 (Version 7) of the Study 0610-02 protocol for content specific to the Phase 1 portion of 0610-02.

Sponsor:

Constellation Pharmaceuticals, Inc. (CPI)

Study Title:

A Phase 1/2 Study of CPI-0610, a Small Molecule Inhibitor of BET Proteins: Phase 1 (Dose Escalation of CPI-0610 in Patients with Hematological Malignancies) and Phase 2 (Dose Expansion of CPI-0610 with and without Ruxolitinib in Patients with Myeloproliferative Neoplasms)

Study Number: 0610-02

Study Phase: 1/2

Investigational Product; Dose; and Mode of Administration:

Phase 2 (Myeloproliferative neoplasm [MPN] expansion):

As of Amendment 6 (Version 7), the expansion arm doses for myelofibrosis (MF) patients previously treated (or ineligible to receive treatment) with a JAK inhibitor (**Prior JAKi**) or currently treated with a JAKi (**Add-on to JAKi**) are:

Arm 1: Prior JAKi Monotherapy Arm (MF patients treated with pelabresib alone):

Pelabresib at initial dose of 125 mg once daily (QD) for 14 days followed by a 7-day break (upward titration allowed; 1 cycle = 21 days)

Arm 2: Add-on to JAKi Combination Arm (MF patients treated with pelabresib in combination with ruxolitinib):

Pelabresib at initial dose of 125 mg QD for 14 days followed by a 7-day break (upward titration allowed); ruxolitinib at dose patient is taking at the time of screening (1 cycle = 21 days)

NOTE: As of Amendment 7 (Version 8), there are 2 cohorts within Arm 1: Cohort 1A (transfusion-dependent [TD]) and Cohort 1B (non-TD) and 2 cohorts within Arm 2: Cohort 2A (TD) and Cohort 2B (non-TD).

As of Amendment 7 (Version 8), a new Combination Arm has been added for MF patients who have not previously been treated with a JAKi (JAKi Naïve):

Arm 3: JAKi Naïve Combination Arm (MF patients treated with pelabresib in combination with ruxolitinib):

Pelabresib at initial dose of 125 mg QD for 14 days followed by a 7-day break (upward titration allowed); ruxolitinib at initial dose dependent on applicable approved package insert with upward titration allowed (1 cycle = 21 days).

As of Amendment 8 (Version 9), as per the recommendation by the Safety Review Committee (SRC), the starting dose for **JAKi Naïve Combination Arm 3** will be pelabresib 125 mg QD and ruxolitinib one dose level below (by 5 mg) the recommended dose per platelet count at baseline and as described in the applicable approved package insert.

As of Amendment 9 (Version 10.0), the maximum dose of ruxolitinib that may be administered to Arm 3 patients was increased to the maximum dose per product labeling, and the maximum dose of pelabresib that may be administered to Arm 3 patients was lowered to 175 mg QD.

As of Amendment 10 (Version 11), **Essential Thrombocythemia (ET) Monotherapy Arm 4** has been added for high-risk ET patients who are resistant or intolerant to hydroxyurea (HU). In addition, Cohort 1B was expanded to enroll up to 50 patients, Arm 3 was reduced to a maximum of 81 patients, guidance for dose reductions/modifications for pelabresib and ruxolitinib were revised, and guidelines were added that 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 participants.

Study Objectives

Phase 2 (MF Expansion-Prior JAKi Arm 1 and Add-on to JAKi Arm 2) Primary Objectives:	**Phase 2 (MF Expansion-Prior JAKi Arm 1 and Add-on to JAKi Arm 2) Primary Endpoints:**
To evaluate splenic response rate by imaging after 24 weeks of treatment in Cohorts 1B and 2B (ie, in non-TD cohorts)	The splenic response rate is defined as the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) after 24 weeks of treatment (Cycle 9, Day 1)
To evaluate the rate of conversion from red blood cell (RBC) TD to RBC transfusion independence (TI) in Cohorts 1A and 2A (ie, in TD cohorts)	The conversion rate is defined as the proportion of patients who convert from TD to TI, where TD is defined as receiving an average of ≥ 2 RBC transfusions per month (total of ≥ 6 RBC transfusions during the prior 12 weeks) prior to enrollment and TI is defined as absence of RBC transfusions over any consecutive 12 week period

Phase 2 (MF Expansion-Prior JAKi Arm 1 and Add-on to JAKi Arm 2) Secondary Objectives:	**Phase 2 (MF Expansion-Prior JAKi Arm 1 and Add-on to JAKi Arm 2) Secondary Endpoints:**
To evaluate the change in patient-reported outcomes (PROs) and the rate of patients who achieve a ≥ 50% reduction in total symptom score (TSS) after 12 and 24 weeks of treatment (all cohorts)	PROs will be evaluated using the Myelofibrosis Symptom Assessment Form Version 4.0 (MFSAF v4.0) and the Patient Global Impression of Change (PGIC). Changes from baseline in the TSS from the MFSAF v4.0 and PGIC will be described. The proportion of patients who achieve a ≥ 50% reduction in TSS after 12 weeks (Cycle 5, Day 1) and 24 weeks of treatment (Cycle 9, Day 1) will also be reported.
To evaluate overall splenic response rate (all cohorts) and the splenic response rate after 12 weeks (all cohorts) and 24 weeks of treatment (Cohorts 1A and 2A)	The overall splenic response rate is the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT); The reduction in spleen size from baseline by imaging (MRI or CT) after 12 weeks (Cycle 5, Day 1) and 24 weeks of treatment (Cycle 9, Day 1) will also be evaluated.
To evaluate the duration of TI in Cohorts 1A and 2A	The duration of TI is defined as the time from the first onset date of TI to the earliest onset date of loss of TI
To evaluate the early anemic response rate in Cohorts 1A and 2A	The early anemic response rate is defined as the proportion of patients who achieve a hemoglobin (Hgb) increase of ≥ 1g/dL from baseline over any consecutive 8-week period in the absence of RBC transfusions
To evaluate the anemic response rate in patients who enroll as TI in Cohorts 1B and 2B	The anemic response rate is defined as the proportion of patients who enroll as TI and achieve ≥ 1.5 g/dL Hgb increase from baseline over any consecutive 12-week period in the absence of RBC transfusions
To evaluate the duration of splenic response by imaging (all cohorts)	Duration of the splenic response is defined as the time when splenic response criteria are first met (a ≥ 35% reduction from baseline spleen size) until the first-time spleen volume reduction is < 35% from baseline and is increased by ≥ 25% from nadir in spleen volume by imaging
To evaluate the safety of pelabresib in patients with MF	The incidence of adverse events (AEs) and serious adverse events (SAEs) and changes

	from baseline in vital signs, and laboratory values
To characterize the pharmacokinetics (PK) of pelabresib (all cohorts)	Maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), predose (trough) concentration collected at the end of a dosing interval (C_{trough}), area under the concentration-time curve from time 0 to the last observed concentration (AUC_{last}), area under the concentration-time curve from time 0 to 8 hours postdose ($AUC_{0-8,ss}$) at steady state, C_{max} at steady state ($C_{max,ss}$), t_{max} at steady state ($t_{max,ss}$)
To characterize the effects, if any, of pelabresib on the PK of ruxolitinib in Arm 2	C_{max}, t_{max}, C_{trough}, AUC_{last}, $AUC_{0-8,ss}$
Phase 2 (MF Expansion-Prior JAKi Arm 1 and Add-on to JAKi Arm 2) **Exploratory Objectives:**	**Phase 2 (MF Expansion-Prior JAKi Arm 1 and Add-on to JAKi Arm 2)** **Exploratory Endpoints:**

[redacted]

Phase 2 **(MF Expansion- JAKi Naïve Arm 3)** **Primary Objective:**	**Phase 2** **(MF Expansion – JAKi Naïve Arm 3)** **Primary Endpoint:**
To evaluate splenic response rate by imaging after 24 weeks of treatment	The splenic response rate is defined as the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT) after 24 weeks of treatment (Cycle 9, Day 1)
Phase 2 **(MF Expansion-JAKi Naïve Arm 3)** **Secondary Objectives:**	**Phase 2** **(MF Expansion-JAKi Naïve Arm 3)** **Secondary Endpoints:**
To evaluate the change in patient reported outcomes (PROs) and the rate of ≥ 50% reduction in TSS after 12 and 24 weeks of treatment	PROs will be evaluated using the MFSAF v4.0 and the PGIC. Changes from baseline in the TSS from the MFSAF and PGIC will be described. The proportion of patients who achieve a ≥ 50% reduction in TSS after 12 weeks (Cycle 5, Day 1) and 24 weeks of treatment (Cycle 9, Day 1) will also be reported.

To evaluate splenic response rate by imaging after 12 weeks of treatment	The splenic response rate is defined as the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT) after 12 weeks of treatment (Cycle 5, Day 1)
To evaluate the anemic response rate in patients who enroll as TI	The anemic response rate is defined as the proportion of patients who enroll as TI and achieve ≥ 1.5 g/dL Hgb increase from baseline over any consecutive 12-week period in the absence of RBC transfusions
To evaluate the overall splenic response rate and the duration of splenic response	The overall splenic response rate is the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT); duration of the splenic response is defined as the time when splenic response criteria are first met (a ≥ 35% reduction from baseline spleen size) until the first-time spleen volume reduction is < 35% from baseline and is increased by ≥ 25% from nadir in spleen volume by imaging
To evaluate the safety of pelabresib in patients with MF	The incidence of AEs and SAEs and changes from baseline in vital signs, and laboratory values
To characterize the PK of pelabresib (all cohorts) To characterize the effects, if any, of pelabresib on the PK of ruxolitinib	C_{max}, t_{max}, C_{trough}, AUC_{last}, $AUC_{0-8,ss}$, $C_{max,ss}$, $t_{max,ss}$ C_{max}, t_{max}, C_{trough}, AUC_{last}, $AUC_{0-8,ss}$
Phase 2 **(MF Expansion-JAKi Naïve Arm 3)** **Exploratory Objectives:**	**Phase 2** **(MF Expansion-JAKi Naïve Arm 3)** **Exploratory Endpoints:**
CCI	


CCI

Phase 2 (ET Expansion Arm 4) Primary Objective:	**Phase 2 (ET Expansion Arm 4) Primary Endpoint:**
To evaluate the complete hematological response rate	The proportion of patients who meet the criteria for a complete hematological response (CHR), as assessed by modified European Leukemia Net criteria (Barosi et al. 2009) • Normalization of platelet count ($\leq 400 \times 10^9$/L) • White blood cell (WBC) count within normal range ($\leq 10 \times 10^9$/L) • Laboratory results confirmed after 1 cycle (after 3 weeks) • Normal spleen size (by palpation or imaging)
Phase 2 (ET Expansion Arm 4) Secondary Objectives:	**Phase 2 (ET Expansion Arm 4) Secondary Endpoints:**
To assess symptom improvement	The proportion of patients with ≥ 50% reduction from baseline in the Myeloproliferative

	Neoplasm Symptom Assessment Form (MPN-SAF) total score (Scherber et al. 2015) PGIC will also be summarized.
To evaluate the partial hematological response rate	The proportion of patients who meet the following criteria for a partial hematological response: • Platelets 400-600 × 10^9/L • WBC within normal range (≤ 10 × 10^9/L) • Laboratory results confirmed after 1 cycle (after 3 weeks)
To evaluate the overall hematological response rate and duration of response	The proportion of patients with either a complete or partial hematological response at any time point and duration of response
To evaluate the duration of response	The time from the first onset date of response to the earliest onset date of loss of response, including: • Hematologic response • Symptom improvement
To evaluate the rate of hemorrhagic and thromboembolic (TE) events	The proportion of patients with hemorrhagic or TE events
To evaluate the safety of pelabresib in patients with ET	The incidence of AEs and SAEs and changes from baseline in vital signs, and laboratory values
To characterize the PK of pelabresib	C_{max}, t_{max}, C_{trough}, AUC_{last}, $AUC_{0-8,ss}$, $C_{max,ss}$, $t_{max,ss}$
Phase 2 **(ET Expansion Arm 4)** **Exploratory Objectives:**	**Phase 2** **(ET Expansion Arm 4)** **Exploratory Endpoints:**
CCI	

Number of Patients:

It is estimated that up to 341 evaluable patients may be enrolled. This estimate is based on the observed accrual of 44 patients with acute leukemia, myelodysplasia (MDS) or MDS/MPN to Phase 1 (dose escalation) of the study, and on the plan for 4 expansion arms (n = up to 60 evaluable MF patients each in Cohorts 1A and 2A, up to 50 evaluable MF patients in Cohort 1B, and up to 25 evaluable MF patients in Cohort 2B in Arms 1 and 2; n = up to 81 evaluable MF patients in Arm 3; and n = up to 21 evaluable ET patients in Arm 4) in Phase 2 (dose expansion).

Study Design:

This is a Phase 1/2, multicenter, open-label, dose escalation study (Phase 1) of pelabresib in patients with AML, MDS, MDS/MPN or MF and expansion study (Phase 2) of pelabresib as a single agent in patients with MF or ET and in combination with ruxolitinib (a JAKi approved for the treatment of patients with MF) in patients with MF.

In both phases of the study, pelabresib will be given QD once daily for 14 consecutive days followed by a 7-day break (1 cycle = 21 days), with 3-week cycles of treatment repeated as long as pelabresib is well tolerated and there is no evidence of disease progression.

Phase 2 (MPN Expansion):

The Phase 2 (MPN expansion) portion of the study will evaluate pelabresib in 4 arms (2 arms in the **Prior and Add-on to JAKi** MF population, 1 arm in the **JAKi Naïve** MF population, and 1 arm in the **ET** population):

Arm 1: Prior JAKi Monotherapy Arm (MF patients treated with pelabresib alone):

- Cohort 1A: Open to patients with MF who are TD and who have previously been treated with a JAKi and are intolerant, resistant, refractory, or lost response to the JAKi, or are ineligible to be treated with a JAKi.

- Cohort 1B: Open to patients with MF who are not TD and who have previously been treated with a JAKi and are intolerant, resistant, refractory, or lost response to the JAKi, or are ineligible to be treated with a JAKi.

Evidence for refractoriness, resistant, or lost response would include no spleen size reduction or symptom improvement after 6 months of therapy, disease progression, or intolerant to ruxolitinib (ie, platelet count $< 50 \times 10^9$/L and/or absolute neutrophil count (ANC) $\leq 0.5 \times 10^9$/L despite recommended dose adjustments and interruptions per approved ruxolitinib label; bleeding; or other severe [ie, $\geq$ Grade 3 non-hematological] toxicity).

Ineligible to be treated with a JAKi is defined as those patients for whom ruxolitinib is indicated, but the healthcare provider is reluctant to initiate ruxolitinib due to prior history of severe infections such as tuberculosis (TB), progressive multifocal leukoencephalopathy (PML), skin malignancies that are known to be associated or exacerbated by ruxolitinib, or other significant considerations as documented by the treating Investigator (see the approved package insert for ruxolitinib).

Arm 2: Add-on to JAKi Combination Arm (MF patients treated with pelabresib in combination with ruxolitinib):

- Cohort 2A: Open to patients with MF who are TD and are currently taking ruxolitinib for > 6 months and be on a stable dose for a minimum 8 weeks prior to start of study drug but have disease that is not being adequately controlled by ruxolitinib.

- Cohort 2B: Open to patients with MF who are not TD and are currently taking ruxolitinib for > 6 months and be on a stable dose for a minimum 8 weeks prior to

start of study drug but have disease that is not being adequately controlled by ruxolitinib.

Arm 3: JAKi Naïve Combination Arm (MF patients treated with pelabresib in combination with ruxolitinib):

- Open to patients with MF who are eligible to receive ruxolitinib and have not previously been treated with a JAKi.

NOTE: MF patients may have primary MF or MF that has evolved from ET or polycythemia vera.

Arm 4: ET Arm (high-risk ET patients treated with pelabresib alone):

- Open to patients with high-risk ET who are resistant or intolerant to HU.

Study Population:

Patients must meet all of the following criteria to be enrolled in this study:

Key Eligibility Criteria: Prior JAKi Arm 1 and Add-on to JAKi Arm 2 Inclusion criteria

- Patients with confirmed diagnosis of MF who meet all of the following criteria:
  - Dynamic International Prognostic Scoring System (DIPSS) risk category of intermediate-2 or higher
  - Platelet count $\geq 75 \times 10^9$/L without the assistance of thrombopoietic factors or transfusions
  - ANC $\geq 1 \times 10^9$/L without the assistance of granulocyte growth factors
  - Spleen volume of ≥ 450 cm^3 by CT or MRI for Cohorts 1B and 2B OR RBC TD (defined as an average of ≥ 2 units of RBC transfusions per month [total of ≥ 6 RBC transfusions over the 12 weeks] prior to enrollment) for Cohorts 1A and 2A
  - Peripheral blood blast count $< 10\%$
  - At least 2 symptoms measurable (score ≥ 1) using the MFSAF v4.0
  - Monotherapy Arm (Arm 1) patients only: Previously treated with a JAKi and be intolerant, resistant, refractory, or lost response to the JAKi; have not received the JAKi within 2 weeks prior to start of study drug, or are ineligible to be treated with a JAKi
  - Combination Arm (Arm 2) patients only: Must have received ruxolitinib for at least 6 months and be on a stable ruxolitinib dose for a minimum 8 weeks (prior to start of study drug)
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
  - Serum direct bilirubin $< 2 \times$ upper limit of normal (ULN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ ULN. The AST and /or ALT may

be elevated up to 5 × ULN if the elevation can be reasonably ascribed to liver involvement.

- Calculated or measured creatinine clearance (CrCl) ≥ 45 mL/min
- No prior treatment with any bromodomain and extra-terminal domain (BET) inhibitor

Key Eligibility Criteria: JAKi Naïve Arm 3 Inclusion criteria

- Patients with confirmed diagnosis of MF who meet all of the following criteria:
  - DIPSS risk category of intermediate-2 or higher
  - Platelet count ≥ 100 × 10^9/L without the assistance of thrombopoietic factors or transfusions
  - ANC ≥ 1 × 10^9/L without the assistance of granulocyte growth factors
  - Spleen volume of ≥ 450 cm^3 by MRI/CT
  - Peripheral blood blast count < 10%
  - At least 2 symptoms measurable (score ≥ 3) or a total score of ≥ 10 using the MFSAF v4.0
  - No prior treatment with JAKi allowed
- ECOG performance status ≤ 2
- Life expectancy of > 24 weeks
- Serum direct bilirubin < 2.0 × ULN; AST and ALT ≤ 2.5 × ULN. The AST and /or ALT may be elevated up to 5 × ULN if the elevation can be reasonably ascribed to liver involvement.
- Calculated or measured CrCl ≥ 45 mL/min
- No prior treatment with any BET inhibitor

Key Eligibility Criteria: ET Expansion Arm 4 Inclusion criteria

- Patients with confirmed diagnosis of ET who meet all of the following criteria:
  - High-risk disease, defined as meeting <u>at least one</u> of the following criteria (modified from (Barosi et al. 2007))
    - Age > 60 years
    - Platelet count > 1500 × 10^9/L (at any point during the patient's disease)
    - Previously documented thrombosis (including Transient Ischemic Attack [TIA]), erythromelalgia, or migraine (severe, recurrent, requiring medications, and felt to be secondary to the MPN) either after diagnosis or within 10 years before diagnosis and considered disease-related
    - Previous hemorrhage related to ET

- Diabetes or hypertension requiring pharmacological therapy for > 6 months

- Have at least 2 symptoms with an average score ≥ 3 over the 7-day period prior to Cycle 1 Day 1 or an average total score of ≥ 15 over the 7-day period prior to Cycle 1 Day 1 using the MPN-SAF (Appendix 7; (Scherber et al. 2015)
- Platelets > 600 × 10^9/L
- Resistant or intolerant to HU, defined as meeting any of the following criteria:
  - Platelet count > 600 × 10^9/L after 8 weeks of at least 2 g/day or MTD of HU (2.5 g/day in patients with a body weight > 80 kg)
  - Platelet count > 400 × 10^9/L and WBC < 2.5 × 10^9/L at any dose of HU (for a period of at least 8 weeks)
  - Platelet count > 400 × 10^9/L and Hgb < 110 g/L at any dose of HU (for a period of at least 8 weeks)
  - Platelet count persistently < 100 × 10^9/L at any dose of HU (for a period of at least 8 weeks)
  - Progressive splenomegaly or hepatomegaly, ie, enlargement by more than 5 cm or appearance of new splenomegaly or hepatomegaly on HU treatment
  - Not achieving the desired reduction of hematocrit or packed cell volume with the addition of HU in patients who do not tolerate frequent venesections after 8 weeks of at least 2 g/day of HU (2.5 g/day in patients with a body weight > 80 kg)
  - Not achieving the desired stable reduction of WBC when leukocytes are a target of therapy after 8 weeks of at least 2 g/day or MTD of HU (2.5 g/day in patients with a body weight > 80 kg)
  - Thrombosis or hemorrhage (including TIA) while on therapy
  - Presence of leg ulcers or other unacceptable HU-related non-hematological toxicities, such as unacceptable mucocutaneous manifestations, gastrointestinal (GI) symptoms, pneumonitis, or fever at any dose of HU
  - Disease-related symptoms not controlled by HU
- ECOG performance status ≤ 2
- Life expectancy of > 24 weeks.
- ANC ≥ 1 × 10^9/L in the absence of growth factors
- Serum direct bilirubin < 2.0 × ULN; AST and ALT ≤ 2.5 × ULN
- Calculated or measured CrCl ≥ 45 mL/min
- No prior treatment with any BET inhibitor

Study Duration:

In the absence of disease progression, and if pelabresib treatment (or the combination of pelabresib plus ruxolitinib) is being well tolerated, patients may continue to receive successive cycles of treatment.

End of Study:

The date of the end of the study for all arms (ie, study completion) is defined as the date at least 42 months after the last Arm 3 patient is enrolled. A patient who is still on study without disease progression may be consented to an extension protocol to continue receiving access to drug if they are deriving clinical benefit or monitored for long-term follow-up or compassionate use protocol or transition to commercial supply if available at the time. The Sponsor may end the trial when the availability of a rollover study exists into which any patient may enter if they are deriving clinical benefit or being monitored for long-term follow-up. Such a protocol would be written for pelabresib if not yet commercially available.

Safety Assessments:

Safety will be assessed by monitoring AEs, SAEs, hematology, and clinical chemistry values, vital signs, physical examinations, electrocardiograms (ECGs), ECOG performance status, and the use of concomitant medications.

Pharmacokinetic Assessments:

As of Amendment 12 (Version 13) the collection of pharmacokinetic samples has been completed.

Serial blood samples for the measurement of circulating concentrations of pelabresib will be collected before and after dosing with pelabresib. The sampling strategy outlined in the protocol should allow characterization of pelabresib's PK at steady state. In the Phase 2 Combination Arms, it will also allow an evaluation of the PK profile of ruxolitinib when given in combination with pelabresib. In Phase 2, serial blood samples will also be collected before and after dosing with pelabresib when upward dose titration above the starting dose or dose re-escalation above the starting dose occurs.

Phase 2: Pharmacodynamic Biomarker Assessments:
Peripheral blood samples will be collected at screening and serially during the study for the measurement of circulating concentrations of cytokines and mutant allele burden of selected genes, and for assessment of changes in genes associated with MF and BET target genes. Peripheral blood samples will be collected pre-and post-treatment for assessment of changes in hematopoietic cell populations, changes in signaling pathway activity and/or changes in mutational/transcriptional profiles and to evaluate gene expression changes in circulating leukocytes. Bone marrow biopsy samples will be collected pre- and post-treatment for grading of bone marrow fibrosis and for exploratory assessment CCI [redacted]

Phase 2: CCI [redacted] Assessments:
All blood and bone marrow samples collected may be used for additional exploratory analysis CCI [redacted]

Efficacy Assessments:

Phase 2: Efficacy assessments in patients with MF

Response assessment in Phase 2 patients with MF will rely on the evaluation of peripheral blood counts, transfusion requirements, MF-associated symptom scores, spleen size (by palpation and MRI or CT), extent of fibrosis (with bone marrow biopsy) and of changes in mutated allele burden (in peripheral blood). Disease response including splenic response, CCI [redacted], anemic response, change in PROs, CCI [redacted]. Peripheral blood and bone marrow blasts will also be used to monitor for conversion to AML. A CT or MRI scan will be performed at screening, after 12 weeks of treatment (Cycle 5, Day 1), after 24 weeks of treatment (Cycle 9, Day 1) and then every 12 weeks (4 cycles) thereafter.

Phase 2: Efficacy assessments in patients with ET

Response assessment in Phase 2 patients with ET will rely on the evaluation of hematological response, including platelet and WBC counts and spleen size, and by the duration of response and symptom improvement (TSS). Disease response including CHR, symptom improvement, change in PROs, etc. will be evaluated. Peripheral blood and bone marrow blasts will also be used to monitor for conversion to MF or AML. An MRI or CT scan will be performed at screening, after 24 weeks of treatment (Cycle 9, Day 1), after 48 weeks of treatment (Cycle 17, Day 1) and then yearly thereafter.

Statistical Methods:

Phase 2 (MPN expansion)

In Phase 2 (MPN expansion), pelabresib will be evaluated in 4 arms: Arm 1: Prior JAKi Monotherapy Arm (MF patients treated with pelabresib alone), Arm 2: Add-on to JAKi Combination Arm (MF patients treated with pelabresib in combination with ruxolitinib), Arm 3: JAKi Naïve Combination Arm (MF patients treated with pelabresib in combination with ruxolitinib), and Arm 4: ET Arm (high-risk ET patients treated with pelabresib alone). The Prior and Add-on to JAKi arms (Arms 1 and 2) are further stratified into TD cohorts (Cohorts 1A and 2A) and non-TD cohorts (Cohorts 1B and 2B). The primary endpoint in Cohorts 1B and 2B and in Arm 3 is splenic response rate via imaging after 24 weeks of treatment. The primary endpoint for Cohorts 1A and 2A is the rate of conversion from TD to TI. A Simon's two-stage design will be used for Cohorts 1A and 2A in the Prior and Add-on to JAKi Arms to allow the possibility of early stopping for futility. Conversion from TD to TI will be used to guide the Simon's two-stage design.

For Cohorts 1A and 2A, the null hypothesis that the true conversion rate is 2% will be tested against a one-sided alternative. The null rate of 2% is based on the fact that conversion from TD to TI is very unlikely in the Prior and Add-on to JAKi population and is not expected to happen spontaneously. In the first stage, 6 evaluable patients will be accrued in each cohort. If there are 1 or more conversions in these 6 evaluable patients, 10 additional evaluable patients will be accrued for a total of 16 in each cohort. The null hypothesis will be rejected for a given cohort if 2 or more conversions are observed in 16 evaluable patients. This design yields a type I error rate of 0.05 and power of 80% assuming the true conversion rate is 25%. **NOTE:** As of 29 September 2020, 3 of the 14 evaluable patients in Cohort 1A have converted from TD to TI, therefore, the null hypothesis is rejected in favor of a true TD-to-TI conversion rate of 25%. To estimate the conversion rate with higher precision, Cohort 1A and Cohort 2A were each further expanded to enroll an additional 44 evaluable patients (for a total of 60) so that each cohort will provide 85% power for the lower bound of a two-sided 95% exact binomial confidence interval estimate of the conversion rate to exclude 10%.

For Cohorts 1B and 2B, a sample size of 25 patients is required in each cohort to distinguish between a maximum futility splenic response rate of 10% and a minimum efficacy splenic response rate of 30% at Week 24, with an actual one-sided significance level of 0.033 and actual power of 80.65%. Five or more splenic responses are required in a cohort to find in favor of the treatment for that cohort. As of this amendment, 5 splenic responses have been observed in Cohort 1B. To increase the precision of estimate, Cohort 1B will be expanded to enroll 25 additional evaluable patients for a total of 50 evaluable patients. Assuming a true splenic response rate of 30%, a sample size of 50 evaluable patients will provide 86% power for the lower bound of a two-sided 95% exact binomial confidence interval to exclude a splenic response rate of 12.5%.

For JAKi Naïve Combination Arm (Arm 3), a total of 81 patients will be enrolled and an optimal Simon's two-stage design will be used. The primary endpoint for Arm 3 is splenic response rate after 24 weeks of treatment. The null hypothesis that the true splenic response rate is 30% will be tested against a one-sided alternative. The null hypothesis is constructed based on the splenic response rate at 24 weeks reported for ruxolitinib in the SIMPLIFY-1 trial (Mesa et al. 2017). In the first stage, 27 patients will be accrued. If there are 9 or fewer responses in these 27 patients, the study will be stopped. Otherwise, 54 additional patients will be accrued in Stage 2 for a total of 81. The null hypothesis will be rejected if 31 or more responses are observed in 81 patients. This design yields a type I error rate of 0.05 and power of 80% when the true splenic response rate is 45%.

For the ET Arm (Arm 4), a sample size of 21 patients is required to distinguish between a maximum futility CHR rate of 8% and a minimum efficacy CHR rate of 30% with an actual one-sided significance level of 0.023 and actual power of 80.16%. Four or more complete hematologic responses are required to find in favor of the treatment.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT (SGPT)	alanine aminotransferase
AML	acute myelogenous leukemia
ANA	anagrelide
ANC	absolute neutrophil count
ARDS	acute respiratory distress syndrome
AST (SGOT)	aspartate aminotransferase
AUC_{0-8}	area under the concentration-time curve from time 0 to 8 hours postdose
$AUC_{0-8,ss}$	area under the concentration-time curve from time 0 to 8 hours postdose steady state
AUC_{inf}	area under the concentration-time curve from time 0 extrapolated to infinity
AUC_{last}	area under the concentration-time curve from time 0 to the last observed concentration
BAT	best available therapy
BET	bromodomain and extra-terminal
CALR	calreticulin
CHR	complete hematological response
CI	clinical improvement
C_{max}	maximum observed plasma concentration
C_{trough}	predose (trough) concentration collected at the end of a dosing interval
CR	complete response/remission
CrCl	creatinine clearance
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DIPSS	Dynamic International Prognostic Scoring System
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
EC_{50}	50% effective concentration
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELN	European LeukemiaNet

Abbreviation	Definition
EMH	extramedullary hemopoiesis
EOS	End of Study (visit)
EOT	End of Treatment (visit)
EPO	erythropoietin
ET	essential thrombocythemia
HSCT	hematopoietic stem cell transplant
HU	hydroxyurea
IC_{50}	50% inhibitory concentration
IFN-α	interferon-α
IL	interleukin
IMP	investigational medicinal product
IWG	International Working Group
CCI [redacted]	[redacted]
JAKi	JAK inhibitor
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFTs	liver function tests
LPS	lipopolysaccharide
MDS	myelodysplastic syndrome
MF	myelofibrosis
MFSAF v.4.0	Myelofibrosis Symptom Assessment Form Version 4.0
MPN	myeloproliferative neoplasm
MPN-SAF	Myeloproliferative Neoplasm Symptom Assessment Form
MRI	magnetic resonance imaging
MRT	Myeloproliferative Neoplasms Research and Treatment
MT-1	melatonin type 1 receptor
MTD	maximum tolerated dose
NCI	National Cancer Institute
NF-κB	nuclear factor kappa-B
PGIC	Patient Global Impression of Change
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PO	per oral; orally
PRO	patient-reported outcome

Abbreviation	Definition
QD	once daily
QTcF	corrected QT interval by Fredericia
SD	standard deviation
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	elimination half-life
TD	transfusion-dependent/dependence
TGI	tumor growth inhibition
TI	transfusion-independent/independence
t_{max}	time to reach C_{max}
TIA	transient ischemic attack
TPO	thrombopoietin
TSS	total symptom score
ULN	upper limit of normal
WBC	white blood cell
β-hCG	beta-human chorionic gonadotropin

1. INTRODUCTION

NOTE: As of Amendment 6, Phase 1 is complete and all new patients will be enrolled in Phase 2. See Amendment 6 (Version 7) of the Study 0610-02 protocol for content specific to the Phase 1 portion of 0610-02.

1.1. BET Proteins

Bromodomain and extra-terminal (BET) bromodomain inhibition with small molecules is a novel therapeutic strategy in the treatment of cancer. The BET family of proteins has 4 members: BRD2, BRD3, BRD4, and BRDT. Each member contains 2 bromodomains, small, well-defined clefts in the surface of these proteins, designated BD1 and BD2. BD1 and BD2 allow the BET proteins to bind to chromatin and, rather than affecting an upstream signaling pathway (as do many protein kinase inhibitors), the BET proteins facilitate the transcription of a small set of genes that integrate a diverse array of abnormal signals. They do this by recruiting transcriptional co-regulators, like the cyclin dependent kinase P-TEFb, to specific sites on chromatin and providing a "scaffolding" function for the assembly of the transcriptional machinery needed for gene expression. The BET inhibitor pelabresib (see Section 1.2) antagonizes the binding of BET proteins to chromatin through its ability to disrupt the interaction between the BET bromodomains and acetylated lysine residues on the tails of histones.

Several of the genes inhibited by BET proteins are involved in cancer. For example, BET proteins facilitate the expression of *MYC* and *BCL-2*, 2 oncogenes implicated in the pathogenesis

of a wide range of human malignancies. Initially, the clinical development program for pelabresib was centered on its ability to rapidly and reversibly suppress expression of the *MYC* gene. However, BET proteins are also involved in regulating the expression of a subset of nuclear factor kappa-B kinase (NF-κB)-dependent genes that play roles in both inflammation (eg, interleukin [IL]-6) and some malignancies. Mechanistically, BET inhibition elicits these alterations of the NF-κB pathway by blocking the inhibitor of NF-κB subunit beta (IKKβ). This results in stabilization of IκB, subsequently inhibiting the NF-κB pathway by sequestration of NF-κB proteins in the cytoplasm (Ceribelli et al. 2014). Following exposure to lipopolysaccharide (LPS) and treatment with compound for 16 hours, pelabresib inhibited the release of IL-6 with a half maximal inhibitory concentration (IC_{50}) of 69 nM in the THP-1 acute leukemia cell line and reduced IL-8 levels in peripheral blood of patients treated with pelabresib in Phase 1 clinical studies. It was the demonstrated effects of pelabresib on inflammatory cytokines, as well as its consistent effects on platelet counts in advanced cancer patients (see Section 1.3.6.1), along with the known role of BET proteins in other biological processes that redirected the focus of the pelabresib clinical development program toward myelofibrosis (MF); see Section 1.3.3.

1.2. Pelabresib

1.2.1. Description

Pelabresib is a small molecule inhibitor of BET protein bromodomains being developed to treat patients with MF and other hematological malignancies. Pelabresib has a molecular weight of 365.81 g/mol. CCI [redacted] As of Amendment 6, all patients enrolled into Study 0610-02 will receive the tablet formulation.

The following sections summarize the preclinical and clinical data for pelabresib. Additional details are available in the Investigator's Brochure.

1.2.2. Nonclinical Information

CCI [redacted]


CCI


CCI


CCI


CCI

1.3. Study Rationale and Design

1.3.1. Acute Leukemia, Myelodysplastic Syndrome or Myelodysplastic Syndrome/Myeloproliferative Neoplasm for Phase 1

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

1.3.2. Myeloproliferative Neoplasms for Phase 2

1.3.2.1. Myelofibrosis for Phase 2 (MF Expansion) and JAK Inhibition

MF is a clonal myeloproliferative disease. It shares many of the characteristics of the other myeloproliferative diseases (essential thrombocythemia [ET] and polycythemia vera), but is characterized by more exaggerated abnormalities in megakaryocytes (Ciurea et al. 2007) and by a more aggressive disease course with complications from cytopenias and transformation to acute leukemia. 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. They release abnormal amounts of TGF-beta into the bone marrow, and TGF-beta stimulates the proliferation of fibroblasts in the bone marrow (Kuter et al. 2007). The deposition of collagen in the bone marrow by fibroblasts leads 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 JAKis have activity in this disease. In addition, approximately 50% of patients with MF have activating mutations in JAK2 (Tefferi et al. 2011; Pikman et al. 2006). 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 extramedullary hemopoiesis (EMH). The fibrosis and EMH are several of the key factors leading to anemia, one of the signature features of MF (Naymagon and Mascarenhas 2017). In fact, at the time of diagnosis, approximately 40% of patients have anemia (defined as a hemoglobin [Hgb] < 10 g/dL), and approximately 25% of patients require red blood cell (RBC) transfusions (Tefferi et al. 2012).

While JAK inhibition is useful in the management of patients with MF, its efficacy is limited. The only JAKi currently approved for use in patients with MF is ruxolitinib (Harrison et al. 2012; Verstovsek, Mesa RA, et al. 2012; Passamonti, Caramazza, and Maffioli 2014; Guglielmelli et al. 2014; Mesa et al. 2013; Verstovsek et al. 2010; Cervantes et al. 2013). In Phase 3 trials a greater than 50% improvement in symptom scores was seen in 46% of patients treated with ruxolitinib compared to 5% of patients treated with placebo. A 35% or greater reduction in spleen volume occurred in 29% to 42% of patients compared to 1-5% of patients treated with placebo or best available therapy (BAT). While ruxolitinib was effective in relieving constitutional symptoms and spleen size, there was little evidence to suggest that it modified the underlying disease, with infrequent histomorphologic changes in the marrow or reduction in mutated JAK2 allele burden. Unfortunately, anemia and thrombocytopenia occur frequently with ruxolitinib, and reach Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 levels in 45% and 13% of patients, respectively. In general, anemia is of concern for any patient. Maintenance of sufficient oxygen in the presence of anemia requires a compensatory increase in cardiac output, stressing the cardiovascular system (Weiss and Goodnough 2005). In MF in particular, anemia is associated with a poorer prognosis (Cervantes and Pereira 2012) and a lesser quality of life (Mesa et al. 2007; Tefferi et al. 2013).Chronic transfusions can lead to a variety of complications, but of more concern in MF, transfusion dependence (TD) in this setting is an indicator of end-stage disease (Naymagon and Mascarenhas 2017). Hence there remains a need for better treatments for MF, particularly in patients with anemia.

