Clinical Trial Protocol: 0610-02

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 Myelofibrosis)

Study Number: 0610-02 / NCT02158858

Study Phase: 1

Product Name: CPI-0610

Indication: Acute Leukemia, Myelodysplastic Syndrome, Myelodysplastic/Myeloproliferative Neoplasms, and Myelofibrosis

Study Sponsor: Constellation Pharmaceuticals
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Medical Monitor: PPD

Constellation Pharmaceuticals
PPD

	Date
Original Protocol (Version 1):	13 September 2013
Amendment 1 (Version 2):	16 April 2014
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Amendment 3 (Version 4):	02 November 2015
Amendment 4 (Version 5):	11 December 2015
Amendment 5 (Version 6):	03 August 2016
Amendment 6 (Version 7):	04 January 2018

PRINCIPAL INVESTIGATOR SIGNATURE

I have read the attached Protocol 0610-02, entitled "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 Myelofibrosis)" dated 04 January 2018. I agree to abide by all provisions set forth herein. I agree to comply with the International Conference on Harmonization Tripartite Guidelines on Good Clinical Practice, effective in the United States from 9 May 1997, and applicable United States Food and Drug Administration regulations set forth in 21 CFR §50, 54, 56, and 312. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of this clinical investigation without the prior written consent of Constellation Pharmaceuticals.

Principal Investigator Printed Name	Principal Investigator Signature	Date

Investigational Site or Name of Institution and Location

PPD

Medical Monitor Printed Name	Medical Monitor Signature	4-January-2018 Date

SYNOPSIS

NOTE: As of Amendment 6, Phase 1 is complete and all new patients will be enrolled in Phase 2.

Sponsor:
Constellation Pharmaceuticals

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

Study Number: 0610-02

Study Phase: 1/2

Investigational Product; Dose; and Mode of Administration:

Phase 1 (dose escalation): CPI-0610; starting dose 6 mg PO QD; patients will take CPI-0610 by mouth for 14 days followed by a 7-day break (1 cycle = 21 days)

Phase 2 (MF expansion): As of Amendment 6 (Version 7), the expansion arm doses for myelofibrosis (MF) patients are:

Monotherapy Arm (MF patients treated with CPI-0610 alone):

CPI-0610 at initial dose of 125 mg QD for 14 days followed by a 7-day break (upward titration allowed; 1 cycle = 21 days)

Combination Arm (MF patients treated with CPI-0610 in combination with ruxolitinib):

CPI-0610 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)

Phase 1 (Dose Escalation) Primary Objective:	**Phase 1 Primary Endpoint:**
To determine the maximum tolerated dose (MTD) of CPI-0610 and characterize its dose-limiting toxicities (DLTs) in patients with acute leukemia, myelodysplastic syndrome (MDS), or myelodysplastic/myeloproliferative neoplasms (MDS/MPN), and in patients with myelofibrosis (MF), when given once daily by mouth for 14 consecutive days and followed by a 7-day break	The frequency of DLTs associated with CPI-0610 administration during the first cycle (first 21 days) of treatment

Phase 1 (Dose Escalation) Secondary Objectives:	**Phase 1 Secondary Endpoints:**

To characterize the safety and tolerability of CPI-0610	Adverse events and serious adverse events; changes in hematology and clinical chemistry values; changes in the physical examination, vital signs, electrocardiogram, echocardiogram (ECHO) and Eastern Cooperative Oncology Group (ECOG) performance status
To characterize the pharmacokinetics of CPI-0610 and profile its potential metabolites	$AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, $AUC_{tau,ss}$, T_{max}, C_{max}, C_{trough}, $T_{1/2}$, Vd/F, CL/F
To characterize the pharmacodynamic effects of CPI-0610 in peripheral blood leukocytes by assessing changes in the expression of genes sensitive to BET inhibition	Post-treatment changes from baseline in the expression of *MYC* and other sensitive genes in leukemic cells by qPCR or RNA Seq Post-treatment changes from baseline in the expression of *CCR2* and six additional genes in peripheral blood mononuclear cells (PBMCs) by qPCR
To characterize the pharmacodynamic effects of CPI-0610 in leukemic cells in the bone marrow	Post-treatment changes from baseline in the expression of *MYC* and other genes that are sensitive to BET inhibition, assessed by measuring levels of their corresponding mRNA and/or protein Post-treatment changes from baseline in the expression of markers of cellular proliferation and apoptosis
To characterize any anti-leukemic, anti-MDS or anti-MDS/MPN activity associated with CPI-0610 treatment	Leukemia, MDS, MDS/MPN, and MF response as assessed by the investigator using the 2013 NCCN criteria for ALL, the 2003 Cheson criteria for AML, the 2006 modified International Working Group (IWG) criteria for MDS and MDS/MPN
Phase 2 (MF Expansion) Primary Objective:	**Phase 2 Primary Endpoint:**
To evaluate splenic response by imaging after 24 weeks of treatment	Evaluation of the reduction in spleen size from baseline by imaging (MRI or CT)after 24 weeks of treatment (Cycle 9, Day 1)
To evaluate the RBC transfusion independence rate	The rate is defined as the proportion of patients who are transfusion independent where transfusion independence is defined as absence of RBC transfusion and no hemoglobin level below 8 g/dL in the prior 12 weeks
Phase 2 (MF Expansion) Secondary Objectives:	**Phase 2 Secondary Endpoints:**
To evaluate splenic response by palpation after 24 weeks of treatment	Evaluation of the reduction in spleen size from baseline by palpation after 24 weeks of treatment (Cycle 9, Day 1)

To evaluate the duration of splenic response by imaging	Duration of the spleen response is defined as the time when splenic response criteria are first met (a ≥ 35% reduction from baseline spleen size) until the time at which an increase of ≥ 25% in spleen volume by imaging compared to baseline is documented
To evaluate the duration of splenic response by palpation	Duration of the spleen response is defined as the time when the splenic response criteria are first met (≥ 50% reduction from baseline spleen size) until the time at which an increase of ≥ 50% in spleen length by palpation compared to baseline is documented
To evaluate response categories per the revised 2013 IWG-MRT response criteria	Rate of response categories (such as CR, PR, CI, SD, PD and relapse) after 24 weeks of treatment and every 6 months thereafter based on the revised 2013 IWG-MRT response criteria
To evaluate the change in patient reported outcomes (PROs)	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 total symptom score (MFSAF) and PGIC will be described.
To evaluate the rate of RBC transfusion To evaluate the RBC transfusion dependence rate	The rate is defined as the average number of RBC units per subject-month The rate is defined as the proportion of subjects who are transfusion dependent, where transfusion dependence is defined as at least 4 units of RBC transfusions, or a hemoglobin level below 8 g/dL in the prior 8 weeks
To characterize the pharmacokinetics of CPI-0610 To characterize the effects, if any, of CPI-0610 on the PK of ruxolitinib	$AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $AUC_{tau,ss}$, T_{max}, C_{max}, C_{trough}, $T_{1/2}$, Vd/F, CL/F $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $AUC_{tau,ss}$, T_{max}, C_{max}, C_{trough}, $T_{1/2}$, Vd/F, CL/F
Phase 2 (MF Expansion) Exploratory Objectives:	**Phase 2 Exploratory Endpoints:**
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Study Population:

Phase 1 (dose escalation) eligible patients must be adults (aged ≥ 18 years) who have one of the following hematologic malignancies: acute leukemia, including acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), and acute undifferentiated or biphenotypic leukemia; chronic myelogenous leukemia (CML) in blast crisis; myelodysplastic syndrome (MDS); myelodysplastic/myeloproliferative neoplasms (MDS/MPN); or myelofibrosis (MF). They must be patients for whom effective standard treatment is not available; eligibility criteria regarding prior therapies specific for each of these diseases are described below. Phase 2 (MF expansion) eligible patients must be adults (aged ≥ 18 years) who must have primary MF or MF that has evolved from essential thrombocythemia or polycythemia vera.

As of Amendment 6, Phase 1 is complete and all new MF patients will be enrolled in Phase 2.

It is estimated that up to 114 patients will be enrolled. This is based on the observed accrual of 44 patients with acute leukemia, MDS or MDS/MPN to Phase 1 (dose escalation) of the study and on the plan for two expansion arms in Phase 2 (up to 35 patients each) in patients with MF.

Phase 1: Acute Leukemia
Patients with newly diagnosed acute leukemia should have been treated with a standard induction chemotherapeutic regimen or with another anti-leukemic agent before they are considered for participation in this study. However, patients who have newly diagnosed and previously untreated acute myelogenous leukemia may participate if the marrow contains myelodysplasia-related changes and 20-30% blasts.

Patients with relapsed or refractory acute leukemia are eligible if they are considered to not be candidates for further induction chemotherapy. Patients whose disease has relapsed 6 or more months following allogeneic stem cell transplantation are eligible, but they must not be taking more than 10 mg of prednisone (or the equivalent dose of another corticosteroid) per day or any other immunosuppressive medication.

Phase 1: CML
Patients with CML in blast crisis (a form of acute myelogenous leukemia) must have been previously treated with at least two Bcr-Abl TKIs (e.g., with imatinib, nilotinib, dasatinib, bosutinib, ponatinib) and must not be candidates for high dose chemotherapy followed by allogeneic stem cell transplantation.

Phase 1: MDS
Patients with newly diagnosed and previously untreated MDS may participate if they have intermediate, high or very high risk disease according to the revised International Prognostic Scoring System (IPSS-R). All patients with MDS that has been previously treated with a hypomethylating agent (e.g., 5-azacytidine, decitabine) and/or with an immunomodulatory agent (e.g., lenalidomide, thalidomide) are eligible.

Phase 1: MDS/MPN
Patients with MDS/MPN may participate if they have one of the following diseases: chronic myelomonocytic leukemia (CMML), atypical (Bcr-Abl negative) chronic myeloid leukemia, or MDS/MPN-unclassifiable. Patients with MDS/MPN are eligible regardless of whether they have or have not been previously treated.

Phase 1: MF
Patients with MF must have primary myelofibrosis or myelofibrosis that has evolved from essential thrombocythemia or polycythemia vera. Patients with MF may participate if they have disease that has not responded to or that is not being adequately controlled by treatment with a JAK inhibitor, disease that has progressed in spite of treatment with a JAK inhibitor, or if they are intolerant of treatment with a JAK inhibitor.

Phase 2: MF

Patients with MF must have primary myelofibrosis or myelofibrosis that has evolved from essential thrombocythemia or polycythemia vera.

- Monotherapy Arm: patients with MF may participate if they have previously been treated with a JAK inhibitor and are intolerant, resistant, refractory or lost response to the JAK inhibitor.

- Combination Arm: patients with MF may participate if they are taking ruxolitinib at the time of enrollment but have disease that is not being adequately controlled by ruxolitinib.

Study Design:

This is a Phase 1/2, multi-center, open-label, dose escalation study (Phase 1) of CPI-0610 in patients with acute leukemia, MDS, MDS/MPN or MF and expansion study (Phase 2) of CPI-0610 as a single agent and in combination with ruxolitinib (a JAK inhibitor approved for the treatment of patients with MF) in patients with MF.