In regard to the anemia associated with ruxolitinib, this side effect is related to ruxolitinib's mechanism of action. The hormone responsible for endogenous RBC production is erythropoietin (EPO), which, when bound to its receptor, activates JAK2, eventually leading to the production of RBCs. Ruxolitinib treatment can therefore worsen anemia via inhibition of JAK2 (McMullin et al. 2015). There is a typical pattern of anemia associated with ruxolitinib therapy (Al-Ali et al. 2016) as highlighted in data from the Phase 3 trial of ruxolitinib versus placebo in JAKi naïve patients with MF (COMFORT-1) (Verstovsek, Mesa RA, et al. 2012). In this study, the mean Hgb in ruxolitinib treated patients decreased from baseline over time, reaching a nadir after 2-3 months of treatment prior to recovery to a new steady state after 6 months of treatment. While the new steady state level was stable, it was lower than that at baseline (the proportion of ruxolitinib patients requiring at least 1 transfusion followed a similar pattern) (Verstovsek, Mesa, et al. 2012). Mean Hgb levels in the placebo group remained stable throughout the study. In a separate Phase 3 randomized trial of ruxolitinib versus an investigational JAKi in JAKi naïve patients (SIMPLIFY-1), the mean percent change in Hgb

over the first 6 months of treatment was -6.5% in the ruxolitinib group. The rate of patients randomized to ruxolitinib who were RBC TD in this study increased over the first 6 months of treatment (24.7% to 40.1%), when TD was defined as ≥ 4 RBC transfusions or Hgb < 8 g/dL in the prior 8 weeks. Similarly, the rate of those who were RBC transfusion-independent (TI) decreased over that same timeframe (70% to 49.3%) when transfusion independence was defined as 0 RBC transfusions and Hgb ≥ 8 g/dL in the prior 12 weeks (Mesa et al. 2017).

1.3.2.2. Essential Thrombocythemia for Phase 2 (ET Expansion) and BET Inhibition

ET is one of the 3 Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), along with polycythemia vera and primary MF. ET is a clonal stem cell disorder classified by unexplained, autonomous thrombocytosis(Tefferi A 2018b). Similar to MF, aberrant megakaryocytes are drivers of altered hematopoiesis and inflammation in ET. Approximately 90% of patients with ET have somatically acquired mutations in *JAK2V617F*, calreticulin (*CALR*), or thrombopoietin receptor (*MPL*) (Tefferi A 2018b). The 3 MPNs share similar well-known mutations in JAK/STAT signaling components that lead to constitutive stimulation of the JAK/STAT pathway and cause the increased proliferation of myeloid cells with varying morphologic maturity and hematopoietic efficiency (Tefferi A 2018b).

ET is characterized by excessive clonal platelet production (Barbui et al. 2018; Harrison et al. 2017b) resulting from inordinate platelet production rather than from prolonged platelet survival in peripheral blood (Tefferi A 2018b). The term "essential" refers to an innate problem of hematopoiesis in the bone marrow. This contrasts with "secondary thrombocytosis," which is a high platelet count in reaction to another issue in the patient's body (eg, splenectomy) (Leuk and Lymphoma 2012). Platelet kinetic data suggest that megakaryocyte proliferation occurs autonomously of circulating thrombopoietin (TPO) levels in ET. The simultaneous normal or slightly elevated plasma TPO concentrations and lower *MPL* (TPO receptor) expression in platelets and megakaryocytes result in a net overall normal clearance of TPO (Ng et al. 2014). Because TPO levels do not influence megakaryocyte proliferation in ET, therapeutic agents that directly affect megakaryocytes may be useful treat this disease.

In ET, similar to MF, driver mutations deregulate the normally occurring endomitosis that generates polyploidy in megakaryocytes, resulting in mild-to-moderate megakaryocyte hyperplasia with hyperploid nuclei (Guo et al. 2018). Recent preclinical models and clinical studies have shown that NF-κB pathway activation in both mutant and nonmutant hematopoietic cells drive expression of pro-inflammatory cytokines that typify the MPNs (Verstovsek, Mesa, et al. 2012; Pardanani et al. 2015; Kleppe et al. 2018). The resulting continuously activated leukocytes and platelets release greatly elevated inflammatory cytokines that perpetuate inflammation in the MPN microenvironment, engendering MPN-associated symptoms (Kleppe et al. 2018; Lussana and Rambaldi 2017).

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 (Agarwal et al. 2016; Kleppe et al. 2018). Pelabresib has the potential through its multiple mechanisms of action to reduce abnormal megakaryocytes, the major contributor to the pathogenesis of ET, through its inhibitory effects: (I) megakaryocyte differentiation and proliferation; (II) the inflammatory cytokine expression and release via the NF-κB signaling pathway (pelabresib treatment may diminish the quantity of platelets and the pro-inflammatory

cytokines that are released from megakaryocytes); and (III) targeting genes of TGF-ß signaling, especially secretion of collagen by fibroblasts (pelabresib may diminish bone marrow fibrosis by BET inhibition of pro-fibrotic pathways).

Although not approved for the treatment of ET in the United States, hydroxyurea (HU) serves as standard of care for high-risk ET and is recommended as first-line cytoreductive therapy for these patients (Barbui et al. 2018; Storen and Tefferi 2001; Cortelazzo et al. 1995). HU offers clinical benefits; however, it also carries major risks, including development of anemia, cutaneous complications, and leukemic transformation. HU may control platelet production but is associated with worsening neutrophil and Hgb levels (Briere 2007). Patients with high-risk ET receiving long-term HU therapy have also experienced notable cutaneous complications, including painful leg ulcers, anemia, fever, and squamous and basal cell carcinomas, AEs that may require therapy discontinuation (Callot-Mellot et al. 1996; Prassopoulos et al. 1997; Birgegard 2009). Furthermore, patients solely treated with HU have a 3-4% incidence of leukemic transformation (Harrison et al. 2005). Once leukemic transformation occurs, median survival ranges from 2-7 months (Tefferi and Barbui 2019) . Moreover, approximately 20% of patients who take HU become refractory and/or intolerant to the drug, as defined by the European LeukemiaNet (ELN) (Harrison et al. 2005; Barosi et al. 2007). Life expectancy for patients with HU resistance/intolerance is shorter than for patients who respond to HU, as defined by ELN response criteria (Barosi et al. 2009). In a 14-year retrospective study involving 166 patients with high-risk ET treated with HU for a median of 4.5 years, 38 (23%) patients died at a median follow-up of 7 years from ET diagnosis, resulting in a 65% survival at 10 years from the beginning of HU treatment (Hernandez-Boluda et al. 2011). Overall, 70% of the patients had complete response at 1-year per ELN criteria. Patients who achieved a complete response (platelet count $\leq 400 \times 10^9$/L, white blood cell (WBC) count $\leq 10 \times 10^9$/L, normal spleen size, and no disease-related symptoms) to HU had a 79% 10-year overall survival; comparatively, those with HU resistance had a 26% 10-year overall survival. These data highlight a significant unmet need in the patient population with HU resistance.

In 1997, anagrelide (ANA) became the only drug approved by the Food and Drug Administration (FDA) for the treatment of thrombocythemia, secondary to MPNs, for the reduction of elevated platelet count, reduction of thrombotic risk, and amelioration of symptoms including thrombo-hemorrhagic events (AGRYLIN. 2018, 1998) Unfortunately, the use of ANA has been associated with several side effects, including anemia (Birgegard 2009; Storen and Tefferi 2001). Furthermore, ANA does not necessarily prevent thrombohemorrhagic events (Harrison et al. 2005). Although ANA is approved for the treatment of thrombocythemia, secondary to myeloproliferative neoplasms, based on a meta-analysis of the literature between 2011 to 2017 (using MEDLINE and EMBASE), experts in a LeukemiaNet panel could not reach a consensus on recommending ANA in a first-line setting (Barbui et al. 2018).

Another treatment option for high-risk ET, IFN-α, reduces platelet count and the risk of thromboembolic complications in ET (Birgegard 2009). IFN-α is not approved for the treatment of patients with high-risk ET in the US. Although IFN-α has demonstrated reasonable effects on thrombocytosis, it does not appear to have a significant effect on the neoplastic clone in younger patients (Tefferi and Barbui 2019; Bentley et al. 1999) In a study involving 21 female patients with high-risk ET with a median age of 41 years (range: 14-68 years) who finished 2 years of IFN-α therapy, IFN-α elicited complete hematological responses (CHRs) (platelet count < 400 ×

10^9/L) in 13 (62%) patients and partial hematological responses (platelet count 400-600 × 10^9/L) in 7 (33%) patients (Bentley et al. 1999). However, within 1-4 months of therapy discontinuation, platelet counts either rebounded or patients needed to restart therapy, suggesting IFN-α did not induce a sustained, unmaintained hematologic remission (Bentley et al. 1999). IFN-α has also been associated with several clinically significant toxicities. Patients who take IFN-α experience the same flu-like symptoms from which they seek relief, such as nausea, myalgia, depression, and fatigue, with these side effects occurring in nearly all patients at the start of treatment (Birgegard 2009; Kiladjian, Chomienne, and Fenaux 2008). Despite the general abatement in side effects that occurs during treatment, dropout rates between 15% and 66% have been reported in multiple studies (Birgegard 2009). To reduce these widely recognized dose-dependent symptoms, physicians must administer lower, potentially suboptimal doses, which could undermine the treatment efficacy and lead to ET complications that otherwise would have been prevented through cytoreductive therapy (Kiladjian, Chomienne, and Fenaux 2008).

More recently, a Phase 2, randomized controlled trial (MAJIC-ET) evaluated ruxolitinib against a second-line best available therapy (BAT) control arm (ANA, IFN-α, or continuation of HU) in patients with high-risk, HU-resistant and/or intolerant ET (Harrison, Vannucchi, and Platzbecker 2017a). High-risk ET and HU resistance/intolerance were defined by standard criteria (see Section 6.1). One hundred-ten patients were randomized 1:1 to receive either ruxolitinib (starting dose 25 mg BID or 20 mg BID, if baseline platelets were 100 to 200 × 10^9/L) or BAT (ANA or IFN-α, with add-on busulfan, ^{32}P, and HU). Ruxolitinib failed to achieve a statistically significant difference in the primary endpoint, complete response (platelet count ≤ 400 × 10^9/L, WBC count ≤ 10 × 10^9/L, and normal spleen size on imaging), as defined by ELN criteria within a year of treatment (Barosi et al. 2009). There was no difference in complete response in patients treated with ruxolitinib (27; 46.6%) vs patients treated with BAT (23; 44.2%) ($P = 0.40$). Analysis of 2 clinically relevant secondary endpoints, thrombohemorrhagic events and disease transformation, revealed no significant difference in thrombotic and hemorrhagic event-free survival between each arm after 1 year ($P = 0.09$ and $P = 0.14$, respectively) and no significant difference in transformation-free probability between each arm after 1 year ($P = 0.29$). In addition to the nonsignificant difference between ruxolitinib and BAT with respect to platelets and patient-reported outcomes (PROs) in the MAJIC-ET trial, because JAK2 interferes with TPO and EPO signaling, ruxolitinib was associated with hematological toxicities, hindering patients with ET from achieving favorable hematological responses (Pettit and Odenike 2017). Grade 3 or 4 anemia was reported in 12 (21%) patients taking ruxolitinib and in none of the patients taking BAT; Grade 3 or 4 thrombocytopenia occurred in 2 (3.4%) patients in the ruxolitinib arm and in none of the patients in the BAT arm. Two patients discontinued ruxolitinib due to anemia, but no patients discontinued ruxolitinib or BAT due to thrombocytopenia. The study concluded that ruxolitinib elicited better symptom responses than BAT, but it did not have improved efficacy compared to BAT for most clinically significant events, including control of blood counts, transformation, thrombosis, or hemorrhage. In the MAJIC-ET trial, patients taking BAT (which consisted of ANA or IFN-α) did not experience any total symptom score (TSS) reduction in the first 12 months of treatment compared to ruxolitinib (0% vs 32%; $P = 0.03$) (Harrison, Vannucchi, and Platzbecker 2017a). Of note, patients in the MAJIC study had a lower baseline symptom score than previously reported in this population: baseline mean TSS score of 1.8 (SD: 1.6) by using the 10 symptom based Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) (Scherber et al. 2015). MPN-SAF was

established based on a prospective survey performed in MPN patients with ET, PV, and MF (Emanuel et al. 2012). The survey in 594 ET patients have shown mean TSS of 18.7 (SD: 15.3) by using MPN-SAF form based on 10 questions (fatigue, early satiety, abdominal discomfort, inactivity, concentration problems, high sweats, itching, bone pain, fever, weight loss). Although ruxolitinib, the standard of care agent for MF and polycythemia vera, demonstrated some symptomatic improvement in the MAJIC study, ruxolitinib failed to demonstrate superiority over ET standard of care agents in eliciting CHR, preventing thrombohemorrhagic events, controlling platelet count, or preventing disease transformation.

Based on the data presented above, there remains a high unmet need for patients with high-risk, HU-resistant and/or intolerant ET who urgently need an agent that may provide early resolution of thrombocytosis without detrimental effects on the other blood lineages and provide early and sustained symptomatic improvement.

1.3.3. Potential Role for Pelabresib as Monotherapy and in Combination With JAKi in MPN

There are multifaceted mechanisms by which pelabresib has the potential to address both the symptoms and the underlying disease of MF and ET, supporting its evaluation in these indications. Through its inhibitory effects on megakaryocyte differentiation and proliferation, the quantity of platelets and the pro-inflammatory cytokines that are released from megakaryocytes may be diminished and the mutant allele burden may also be reduced. Since the NF-κB signaling pathway has been implicated in MF and is affected by BET proteins, pelabresib may be able to reduce the levels of these pro-inflammatory cytokines and their associated constitutional symptoms and EMH. Of note, different inflammatory cytokines are affected by the NF-κB and JAK/STAT signaling pathways and so complementary activity of pelabresib with JAKis may be possible in reducing pro-inflammatory cytokines. In addition, BET inhibition affects the target genes of TGF-ß signaling, especially secretion of collagen by fibroblasts (Ding et al. 2015). Further, published studies have demonstrated that the BET protein BRD4 is associated with genes involved in multiple pro-fibrotic pathways and that BET inhibition in animal models of organ fibrosis (heart, liver, kidney, etc.) results in prevention of proliferation and differentiation of precursor cells into myofibroblasts and reduction of collagen production by the myofibroblasts (Ding et al. 2015; Stratton, Haldar, and McKinsey 2017). Thus, through its inhibitory effects on TGF-ß-induced signaling and on pro-fibrotic pathways, pelabresib may be able to reduce bone marrow fibrosis and the resultant EMH.

Support of the potential activity of pelabresib as monotherapy and in combination with JAK inhibition comes from a recent publication where BET inhibition was evaluated alone and in combination with ruxolitinib in mouse MF models (Kleppe et al. 2018). In the MF models, BET inhibition resulted in reduced pro-inflammatory cytokines, platelet counts, spleen volume, mutant allele burden in peripheral blood, and fibrosis. Significantly, many of these effects were of greater magnitude when the BET inhibitor was combined with ruxolitinib further supporting the complementary activity of BET and JAKi.

1.3.4. Phase 2 Study Design in MF

As of Amendment 6 of Study 0610-02, 2 Phase 2 MF expansion arms were defined: the Monotherapy Arm for patients previously treated with a JAKi (or ineligible to be treated with a JAKi), and the Combination Arm for patients currently on a stable dose of ruxolitinib. As of

Amendment 7, these arms are now denoted as Arm 1: Prior JAKi Monotherapy Arm and Arm 2: Add-on to JAKi Combination Arm. Prior treatment with a JAKi is required for Arm 1 (unless a patient is ineligible to be treated with a JAKi) to determine the benefit of pelabresib after patients fail standard of care JAK inhibition, where failure is defined as intolerant of, resistant, refractory, or loss of response to prior JAKi therapy. Currently, the options available for patients after they fail ruxolitinib are limited.

Because of the symptomatic benefit provided by ruxolitinib and because of the rapid symptomatic deterioration that can occur when it is stopped, some patients continue to be treated with ruxolitinib even when other manifestations of the disease (cytopenias, organomegaly) worsen. It is therefore also important to determine whether a new agent introduced for the treatment of patients with MF can be combined with ruxolitinib. Hence, in addition to evaluating pelabresib as a single agent therapy in patients with MF who are previously treated with a JAKi (Arm 1), this study separately evaluates pelabresib given in combination with ruxolitinib in patients who have been on a stable dose of ruxolitinib (Arm 2).

After a review of the safety data on pelabresib as monotherapy across 3 Phase 1 trials in hematological malignancies (described in Section 1.3.6), 225 mg QD (tablet formulation) was determined to be the MTD of pelabresib as monotherapy. Rather than starting at the MTD, as of Amendment 6 (Version 7) of Study 0610-02, a lower starting dose of 125 mg of pelabresib was chosen for the Phase 2 (MF expansion, Arms 1 and 2) based on the experience with pelabresib in the treatment of patients with lymphoma from Study 0610-01 (see Section 5.7.1 for rationale). Patients will be allowed to undergo upward titration (see Sections 5.7.3 and 5.7.7) of their pelabresib dose based on platelet count, Hgb levels, and safety evaluation. The maximum dose permitted must not exceed 225 mg QD (the monotherapy MTD) for Arms 1 and 2 and 175 mg QD for Arm 3. This is similar to the approach used in clinical practice with ruxolitinib.

As of Amendment 8 (Version 9), Arm 3 will enroll patients who are eligible to receive ruxolitinib and have not previously been treated with a JAKi, and will be treated with pelabresib in combination with ruxolitinib (Arm 3: JAKi Naïve Combination Arm). The complementary mechanisms between the 2 classes of agents, preclinical data, and early clinical evidence of synergy when BET and JAK inhibition are combined (see Sections 1.3.3 and 1.3.6.4) support evaluating this therapy in the frontline treatment of patients with MF. The first 6 patients have been enrolled and treated at an initial dose of 125 mg (with upward titration allowed) as in Arms 1 and 2. The initial ruxolitinib dose was as per the applicable approved package insert. The Safety Review Committee (SRC) has reviewed all data from the first 6 patients enrolled to determine whether any change in the starting dose is required. As of Amendment 8 (Version 9), as per the recommendation by the SRC, the starting dose for JAKi Naïve Combination Arm 3 will be pelabresib 125 mg QD and ruxolitinib one dose level below (by 5 mg) the recommended dose per platelet count at baseline and as described in the applicable approved package insert.

Rationale for Focus on TD Population (MF Expansion Arms)
As of Amendment 7 (Version 8), the Prior and Add-on to JAKi arms (Arms 1 and 2) have been stratified into TD cohorts (Cohorts 1A and 2A) and non-TD cohorts (Cohorts 1B and 2B) where TD is defined as receiving an average of ≥ 2 RBC transfusions per month (total of ≥ 6 RBC transfusions during the 12 weeks) prior to enrollment. The primary objective for the TD cohorts is to evaluate the rate of conversion from TD to TI (defined as no RBC transfusions over a period

of 12 weeks) (Gale et al. 2011). The primary objective for the non-TD cohorts is to evaluate the splenic response rate by imaging after 24 weeks of treatment (the original objective for the Prior and Add-on to JAKi arms). As described in more detail in Section 1.3.6.4, the first 4 evaluable Prior and Add-on to JAKi MF patients treated with pelabresib as monotherapy or in combination with ruxolitinib (all 4 of whom have received at least 6 months of treatment) have experienced a reduction in their constitutional symptoms, a decrease in spleen volume, and an increase in Hgb. The one patient who was TD at study entry became TI (as of July 2018, 7 months had elapsed since this patient's last transfusion). These findings are of relevance because, as described in Section 1.3.2, many MF patients present with low Hgb levels and mechanistically JAK inhibition can further reduce Hgb leading to TD in a proportion of patients treated with ruxolitinib. Stratifying the Prior and Add-on to JAKi arms into TD and non-TD cohorts will allow evaluation of endpoints particularly relevant to the TD group (eg, conversion from TD to TI) separately from the non-TD group. A Simon's two-stage design will be implemented for each TD cohort, which will allow for early stopping for futility. NOTE: See Investigator Brochure for further updates of the 0610-02-MF Phase 2 study.

The synergy reported in the preclinical study combining BET and JAK inhibition (see Section 1.3.3) support evaluation of pelabresib and ruxolitinib combination in the first-line JAKi naïve setting. The primary objective of Arm 3 is to evaluate the splenic response rate via imaging after 24 weeks of treatment. This combination may also be particularly relevant given the known reduction in Hgb associated with JAKi ruxolitinib, especially during the first 12 weeks of ruxolitinib therapy (see Section 1.3.2). Combining the 2 classes of drugs upfront may prevent or minimize any reduction in Hgb and prevent or reverse TD in this JAKi Naïve MF patient population.

1.3.5. Phase 2 Study Design in ET

As of Amendment 10 (Version 11), Arm 4 will enroll patients with high-risk ET who are resistant or intolerant to HU.

After a review of the safety data on pelabresib as monotherapy across 3 Phase 1 trials in hematological malignancies (described in Section 1.3.6), 225 mg QD (tablet formulation) was determined to be the MTD of pelabresib as monotherapy, and this will be the starting dose for patients with ET. Dose modifications due to toxicity will be permitted, as will dose re-escalation (up to a maximum dose of 225 mg QD) following recovery from toxicity. Refer to Section 5.7.13 and Section 5.7.14 for further details.

1.3.6. Clinical Development of Pelabresib

As of 27 June 2019, single-agent pelabresib has been studied in 138 patients in 3 Phase 1 clinical trials in hematologic malignancies (Table 2).

Initially, the clinical development program for pelabresib was centered on its ability to rapidly and reversibly suppress expression of the *MYC* gene, a gene broadly implicated in both hematologic malignancies and solid tumors. Based on its demonstrated anti-proliferative effects in vitro against lymphoma cell lines and antitumor effects in mouse xenograft models of lymphoma and leukemia, 3 Phase 1 clinical studies were conducted concurrently in the following patient populations: lymphoma (Study 0610-01); acute leukemia, Myelodysplastic Syndrome (MDS), MDS/MPN (in the present study, Study 0610-02); and multiple myeloma (Study 0610-03).

The focus of the pelabresib clinical development program has since shifted to MF given the inhibitory effects of pelabresib on megakaryocyte differentiation and proliferation in preclinical studies, the inhibitory effects of pelabresib on inflammatory cytokine expression and release and the effects of BET inhibition on treating organ fibrosis and MF in preclinical models; see Section 1.3.3.

Table 2 Phase 1 Clinical Studies With Pelabresib

Study	No. of Patients	Indication
0610-01	64	Lymphoma
0610-02[a]	44	Acute hematologic malignancies (AML, MDS, MDS/MPN, MF)
0610-03	30	Multiple myeloma

See Investigator Brochure for status of the 0610-02-MF Phase 2 study.

AML = acute myelogenous leukemia; MDS = myelodysplastic syndrome; MF = myelofibrosis; MPN = myeloproliferative neoplasm.

1.3.6.1. Clinical Safety Overview

As of Amendment 6, Phase 1 (dose escalation) of the present study (Study 0610-02) in patients with acute leukemia, MDS, MDS/MPN or MF is complete. All 3 Phase 1 studies (Studies 0610-01, 0610-02, and 0610-03) evaluated escalating doses of pelabresib when administered in treatment cycles comprised of a 14-day treatment period and a 7-day off-treatment period. Pelabresib was first evaluated in a capsule formulation across the dose range of 6 to 400 mg QD and 85-150 mg BID and subsequently in a tablet formulation at doses of 125, 225, and 275 mg QD. The tablet formulation includes micronized drug substance to improve the solubility of pelabresib at higher gastric pH and thereby increase bioavailability, particularly at higher doses of pelabresib. The exposure (C_{max} and AUC) achieved with the 225 and 275 mg QD tablet doses exceeded that achieved with the 300 and 400 mg capsule doses, supporting the switch to the tablets. Pelabresib is currently available in 25 mg and 100 mg strength tablets for oral administration.

The 225 mg QD dose in tablet form had been administered to more patients than any other dose (N = 23) and has been identified as the MTD for patients with lymphoma (Study 0610-01), and for patients with other hematologic malignancies (acute leukemia, MDS, MDS/MPN or MF; Study 0610-02, see Section 1.3.6.2) when given in the 2-week-on-1-week-off dosing regimen.

Pelabresib had a similar safety profile in all of these indications. In all 3 Phase 1 studies, hematologic changes and GI AEs were reported with the highest frequencies, and also with the highest incidence of study drug-related AEs and CTCAE Grade 3 or higher AEs that were considered related to study drug.

Thrombocytopenia (including platelet count decreased) was the most common treatment-related AE, reported in 33% of the 138 patients treated in all 3 Phase 1 clinical studies. There was a lower frequency reported in patients with leukemia and the other hematologic malignancies evaluated in the Phase 1 portion of Study 0610-02 (16%) than the other studies, which is likely due to the difficulty in discriminating between disease-related and treatment-related

thrombocytopenia in these patient populations. Approximately half the patients with treatment-related thrombocytopenia (26 of 46 patients) had thrombocytopenia of CTCAE Grade 3 or higher (17% of the 138 patients treated in all 3 Phase 1 studies). The thrombocytopenia reported was dose-dependent (increasing in incidence and severity with pelabresib exposure), reversible, and noncumulative. An additional week off treatment prior to initiation of the subsequent treatment cycle was needed for platelet recovery for some patients.

The other treatment-related hematological changes that were reported with higher frequencies in the Phase 1 clinical studies included anemia, neutropenia (including neutrophil count decreased) and lymphocyte count decreased; they also had a higher incidence of CTCAE Grade 3 or greater study drug-related AEs. The incidence of treatment-related anemia, neutropenia and lymphocyte count decreased was 13% (18 patients), 9% (13 patients) and 8% (11 patients), respectively, across the 3 Phase 1 clinical studies. The reporting of these hematological changes is confounded by the advanced disease populations evaluated in the Phase 1 hematological studies; no clear dose response was observed. Of all the hematologic changes reported in all 3 Phase 1 clinical studies, only one case of thrombocytopenia in Study 0610-02 and one case of febrile neutropenia in Study 0610-01 were reported as treatment-related SAEs.

The study drug-related GI AEs reported with higher frequencies were nausea, diarrhea, and vomiting, with incidences of 27% (37 patients), 20% (27 patients) and 17% (23 patients), respectively, across all 3 Phase 1 clinical studies. Many of these GI events were of low severity and manageable with adequate treatment. Apart from hypertension (reported in 2 patients), diarrhea, vomiting and nausea were the only SAEs that were considered to be related to study drug in more than one patient (5, 2 and 2 patients, respectively).

The other frequently reported study drug-related AEs were fatigue (33 patients; 24%), decreased appetite (29 patients; 21%), and dysgeusia (19 patients; 14%), most of which were of low severity.

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

1.3.6.2. Clinical Safety of Study 0610-02

In the present study (Study 0610-02), a total of 44 patients with acute leukemia, MDS or MDS/MPN were enrolled during Phase 1 (dose escalation) into the following cohorts:

Cohort 1: 24 mg QD (capsule formulation)
Cohort 2: 48 mg QD (capsule formulation)
Cohort 3: 120 mg QD (capsule formulation)
Cohort 4: 170 mg QD (capsule formulation)
Cohort 5: 230 mg QD (capsule formulation)
Cohort 6: 300 mg QD (capsule formulation)
Cohort 7: 400 mg QD (capsule formulation)
Cohort 8: 275 mg QD (tablet formulation)
Cohort 9: 225 mg QD (tablet formulation)

Of the 6 patients enrolled into Cohort 8 (275 mg QD tablet formulation), 2 of those patients experienced dose-limiting toxicity (DLTs). One patient experienced Grade 3 nausea and another patient experienced Grade 4 hypotension both of which were considered to be dose-limiting. Cohort 9 enrolled 6 patients to evaluate the lower dose of 225 mg QD tablet formulation. Of the 6 patients enrolled into Cohort 9, one patient experienced Grade 3 hyperbilirubinemia. Therefore, the MTD was defined as 225 mg QD (tablet formulation).

Since 27 June 2017, additional patients with MF have been enrolled in Study 0610-02 under Amendment 5 (Version 6). These patients will be included in the Phase 2 analysis.

Treatment of pelabresib alone and in combination with ruxolitinib in the 5 MF patients treated as of 27 June 2018 has been well tolerated, with 4 patients having received a minimum of 6 months (10 treatment cycles) of pelabresib as either monotherapy or in combination with ruxolitinib. Three of the 5 patients with MF who were treated with pelabresib alone or in combination with ruxolitinib reported at least one adverse drug reaction. The following adverse drug reactions were reported by a single patient each: thrombocytopenia, diarrhea, nausea, malaise, dizziness, and rash maculo-papular. Only the incidence of thrombocytopenia was of CTCAE Grade 3 or higher.

One SAE was reported by a single MF patient. The patient experienced CTCAE Grade 4 depression that was considered to be unrelated to study drug (pelabresib and ruxolitinib).
NOTE: See Investigator's Brochure for further updates of the 0610-02-MF Phase 2 study.

Treatment withdrawal syndrome: Two cases of acute respiratory distress syndrome (ARDS) were observed during the safety follow-up period in the present study (0610-02) in patients with MF treated with the combination of ruxolitinib and pelabresib. Respiratory distress was observed in 2 patients treated on Arm 3 of the study after treatment discontinuation. Patients remained on study for 22 and 26 cycles, respectively, before a decision was made to discontinue treatment due to Grade 3 thrombocytopenia in the setting of progressive disease. The events of ARDS were reported for both patients 5 days after last ruxolitinib dose and 12 days after last pelabresib dose. Both patients experienced clinical worsening and eventually died. The treating Investigator had considered these 2 cases to be consistent with ruxolitinib discontinuation syndrome (RDS) and to be unrelated to pelabresib. However, considering the investigational nature of pelabresib, the Sponsor is assessing the event of respiratory failure with fatal outcome as possibly related to the combination of pelabresib with ruxolitinib. Instances of severe AEs 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. Additional information about these cases, the risk of RDS, and guidance for the Investigator may be found in the pelabresib Investigator's Brochure.

Of note, no case reports of ARDS have been reported to date in patients with MF who were treated with pelabresib monotherapy (n = 78 in Arm 1) either during treatment or within 30 days of treatment discontinuation. The recommendations on RDS risk mitigation are presented in Section 5.8.5.

More detailed information about the known and expected benefits and risks may be found in the Investigator Brochure.

1.3.6.3. Clinical Pharmacokinetics

The PK profile of pelabresib when administered QD has been fairly consistent across the 3 Phase 1 clinical studies. CCI [redacted]

1.3.6.4. Clinical Efficacy

In Study 0610-01, 5 patients have achieved an objective response to pelabresib. One patient with T-cell and histiocyte-rich large B-cell lymphoma, 3 patients with DLBCL, and 1 patient with follicular lymphoma. Nineteen additional lymphoma patients achieved stable disease, and of these 19 patients, 6 patients maintained stable disease for 6 or more cycles of treatment. There have been no objective responses in unselected populations of patients with acute leukemia, MDS or MDS/MPN (Phase 1 of the present study 0610-02) or multiple myeloma (Study 0610-03).

All MF patients enrolled in Study 0610-02 under Amendment 5 will be included in the Phase 2 analysis. Prior to Amendment 7 and as of July 2018, 5 patients with MF have been treated with pelabresib in Study 0610-02 within the Prior and Add-on to JAKi cohorts, 4 of whom are evaluable. All 4 evaluable patients have received at least 6 months of treatment and have demonstrated clinical benefit that has extended at least that long. Two each are on the monotherapy and combination arms. All 4 patients were considered resistant/intolerant to ruxolitinib therapy at study entry, and all 4 have experienced a reduction in their constitutional symptoms, a decrease in spleen volume, and an increase in Hgb. The single patient who was TD at study entry became TI on combination treatment with pelabresib and ruxolitinib. This patient also experienced a spleen reduction > 35% by magnetic resonance imaging (MRI) and significant improvement in MF-related symptoms.

In addition, the one patient who entered the study with uncontrolled thrombocytosis associated with disabling headaches (and requiring hospital admission for pain control) experienced a normalization of platelet counts within the first month of monotherapy treatment with pelabresib along with disappearance of concomitant headaches. These effects were also associated with spleen shrinkage.

Finally, one patient in the Monotherapy Arm had an improved fibrosis bone marrow score from 3+ to 2+ after 6 months of therapy.

NOTE: See Investigator Brochure for further updates of the 0610-02-MF Phase 2 study.

1.3.6.5. Benefit-risk assessment

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

1.3.6.3.1 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.
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- **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.
- **Leukemic transformation:** An imbalance in MANIFEST-2 was identified with more patients experiencing increased blasts ≥10% in the pelabresib + ruxolitinib arm compared with the placebo + ruxolitinib arm. All patients identified were found to have one or more risk factors of leukemic transformation. The data did not reveal any consistent patterns in terms of demographics including mutational status, onset latency, or duration of underlying MF. A biological mechanism for an imbalance in patients with blast count increases ≥10% in the MANIFEST-2 study could not be identified. Disease progression in myeloproliferative neoplasms due to leukemic transformation is a serious event in the natural history of the disease. Additional information about the risk of leukemic transformation is found in the pelabresib IB.

1.3.6.3.2 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 (Mascarenhas et al. 2023). 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.

1.3.6.5.3 Overall Benefit-risk conclusion

The improvements in spleen volume, disease 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.

2. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 3, Table 4 and Table 5.

Table 3 Phase 1 (Dose Escalation - COMPLETED): Study Objectives and Endpoints

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

NOTE: The MF patients enrolled under Amendment 5 will be included in Phase 2 (see Table 4 for objectives).

Table 4 Phase 2 (MF Expansion-Prior JAKi Arm 1 and Add-on to JAKi Arm 2): Study Objectives and Endpoints

	Objectives	Endpoints
Primary	To evaluate splenic response rate by imaging after 24 weeks of treatment in Cohorts 1B and 2B (ie, in non-TD cohorts)	The splenic response rate is defined as the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT) after 24 weeks of treatment (Cycle 9, Day 1)
	To evaluate the rate of conversion from RBC TD to RBC TI in Cohorts 1A and 2A (ie, in TD cohorts)	Conversion rate is defined as the proportion of patients who convert from TD to TI, where TD is defined as receiving an average of ≥ 2 units of RBC transfusions per month (total of ≥ 6 RBC transfusions during the 12 weeks) prior to enrollment and TI is defined as absence of RBC transfusions over any consecutive 12 week period
Secondary	To evaluate the change in PROs and the rate of patients who achieve a ≥ 50% reduction in the TSS after 12 and 24 weeks of treatment (all cohorts)	PROs will be evaluated using the MFSAF v4.0 and the PGIC. Changes from baseline in the TSS from the MFSAF and PGIC will be described. The proportion of patients who achieve a ≥ 50% reduction in the TSS after 12 weeks (Cycle 5, Day 1) and 24 weeks of treatment (Cycle 9, Day 1) will also be reported
	To evaluate overall splenic response rate (all cohorts) and the splenic response rate after 12 weeks (all cohorts) and 24 weeks of treatment (Cohorts 1A and 2A)	The overall splenic response rate is the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT). The reduction in spleen size from baseline by imaging (MRI or CT) after 12 weeks (Cycle 5, Day 1) and after 24 weeks of treatment (Cycle 9, Day 1) will also be evaluated.
	To evaluate the duration of TI in Cohorts 1A and 2A	The duration of TI is defined as the time from the first onset date of TI to the earliest onset date of loss of TI
	To evaluate the early anemic response rate in Cohorts 1A and 2A	The early anemic response rate is defined as the proportion of patients who achieve a Hgb increase of ≥ 1g/dL from baseline over any consecutive 8 week period in the absence of RBC transfusions
	To evaluate the anemic response rate in patients who enroll as TI in Cohorts 1B and 2B	The anemic response rate is defined as the proportion of patients who enroll as TI and achieve ≥ 1.5 g/dL Hgb increase from baseline over any consecutive 12-week period in the absence of RBC transfusions

	Objectives	Endpoints
	To evaluate the duration of splenic response by imaging (all cohorts)	Duration of the splenic response is defined as the time when splenic response criteria are first met (a ≥ 35% reduction from baseline spleen size) until the first-time spleen volume reduction is < 35% from baseline and is increased by ≥ 25% from nadir in spleen volume by imaging
	To evaluate the safety of pelabresib in patients with MF	The incidence of AEs and SAEs and changes from baseline in vital signs, and laboratory values
	To characterize the PK of pelabresib (all cohorts)	C_{max}, t_{max}, C_{trough}, AUC_{last}, $AUC_{0-8,ss}$ $C_{max,ss}$, $t_{max,ss}$
	To characterize the effects, if any, of pelabresib on the PK of ruxolitinib in Arm 2	C_{max}, t_{max}, C_{trough}, AUC_{last}, $AUC_{0-8,ss}$
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Objectives	Endpoints
CCI	

Table 5 Phase 2 (MF Expansion-JAKi Naïve Arm 3): Study Objectives and Endpoints

	Objectives	Endpoints
Primary	To evaluate splenic response rate by imaging after 24 weeks of treatment	The splenic response rate is defined as the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT) after 24 weeks of treatment (Cycle 9, Day 1)
Secondary	To evaluate the change in PROs and the rate of ≥ 50% reduction in TSS after 12 and 24 weeks of treatment.	PROs will be evaluated using the MFSAF v4.0 and the PGIC. Changes from baseline in the TSS from the MFSAF and PGIC will be described. The proportion of patients who achieve a ≥ 50% reduction in TSS after 12 weeks (Cycle 5, Day 1) and 24 weeks of treatment (Cycle 9, Day 1) will also be reported.

	Objectives	Endpoints
	To evaluate splenic response rate by imaging after 12 weeks of treatment	The splenic response rate is defined as the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT) after 12 weeks of treatment (Cycle 5, Day 1)
	To evaluate the anemic response rate in patients who enroll as TI	The anemic response rate is defined as the proportion of patients who enroll as TI and achieve ≥ 1.5 g/dL Hgb increase from baseline over any consecutive 12-week period in the absence of RBC transfusions
	To evaluate the overall splenic response rate and the duration of splenic response	The overall splenic response rate is the proportion of patients who achieve a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT). Duration of the splenic response is defined as the time when splenic response criteria are first met (a ≥ 35% reduction from baseline spleen size) until the first-time spleen volume reduction is < 35% from baseline and is increased by ≥ 25% from nadir in spleen volume by imaging
	To evaluate the safety of pelabresib in patients with MF	The incidence of AEs and SAEs and changes from baseline in vital signs, and laboratory values
	To characterize the PK of pelabresib (all cohorts)	C_{max}, t_{max}, C_{trough}, AUC_{last}, $AUC_{0\text{-}8,ss}$, $C_{max,ss}$, $t_{max,ss}$
	To characterize the effects, if any, of pelabresib on the PK of ruxolitinib	C_{max}, t_{max}, C_{trough}, AUC_{last}, $AUC_{0\text{-}8,ss}$
Exploratory	CCI	

Objectives	Endpoints
CCI	


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Table 6 Phase 2 (ET Expansion Arm 4): Study Objectives and Endpoints

	Objectives	Endpoints
Primary	To evaluate the CHR	The proportion of patients who meet the criteria for a CHR, as assessed by modified ELN criteria (Barosi et al. 2009) • Normalization of platelet count ($\leq 400 \times 10^9$/L) • WBC count within normal range ($\leq 10 \times 10^9$/L) • Laboratory results confirmed after 1 cycle (after 3 weeks) • Normal spleen size (by palpation or imaging)
Secondary	To assess symptom improvement	The proportion of patients with $\geq$ 50% reduction from baseline in the MPN-SAF total score (Scherber et al. 2015). PGIC will also be summarized.
	To evaluate the partial hematological response rate	The proportion of patients who meet the following criteria for a partial hematological response: • Platelets 400-600 $\times 10^9$/L • WBC within normal range ($\leq 10 \times 10^9$/L) • Laboratory results confirmed after 1 cycle (after 3weeks)
	To evaluate the overall hematological response rate and duration of response	The proportion of patients with either a complete or partial hematological response at any time point and duration of response
	To evaluate the duration of response	The time from the first onset date of response to the earliest onset date of loss of response, as measured by: • Hematologic response • Symptom improvement
	To evaluate the rate of hemorrhagic and TE events	The proportion of patients with hemorrhagic or TE events
	To evaluate the safety of pelabresib in patients with ET	The incidence of AEs and SAEs and changes from baseline in vital signs, and laboratory values
	To characterize the PK of pelabresib	C_{max}, t_{max}, C_{trough}, AUC_{last}, $AUC_{0\text{-}8,ss}$, $C_{max,ss}$, $t_{max,ss}$
Exploratory	CCI	

Objectives	Endpoints
CCI	

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3. STUDY DESIGN

3.1. Overview of Study Design

This is a Phase 1/2, multicenter, open-label, dose escalation study (Phase 1) of pelabresib in patients with AML, MDS, MDS/MPN or MF and expansion study (Phase 2) of pelabresib in patients with MF previously or currently treated with a JAKi as a single agent (Arm 1: Prior JAKi Monotherapy Arm) and in combination with ruxolitinib (Arm 2: Add-on to JAKi Combination Arm), in patients with MF who are JAKi naïve in combination with ruxolitinib (Arm 3: JAKi Naïve Combination Arm), and in high-risk patients with ET who are resistant or intolerant to HU (Arm 4: ET Monotherapy Arm). Arms 1 and 2 are further stratified into TD cohorts (Cohorts 1A and 2A) and non-TD cohorts (Cohorts 1B and 2B).

The primary objective of Phase 1 (dose escalation) was to determine the DLTs and MTD of pelabresib in patients with acute leukemia, MDS, MDS/MPN or MF. As of Amendment 6, Phase 1 is complete. The primary objective of Phase 2 (MF expansion-Prior and Add-on to JAKi) depends on the cohort. The primary objective in Cohorts 1B, 2B and 3 is to evaluate splenic response rate by imaging after 24 weeks of treatment and the primary objective in Cohorts 1A and 2A is to evaluate the rate of conversion from TD to TI. The primary objective in

Cohort 4 (ET) is to evaluate complete hematologic response rate. **NOTE:** as of Amendment 6, separate dose escalation in MF will not be pursued (see Section 1.3.4 for details).

In both phases of the study, pelabresib will be administered PO QD for 14 days followed by a 7-day break, with cycles of treatment repeated every 21 days. This dosing regimen was originally chosen based on the aims of achieving continuous inhibition of the expression *MYC* and other genes (like *BCL-2*) for approximately 2 weeks, since preclinical studies suggest that longer exposure times are associated with greater antitumor activity. The 7-day break from treatment built into each cycle of treatment acknowledges the possible need for recovery from on-target normal tissue toxicity when pharmacologically active doses of pelabresib are given.

Phase 1 (Dose Escalation -COMPLETED):

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

Phase 2 (MPN Expansion):

The expansion phase of the study will evaluate pelabresib in 4 arms (2 arms in the **Prior and Add-on to JAKi** MF population, one arm in the **JAKi Naïve** MF population, and one arm in the **high-risk ET** population):

Arm 1: Prior JAKi Monotherapy Arm (MF patients treated with pelabresib alone):

- Cohort 1A: Open to patients with MF who are TD (defined as receiving an average of ≥ 2 units of RBC transfusions per month [total of ≥ 6 RBC transfusions over the 12 weeks] prior to enrollment) and who have previously been treated with a JAKi and are intolerant, resistant, refractory, or lost response to the JAKi, or are ineligible to be treated with a JAKi.

- Cohort 1B: Open to patients with MF who are not TD and who have previously been treated with a JAKi and are intolerant, resistant, refractory, or lost response to the JAKi, or are ineligible to be treated with a JAKi.

  Evidence of refractoriness, resistance, or loss of response would include no spleen size reduction or symptom improvement after 6 months of therapy, disease progression, or intolerance to ruxolitinib (ie, platelet count $< 50 \times 10^9$/L and/or absolute neutrophil count (ANC) $\leq 0.5 \times 10^9$/L despite recommended dose adjustments and interruptions per approved ruxolitinib label; bleeding; or other severe [eg, ≥ Grade 3 non-hematological] toxicity).

  Ineligible to be treated with a JAKi is defined as those patients for whom ruxolitinib is indicated, but the healthcare provider is reluctant to initiate ruxolitinib due to prior history of severe infections such as tuberculosis (TB), progressive multifocal leukoencephalopathy (PML), skin malignancies that are known to be associated or exacerbated by ruxolitinib, or other significant considerations as documented by the treating investigator (see the approved package insert for ruxolitinib).

Arm 2: Add-on to JAKi Combination Arm (MF patients treated with pelabresib in combination with ruxolitinib):

a. Cohort 2A: Open to patients with MF who are TD and who are currently taking ruxolitinib for > 6 months and be on a stable dose for a minimum 8 weeks prior to start of study drug but have disease that is not being adequately controlled by ruxolitinib.

b. Cohort 2B: Open to patients with MF who are not TD and are currently taking ruxolitinib for > 6 months and be on a stable dose for a minimum 8 weeks prior to start of study drug but have disease that is not being adequately controlled by ruxolitinib.

Arm 3: JAKi Naïve Combination Arm (MF patients treated with pelabresib in combination with ruxolitinib):
Open to patients with MF who are eligible for ruxolitinib and have not previously received a JAKi.

Arm 4: ET Arm (high-risk ET patients treated with pelabresib alone)

- Open to high-risk ET patients who are resistant or intolerant to HU

Because both pelabresib and ruxolitinib cause reversible thrombocytopenia, patients enrolled in the JAKi Naïve Combination Arm 3 will be required to have a platelet count $\geq 100 \times 10^9$/L in order to be eligible. A platelet count $\geq 75 \times 10^9$/L is required for patients on the Prior JAKi Monotherapy Arm 1 and Add-on to JAKi Combination Arm 2. In addition, Add-on to JAKi Combination Arm 2 patients will also be required to be on a stable dose of ruxolitinib for a minimum 8 weeks at the time of enrollment.

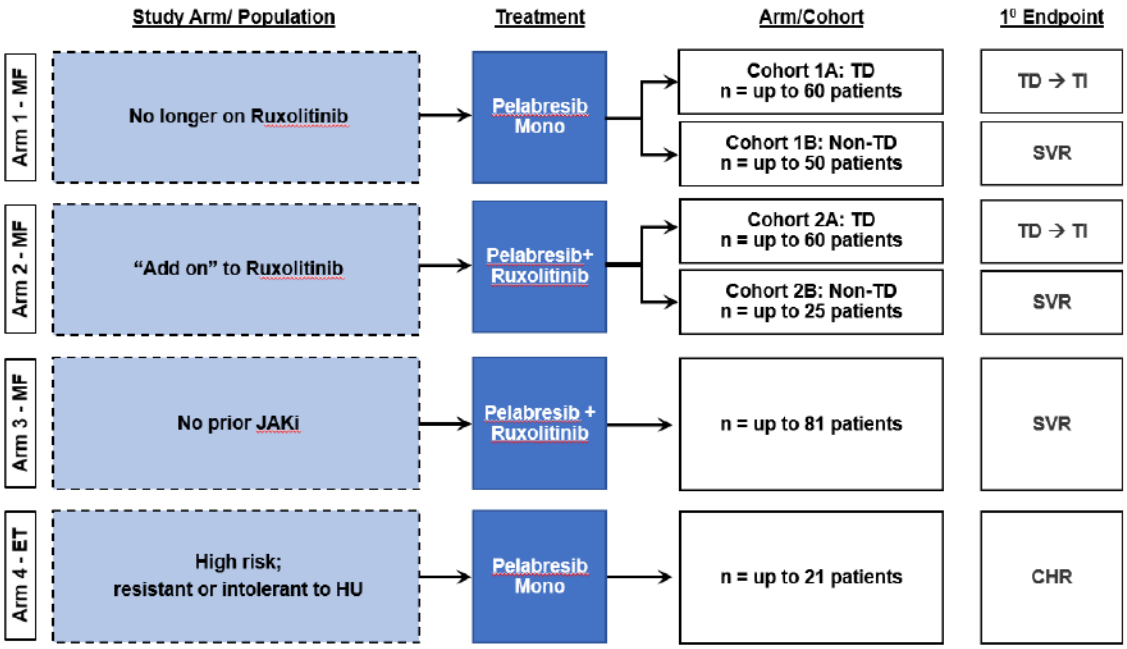
For Cohorts 1A and 2A, a Simon's two-stage design will be used to allow the possibility of early stopping for futility. For Cohorts 1A and 2A, the two-stage design will be based on conversion from TD to TI (see definitions in Section 7.2.4.3). Stage 1 for each cohort will enroll 6 evaluable patients. If 1 or more patients have a conversion, then an additional 10 evaluable patients will be enrolled in Stage 2 (see Figure 1). **NOTE:** All patients with MF enrolled under Amendment 5 will be included in Phase 2. **NOTE:** As of Amendment 8 (Version 9), 2 Cohort 2A patients have converted from TD to TI, therefore, the null hypothesis is rejected in favor of a true TD-to-TI conversion rate of 25%. To estimate the conversion rate with higher precision, Cohort 2A will be further expanded to enroll an additional 44 evaluable patients (for a total of 60) so that the study will have 85% power to exclude 10% from the lower bound of a two-sided 95% exact binomial confidence interval. Similarly, if the null hypothesis is rejected in the Simon's two-stage design of Cohort 1A, the cohort will be expanded to a total of 60 evaluable patients.

For Cohorts 1B and 2B, a sample size of 25 patients is required in each cohort to distinguish between a maximum futility splenic response rate of 10% and a minimum efficacy splenic response rate of 30% at Week 24, with an actual one-sided significance level of 0.033 and actual power of 80.65%. Five or more splenic responses are required in a cohort to find in favor of the treatment for that cohort. As of this amendment, 5 splenic responses have been observed in Cohort 1B. To increase the precision of estimate, Cohort 1B will be expanded to enroll 25 additional evaluable patients for a total of 50 evaluable patients. Assuming a true splenic response rate of 30%, a sample size of 50 evaluable patients will provide 86% power for the lower bound of a two-sided 95% exact binomial confidence interval to exclude a splenic response rate of 12.5%.

For JAKi Naïve Combination Arm (Arm 3), a total of 81 patients will be enrolled and an optimal Simon's two-stage design will be used. The primary endpoint for Arm 3 is splenic response rate after 24 weeks of treatment. The null hypothesis that the true splenic response rate is 30% will be tested against a one-sided alternative. The null hypothesis is constructed based on the splenic response rate at 24 weeks reported for ruxolitinib in the SIMPLIFY-1 trial (Mesa et al. 2017). In the first stage, 27 patients will be accrued. If there are 9 or fewer responses in these 27 patients, the study will be stopped. Otherwise, 54 additional patients will be accrued in Stage 2 for a total of 81. The null hypothesis will be rejected if 31 or more responses are observed in 81 patients. This design yields a type I error rate of 0.05 and power of 80% when the true splenic response rate is 45%.

For the ET arm (Arm 4), a sample size of 21 patients is required to distinguish between a maximum futility CHR rate of 8% and a minimum efficacy CHR rate of 30% with an actual one-sided significance level of 0.023 and actual power of 80.16%. Four or more complete hematologic responses are required to find in favor of the treatment.

Figure 1 Study Design Schematic



A patient may remain on study, despite confirmation of PD, if clinical benefit is derived until end of study is reached (see Section 6.5 for potential treatment after end of study). Clinical benefit is determined by the Investigator and may include improvement in TSS scores and blood counts.

3.2. Number of Patients

It is estimated that up to 341 evaluable patients may be enrolled. This estimate is based on the observed accrual of 44 patients with acute leukemia, myelodysplasia (MDS) or MDS/MPN to Phase 1 (dose escalation) of the study, and on the plan for 4 expansion arms (n = up to 60 evaluable MF patients each in Cohorts 1A and 2A, up to 50 evaluable MF patients in Cohort 1B,

and up to 25 evaluable MF patients in Cohort 2B in Arms 1 and 2; n = up to 81 evaluable MF patients in Arm 3; and n = up to 21 evaluable ET patients in Arm 4) in Phase 2 (dose expansion). **NOTE**: All patients with MF enrolled under Amendment 5 will be included in Phase 2.

4. STUDY POPULATION

4.1. Phase 1 (Dose Escalation - COMPLETED) Inclusion Criteria

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

4.2. Phase 1 (Dose Escalation - COMPLETED) Exclusion Criteria

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

4.3. Phase 2 Arm 1 (MF Expansion – Prior JAKi) and Arm 2 (Add-on to JAKi) Inclusion Criteria

Patients must meet all of the following criteria to be enrolled in this study:

1. Adult (aged ≥ 18 years)
2. Patients with confirmed diagnosis of MF who meet all of the following criteria:
   a. Dynamic International Prognostic Scoring System (DIPSS; see Appendix 3) risk category of intermediate-2 or higher.
   b. Platelet count ≥ 75×10^9/L without the assistance of thrombopoietic factors or transfusions
   c. ANC ≥ 1×10^9/L without the assistance of granulocyte growth factors
   d. Spleen volume of ≥ 450 cm^3 by MRI or CT for Cohorts 1B and 2B **OR** RBC TD (defined as an average of ≥ 2 units of RBC transfusions per month [total of ≥ 6 RBC transfusions over the 12 weeks] prior to enrollment) for Cohorts 1A and 2A
   e. Peripheral blood blast count < 10%
   f. At least 2 symptoms measurable (score ≥ 1) using the Myelofibrosis Symptom Assessment Form Version 4.0 (MFSAF v4.0)
   g. Monotherapy Arm (Arm 1) patients only: Previously treated with a JAKi and be intolerant, resistant, refractory, or lost response to the JAKi (defined as no spleen size reduction or symptom improvement after 6 months of therapy, disease progression, or intolerant to ruxolitinib [ie, platelet count < 50×10^9/L and/or ANC ≤ 0.5×10^9/L despite recommended dose adjustments and interruptions per approved ruxolitinib label; bleeding; or ≥ Grade 3 non-hematological toxicity]); have not received the JAKi within 2 weeks prior to start of study drug; or are ineligible to be treated with a JAKi (defined as those patients for whom ruxolitinib is indicated, but the healthcare provider is reluctant to initiate ruxolitinib due to prior history of severe infections such as TB, PML, skin malignancies that are known to be associated or exacerbated

by ruxolitinib, or other significant considerations as documented by the treating investigator [see the approved package insert for ruxolitinib]).

h. Combination Arm (Arm 2) patients only: Must have received ruxolitinib for at least 6 months and be on a stable ruxolitinib dose for a minimum 8 weeks (prior to start of study drug) but have disease that is not being adequately controlled by ruxolitinib

3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
4. Serum direct bilirubin < 2 × upper limit of normal (ULN)
5. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN. The AST and /or ALT may be elevated up to 5 × ULN if the elevation can be reasonably ascribed to liver involvement.
6. Calculated or measured creatinine clearance (CrCl) ≥ 45 ml/min (either measured or estimated by the Cockcroft-Gault formula).

   [Cockcroft-Gault formula for eCrCl: eCrCl = (140 – Age) × Mass (kg) × [0.85 if Female]/ 72 × Serum Creatinine (mg/dL)]
7. Patients must have fully recovered from major surgery and from the acute toxic effects of prior chemotherapy and radiotherapy (residual CTCAE Grade 1 toxicity, eg, Grade 1 peripheral neuropathy, and residual alopecia are allowed).
8. Both male and WOCBP 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 5.10, 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 pelabresib for male patients and male partners of WOCBP, and for 184 days after the last dose of study drug for WOCBP and female partners of male patients. **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.
9. Patients must give written informed consent to participate in this study before the performance of any study-related procedure.

4.4. Phase 2 Arm 1 (MF Expansion – Prior JAKi) and Arm 2 (Add-on to JAKi) Exclusion Criteria

Patients who meet any of the following criteria will not be enrolled in the study:

1. Patients in Cohorts 1B and 2B only: Patients who have had prior splenectomy
2. Patients in Cohorts 1B and 2B only: Patients who have had splenic irradiation within 3 months of starting study drug
3. Current known active or chronic infection with human immunodeficiency virus (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. 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.

4. Patients with active clinically significant infection will not be eligible for enrollment until recovery for at least 2 weeks prior to the first dose of study drug.
5. Patients with anemia deemed clinically significant by the investigator from iron deficiency, B12 and folate deficiencies, or hemolytic anemia.
6. Patient with a major bleeding event causing a decrease in Hgb of ≥ 2g/dL or leading to transfusion of ≥ 2 units of packed red cells in the last 6 months prior to enrollment.
7. Patients with liver cirrhosis Child-Pugh Class B or C (see Appendix 6)
8. Impairment of GI function or GI disease that could significantly alter the absorption of pelabresib and/or ruxolitinib, including any unresolved nausea, vomiting, or diarrhea > CTCAE Grade 1.
9. 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 on the screening ECG
     - All countries other than France and Germany: > 500 msec
     - France and Germany only: > 450 msec
   - Uncontrolled clinically significant cardiac arrhythmia (patients with rate-controlled atrial fibrillation are not excluded)

   Note that patients with a history of coronary artery disease and revascularization are not excluded.
10. Ongoing uncontrolled hypertension despite maximal antihypertensive treatment
11. 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, or active or uncontrolled infections.
12. Systemic anticancer treatment (other than ruxolitinib for the Combination Arm [Arm 2]; see inclusion criterion #2) other than HU and ANA less than 2 weeks (or 5 half-lives, whichever is longer) before the first dose of pelabresib. **NOTE:** HU and ANA are permitted to be used up to 24 hours prior to start of study drug.
13. 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 pelabresib.
14. Prior treatment with a BET inhibitor.

15. 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.
16. Patients in the Combination Arm (Arm 2) who are receiving treatment with fluconazole. **NOTE:** Patients in the Combination Arm who, at the time of screening, are already on a strong CYP3A4 inducer or inhibitor may be eligible, provided they meet all the other eligibility criteria. **Initiation of treatment** of a strong CYP3A4 inhibitor or inducer (listed in Appendix 4) during study treatment in Combination Arm patients is prohibited.
17. Systemic corticosteroids at daily doses ≥ 10 mg of oral prednisone or equivalent within 4 weeks before the first dose of study drug. **NOTE:** Patients who received daily doses of > 5 and < 10 mg oral prednisone or equivalent for ≤ 10 days within 2 weeks before the first dose of study drug may be eligible after consultation with the CPI Medical Monitor or designee. Topical, intra-articular injection, nasal and inhaled corticosteroids or daily doses of ≤ 5 mg oral prednisone or equivalent are allowed.
18. 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
19. Females who are breastfeeding or pregnant (as documented by a highly sensitive urine or serum beta-human chorionic gonadotropin [β-hCG] pregnancy test consistent with pregnancy, obtained within 72 hours prior to the first dose of pelabresib) 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 pelabresib. Females of non-childbearing potential (postmenopausal for more than 1 year; underwent a hysterectomy or bilateral salpingectomy or bilateral oophorectomy) do not require a serum pregnancy test.
20. Patients unwilling or unable to comply with this study protocol.

4.5. Phase 2 Arm 3 (MF Expansion – JAKi Naïve) Inclusion Criteria

Patients must meet all of the following criteria to be enrolled in this study:

1. Adult (aged ≥ 18 years)
2. Patients with confirmed diagnosis of MF who meet all of the following criteria:
    a. DIPSS (see Appendix 3) risk category of intermediate-2 or higher
    b. Platelet count ≥ 100 × 10^9/L without the assistance of thrombopoietic factors or transfusions
    c. ANC ≥ 1 × 10^9/L without the assistance of granulocyte growth factors

d. Spleen volume of ≥ 450 cm^3 by MRI/CT

e. Peripheral blood blast count < 10%

f. At least 2 symptoms measurable (score ≥ 3) or a total score of ≥ 10 using the MFSAF v4.0

g. No prior treatment with JAKi allowed

3. ECOG performance status ≤ 2
4. Life expectancy of > 24 weeks
5. Serum direct bilirubin < 2.0 × ULN
6. AST and ALT ≤ 2.5 × ULN. The AST and /or ALT may be elevated up to 5 × ULN if the elevation can be reasonably ascribed to liver involvement.
7. Calculated or measured CrCl ≥ 45 mL/min (either measured or estimated by the Cockcroft-Gault formula)

   [Cockcroft-Gault formula for eCrCl: eCrCl = (140 – Age) × Mass (kg) × [0.85 if Female]/ 72 × Serum Creatinine (mg/dL)]
8. Patients with a history of transfusions must have a documented transfusion record during the 12 weeks prior to the first dose of study drug
9. Patients must have fully recovered from major surgery and from the acute toxic effects of prior chemotherapy and radiotherapy (residual CTCAE Grade 1 toxicity, eg, Grade 1 peripheral neuropathy, and residual alopecia are allowed).
10. Both male and WOCBP 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 5.10, 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 pelabresib for male patients and male partners of WOCBP, and for 184 days after the last dose of study drug for WOCBP and female partners of male patients. **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.
11. Patients must give written informed consent to participate in this study before the performance of any study-related procedure.

4.6. Phase 2 Arm 3 (MF Expansion – JAKi Naïve) Exclusion Criteria

Patients who meet any of the following criteria will not be enrolled in the study:

1. Prior treatment with a BET inhibitor
2. Patients who have had a prior splenectomy
3. Patients who have had splenic irradiation within 3 months of starting study drug
4. 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. 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.

5. Patients with active clinically significant infection will not be eligible for enrollment until recovery for at least 2 weeks prior to the first dose of study drug.
6. Patients with anemia deemed clinically significant by the investigator from iron deficiency, B12 and folate deficiencies, or hemolytic anemia
7. Patient with a major bleeding event causing a decrease in Hgb of ≥ 2 g/dL or leading to transfusion of ≥ 2 units of packed red cells in the last 6 months prior to enrollment
8. Patients with liver cirrhosis Child-Pugh Class B or C (see Appendix 6)
9. Impairment of GI function or GI disease that could significantly alter the absorption of pelabresib and/or ruxolitinib, including any unresolved nausea, vomiting, or diarrhea > CTCAE Grade 1
10. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption or patients with hypersensitivity to any ingredient in the formulation of ruxolitinib
11. Patients who have or have had PML
12. 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 on the screening ECG
        - All countries other than France and Germany: > 500 msec
        - France and Germany only: > 450 msec
    - Uncontrolled clinically significant cardiac arrhythmia (patients with rate-controlled atrial fibrillation are not excluded)

    Note that patients with a history of coronary artery disease and revascularization are not excluded.
13. Ongoing uncontrolled hypertension despite maximal antihypertensive treatment
14. 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, or active or uncontrolled infections.

15. Systemic anticancer treatment other than HU and ANA less than 2 weeks (or 5 half-lives, whichever is longer) before the first dose of pelabresib. **NOTE:** HU and ANA are permitted to be used up to 24 hours prior to start of study drug.
16. 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 pelabresib
17. 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. Patients receiving treatment with fluconazole, or who have received a strong CYP3A4 inhibitor or inducer (listed in Appendix 4) within 2 weeks prior to the first dose of study drug. Initiation of treatment of a strong CYP3A4 inhibitor or inducer during study treatment is prohibited.
19. Systemic corticosteroids at daily doses ≥ 10 mg of oral prednisone or equivalent within 4 weeks before the first dose of study drug. **NOTE:** Patients who received daily doses of > 5 and < 10 mg oral prednisone or equivalent for ≤ 10 days within 2 weeks before the first dose of study drug may be eligible after consultation with the CPI Medical Monitor or designee. Topical, intra-articular injection, nasal and inhaled corticosteroids, or daily doses of ≤ 5 mg oral prednisone or equivalent are allowed.
20. 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
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 pelabresib) 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 pelabresib. Females of non-childbearing potential (postmenopausal for more than 1 year; underwent a hysterectomy or bilateral salpingectomy or bilateral oophorectomy) do not require a serum pregnancy test.
22. Patients unwilling or unable to comply with this study protocol

4.7. Phase 2 Arm 4 (ET Expansion) Inclusion Criteria

Patients must meet all of the following criteria to be enrolled in this study:

1. Adult (aged ≥ 18 years)
2. A confirmed diagnosis of ET according to the 2016 World Health Organization (WHO) criteria (Swerdlow 2017)
3. High-risk disease, defined as meeting at least one of the following criteria:

- Age > 60 years
- Platelet count > 1500 × 10^9/L (at any point during the patient's disease)
- Previously documented thrombosis (including Transient Ischemic Attack [TIA]), erythromelalgia, or migraine (severe, recurrent, requiring medications, and felt to be secondary to the MPN) either after diagnosis or within 10 years before diagnosis and considered disease-related
- Previous hemorrhage related to ET
- Diabetes or hypertension requiring pharmacological therapy for > 6 months

4. Have at least 2 symptoms with an average score ≥ 3 over the 7-day period prior to Cycle 1 Day 1 or an average total score of ≥ 15 over the 7-day period prior to Cycle 1 Day 1 using the using the MPN-SAF (Appendix 7); (Scherber et al. 2015)
5. Platelets > 600 × 10^9/L
6. Resistant or intolerant to HU, defined as meeting any of the following criteria (Barosi et al. 2007):
    - Platelet count > 600 × 10^9/L after 8 weeks of at least 2 g/day or MTD of HU (2.5 g/day in patients with a body weight > 80 kg)
    - Platelet count > 400 × 10^9/L and WBC < 2.5 × 10^9/L at any dose of HU (for a period of at least 8 weeks)
    - Platelet count > 400 × 10^9/L and Hgb < 110 g/L at any dose of HU (for a period of at least 8 weeks)
    - Platelet count persistently < 100 × 10^9/L at any dose of HU (for a period of at least 8 weeks)
    - Progressive splenomegaly or hepatomegaly, ie, enlargement by more than 5 cm or appearance of new splenomegaly or hepatomegaly on HU treatment
    - Not achieving the desired reduction of hematocrit or packed cell volume with the addition of HU in patients who do not tolerate frequent venesections after 8 weeks of at least 2 g/day of HU (2.5 g/day in patients with a body weight > 80 kg)
    - Not achieving the desired stable reduction of WBC when leukocytes are a target of therapy after 8 weeks of at least 2 g/day or MTD of HU (2.5 g/day in patients with a body weight > 80 kg)
    - Thrombosis or hemorrhage (including TIA) while on therapy
    - Presence of leg ulcers or other unacceptable HU-related non-hematological toxicities, such as unacceptable mucocutaneous manifestations, GI symptoms, pneumonitis, or fever at any dose of HU. OR Cycling platelet counts on therapy
    - Disease-related symptoms not controlled by HU
7. ECOG performance status ≤ 2
8. Life expectancy of > 24 weeks

9. ANC $\geq 1 \times 10^9$/L in the absence of growth factors
10. Serum direct bilirubin $< 2.0 \times$ ULN
11. AST and ALT $\leq 2.5 \times$ ULN
12. Calculated or measured CrCl ≥ 45 mL/min (either measured or estimated by the Cockcroft-Gault formula)

    [Cockcroft-Gault formula for eCrCl: eCrCl = (140 – Age) × Mass (kg) × [0.85 if Female]/ 72 × Serum Creatinine (mg/dL)]
13. Patients must have fully recovered from major surgery and from the acute toxic effects of prior chemotherapy and radiotherapy (residual CTCAE Grade 1 toxicity, eg, Grade 1 peripheral neuropathy, and residual alopecia are allowed).
14. Both male and WOCBP 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 5.10, 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 pelabresib for male patients and male partners of WOCBP, and for 184 days after the last dose of study drug for WOCBP and female partners of male patients. **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.
15. Patients must give written informed consent to participate in this study before the performance of any study-related procedure.

4.8. Phase 2 Arm 4 (ET Expansion) Exclusion Criteria

Patients who meet any of the following criteria will not be enrolled in the study:

1. Prior treatment with a BET inhibitor
2. 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. 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.
3. Patients with active clinically significant infection will not be eligible for enrollment until recovery for at least 2 weeks prior to the first dose of study drug.
4. Patients with liver cirrhosis Child-Pugh Class B or C (see Appendix 6)
5. Impairment of GI function or GI disease that could significantly alter the absorption of pelabresib, including any unresolved nausea, vomiting, or diarrhea > CTCAE Grade 1

6. 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 on the screening ECG
        - All countries other than France and Germany: > 500 msec
        - France and Germany only: > 450 msec
    - Uncontrolled clinically significant cardiac arrhythmia (patients with rate-controlled atrial fibrillation are not excluded)

    Note that patients with a history of coronary artery disease and revascularization are not excluded.
7. Ongoing uncontrolled hypertension despite maximal antihypertensive treatment
8. 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, or active or uncontrolled infections.
9. Systemic treatment for ET other than HU and ANA less than 2 weeks (or 5 half-lives, whichever is longer) before the first dose of pelabresib. **NOTE**: HU and ANA are permitted to be used up to 24 hours prior to start of study drug.
10. 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 pelabresib
11. Hematopoietic growth factor (granulocyte growth factor, erythropoiesis stimulating agent, TPO mimetic) or androgenic steroids less than 4 weeks before the first dose of study drug
12. Systemic corticosteroids at daily doses ≥ 10 mg of oral prednisone or equivalent within 4 weeks before the first dose of study drug. **NOTE:** Patients who received daily doses of > 5 and < 10 mg oral prednisone or equivalent for ≤ 10 days within 2 weeks before the first dose of study drug may be eligible after consultation with the CPI Medical Monitor or designee. Topical, intra-articular injection, nasal and inhaled corticosteroids, or daily doses of ≤ 5 mg oral prednisone or equivalent are allowed.
13. 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
14. 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 pelabresib) 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 pelabresib. Females of non-childbearing potential (postmenopausal for more than 1 year; underwent a hysterectomy or bilateral salpingectomy or bilateral oophorectomy) do not require a serum pregnancy test.

15. Patients unwilling or unable to comply with this study protocol.

5. STUDY TREATMENT

5.1. Study Drug

The term "study drug" refers to pelabresib, CPI's investigational inhibitor of BET proteins, formulated as tablets for oral administration. No control drug will be used in this study.

Pelabresib tablets, 25 mg and 100 mg contain the active pharmaceutical ingredient (pelabresib) CCI

All tablets are supplied in high density polyethylene (HDPE) bottles with child-resistant caps.

5.1.1. Study Drug Administration

Pelabresib will be administered PO, once a day for 14 consecutive days followed by a 7-day break. The 14 days of pelabresib dosing and the 7-day rest period together constitute 1 cycle of treatment. The first dose will be administered in the clinic on Day 1 of Cycle 1; thereafter, patients will take their daily dose at home unless otherwise instructed (explained below).

See Amendment 6 (Version 7) of the Study 0610-02 protocol for information on pelabresib dosing during Phase 1.

Patients will be given a dosing diary in which they should record relevant information regarding their study drug (eg, confirmation that each daily dose was taken, reasons for missed doses).

5.1.1.1. Once Daily Administration of Pelabresib

Patients should be instructed to take their daily dose at approximately the same time each day. Pelabresib should be taken in the morning unless otherwise instructed (see supportive care guidelines for nausea and vomiting in Section 5.8.1). Each dose should be taken with a glass of water and consumed over as short a time as possible (eg, all tablets within 5 minutes). Patients should be instructed to swallow tablets whole and to not chew them.

No food should be consumed for 2 hours prior to and 1 hour after oral administration of pelabresib. 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 dose of pelabresib 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 morning dose, then he/she should take pelabresib 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.

5.1.2. Packaging and Labeling

The study drug will be provided by CPI. The study drug will be labeled and handled at the investigational site as open-label material. Study drug labels will fulfill all requirements specified by relevant governing regulations. There will be no information about the patient on the study drug label. The storage conditions for study drug will be provided on the study drug label.

5.1.3. How Supplied

Pelabresib tablets will be supplied to the site pharmacy. The site pharmacist will dispense the appropriate number of bottles to each patient to ensure sufficient supply prior to the next study visit.

Please see Appendix 8 for changes due to unforeseen circumstances (including pandemics).

5.1.4. Storage, Handling, and Accountability

The study drug must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the pharmacist and designated assistants have access. Upon receipt, the study drug should be stored according to the instructions specified on the drug labels. Tablets should remain in the bottle provided until they are dispensed to patients. The bottles should be stored at the investigational site at controlled room temperature. Clinical supplies are to be dispensed only in accordance with the protocol.

Containers should be kept closed during storage.

Because this is an investigational agent, it should be handled with due care.

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be evaluated by the field monitor during site visits and at the completion of the study. All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed to do so by CPI, the Investigator must not destroy any drug labels, or any partly used or unused drug supply.

Please see Appendix 8 for changes in the drug shipment process due to unforeseen circumstances such as the COVID-19 pandemic.

5.2. Ruxolitinib for Phase 2 (MF Expansion - Add-on to JAKi Combination Arm [Arm 2] and MF Expansion-JAKi Naïve Combination Arm [Arm 3])

5.2.1. Starting Dose (MF Expansion - Add-on to JAKi Combination Arm [Arm 2])

Patients enrolled in the Phase 2 Add-on to JAKi Combination Arm (Arm 2) will already be on a stable fixed dose of ruxolitinib PO BID. Patients in this arm will remain on this same dose throughout the trial unless a dose reduction is required for toxicity (see Section 5.7.4).

5.2.2. Starting Dose (MF Expansion - JAKi Naïve Combination Arm [Arm 3])

As of Amendment 8 (Version 9), as per the recommendation by the SRC, the starting dose for JAKi Naïve Combination Arm 3 will be pelabresib 125 mg QD and ruxolitinib one dose level below (by 5 mg BID) the recommended dose per platelet count at baseline and as described in the applicable approved package insert. Refer to Section 5.7.2 for further details.

5.2.3. Patient Diary

Patients will be given a dosing diary in which they should record relevant information regarding ruxolitinib (eg, confirmation that each dose was taken, reasons for missed doses).

5.2.4. Ruxolitinib Administration

Patients will take ruxolitinib PO BID on a continuous basis for 21 consecutive days of each 21-day cycle. Patients will be instructed not to take the first dose of the drug on Day 1 of Cycle 1 until it can be administered in the clinic; thereafter, patients will take their daily dose at home unless otherwise instructed (see Section 5.2.4.1).

5.2.4.1. BID Administration of Ruxolitinib

Patients should be instructed to take their BID doses at approximately the same time each day. Each dose should be taken with a glass of water. Patients should be instructed to swallow tablets whole and to not chew them. On the days that pelabresib is also taken, the first ruxolitinib dose of the day should be swallowed whole with water at home first thing in the morning immediately after the pelabresib dose except for days that study drug will be administered in the study center under the observation of the study personnel.

Since pelabresib tablets must be taken on an empty stomach, no food should be consumed for 2 hours prior to and 1 hour after oral administration of the first daily dose of ruxolitinib on the days both drugs are to be administered. For the second ruxolitinib dose of the day, and on days that pelabresib is not administered, ruxolitinib can be taken with or without food.