In both phases of the study, CPI-0610 will be given 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 CPI-0610 is well tolerated and there is no evidence of disease progression.

Phase 1 (Dose Escalation):

NOTE: As of Amendment 6, Phase 1 is complete. A separate dose escalation was initially planned for MF patients with and without ruxolitinib. However, after a review of the safety data on CPI-0610 as monotherapy across 3 Phase 1 trials in hematological malignancies, 225 mg QD (tablet formulation) was determined to be the MTD of CPI-0610 as monotherapy. Therefore, as of Amendment 6, rather than dose escalation within cohorts, all MF patients enrolled to either the Monotherapy Arm or the Combination Arm of Phase 2 will start CPI-0610 at a dose of 125 mg QD with upward titration of their CPI-0610 dose allowed (up to a maximum dose of 225 mg QD) based on platelet count, hemoglobin levels and safety evaluation.

The CPI-0610 starting dose will be 6 mg PO once daily. However, if sufficient data is available from preceding trials of CPI-0610 in patients with lymphoma or myeloma, that data may be used to support a higher starting dose for this trial.

Increasing doses of CPI-0610 will be evaluated in successive cohorts of 3-6 patients with acute leukemia, MDS, or MDS/MPN until the MTD is determined. Dose escalation decisions and determination of the MTD will be guided by a standard "3+3 rule-based algorithm. The MTD is the highest dose that causes dose-limiting toxicity in less than 2 of 6 patients. Following three initial dose doublings, the maximal allowable increase in dose from one cohort of patients to the next will be defined by the modified Fibonacci series.

In patients with acute leukemia, MDS, or MDS/MPN, dose-limiting hematologic toxicity will be defined as the presence of CTCAE grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L) and/or grade 4 thrombocytopenia ($<25 \times 10^9$/L) in the absence of any morphologic evidence of residual disease (acute leukemia, MDS or MDS/MPN), 21 or more days after suspending dosing with CPI-0610. This definition of hematologic dose-limiting toxicity allows patients to continue to receive CPI-0610 in the face of severe peripheral cytopenias as long as the underlying disease is improving or at least not worsening.

In patients with MF, dose-limiting hematologic toxicity will be defined as grade 4 neutropenia lasting for more than 7 days, febrile neutropenia of any duration, grade 4 neutropenia resulting in the omission of more than 1, 2 or 3 of the planned 7, 14 or 21 doses in a cycle of treatment, grade 3 or greater thrombocytopenia with bleeding or any requirement for platelet transfusion, or any platelet count less than 10×10^9/L.

Dose-limiting non-hematologic toxicity will generally be defined as CTCAE grade 3 or higher adverse events and laboratory abnormalities that are considered to be unrelated to the patient's underlying hematologic malignancy, unrelated to complications of the malignancy (like infection and bleeding), and unrelated to other concurrent medications.

Phase 2 (MF Expansion):

Following completion of Phase 1 (dose escalation), the MTD of single agent CPI-0610 was defined as 225 mg QD (tablet formulation). The Phase 2 (MF expansion) portion of the study will evaluate CPI-0610 in two separate groups of patients:

Monotherapy Arm (MF patients treated with CPI-0610 alone):

- Open to patients with MF who have previously been treated with a JAK inhibitor and are intolerant, resistant, refractory or lost response to the JAK inhibitor. The initial dose of CPI-0610 will be 125 mg QD (tablet formulation). Upward titration of CPI-0610 is allowed (up to a maximum dose of 225 mg QD) based on platelet count, hemoglobin levels and safety evaluation.

Combination Arm (MF patients treated with CPI-0610 in combination with ruxolitinib):

- Open to patients with MF who are currently taking ruxolitinib but have disease that is not being adequately controlled by ruxolitinib. The initial dose of CPI-0610 will be 125 mg QD (tablet formulation) and the initial dose of ruxolitinib will be the dose on which each patient is on at the time of screening. Upward titration of CPI-0610 is allowed (up to a maximum dose of 225 mg QD) based on platelet count, hemoglobin levels and safety evaluation.

Study Duration:

Patients with acute leukemia, MDS, or MDS/MPN will have their disease assessed with peripheral blood counts and with bone marrow biopsy and aspiration at baseline, after the completion of every 2 cycles of treatment for the first 6 cycles, and thereafter following the completion of every 4 cycles of treatment.

Patients with MF will have their disease assessed with peripheral blood counts, history/documentation of transfusion requirements, measurement of spleen and liver size (by palpation and CT or MRI), MF-associated symptom scoring, extent of marrow fibrosis by bone marrow biopsy and measurement of mutated allele burden (in peripheral blood). A CT or MRI scan will be done 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. In the absence of disease progression, and if CPI-0610 treatment (or the combination of CPI-0610 plus ruxolitinib) is being well tolerated, patients may continue to receive successive cycles of treatment.

Patients experiencing disease progression will have study treatment discontinued. In Phase 1, patients experiencing dose-limiting toxicity will have therapy with CPI-0610 discontinued or, after recovery from the DLT, they may resume therapy at a lower dose of CPI-0610 if there is no evidence of disease progression.

Patients will be discontinued from the study if they withdraw consent, refuse treatment or request to stop treatment, fail to return for follow-up, begin an alternative medication, or if the investigator judges that further therapy with CPI-0610 is no longer in the patient's best interest for example, due to an adverse event, intercurrent illness, etc. Investigators also have the right to withdraw patients from the study for protocol violation or for administrative reasons.

Safety Assessments:

Safety will be assessed by monitoring adverse events (AEs), serious adverse events (SAEs), hematology and clinical chemistry values, vital signs, physical examinations, ECGs, ECHOs (Phase 1 only), ECOG performance status, and the use of concomitant medications.

Pharmacokinetic Assessments:

During the first cycle of treatment serial blood samples for the measurement of circulating concentrations of CPI-0610 will be collected before and after dosing with CPI-0610. The sampling strategy outlined in the protocol should allow characterization of CPI-0610's pharmacokinetics after the first dose as well as at steady-state, and will facilitate an estimate of CPI-0610's elimination half-life. In the Phase2 Combination Arm, it will also allow an evaluation of the pharmacokinetic profile of ruxolitinib when given in combination with CPI-0610. In Phase 1, one additional blood sample for CPI-0610 concentration determination and metabolite profiling will be collected during the first cycle of treatment at the time that an additional bone marrow aspirate and biopsy are collected (between Days 8 and 13) for pharmacodynamic assessments. In Phase 2, serial blood samples will also be collected before and after dosing with CPI-0610 when upward dose titration occurs.

CCI [redacted]

Phase 1: Pharmacodynamic Biomarker Assessments in Patients with Acute Leukemia, MDS or MDS/MPN:

Before the start of CPI-0610 administration and at selected time points during the first cycle of treatment peripheral blood, bone marrow biopsies and bone marrow aspirates will be collected in order to assess the effects of CPI-0610 on gene expression in leukemic cells and to detect corresponding phenotypic effects, such as inhibition of cellular proliferation and induction of apoptosis. Peripheral blood for these pharmacodynamic assessments will be collected at selected PK sampling time points during the first cycle of treatment, for comparison to a pre-treatment sample. A bone marrow biopsy and aspirate for pharmacodynamic assessments will be collected between Days 8 and 13 of the first cycle of treatment, for comparison with pharmacodynamic assessments made in the pre-treatment bone marrow biopsy and aspirate.

Based on studies of leukemic cell lines and freshly isolated human leukemic blasts, there are approximately 100 genes, such as *MYC* and *HEXIM1,* whose expression is expected to be affected by BET protein bromodomain inhibition. The expression of a subset of these genes in leukemic cells will be assessed using slides prepared from the bone marrow biopsies and aspirates, employing IHC for proteins and *in situ* hybridization (ISH) for mRNA. These same slides may be assessed by immunohistochemistry (IHC) for evidence of changes in leukemic cell proliferation (Ki67) and/or apoptosis (cleaved caspase 3).

Peripheral blood will be collected into PAXgene RNA tubes for the isolation of leukocyte-derived RNA. In patients without circulating leukemic cells, samples will be assessed by qPCR for changes in the expression of 7 genes, including *CCR2, CCR1* and *THBS1*, which are known to be sensitive to BET protein bromodomain inhibition. In patients with circulating leukemic cells changes in the expression of the broader set of approximately 100 genes will also be assessed. Changes in gene expression in patients with circulating leukemic cells may also be assessed in a global, unbiased manner using RNA Seq.

Phase 1: Predictive Biomarker Assessments in Patients with Acute Leukemia, MDS or MDS/MPN:

In patients with acute leukemia, MDS or MDS/MPN the bone marrow aspirates and accompanying blood samples obtained before the start of treatment and between Days 8 and 13 of the first cycle of treatment will be processed to isolate leukemic cells and to extract from those cells both DNA and RNA. Leukemic cells will be isolated from the marrow aspirates using antibodies directed against specific surface antigens (e.g., CD33 in myeloid leukemia) coupled to magnetic particles. The DNA and RNA will then potentially be

sequenced in order to provide initial hypotheses regarding mutations or patterns of gene expression associated with response or resistance to CPI-0610.

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Phase 2: Pharmacodynamic Biomarker Assessments in Patients with MF:
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 myelofibrosis 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 CCI [redacted] Bone marrow biopsy samples will be collected pre and post treatment for grading of bone marrow fibrosis and for exploratory assessment CCI [redacted]

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

Efficacy Assessments:

Phase 1: Efficacy assessments in patients with acute leukemia, MDS or MDS/MPN

Response assessment in Phase 1 (patients with acute leukemia, MDS or MDS/MPN) will rely primarily on the evaluation of peripheral blood counts, bone marrow biopsies and bone marrow aspirates. Other assessments (e.g., spinal fluid cytology, radiographic imaging studies) may be required in some patients to assess sites of potential extramedullary disease. Categorization of response will be determined by the investigator. The criteria used to assess response will include the 2013 National Comprehensive Cancer Network (NCCN) criteria for ALL, the 2003 Cheson criteria for AML, and the 2006 modified IWG criteria for MDS and MDS/MPN.

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 and liver size (by palpation and CT or MRI), extent of fibrosis (with bone marrow biopsy) and of changes in mutated allele burden (in peripheral blood). Disease response including splenic response, change in PROs, RBC transfusion status and response as assessed by the investigator following the 2013 revised IWG-MRT criteria will be evaluated. Peripheral blood will also be used to monitor for conversion to AML.

Statistical Methods:
Phase 1 (dose escalation)

In Phase 1 (dose escalation), the statistical methods employed will be primarily descriptive. Determination of the MTD of CPI-0610 will be achieved using a standard deterministic algorithm, commonly described as the "3+3 design" in conjunction with a modified Fibonacci dose escalation scheme.