On days when PK and/or pharmacodynamic samples need to be collected, the patient should take that day's first dose of ruxolitinib 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 a dose of ruxolitinib, the patient should not take an additional dose, but should take the next usual prescribed dose.

5.2.5. How Supplied

Ruxolitinib is available as tablets formulated in 5, 10, 15, and 20 mg strengths. In the US, a 25 mg strength is also available. See the see the approved package insert for ruxolitinib for more details.

5.2.6. Adverse Events

As of the December 2017 US Prescribing Information for ruxolitinib, the most common adverse reactions associated with ruxolitinib in the double-blind, placebo-controlled trial of ruxolitinib in patients with MF were (% of patients, all grade): bruising (23%), dizziness (18%), headache (15%), urinary tract infections (9%), weight gain (7%), flatulence (5%) and herpes zoster (2%). Less than 1% of any adverse reaction was Grade 3, and none were Grade 4. The most common hematological laboratory abnormalities were (% of patients) thrombocytopenia (70% all grades, 9% Grade 3, 4% Grade 4); anemia (96% all grades, 34% Grade 3, 11% Grade 4); and neutropenia (19% all grades, 5% Grade 3 and 2% Grade 4). In addition, 25% of patients on ruxolitinib developed newly occurring or worsening Grade 1 abnormalities in ALT, 2% developed ≥ Grade 2 elevations. Seventeen percent of patients on ruxolitinib developed newly

occurring or worsening Grade 1 abnormalities in AST, < 1% developed Grade 2 elevations. Seventeen percent of patients on ruxolitinib developed newly occurring or worsening Grade 1 elevations in cholesterol, < 1% developed Grade 2 elevations.

The following warnings and precautions associated with the use of ruxolitinib:

- Thrombocytopenia, anemia, and neutropenia

In the Phase 3 study, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50000 was 14 days. Platelet transfusions were administered to 5% of patients. Discontinuation of treatment because of thrombocytopenia occurred in < 1% of patients. Patients with a platelet count of 100 to 200 × 109/L before starting ruxolitinib had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count > 200 × 109/L (17% versus 7%).

In the Phase 3 study, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (< 1%) discontinued treatment because of anemia. Mean decreases in Hgb reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy.

Sixty percent of patients treated with ruxolitinib and 38% of patients receiving placebo received RBC transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with ruxolitinib and 1.7 in placebo treated patients.

In the Phase 3 study, 1% of patients reduced or stopped ruxolitinib because of neutropenia.

- Risk of infection

Serious bacterial, mycobacterial, fungal, and viral infections have occurred including TB, PML, herpes zoster, and herpes simplex. Herpes simplex virus reactivation and/or dissemination has been identified post-approval in patients receiving ruxolitinib. Hepatitis B viral load increases, with or without associated elevations in AST and ALT have been reported in patients with chronic Hepatitis B infection.

- Symptom exacerbation following interruption or discontinuation of ruxolitinib

Following discontinuation of ruxolitinib, symptoms from MF may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following AEs after discontinuing ruxolitinib: fever, respiratory distress, hypotension, DIC, or multi-organ failure.

- Nonmelanoma skin cancer

Nonmelanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with ruxolitinib.

- Lipid elevations

Treatment with ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

5.3. Patient Numbering

Each patient in the study is identified by a unique patient number. 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 CPI to each investigative site.

The procedures for patient numbering and coordination between the study sites will be provided in a separate document prior to study start. Upon signing the informed consent form, the patient is assigned a patient number. Once assigned to a patient, a patient number will not be reused.

Informed consent must be obtained before performing any test to assess a patient's eligibility for this study.

5.4. Treatment Assignment

The assignment of a patient to a given dose cohort in Phase 1 was coordinated by the Sponsor. During Phase 2, all patients will be assigned to either Arm 1: Prior JAKi Monotherapy Arm (pelabresib alone), Arm 2: Add-on to JAKi Combination Arm (pelabresib plus ruxolitinib), Arm 3: JAKi Naïve Combination Arm (pelabresib plus ruxolitinib), or Arm 4: high-risk ET patients who are intolerant of or resistant to HU based on the eligibility criteria. Patients assigned to Arms 1 or 2 will also be assigned to either a TD cohort (Cohort 1A or 2A) or a non-TD cohort (Cohort 1B or 2B) based on TD status at enrollment.

5.5. Treatment Blinding

This is an open-label study and treatment blinding is not applicable.

5.6. Phase 1 (Dose Escalation - COMPLETED)

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

5.7. Phase 2 (MPN Expansion)

The expansion phase of the study will evaluate pelabresib in 4 arms (2 arms in the **Prior and Add-on to JAKi** MF population, one arm in the **JAKi Naïve** MF population, and one arm in the **ET population**):

Arm 1: Prior JAKi Monotherapy Arm (MF patients treated with pelabresib alone)

- For both Cohort 1A and Cohort 1B, the initial dose of pelabresib will be 125 mg QD (tablet formulation). Upward titration (see Section 5.7.3) of pelabresib is allowed (up to a maximum dose of 225 mg QD) based on platelet count, Hgb levels, and safety evaluation. Dose modification using downward titration will be utilized for patients who meet the dose adjustment criteria as outlined in Section 5.7.5. Pelabresib may be re-escalated after dose reduction provided the criteria in Section 5.7.6 are met.

Arm 2: Add-on to JAKi Combination Arm (MF patients treated with pelabresib in combination with ruxolitinib)

- For both Cohort 2A and Cohort 2B, the initial dose of pelabresib will be 125 mg QD (tablet formulation) and the initial dose of ruxolitinib will be the dose each patient is on at the time of screening. Dose modification using both an upward titration (for pelabresib only up to a maximum dose of 225 mg QD based on platelet count, Hgb levels, and safety evaluation; see Section 5.7.3) and downward titration (for either pelabresib or for ruxolitinib; see Section 5.7.5) will be utilized for patients who meet the dose adjustment criteria. **NOTE**: no dose above the original dose of ruxolitinib is allowed. Pelabresib may be re-escalated after dose reduction provided the criteria in Section 5.7.6 are met. **NOTE:** Patients in the Prior JAKi Combination Arm are required to have been on a stable dose of ruxolitinib for ≥ 8 weeks prior to start of study drug. Therefore, for US patients, dose modifications based on insufficient response and/or presence of Child-Pugh Class A or moderate renal impairment should have already been taken into account prior to enrollment on this trial.

Arm 3: JAKi Naïve Combination Arm (MF patients treated with pelabresib in combination with ruxolitinib)

- The starting dose for JAKi Naïve Combination Arm 3 is pelabresib 125 mg QD and ruxolitinib one dose level below (by 5 mg BID) the recommended dose per platelet count at baseline and as described in the applicable approved package insert. Refer to Section 5.7.2 for further details. Dose modification using upward titration is allowed for both pelabresib (only up to a maximum dose of 175 mg QD based on platelet count, Hgb levels, and safety evaluation; see Section 5.7.7) and ruxolitinib (see Section 5.7.8). Dose modification using downward titration will also be utilized for pelabresib and ruxolitinib (see Section 5.7.10) for patients who meet the dose adjustment criteria. Pelabresib and ruxolitinib may be re-escalated after dose reduction provided the criteria in Section 5.7.12 are met.

Arm 4: ET Arm (high-risk ET patients treated with pelabresib alone)

- For this arm, the initial dose of pelabresib will be 225 mg QD (tablet formulation). Dose modification using downward titration will be utilized for patients who meet the dose adjustment criteria as outlined in Section 5.7.13. Pelabresib may be re-escalated (up to a maximum dose of 225 mg QD) after dose reduction provided the criteria in Section 5.7.14 are met.

5.7.1. Rationale for Starting Dose of Pelabresib

Following completion of Phase 1 (dose escalation), and after evaluation of 3 Phase 1 trials, the MTD of single-agent pelabresib across all hematological malignancies was defined as 225 mg QD (tablet formulation). In patients with ET (Arm 4), the starting dose will be 225 mg QD. However, in patients with MF, the starting dose will be 125 mg QD using pelabresib tablets. The selection of the 125 mg QD tablet starting dose in patients with MF is based on Phase 1 experience and the relationship between pelabresib dose and thrombocytopenia, as detailed below.

CCI [redacted]

In contrast to the patient population with MF, a decrease in platelet count is a desired effect in patient population with ET, therefore the starting dose in Arm 4 (ET cohort) will be the established pelabresib MTD of 225 mg daily.

The capsule formulation of pelabresib that has been used to date in clinical studies of pelabresib has been replaced with a new tablet formulation. CCI [redacted] The tablets are currently supplied in 25 and 100 mg strengths.

5.7.2. Safety Review Committee

Throughout Phase 2 (all arms), review of data will be provided by the SRC comprised of a subset of study investigators, the sponsor, and other representatives of the Sponsor. **NOTE**: Per Amendment 7 (Version 8), the SRC has reviewed the safety data from the first 6 patients enrolled in the JAKi Naïve Arm 3 and treated with the ruxolitinib and pelabresib combination therapy (see Section 5.7.2.1). The SRC has recommended the starting dose for both pelabresib and ruxolitinib as described in Section 5.7.2.2.

Other details on the members and responsibilities of the SRC are provided in the SRC charter, provided as a document separate from this protocol.

5.7.2.1. Summary of Safety Data from the First 6 Patients Enrolled in JAKi Naïve Combination Arm (Arm 3)

On 07 June 2019, SRC reviewed the safety for the first 6 patients treated for at least 1 cycle. All patients were treated with pelabresib 125 mg QD and ruxolitinib (2 patient each) either 10 BID or 15 BID or 20 mg BID.

Although 6 of 6 patients had some reductions in platelets, as expected from both agents, only 2 had Grade 2 platelet count decrease. One of these 2 patients required dose reduction of both pelabresib and ruxolitinib; the other patient required dose reduction of pelabresib and has remained stable on the modified dose. The other 4 patients had acceptable platelet count ($\geq 100 \times 10^9$/L) and remained on the starting dose of pelabresib and ruxolitinib. In addition, one patient was able to have an upward pelabresib dose titration to 150 mg PO QD. No ≥ 3 Grade AEs (including thrombocytopenia) and no SAEs were reported. There was no treatment discontinuation; all patients are active on treatment.

5.7.2.2. Summary of Recommendations for Pelabresib and Ruxolitinib Starting Dose in JAKi Naïve Combination Arm (Arm 3)

Based on the safety data review for the first 6 patients, the SRC recommended the following regimen as the starting dose for patients in the JAKi Naïve Combination Arm starting in Amendment 8 (Version 9.0). The starting dose for JAKi Naïve Combination Arm 3 will be pelabresib 125 mg QD and ruxolitinib one dose level below (by 5 mg BID) the recommended dose per platelet count at baseline and as described in the applicable approved package insert, as shown in Table 7.

Starting dose at Cycle 1 Day 1 is the combination of pelabresib at 125 mg QD and ruxolitinib at 10 mg BID when the platelet count is 100 - 200 $\times 10^9$/L. If the platelet count is > 200 $\times 10^9$/L, ruxolitinib starting dose should be 15 mg BID.

It is mandatory to increase ruxolitinib by 5 mg BID / cycle at Cycle 3 Day 1 regardless of percent change in spleen size by palpation from pretreatment baseline. Further upward dose titration of ruxolitinib up to a maximum dose of 25 mg BID should be considered if the criteria as defined in Section 5.7.7 are met.

Then increase pelabresib from Cycle 5 Day 1 and thereafter by 25 mg increments, not more frequently than once every 2 cycles, to a maximum dose of 175 mg QD if the upward dose titration criteria as defined in Section 5.7.8 are met.

NOTE that both ruxolitinib and pelabresib dose cannot be increased in the same cycle.

Table 7 Starting Doses of Ruxolitinib and Pelabresib and Uptitration Rules

Treatment Cycle/Day	Ruxolitinib (mg BID)	Pelabresib (mg QD)	Treatment Cycle
C1D1 (starting dose)	10 (if PLT 100-200 $\times 10^9$/L) / 15 (if PLT > 200 $\times 10^9$/L)	125	MANDATORY to start ruxolitinib at 10 or 15 mg BID (one dose level below the recommended dose per PLT count at baseline and as described in the applicable approved package insert) • Regardless of Hgb or transfusion status at C1D1

Treatment Cycle/Day	Ruxolitinib (mg BID)	Pelabresib (mg QD)	Treatment Cycle
C3D1 (dose increase)	10 to 15 / 15 to 20	125	MANDATORY to ↑ ruxolitinib dose by 5 mg BID • If PLT ≥ 125 × 10^9/L and ANC > 0.75 • Regardless of % change in spleen size by palpation from pretreatment baseline • No ≥ G3 non-hematological toxicity in C1 requiring dose interruption or reduction

ANC = absolute neutrophil count; BID = twice daily; C = Cycle; D = Day; G3 = Grade 3; Hgb = hemoglobin; PLT = platelet; QD = once daily.

5.7.3. Upward Titration Criteria for Pelabresib in Prior and Add-on to JAKi Patients (Arm 1 and Arm 2)

The starting dose of pelabresib for all Prior and Add-on to JAKi patients in Phase 2 will be 125 mg QD. Upward titration of pelabresib to a maximum dose of 225 mg QD is permitted in patients who are not progressing and who meet the upward titration criteria starting from Cycle 2 Day 1 (Monotherapy Arm [Arm 1]) or Cycle 3 Day 1 (Combination Arm [Arm 2]).

The following criteria must be met in order for the dose of pelabresib to be upward titrated by 25 mg on Day 1 of a cycle:

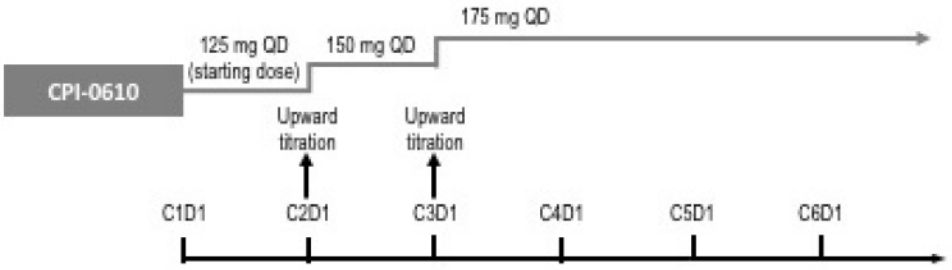
- Platelet count has been > 75 × 10^9/L over the course of the prior 1 cycle
- No safety concerns requiring pelabresib interruption, dose reduction, or discontinuation on the day the dose increase is under consideration

If a dose reduction of pelabresib was previously required for toxicity, re-escalation back to the original dose is allowed, provided the patient meets the criteria as described in Section 5.7.6. Once the patient is back on their original dose, further upward titration of their dose may be considered if the patient meets the criteria as described earlier here in this section.

For Arm 2 patients, the dose of ruxolitinib should remain the same during the treatment, unless a dose modification is required for toxicity (see Section 5.7.5).

Figure 2 and Figure 3 provide 2 examples of how upward titration of pelabresib may work for the Prior JAKi Monotherapy Arm 1, depending on the patient's clinical scenario. Figure 4 and Figure 5 provide 2 examples of how upward titration of pelabresib may work for the Add-on to JAKi Combination Arm 2.

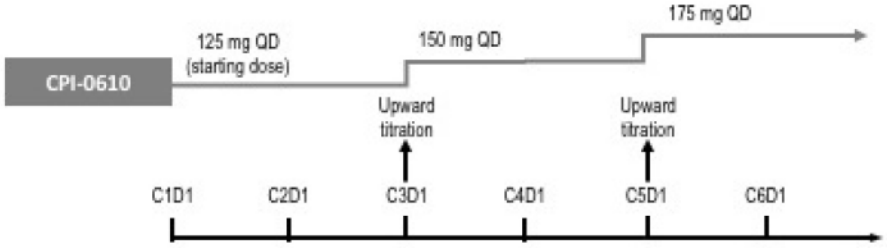
Figure 2 Example 1: Upward Titration of Pelabresib for Monotherapy Arm 1 Patients



Criteria for upward titration are met on C2D1 as per Section 5.7.3, CPI-0610 can be increased to 150 mg QD
Criteria for upward titration are met on C3D1 as per Section 5.7.3, CPI-0610 can be increased to 175 mg QD

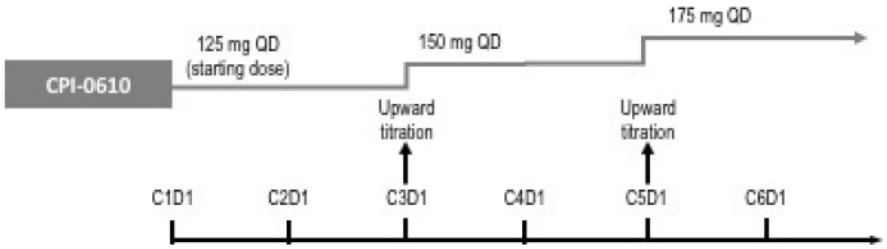
C = Cycle; D = Day; QD = once daily.

Figure 3 Example 2: Upward Titration of Pelabresib for Monotherapy Arm 1 Patients



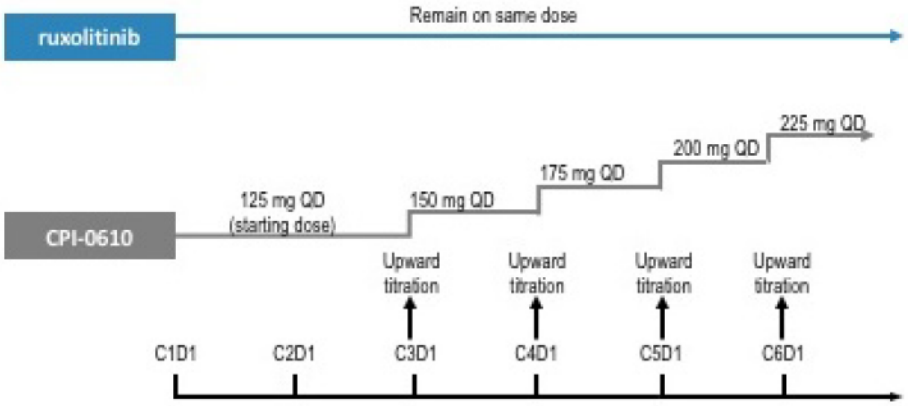
Criteria for upward titration are NOT met on C2D1 as per Section 5.7.3, and no dose reduction required as per Section 5.7.5; CPI-0610 dose remains at 125 mg QD
Criteria for upward titration are met on C3D1 as per Section 5.7.3, CPI-0610 can be increased to 150 mg QD
Criteria for upward titration are NOT met on C4D1 as per Section 5.7.3, and no dose reduction required as per Section 5.7.5; CPI-0610 dose remains at 150 mg QD
Criteria for upward titration are met on C5D1 as per Section 5.7.3, CPI-0610 can be increased to 175 mg QD

C = Cycle; D = Day; QD = once daily.

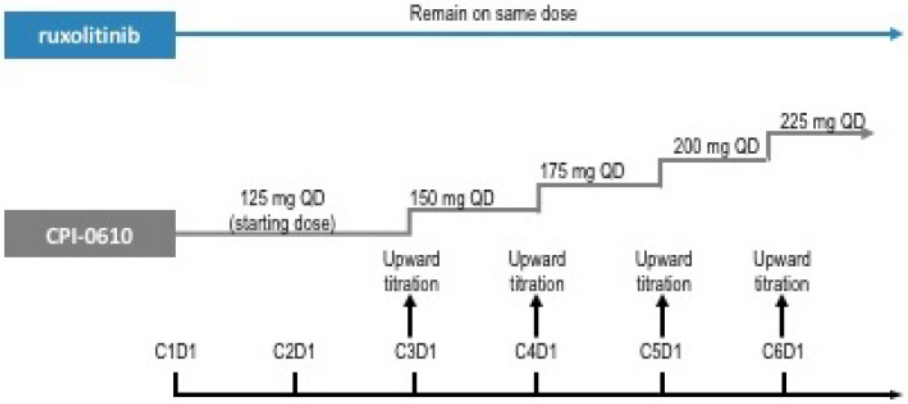


Criteria for upward titration are NOT met on C2D1 as per Section 5.7.3, and no dose reduction required as per Section 5.7.5; CPI-0610 dose remains at 125 mg QD
Criteria for upward titration are met on C3D1 as per Section 5.7.3, CPI-0610 can be increased to 150 mg QD
Criteria for upward titration are NOT met on C4D1 as per Section 5.7.3, and no dose reduction required as per Section 5.7.5; CPI-0610 dose remains at 150 mg QD
Criteria for upward titration are met on C5D1 as per Section 5.7.3, CPI-0610 can be increased to 175 mg QD

Figure 4 Example 1: Upward Titration of Pelabresib for Combination Arm 2 Patients



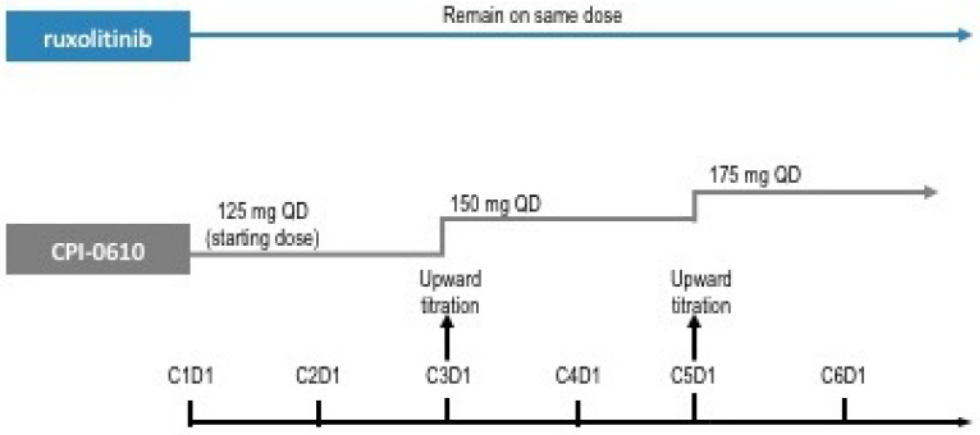
Criteria for upward titration are met on C3D1 as per Section 5.7.3, CPI-0610 can be increased to 150 mg QD
Criteria for upward titration are met on C4D1 as per Section 5.7.3, CPI-0610 can be increased to 175 mg QD
Criteria for upward titration are met on C5D1 as per Section 5.7.3, CPI-0610 can be increased to 200 mg QD
Criteria for upward titration are met on C6D1 as per Section 5.7.3, CPI-0610 can be increased to 225 mg QD



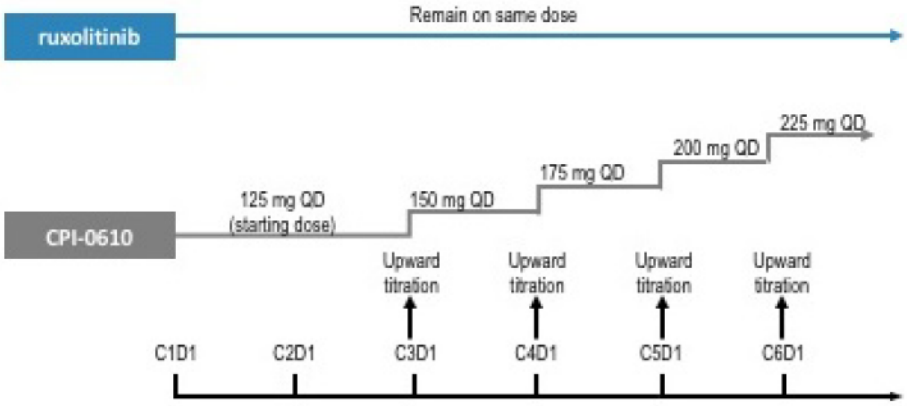
Criteria for upward titration are met on C3D1 as per Section 5.7.3, CPI-0610 can be increased to 150 mg QD
Criteria for upward titration are met on C4D1 as per Section 5.7.3, CPI-0610 can be increased to 175 mg QD
Criteria for upward titration are met on C5D1 as per Section 5.7.3, CPI-0610 can be increased to 200 mg QD
Criteria for upward titration are met on C6D1 as per Section 5.7.3, CPI-0610 can be increased to 225 mg QD

C = Cycle; D = Day; QD = once daily.

Figure 5 Example 2: Upward Titration of Pelabresib for Combination Arm 2 Patients



Criteria for upward titration are met on C3D1 as per Section 5.7.3, CPI-0610 can be increased to 150 mg QD
Criteria for upward titration are NOT met on C4D1 as per Section 5.7.3, and no dose reduction required as per Section 5.7.5; CPI-0610 dose remains at 150 mg QD
Criteria for upward titration are met on C5D1 as per Section 5.7.3, CPI-0610 can be increased to 175 mg QD
Criteria for upward titration are NOT met on C6D1 as per Section 5.7.3, and no dose reduction required as per Section 5.7.5; CPI-0610 dose remains at 175 mg QD



Criteria for upward titration are met on C3D1 as per Section 5.7.3, CPI-0610 can be increased to 150 mg QD
Criteria for upward titration are met on C4D1 as per Section 5.7.3, CPI-0610 can be increased to 175 mg QD
Criteria for upward titration are met on C5D1 as per Section 5.7.3, CPI-0610 can be increased to 200 mg QD
Criteria for upward titration are met on C6D1 as per Section 5.7.3, CPI-0610 can be increased to 225 mg QD

C = Cycle; D = Day; QD = once daily.

5.7.4. Dose Modification Rules for Prior and Add-on to JAKi Patients (Arm 1 and Arm 2)

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 Schedule of Events Table (see Table 15). Toxicity will be assessed according to the National Cancer Institute

(NCI) CTCAE, v4.03. The investigator should carefully assess all treatment-associated toxicities and in the Add-on to JAKi Combination Arm (Arm 2), whenever possible, determine if they can be attributed to pelabresib alone, ruxolitinib alone or to the combination of pelabresib plus ruxolitinib.

If patients experience pelabresib drug toxicity as specified in Table 8, follow the actions required. If Arm 2 patients experience ruxolitinib drug toxicity as specified in Table 8, follow the actions required.

Arm 1 (pelabresib alone):

- For pelabresib dose reduction, the dose will be downwards titrated by 25 mg/day (minimum dose level 50 mg QD**).

Arm 2 (pelabresib plus ruxolitinib):

- For pelabresib dose reduction, the dose will be downwards titrated by 25 mg/day (minimum dose level 50 mg QD**).
- For ruxolitinib dose reduction, the dose will be downwards titrated by 5 mg/day (minimum dose level 5 mg QD).

**Dose reductions of pelabresib below the starting dose of 125 mg QD should be carried out in accordance with Table 9 (Arm 1) and Table 11 (Arm 2). If it is deemed that a dose reduction below 50 mg QD is not appropriate, pelabresib may be permanently discontinued and the patient followed-up per protocol.

If pelabresib must be held for > 28 days due to toxicities (ie, if a break of > 35 days is required), pelabresib must be permanently discontinued (unless patient has evidence of clinical benefit, as assessed by the Investigator and discussed with the sponsor) and the patient followed-up per protocol.

If pelabresib is permanently discontinued in a patient in Arm 2, but the patient is indicated for continued treatment of ruxolitinib at the discretion of the investigator, then this will be regarded as a new anti-cancer therapy and the procedures as indicated in the study schedule will be followed to discontinue the patient from the study.

If a ruxolitinib dose below 5 mg PO BID is required, and/or if ruxolitinib must be held for > 28 days due to toxicities, ruxolitinib must be discontinued (unless patient has evidence of clinical benefit, as assessed by the Investigator). Gradual tapering of ruxolitinib should be considered when possible, to mitigate risk of RDS (see Section 5.8.5); ruxolitinib treatment may be restarted after a 28-day discontinuation if considered clinically necessary as per the Investigator's judgement after consultation with the sponsor. After 24 weeks, if a patient is required to discontinue ruxolitinib, the patient may be allowed to stay on trial and to receive pelabresib monotherapy, provided patient has evidence of clinical benefit, as assessed by the Investigator and after discussion with the sponsor.

Cycles are defined throughout the trial as every 3 weeks. In the event that dosing with pelabresib (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, they will still remain off pelabresib for Days 15-21 (the prescribed 7-day off period).

In case a patient becomes infected with COVID-19 during the study, pelabresib 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 judgement depending on patient's symptoms, disease status, comorbidities, concomitant medications, and according to local and institutional standards of care.

5.7.5. Dose Modification for Toxicities in Prior and Add-on to JAKi Patients (Arm 1 and Arm 2)

Table 8 provides rules on holding and/or dose modifying pelabresib (Arms 1 and 2) and ruxolitinib (Arm 2 only) for drug-related toxicities. Dose adjustment of pelabresib and/or ruxolitinib other than in Table 8 may be considered as per Investigator's clinical judgement after consultation with the sponsor, based on patient history and current clinical status, concomitant medications, laboratory findings, AEs, potential of RDS (Arm 2 only), and other observations with regards to risk/benefit considerations. See Section 5.7.6 for possible re-escalation of pelabresib and ruxolitinib after any dose reduction required for toxicity.

Table 8 Dose Modification Table for Toxicities in Prior and Add-on to JAKi Patients (Arm 1 and Arm 2)

Toxicity	Actions Required
Hematology	
Grade 4 neutropenia (ANC < 0.5 × 10^9/L)	• Hold pelabresib for up to 28 days. Repeat CBC at least twice weekly until resolution to ≤ Grade 3. NOTE: if an Arm 2 patient is considered to be at high risk for ruxolitinib discontinuation syndrome (RDS, see Section 5.8.5), 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 judgement. • Once resolved to ≤ Grade 3, restart pelabresib reduced by one dose level. • In the Combination Arm (Arm 2), if Grade 4 recurs despite pelabresib dose reduction, then hold pelabresib and ruxolitinib for up to 28 days. • Repeat CBC at least twice weekly until resolution to ≤ Grade 3 • Once resolved to ≤ Grade 3, restart pelabresib at the same dose and ruxolitinib reduced by one dose level.
Grade 2 thrombocytopenia (platelets 50 to < 75 × 10^9/L)	• Repeat CBC at least once weekly until resolution to ≤ Grade 1. • Follow dose modification in Table 9 (Arm 1) and Table 11 (Arm 2).
≥ Grade 3 thrombocytopenia (platelets < 50 × 10^9/L)	• Repeat CBC at least once weekly until resolution to ≤ Grade 1. • Follow dose modification in Table 9 (Arm 1) and Table 11 (Arm 2). NOTE: if an Arm 2 patient is considered to be at high risk for ruxolitinib discontinuation syndrome (RDS, see Section 5.8.5), 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 judgement.

Toxicity	Actions Required

Peripheral blood blasts ≧10% and/or clinical symptoms of potential transformation to blast phase	• HOLD pelabresib for up to 35 days
	• Collect a bone marrow biopsy:
	  • If transformation to blast phase (blasts ≥20%) is confirmed, permanently discontinue pelabresib
	  • If accelerated phase (≥10 to <20% blasts) is confirmed, permanently discontinue pelabresib
	  • If the bone marrow biopsy does not confirm accelerated phase (biopsy contains <10% of blasts), BUT there are at least 2 consecutive results in the peripheral blood blast of ≥10%, permanently discontinue study treatment
	• Resume pelabresib if the above criteria are not met

Hepatic	
≥ Grade 3 direct bilirubin (> 3 × ULN)	• Hold pelabresib up to 28 days. • Repeat direct bilirubin at least weekly until resolution to ≤ Grade 1. • Once resolves to ≤ Grade 1, restart pelabresib reduced by one dose level. • In the Combination Arm (Arm 2), if ≥ Grade 3 recurs despite pelabresib reduction, continue pelabresib at the reduced dose and hold ruxolitinib for up to 28 days. • Repeat direct bilirubin at least weekly until resolution to ≤ Grade 1 • Once resolved to ≤ Grade 1, restart ruxolitinib reduced by one dose level.
≥ Grade 3 ALT (> 5 × ULN) in patients who enroll with ≤ Grade 1 ALT **OR** Tripling of ALT in patients who enroll with Grade 2 ALT	• Hold pelabresib up to 28 days. • Repeat serum transaminases at least weekly until resolved to ≤ Grade 1 or baseline. • Once resolves to ≤ Grade 1 or baseline, restart pelabresib reduced by one dose level. • In the Combination Arm (Arm 2), if toxicity recurs despite pelabresib reduction, continue pelabresib at the reduced dose and hold ruxolitinib for up to 28 days. • Repeat serum transaminases at least weekly until resolved to ≤ Grade 1 or baseline. • Once resolved to ≤ Grade 1or baseline, restart ruxolitinib reduced by one dose level.
≥ Grade 2 total bilirubin (> 1.5 × ULN or > 3 × ULN for patients with Gilbert syndrome not attributable to Gilbert syndrome) **AND** ≥ Grade 2 ALT (> 3 × ULN) in patients who enroll with ≤ Grade 1 ALT **OR** ≥ Grade 2 total bilirubin (> 1.5 × ULN or > 3 × ULN for patients with Gilbert syndrome not attributable to Gilbert syndrome) **AND** tripling of ALT in patients who enroll with Grade 2 ALT	• Hold pelabresib up to 28 days. • Hold ruxolitinib up to 28 days. • Once resolved to ≤ Grade 1 or baseline, if another cause is identified, restart pelabresib and ruxolitinib at same dose. • Permanently discontinue pelabresib 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	

Toxicity	Actions Required
≥ Grade 3 vomiting, diarrhea or Grade 3 nausea	• Treat with optimal supportive care as per institutional guidelines (see Section 5.8.1 and Section 5.8.2) until resolution to ≤ Grade 1 • Hold pelabresib up to 28 days. • Patient must be contacted by investigator or study nurse daily until resolution to ≤ Grade 1 or a decision is made to increase support (eg, hospitalization). • Resume pelabresib in the presence of symptomatic prophylaxis at same dose if duration is ≤ 72 hours, or resume with dose reduced by one level if the duration is > 72 hours or if hospitalization is required despite optimal supportive care. • For the Combination Arm (Arm 2), if ≥ Grade 3 persists > 72 hours despite holding pelabresib dose, then also hold ruxolitinib for up to 28 days. • Resume ruxolitinib at same dose once recovers to ≤ Grade 1 and resume pelabresib in the presence of symptomatic prophylaxis at same dose if duration is ≤ 72 hours, or resume with dose reduced by one level if the duration is > 72 hours or if hospitalization is required despite optimal supportive care. **NOTE:** If toxicity recurs in the Combination Arm (Arm 2), and a hold of ruxolitinib was previously required because the duration was > 72 hours, hold both pelabresib and ruxolitinib for up to 28 days In some instances, separation of pelabresib and ruxolitinib intake by a few hours or pelabresib intake in the evening prior to bedtime has mitigated GI AEs.
Infection*	
≥ Grade 3	• Provide supportive care. • Hold pelabresib until infection resolves to ≤ Grade 1.
Grade 4	• Provide supportive care. • Hold all study treatment (both pelabresib and ruxolitinib as applicable) until infection resolves to ≤ Grade 1.
Rash	
≤ Grade 2	Provide supportive care (see Section 5.8.3).
Grade 3	• Provide supportive care (see Section 5.8.3). • If resolution to ≤ Grade 1 takes > 72 hours, hold pelabresib until resolution to ≤ Grade 1. • Resume pelabresib with dose reduced by 25 mg/day.
Grade 4	• Provide supportive care (see Section 5.8.3). • Permanently discontinue pelabresib treatment.
Other Nonspecified	
≥ Grade 2 that, in the opinion of the investigator, requires dose reduction	• For Grade 2, consider dose reduction of pelabresib by 25 mg daily; for Grade 3, HOLD offending agent(s) up to 28 days. • Evaluate at least once weekly until toxicity resolves to ≤ Grade 1 or stabilized. • Resume with dose of offending agent(s) reduced by one level.
Any toxicity caused by pelabresib that requires > 28 days hold	• Permanently discontinue pelabresib if a break of > 35 days off is required unless clear evidence of clinical benefit, as assessed by the Investigator.
Any toxicity caused by ruxolitinib that requires > 28 days hold	• Discontinue ruxolitinib. NOTE: if an Arm 2 patient is considered to be at high risk for RDS (see Section 5.8.5), consider tapering ruxolitinib instead of an abrupt stop.

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; CBC = complete blood count; GI = gastrointestinal; JAKi = JAK inhibitor; ULN = upper limit of normal.

*Please refer to ruxolitinib package insert for guidance in case of herpes simplex infections

Table 9 Pelabresib Dose Modification for Arm 1 for Reduction in Platelet Count

Platelet Count on Day 1 of any Cycle	Scenario	Pelabresib Dose at Time of Platelet Decline[a,b]						
		225 mg QD	200 mg QD	175 mg QD	150 mg QD	125 mg QD	100 mg QD	75 mg QD
		New Dose	New Dose	New Dose	New Dose	New Dose	New Dose	New Dose
100 - < 125 × 10^9/L		No Change						
75 - < 100 × 10^9/L		No Change						
50 - < 75 × 10^9/L (Grade 2)		175 mg QD	175 mg QD	150 mg QD	125 mg QD	100 mg QD	75 mg QD	50 mg QD
25 - < 50 × 10^9/L (Grade 3)[c]		75 mg QD	75 mg QD	75 mg QD	75 mg QD	75 mg QD	50 mg QD	50 mg QD
< 25 × 10^9/L (Grade 4)	First instance	**HOLD**						
		If HOLD, then restart when resolved to ≤ Grade 2 - Pelabresib dose reduced by 50 mg/day, except if the dose was 75 or 100 mg QD at the time of HOLD, then restart at 50 mg QD (increase to 75 mg QD ≤ Grade 2 platelet count is maintained for at least 2 cycles)						
	Second instance	Discontinue						

QD = once daily.

[a] If HOLD, restart when resolved to ≤ Grade 2

Discontinue treatment if HOLD for > 28 days

HOLD if associated with severe bleeding, ie, bleeding with clinical significance

5.7.6. Re-escalation of Pelabresib and Ruxolitinib After Dose Reduction for Toxicity in Prior and Add-on to JAKi Patients (Arm 1 and Arm 2)

If a dose of pelabresib and/or ruxolitinib has been reduced for a given patient and the indicated toxicity in Table 8 resolves (with exceptions noted below) for at least 1 cycle, the dose level may be upward titrated one dose level higher per cycle (25 mg/day for pelabresib and 5 mg /day for ruxolitinib). First increase the ruxolitinib dose, and then increase the pelabresib dose. Both pelabresib and ruxolitinib dose cannot be increased in the same cycle. This can be repeated until the original dose level (defined as the dose level before receiving the downwards titration) is reached for each agent. Ruxolitinib may not be re-escalated beyond the starting dose.

Exceptions: Upward titration of the pelabresib and ruxolitinib dose for patients who require dose reduction for Grade 4 non-hematological toxicity is not allowed. Treatment discontinuation may be considered based on the Investigator's judgement. If a patient experiences Grade 4 neutropenia, and the toxicity resolves for at least 1 cycle, the dose level may be titrated upwards one dose level per cycle. However, if Grade 4 neutropenia recurs, no subsequent upward dose titration will be permitted, even after the toxicity resolves. If a patient experiences any grade thrombocytopenia, all dose modifications must be made per Table 9 and Table 11. Re-escalation decisions must be made in accordance to criteria defined in Section 5.7.3 for pelabresib.

5.7.7. Upward Titration Criteria for Ruxolitinib in JAKi Naïve Patients (Arm 3)

As described in Section 5.7.2.2, if the starting dose of ruxolitinib is 10 or 15 mg BID, it is mandatory to increase the ruxolitinib dose by 5 mg BID at Cycle 3 Day 1 regardless of percent change in spleen size by palpation from pretreatment baseline and if platelet count is > 125 × 10^9/L and ANC is > 0.75 at Cycle 2 Day 1 (see Table 7). The ruxolitinib dose should be increased in 5 mg BID increments from Cycle 4 Day 1 or thereafter if all criteria outlined below are met. If all of these criteria are met, the ruxolitinib dose should be increased in 5 mg BID increments, not more frequently than once every cycle, up to 25 mg BID.

- Failure to achieve a reduction from pretreatment baseline in either palpable spleen length of ≥ 50% or spleen volume (as measured by MRI or CT) of ≥ 35% at Week 12
- Platelet count > 125 × 10^9/L over the course of the prior 1 cycle
- ANC > 0.75 × 10^9/L
- No AE requiring any dose interruption and/or reduction in the previous cycle when the ruxolitinib dose increase is under consideration

If the above criteria are met, upward dose titration for ruxolitinib should be followed.

NOTE that no dose reduction of ruxolitinib will be allowed based on Hgb levels during the first 24 weeks of treatment.

NOTE that both ruxolitinib and pelabresib dose cannot be increased in the same cycle.

5.7.8. Upward Titration Criteria for Pelabresib in JAKi Naïve Patients (Arm 3)

Pelabresib dose uptitration 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 pelabresib from Cycle 5 Day 1 or thereafter only if all the following criteria are met. If these criteria are met, the pelabresib 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 in order for the dose of pelabresib to be considered for upward titration Day 1 of a cycle (from Cycle 5 Day 1):

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

If the above criteria are met, investigator may consider an upward dose titration for pelabresib.

NOTE that both ruxolitinib and pelabresib dose cannot be increased in the same cycle. If pelabresib dose was reduced in a prior cycle, see Section 5.7.12 for possible re-escalation and subsequent upward titration of dose.

5.7.9. Dose Modification Rules for JAKi Naïve Patients (Arm 3)

Investigators should follow the ruxolitinib local approved product labeling and local clinical practice for dose modifications. Guidance for dose modification of ruxolitinib, in line with the ruxolitinib local approved product labeling, when given in combination with pelabresib, is outlined below.

If patients experience pelabresib or ruxolitinib drug toxicity as specified in Table 10 and Table 11, follow the actions required. A summary of the dose modification schema for platelet count decrease is presented as Figure 6.

Arm 3 (pelabresib plus ruxolitinib):

- For pelabresib dose reduction, the dose will be downwards titrated by 25 mg/day (minimum dose level 50 mg QD**).
- For ruxolitinib dose reduction, the dose will be downwards titrated by 5 mg BID (minimum dose level 5 mg BID[##]).

**Dose reductions of pelabresib for platelet count decrease should be carried out in accordance with Table 11. Doses below 50 mg QD are not allowed. In case of ongoing toxicity at the dose of 50 mg daily, pelabresib will be permanently discontinued and the patient followed-up per protocol.

[##] **NOTE**: No dose reduction of ruxolitinib is allowed based on Hgb levels during the first 24 weeks of treatment.

If pelabresib must be held for > 28 days due to toxicities as in the footnote in Figure 6 (ie, if a break of > 35 days is required), pelabresib must be permanently discontinued (unless patient has evidence of clinical benefit, as assessed by the Investigator and discussed with the sponsor) and the patient followed-up per protocol.

If pelabresib is permanently discontinued in a patient in Arm 3, but the patient is indicated for continued treatment of ruxolitinib at the discretion of the investigator, then this will be regarded as a new anti-cancer therapy. EOT, EOS and survival follow up procedures should be followed as appropriate.

If a ruxolitinib dose below 5 mg PO BID is required, and/or if ruxolitinib must be held for > 28 days due to toxicities, ruxolitinib must be discontinued. Gradual tapering of ruxolitinib should be considered when possible to mitigate risk of RDS (see Section 5.8.5); ruxolitinib treatment may be restarted after a 28-day discontinuation if considered clinically necessary as per the Investigator's judgement after consultation with the sponsor. After 24 weeks, if a patient is required to discontinue ruxolitinib, the patient may be allowed to stay on trial and to receive

pelabresib monotherapy, provided patient has evidence of clinical benefit, as assessed by the Investigator and after discussion with the sponsor.

Cycles are defined throughout the trial as every 3 weeks. In the event that dosing with pelabresib (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, they will still remain off pelabresib for Days 15-21 (the prescribed 7-day off period).

In case a patient becomes infected with COVID-19 during the study, pelabresib 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 judgement depending on patient's symptoms, disease status, comorbidities, concomitant medications, and according to local and institutional standards of care.

5.7.10. Dose Modification for Toxicities for JAKi Naïve Patients (Arm 3)

Table 10 provides rules on holding and/or dose modifying pelabresib and ruxolitinib for drug-related toxicities. See Section 5.7.12 for possible re-escalation of pelabresib after any dose reduction required for toxicity. See Section 5.7.11 for possible re-escalation of ruxolitinib after dose reduction required for toxicity.

Table 10 Dose Modification Table for Toxicities in JAKi Naïve Patients (Arm 3)

Toxicity	Actions Required
Hematology	
Grade 4 neutropenia (ANC < 0.5 × 10^9/L)	• Hold pelabresib and ruxolitinib for up to 28 days. Repeat CBC at least twice weekly until resolution to > 0.75 × 10^9/L. NOTE: if a patient is considered to be at high risk for ruxolitinib discontinuation syndrome (RDS, see Section 5.8.5), 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 judgement. • Once resolved to > 0.75 × 10^9/L, restart pelabresib dose reduced by 25 mg/day and ruxolitinib reduced by 5 mg per dose.
Reduction in platelet count	• For any reduction in platelet count to less than 100 × 10^9/L, see Table 11 for guidance on pelabresib and ruxolitinib dosing. • Repeat CBC as clinically indicated and at least once weekly until resolution to ≤ Grade 2.
Anemia	• For severe (Hgb < 8.0 g/dL) and/or symptomatic anemia, blood transfusion should be considered. • Ruxolitinib dose reduction/modification for anemia is not permitted in the first 24 weeks.

Peripheral blood blasts ≥10% and/or clinical symptoms of potential transformation to blast phase	• HOLD pelabresib for up to 35 days
	• Collect a bone marrow biopsy:
	  • If transformation to blast phase (blasts ≥20%) is confirmed, permanently discontinue pelabresib
	  • If accelerated phase (≥10 to <20% blasts) is confirmed, permanently discontinue pelabresib
	  • If the bone marrow biopsy does not confirm accelerated phase (biopsy contains <10% of blasts), BUT there are at least 2 consecutive results in the peripheral blood blast of ≥10%, permanently discontinue study treatment
	• Resume pelabresib if the above criteria are not met

Hepatic	
≥ Grade 3 direct bilirubin (> 3 × ULN)	• Hold pelabresib up to 28 days. • Repeat direct bilirubin at least weekly until resolution to ≤ Grade 1. • Once resolved to ≤ Grade 1, restart pelabresib reduced by 25 mg/day. • If ≥ Grade 3 recurs despite pelabresib reduction, continue pelabresib at the reduced dose and hold ruxolitinib for up to 28 days. • Repeat direct bilirubin at least weekly until resolution to ≤ Grade 1. • Once resolved to ≤ Grade 1, restart ruxolitinib reduced by 5mg per dose.
≥ Grade 3 ALT (> 5 × ULN) in patients who enroll with ≤ Grade 1 ALT **OR** Tripling of ALT in patients who enroll with Grade 2 ALT	• Hold pelabresib up to 28 days. • Repeat serum transaminases at least weekly until resolved to ≤ Grade 1 or baseline. • Once resolved to ≤ Grade 1or baseline, restart pelabresib reduced by 25 mg/day. • If toxicity recurs despite pelabresib reduction, continue pelabresib at the reduced dose and hold ruxolitinib for up to 28 days. • Repeat serum transaminases at least weekly until resolved to ≤ Grade 1 or baseline. • Once resolved to ≤ Grade 1or baseline, restart ruxolitinib reduced by 5mg per dose.

Toxicity	Actions Required
≥ Grade 2 total bilirubin (> 1.5 × ULN or > 3 × ULN for patients with Gilbert syndrome not attributable to Gilbert syndrome) **AND** ≥ Grade 2 ALT (> 3 × ULN) in patients who enroll with ≤ Grade 1 ALT **OR** ≥ Grade 2 total bilirubin (> 1.5 × ULN or > 3 × ULN for patients with Gilbert syndrome not attributable to Gilbert syndrome) **AND** tripling of ALT in patients who enroll with Grade 2 ALT	• Hold pelabresib up to 28 days. • Hold ruxolitinib up to 28 days. • Once resolved to ≤ Grade 1 or baseline, if another cause is identified, restart pelabresib and ruxolitinib at same dose. • Permanently discontinue pelabresib 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	
≥ Grade 3 vomiting, diarrhea, or Grade 3 nausea	• Treat with optimal supportive care as per National Comprehensive Cancer Network or institutional guidelines (see Section 5.8.1 and Section 5.8.2) until resolution to ≤ Grade 1. • Hold pelabresib up to 28 days. • Patient must be contacted by investigator or study nurse daily until resolution to ≤ Grade 1 or a decision is made to increase support (eg, hospitalization). • Resume pelabresib 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 ≥ Grade 3 persists > 72 hours despite holding pelabresib 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 5.8.5), consider tapering ruxolitinib instead of an abrupt stop. • Resume ruxolitinib at same dose once recovers to ≤ Grade 1 and resume pelabresib 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 both pelabresib and ruxolitinib for up to 28 days. In some instances, separation of pelabresib and ruxolitinib intake by a few hours or pelabresib intake in the evening prior to bedtime has mitigated GI AEs.
Infection*	
≥ Grade 3	• Provide supportive care. • Hold pelabresib until infection resolves to ≤ Grade 1.
Grade 4	• Provide supportive care. • Hold all study treatment (both pelabresib and ruxolitinib as applicable) until infection resolves to ≤ Grade 1.
Rash	
≤ Grade 2	• Provide supportive care (see Section 5.8.3).
Grade 3	• Provide supportive care (see Section 5.8.3).

Toxicity	Actions Required
	• If resolution to ≤ Grade 1 takes > 72 hours, hold pelabresib until resolution to ≤ Grade 1. • Resume pelabresib with dose reduced by 25 mg/day.
Grade 4	• Provide supportive care (see Section 5.8.3). • Permanently discontinue pelabresib treatment.
Other Nonspecified	
≥ Grade 2 that, in the opinion of the investigator, requires dose reduction	• For Grade 2, consider dose reduction of pelabresib by 25 mg daily; for Grade 3, HOLD offending agent(s) up to 28 days. • Evaluate at least once weekly until toxicity resolves to ≤ Grade 1 or stabilizes. • Resume with dose of offending agent(s) reduced by one level (ie, 25 mg/day for pelabresib or 5mg per dose for ruxolitinib).
	•
Any toxicity caused by pelabresib that requires > 28 days hold	• Permanently discontinue pelabresib if a break of > 35 days off is required unless clear evidence of clinical benefit, as assessed by the Investigator.
Any toxicity caused by ruxolitinib that requires > 28 days hold	• Discontinue ruxolitinib. NOTE: if a patient is considered to be at high risk for RDS (see Section 5.8.5), consider tapering ruxolitinib instead of an abrupt stop.

AE – adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; CBC = complete blood count; GI = gastrointestinal; Hgb = hemoglobin; JAKi = JAK inhibitor; ULN = upper limit of normal.

*Please refer to ruxolitinib package insert for guidance in case of herpes simplex infections

Table 11 Pelabresib and Ruxolitinib Dose Modification for Arm 2 and Arm 3 for Reduction in Platelet Count

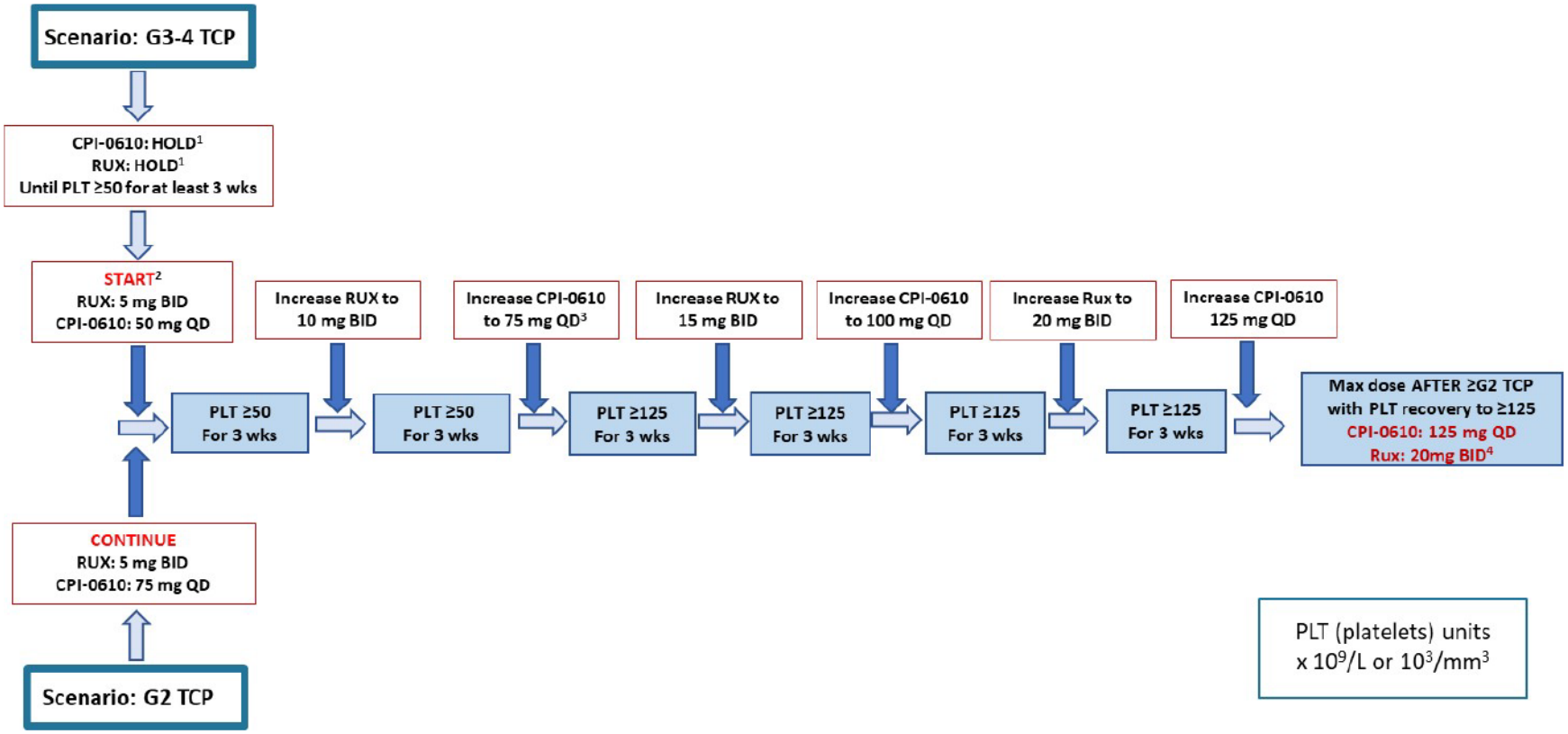
Platelet Count on Day 1 of any Cycle	Ruxolitinib Dose at time of Platelet Decline[a]					Pelabresib Dose Modification[a]
	25 mg BID	20 mg BID	15 mg BID	10 mg BID	5 mg BID	
100 - < 125 × 10^9/L	20 mg BID	15 mg BID	No Change	No Change	No Change	No Change
75 - < 100 × 10^9/L	10 mg BID	10 mg BID	10 mg BID	No Change	No Change	75 mg QD
50 - < 75 × 10^9/L (Grade 2)	• Ruxolitinib 5 mg BID and pelabresib 75 mg QD. • If PLT ≥ 50 × 10^9/L for at least 3 wks, may increase ruxolitinib to 10 mg BID and maintain pelabresib. • Maintain the above dose regimen until PLT recovers to ≥ 125 × 10^9/L and follow Figure 6 for further dose escalation.					
< 50 × 10^9/L (Grade 3-4)	• HOLD both ruxolitinib and pelabresib until PLT recovery to ≥ 50 × 10^9/L. NOTE: if a patient is considered to be at high risk for RDS (see Section 5.8.5), 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 judgement. 1. If PLT recovers to ≥ 50 × 10^9/L for at least 3 weeks, restart ruxolitinib 5 mg BID and pelabresib at 50 mg QD on Day 1 of upcoming cycle. 2. If PLT ≥ 50 × 10^9/L for at another 3 weeks: ↑ ruxolitinib to 10 mg BID, maintain pelabresib 50 mg QD on Day 1 of upcoming cycle. 3. If PLT ≤ Grade 2 for another 3 weeks: maintain ruxolitinib 10 mg BID, ↑ pelabresib to 75 mg QD on Day 1 of upcoming cycle.					

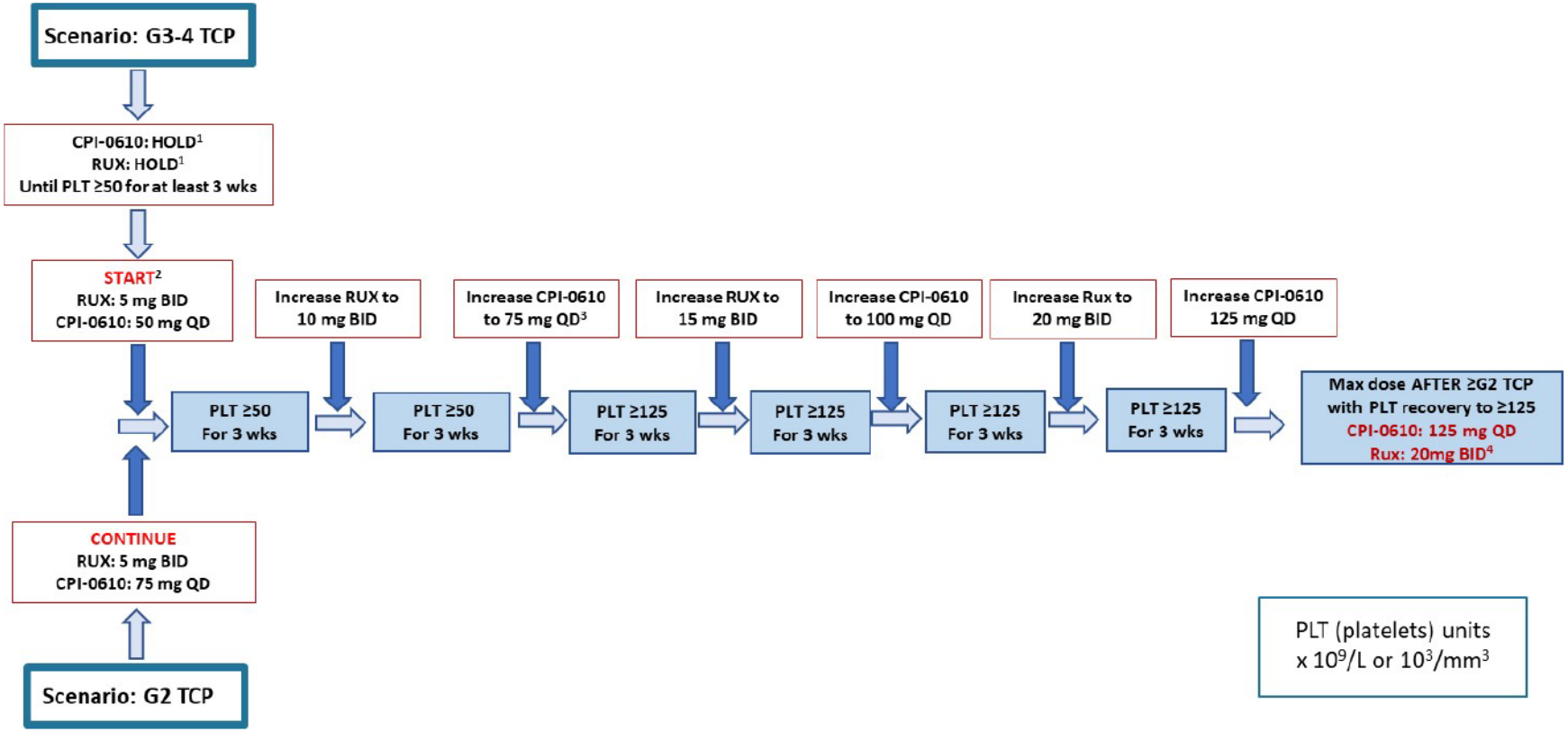
- Maintain the above dose regimen until PLT recovers to ≥ 125 × 10^9/L and follow Figure 6 for further dose escalation
- If Grade 3 PLT recurs after start of treatment, HOLD both ruxolitinib and pelabresib until PLT recovers to ≥ 50 × 10^9/L and follow steps 1-3 above.
- If Grade 4 PLT recurs after start of treatment, DISCONTINUE treatment
- If ruxolitinib and pelabresib is held > 28 days, DISCONTINUE treatment

BID = twice daily; PLT = platelet; QD = once daily.

[a] Both ruxolitinib and pelabresib dose cannot be increased in the same cycle

Figure 6 Pelabresib and Ruxolitinib Dose Modification and Re-escalation Schema After ≥ Grade 2 Platelet Count Decrease (Arm 2 and Arm 3)





BID = twice daily; C = Cycle; D = Day; G = Grade; PLT = platelet; QD = once daily; RDS = ruxolitinib discontinuation syndrome; RUX = ruxolitinib; TCP = thrombocytopenia.

[1] If pelabresib or ruxolitinib dosing is HOLD > 28 days, DISCONTINUE study treatment. If a patient is considered to be at high risk for RDS (see Section 5.8.5), HOLD pelabresib and consider tapering ruxolitinib instead of an abrupt stop. The risk of neutropenia versus the 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 judgement.

[2] If Grade 4 recurs after starting ruxolitinib 5 mg BID and pelabresib 50 mg QD, DISCONTINUE study treatment.

[3] If pelabresib is already 75 mg QD, please wait until PLT ≥ 125 × 10^9/L for further dose escalation.

[4] In Arm 2, ruxolitinib may not be re-escalated beyond the starting dose.

Note: Both ruxolitinib and pelabresib doses cannot be increased in the same cycle.

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

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

5.7.11. Re-escalation of Ruxolitinib After Dose Reduction for Toxicity JAKi Naïve Patients (Arm 3)

When considering re-escalation of ruxolitinib dose, the goal should be to keep increasing the dose regardless spleen response until it reaches the dose 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 spleen volume (as measured by MRI or CT scan) of ≥ 35% at Week 12.

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

- If dose reduced due to thrombocytopenia, refer to Table 11 and Figure 6 for information on dose re-escalation.
- If dose reduced due to neutropenia, a dose increase cannot be instituted until the ANC is $> 0.75 \times 10^9$/L for at least 1 cycle; refer to Table 10 for dose re-escalation.
- No safety concerns requiring pelabresib interruption, dose reduction, or discontinuation 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 dose increase is prohibited.

If the above criteria are met, upward dose titration for ruxolitinib can be considered. After the dose level prior to dose reduction is reached, subsequent upward dose titration of ruxolitinib is allowed provided that the criteria described in Section 5.7.7 are met.

NOTE that both ruxolitinib and pelabresib dose cannot be increased in the same cycle.

5.7.12. Re-escalation of Pelabresib After Dose Reduction for Toxicity in JAKi Naïve Patients (Arm 3)

NOTE: For restarting rules of pelabresib after a dose is held for toxicity, see Table 10. This section only addresses re-escalation (ie, dose increases after a dose reduction).

If a dose of pelabresib has been reduced for a given patient, the dose may be increased on Day 1 of a cycle. The following criteria must be met in order for the dose of pelabresib to be considered for re-escalation:

- The ruxolitinib dose has reached at least 10 mg BID for at least 3 weeks (see Table 11 and Figure 6).
- If dose reduced due to thrombocytopenia, refer to Table 11 and Figure 6 for information on dose re-escalation.

- If dose reduced due to neutropenia, a dose increase cannot be instituted until the ANC is $> 0.75 \times 10^9$/L for at least 1 cycle; refer to Table 10 for dose re-escalation.
- No safety concerns requiring pelabresib or ruxolitinib interruption, dose reduction, or discontinuation on the day the pelabresib dose increase is under consideration
- If dose reduced to Grade 4 non-hematologic toxicity, a dose increase is prohibited
- If dose reduced for other non-hematologic toxicity, a dose increase cannot be instituted until the toxicity has resolved to ≤ Grade 1 for at least 1 cycle. If a toxicity recurs after dose re-escalation, further dose increases are prohibited

If the above criteria are met, re-escalation of the pelabresib dose can be considered.

NOTE that both ruxolitinib and pelabresib dose cannot be increased in the same cycle.

5.7.13. Dose Modification for Toxicities for ET Patients (Arm 4)

In case a patient becomes infected with COVID-19 during the study, pelabresib 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 judgement depending on patient's symptoms, disease status, comorbidities, concomitant medications, and according to local and institutional standards of care.

Table 12 and Table 13 provide recommendations for dose modification for pelabresib (Arm 4) for drug-related toxicities.

Table 12 Dose Modification Table for Toxicities in ET Patients (Arm 4)

Toxicity	Actions Required
Hematology	
Grade 4 neutropenia (ANC < 0.5×10^9/L)	• Hold pelabresib for up to 28 days. Repeat CBC at least twice weekly until resolution to ≤ Grade 3. • Once resolved to ≤ Grade 3, restart pelabresib reduced by one dose level.
Reduction in platelet count	• For any reduction in platelet count to less than 125×10^9/L, see Table 13 for guidance on pelabresib and ruxolitinib dosing. • Repeat CBC as clinically indicated and at least once weekly until resolution to ≤ Grade 2.

Peripheral blood blasts ≥10% and/or clinical symptoms of potential transformation to blast phase	• HOLD pelabresib for up to 35 days
	• Collect a bone marrow biopsy:
	  • If transformation to blast phase (blasts ≥20%) is confirmed, permanently discontinue pelabresib
	  • If accelerated phase (≥10 to <20% blasts) is confirmed, permanently discontinue pelabresib
	  • If the bone marrow biopsy does not confirm accelerated phase (biopsy contains <10% of blasts), BUT there are at least 2 consecutive results in the peripheral blood blast of ≥10%, permanently discontinue study treatment
	• Resume pelabresib if the above criteria are not met

Toxicity	Actions Required
Hepatic	
≥ Grade 3 direct bilirubin (> 3 × ULN)	• Hold pelabresib up to 28 days. • Repeat direct bilirubin at least weekly until resolution to ≤ Grade 1 • Once resolves to ≤ Grade 1, restart pelabresib reduced by one dose level.
≥ Grade 3 ALT (> 5 × ULN) in patients who enroll with ≤ Grade 1 ALT **OR** Tripling of ALT in patients who enroll with Grade 2 ALT	• Hold pelabresib up to 28 days. • Repeat serum transaminases at least weekly until resolved to ≤ Grade 1 or baseline. • Once resolves to ≤ Grade 1 or baseline, restart pelabresib reduced by one dose level.
≥ Grade 2 total bilirubin (> 1.5 × ULN or > 3 × ULN for patients with Gilbert syndrome not attributable to Gilbert syndrome) **AND** ≥ Grade 2 ALT (> 3 × ULN) in patients who enroll with ≤ Grade 1 ALT **OR** ≥ Grade 2 total bilirubin (> 1.5 × ULN or > 3 × ULN for patients with Gilbert syndrome not attributable to Gilbert syndrome) **AND** tripling of ALT in patients who enroll with Grade 2 ALT	• Hold pelabresib up to 28 days • Once resolved to ≤ Grade 1 or baseline, if another cause is identified, restart pelabresib at same dose • Permanently discontinue pelabresib in the absence of biliary obstruction or other potential causes deemed responsible for the concurrent elevation of direct bilirubin and ALT.
Gastrointestinal	
≥ Grade 3 vomiting, diarrhea, or Grade 3 nausea	• Treat with optimal supportive care as per institutional guidelines (see Section 5.8.1 and Section 5.8.2) until resolution to ≤ Grade 1. • Hold pelabresib up to 28 days. • Patient should be contacted by investigator or study nurse daily until resolution to ≤ Grade 1 or a decision is made to increase support (eg, hospitalization). • Resume pelabresib in the presence of symptomatic prophylaxis at same dose if duration is ≤ 72 hours, or resume with dose reduced by one level if the duration is > 72 hours or if hospitalization is required despite optimal supportive care.
Infection	
Grade 3	• Provide supportive care (see Section 5.8.4). • If resolution to ≤ Grade 1 takes > 72 hours, hold pelabresib until resolution to ≤ Grade 1.
Grade 4	• Provide supportive care (see Section 5.8.4). • Hold pelabresib until resolution to ≤ Grade 1.
Rash	
≤ Grade 2	• Provide supportive care (see Section 5.8.3).
Grade 3	• Provide supportive care (see Section 5.8.3). • If resolution to ≤ Grade 1 takes > 72 hours, hold pelabresib until resolution to ≤ Grade 1. • Resume pelabresib with dose reduced by 25 mg/day.

Toxicity	Actions Required
Grade 4	• Provide supportive care (see Section 5.8.3). • Permanently discontinue pelabresib.
Other Nonspecified	
≥ Grade 2 that, in the opinion of the investigator, requires dose reduction	• For Grade 2, consider dose reduction of pelabresib by 25 mg daily; for Grade 3, HOLD pelabresib up to 28 days. • Evaluate at least once weekly until toxicity resolves to ≤ Grade 1 or stabilizes. • Resume with dose of pelabresib reduced by one level.
Any toxicity caused by pelabresib that requires > 28 days hold	• Permanently discontinue pelabresib if a break of > 35 days off is required unless clear evidence of clinical benefit, as assessed by the Investigator.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; CBC = complete blood count; ET = essential thrombocythemia; ULN = upper limit of normal.

Table 13 Pelabresib Dose Modification for ET Patients (Arm 4) for Reduction in Platelet Count

Platelet Count on Day 1 of any Cycle	Pelabresib Dose at Time of Platelet Decline[a]						
	225 mg QD	**200 mg QD**	**175 mg QD**	**150 mg QD**	**125 mg QD**	**100 mg QD**	**75 mg QD**
	New Dose	New Dose	New Dose	New Dose	New Dose	New Dose	New Dose
100 - < 125 × 10^9/L	200 mg QD	175 mg QD	150 mg QD	125 mg QD	125 mg QD	100 mg QD	75 mg QD
75 - < 100 × 10^9/L	175 mg QD	150 mg QD	125 mg QD	125 mg QD	100 mg QD	75 mg QD	75 mg QD
50 - < 75 × 10^9/L (Grade 2)	Decrease or continue at 75 mg QD If PLT recovers ≥ 75 × 10^9/L for at least 3 weeks, dose may be upward titrated by 25 mg QD per cycle						
< 50 × 10^9/L (Grade 3/4)	HOLD[b] treatment until PLT recovers to ≥ 50 × 10^9/L 1. If PLT recovers ≥ 50 × 10^9/L for at least 3 weeks, restart treatment at 75 mg QD 2. For all countries other than Canada: If PLT recovers ≥ 75 × 10^9/L for at least 3 weeks, dose may be upward titrated by 25 mg QD per cycle For Canada only: If Grade 4 PLT recurs after restart of treatment, DISCONTINUE treatment						

BID = twice daily; ET = essential thrombocythemia; PLT = platelet; QD = once daily
[a] HOLD treatment if associated with severe bleeding, ie bleeding with clinical significance
[b] Discontinue treatment if HOLD for > 28 days

5.7.14. Re-escalation of Pelabresib After Dose Reduction for Toxicity in ET Patients (Arm 4)

NOTE: For restarting rules of pelabresib after a dose is held for toxicity, see Table 12 and Table 13. This section only addresses re-escalation (ie, dose increases after a dose reduction).

If a dose of pelabresib has been reduced for a given patient, the dose may be increased on Day 1 of a cycle. The following criteria must be met in order for the dose of pelabresib to be considered for re-escalation:

- If dose reduced due to thrombocytopenia, refer to Table 13 for information on dose re-escalation.
- If dose reduced due to neutropenia, a dose increase cannot be instituted until the ANC is $\geq 0.75 \times 10^9$/L for at least 1 cycle; refer to Table 12 for dose re-escalation.
- No safety concerns requiring pelabresib interruption, dose reduction, or discontinuation on the day the pelabresib dose increase is under consideration
- If dose reduced to Grade 4 non-hematologic toxicity, a dose increase is prohibited
- If dose reduced for other non-hematologic toxicity, a dose increase cannot be instituted until the toxicity has resolved to ≤ Grade 1 for at least 1 cycle. If a toxicity recurs after dose re-escalation, further dose increases are prohibited

If the above criteria are met, re-escalation of the pelabresib dose can be considered.

5.8. Supportive Care

5.8.1. Nausea and/or Vomiting

5.8.1.1. Prophylaxis for Nausea and/or Vomiting

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

5.8.1.2. Management of Nausea and/or Vomiting

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

In addition to using prophylactic/supportive medications for these GI 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.

In some instances, separation of pelabresib and ruxolitinib intake by a few hours or pelabresib intake in the evening prior to bedtime has mitigated GI AEs, ie, nausea and vomiting.

Refer to Table 8 (Arms 1 and 2), Table 10 (Arm 3), and Table 12 (Arm 4) for dose hold and restarting criteria for nausea and vomiting.

5.8.2. Management of Diarrhea

Patients who develop diarrhea should be treated with anti-diarrhea medications as per standards of care and/or institutional guidelines. As an example, patients may be instructed to take loperamide, 4 mg, at the occurrence of the first loose stool and then 2 mg every 2 hours until they are diarrhea-free for at least 12 hours. During the night, patients may take 4 mg of loperamide every 4 hours. Fluid intake should be maintained to avoid dehydration.

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

In some instances, separation of pelabresib and ruxolitinib intake by a few hours or pelabresib intake in the evening prior to bedtime has mitigated GI AEs including diarrhea.

Refer to Table 8 (Arms 1 and 2), Table 10 (Arm 3), and Table 12 (Arm 4) for dose hold and restarting criteria for diarrhea.

5.8.3. Management of Rash

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

Refer to Table 8 (Arms 1 and 2), Table 10 (Arm 3), and Table 12 (Arm 4) for dose hold and restarting criteria for rash.

5.8.4. Management of Infection

Ruxolitinib has immunosuppressive effects, including down regulation of T cells and impairment of dendritic cell function, leading to serious opportunistic infections in patients on ruxolitinib therapy. It is recommended to stop ruxolitinib in case of an active severe infection, or, if the treating investigator is concerned about ruxolitinib symptom flare, ruxolitinib should be reduced to 5 mg BID until resolution of the infection when it can be uptitrated. The effects of pelabresib on the immune system are unknown. Thus, study intervention interruption is required in patients with a new onset of a > Grade 2 infection until resolved. Treatment may restart once the infection resolves to ≤ Grade 1.

Refer to Table 8 (Arms 1 and 2), Table 10 (Arm 3), and Table 12 (Arm 4) for dose hold and restarting criteria for infection.

5.8.5. Management of Ruxolitinib Discontinuation Syndrome (RDS)

Instances of SAEs 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 hematopoietic stem cell transplant [HSCT] delay) occurring in 1-11% of cases (Palandri et al. 2021; Shanavas et al. 2016; Tefferi and Pardanani 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 and Pardanani 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)

5.9. Concomitant Medications

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. 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 permitted during the study. 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 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 judgement, local and institutional regulations, and standards of care.

5.9.1. Antineoplastic Therapy

See Amendment 6 (Version 7) of the Study 0610-02 protocol for rules on antineoplastic therapy during Phase 1.