Phase 2 (MF expansion)

In Phase 2 (MF expansion), two separate groups of patients will be evaluated: Monotherapy Arm (MF patients treated with CPI-0610 alone) and Combination Arm (MF patients treated with CPI-0610 in combination with ruxolitinib). The primary endpoint is splenic response via imaging after 24 weeks of treatment or for patients who are transfusion dependent, the transfusion independence rate. Since the appropriate reduction in spleen volume to define splenic response or the approximate transfusion independence rate is not clear for the patient population being enrolled in this study, the analysis of splenic response and transfusion independence will be primarily descriptive. However, a Simon's two-stage design will be used for each arm to allow the possibility of early stopping for futility. For the purpose of the two-stage design, a response will be defined as a ≥35% reduction from baseline spleen size by imaging (MRI or CT) or conversion from RBC transfusion dependent to independent (see definitions in Section 7.2.4.3) The null hypothesis that the true response rate is 6% will be tested against a one-sided alternative. The null rate of 6% is based on the splenic response rate seen in the best alternative therapy arm of the Phase 3 SIMPLIFY-2 trial. In the first stage, 17 patients will be accrued in each arm. If there are 1 or fewer responses in these 17 patients, that arm will be stopped. Otherwise, 18 additional patients will be accrued for a total of 35 in each arm. The null hypothesis will be rejected for a given arm if 5 or more responses are observed in 35 patients. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 20%. If an arm is stopped after Stage 1, the sample size (n=17) is still adequate for descriptive analyses of splenic response. This data will be used to design subsequent trials.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT (SGOT)	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
APL	acute promyelocytic leukemia
aPTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase
AUC	area under the curve
BET	bromodomain and extra-terminal
BAT	best alternative therapy
BID	twice daily
BUN	blood urea nitrogen
CBC	complete blood count
ChIP	chromatin immunoprecipitation
CL	Clearance
C_{max}	maximum concentration
CML	chronic myeloid leukemia
CMML	chronic myelomonocytic leukemia
CNS	central nervous system
CR	complete response/remission
CrCl	creatinine clearance
CRi	complete response/remission with blood count recovery
CRO	contract research organization
CRu	complete response, unconfirmed
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
cTn	cardiac troponin
CYP	cytochrome P450
DFS	disease-free survival
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid

EC_{50}	50% effective concentration
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRCL	estimated creatinine clearance (by the Cockcroft-Gault formula)
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study (visit)
EOT	End of Treatment (visit)
FAB	French-American-British
FDA	Food and Drug Administration
FISH	fluorescent *in situ* hybridization
GCP	Good Clinical Practice
GI	Gastrointestinal
GI_{50}	concentration producing 50% inhibition of growth
GLP	Good Laboratory Practice
HCT	hematopoietic cell transplantation
HDPE	high density polyethylene
Hgb	Hemoglobin
HI	hematologic improvement
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HPMC	hydroxypropyl methyl cellulose
HSC	hematopoietic stem cells
IC_{50}	50% inhibitory concentration
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	Immunohistochemistry
IL-6	interleukin-6
IPSS-R	revised International Prognostic Scoring System
IRB	institutional review board
ISH	*in situ* hybridization
IWG	International Working group
KO	Knockout
LDH	lactate dehydrogenase

LFTs	liver function tests
LPS	Lipopolysaccharide
LVEF	left ventricular ejection fraction
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MEFs	murine embryonic fibroblasts
MF	Myelofibrosis
MFSAF v.4.0	Myelofibrosis Symptom Assessment Form Version 4.0
MPN	myeloproliferative neoplasm
MRC	Medical Research Council
mRNA	messenger ribonucleic acid
MT-1	melatonin type 1 receptor
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOAEL	no-observed-adverse effect level
NR	no response
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PO	Orally
PR	partial response/remission
PROs	patient reported outcomes
PRBCs	packed red blood cells
PT	prothrombin time
QD	once daily
RBC	red blood cell
Rel	relapse
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose

SAEs	serious adverse events
shRNA	small hairpin ribonucleic acid
SPD	sum of the product of the greatest perpendicular diameters
STD_{10}	severely toxic dose for 10% of the animals
SUSARs	suspected unexpected serious adverse reactions
$T_{1/2}$	elimination half-life
TGI	tumor growth inhibition
TLH	trilineage hematopoiesis
T_{max}	time to maximum concentration
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
URL	upper reference limit
WBC	white blood count
WHO	World Health Organization
β-hCG	beta-human chorionic gonadotropin

NOTE: As of Amendment 6, Phase 1 is complete and all new patients will be enrolled in Phase 2.

1 INTRODUCTION

1.1 BET proteins in oncology

1.1.1 Introduction

The BET (bromodomain and extra-terminal) family of proteins has four members: BRD2, BRD3, BRD4, and BRDT. Each member contains two bromodomains, designated BD1 and BD2. Bromodomains are small binding pockets that engage acetylated lysine residues on the tails of histones. The BET proteins bind to chromatin through their bromodomains and are involved in regulating the expression of set of genes, several of which are involved in cancer and/or inflammation. For example, BET proteins facilitate the expression of *MYC* and *BCL-2*, two oncogenes implicated in the pathogenesis of a wide range of human malignancies. BET proteins are also involved in regulating the expression of a subset of NF-κB-dependent genes that play roles in both inflammation and some malignancies.

1.1.2 BET protein regulation of gene transcription

The mechanism whereby BET proteins regulate gene expression has been best described for BRD4.[1] Following the exposure of innate immune cells to various inflammatory stimuli NF-κB is released from Iκβα in the cytosol and then translocates to the nucleus. In the nucleus NF-κB binds near the promoter of the genes it regulates and recruits to the same region other proteins that acetylate lysine residues on histones H3 and H4. BRD4 then binds to these acetylated lysine residues and recruits P-TEFb, which phosphorylates and thereby activates RNA polymerase II to support transcript elongation. BRD4 therefore provides a "scaffolding" function for the assembly of the transcriptional machinery. This same scaffolding function has now been described by several groups for BRD4's regulation of *MYC* transcription in leukemia, lymphoma and myeloma cell lines.[2-4] In myeloma and lymphoma cell lines where *MYC* is translocated to an IgH enhancer, chromatin immunoprecipitation (ChIP) experiments demonstrate the release of BRD4 from regions proximal to the transcription start site with the coincident loss of proteins (like CDK9) that form transcriptional complexes.

Given the broad distribution of BET proteins across the genome it could be expected that interference with the binding of BET proteins to chromatin would have widespread effects on gene transcription. While BET protein knock-down and knock-out indeed have widespread effects on gene transcription, interference with BET protein binding to chromatin using small molecule inhibitors of their bromodomains has more circumscribed and selective effects. For example, BET protein knock-down prevents the production of both interleukin-6 (IL-6) and TNF-α by dendritic macrophages after exposure to lipopolysaccharide (LPS), but antagonism of BET protein binding to chromatin with a small molecule inhibitor affects only the production of IL-6; TNF-α is unaffected.[5] Moreover, the number of genes up- or down-regulated 2-fold or more by prototypic BET bromodomain inhibitors is far smaller than the number of genes that display BET protein occupancy as determined by chromatin binding studies.[3-6]

1.1.3 BET proteins in oncology: midline carcinoma

A potential role for small molecule BET protein inhibition in oncology therapeutics was described by Filippakopoulos and colleagues in midline carcinoma.[7] This exceedingly rare solid tumor occurs mainly in children and adolescents and is known to be the result of translocations that create either a BRD4- or BRD3-NUT fusion protein. Using JQ1, a small molecule BET bromodomain inhibitor related to compounds discovered by Mitsubishi Tanabe in an empiric screen for new anti-inflammatory chemical matter, these investigators demonstrated that midline carcinoma cells are sensitive to BET inhibition both *in vitro* and *in vivo*, with the principal effect being their terminal squamous differentiation. This effect of JQ1 is due to its ability to bind to the bromodomains of BET proteins and antagonize their interaction with acetylated lysine residues on histones; indeed, an enantiomer of JQ1 without the ability to bind to BET bromodomains had no activity. However, a broader role for BET inhibition in oncology was not obvious until the results of more empiric studies became available.

1.1.4 BET proteins in oncology: hematologic malignancies

Zuber and colleagues[8] discovered a connection between BRD4 and leukemogenesis as the result of screening a library of small hairpin RNAs (shRNAs). The library was focused against 243 known chromatin regulators, i.e., against the 'writers', 'erasers', and 'readers' of epigenetic marks. The model screened was a murine model of acute myeloid leukemia (AML) driven by MLL-AF9 and $Nras^{G12D}$, chosen in the light of previous studies indicating that AML1-ETO and MLL fusion proteins induce self-renewal programs in part through reprogramming of epigenetic pathways. Several shRNAs against *Brd4* had the strongest effects in this screen, and there was good correspondence between knockdown efficiency and growth inhibition. shRNAs against *Brd4* also induced cell-cycle arrest in two human MLL-$AF9^{+}$ AML lines. The potential selectivity of *Brd4* for leukemia cell viability was suggested by a lack of phenotypic consequences from *Brd4* knockdown in immortalized murine embryonic fibroblasts (MEFs) and in non-transformed (G1E) erythroblasts. It should be noted that *Brd4* is neither mutated nor over-expressed in most malignancies, but this study and others have demonstrated that maintenance of the malignant phenotype can be dependent on *Brd4*.

Zuber and other investigators[2-4] evaluated the activity of small molecule inhibitors of BET proteins in preclinical models of acute leukemia, myeloma and lymphoma. While the initial screen of Zuber and colleagues identified *Brd4* as the critical target, small molecule inhibitors of BET protein bromodomains do not discriminate between the four BET family members. This is because the bromodomains of these proteins have very similar structures. As anticipated, small molecule inhibitors of BET bromodomains proved to be broadly active in cell lines and xenograft models of all three groups of hematologic malignancies. No specific genetic or molecular feature of these models has yet been shown to be predictive of a tumor's sensitivity to BET inhibition, although it is likely that dependence of a tumor on *MYC* expression is one determinant of sensitivity. Importantly, anti-tumor activity in *in vivo* models can be achieved at well tolerated doses.

1.1.5 BET proteins in oncology: the central role of *MYC*

Three groups[2-4] have now independently confirmed the dominant role that inhibition of *MYC* transcription plays in mediating the phenotypic effects of BET inhibition. Following exposure of leukemia, myeloma or lymphoma cells to a small molecule BET inhibitor (e.g., JQ1, IBET) there is a rapid decrease in *MYC* mRNA. Maximal inhibition of transcription is achieved within approximately 4 hours, and is accompanied by decreases in the level of MYC protein. Following drug washout *MYC* transcription is rapidly restored to baseline levels. The tumor suppressor gene, p21, is known to be tightly regulated by *MYC*, and as *MYC* transcription is inhibited there is a concomitant and marked increase in the transcription of p21. Evaluation of whole genome expression profiles before and at 4 hours following exposure to JQ1 demonstrates that the genes affected are primarily *MYC* and *MYC* target genes. The importance of *MYC* suppression to the phenotypic effects observed has been supported by experiments in which cells are transduced with a doxycycline-inducible *MYC* expression construct that is resistant to the effects of BET bromodomain inhibition. The addition of doxycycline to these transduced cells largely prevents JQ1-induced G1 arrest, and it also prevents the transcriptional deregulation of genes (like *p21*) know to be downstream targets of *MYC*. Importantly, small molecule inhibitors of BET proteins can suppress the expression of *MYC* in the context of translocation, amplification, or when the gene is structurally normal.