During Phase 2, patients are prohibited from receiving concomitant treatment with HU and should discontinue treatment at least 24 hours prior to starting pelabresib.

Apart from the use of ruxolitinib in patients enrolled in the Phase 2 Add-on to JAKi Combination Arm (Arm 2) and JAKi Naïve Combination Arm (Arm 3), patients are prohibited from receiving any antineoplastic therapy other than pelabresib during the course of this study. If alternative therapy is required for treatment of the patient's disease, the patient should be removed from this study and the reason for removal recorded in the electronic case report form (eCRF).

5.9.2. Corticosteroids (Phase 2)

Systemic corticosteroids at daily doses ≥ 10 mg of oral prednisone or equivalent are prohibited within 4 weeks of the first dose of pelabresib.

During the trial, systemic steroids above the equivalent of 10 mg/day prednisone are allowed if only required for ≤5 days. Pelabresib dosing should not be administered during this time. Concomitant use of topical, nasal, intra-articular, and inhaled corticosteroids is allowed without requiring a dose hold of pelabresib. During the trial, daily doses up to 20 mg of oral prednisone or equivalent may be allowed for ≤ 7 days if indicated, after consultation with the sponsor or designee. Pelabresib dose hold is required and can be resumed at least one week after completion of the higher dose (≥ 10 mg/day) steroid treatment.

No concomitant immunosuppressants are allowed during the trial.

5.9.3. Hematopoietic Growth Factors and Androgenic Steroids

Patients who have received a myeloid, erythroid or TPO growth factor or androgenic steroids within 4 weeks of the first dose of study drug will not be eligible for Phase 2 (MPN expansion). During Phase 2, use of any of these growth factors or androgenic steroids is prohibited as they may be associated with spleen size changes. However, on a case-by-case situation, particularly in patients with evidence of clinical benefit (as assessed by the Investigator), upon CPI consultation, patients may be allowed to receive growth factors.

5.9.4. Guidelines Regarding Potential Drug-drug Interactions With Concomitant Medications

5.9.4.1. CYP450 (CYP) Enzyme Inhibitors and Inducers

Concomitant administration of ruxolitinib with fluconazole doses > 200 mg QD may increase ruxolitinib exposure due to inhibition of both the CYP3A4 and CYP2C9 metabolic pathways. Therefore, **concomitant use** of fluconazole is prohibited in this trial for patients in the Phase 2 Add-on to JAKi Combination Arm (Arm 2) and in the JAKi Naïve Combination Arm (Arm 3). Concomitant administration of ruxolitinib with strong CYP3A4 inhibitors may increase ruxolitinib exposure, and strong CYP3A4 inducers may decrease ruxolitinib exposure. Therefore, **initiation of** strong CYP3A4 inhibitors or inducers is prohibited in this trial for patients in the Phase 2 Combination Arms; see Appendix 4. **NOTE:** Patients who require fluconazole at the time of screening will not be eligible for the Phase 2 Combination Arms. Patients who, at the time of screening, are already on a strong CYP3A4 inducer or inhibitor may be eligible for the Phase 2 Add-on to JAKi Combination Arm 2, provided they meet all the other eligibility criteria. **Initiation of treatment** of a strong CYP3A4 inhibitor or inducer (listed in Appendix 4) during study treatment with ruxolitinib in the Add-on to JAKi Combination Arm 2

patients is prohibited. Patients who require strong CYP3A4 inhibitors or inducers at the time of screening will **not** be eligible for the Phase 2 JAKi Naïve Combination Arm. Initiation of treatment with a strong CYP3A4 inhibitor or inducer during study treatment with ruxolitinib in the JAKi Naïve Combination Arm is prohibited.

CCI [redacted]

[redacted]

[redacted]

5.9.4.2. Drugs That Prolong the QT Interval

CCI [redacted] Despite this, it is recommended that treatment with medications that are known to prolong the QT interval be used with caution. See https://www.crediblemeds.org. NOTE: Access to the lists of QT drugs on this website by risk category (ie, known, possible, conditional) requires registration (which is free). These lists are frequently revised, and via registration, users will be notified when lists have been revised.

5.9.4.3. Drugs That Decrease the Heart Rate or Prolong the PR Interval

For patients enrolled at Canadian sites who are being treated with ruxolitinib, the Canadian Product Monograph for ruxolitinib should be consulted for guidance on the concomitant use of drugs that decrease the heart rate or prolong the PR interval.

5.10. Contraception

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

5.10.1. Female Patients

WOCBP are required to use at least one highly effective method of contraception (preferably low user dependency contraception methods, 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 posthysterectomy, 6 months post-surgical bilateral oophorectomy, or 6 months post-surgical salpingectomy.

In accordance with Clinical Trials Facilitation and Coordination Group (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*#
- Bilateral tubal occlusion*
- Vasectomized partner for females*+
- Sexual abstinence if the preferred and usual lifestyle of the male and female subjects, and partners of subjects

** Contraception methods that are considered to have low user dependency*

[redacted]

*** 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.*

+ 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 WOCBP to use additional highly effective contraception methods (listed below) in combination.

5.10.2. 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 pelabresib.

Men with documented infertility or surgical sterilization (performed at least 6 months before the first dose of study drug) are exempt from the highly effective contraception requirement. Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens on ultrasound before the first dose of study drug (Day 1).

Male patients with female partners who are able to have children are required to use at least one highly effective method of contraception while receiving study drug and for 94 days after the last dose of study drug. The highly effective contraceptive methods for men are:

- Male condom with spermicide with a female occlusive cap with spermicide (eg, diaphragm or cervical cap)
- Vasectomy (confirmed azoospermia)*
- Sexual abstinence if the preferred and usual lifestyle of the participant

* *Contraception methods that are considered to have low user dependency*

5.10.3. 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 while male partner is receiving study drug and for 94 days after the last dose of pelabresib.

5.10.4. 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.

5.11. Withdrawal of Patients from Protocol-mandated Treatment

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

- Development of PD
- Confirmation of accelerated phase (≥10% to <20% blasts in bone marrow or in 2 consecutive peripheral blood measurements)
- Occurrence of an unacceptable treatment-related AE
- Female patient becomes pregnant or suspects pregnancy
- Alternative therapy or medication
- Patient becomes eligible for allogeneic stem cell transplantation (allowed after 24 weeks of treatment are completed)

- Refusal of treatment/patient request

PD is defined by meeting one of the following criteria:

- Progressive splenomegaly, defined as enlargement of spleen volume by MRI (or CT scan in patients with contraindications for MRI) of ≥ 25% compared to baseline value.
- Leukemic transformation, confirmed by a bone marrow blast count of ≥ 20%
- Leukemic transformation, confirmed with a peripheral blood blast percentage of ≥ 20% associated with an absolute blast count of ≥ 1 × 109/L that persists for at least 2 weeks

An End of Treatment (EOT) visit is required for all patients within 7 days of the last dose of study treatment or since the decision has been made to discontinue treatment. In addition, all patients must have assessments for safety within 30 days after the last dose of study treatment. All patients will be followed for AEs and SAEs for 30 days following the last dose of pelabresib. Patients who discontinue study treatment and refuse to return for the EOT visit will be contacted for safety evaluations during the 14 days following the last dose of study drug. Ruxolitinib may be continued as monotherapy at the discretion of the investigator.

Patients may receive treatment in the study until disease progression, discontinuation, or withdrawal from treatment, whichever occurs first, and will subsequently be followed for splenic progression (for MF arms 1, 2, 3) and overall survival (for Arm 3 patients only). Patients who discontinue treatment for reasons other than documented splenic progression or withdrawal from study should receive follow-up visits every 12 weeks (with a visit window of ± 2 weeks) starting from the EOT visit to document splenic progression by imaging every 12 weeks, , until initiation of next anticancer therapy, splenic progression, or death, whichever comes first. Information on subsequent anti-MF therapy will also be collected in the follow-up period. Withdrawal of Patients from Study

Patients will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care. Additionally, the Sponsor may terminate the study. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Patient withdrew consent
- Refusal of treatment/patient request
- Protocol violation
- Failure to return for follow-up/noncompliance
- Alternative therapy or medication
- Administrative reasons
- Intercurrent illness
- Adverse event
- Eligible to undergo bone marrow transplant after at least 24 weeks of study treatment
- Death

All patients should be encouraged to continue, if possible, with the scheduled study and follow-up visits. If a patient is withdrawn, he or she should complete the EOT visit. The reason(s) for a patient's withdrawal from the study are to be recorded in the patient's source record and on the eCRF. For OS data, an investigator may consult publicly available sources of information to determine a patient's vital status (and if deceased, cause of death) after a patient withdraws from the study. This activity does not require patient consent because the information is publicly available. If information is obtained through publicly available information, the information is to be recorded in the patient's source record and on the eCRF.

Following withdrawal of consent to participate in this study by a patient, no new information will be collected from that patient and added to the existing data or any database, if requested by the patient. However, every effort will be made to follow all patients for safety.

5.12. Lost to Follow-up

A patient will be considered lost to follow-up if they repeatedly fail 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.
- 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 and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). 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 with a primary reason of lost to follow-up.

6. STUDY CONDUCT

6.1. Arrangements 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 institutional review board (IRB) or independent ethics committee (IEC).

6.2. Schedule of Events

Study schedules, including all procedures to be performed during the study, are presented for the dosing regimen used during Phase 1 (dose escalation) [14 days of daily dosing, 7-day break (21-day cycle)] in Table 14 (see Amendment 6 Version 7 of the Study 0610-02 protocol). A separate Schedule of Events is presented for patients in Phase 2 (MPN expansion) in Table 15 (Arms 1 and 2), Table 16 (Arm 3), and Table 17 (Arm 4).

The screening period includes the 28 days before the first dose of pelabresib.

See Amendment 6 (Version 7) of the Study 0610-02 protocol for information on allowed windows for each visit, and for the volume of blood to be collected during the Phase 1 part of the study. In Phase 2, for logistical reasons (such as holidays), a window of -3 days applies to the visit on Cycle 1, Day 14. A window of ± 3 days applies to each study visit after Cycle 1. Cycles are defined throughout the trial as every 3 weeks. In the event that dosing with pelabresib (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, they will still remain off pelabresib for Days 15-21 (the prescribed 7-day break). Because pelabresib is dispensed on Day 1 of each cycle, if the window for a study visit must be utilized, it is strongly encouraged that the (-) window be used, as this will minimize unnecessarily missing doses of pelabresib. However, the dosing of pelabresib should resume for the new cycle after a minimum of a 7-day break. If a (+) window is utilized, missed doses cannot be made up.

Please see Appendix 8 for changes in study conduct due to unforeseen circumstances (including pandemics).

Table 14 Phase 1 (Dose Escalation - COMPLETED) Schedule of Events: Patients With Acute Leukemia, MDS, MDS/MPN: 14 days of daily dosing, 7-day break (21-day cycle)

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

Table 15 Phase 2 Arms 1 and 2 (MF Expansion) Schedule of Events: 14 days of daily dosing, 7-day break (21-day cycle)

	Screening	Cycle 1		Cycle 2 & 3 and every odd numbered cycle (ie, 5, 7, 9, etc.)	Cycle 4 and every even numbered cycle (ie, 6, 8, 10, etc.)	EOT (within 7 days of last dose of pelabresib)	Post-EOT 30-day safety follow-up[a]	LTFU[b] Q12w ± 2 weeks	EOS[c]
Assessment (+/- days)	**Days** (-28 to Prior to Dosing)	**Day 1**	**Day 14**	**Day 1** (+/- 3)	**Day 1** (+/- 3)				
Informed consent	X								
Inclusion/ exclusion criteria	X								
Demographics	X								
Medical history	X								
Physical examination	X[d,e]	X[d,e]		X[e]		X[e]			
MFSAF v4.0	Completed every day for 7 days prior to Day 1 of each cycle[f]								
PGIC		X[g]		X[g]		X[g]			
ECOG performance status	X	X[h]		X[h]		X			
Vital signs	X	X[h,i]		X[h,i]		X[i]			
ECG	X	X[d]		X		X			
Transfusion documentation	X[j]	X[j]		X[j]	X[j]	X[j]		X[j]	X[j]
Coagulation	X[k]			X[h,k]		X[k]			
Hematology	X[d,k]	X[d,k]	X[k]	X[h,k]	X[h,k]	X[k]			
Clinical chemistry	X[d,k]	X[d,k]	X[k]	X[h,k]	X[h,k]	X[k]			
Serum lipids	X[k]			See footnote k					
Pregnancy testing	X[k]	X[h,k]		X[h,k]	X[h,k]	X[k]			
PK sampling		X[l]	X[l]	See footnote l (As of Amendment 12 (v13) no further PK samples for up-titrations will be collected)					
Leukocyte gene expression (peripheral blood sample)		X[m]	X[m]	See footnote m					
Cytokine assessment (peripheral blood sample)		X[n]	X[n]	See footnote n		X[n]			
Viable cells (peripheral blood sample)		X[o]		See footnote o		X[o]			

	Screening	Cycle 1		Cycle 2 & 3 and every odd numbered cycle (ie, 5, 7, 9, etc.)	Cycle 4 and every even numbered cycle (ie, 6, 8, 10, etc.)	EOT (within 7 days of last dose of pelabresib)	Post-EOT 30-day safety follow-up[a]	LTFU[b] Q12w ± 2 weeks	EOS[c]
Assessment (+/- days)	**Days** (-28 to Prior to Dosing)	**Day 1**	**Day 14**	**Day 1** (+/- 3)	**Day 1** (+/- 3)				
Mutated allele burden (peripheral blood sample)		X[p]		As of Amendment 12 (v 13) no further required. See footnote p		X[p]			
Bone marrow biopsy	X[q]			See footnote r		X[s]			
MRI (or CT) scan	X[t]			See footnote t		X[s]		X	X
Pelabresib administration		Administered on Days 1-14 of each cycle							
Ruxolitinib administration (Arm 2 only)		Administered daily BID							
Adverse events	X	Collected continuously while the patient is on study[u]					X[u]		
Concomitant medications	X	Collected continuously while the patient is on study[u]					X[u]		
AML (leukemic) transformation		X[k,v]					X[a,,v]		X[v]
Next anti-cancer therapy							X	X	X

ALT (SGPT) = alanine aminotransferase; AML = acute myelogenous leukemia; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase; BID = twice daily; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; EOT = End of Treatment; EPO = erythropoietin; ePRO – electronic patient-reported outcome; eCRF = electronic case report form; HDL = high density lipoprotein; Hgb = hemoglobin; INR = international normalized ratio; IWG-MRT = International Working Group- Myeloproliferative Neoplasms Research and Treatment; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LFTs = liver function tests; LTFU = long-term follow-up; MF = myelofibrosis; MFSAF = Myelofibrosis Symptom Assessment Form; MRI = magnetic resonance imaging; PD = progressive disease; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; PT = prothrombin time; Q12w = every 12 weeks; RBC = red blood cell; TB = tuberculosis; WBC = white blood cell.

[a] The "30-day safety follow-up visit" should occur 30 days (± 3 days) after the last dose of study treatment (pelabresib) or at the time of documented disease progression or, for patients initiating a next anticancer therapy, just prior to initiation of next therapy, whichever comes first. This visit may be conducted by telephone. Leukemic transformation and accelerated blast phase will be collected as AESI until 30-day safety follow-up or death, whichever comes first.

[b] Long-term follow-up (LTFU):

Splenic progression follow-up: Patients who discontinue treatment for reasons other than documented splenic progression or withdrawal from study should receive follow-up visits every 12 weeks (with a visit window of ± 2 weeks) starting from the EOT visit to document splenic progression by imaging every 12 weeks,until initiation of next anticancer therapy, progression, or death, whichever comes first.

Transfusion requirements: Transfusions for the first 12 weeks starting from EOT will be collected.

[c] If the subject is discontinued from LTFU, the reason of discontinuation should be recorded on EOS eCRF. An MRI (or CT) scan will be performed at the EOS visit only if splenic progression has not been previously documented or, in the absence of documented splenic progression, if imaging has not been performed within the previous 6 weeks. Transfusion requirements will be documented up to 12 weeks after last study drug.

[d] The screening physical examination, ECG, hematology, and clinical chemistry results do not need to be repeated on Cycle 1, Day 1 if they are conducted ≤ 72 hours before the first dose of pelabresib.

[e] Complete physical examination at screening, including height, weight, clinical signs and symptoms, and palpable spleen* length, measured with a ruler. *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. The complete physical examination will include assessment of splenomegaly. Subsequent physical exams (within 72 hours prior to the start of Cycle 2, 3 and then every odd numbered cycle, and at the EOT visit) may be targeted to areas of known disease and potential areas of MF involvement. Targeted physical examination must include weight and examination of the abdomen to assess the spleen length by palpation.

[f] Symptom assessment via MFSAF v.4.0. During screening, patients will complete the 24-hour symptom diary every day for 7 days prior to Cycle 1, Day 1. For each subsequent cycle, patients will complete the 24-hour symptom diary every day for 7 days prior to Day 1 of the cycle (ie, Days 15 to 21 of the previous cycle). **NOTE:** patients who are on the ePRO devices will be prompted to fill out the MFSAF assessment daily. Sites will be notified and trained accordingly for implementation of the e-diary.

[g] The PGIC assessment should be completed prior to any other visit assessments on the visit day. The PGIC will be collected on Day 1 of Cycles 1, 2, and 3 and then every subsequent odd numbered cycle, and at the EOT visit. **NOTE:** patients may be requested to complete the symptom diary daily, if an electronic (e) system for symptom capture becomes available. Sites will be notified and trained accordingly for implementation of the e-diary.

[h] Performed ≤ 72 hours before the start of the scheduled cycle, as indicated.

[i] Vital signs must include: temperature, pulse, respiratory rate, and blood pressure.

[j] A complete transfusion history for the 12 weeks prior to enrollment will be taken during screening to include the date, type (eg, whole blood, platelets, packed cells), number of units of the transfusion, as well as the Hgb or platelet value at the time of the transfusion. Furthermore, transfusion history from medical records dating up to 1 year prior to study enrollment will be collected for patients enrolled in Arm 2A whenever available. An assessment of transfusion events will be collected on Day 1 of every cycle, at the EOT visit, and at the first 12-week long-term follow-up visit (for patients who discontinued for reasons other than disease progression).

[k] Coagulation parameters must include PT, aPTT, and INR. PT, aPTT, and INR will be determined during screening for all patients, ≤ 72 hours before the start of Cycle 2, 3 and then every odd numbered cycle of treatment as indicated, and at the EOT visit.

Hematology parameters must include a CBC with differential (ie, RBC, Hgb, hematocrit, platelet count, total WBC count, neutrophils, eosinophils, basophils, lymphocytes, monocytes) and a peripheral blood smear (ie, blast cells, nucleated erythrocytes, bands/stabs, myelocytes, metamyelocytes, and promyelocytes). Hematology will be obtained at screening, ≤ 72 hours before the start of each cycle of treatment, at Cycle 1 Day 14, and at the EOT visit.

NOTE: Peripheral blood blasts need to be collected and assessed at every cycle. Please confirm with your laboratory that a line for blast count of 0% is still included in the laboratory report even if no blast cells were detectable.

Chemistry parameters must include sodium, potassium, total carbon dioxide, chloride, serum glucose, BUN, serum creatinine, total and direct bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), LDH, uric acid, calcium, phosphorus, EPO, CRP, iron*, iron binding capacity*, ferritin* and transferrin saturation*. The chemistry parameters will be obtained at screening, at Cycle 1 Day 14, ≤ 72 hours before the start of Cycle 2, 3, and then every odd numbered cycle of treatment, and at the EOT visit. **NOTE:** on Cycle 4 and every even numbered cycle thereafter, only LFTs will be collected including total and direct bilirubin, AST, and ALT. *Only required at screening, after 12 weeks of treatment (Cycle 5, Day 1), after 24 weeks of treatment (Cycle 9, Day 1), and then every 12 weeks (4 cycles) thereafter and at the EOT visit.

Serum lipids must include total cholesterol, cholesterol LDL, cholesterol HDL, and triglycerides. Serum lipids will be obtained at screening, after 6 weeks of treatment (Cycle 3, Day 1) and then every 12 weeks (4 cycles) thereafter.

Pregnancy test is only required in women of child bearing potential. Should be performed at monthly intervals after EOT until 184 days after the last dose of study drug.

[l] As of Amendment 12 (v13) PK sampling for this study has been completed. Information on the previous sampling strategy is outlined in Section 6.3.14.2.

[m] A peripheral blood sample for leukocyte gene expression will be collected prior to dosing on Cycle 1, Day 1 and Day 14 and Cycle 3 Day 1, and at 4 hours after pelabresib dosing on Cycle 1, Day 1 and Day 14 and on Cycle 3 Day 1. In addition, samples will be collected on Day 1 of any cycle where the dose of pelabresib is changed (predose and 4 hours after pelabresib).

[n] A peripheral blood sample for measurement of plasma cytokine concentrations and hepcidin will be collected prior to dosing on Cycle 1, Day 1, anytime on Cycle 1, Day 14, Day 1 Cycle 3, 5, 7 and 9 and at the EOT visit.

[o] A peripheral blood sample (in 3 tubes) for collection of viable cells will be collected prior to dosing on Cycle 1, Day 1, and then anytime on Day 1 of Cycle 3, 5, 7 and 9 and at the EOT visit.

[p] As of Amendment 12 (Version 13) the collection of samples for allele burden assessment has been completed, except for the sample at EOT. For further information please refer to Section 6.3.17.4.

[q] The bone marrow biopsy sample will be accepted as the screening sample if obtained within 3 months of Cycle 1, Day 1.

[r] Bone marrow biopsy will be performed for fibrosis grading after 24 weeks of treatment (Cycle 9, Day 1) and then every 24 weeks (8 cycles) thereafter. A window of ± 2 weeks applies to these assessments. NOTE: Following the bone marrow biopsy after 72 weeks (Cycle 25 Day 1), subsequent biopsies will be performed every 48 weeks (16 cycles).

[s] The EOT bone marrow biopsy does not need to be collected if a biopsy has been performed within the previous 12 weeks. An MRI (or CT) scan will be performed at the EOT visit only if PD has not been previously documented or, in the absence of documented PD, if imaging has not been performed within the previous 6 weeks.

[t] An MRI (or CT) scan to measure spleen size will be performed during screening, after 12 weeks of treatment (Cycle 5, Day 1), after 24 weeks of treatment (Cycle 9, Day 1), and then every 12 weeks (4 cycles) thereafter. A window of ± 2 weeks applies to these assessments. NOTE: preference is for MRI if possible. Details on calculating spleen volume are provided in Section 6.3.7.

[u] This information will be collected during clinic visits by study staff. Adverse events and concomitant medications should be collected for the first 30 days after the last dose of study treatment.

[v] AML (leukemic) transformation can be assessed by either 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 persists for at least 2 weeks.

Table 16 Phase 2 Arm 3 (MF Expansion) Schedule of Events: 14 days of daily dosing, 7-day break (21-day cycle)

	Screening	Cycle 1		Cycle 2 & 3 and every odd numbered cycle (ie, 5, 7, 9, etc.)	Cycle 4 and every even numbered cycle (ie, 6, 8, 10, etc.)	EOT (within 7 days of last dose of pelabresib)	Post-EOT 30 day safety follow-up[a]	LTFU[a,b] Q12w ± 2 weeks	EOS[c]
Assessment (+/- days)	**Days** (-28 to Prior to Dosing)	**Day 1**	**Day 14**	**Day 1** (+/- 3)	**Day 1** (+/- 3)				
Informed consent	X								
Inclusion/ exclusion criteria	X								
Demographics	X								
Medical history	X								
TB testing (Arm 3 only)	X[d]								
Physical examination	X[e,f]	X[e,f]		X[f]		X[f]			
MFSAF v4.0	Completed every day for 7 days prior to Day 1 of each cycle[g]								
PGIC		X[h]		X[h]		X[h]			
ECOG performance status	X	X[i]		X[i]		X			
Vital signs	X	X[i,j]		X[i,j]		X[j]			
ECG	X	X[e]		X		X			
Transfusion documentation	X[k]	X[k]		X[k]	X[k]	X[k]		X[k]	X
Coagulation	X[l]			X[i,l]		X[l]			
Hematology	X[e,l]	X[e,l]	X[l]	X[i,l]	X[i,l]	X[l]			
Clinical chemistry	X[e,l]	X[e,l]	X[l]	X[i,l]	X[i,l]	X[l]			
Serum lipids	X[l]			See footnote l					
Pregnancy testing	X[l]	X[i,l]		X[i,l]	X[i,l]	X[l]			
PK sampling		X[m]	X[m]	See footnote m (As of Amendment 12 (v13) no further PK samples for up-titrations will be collected.)					
Leukocyte gene expression (peripheral blood sample)		X[n]	X[n]	See footnote n					
Cytokine assessment (peripheral blood sample)		X[o]	X[o]	See footnote [o]		X[o]			
Viable cells (peripheral blood sample)		X[p]		See footnote [p]		X[p]			

	Screening	Cycle 1		Cycle 2 & 3 and every odd numbered cycle (ie, 5, 7, 9, etc.)	Cycle 4 and every even numbered cycle (ie, 6, 8, 10, etc.)	EOT (within 7 days of last dose of pelabresib)	Post-EOT 30 day safety follow-up[a]	LTFU[a,b] Q12w ± 2 weeks	EOS[c]
Assessment (+/- days)	**Days** (-28 to Prior to Dosing)	**Day 1**	**Day 14**	**Day 1** (+/- 3)	**Day 1** (+/- 3)				
Mutated allele burden (peripheral blood sample)		X[q]		As of Amendment 12 (v 13) no further required. See footnote [q]		X[q]			
Bone marrow biopsy	X[r]			See footnote [s]		X[t]			
MRI (or CT) scan	X[u]			See footnote [u]		X[t]		X	X
Pelabresib administration		Administered on Days 1-14 of each cycle							
Ruxolitinib administration (Arm 3 only)		Administered daily BID (see footnote v)							
Adverse events	X	Collected continuously while the patient is on study[w]					X[w]		
Concomitant medications	X	Collected continuously while the patient is on study[w]					X[w]		
AML (leukemic) transformation		X[l,x]					X [a,x]	X [a,b,x]	X[x]
Next anti-cancer therapy							X	X	X
Survival follow-up							X	X	X

ALT (SGPT) = alanine aminotransferase; AML = acute myelogenous leukemia; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase; BID = twice daily; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EOS = End of Study; EOT = End of Treatment; EPO = erythropoietin; ePRO = electronic patient-reported outcome; HDL = high density lipoprotein; Hgb = hemoglobin; International Working Group-Myeloproliferative Neoplasms Research and Treatment; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LFTs = liver function tests; LTFU = long-term follow-up; MF = myelofibrosis; MFSAF = Myelofibrosis Symptom Assessment Form; MRI = magnetic resonance imaging; PD = progressive disease; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; PT = prothrombin time; Q12w = every 12 weeks; RBC = red blood cell; TB = tuberculosis; WBC = white blood cell.

[a] The 30-day safety follow-up visit should occur 30 days (±3 days) after the last dose of study treatment (pelabresib) or at the time of documented disease progression or, for patients initiating a next anticancer therapy, just prior to initiation of next therapy, whichever comes first. This visit may be conducted by telephone. Leukemic transformation and accelerated blast phase will be collected as AESI until 30-day safety follow-up or death, whichever comes first.

Long-term follow-up (LTFU):

Splenic progression follow-up: Patients who discontinue treatment for reasons other than documented splenic progression or withdrawal from study should receive follow-up visits every 12 weeks (with a visit window of ± 2 weeks) starting from the EOT visit to document splenic progression by imaging every 12 weeks, until initiation of next anticancer therapy, progression, or death, whichever comes first.

Transfusion requirements: Transfusions for the first 12 weeks starting from EOT will be collected. AML (leukemic) transformation follow-up: All patients will be followed up for AML (leukemic) transformation records (by biopsy if applicable) will be collected every 12 weeks until documented AML transformation or the patient's death, whichever comes first. Follow up for AML transformation can be conducted by telephone if clinic visit is not planned.

[b] If the subject is discontinued from LTFU, the reason of discontinuation should be recorded on EOS eCRF. An MRI (or CT) scan will be performed at the EOS visit only if splenic progression has not been previously documented or, in the absence of documented splenic progression, if imaging has not been performed within the previous 6 weeks. Transfusion requirements will be documented up to 12 weeks after last study drug.

[c] In Arm 3, patients should be evaluated for TB risk factors, and those at higher risk should be tested for latent infection as outlined in the approved package insert for ruxolitinib and according to local regulations.

[d] The screening physical examination, ECG, hematology, and clinical chemistry results do not need to be repeated on Cycle 1, Day 1 if they are conducted ≤ 72 hours before the first dose of pelabresib.

[e] Complete physical examination at screening, including height, weight, clinical signs and symptoms, and palpable spleen* length, measured with a ruler. *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. The complete physical examination will include assessment of splenomegaly. Subsequent physical exams (within 72 hours prior to the start of Cycle 2, 3 and then every odd numbered cycle and at the EOT visit) may be targeted to areas of known disease and potential areas of MF involvement. Targeted physical examination must include weight and examination of the abdomen to assess the spleen length by palpation.

[f] Symptom assessment via MFSAF v.4.0. During screening, patients will complete the 24-hour symptom diary every day for 7 days prior to Cycle 1, Day 1. For each subsequent cycle, patients will complete the 24-hour symptom diary every day for 7 days prior to Day 1 of the cycle (ie, Days 15 to 21 of the previous cycle). **NOTE:** patients who are on the ePRO devices will be prompted to fill out the MFSAF assessment daily. Sites will be notified and trained accordingly for implementation of the e-diary.

[g] The PGIC assessment should be completed prior to any other visit assessments on the visit day. The PGIC will be collected on Day 1 of Cycles 1, 2, and 3 and then every subsequent odd numbered cycle, and at the EOT visit. **NOTE:** patients may be requested to complete the symptom diary daily, if an electronic (e) system for symptom capture becomes available. Sites will be notified and trained accordingly for implementation of the e-diary.

[h] Performed ≤ 72 hours before the start of the scheduled cycle, as indicated.

[i] Vital signs must include: temperature, pulse, respiratory rate, and blood pressure.

[j] A complete transfusion history for the 12 weeks prior to enrollment will be taken during screening to include the date, type (eg, whole blood, platelets, packed cells), number of units of the transfusion as well as the Hgb or platelet value at the time of the transfusion. Furthermore, transfusion history from medical records dating up to 1 year prior to study enrollment will be collected for patients enrolled in Arm 2A whenever available. An assessment of transfusion events will be collected on Day 1 of every cycle, at the EOT visit, and at the Q12w follow-up visits for progression (for patients who discontinued for reasons other than disease progression).

[k] Coagulation parameters must include PT, aPTT, and INR. PT, aPTT, and INR will be determined during screening for all patients, ≤ 72 hours before the start of Cycle 2, 3 and then every odd numbered cycle of treatment as indicated, and at the EOT visit.

Hematology parameters must include a CBC with differential (ie, RBC, Hgb, hematocrit, platelet count, total WBC count, neutrophils, eosinophils, basophils, lymphocytes, monocytes) and a peripheral blood smear (ie, blast cells, nucleated erythrocytes, bands/stabs, myelocytes, metamyelocytes, and promyelocytes). Hematology will be obtained at screening, ≤ 72 hours before the start of each cycle of treatment, at Cycle 1 Day 14, and at the EOT visit.

NOTE: Peripheral blood blasts need to be collected and assessed at every cycle. Please confirm with your laboratory that a line for blast count of 0% is still included in the laboratory report even if no blast cells were detectable.

Chemistry parameters must include sodium, potassium, total carbon dioxide, chloride, serum glucose, BUN, serum creatinine, total and direct bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), LDH, uric acid, calcium, phosphorus, EPO, CRP, iron*, iron binding capacity*, ferritin* and transferrin saturation*. The

chemistry parameters will be obtained at screening, at Cycle 1 Day 14, ≤ 72 hours before the start of Cycle 2, 3, and then every odd numbered cycle of treatment and at the EOT visit. **NOTE:** on Cycle 4 and every even numbered cycle thereafter, only LFTs will be collected including total and direct bilirubin, AST, and ALT. *Only required at screening, after 12 weeks of treatment (Cycle 5, Day 1), after 24 weeks of treatment (Cycle 9, Day 1), and then every 12 weeks (4 cycles) thereafter and at the EOT visit.

Serum lipids must include total cholesterol, cholesterol LDL, cholesterol HDL and triglycerides. Serum lipids will be obtained at screening, after 6 weeks of treatment (Cycle 3, Day 1) and then every 12 weeks (4 cycles) thereafter.

Pregnancy test is only required in women of child bearing potential. Should be performed at monthly intervals after EOT until 184 days after the last dose of study drug.

[l] As of Amendment 12 (v13) PK sampling for this study has been completed. Information on the previous sampling strategy is outlined in Section 6.3.14.2.

[m] A peripheral blood sample for leukocyte gene expression will be collected prior to dosing on Cycle 1, Day 1 and Day 14 and Cycle 3 Day 1, and at 4 hours after pelabresib dosing on Cycle 1, Day 1, and Day 14 and on Cycle 3 Day 1. In addition, samples will be collected on Day 1 of any cycle where the dose of pelabresib is changed (predose and 4 hours after pelabresib).

[n] A peripheral blood sample for measurement of plasma cytokine concentrations and hepcidin will be collected prior to dosing on Cycle 1, Day 1, anytime on Cycle 1, Day 14, Day 1 of Cycle 3, 5, 7 and 9 and at the EOT visit.

[o] A peripheral blood sample (in 3 tubes) for collection of viable cells will be collected prior to dosing on Cycle 1, Day 1, and then anytime on Day 1 of Cycle 3, 5, 7 and 9, and at the EOT visit.

[p] As of Amendment 12 (Version 13) the collection of samples for allele burden assessment has been completed, except for the sample at EOT. For further information please refer to Section 6.3.17.4.

[q] The bone marrow biopsy sample will be accepted as the screening sample if obtained within 3 months of Cycle 1, Day 1.

[r] Bone marrow biopsy will be performed for fibrosis grading after 24 weeks of treatment (Cycle 9, Day 1) and then every 24 weeks (8 cycles) thereafter. A window of ± 2 weeks applies to these assessments. NOTE: Following the bone marrow biopsy after 72 weeks (Cycle 25 Day 1), subsequent biopsies will be performed every 48 weeks (16 cycles).

[s] The EOT bone marrow biopsy does not need to be collected if a biopsy has been performed within the previous 12 weeks. An MRI (or CT) scan will be performed at the EOT visit only if PD has not been previously documented or, in the absence of documented PD, if imaging has not been performed within the previous 6 weeks.

[t] An MRI (or CT) scan to measure spleen size will be performed during screening, after 12 weeks of treatment (Cycle 5, Day 1), after 24 weeks of treatment (Cycle 9, Day 1), and then every 12 weeks (4 cycles) thereafter. A window of ± 2 weeks applies to these assessments. NOTE: preference is for MRI if possible. Details on calculating spleen volume are provided in Section 6.3.7.

[u] For Arm 3, the first ruxolitinib dose on Cycle 1 Day 1 should be administered after the 4h sample collection (see footnote n).

[v] This information will be collected during clinic visits by study staff. Adverse events and concomitant medications should be collected for the first 30 days after the last dose of study treatment.

[x] AML (leukemic) transformation can be assessed by either 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 persists for at least 2 weeks.

Table 17 Phase 2 Arm 4 (ET Expansion) Schedule of Events: 14 days of daily dosing, 7-day break (21-day cycle)

	Screening	Cycle 1		Cycle 2 & 3 and every odd numbered cycle (ie, 5, 7, 9, etc.)	Cycle 4 and every even numbered cycle (ie, 6, 8, 10, etc.)	EOT[a] (within 7 days of last dose of pelabresib)	Post-EOT 30-day safety follow-up EOS[b]
Assessment (+/- days)	**Days** (-28 to Prior to Dosing)	**Day 1**	**Day 14**	**Day 1** (+/- 3)	**Day 1** (+/- 3)		
Informed consent	X						
Inclusion/exclusion criteria	X						
Demographics	X						
Medical history	X						
Physical examination	X[c,d]	X[c,d]		X[d]		X[d]	
MPN-SAF	X[e]	To be completed on Days 15-21 of Cycles 1, 2, 4, 8, and every 4 cycles thereafter					
PGIC		X[f]		X[f]		X[f]	
ECOG performance status	X	X[g]		X[g]		X	
Vital signs	X	X[g,h]		X[g,h]		X[h]	
ECG	X	X[c]	X	X		X	
Transfusion documentation	X[i]	X[i]		X[i]	X[i]	X[i]	
Coagulation	X[i]			X[g,i]		X[i]	
Hematology	X[c,i]	X[c,i]	X[i]	X[g,i]	X[g,i]	X[i]	
Clinical chemistry	X[c,i]	X[c,i]	X[i]	X[g,i]	X[g,i]	X[i]	
Serum lipids	X[i]			See footnote i			
Pregnancy testing	X[i]	X[g,i]		X[g,i]	X[g,i]	X[i]	
PK sampling		X[j]	X[j]	See footnote j			
Leukocyte gene expression (peripheral blood sample)		X[k]	X[k]	See footnote k			

Cytokine assessment (peripheral blood sample)		X[l]	X[l]	See footnote l		X[l]	
Viable cells (peripheral blood sample)		X[m]		See footnote m		X[m]	
Mutated allele burden (peripheral blood sample)		X[n]		As of Amendment 12 (v 13) no further required. See footnote n		X[n]	
Bone marrow biopsy	X[o]			See footnote p		X[q]	
MRI (or CT) scan	X[r]			See footnote r		X[r,q]	
Pelabresib administration		Administered on Days 1-14 of each cycle					
Adverse events	X	Collected continuously while the patient is on study[s]					X[s]
Concomitant medications	X	Collected continuously while the patient is on study[s]					X[s]
AML (leukemic) transformation		X[t,i]				X [b,t]	X [b,t]

ALT (SGPT) = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; EOT = End of Treatment; EPO = erythropoietin; ET = essential thrombocythemia; HDL = high density lipoprotein; Hgb = hemoglobin; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LFTs = liver function tests; MF = myelofibrosis; MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form; MRI = magnetic resonance imaging; PD = progressive disease; PGIC = Patient Global Impression of Change; PK = pharmacokinetic; PT = prothrombin time; Q12w = every 12 weeks; RBC = red blood cell; TB = tuberculosis; WBC = white blood cell.