While effects on *MYC* transcription therefore have a dominant effect in many malignant cells, it is clear that effects on the transcription of other genes may play a role as well. For example, BET inhibition reduces the expression of *BCL-2*, potentially via the association of BRD2 and BRD4 with a *BCL-2* enhancer. Overexpression of *BCL-2* was able to block the phenotypic effects of BET inhibition in a mixed lineage leukemia cell line.

1.1.6 Role of *MYC* in normal tissues

While the initial *in vivo* studies with JQ1 and IBET suggest that tumors may be more susceptible to the effects of small molecule BET inhibition than normal tissues, it is expected that BET inhibition will suppress the expression of *MYC* in normal tissues. Hence studies of the inhibition of *MYC* expression in normal tissues may anticipate some of the toxicities that will be observed with BET inhibition. Studies of whole body *MYC* knock-out mice are not very informative, since mouse embryos do not survive beyond day ten.[9-11] The potential consequences of *MYC* suppression in the adult are therefore better anticipated from studies investigating postnatal conditional overexpression of a dominant mutant form of *MYC* or of conditional and tissue-selective *MYC* knock-out.

One study assessed the effects of whole body suppression of *MYC* expression in mice using a dominant mutant form of *MYC*, known as Omomyc.[12] Omomyc homodimerizes with all three Myc proteins (c-Myc, N-Myc and L-Myc), but Myc-Omomyc heterodimers cannot interact with Max, which is required for *MYC*-driven gene transcription. As expected, the effects of Omomyc expression were restricted to proliferating tissues, i.e., to the skin, gastrointestinal epithelium, bone marrow and testis. Organs with low proliferative indices (e.g., pancreas, kidney, liver, heart and lung) were unaffected. In spite of these effects on proliferating tissues the mice retained normal body weight and blood chemistry values. Upon withdrawal of tetracycline

(which forces the expression of Omomyc) all of these histopathologic effects were completely reversed within 4-14 days.

Deletion of *c-Myc* alone results in severe bone marrow hypocellularity and pancytopenia.[13] Hematopoietic stem cells (HSCs) survive and maintain the capacity for self-renewal, but fail to give rise to more differentiated progenitor cells. The survival of the HSCs is attributable to the remaining expression of *N-Myc*: when both *c-Myc* and *N-Myc* are deleted, both differentiated hematopoietic progenitors and HSCs are lost.[14]

The effects of conditional *c-Myc* knockout (KO) in the skin of mice have also been described,[15] and are also more severe than those described in the Omomyc model. Deletion of *c-Myc* in the skin resulted in tight, fragile skin that easily tore with mechanical friction and displayed impaired wound healing. The epidermis was thinner, with a loss of cellularity and the appearance of early markers of differentiation in the basal (proliferative) layer.

Consistent with the idea that *MYC* is more important in rapidly proliferating tissues, conditional knockout of *c-Myc* in the liver was found to have no effect during the postnatal period on normal liver growth, restoration of liver mass following partial hepatectomy, or recovery from fasting.[16]

1.1.7 Summary

Small molecule inhibition of BET bromodomain binding to chromatin represents a novel approach to cancer treatment. Rather than affecting an upstream signaling pathway (as do many protein kinase inhibitors) it inhibits the transcription of a small set of genes that integrate a diverse array of abnormal signals. The most important of these genes appears to be *MYC*, although it is likely that the transcription of other genes, like *BCL-2*, is also important for its anti-tumor activity. To date the published data support the idea that BET bromodomain inhibition may be broadly active in hematologic malignancies, although identifying the most sensitive of these malignancies remains a challenge for future investigation.

While the preclinical investigations of BET inhibition suggest that efficacy can be achieved with good tolerability, in light of the effects on *MYC* expression it is expected that BET inhibition may be associated with reversible toxicity in rapidly proliferating tissues like the gut, bone marrow, skin and testes. Moreover, since BET inhibition affects the transcription of genes other than *MYC*, it is possible that additional toxicities will be identified.

1.2 CPI-0610

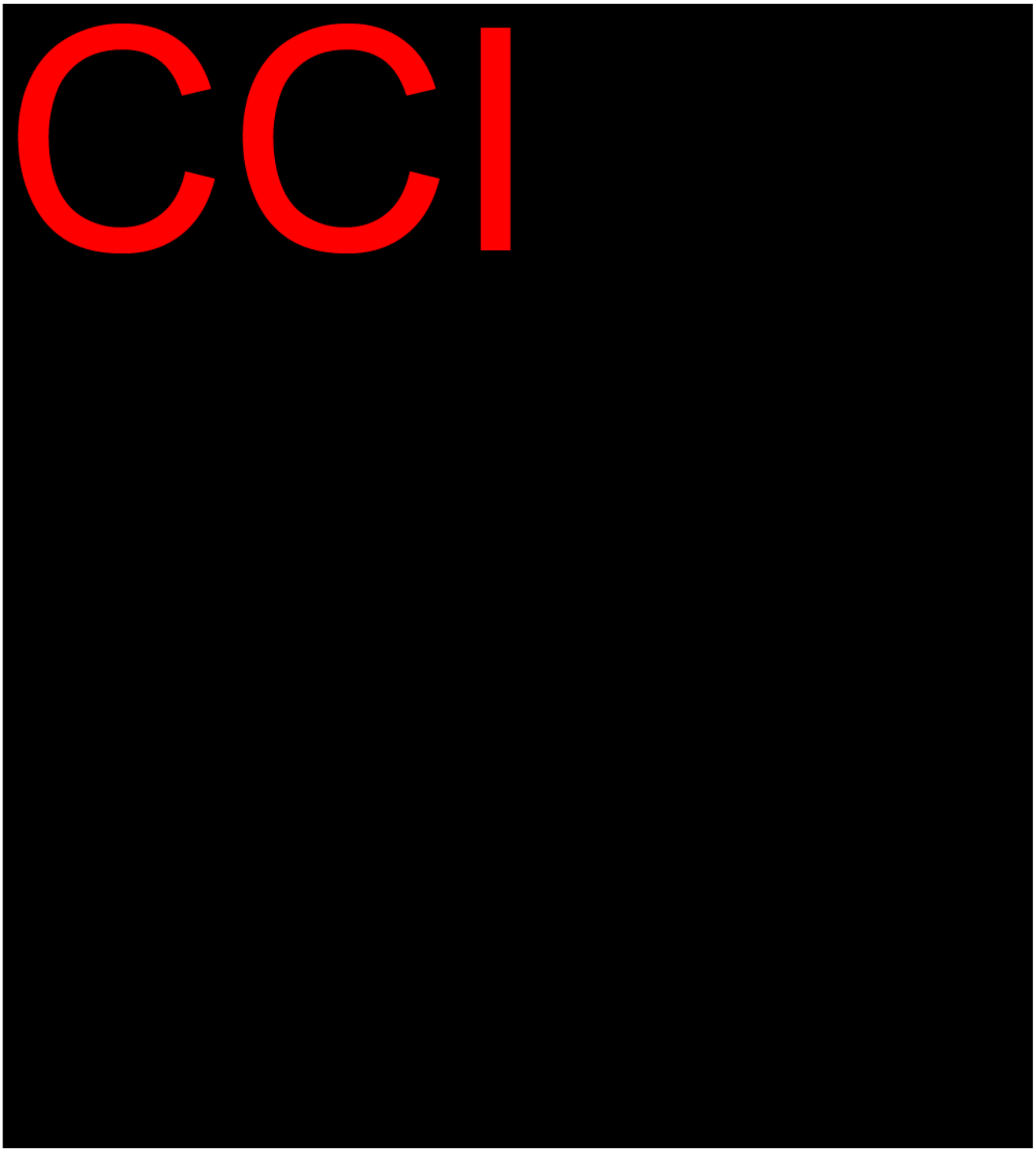
1.2.1 Description

CPI-0610 is small molecule inhibitor of BET protein bromodomains. CPI-0610 has a molecular weight of 365.81 g/mol. CCI [redacted]

CCI

The following sections summarize the preclinical data for CPI-0610. Additional details are available in the Investigator's Brochure.

1.2.2 Nonclinical information

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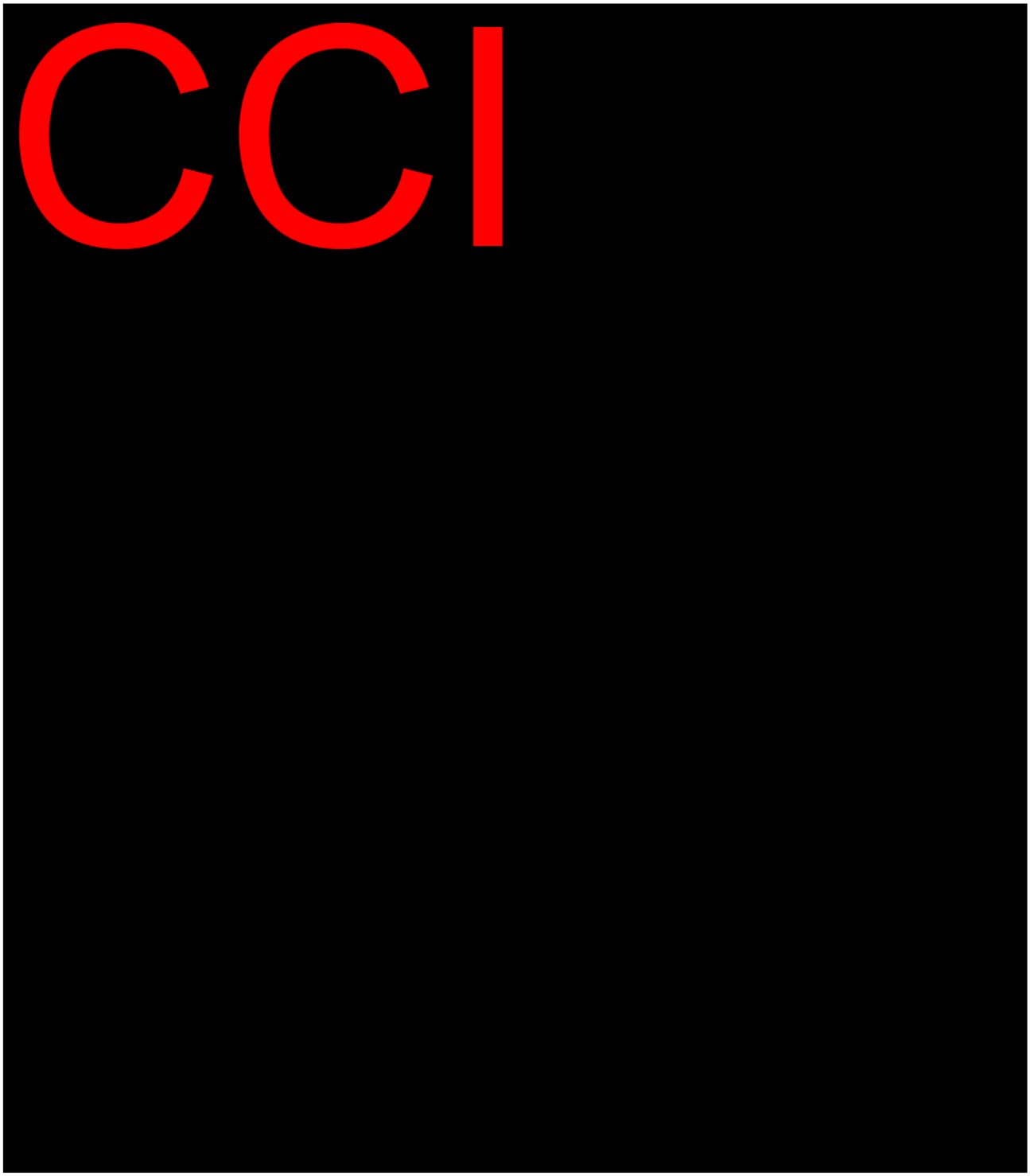