[a] EOT visit should occur within 7 days of last dose of pelabresib.

[b] The post-EOT 30-day safety follow-up visit should occur 30 days (±3 days) after last study drug or at the time of documented disease progression or, for patients initiating a next anticancer therapy., Leukemic transformation and accelerated blast phase will be collected as AESI until 30-day safety follow-up or death, whichever comes first. This visit may be conducted by telephone.

[c] The screening physical examination, ECG, hematology, and clinical chemistry results do not need to be repeated on Cycle 1, Day 1 if they are conducted ≤ 72 hours before the first dose of pelabresib.

[d] Complete physical examination at screening, including height, weight, clinical signs and symptoms, and palpable spleen* length, measured with a ruler. *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. The complete physical examination will include assessment of splenomegaly. Subsequent physical exams (within 72 hours prior to the start of Cycles 1, 2, and 3 and

then every odd numbered cycle, and at the EOT visit) may be targeted to areas of known disease and potential areas of MPN involvement. Targeted physical examination must include weight and examination of the abdomen to assess the spleen length by palpation.

[e] Symptom assessment via MPN-SAF (Appendix 7) Patients will complete the assessment every day for the 7 days prior to Cycle 1 Day 1. In addition, patients will complete the assessment on Days 15 to 21 of Cycles 1, 2, 4, 8, and every 4 cycles thereafter.

[f] The PGIC assessment should be completed prior to any other visit assessments on the visit day. The PGIC will be collected on Day 1 of Cycles 1, 2, and 3 and then every subsequent odd numbered cycle, and at the EOT visit.

[g] Performed ≤ 72 hours before the start of the scheduled cycle, as indicated.

[h] Vital signs must include: temperature, pulse, respiratory rate, and blood pressure.

[i] A complete transfusion history for the 12 weeks prior to enrollment will be taken during screening to include the date, type (eg, whole blood, platelets, packed cells), number of units of the transfusion as well as the Hgb or platelet value at the time of the transfusion. An assessment of transfusion events will be collected on Day 1 of every cycle and at the EOT visit.

Coagulation parameters must include PT, aPTT, and INR. PT, aPTT, and INR will be determined during screening for all patients, ≤ 72 hours before the start of Cycle 2, 3 and then every odd numbered cycle of treatment as indicated, and at the EOT visit.

Hematology parameters must include a CBC with differential (ie, RBC, Hgb, hematocrit, platelet count, total WBC count, neutrophils, eosinophils, basophils, lymphocytes, monocytes) and a peripheral blood smear (ie, blast cells, nucleated erythrocytes, bands/stabs, myelocytes, metamyelocytes, and promyelocytes). Hematology will be obtained at screening, ≤ 72 hours before the start of each cycle of treatment, at Cycle 1 Day 14, and at the EOT visit.

NOTE: Peripheral blood blasts need to be collected and assessed at every cycle. Please confirm with your laboratory that a line for blast count of 0% is still included in the laboratory report even if no blast cells were detectable.

Chemistry parameters must include sodium, potassium, total carbon dioxide, chloride, serum glucose, BUN, serum creatinine, total and direct bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), LDH, uric acid, calcium, phosphorus, EPO, CRP, iron*, iron binding capacity*, ferritin* and transferrin saturation*. The chemistry parameters will be obtained at screening, at Cycle 1 Day 14, ≤ 72 hours before the start of Cycle 2, 3, and then every odd numbered cycle of treatment and at the EOT visit. **NOTE:** on Cycle 4 and every even numbered cycle thereafter, only LFTs will be collected including total and direct bilirubin, AST, and ALT. *Only required at screening, after 12 weeks of treatment (Cycle 5, Day 1), after 24 weeks of treatment (Cycle 9, Day 1), and then every 12 weeks (4 cycles) thereafter and at the EOT visit.

Serum lipids must include total cholesterol, cholesterol LDL, cholesterol HDL and triglycerides. Serum lipids will be obtained at screening, after 6 weeks of treatment (Cycle 3, Day 1) and then every 12 weeks (4 cycles) thereafter.

Pregnancy test is only required in women of child bearing potential. Should be performed at monthly intervals after EOT until 184 days after the last dose of study drug.

[j] PK sampling for this study is completed and no further sample collection will be required. Information on the PK sampling strategy is outlined in Section 6.3.14.2.

[k] A peripheral blood sample for leukocyte gene expression will be collected prior to dosing on Cycle 1, Day 1 and Day 14 and Cycle 3 Day 1, and at 4 hours after pelabresib dosing on Cycle 1, Day 1, and Day 14 and on Cycle 3 Day 1. In addition, samples will be collected on Day 1 of any cycle where the dose of pelabresib is changed (predose and 4 hours after pelabresib).

[l] A peripheral blood sample for measurement of plasma cytokine concentrations and hepcidin will be collected prior to dosing on Cycle 1, Day 1, anytime on Cycle 1, Day 14, Day 1 of Cycle 3, 5, 7 and 9 and, at the EOT visit.

[m] A peripheral blood sample (in 3 tubes) for collection of viable cells will be collected prior to dosing on Cycle 1, Day 1, and then anytime on Day 1 of Cycle 3, 5, 7 and 9 and at EOT visit.

[n] As of Amendment 12 (Version 13) the collection of samples for allele burden assessment has been completed, except for the sample at EOT. For further information please refer to Section 6.3.17.4.

[o] The bone marrow biopsy sample will be accepted as the screening sample if obtained within 3 months of Cycle 1, Day 1.

[p] Bone marrow biopsy will be performed after 48 weeks of treatment (Cycle 17, Day 1) and then yearly thereafter for 3 years after the start of the study. A window of ± 2 weeks applies to these assessments.

[q] The EOT bone marrow biopsy does not need to be collected if a biopsy has been performed within the previous 12 weeks. An MRI (or CT) scan will be performed at the EOT visit only if PD has not been previously documented or, in the absence of documented PD, if imaging has not been performed within the previous 12 weeks.

[r] An MRI or CT scan will be performed at screening, after 24 weeks of treatment (Cycle 9, Day 1), after 48 weeks of treatment (Cycle 17, Day 1) and then yearly thereafter. A window of ± 2 weeks applies to these assessments. **NOTE**: preference is for MRI if possible. Details on calculating spleen volume are provided in Section 6.3.7.

[s] This information will be collected during clinic visits by study staff. Adverse events and concomitant medications should be collected for the first 30 days after the last dose of study treatment.

[t] AML (leukemic) transformation can be assessed by either 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 persists for at least 2 weeks.

6.3. Study Procedures

6.3.1. Informed Consent

Each patient must provide written informed consent before any study-related procedures are conducted, unless those procedures are performed as part of the patient's standard care.

Written informed consent will be obtained from patients who are still alive to collect survival follow-up data. After the End of Study (EOS) visit, the study site will call the patient (or the patient's family) every 84 days (± 2 weeks) to cover a duration of up to 42 months from Cycle 1 Day 1 of the last Arm 3 patient to inquire about the patient's status, new treatments started since EOS and in case of death, cause and date of death. Collection of informed consent and survival follow-up data will be recorded in the patient's source records and on the eCRF.

For patients who are lost to follow-up or unreachable (for definition see Section 5.12), a study site may consult publicly available sources of information to determine a patient's vital status (and if deceased, cause and date of death) after a patient withdraws from the study. This activity does not require patient's written informed consent. If information is obtained through publicly available sources, the information will be recorded in the patient's source record and on the eCRF.

Please see Appendix 8 for changes in study conduct due to unforeseen circumstances (including pandemics).

6.3.2. Clinic Visits

Patients should be seen in the clinic by the investigator during screening, and on Day 1 and Day 14 of Cycle 1. Subsequently, patients should be seen in the clinic by the investigator and study personnel on Day 1 of each new cycle of treatment to assess their wellbeing and compliance with the study.

See Amendment 6 (Version 7) of the Study 0610-02 protocol for information on Phase 1. During Phase 2, patients will have safety labs collected ≤ 72 hours before the start of each cycle of treatment and at the EOT visit. The schedule for blood collection for PK and biomarker assessments is outlined in the Schedule of Events (Table 15).

Based on patient reports and/or laboratory findings, additional clinic visits should be scheduled by the investigator and study site staff as deemed necessary.

6.3.3. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria will be assessed during screening (≤ 28 days before the first dose of pelabresib). A patient is considered to be enrolled in the study once written informed consent to study participation has been obtained, all inclusion criteria have been met, all exclusion criteria have been determined to not exist, and the enrollment form has been completed.

6.3.4. Demographics

Patient demographics will be documented during screening and will include patient birth date, gender, ethnicity, and race.

6.3.5. Medical History

During the screening period the patient will have a complete medical history taken to include all medical conditions. The medical history will also include details on the cancer diagnosis with a description of all related prior therapies. For Phase 2 this includes 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 of screening.

6.3.6. Tuberculosis Testing (Arm 3 Only)

In Arm 3, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection as outlined in the approved package insert for ruxolitinib and according to local regulations.

6.3.7. Splenic Volume

Splenic volume will be assessed during Phase 2 as noted in the Schedule of Events (Table 15). The method of splenic volume assessment at the site should be consistent throughout the study. Typically, a volumetric segmentation method would be used with a resulting overall spleen volume calculation, and this result needs to be noted by the radiologist in the radiology report. If a volumetric method is not available at the site, the following formula should be used to estimate volume of the spleen on cross-sectional imaging methods by measuring 3 dimensions - caudocranial (L), maximum size in axial plane (D), and maximum thickness in axial plane (T) (Prassopoulos et al. 1997):

$$\text{Volume [mL]} = 30 + 0.58 \times L \times D \times T$$

6.3.8. Transfusions (Phase 2)

During Phase 2, a complete transfusion history will be taken during screening to include the date, type (eg, whole blood, platelets, packed cells), number of units of the transfusion as well as the Hgb and platelet value at the time of the transfusion. In order to more comprehensively describe the baseline transfusion needs, in addition to the mandatory 12-week period for documenting transfusions, whenever the data are available in medical records, administered transfusions will be collected for a period up to 1 year prior to study enrollment for patients in Cohort 2A.

An assessment of transfusion events will also be collected on Day 1 of every cycle and at the EOT visit.

6.3.9. Pelabresib Administration (All Patients)

Patients will receive pelabresib during the treatment period as outlined in Section 5.1.1. The first day of study treatment will be considered Day 1 of Cycle 1. Pelabresib will be given for 14 consecutive days and followed by a 7-day break from dosing, creating 21-day cycles of treatment. Cycles of treatment will be repeated as long as the patient's disease has not progressed or until precluded by toxicity. Patient may continue to receive treatment, despite confirmation of PD, if clinical benefit is derived. Clinical benefit is determined by the Investigator and may include improvement in TSS scores and blood counts; continuation of therapy has to be discussed with the sponsor.

See Amendment 6 (Version 7) of the Study 0610-02 protocol for information on Phase 1. During Phase 2, dose modification rules are provided in Sections 5.7.3-5.7.6 for Prior JAKi Arm 1 and Add-on to JAKi Arm 2), in Sections 5.7.7-5.7.12 for the JAKi Naïve Arm 3, and in Section 5.7.13 for the ET Monotherapy Arm 4.

6.3.10. Ruxolitinib Administration (Phase 2 Combination Arms)

Patients in the Phase 2 Combination Arms (Arms 2 and 3) will receive ruxolitinib BID on a continuous basis for 21 consecutive days of each 21-day cycle as outlined in Section 5. The first day of study treatment will be considered Day 1 of Cycle 1. Cycles of treatment will be repeated as long as the patient's disease has not progressed or until precluded by toxicity. Patient may continue to receive treatment, despite confirmation of PD, if clinical benefit is derived. Clinical benefit is determined by the Investigator and may include improvement in TSS scores and blood counts; continuation of therapy has to be discussed with sponsor. Dose modification rules are provided in Sections 5.7.3-5.7.6 for Prior JAKi Arm 1 and Add-on to JAKi Arm 2) and in Sections 5.7.7-5.7.12 for the JAKi Naïve Arm 3.

6.3.11. Phase 2: PROs

6.3.11.1. Arms 1-3: MFSAF v4.0

The MFSAF assessment should be completed every day for 7 days prior to Day 1 of each cycle, including during the screening period for the 7 days prior to Cycle 1 Day 1. **NOTE:** patients may be requested to complete the symptom diary daily, if an electronic (e) system for symptom capture becomes available. Sites will be notified and trained accordingly for implementation of the e-diary. The MFSAF uses a 24-hour recall format and asks patients to rate the severity of each symptom (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. The MFSAF asks patients to report symptom severity at its worst for each of the 7 items on a 0 (Absent) to 10 (Worst Imaginable) numeric rating scale (see Appendix 5).

6.3.11.2. Arm 4: MPN-SAF

The MPN-SAF assessment (see Appendix 5) should be completed as follows:

- During the screening period, every day for the 7 days prior to Cycle 1 Day 1
- Day 15 to Day 21 of Cycles 1, 2, 4, 8, and every 4 cycles thereafter.

6.3.11.3. Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) assessment should be completed prior to any other visit assessments on the visit day. The PGIC will be collected on Day 1 of Cycle 1, 2, and 3, every subsequent odd numbered cycle, and at the EOT visit. **NOTE:** patients may be requested to complete the symptom diary daily, if an electronic (e) system for symptom capture becomes available. Sites will be notified and trained accordingly for implementation of the e-diary. The PGIC is a single question to assess the patient's impression of change in their MPN 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 study, my overall status is (1) Very much improved,

(2) Much improved, (3) Minimally improved, (4) No change, (5) Minimally worse, (6) Much worse, (7) Very much worse."

6.3.12. Safety Assessments

6.3.12.1. Adverse Events

AEs will be monitored throughout the study period beginning from the time of informed consent and for 30 days following the last dose of pelabresib. All AEs and SAEs that occur during the reporting period will continue to be followed until the event resolves, the investigator assesses the event as stable, the event is determined to be irreversible, or the patient is lost to follow-up. Definitions, documentation, and reporting of AEs are described in detail in Section 9.2.

6.3.12.2. ECOG Performance Status

ECOG performance status will be assessed during screening, ≤ 72 hours before the start of Cycle 1, 2, and 3, every subsequent odd numbered cycle of treatment and at the EOT visit and at the EOS visit (Phase 1 only).

6.3.12.3. Signs and Symptoms/Physical Examination

Phase 1: See Amendment 6 (Version 7) of the Study 0610-02 protocol.

Phase 2:

At screening a complete physical examination (including height, weight, clinical signs and symptoms, and palpable spleen* and liver length measured with a ruler) will be conducted. The complete physical examination will include assessment of splenomegaly and hepatomegaly. If the screening physical examination is conducted ≤ 72 hours before the first dose of pelabresib, it does not need to be repeated on Cycle 1, Day 1. *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.

Subsequent physical exams (within 72 hours prior to the start of Cycle 1, 2, and 3, every subsequent odd numbered cycle, and at the EOT visit) may be targeted to areas of known disease and potential areas of MPN involvement. The targeted physical examination must include weight and examination of the abdomen to assess the spleen length by palpation.

6.3.12.4. Vital Signs

Phase 1: See Amendment 6 (Version 7) of the Study 0610-02 protocol.

Phase 2: Vital signs (temperature, pulse, respiratory rate, and blood pressure) will be taken at screening, ≤ 72 hours before the start of Cycle 1, 2, and 3, every subsequent odd numbered cycle of treatment, and at the EOT visit.

6.3.12.5. Electrocardiograms

Phase 1: See Amendment 6 (Version 7) of the Study 0610-02 protocol.

Phase 2:

A 12-lead ECG will be obtained as part of the screening evaluation, then performed ≤ 72 hours before the start of Cycle 1, 2, and 3, every subsequent odd numbered cycle of treatment and at the EOT visit.

For ≥ Grade 3 plasma potassium increase, an ECG must be conducted to determine whether this potential elevation has any clinical consequence (ie, tall peaked T waves, loss of P waves, widening of QRS, sine wave and ventricular arrhythmia) and treated as needed.

6.3.12.6. Left Ventricular Ejection Fraction by Echocardiography (Phase 1 Only)

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

6.3.12.7. Concomitant Medications and Supportive Therapies

All concomitant medications and supportive therapies will be recorded from screening through the end of the study. Concomitant medications and therapies that are prohibited or allowed are described in Section 5.

6.3.12.8. Clinical Laboratory Evaluations

Coagulation parameters

PT and activated partial thromboplastin time will be determined during screening for all patients, ≤ 72 hours before the start of Cycle 2 and 3, every subsequent odd numbered cycle of treatment and at the EOT visit.

Hematology

Phase 1:

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

Phase 2:

A complete blood count (CBC) with differential and a peripheral blood smear will be obtained at screening, ≤ 72 hours before the start of each cycle of treatment, at Cycle 1, Day 14, and at the EOT visit. If the screening assessment is conducted ≤ 72 hours before the first dose of pelabresib, it does not need to be repeated on Cycle 1, Day 1. If the results of pretreatment laboratory assessment on Cycle 1, Day 1 fall outside of the parameters listed in the eligibility criteria, the treating physician should undertake the following steps:

- Consider repeating the laboratory assessment if an error or artefact is suspected.
- Evaluate the patient for possible clinical explanation for the change in laboratory values, such as infection, dehydration, or another AE, treat the underlying cause and delay Cycle 1, Day 1 accordingly until the AE is resolved.
- If the repeat laboratory values still do not meet eligibility criteria, contact the study monitor.

The CBC with differential consists of the following: RBC, Hgb, hematocrit, platelet count, total WBC count, neutrophils, eosinophils, basophils, lymphocytes, monocytes. A reticulocyte count should also be performed.

Peripheral blood smear consists of the following: blast cells, nucleated erythrocytes, bands/stabs, myelocytes, metamyelocytes, and promyelocytes.

Clinical chemistry
Phase 1: See Amendment 6 (Version 7) of the Study 0610-02 protocol.

Phase 2:

A clinical chemistry panel will be obtained at screening, at Cycle 1 Day 14, ≤ 72 hours before the start of Cycle 2, 3, and then every odd numbered cycle of treatment and at the EOT visit. If the screening assessment is conducted ≤ 72 hours before the first dose of pelabresib, it does not need to be repeated on Cycle 1, Day 1. **NOTE:** on Cycle 4 and every even numbered cycle thereafter, only liver function tests (LFTs) will be collected including total and direct bilirubin, AST, and ALT.

The clinical chemistry panel consists of the following: sodium, potassium, total carbon dioxide, chloride, serum glucose, blood urea nitrogen (BUN), serum creatinine, total and direct bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), lactate dehydrogenase (LDH), cardiac troponin (Phase 1 only), uric acid, calcium, phosphorus, EPO, C-reactive protein, iron*, iron binding capacity*, ferritin* and transferrin saturation*.

*Only required in Phase 2 at screening, after 12 weeks of treatment (Cycle 5, Day 1), after 24 weeks of treatment (Cycle 9, Day 1), and then every 12 weeks (4 cycles) thereafter.

If ≥ Grade 2 plasma potassium increase is observed, repeat plasma potassium using Li-Heparin or Na-Heparin tubes for confirmation.

Serum lipids
Serum lipids will be obtained at screening, after 6 weeks of treatment (Cycle 3, Day 1), and then every 12 weeks (4 cycles) thereafter.

The serum lipid panel includes total cholesterol, cholesterol LDL, cholesterol HDL, and triglycerides.

Pregnancy testing
A serum β-hCG pregnancy test will be performed for WOCBP during screening and at baseline (≤ 72 hours before the start of Cycle 1). Both results must be negative before the first dose of pelabresib is given. In WOCBP, a highly sensitive urine or serum pregnancy test will be repeated ≤ 72 hours before the start of every cycle during treatment with pelabresib, at the EOT visit, and thereafter at monthly intervals until the end of relevant systemic exposure (184 days after the last dose of study drug).

If a female 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 and the patient must be discontinued from the study.

If 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.

ACTH stimulation testing (Phase 1 Only):
See Amendment 6 (Version 7) of the Study 0610-02 protocol.

6.3.13. Efficacy Measurements

6.3.13.1. Disease Response Assessment

Patients with acute leukemia, MDS or MDS/MPN (Phase 1)
See Amendment 6 (Version 7) of the Study 0610-02 protocol.

Patients with MF (Phase 2)
Disease response including splenic response, CCI anemic response, change in PROs, CCI

The patient's disease status will be evaluated with measurement of peripheral blood counts (see Section 6.3.12.8), history/documentation of transfusion requirements (see Section 6.3.8), MF-associated symptoms (see Section 6.3.11), spleen size by palpation (see Section 6.3.12.3) and by CT or MRI (see below), extent of marrow fibrosis (with bone marrow biopsy; see Section 6.3.17.5), and mutant allele burden (in peripheral blood; see Section 6.3.17.4).

An MRI (preferred) or CT scan will be performed at screening, after 12 weeks of treatment (Cycle 5, Day 1), after 24 weeks of treatment (Cycle 9, Day 1) and then every 12 weeks (4 cycles) thereafter. A window of ± 2 weeks applies to these assessments. An MRI or CT scan should be repeated at the EOT visit only if PD has not been previously documented or, in the absence of documented PD, if imaging has not been performed within the previous 6 weeks. Imaging data for spleen volume measurement (imaging studies, derived assessments, and reports) will be stored according to usual practice by the sites and will be available upon request for review by the Sponsor or independent radiology reviewers for central radiology review. Details on the central radiology review will be provided in a charter, provided as a document separate from the protocol.

Peripheral blood will also be used to monitor for conversion to acute myelogenous leukemia (AML).

Patients with ET (Phase 2)
Disease response including CHR, symptom improvement, splenic response, change in PROs, etc. will be evaluated. These response criteria are provided in Section 7.2.5.

The patient's disease status will be evaluated with measurement of platelet and WBC counts (see Section 6.3.12.8), spleen size by palpation (see Section 6.3.12.3) and by MRI or CT (see below), and by the incidence of hemorrhagic and thromboembolic events.

An MRI or CT scan will be performed at screening, after 24 weeks of treatment (Cycle 9, Day 1), after 48 weeks of treatment (Cycle 17, Day 1) and then yearly thereafter. A window of ± 2 weeks applies to these assessments. An MRI or CT scan should be repeated at the EOT visit only if PD has not been previously documented or, in the absence of documented PD, if imaging has not been performed within the previous 6 weeks. Imaging data for spleen volume measurement (imaging studies, derived assessments, and reports) will be stored according to usual practice by the sites and will be available upon request for review by the Sponsor or independent radiology reviewers for central radiology review.

Peripheral blood will also be used to monitor for conversion to MF or AML.

6.3.14. Pharmacokinetic Measurements

As of Amendment 12 (Version 13), the collection of PK samples has been completed. No further sample collection will be required. Current activities are limited to the analysis of previously collected PK samples.

6.3.14.1. Overview of the Pharmacokinetic Sampling Strategy

Serial peripheral blood samples (approximately 4 mL each) will be drawn before and after dosing with pelabresib in order to determine circulating concentrations of pelabresib, and in the Phase 2 Combination Arms, to evaluate the PK profile of ruxolitinib when given in combination with pelabresib. See the specific time points for sampling outlined in Section 6.3.14.2. In Phase 2, serial blood samples will also be collected after dosing with pelabresib when upward dose titration above the starting dose or dose re-escalation above the starting dose occurs. **NOTE:** for the JAKi Naïve Arm (Arm 3), PK for evaluation of initial steady state of pelabresib will be collected from at least 15 patients, and from at least 15 patients who undergo upward dose titration above the starting dose or dose re-escalation of pelabresib above the starting dose. PK is required in all patients enrolled in the Prior and Add-on to JAKi arms (Arm 1 and Arm 2) and the ET arm (Arm 4). However, if this is not feasible, a blood sample for PK may be omitted from a patient in Arm 1, Arm 2, or Arm 4 only after consultation with the Sponsor.

See Amendment 6 (Version 7) of the Study 0610-02 protocol for additional details on Phase 1 blood collection for PK.

6.3.14.2. Specific Time Points for Pharmacokinetic Sampling

See Amendment 6 (Version 7) of the Study 0610-02 protocol for additional details on Phase 1 blood collection for PK.

The total volume of blood drawn in the Phase 2 Arms will be approximately 32 mL in Cycle 1 and 28 mL in cycles where upward titration or dose re-escalation above the starting dose occurs.

Table 18 Phase 1 Pharmacokinetic Sampling Schedule

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

Table 19 Pharmacokinetic Sampling Schedule: Phase 2 (Arms 1, 2, 3[a], and 4)

Cycle Day	Time point	Total approximate amount of blood per study day
C1D1	Prior to dosing	4 mL
C1D14 (a -3 day window applies to this visit)	Prior to dosing 30 minutes (± 10 min) after dosing 1 hour (± 15 min) after dosing 2 hours (± 30 min) after dosing 4 hours (± 30 min) after dosing 6 hours (± 1 hr) after dosing 8 hours (± 1 hr) after dosing	28 mL
CXD4-14[b] (X = cycle when upward dose titration of pelabresib occurs)	Prior to dosing 30 minutes (± 10 min) after dosing 1 hour (± 15 min) after dosing 2 hours (± 30 min) after dosing 4 hours (± 30 min) after dosing 6 hours (± 1 hr) after dosing 8 hours (± 1 hr) after dosing	28 mL

C = cycle; D = day; ET = early termination; JAKi = JAK inhibitor; PK = pharmacokinetic.

[a] For the JAKi Naïve Arm (Arm 3), PK for evaluation of initial steady state of pelabresib will be collected from at least 15 patients, and from at least 15 patients who undergo upward dose titration above the starting dose or re-escalation of pelabresib above the starting dose. PK is required in all patients enrolled in the Prior and Add-on to JAKi arms (Arm 1 and Arm 2) and the ET arm (Arm 4).

[b] Once an upward titration or re-escalation of pelabresib above the starting dose has occurred on CXD1, the patient can come in any day from CXD4 to CXD14 for PK sampling.

The timing, but not the number (unless fewer) of blood samples drawn for pelabresib and/or ruxolitinib plasma concentration determination may be changed if the emerging data indicate that an alteration in the sampling scheme is needed to better characterize pelabresib's and/or ruxolitinib's PK.

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

6.3.15. Phase 1: Pharmacodynamic Biomarker Measurements in Patients With Acute Leukemia, MDS or MDS/MPN

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

Table 20 Peripheral Blood Pharmacodynamic Sampling Schedule

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

Table 21 Bone marrow Biopsy and Aspirate for Pharmacodynamic Assessments

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

6.3.16. Phase 1: Predictive Biomarker Measurements in Patients With Acute Leukemia, MDS or MDS/MPN

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

6.3.17. Phase 2: Pharmacodynamic Biomarker Measurements in Patients With MF or ET

6.3.17.1. Peripheral Blood Samples for Assessment of Gene Expression Changes in Circulating Leukocytes

Peripheral blood samples (approximately 5 mL of whole blood at each time point) will be collected for the assessment of gene expression changes in circulating leukocytes. Samples will be collected predose and 4 hours after administration of pelabresib on Cycle 1, Day 1, and Day 14, and on Cycle 3 Day 1 (see Table 22). In addition, these samples will be collected on Day 1 of any cycle where the dose of pelabresib is increased. The blood samples will be collected into PAXgene blood RNA tubes, and RNA will be subsequently isolated. These RNA samples will be assessed for changes in the expression of genes predicted to be sensitive to exposure to pelabresib.

Table 22 Peripheral Blood Circulating Leukocytes Sampling Schedule

Cycle Day	Time point
C1D1	Predose 4 hours after dosing
C1D14	Predose 4 hours after dosing
C3D1	Predose 4 hours after dosing
CXD1 (upon any dose change)	Predose 4 hours after dosing

C = cycle; D = day.

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

6.3.17.2. Peripheral Blood Samples for Cytokine and Hepcidin 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 pelabresib on Cycle 1, Day 1, on Cyc1e 1, Day 14, on Day 1 of Cycle 3, 5, 7, 9, and at the EOT visit (see Table 23). An aliquot of the sample collected for cytokine evaluation will also be used for hepcidin assay.

Table 23 Peripheral Blood Cytokine Sampling Schedule

Cycle Day	Time point
C1D1	Predose
C1D14	Anytime
C3D1	Anytime
CXD1 (C5, C7, C9)	Anytime
EOT	Anytime

C = cycle; D = day; EOT = End of Treatment.

Samples will be immediately placed on ice and centrifuged under refrigeration to obtain plasma. Plasma will be frozen and maintained at -80°C until the time of analysis of plasma cytokine concentrations and hepcidin assay.

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

6.3.17.3. Peripheral Blood Samples for Collection of Viable Cells

Peripheral blood samples (approximately 30 mL of whole blood at each time point) will be collected in 3 EDTA tubes for cryopreservation of viable mononuclear cells for assessment of changes in genes associated with MF and BET target genes, to assess changes in signaling pathways and to evaluate changes in hematopoietic cell populations. Samples will be collected prior to the administration of pelabresib on Cycle 1, Day 1, on Cycle 3 Day 1 and on Day 1 of Cycle 5, 7, 9 and at the EOT visit (see Table 24).

Table 24 Peripheral Blood Viable Cell Sampling Schedule

Cycle Day	Time point
C1D1	Predose
C3D1	Anytime
CXD1 (C5, C7, C9)	Anytime
EOT	Anytime

C = cycle; D = day; EOT = End of Treatment.

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

6.3.17.4. Peripheral Blood Samples for Allele Burden Assessment

As of Amendment 12 (Version 13) the collection of samples for allele burden assessment has been completed, **except for the EOT sample collection**. Already collected samples as well as EOT samples are subject to analysis.

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 (eg, *JAK2*, *CALR*) using a focused next-generation sequencing assay. Samples will be collected Cycle 1, Day 1, after 24 weeks of treatment (Cycle 9, Day 1), every 24 weeks (8 cycles) thereafter and at the EOT visit (see Table 25). Correlation of mutation profile and response to pelabresib as a single agent and in combination with ruxolitinib will be used to identify predictive biomarkers. Additionally, changes in allelic burden of specific mutations in patients treated with pelabresib may identify hypersensitivity of certain mutational contexts to pelabresib.

Table 25 Peripheral Blood Mutant Allele Sampling Schedule

Cycle Day	Time point
C1D1	Anytime
CXD1 (X = every 8 cycles, ie, C9, C17, etc.)	Anytime
EOT	Anytime

C = cycle; D = day; EOT = End of Treatment.

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

6.3.17.5. Bone Marrow Biopsies for Grading of Fibrosis

In Arms 1, 2, and 3, bone marrow biopsy samples will be collected and assessed by a local hematopathologist for grading of bone marrow fibrosis following the European classification (Thiele et al. 2005) during screening, after 24 weeks of treatment (Cycle 9, Day 1), every 24 weeks (8 cycles) thereafter and at the EOT visit (see Table 26). The EOT bone marrow biopsy does not need to be collected if a biopsy has been performed within the previous 12 weeks. The percentage of blasts is required to be reported as part of the bone marrow pathology assessment by the local hematopathologist for the purpose of monitoring AML (leukemic) transformation. Refer to Section 7.2.4.6 for further details.

After the bone marrow biopsy has been assessed locally by the institution's hematopathologist for grading of bone marrow fibrosis, 3 stained slides should be sent to central review laboratory. Stained slides need to include:

- --H&E
- --Reticulin
- --Trichrome

A retrospective central review of bone marrow slides will be performed. For this purpose, histopathology data for bone marrow biopsy (slides, assessments, and reports) from the Phase 2 study will be stored according to usual practice by the sites and may be requested for review by the Sponsor or by independent reviewers for central pathology review.

Bone marrow samples may also be used for exploratory assessment CCI [redacted]

Table 26 Bone Marrow Sampling Schedule

Cycle Day	Time point
Screening[a]	Anytime
CXD1 (X = every 8 cycles, ie, C9, C17, etc.)	Anytime
EOT[b]	Anytime

C = cycle; D = day; EOT = End of Treatment.

[a] The bone marrow biopsy will be accepted as the screening sample if it is obtained within 3 months 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.

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

For patients in Arm 4, see Table 17 for details on the timing of bone marrow biopsies.

6.3.18. Phase 2: CCI [redacted] Evaluation

All blood and bone marrow samples collected as detailed in Section 6.3.17 may be used for additional exploratory analysis CCI [redacted]

CCI [redacted]

6.3.19. Long-term Follow-up (LTFU)

Splenic progression follow-up (Arms 1, 2, and 3): Patients who discontinue treatment for reasons other than documented splenic progression or withdrawal from study should receive follow-up visits every 12 weeks (with a visit window of ± 2 weeks) starting from the EOT visit to document splenic progression by imaging every 12 weeks until initiation of next anticancer therapy, progression, or death, whichever comes first. Transfusion requirements (Arms 1, 2, and 3): Transfusions for the first 12 weeks starting from EOT will be collected.

AML (leukemic) transformation follow-up: Arm 3 patients will be followed up for AML (leukemic) transformation and records (by biopsy if applicable) will be collected every 12 weeks until documented AML (leukemic) transformation or the patient's death, whichever comes first. Follow-up for AML (leukemic) transformation can be conducted by telephone if clinical visit is not planned.

If the subject is discontinued from LTFU, the reason of discontinuation should be recorded on EOS eCRF. An MRI (or CT) scan will be performed at the EOS visit only if PD has not been previously documented or, in the absence of documented PD, if imaging has not been performed within the previous 6 weeks. Transfusion requirements will be documented up to 12 weeks after last study drug.

6.3.20. Patient Contact

Patients who complete an EOS visit less than 30 days after the last pelabresib dose should be contacted by telephone on Day 30 post-treatment to assess new or ongoing AEs or SAEs that may have occurred since the last visit. Patients in Arm 3 will also be contacted every 12 weeks for data collection on OS until death of any cause or end of Study (see Section 6.5), whichever comes first.

6.4. Study Compliance

Pelabresib will be administered only to eligible patients under supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing, including the following: applicable lot numbers and total drug administered in milligrams (mg). Any discrepancy regarding the dose administered and the reason for the discrepancy will be documented in the source records and eCRF.

Patients will receive a drug diary that includes the instructions for home administration of pelabresib (and if applicable ruxolitinib), including that pelabresib must be administered as intact tablets. There will be a place to record the date and time of each dose as well as the number and strength (mg) of tablets taken.

Patients will receive a sufficient quantity of pelabresib for each treatment cycle. The study center staff will check the patient's diary versus the patient's supply of remaining pelabresib

tablets at each study center visit and at the EOT visit to ensure proper compliance with dosing. Patients who are not compliant with the dosing schedule may be withdrawn from the study.

In addition, patients will receive instructions on the MFSAF v4.0 diary to be completed as detailed in Section 6.3.11.1.

6.5. End of Study

The date of the end of the study for all arms (ie, study completion) is defined as the date at least 42 months after the last Arm 3 patient is enrolled. A patient who is still on study without disease progression may be consented to an extension protocol to continue receiving access to drug if they are deriving clinical benefit or monitored for long term-term follow-up or compassionate use protocol or transition to commercial supply if available at the time. The Sponsor may end the trial when the availability of a rollover study exists into which any patient may enter if they are deriving clinical benefit or being monitored for long term-term follow-up. Such a protocol would be written for pelabresib if not yet commercially available.

6.6. Post-end of Study

Following the end of the study, no further medical care or treatment will be provided to patients through this study by the study investigator(s). Thereafter, patients will receive medical care at the discretion of their physician. If a new event occurs after the termination of the trial that is likely to change the risk/benefit analysis of the trial and could still have an impact on the trial participants, the Sponsor should notify the competent authority and ethics committees concerned and provide a proposed course of action.

7. STUDY ENDPOINTS

The measurements that will be used to assess the safety, efficacy, PK, pharmacodynamics, and pharmacogenetics of pelabresib and pelabresib plus ruxolitinib in this study are outlined below.

7.1. Safety

Assessment of the safety of pelabresib and pelabresib plus ruxolitinib treatment will rely on the continuous evaluation of AEs and SAEs by type, frequency, severity, and their potential relationship to the study medication, on serial assessments of ECOG performance status, on monitoring of clinically significant abnormal laboratory values (with an emphasis on hematologic parameters, LFTs, and renal function), on monitoring of vital signs and physical examination, and on the evaluation of serial ECGs and echocardiograms (Phase 1 only). Concomitant medications will also be recorded.

7.2. Efficacy Measurements

The following section describes the efficacy measurements that will be obtained during the study.

In Phase 2, disease response to treatment with pelabresib and pelabresib plus ruxolitinib will be assessed through the evaluation of peripheral blood counts, transfusion requirements, symptom scores, spleen size (by palpation and CT/MRI), mutated allele burden and extent of marrow fibrosis. Response will include splenic response, CHR, CCI , anemic response, change in PROs, CCI

7.2.1. Acute Lymphoblastic Leukemia (Phase 1)

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

7.2.2. Acute Myelogenous Leukemia (Phase 1)

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

7.2.3. MDS (Phase 1)

Table 27 and Table 28 describe the response criteria for altering the natural history of MDS and hematologic improvement, respectively.