1.3 Study rationale

1.3.1 Acute leukemia, MDS or MDS/MPN

The treatment of patients with AML has not significantly changed since the development of induction therapy with cytosine arabinoside and an anthracycline nearly 40 years ago. Acute

promyelocytic leukemia (APL) is the one exception to this general statement, and in this form of AML > 75% of patients are cured with a combination of anthracycline-based chemotherapy, all-trans retinoic acid, and arsenic trioxide. Unfortunately for all other subtypes of AML the outcome of treatment remains poor. Although initial induction chemotherapy produces complete remission in 70-80% of patients < 60 years of age, almost all patients experience disease relapse and overall survival at 5 years is 40-50%.[18,19] In patients > 60 years of age with a good performance status the rate of complete remission is only 40-50%, cure rates are < 10%, and median survival is < 1 year.[20,21] High dose chemotherapy with allogeneic stem cell transplantation is an option for a small proportion of patients, but its application is limited to patients for whom appropriately HLA-matched donors can be identified and who are sufficiently fit to withstand both the acute toxicities of this treatment and its long term effects, including graft versus host disease.

In contrast to AML, significant advances have been made in the treatment of chronic myeloid leukemia (CML) with the introduction of small molecule inhibitors of the bcr-abl fusion kinase that is typically the sole molecular abnormality at the time of initial diagnosis. Nevertheless, over time resistance to these drugs emerges in a small proportion of patients, and the disease may evolve into a form of AML, called CML in blast crisis. Some patients will develop leukemic blasts that have lymphoid characteristics, and these patients may transiently benefit from chemotherapy with vincristine and prednisone-based chemotherapy.

While the treatment of children with acute lymphoblastic leukemia (ALL) is one of the successes in the development of cytotoxic chemotherapy, adults with ALL have outcomes similar to those of adults with AML. Initial induction chemotherapy, based on regimens that contain vincristine, prednisone, and an anthracycline as well as other agents, achieves a complete remission in approximately 80% of patients. But after further consolidation and maintenance chemotherapy less than half of these patients will have long-term leukemia-free survival, and the majority of adults with ALL will ultimately relapse. For example, in the Medical Research Council (MRC)/Eastern Cooperative Oncology Group (ECOG) UKALL12/ECOG2993 study of 609 adults with ALL, the rates of five-year overall survival (OS) were 38 and 7 percent in those with newly diagnosed or relapsed ALL, respectively.[22] However, allogeneic hematopoietic cell transplantation (HCT) after initial cytoreduction or in second CR offers a chance of cure in a small, highly selected group of patients.[23]

Myelodysplastic syndrome (MDS) is a term used to describe a heterogeneous group of diseases characterized by inadequate production of red cells, neutrophils, and platelets by a bone marrow whose precursors of these mature cells bear dysplastic features (megaloblatosis in normoblasts; ringed sideroblasts; pseudo-Pelger-Huet abnormality in neutrophils; micromegakaryocytes, hypogranular or giant platelets in the blood). MDS has a propensity to evolve into AML, and it is common even in absence of frank leukemia to find increased numbers of myeloblasts in the bone marrow. Many of these patients can be managed with transfusion support, erythropoietin and antibiotics, but as the number of blasts increases and peripheral cytopenias worsen more aggressive treatments are used. Patients with an uncommon form of MDS characterized by loss of the long arm of chromosome 5 (5 q- syndrome) often experience hematologic improvement following treatment with lenalidomide, an immunomodulating agent. However, the cytotoxic demethylating agents 5-azacytidine and decitabine are currently the two most common drugs used to treat patients with more advanced forms of MDS. While improvement in peripheral

blood counts is common with these agents, complete remission occurs in 10% or fewer cases[24-27]; their impact on long term outcomes is therefore limited.

There are also a number of myeloid diseases that may have both proliferative and dysplastic features. These diseases can be difficult to categorize, and are simply described as MDS/myeloproliferative neoplasm- (MPN-) unclassifiable. However, some forms of MDS/MPN are more readily recognized, e.g., chronic myelomonocytic leukemia (CMML) and atypical (Bcr-Abl negative) chronic myeloid leukemia. These diseases also tend to evolve into acute myeloid leukemia, and are poorly served by currently available therapies.

Several groups, including investigators at Constellation Pharmaceuticals, have now reported that small molecule inhibitors of BET bromodomains are effective in preclinical models of acute leukemia as well as in models of lymphoma and myeloma. In addition to having activity against human leukemia cell lines grown in tissue culture, these studies have shown BET inhibitors to be effective in murine models of leukemia, in human leukemia xenografts in mice, and against leukemia cells isolated from the peripheral blood or bone marrow of patients and grown *ex vivo* for several days. These studies have been remarkably consistent in demonstrating the high sensitivity of leukemic cells to BET inhibitors and in demonstrating that a major component of this sensitivity is related to the suppression of *MYC* transcription.

1.3.2 Myelofibrosis

Myelofibrosis (MF) is a clonal myeloproliferative disease. It shares many of the characteristics of the other myeloproliferative diseases (essential thrombocythemia and polycythemia vera), but is characterized by more exaggerated abnormalities in megakaryocytes[28] 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.[29] 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 JAK inhibitors have activity in this disease. In addition, approximately 50% of patients with MF have activating mutations in JAK2.[30,31] Regardless of the JAK2 mutational status of patients, it is thought that patients with myelofibrosis have deregulated JAK-STAT signaling, which is why they respond to JAK inhibitor therapy regardless of their mutational status.

While JAK inhibition is useful in the management of patients with MF, its efficacy is limited. The only JAK inhibitor currently approved for use in patients with MF is ruxolitinib.[32-38] In Phase III 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. And 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. 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. However, recent analysis of 5-year survival from a registrational Phase III study suggests that there may be a survival advantage associated with ruxolitinib treatment when compared to best available therapy.[39-40] 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. Hence there remains a need for better treatments for MF.

BET bromodomain inhibition has the potential to be an effective treatment for patients with MF because its effects on gene transcription intersect with the mechanisms that drive this disease. It is now clear that CPI-0610 and other BET inhibitors have significant anti-megakaryocytic effects. The principal toxicity of treatment with CPI-0610 is reversible thrombocytopenia, and mild (CTCAE Grade 2) thrombocytopenia is observed at doses of CPI-0610 that are relatively low and devoid of any other toxicity. In preclinical models where human stem cells are differentiated *ex vivo* into megakaryocytes, megakaryocyte differentiation is inhibited at relatively low concentrations of CPI-0610, and at concentrations that correlate with those where thrombocytopenia is observed in patients. BET bromodomain inhibitors were initially discovered through phenotypic screens for novel anti-inflammatory agents, and it was subsequently shown that their anti-inflammatory effects result from their ability to inhibit the transcription of a subset of NF-κB-dependent cytokines, like IL-6. Hence BET inhibition, like JAK inhibition, may alleviate the constitutional symptoms that are part of this disease. Finally, BET bromodomain inhibition can block the TGF-beta-induced secretion of collagen by fibroblasts, raising the possibility of eventually ameliorating the marrow fibrosis that is part of this disease.

1.3.3 Rationale for Selection of MF for Phase 2 (MF Expansion)

In light of the lack of efficacy in the acute leukemia, MDS or MDS/MPN populations, the need for novel treatment strategies for patients with MF, the initial clinical activity reported with CPI-0610 in MF and the safety profile of CPI-0610 (as described in Section 1.3.4), the MF population was chosen for further evaluation in Phase 2 (MF expansion) of the present study (Study 0610-02).

The rationale for BET inhibition with CPI-0610 as monotherapy in patients with MF is provided in Section 1.3.2. 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 practically 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 CPI-0610 as a single agent therapy in patients with MF (Monotherapy Arm), this study separately evaluates CPI-0610 given in combination with ruxolitinib (Combination Arm).

CPI-0610 is anticipated to have effects in the treatment of MF that are complementary to those of ruxolitinib. CPI-0610 is expected to suppress the expression of a subset of NF-κB-dependent cytokines, and may thereby augment the suppression of cytokines achieved with ruxolitinib. CPI-0610 also has a direct effect on megakaryocyte differentiation and proliferation, and hence may further suppress abnormal cytokine production.

As of Amendment 5 (Version 6) of Study 0610-02, the plan was to conduct separate dose escalations for patients with MF on CPI-0610 as monotherapy, and on CPI-0610 in combination with ruxolitinib. However, after a review of the safety data on CPI-0610 as monotherapy across 3 Phase 1 trials in hematological malignancies (described in Section 1.3.4), 225 mg QD (tablet formulation) was determined to be the maximum tolerated dose (MTD) of CPI-0610 as monotherapy. Therefore, as of Amendment 6 (Version 7) of Study 0610-02, all patients enrolled to either the Monotherapy Arm or the Combination Arm of Phase 2 (CPI-0610 in combination with ruxolitinib), will start CPI-0610 at a dose of 125 mg QD (see Section 5.6.1.2 for rationale of starting dose). Rather than dose escalation within cohorts, patients will be allowed to undergo upward titration (see Section 5.7.1) of their CPI-0610 dose based on platelet count, hemoglobin levels and safety evaluation. The maximum dose permitted must not exceed 225 mg QD. This is similar to the approach used in clinical practice with ruxolitinib.

1.3.4 Clinical Development of CPI-0610

As of 27 June 2017, single-agent CPI-0610 has been studied in 138 patients in 3 Phase 1 clinical trials in hematologic malignancies (Table 1-2).

Table 1-2 Clinical Studies with CPI-0610

Study	# of Patients	Indication
0610-01	64	Lymphoma
0610-02	44	Acute hematologic malignancies (AML, MDS, MDS/MPN, MF*)
0610-03	30	Multiple myeloma
*No MF patients were enrolled as of 27 June 2017		

1.3.4.1 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 three Phase 1 studies evaluated escalating doses of CPI-0610 when administered in treatment cycles comprised of a 14-day treatment period and a 7-day off-treatment period. CPI-0610 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 CPI-0610 at higher gastric pH and thereby increase bioavailability, particularly at higher doses of CPI-0610.

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 1.3.4.2).

CPI-0610 had a similar safety profile in all of these indications. In all three Phase 1 studies, hematologic changes and gastrointestinal adverse events were reported with the highest

frequencies, and also with the highest incidence of treatment-related adverse events (TRAEs) and CTCAE grade 3 or higher adverse events that were considered related to study drug.

Thrombocytopenia was the most common TRAE, reported in 32% of the 138 patients treated in the three Phase 1 clinical studies. There was a lower frequency reported in patients with leukemia and the other hematologic malignancies evaluated in Study 0610-02 (14%) 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 (21 of 44 patients) had thrombocytopenia of CTCAE grade 3 or higher (15% of the 138 patients treated in the three Phase 1 studies). The thrombocytopenia reported was dose-dependent (increasing in incidence and severity with CPI-0610 exposure), reversible, and non-cumulative. An additional week off treatment prior to initiation of the subsequent treatment cycle was needed for platelet recovery for some patients.

Anemia, neutropenia (including neutrophil count decreased) and lymphocyte count decreased were the other commonly reported treatment-related hematologic changes; they also had a higher incidence of CTCAE grade 3 or greater TRAEs. The incidence of treatment-related anemia, neutropenia and lymphocyte count decreased was 12%, 9% and 7%, respectively, across the three clinical studies. These hematologic events did not have a clear dose response. Of all the hematologic changes reported in the three clinical studies, only one case of febrile neutropenia in Study 0610-01 was reported as a treatment-related serious adverse event (SAE).

The treatment-related gastrointestinal adverse events reported with the greatest frequency were nausea, diarrhea and vomiting, with incidences of 27%, 19% and 17%, respectively, across the three clinical studies. The majority of these gastrointestinal events were of low severity. Diarrhea, vomiting and nausea were the only serious adverse events that were considered to be related to study drug in more than one patient (5, 3 and 2 patients, respectively).

The other frequently reported treatment-related adverse events were fatigue (25%), decreased appetite (20%), and dysguesia (14%), most of which were of low severity.

1.3.4.2 Clinical Safety of Study 0610-02 Phase 1 (Dose Escalation)

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 toxicities (DLT). 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 hyperbilrubinemia. 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.

1.3.4.3 Clinical Pharmacokinetics

The pharmacokinetic profile of CPI-0610 when administered once daily has been fairly consistent across the three Phase 1 clinical studies. Maximum exposure of CPI-0610 following tablet administration is achieved within 1-5 hours. The exposure (C_{max} and AUC) achieved following a single 225 mg dose in tablet form was 2021 ng/mL and 19,342 ng·hr/mL, respectively. The half-life was approximately 16 hours, supporting once daily dosing.

1.3.4.4 Clinical Efficacy

In Study 0610-01, five patients have achieved an objective response to CPI-0610. One patient with T-cell and histiocyte-rich large B cell lymphoma, three patients with diffuse large B-cell lymphoma (DLBCL) and one 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.

2 STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 2-1 and Table 2-2.

Table 2-1 Phase 1 (Dose Escalation): Study objectives and endpoints

	Objective	Endpoint
Primary	To determine the maximum tolerated dose (MTD) of CPI-0610 and characterize its dose-limiting toxicities (DLTs) in patients with acute leukemia, myelodysplastic syndrome (MDS), or myelodysplastic/myeloproliferative neoplasms (MDS/MPN), and in patients with myelofibrosis (MF), when given once daily by mouth for 14 consecutive days and followed by a 7-day break	The frequency of DLTs associated with CPI-0610 administration during the first cycle (first 21 days) of treatment
Secondary	To characterize the safety and tolerability of CPI-0610	Adverse events and serious adverse events, changes in hematology and clinical chemistry values; changes in the physical examination, vital signs, ECG, echocardiogram (ECHO) and ECOG performance status
	To characterize the pharmacokinetics of CPI-0610 and profile its potential metabolites	$AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, $AUC_{tau,ss}$, T_{max}, C_{max}, $T_{1/2}$, Vd/F, CL/F
	To characterize the pharmacodynamic effects of CPI-0610 in peripheral blood leukocytes by assessing changes in the expression of genes sensitive to BET inhibition	Post-treatment changes from baseline in the expression of *MYC* and other sensitive genes in leukemic cells by qPCR or RNA Seq Post-treatment changes from baseline in the expression of *CCR2* and six additional genes in peripheral blood mononuclear cells (PBMCs) by qPCR
	To characterize the pharmacodynamic effects of CPI-0610 in leukemic cells in the bone marrow	Post-treatment changes from baseline in expression of *MYC* and other genes that are sensitive to BET inhibition, assessed by measuring levels of their corresponding mRNA and/or protein Post-treatment changes from baseline in the expression of markers of cellular proliferation and apoptosis

	Objective	Endpoint
	To characterize any anti-leukemic, anti-MDS, anti-MDS/MPN activity associated with CPI-0610 treatment	Leukemia, MDS and MDS/MPN response as assessed by the investigator using the 2013 NCCN criteria for ALL, the 2003 Cheson criteria for AML, the 2006 modified International Working Group (IWG) criteria for MDS and MDS/MPN
Exploratory		

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

Table 2-2 Phase 2 (MF Expansion): Study objectives and endpoints

	Objectives	Endpoints
Primary	To evaluate splenic response by imaging after 24 weeks of treatment	Evaluation of the reduction in spleen size from baseline by imaging (MRI or CT) after 24 weeks of treatment (Cycle 9, Day 1)
	To evaluate the RBC transfusion independence rate	The rate is defined as the proportion of patients who are transfusion independent where transfusion independence is defined as absence of RBC transfusion and no hemoglobin level below 8 g/dL in the prior 12 weeks
Secondary	To evaluate splenic response by palpation after 24 weeks of treatment	Evaluation of the reduction in spleen size from baseline by palpation after 24 weeks of treatment (Cycle 9, Day 1)
	To evaluate the duration of splenic response by imaging	Duration of the spleen response is defined as the time when splenic response criteria are first met (a ≥ 35% reduction from baseline spleen size) until the time at which an increase of ≥ 25% in spleen volume by imaging compared to baseline is documented
	To evaluate the duration of splenic response by palpation	Duration of the spleen response is defined as the time when the splenic response criteria are first met (≥ 50% reduction from baseline spleen size) until the time at which an increase of ≥ 50% in spleen length by palpation compared to baseline is documented
	To evaluate response categories per the revised 2013 IWG-MRT response criteria	Rate of response categories (such as CR, PR, CI, SD, PD and relapse) after 24 weeks of treatment and every 6 months thereafter based on the revised 2013 IWG-MRT response criteria
	To evaluate the change in patient reported outcomes (PROs)	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 total symptom score (MFSAF) and PGIC will be described.

	Objectives	Endpoints
	To evaluate rate of RBC transfusion	The rate is defined as the average number of RBC units per subject-month
	To evaluate the RBC transfusion dependence rate	The rate is defined as the proportion of subjects who are transfusion dependent where transfusion dependence is defined as at least 4 units of RBC transfusions, or a hemoglobin level below 8 g/dL in the prior 8 weeks
	To characterize the pharmacokinetics of CPI-0610	$AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, $AUC_{tau,ss}$, T_{max}, C_{max}, C_{trough}, $T_{1/2}$, Vd/F, CL/F
	To characterize the effects, if any, of CPI-0610 on the PK of ruxolitinib	$AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, $AUC_{tau,ss}$, T_{max}, C_{max}, C_{trough}, $T_{1/2}$, Vd/F, CL/F
Exploratory	CCI	

3 STUDY DESIGN

3.1 Overview of study design

This is a Phase 1/2, multi-center, open-label, dose escalation study (Phase 1) of CPI-0610 in patients with acute leukemia, MDS, MDS/MPN or MF and expansion study (Phase 2) of CPI-0610 as a single agent and in combination with ruxolitinib (a JAK inhibitor approved for the treatment of patients with MF) in patients with MF. The primary objective of Phase 1 (dose escalation) is to determine the DLTs and MTD of CPI-0610 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) is to evaluate splenic response by imaging after 24 weeks of treatment and for patients who are transfusion dependent, to evaluate the transfusion independence rate in each of the two expansion arms. **NOTE:** as of Amendment 6, separate dose escalation in MF will not be pursued (see Section 1.3.3 for details). The original dose escalation plan is described in Section 5.6.

In both phases of the study, CPI-0610 will be administered by mouth once daily for 14 days followed by a 7-day break, with cycles of treatment repeated every 21 days. The dosing regimen chosen for this study aims to achieve 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 anti-tumor 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 CPI-0610 are given.

Phase 1 (Dose Escalation):

During the dose escalation phase of the study successive cohorts of 3-6 patients will be enrolled to increasing doses of CPI-0610. Following three initial dose doublings in patients with acute leukemia, MDS or MDS/MPN, the maximum increase in dose from one cohort of patients to the next will be guided by the modified Fibonacci series that automatically decreases the incremental increase in dose between cohorts, even in the absence of treatment-related toxicity. Dose escalation will continue until the MTD is estimated using a standard rule-based algorithm, commonly described as the "3+3 design". In this design the MTD is the highest dose that causes dose-limiting toxicity in less than 2 of 6 patients.

In patients with acute leukemia, MDS or MDS/MPN dose-limiting hematologic toxicity will be defined as the presence of Common Toxicity Criteria for Adverse Events (CTCAE) grade 4 neutropenia (absolute neutrophil count [ANC] $< 0.5 \times 10^9$/L) and/or grade 4 thrombocytopenia ($<25 \times 10^9$/L) in the absence of any morphologic evidence of residual disease (acute leukemia, MDS or MDS/MPN), 21 or more days after suspending dosing with CPI-0610. This definition of hematologic DLT allows patients to continue to receive CPI-0610 in the face of severe peripheral cytopenias as long as the underlying disease is improving or at least is not worsening.

In patients with MF, dose-limiting hematologic toxicity will be defined as grade 4 neutropenia lasting for more than 7 days, febrile neutropenia of any duration, grade 4 neutropenia resulting in the omission of more than 1, 2 or 3 of the planned 7, 14 or 21 doses in a cycle of treatment, grade

3 or greater thrombocytopenia with bleeding or any requirement for platelet transfusion, or any platelet count less than 10 x 10^9/L.

Dose-limiting non-hematologic toxicity will generally be defined as grade 3 or higher adverse events and laboratory abnormalities that are considered to be unrelated to the patient's underlying hematologic malignancy, unrelated to complications of the malignancy (like infection and bleeding), and unrelated to other concurrent medications.

Phase 2 (MF Expansion):

Following completion of Phase 1 (dose escalation), the MTD of single agent CPI-0610 was defined as 225 mg QD (tablet formulation). The expansion phase of the study will evaluate CPI-0610 in two separate groups of patients:

Monotherapy Arm (MF patients treated with CPI-0610 alone):

- Open to patients with MF who have previously been treated with a JAK inhibitor and are intolerant, resistant, refractory or lost response to the JAK inhibitor. The initial dose of CPI-0610 will be 125 mg QD (tablet formulation). Upward titration (see Section 5.7.1) of CPI-0610 is allowed based on platelet count, hemoglobin levels and safety evaluation.