Table 27 Proposed modified International Working Group response criteria for altering natural history of MDS

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

Table 28 Proposed modified International Working Group Response Criteria for Hematologic Improvement[44]

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

7.2.4. Myelofibrosis (Phase 2)

7.2.4.1. Splenic Response

The primary endpoint for the Phase 2 Prior and Add-on to JAKi Cohorts 1B and 2B and the JAKi Naïve Arm (Arm 3) is splenic response rate by imaging after 24 weeks of treatment. This is a secondary objective for Prior and Add-on to JAKi Cohorts 1A and 2A. The percent change in spleen size by MRI or CT from baseline will be documented for each patient. A splenic response is defined as a ≥ 35% reduction from baseline spleen size by imaging (MRI or CT) and will be evaluated after 12 and 24 weeks of treatment and overall. This is the reduction in spleen volume used to define splenic response in several trials including COMFORT-I (Gupta et al. 2016) and SIMPLIFY-2 (Harrison, Vannucchi, and Platzbecker 2017a).

Patients in Cohorts 1A and 2A will be evaluable for splenic response as long as the baseline spleen size on imaging is ≥ 450 cm^3. **NOTE:** Patients in Cohorts 1B and 2B and Arm 3 are evaluable for splenic response.

Duration of splenic response will also be evaluated. For splenic response via imaging, duration of the splenic response is defined as the time when splenic response criteria are first met (a ≥ 35% reduction from baseline spleen size) until the first-time spleen volume reduction is < 35% from baseline and is increased by ≥ 25% from nadir in spleen volume by imaging.

Imaging data for spleen volume measurement (scans, derived assessments and reports) from the Phase 2 study will be stored according to usual practice by the sites and will be available upon request for review by the Sponsor or by independent reviewers for central radiology review. Details on the central radiology review will be provided in a charter, provided as a document separate from the protocol.

7.2.4.2. PROs

The TSS for the 24-hour recall (ie, daily diary) format of the MFSAF v4.0 is the sum of the 7 individual item responses on the 0–10 scale (possible TSS of 0–70). All 7 items must be completed for a daily TSS to be computed. A weekly TSS will be calculated by averaging the daily scores collected over the 7-day interval during screening.

Changes in TSS via the MFSAF and in PGIC will be described for each patient over time. Any ≥ 50% reductions in TSS after 12 and 24 weeks of treatment will also be documented, as will the time to ≥ 50% reduction in TSS, defined as the time from the first dose of pelabresib until the first day of ≥ 50% reduction in TSS.

7.2.4.3. RBC Transfusion Status

The primary endpoint for the Phase 2 Prior and Add-on to JAKi Cohorts 1A and 2A is the rate of conversion from TD to TI. Any RBC units given to each patient will be documented in order to determine RBC transfusion status and to calculate the average number of RBC units per subject-month.

RBC TI is defined as: absence of RBC transfusion in the prior 12 weeks.

RBC TD is defined as: receiving an average of ≥ 2 units of RBC transfusions per month (total of ≥ 6 units of RBC transfusions during the prior 12 weeks).

CCI [redacted]

7.2.4.4. Anemic Response

Peripheral blood will be monitored for Hgb level to evaluate anemic response.

Early anemic response rate will be evaluated in patients who enroll at TD and is defined as the proportion of patients who achieve a Hgb increase of ≥ 1 g/dL from baseline over any consecutive 8-week period in the absence of RBC transfusions.

Anemic response rate will be evaluated in patients who enroll as TI and is defined as the proportion of patients who enroll as TI and achieve ≥ 1.5 g/dL Hgb increase from baseline over any consecutive 12-week period in the absence of RBC transfusions. In addition, time to anemic response (defined as the time from the first dose of pelabresib until the first day of ≥ 1.5 g/dL Hgb increase from baseline) and duration of anemic response (defined as the time from the first day of ≥ 1.5 g/dL Hgb increase from baseline until the first day the Hgb drops below 1.5 g/dL from baseline) will be evaluated in patients who enroll as TI.

CCI [redacted]


CCI


CCI

7.2.4.6. Transformation to AML

AML (leukemic) transformation will be assessed by either 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 (Tefferi et al. 2013).

Accelerated blast phase will be assessed as ≥10 to <20% blast count either by bone marrow biopsy or 2 consecutive peripheral blood measurements.

7.2.5. Essential Thrombocythemia (Phase 2)

7.2.5.1. Hematological Response

The primary endpoint for the Phase 2 ET Arm 4 is the proportion of patients who meet the criteria for a CHR, as assessed by modified ELN criteria (Barosi et al. 2009).

CHR is defined as having a platelet count ≤ 400 × 10^9/L, WBC within normal range (≤ 10 × 10^9/L), laboratory results confirmed after 1 cycle (after 3 weeks), and a normal spleen size by palpation or imaging.

Additionally, a secondary endpoint is partial hematological response, defined as having a platelet count > 400-600 × 10^9/L and WBC within normal range (≤ 10 × 10^9/L) with laboratory results confirmed after 1 cycle (after 3 weeks).

7.2.5.2. PROs

Changes in MPN-SAF total score and in PGIC will be described for each patient over time. Additional details of these analyses will be specified in the Statistical Analysis Plan (SAP).

7.2.5.3. Transformation to MF or AML

AML (leukemic) transformation and accelerated blast phase will be assessed as described in Section 7.2.4.6.

CCI [redacted]

Imaging data for spleen volume measurement (scans, derived assessments, and reports) from the Phase 2 study will be stored according to usual practice by the sites and will be available upon request for review by the Sponsor or by independent reviewers for central radiology review. Details on the central radiology review will be provided in a charter, provided as a document separate from the protocol.

7.3. Pharmacokinetic Measurements

Blood samples for determination of the plasma concentration of pelabresib, and in the Phase 2 Combination Arms to evaluate the PK profile of ruxolitinib when given in combination with pelabresib, will be obtained before and after dosing within the first cycle of treatment. In Phase 2, serial blood samples will also be collected after dosing with pelabresib when upward dose titration above the starting dose or dose re-escalation above the starting dose occurs. Some of the PK parameters to be estimated are $AUC_{0\text{-}8,ss}$, C_{max}, t_{max}, $C_{max,ss}$, and $t_{max,ss}$.

See Amendment 6 (Version 7) of the Study 0610-02 protocol for information on Phase 1 PK measurements.

7.4. Phase 1: Pharmacodynamic Biomarker Measurements in Patients With Acute Leukemia, MDS or MDS/MPN

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

7.5. Phase 1: Predictive Biomarker Measurements in Patients With Acute Leukemia, MDS or MDS/MPN

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

7.6. Phase 2: Pharmacodynamic Biomarker Measurements

Peripheral blood samples will be collected for the measurement of circulating concentrations of cytokines. This assessment will include cytokines commonly found to be increased in the plasma of patients with MF, such as IL-1β, IL-1RA, IL-2R, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, TNF-α, G-CSF, IFN-α, MIP-1α, HGF, IP-10, MIG, MCP-1, and VEGF. Hepcidin will also be measured. Peripheral blood samples will also be collected and processed to allow for cryopreservation of viable mononuclear cells for assessment of changes in BET target genes, as well as ex vivo stimulation assays to assess changes in JAK/STAT signaling pathway, to evaluate changes in hematopoietic cell populations, and to evaluate gene expression changes in circulating leukocytes.

Peripheral blood samples will be collected for the measurement of mutant allele burden of selected genes (eg, *JAK2*, *CALR*) using a focused next-generation sequencing assay. Correlation of mutation profile and response to pelabresib as a single agent and in combination with ruxolitinib will be used to identify predictive biomarkers. Additionally, changes in allelic burden

of specific mutations in patients treated with pelabresib may identify hypersensitivity of certain mutational contexts to pelabresib.

Bone marrow biopsy samples will be collected and assessed by a local hematopathologist for grading of bone marrow fibrosis and bone marrow blast percentage for monitoring of AML (leukemic) transformation. A retrospective central review of bone marrow slides may be performed at the Sponsor's request. Bone marrow samples may also be used for exploratory assessment CCI [redacted]

Histopathology data for bone marrow biopsy (slides, assessments, and reports) from the Phase 2 study will be stored according to usual practice by the sites and may be available upon request for review by the Sponsor or by independent reviewers for central pathology review.

7.7. Phase 2: CCI [redacted] Evaluation

All blood and bone marrow samples collected may be used for additional exploratory analysis CCI [redacted]

7.8. CCI [redacted]

CCI [redacted]

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1. Statistical Methods

8.1.1. Determination of Sample Size

In Phase 2 (MPN expansion), 4 arms will be evaluated: Arm 1: Prior JAKi Monotherapy Arm (MF patients treated with pelabresib alone), Arm 2: Add-on to JAKi Combination Arm (MF patients treated with pelabresib in combination with ruxolitinib), Arm 3: JAKi Naïve Combination Arm (MF patients treated with pelabresib in combination with ruxolitinib), and Arm 4: ET Arm (high-risk ET patients treated with pelabresib alone).

The Prior and Add-on to JAKi arms (Arms 1 and 2) are further stratified into TD cohorts (Cohorts 1A and 2A) and non-TD cohorts (Cohorts 1B and 2B).

The primary endpoint for Cohorts 1A and 2A is the rate of conversion from TD to TI. A Simon's two-stage design will be used for Cohorts 1A and 2A in the Prior and Add-on to JAKi Arms to allow the possibility of early stopping for futility. Conversion from TD to TI is very unlikely in the Prior and Add-on to JAKi population and is not expected to happen spontaneously. Therefore, the null hypothesis that the true conversion rate is 2% will be tested against a one-sided alternative. In the first stage, 6 evaluable patients will be accrued in each cohort. If there are 1 or more conversions in these 6 evaluable patients, 10 additional evaluable patients will be

accrued for a total of 16 in each cohort. The null hypothesis will be rejected for a given cohort if 2 or more conversions are observed in 16 evaluable patients. This design yields a type I error rate of 0.05 and power of 80% assuming the true conversion rate is 25%. **NOTE:** As of Amendment 8 (Version 9), 2 Cohort 2A patients have converted from TD to TI, therefore, the null hypothesis is rejected in favor of a true TD-to-TI conversion rate of 25%. To estimate the conversion rate with higher precision, Cohort 2A will be further expanded to enroll an additional 44 evaluable patients (for a total of 60) so that the study will have 85% power to exclude 10% from the lower bound of a two-sided 95% exact binomial confidence interval. Similarly, if the null hypothesis is rejected in the Simon's two-stage design of Cohort 1A, the cohort will be expanded to a total of 60 evaluable patients.

The primary endpoint in Cohorts 1B and 2B is splenic response rate via imaging after 24 weeks of treatment. A $\geq$ 35% reduction from baseline spleen size was chosen as it is the reduction in spleen volume used to define splenic response in several trials including COMFORT-I (Gupta et al. 2016) and SIMPLIFY-2 (Harrison, Vannucchi, and Platzbecker 2017a). For Cohorts 1B and 2B, a sample size of 25 patients is required in each cohort to distinguish between a maximum futility splenic response rate of 10% and a minimum efficacy splenic response rate of 30% at Week 24, with an actual one-sided significance level of 0.033 and actual power of 80.65%. Five or more splenic responses are required in a cohort to find in favor of the treatment for that cohort. As of this amendment, 5 splenic responses have been observed in Cohort 1B. To increase the precision of estimate, Cohort 1B will be expanded to enroll 25 additional evaluable patients for a total of 50 evaluable patients. Assuming a true splenic response rate of 30%, a sample size of 50 evaluable patients will provide 86% power for the lower bound of a two-sided 95% exact binomial confidence interval to exclude a splenic response rate of 12.5%.

For JAKi Naïve Combination Arm (Arm 3), a total of 81 patients will be enrolled and an optimal Simon's two-stage design will be used. The primary endpoint for Arm 3 is splenic response rate after 24 weeks of treatment. The null hypothesis that the true splenic response rate is 30% will be tested against a one-sided alternative. The null hypothesis is constructed based on the splenic response rate at 24 weeks reported for ruxolitinib in the SIMPLIFY-1 trial (Mesa et al. 2017). In In the first stage, 27 patients will be accrued. If there are 9 or fewer responses in these 27 patients, the study will be stopped. Otherwise, 54 additional patients will be accrued in Stage 2 for a total of 81. The null hypothesis will be rejected if 31 or more responses are observed in 81 patients. This design yields a type I error rate of 0.05 and power of 80% when the true splenic response rate is 45%.

For the ET arm (Arm 4), a sample size of 21 patients is required to distinguish between a maximum futility CHR rate of 8% and a minimum efficacy CHR rate of 30% with an actual one-sided significance level of 0.023 and actual power of 80.16%. Four or more complete hematologic responses are required to find in favor of the treatment. The number of patients enrolled in Phase 1 of this study is driven by the dose escalation scheme and by the point(s) in the dose escalation scheme where DLT may occur. Forty-four patients with acute leukemia, MDS or MDS/MPN were enrolled in Phase 1. Up to 60 evaluable MF patients will be enrolled in each of Cohorts 1A and 2A, up to 50 evaluable MF patients in Cohort 1B, and up to 25 evaluable MF patients in Cohort 2B in Arms 1 and 2, up to 81 evaluable patients will be enrolled in Arm 3, and up to 21 evaluable ET patients will be enrolled in Arm 4 during Phase 2. Therefore, it is estimated that up to 341 evaluable patients will be enrolled into this study.

Additional patients may be enrolled if replacement of non-evaluable patients is needed. **NOTE**: All patients with MF enrolled for Phase 1 under Amendment 5 will be included in Phase 2.

The primary analysis will take place when all patients have either completed their primary endpoint assessment (ie, week 24 visit) or discontinued prematurely. Final analysis will take place when all patients have finished their EOS visit.

8.1.2. Randomization and Stratification

No randomization will be used in this trial. In the Prior and Add-on to JAKi arms, patients will be stratified into TD cohorts (Cohorts 1A and 2A) and non-TD cohorts (Cohorts 1B and 2B).

8.1.3. Populations for Analysis

The patient populations for the purpose of statistical analysis in this study are defined below:

8.1.3.1. Population Evaluable for Safety

The population of patients evaluable for safety is defined as all patients who receive at least one dose of investigational medicinal product (IMP).

8.1.3.2. Population Evaluable for DLT

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

8.1.3.3. Population Evaluable for Efficacy

Evaluation of efficacy will be assessed in all patients, when possible, during Phase 1 and Phase 2.

In Phase 2,

- The population evaluable for the primary endpoint in Cohorts 1B and 2B and Arm 3 of splenic response via imaging after 24 weeks of treatment is defined as all patients who have the baseline and at least one post-baseline imaging results available.
- The population evaluable for the primary endpoint in Cohorts 1A and 2A of rate of conversion from TD to TI is defined as all patients who have RBC transfusions assessed for at least the first 12 weeks after the start of treatment.
- The population evaluable for the primary endpoint of CHR in Arm 4 is defined as all patients who have at least 1 follow-up platelet assessment on study.

8.1.3.4. Population Evaluable for Pharmacokinetics

The population of patients evaluable for pelabresib's PK is defined as all patients who receive at least one dose of pelabresib and have at least one measurable pelabresib concentration. This population will be used for analyses of pelabresib PK parameters. For the Phase 2 Combination Arms, the population of patients evaluable for ruxolitinib's PK is defined as all patients who receive at least one dose of ruxolitinib and have at least one measurable ruxolitinib concentration.

8.1.3.5. Populations Evaluable for Pharmacodynamic Assessments (Phase 1)

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

8.1.3.6. Populations Evaluable for Predictive Biomarker Assessments (Phase 1)

See Amendment 6 (Version 7) of the Study 0610-02 protocol.

8.1.3.7. Populations Evaluable for Pharmacodynamics Assessments (Phase 2)

Peripheral blood and bone marrow biopsies will be collected for evaluation of pharmacodynamic markers. Depending on the adequacy of tissue samples and the technical performance of the assays, a number of different populations may be defined for biomarker assessments.

In order for a patient to be included in a population evaluable for a biomarker assessment appropriate tissue samples must have been acquired before and during dosing with pelabresib (and ruxolitinib in the combination arms), the samples must have been processed according to study procedures, and the sample must be adequate to permit the performance of the assay.

8.1.3.8. CCI

CCI

8.1.4. Procedures for Handling Missing, Unused, and Spurious Data

All available data will be included in data listings. No imputation of values for missing data will be performed. Percentages of patients with AEs or laboratory toxicities will be based on non-missing values.

Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

8.1.5. General Methodology

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. Appropriate confidence intervals will also be presented. Safety, efficacy, PK, and pharmacodynamic evaluations will be assessed in the appropriate treated populations. These data will be descriptively summarized by each dose level in Phase 1, for each arm and cohort in Phase 2, and overall, as appropriate.

8.1.6. Baseline Comparisons

There are no treatment groups to be compared with respect to their baseline characteristics. The demographic and baseline characteristics will be descriptively evaluated. Data to be evaluated will include age, sex, race, and baseline characteristics.

8.1.7. Efficacy Analysis

See Amendment 6 (Version 7) of the Study 0610-02 protocol for a description of efficacy analyses during Phase 1.

For Arms 1, 2, and 3, the percent of patients with 35% or more reduction from baseline in spleen size at week 12 and week 24 by imaging will be calculated and summarized for each arm and cohort. In addition, the % change from baseline in the spleen size will be summarized and presented using a waterfall plot, for all scheduled imaging visits. Similarly, the percent of patients achieving conversion from TD to TI will be summarized for each arm and cohort as appropriate. For Arm 4, the percent of ET patients achieving CHR will be calculated and summarized over time.

To summarize the change in PROs, the percent of patients with 50% or more reduction from baseline in TSS will also be calculated for each arm and cohort.

More details of analyses will be specified in SAP. In general, Binary variables (eg, response rates and conversion rates) will be estimated and reported along with exact 95% confidence intervals. Time to event variables (eg, duration of splenic response, time to conversion from TD to TI, Overall Survival) will be described using the method of Kaplan and Meier.

8.1.8. Pharmacokinetic Analysis

Descriptive statistics will be used to summarize PK parameters for each dose group in Phase 1, for each arm and cohort in Phase 2 and, where appropriate, for the entire population. PK parameters will include (but are not limited to) C_{max}, T_{max}, AUC, and $T_{1/2}$. CCI [redacted]. The population evaluable for PK will be used for these analyses.

CCI [redacted]

8.1.9. Pharmacodynamic Analysis

CCI [redacted]

8.1.10. Safety Analysis

The incidence of DLT will be tabulated for each dose group in Phase 1. In addition, to assess the relationship between toxicities and pelabresib dose, the preferred term of individual toxicities will be summarized by their frequency and intensity for each dose group.

Safety will also be evaluated by the incidence of treatment-emergent AEs, severity, and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory results using the population evaluable for safety. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent AEs will be tabulated where treatment-emergent is defined as any AE that occurs after administration of the first dose of study treatment and through 30 days after the last dose of study medication, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in severity after baseline or is subsequently considered drug-related by the investigator. AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class, high level terms, and preferred terms and will include the following categories:

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- Treatment-emergent AEs resulting in study drug discontinuation
- Treatment-emergent serious AEs (SAEs)
- Treatment-emergent AEs resulting in death

The most commonly reported treatment-emergent AEs (ie, those events reported by ≥ 10% of all patients) will be tabulated by high level term and preferred term.

Descriptive statistics for the actual values of clinical laboratory parameters and change from baseline in clinical laboratory parameters will be presented for all scheduled measurements 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 4.03).

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

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

Additional safety analyses may be determined in order to most clearly enumerate rates of toxicities and to further define the safety profile of pelabresib and pelabresib plus ruxolitinib.

8.1.11. CCI [redacted] Analysis

CCI [redacted]

8.1.12. Interim Analysis

See Amendment 6 (Version 7) of the Study 0610-02 protocol for a description of interim analyses during Phase 1.

During Phase 2, an interim analysis will occur after 6 evaluable patients are accrued in Cohorts 1A and 2A and after 27 evaluable patients are accrued in Arm 3 (after Stage 1 of the Simon's two-stage design). See Section 8.1.1 for details.

9. ADVERSE EVENTS

9.1. Definitions

9.1.1. Adverse Event Definition

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

9.1.2. Serious Adverse Event Definition

An SAE is any AE occurring at any dose and regardless of causality that:

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Requires in patient **hospitalization or prolongation of existing hospitalization** (see clarification in paragraph below Section 9.2 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. Overnight stays for observation, stays at an emergency department, or treatment on an out-patient basis do not constitute hospitalizations. However, medical judgement must always be exercised, and when in doubt the case should be considered serious (ie, 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 judgement, it may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions 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.

Clarification should be made between the terms "serious" and "severe" since they ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be

of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.2. Procedures for Recording and Reporting 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. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE and must be recorded in the appropriate sections of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

All SAEs that occur during the course of the study, as defined in Section 9.1.2, must be reported by the investigator to the study contract research organization, PPD, within 24 hours from the point in time when the investigator becomes aware of the SAE. In addition, all SAEs, including all deaths that occur through 30 days after administration of the last dose of study drug must be reported to PPD within 24 hours of the site's knowledge of the event.

All SAEs and deaths must be reported whether or not considered causally related to the study drug. 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 drug. The causal relationship to study interventions will be determined by the Investigator according to best medical judgement, 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 SAE and administration of study interventions. The SAE is unlikely to be caused by a concurrent and/or underlying illness, other drugs, or procedures. If applicable, the SAE follows a clinically consistent resolution pattern upon withdrawal of study interventions.

- Possibly related: There is a clinically plausible time sequence between onset of the SAE and administration of study interventions, but the SAE could also have been caused by the concurrent/underlying illness, other drugs, or procedures. Information regarding withdrawal of study interventions may be lacking or unclear. "Possible" should be used when study intervention administration is 1 of several biologically plausible causes of the SAE.

- Unlikely related: The SAE is most likely due to a non-study intervention-related cause. However, association with study interventions cannot be completely ruled out.
- Unrelated: 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 interventions and/or a causal relationship is considered biologically implausible.

Follow-up information on the SAE may be requested by CPI or PPD.

Table 30 SAE Reporting Contact Information

PPD
Submit to PPD by email: MorphoSysClinicalTrialPV.sm@ppd.com Or by FAX: For country-specific FAX numbers, refer to the contact list.

In accordance with local guidelines, CPI or its designee will notify, in an expedited manner, the appropriate competent authorities, applicable IRBs, and investigators of suspected unexpected serious adverse reactions (SUSARs) associated with the use of the study drug.

Planned hospital admissions or surgical procedures for an illness or disease which existed before the patient was enrolled in the trial or before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, 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).

For both SAEs and nonserious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. Intensity for each AE, including any laboratory abnormality will be determined by using the NCI CTCAE, Version 4.03, as a guideline, wherever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html. In those cases where the NCI CTCAE criteria do not apply, intensity should be defined according to the following criteria:

Table 31 Severity Criteria

Mild	Awareness of sign or symptom but easily tolerated
Moderate	Discomfort enough to cause interference with normal daily activities
Severe	Inability to perform normal daily activities
Life-Threatening	Immediate risk of death from the reaction as it occurred

Relationship to study drug administration and/or ruxolitinib will be determined by the investigator responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug/ruxolitinib?

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 are at risk for many AEs as a result of their disease and the consequences of prior therapy. Expected events due to acute leukemia, chronic myeloid leukemia currently in blast crisis, MDS, MDS/MPN, MF or to the treatment of these diseases are listed below and should not be reported as SUSARs unless they are thought to be study drug-related:

1. Adverse events related to myelosuppression:
    a. Febrile or infection episodes not requiring management in the intensive care unit
    b. Epistaxis or bleeding except for catastrophic central nervous system or pulmonary hemorrhage
    c. Anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia, leukocytosis
    d. Disease-related events
    e. Symptoms associated with anemia: fatigue, weakness, shortness of breath
2. Electrolyte abnormalities (sodium, potassium, bicarbonate, total carbon dioxide, magnesium)
3. Chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)
4. Coagulation abnormalities
5. Alopecia
6. Bone, joint, or muscle pain
7. Renal failure related to tumor lysis syndrome or antibiotic/antifungal therapy

The occurrence of these AEs will be monitored by CPI and an expedited report will be submitted if an aggregate analysis indicates that the events are occurring more frequently than in historical control groups.

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.

9.3. Monitoring of AEs and Period of Observation

Monitoring of AEs and SAEs will be conducted throughout the study. AEs, both serious and nonserious, and deaths will be recorded on the eCRF from the time of informed consent until 30 days after administration of the last dose of study drug. All AEs and SAEs that occur during the reporting period will continue to be followed until the event resolves, the investigator assesses the event as stable, the event is determined to be irreversible, or the patient is lost to follow-up.

Any SAE that occurs at any time after completion of the study and the designated 30-day follow-up period, which the investigator considers to be related to study drug, must be reported to PPD.

9.4. 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 PPD. For the time period beginning when the ICF is signed through 30 days after administration of the last dose of study drug or the start of alternative (off-study) treatment for MF, whichever is earlier, any AESI, or follow up to an existing AESI, whether related to study drug or not, must be reported within 24 hours to PPD.

AESIs 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. ARDS
3. Accelerated phase* (≥10% and <20% blasts): confirmed by bone marrow biopsy or by 2 consecutive peripheral blood measurements
4. Transformation to blast phase* (≥20% blasts): confirmed by a bone marrow blast count of ≥20% or peripheral blood blast count of ≥20% associated with absolute blast count of $\geq 1 \times 10^9$/L that persists for at least 2 weeks

*All AESIs of accelerated phase and transformation to blast phase must be captured in the clinical database and reported to the Safety CRO as a serious AESI using the serious criterion of important medical event unless the event meets one of the other serious criteria (i.e., hospitalization, life-threatening, death, etc.) as described in Section 9.1.2. The occurrence of these serious AESIs of accelerated phase and transformation to blast phase will be monitored by the Sponsor and submitted as expedited reports.

9.5. Treatment of Overdose

For this study, any dose of study drug greater than the recommended Phase 2 dose of pelabresib (225 mg QD; Section 5.7.1) within a 24-hour time period 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 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 9.2.

9.6. Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a female 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 and the patient must be discontinued from the study.

If 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.

PPD must also be contacted immediately by faxing a completed Pregnancy Form. The pregnancy must be followed through the final pregnancy outcome and one month after the expected due date.

10. ADMINISTRATIVE REQUIREMENTS

10.1. Good Clinical Practice

The study will be conducted in accordance with the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (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 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.

10.2. Data Quality Assurance

Constellation (CPI) 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 participant. Study data will be entered into an eCRF by site personnel using a secure, validated web-based electronic data capture (EDC) application. CPI 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, 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.

10.3. Electronic Case Report Form

CPI 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.

CPI 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.

10.4. Study Monitoring

Monitoring and auditing procedures developed or approved by CPI 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 CPI or its designee. Monitoring will be conducted by personal visits from a representative of the Sponsor or 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, email, and fax).

All unused study drug is to be returned to CPI after the clinical phase of the trial has been completed.

10.5. Ethical Considerations

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, IB, informed consent form, 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.

10.6. Patient Information and Informed Consent

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 CPI or its designee.

Please see Appendix 8 for changes in study conduct due to unforeseen circumstances (including pandemics).

10.7. Patient Confidentiality

In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports and communications will identify the patient by initials where permitted and/or by the assigned patient number. The investigator will grant monitor(s) and auditor(s) from CPI 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.

10.8. Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by CPI, and given approval by the IEC and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without agreement of both the investigator and CPI. Changes to the protocol will require written IEC approval prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. If applicable regulatory authorities(ies) permit, the IEC may provide expedited review and approval for minor change(s) in ongoing trials that have the approval of the IEC. CPI will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the investigator will contact CPI, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the eCRF and source documentation.

10.9. On-site Audits

Regulatory authorities, the IEC, and/or CPI's quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

10.10. Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial 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 CPI (or disposal of the drug, if approved by CPI) 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 CPI. 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.

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 will

be returned to CPI or if authorized, disposed of at the study site and documented. All material containing study drug will be treated and disposed of as hazardous waste in accordance with governing regulations.

10.11. Closure of Study

CPI reserves the right to terminate this study prematurely at any time for reasonable medical or administration reason. Any premature discontinuation will be appropriately documented according to local requirements.

Written notification documenting the reason for study termination will be provided to the investigator or CPI by the terminating party. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or non-evaluable data
- Data supporting key endpoints of the study have been collected
- Plans to modify, suspend, or discontinue the development of the study drug
- Availability of a rollover study

Should the study be closed prematurely, all study materials (study medication, etc.) must be returned to CPI. The site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded.

Within 15 days of premature closure, CPI must notify the FDA and IRBs, providing the reasons for study closure.

10.12. Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and communicate this information to CPI or its designee.

11. USE OF INFORMATION

All information regarding pelabresib supplied by CPI 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 CPI. It is understood that there is an obligation to provide CPI with complete data obtained during the study. The information obtained from the clinical trial will be used toward the development of pelabresib and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical trial and evaluation of results by CPI, 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.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Group, comprising CPI employees and study investigators, will be formed to oversee the publication of the study results that will reflect the experience of all participating study centers. Subsequently, individual investigators may publish results from the study in compliance with their agreements with CPI.

A prepublication manuscript or abstract is to be provided to CPI a minimum of 30 days prior to the intended submission date of the manuscript or abstract to a publisher.

Within 30 days after receipt by CPI of the notification, CPI shall inform the investigational sites whether it has objections to the publication for reasons including, but not limited to, those defined below:

If patentable subject matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from CPI receipt of the proposed publication to allow time for the filing of patent applications covering patentable subject matter.

If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at CPI's request.

12. REFERENCES

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13. APPENDICES

APPENDIX 1: REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS-R) IN MYELODYSPLASTIC SYNDROME

Prognostic variable	Score						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast (percent)	≤ 2		> 2 to < 5		5 to 10	> 10	
Hemoglobin (g/dL)	≥ 10		8 to < 10	< 8			
Platelets (cells/microL)	≥ 100	50 to 100	< 50				
Absolute neutrophil count (cells/microL)	≥ 0.8	< 0.8					

This scoring system was applied to an initial group of 7012 patients with primary MDS by the French-American-British classification who had at least 2 months of stable blood counts, ≤ 30% bone marrow blasts and ≤ 19% peripheral blood blasts, and who were observed until progression to AML transformation or death (did not receive disease-modifying agents for MDS). Patients could be stratified into 5 groups with the following estimated overall survival and progression to AML.

Risk group	IPSS-R score	Median overall survival (years)	Median time to 25% AML evolution (years)
Very low	≤ 1.5	8.8	> 14.5
Low	> 1.5 to 3.0	5.3	10.8
Intermediate	> 3 to 4.5	3.0	3.2
High	> 4.5 to 6	1.6	1.4

Very high	> 6	0.8	0.7
The prognostic value of the IPSS-R was validated in an external cohort of 200 patients with MDS			

AML = acute myeloid leukemia; IPSS-R = International Prognostic Scoring System; MDS = myelodysplastic syndrome.

* Cytogenetic definitions:
Very good: -Y, del(11q).
Good: Normal, del(5q), del(12p), del(20q), double including del(5q).
Intermediate: del(7q), +8, +19, i(17q), any other single or double independent clones.
Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities.
Very poor: Complex: > 3 abnormalities.

APPENDIX 2: STANDARD "3 + 3" PHASE I STUDY DESIGN: DOSE ESCALATION RULES AND OPERATING CHARACTERISTICS

Excerpted from: Rubinstein LV, Simon RM. (2003), "Phase I Clinical Trial Design" in Budman DR, Calvert AH, Rowinsky EK (Eds). Handbook of Anticancer Drug Development. Lippincott Williams & Wilkins, Philadelphia, PA.

Dose Escalation Rules for the Standard Phase I Trial

Outcome: # DLT/# patients	**Action:** Escalate, suspend, or halt dose escalation
0 DLT /3 patients	Escalate dose for the next cohort of 3 patients
1 DLT/3 patients	Treated next cohort of 3 patients at the same dose
≥ 2 DLTs/3 patients	Halt dose escalation: Treat a total of 6 patients at previous dose to determine MTD
1 DLT/6 patients	Escalate dose for next cohort of 3 patients
≥ 2 DLTs/6 patients	Halt dose escalation: Treat a total of 6 patients at previous dose to determine MTD

DLT = dose-limiting toxicity; MTD = the highest dose for which no more than 1 of the 6 treated patients exhibits DLT.

Probabilities of Halting or Continuing Dose Escalation for Various Probabilities of DLT Associated with the Dose Level, for the Standard Phase I Design

True probability of DLT for dose level	0.05	0.1	0.2	0.3	0.4	0.5	0.6	0.7
Probability of halting dose escalation after accruing either 3 or 6 patients (≥ 2 DLTs)[a]	0.03	0.09	0.29	0.51	0.69	0.83	0.92	0.97
Probability of continuing escalation after only 3 patients (0 DLT)[b]	0.86	0.73	0.51	0.34	0.22	0.13	0.06	0.03
Probability of halting escalation after only 3 patients (≥ 2 DLTs)[b]	0.01	0.03	0.10	0.22	0.35	0.50	0.65	0.78

DLT = dose-limiting toxicity.

a. This row gives probabilities of halting dose escalation, at a given dose, if the true probability of DLT for that dose level is indicated.

b. These rows give probabilities of continuing or halting dose escalation after accruing only 3 patients, at a given dose, of the true probability of DLT for that dose level is indicated. We see that, in all cases, the cohort will be limited to 3 patients with at least 50% probability, and for the more extreme DLT probabilities (0.05 and 0.7), the cohort will be expanded to 6 patients with less than 20% probability.

APPENDIX 3: DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM

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

- Age > 65: 1 point
- Leukocyte count > 25×10^9/L: 1 point
- Hemoglobin < 10 g/dL: 2 points
- Circulating blast cells ≥ 1%: 1 point
- 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

APPENDIX 4: INHIBITORS OR INDUCERS OF CYP3A4

The lists of drugs in Appendix 4 were compiled from the following resources:

- 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.

Table 32 Strong CYP3A4 Inhibitors and Inducers

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 (eg, high dose, double strength) or as a "moderate CYP3A4 inhibitor" when another preparation was used (eg, low does, single strength).

[b] The effect of St. John's wort varies widely and is preparation-dependent.

APPENDIX 5: MYELOFIBROSIS SYMPTOM ASSESSMENT FORM V4.0

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

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

APPENDIX 6: CHILD-PUGH SCORE

Points	1	2	3
Encephalopathy	None	Minimal	Advanced (coma)
Ascites	None	Controlled	Refractory
Bilirubin (µmol/L)	< 34 (< 2 mg/dL)	34-51 (2-3 mg/dL)	> 51 (> 3 mg/dL)
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin (sec)[a]	< 4	4-6	> 6

[a] Difference between the patient and the control. Differences of 4 to 6 seconds correspond approximately to a prothrombin ratio of ~50 to 40% of normal, respectively.

Chronic liver disease is classified into Child-Pugh Class A to C by adding up the points based on the factors listed in the table above:

- 5-6 points: Class A
- 7-9 points: Class B
- 10-15 points: Class C

Reference: Durand F, Valla D. 2005. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. J Hepatol. 42:S100-S107.

APPENDIX 7: MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM

Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)

Instructions: Please fill out all questions, as best able, reflecting how these symptoms affected you over the **PAST 24 HOURS** unless directed otherwise. Complete forms until the STOP instruction toward the end of the packet.

Circle the one number that describes, during the past 24 hours, how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal pain	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with headaches	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Dizziness/ Vertigo/ Lightheadedness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/ Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Difficulty sleeping	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Depression or sad mood	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with sexual desire or Function	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Cough	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
What is your overall quality of life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As bad as it can be)

Reference: Scherber R, Dueck AC, et al. 2011. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): International Prospective Validation and Reliability Trial in 402 Patients. Blood. 118(2):401-408

APPENDIX 8: 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 participants, such as during natural disasters (floods, tornadoes, earthquakes, hurricanes) or acts of people (eg, acts of terrorism, riots, strikes, wars), and pandemics (eg, 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 ratio 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

	Section	Description
Consent Process	Inclusion/Exclusion Criteria	Original consent to enter the study must be performed in person at the clinical site.
	6.3.1 Informed Consent 10.6 Patient Information and 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 applications, such as Skype. 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.
IMP Shipment *All Safety assessments must be carried out at the clinical trial site prior to the first treatment cycle and IMP being dispensed to the patient for the first time*	5.1.3 How Supplied 5.1.4 Storage, handling and accountability	If patients are unable to pick up drug, Sites may ship IMP directly to patients per local procedures and using the below guidelines. CPI (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 IMP 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*	6.2 Schedule of Events Table 15 6.3 Study Procedures	If the investigator believes that travel to the study site for a study assessment would place the study participant at increased risk relative to the benefit of the in-person assessment, the assessment can be conducted remotely through telemedicine (phone, Skype, 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 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.
Trial Assessments *Including Imaging and Laboratory Blood Draws* *All Safety assessments must be carried out at the clinical trial site prior to the first treatment cycle and IMP being dispensed to the patient for the first time*	6.2 Schedule of Events Table 15 6.3 Study Procedures	Laboratory assessment can be completed locally and sent to the study site, taking into consideration IMP 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 the importance of patients ePRO assessments. For patients who are using

		paper versions of any assessment forms/questionnaires, extra copies should be sent as needed. • 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.
Samples 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.
Adverse Event Reporting		If physical visits are reduced or postponed, the investigators will continue collecting adverse events from the trial participant through alternative means, eg, by phone calls or telemedicine visits, as appropriate.
Protocol Deviations		Protocol Deviations (eg, out of visit windows, etc.) should be captured per the usual study/institutional requirements.