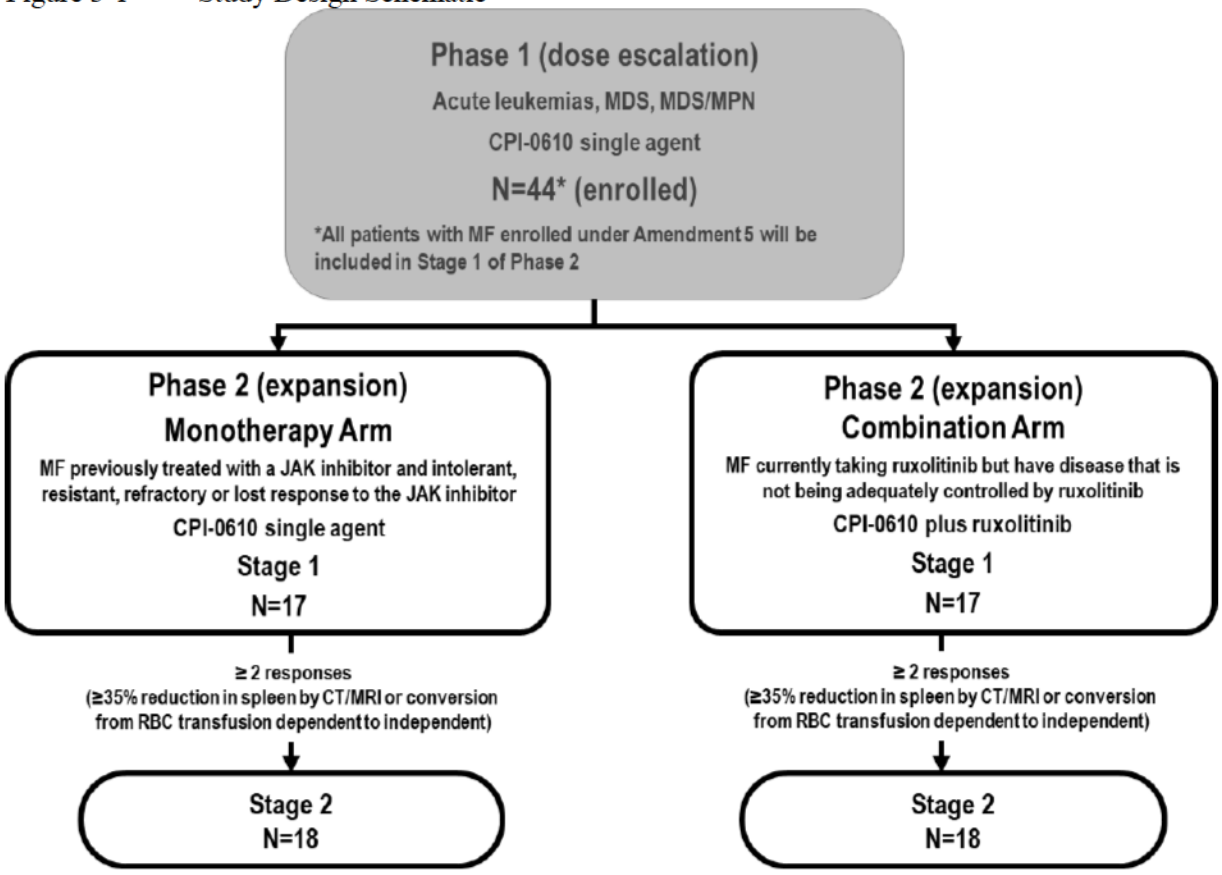
Combination Arm (MF patients treated with CPI-0610 in combination with ruxolitinib):

- Open to patients with MF who are currently taking ruxolitinib but have disease that is not being adequately controlled by ruxolitinib. The initial dose of CPI-0610 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. Upward titration (see Section 5.7.1) of CPI-0610 is allowed based on platelet count, hemoglobin levels and safety evaluation.

Because both CPI-0610 and ruxolitinib cause reversible thrombocytopenia, patients enrolled in the Combination Arm will be required to have a platelet count ≥ 100 x 10^9/L in order to be eligible (a platelet count ≥ 75 x 10^9/L is required for patients on the Monotherapy Arm). Combination Arm patients will also be required to be on a stable dose of ruxolitinib.

The analysis of the primary endpoint, splenic response, will be primarily descriptive. However, a Simon's two-stage design will be used for each arm to allow the possibility of early stopping for futility. For the purpose of the two-stage design, a response will be defined as a ≥35% reduction from baseline spleen size by imaging (MRI or CT) or conversion from RBC transfusion dependent to independent (see definitions in Section 7.2.4.3). Stage 1 of each arm will enroll 17 patients. If 2 or more patients have a response, then an additional 18 patients will be enrolled in Stage 2 (see Figure 1). **NOTE:** All patients with MF enrolled under Amendment 5 will be included in Stage 1 of Phase 2.

Figure 3-1 Study Design Schematic



In the absence of disease progression, and if CPI-0610 treatment (or the combination of CPI-0610 plus ruxolitinib) is being well tolerated, patients may continue to receive successive cycles of treatment.

3.2 Number of patients

It is estimated that up to 114 patients will be enrolled into this study. This estimate is based on the observed accrual of 44 patients with acute leukemia, MDS or MDS/MPN to Phase 1(dose escalation) of the study, and on the plan for two expansion arms (n= up to 35 each) in patients with MF in Phase 2, utilizing a separate Simon's two-stage design within each. **NOTE:** All patients with MF enrolled under Amendment 5 will be included in Stage 1 of Phase 2.

4 STUDY POPULATION

Phase 1 (dose escalation):

Eligible patients must be adults (aged ≥ 18 years) who have one of the following hematologic malignancies: acute leukemia, including acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), and acute undifferentiated or biphenotypic leukemia; chronic myelogenous leukemia (CML) in blast crisis; myelodysplastic syndrome (MDS); myelodysplastic/myeloproliferative neoplasms (MDS/MPN); or myelofibrosis (MF). They must be patients for whom effective standard treatment is not available; eligibility criteria regarding prior therapies specific for each of these diseases are described below.

Acute Leukemia
Patients with newly diagnosed acute leukemia should have been treated with a standard induction chemotherapeutic regimen or with another anti-leukemic agent before they are considered for participation in this study. However, patients who have newly diagnosed and previously untreated acute myelogenous leukemia may participate if the marrow contains myelodysplasia-related changes and 20-30% blasts.

Patients with relapsed or refractory disease are eligible if they are considered to not be candidates for further induction chemotherapy. Patients whose disease has relapsed following allogeneic stem cell transplantation are eligible, but they must not be taking more than 10 mg of prednisone (or the equivalent dose of another corticosteroid) per day or any other immunosuppressive medication.

CML
Patients with CML in blast crisis must have been previously treated with at least two Bcr-Abl TKIs (e.g., imatinib, nilotinib, dasatinib, bosutinib, ponatinib) and must not be candidates for high dose chemotherapy followed by allogeneic stem cell transplantation.

MDS
Patients with newly diagnosed and previously untreated MDS may participate if they have intermediate, high or very high risk disease according to the revised International Prognostic Scoring System, IPSS-R (see Appendix 1). All patients with MDS that has been previously treated with a hypomethylating agent (e.g., 5-azacytidine, decitabine) and/or with an immunomodulatory agent (e.g., lenalidomide, thalidomide) are eligible.

MDS/MPN
Patients with MDS/MPN may participate if they have one of the following diseases: chronic myelomonocytic leukemia (CMML), atypical (Bcr-Abl negative) chronic myeloid leukemia, or MDS/MPN-unclassifiable. Patients with MDS/MPN are eligible regardless of whether they have or have not been previously treated.

Patients must have screening and baseline evaluations performed either ≤ 14 days or ≤ 21 days (radiographic imaging studies only) prior to receiving the first dose of CPI-0610, as described in the Schedule of Events (Section 6). The eligibility of a patient for the study should be established

by evaluating all relevant inclusion and exclusion criteria. A record documenting confirmation of the patient's eligibility must be stored with the source documentation at the study site.

MF
Patients with MF must have primary myelofibrosis or myelofibrosis that has evolved from essential thrombocythemia or polycythemia vera. Patients with MF may participate if they have disease that has not responded to or that is not being adequately controlled by treatment with a JAK inhibitor, disease that has progressed in spite of treatment with a JAK inhibitor, or if they are intolerant of treatment with a JAK inhibitor.

Phase 2 (MF expansion):

Eligible patients must be adults (aged ≥ 18 years) who must have primary MF or MF that has evolved from essential thrombocythemia or polycythemia vera. Monotherapy Arm patients with MF may participate if they have previously been treated with a JAK inhibitor and are intolerant, resistant, refractory or lost response to the JAK inhibitor. Combination Arm patients with MF may participate if they are currently taking ruxolitinib but have disease that is not being adequately controlled by ruxolitinib.

4.1 Phase 1 (Dose Escalation) Inclusion criteria

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

1. Adult (aged ≥ 18 years)
2. Histologically or cytologically confirmed diagnosis of one of the following hematologic malignancies: AML, ALL, acute undifferentiated or biphenotypic leukemia, CML in blast crisis, MDS, MDS/MPN or MF.
3. ECOG performance status ≤2.
4. Serum total bilirubin ≤ 1.5 x ULN (upper limit of normal)
5. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN. The AST and /or ALT may be elevated up to 5 x ULN if the elevation can be reasonably ascribed to leukemic infiltration of the liver.
6. Serum creatinine ≤ 2.0 x ULN or creatinine clearance (CrCl) ≥ 30 ml/min (either measured or estimated by the Cockcroft-Gault formula).

   {Cockcroft-Gault formula for estimated creatinine clearance (eCrCl): eCrCl = (140 – Age) × Mass (kg) × [0.85 if Female]/ 72 × Serum Creatinine (mg/dL)}
7. Platelet count ≥ 50 x 10^9/L and ANC ≥ 1 x 10^9/L (applies only to patients with MF who are not being treated with ruxolitinib).
8. Platelet count ≥ 75 x 10^9/L and ANC ≥ 1 x 10^9/L (applies only to patients with MF who are being treated with ruxolitinib).
9. DIPSS-plus risk category of intermediate-2 or high (applies only to patients with MF).
10. Serum glucose value ≤160 mg/dL. If needed, a fasting serum glucose determination may be obtained to satisfy this criterion. Alternatively, a hemoglobin A1C ≤ 7% (which corresponds

to an average serum glucose concentration ≤ 154 mg/dL) may be used to satisfy this criterion.

11. Patients must have fully recovered from major surgery and from the acute toxic effects of prior chemotherapy and radiotherapy (residual CTCAE grade 1 toxicity, e.g., grade 1 peripheral neuropathy, and residual alopecia are allowed).
12. Female patients who are pre-menopausal or have experienced menopause for less than 2 years must have a negative serum pregnancy test ≤ 72 hours before starting study treatment. Male and female patients with reproductive potential must agree to use appropriate contraceptive methods while on study therapy and for 3 months after the last dose of CPI-0610.
13. Patients must give written informed consent to participate in this study before the performance of any study-related procedure.

4.2 Phase 1 (Dose Escalation) Exclusion criteria

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

1. Newly diagnosed acute leukemia that has not been treated with a standard induction chemotherapeutic regimen or with another anti-leukemic agent.

   However, patients who have newly diagnosed and previously untreated acute myelogenous leukemia may participate if the marrow contains myelodysplasia-related changes and 20-30% blasts.
2. Relapsed or refractory acute leukemia, where additional induction chemotherapy is considered to be of potential clinical benefit.
3. Acute leukemia in relapse less than 6 months following allogeneic stem cell transplantation.
4. CML in blast crisis and previously treated with only one bcr-abl TKI.
5. Very low or low risk MDS without previous treatment.
6. Central nervous system (CNS) (e.g., leptomeningeal) involvement by leukemia. Note that a past history of CNS involvement by leukemia is not an exclusion criterion. Evaluation of the cerebrospinal fluid is only required if there is a clinical suspicion of CNS involvement by leukemia at the time that the patient is being evaluated for participation in this study.
7. Current 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.
8. Impairment of gastrointestinal (GI) function or GI disease that could significantly alter the absorption of CPI-0610, 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 angina pectoris ≤ 6 months prior to starting study drug
- Serum cardiac troponin (cTn) level ≥ 99th percentile of the upper reference limit
- QTcF > 470 msec on the screening ECG
- Left ventricular ejection fraction (LVEF) < 50%

Note that patients with a history of coronary artery disease and revascularization are not excluded.

10. Uncontrolled cardiac arrhythmia (patients with rate-controlled atrial fibrillation are not excluded)
11. A past medical history of other clinically significant heart disease (e.g., uncontrolled hypertension, history of labile hypertension or history of poor compliance with an antihypertensive regimen)
12. Any other concurrent severe and/or uncontrolled concomitant medical condition that could compromise participation in the study (e.g. clinically significant pulmonary disease, clinically significant neurological disorder, active or uncontrolled infection).
13. Systemic anti-cancer treatment with a small molecule therapeutic other than hydroxyurea or radiotherapy less than 2 weeks before the first dose of CPI-0610.
14. Ongoing treatment with a JAK inhibitor or treatment with a JAK inhibitor less than 2 weeks prior to the first dose of CPI-0610 (applies only to patients with MF).
15. Administration of a therapeutic antibody less than 4 weeks before the first dose of CPI-0610. A minimum 2-week period between the last treatment with a therapeutic antibody and the first dose of CPI-0610 may be permitted in patients with rapidly progressive disease following discussion with the medical monitor.
16. Treatment with an investigational small molecule less than 2 weeks before the first dose of CPI-0610. In addition, the first dose of CPI-0610 should not occur before a period equal to or greater than 5 half-lives of the investigational agent has elapsed.
17. Patients who are receiving treatment with medications that are known to be strong inhibitors or inducers of CYP450 enzymes. See Appendix 2 from Amendment 5 (Version 6) of this protocol for a list drugs that are inhibitors or inducers of CYP450 enzymes.
18. Treatment with medications that are known to carry a risk of Torsades de Pointes.

    See Appendix 3 from Amendment 5 (Version 6) of this protocol for a list of drugs that carry both this risk and a risk of QT interval prolongation. Although the co-administration of medications that carry a risk of QT interval prolongation (but not of Torsades de Pointes) is not prohibited, all reasonable effort should be made to minimize their use during treatment with CPI-0610.
19. Immunosuppressive treatment that cannot be discontinued both prior to study entry and for the duration of the study. Immunosuppressive treatment should be discontinued for at least 1 week prior to starting the administration of CPI-0610.

Oral prednisone at a dose of 10 mg or less per day is allowed, as are other oral corticosteroids given at glucocorticoid-equivalent doses. Topical, nasal and inhaled corticosteroids are also allowed.

20. Pregnant or lactating women.
21. Women of child-bearing potential and men with reproductive potential unwilling to use adequate contraception while on study therapy and for 3 months thereafter.
22. Patients unwilling or unable to comply with this study protocol.

4.3 Phase 2 (MF Expansion) 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-1 or higher.

   b. Platelet count (patients are required to have maintained a platelet count above the minimum levels indicated below for least 14 days):

      Monotherapy Arm: Platelet count ≥ 75 x 10^9/L without the assistance of thrombopoietic factors or transfusions

      Combination Arm: Platelet count ≥ 100 x 10^9/L without the assistance of thrombopoietic factors or transfusions

   c. ANC ≥ 1 x 10^9/L without the assistance of granulocyte growth factors

   d. Palpable spleen ≥5 cm that is below the costal margin on physical examination **OR** RBC transfusion dependent (defined as at least 4 units of RBC transfusions, or a hemoglobin level below 8 g/dL in the prior 8 weeks)

   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 patients only: Previously treated with a JAK inhibitor and be intolerant, resistant, refractory or lost response to the JAK inhibitor; have not have received the JAK inhibitor within 2 weeks prior to start of study drug

   h. Combination Arm patients only: Must have received single agent ruxolitinib for at least 12 weeks and be on a stable dose for a minimum 8 weeks (prior to start of study drug)

3. ECOG performance status ≤ 2.
4. Serum direct bilirubin ≤ 1.5 x ULN (upper limit of normal)

5. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN. The AST and /or ALT may be elevated up to 5 x ULN if the elevation can be reasonably ascribed to liver involvement.
6. Serum creatinine ≤ 2.0 x ULN or creatinine clearance (CrCl) ≥ 30 ml/min (either measured or estimated by the Cockcroft-Gault formula).

   {Cockcroft-Gault formula for estimated creatinine clearance (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, e.g., grade 1 peripheral neuropathy, and residual alopecia are allowed).
8. Male and female patients with reproductive potential must agree to use appropriate contraceptive methods while on study therapy and for 3 months after the last dose of CPI-0610.
9. Patients must give written informed consent to participate in this study before the performance of any study-related procedure.

4.4 Phase 2 (MF Expansion) Exclusion criteria

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

1. Patients who have had prior splenectomy
2. Patients who have had splenic irradiation within 3 months of starting study drug
3. Current 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.
4. Patients with Child-Pugh Class B or C
5. Impairment of gastrointestinal (GI) function or GI disease that could significantly alter the absorption of CPI-0610 and/or ruxolitinib, including any unresolved nausea, vomiting, or diarrhea > CTCAE grade 1.
6. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
   a) Acute myocardial infarction or unstable angina pectoris ≤ 6 months prior to starting study drug
   b) QTcF > 500 msec on the screening ECG
   c) 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 anti-cancer treatment (other than ruxolitinib for the Combination Arm; see inclusion criterion #2) other than hydroxyurea less than 2 weeks (or 5 half-lives, whichever is longer) before the first dose of CPI-0610. **NOTE:** Hydroxyurea is 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 CPI-0610.
11. Prior treatment with a BET inhibitor.
12. Hematopoietic growth factor (granulocyte growth factor, erythropoiesis stimulating agent, thrombopoietin mimetic) less than 4 weeks before the first dose of study drug.
13. Patients in the Combination Arm who are receiving treatment with fluconazole.
14. Systemic corticosteroids at daily doses > 10 mg of oral prednisone or equivalent. Topical, nasal and inhaled corticosteroids are also allowed.
15. Women who are lactating or pregnant females as documented by a serum β-hCG pregnancy test consistent with pregnancy, obtained within 72 hours prior to the first dose of CPI-0610. Females with β-hCG values that are within the range for pregnancy but are not pregnant (false-positives) may be enrolled with written consent of the Constellation Pharmaceuticals medical monitor, after pregnancy has been excluded. Females of non-child bearing potential (post-menopausal for more than 1 year; bilateral tubal ligation; hysterectomy) do not require a serum pregnancy test.
16. Patients unwilling or unable to comply with this study protocol.

5 STUDY TREATMENT

5.1 Study drug

The term "study drug" refers to CPI-0610, Constellation's investigational inhibitor of BET proteins, formulated as capsules or tablets for oral administration. No control drug will be used in this study.

NOTE: CPI-0610 capsules were used in the initial clinical studies, including in some of the cohorts of Phase 1 (dose escalation). As of Amendment 6, all patients will receive the tablet formulation.

CPI-0610 monohydrate tablets, 25 mg and 100 mg contain the micronized active pharmaceutical ingredient and several inactive excipients, as described in Table 5-1. Both tablet strengths (25 mg and 100 mg) are supplied in HDPE bottles with heat induction sealed caps. Each bottle contains 100 plain-faced light brown tablets with or without speckles.

Table 5-1 Composition of CPI-0610 Tablets

CCI

5.1.1 Study drug administration

CPI-0610 will be administered PO, once a day for 14 consecutive days followed by a 7-day break. The 14 days of CPI-0610 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).

The CPI-0610 dose to be evaluated in each cohort of patients during Phase 1 (dose escalation) will be rounded down to accommodate the available dose strengths. The dose will not be adjusted for body weight or body surface area; all patients treated in the same cohort/at the same dose level will receive the same total milligram dose of CPI-0610 per day.

Patients will be given a dosing diary at the start of each treatment cycle in which they should record relevant information regarding their study drug (e.g., confirmation that each daily dose was taken, reasons for missed doses).

5.1.1.1 Once daily administration of CPI-0610

Patients should be instructed to take their daily dose at approximately the same time each day, in the morning. Each dose should be taken with a glass of water and consumed over as short a time as possible (e.g., all tablets within 5 minutes). Patients should be instructed to swallow tablets whole and to not chew them.

No food should be consumed for 2 hours prior to and 1 hour after oral administration of CPI-0610. 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 CPI-0610 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 CPI-0610 within 6 hours after the missed dose. If more than 6 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 Constellation. 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

CPI-0610 tablets will be supplied to the site pharmacy as 25 mg or 100 mg strengths in bottles containing 100 tablets. The site pharmacist will dispense the appropriate number of tablets to each patient at the beginning of each cycle.

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. Clinical supplies are to be dispensed only in accordance with the protocol.

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 (20-25°C). 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 Constellation, the Investigator must not destroy any drug labels, or any partly used or unused drug supply.

5.2 Ruxolitinib for Phase 2 (MF Expansion) Combination Arm

Patients enrolled in the Phase 2 Combination Arm will already be on a stable fixed dose of ruxolitinib PO twice daily (BID). Patients in the Combination Arm will remain on this same dose throughout the trial unless a dose reduction is required for toxicity (see Section 5.7.2).

Ruxolitinib is available as tablets formulated in 5, 10, 15, 20 and 25 mg strengths. See the ruxolitinib prescribing information for more details (www.jakafi.com).

Patients will be given a dosing diary at the start of each treatment cycle in which they should record relevant information regarding ruxolitinib (e.g., confirmation that each dose was taken, reasons for missed doses).

5.2.1 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 day 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 5.2.1.1).

5.2.1.1 Twice daily (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 CPI-0610 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 CPI-0610 dose except for days that study drug will be administered in the study center under the observation of the study personnel.

Since CPI-0610 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 CPI-0610 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.

5.2.2 How Supplied

Patients enrolled in the Combination Arm will already be on ruxolitinib, and will continue with the drug supplied in the same manner during the trial.

5.2.3 Adverse Events

As of the October 2017 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 50,000 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 x 10^9/L before starting ruxolitinib had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count > 200 x 10^9/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 hemoglobin 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 red blood cell 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 tuberculosis, progressive multifocal leukoencephalopathy and herpes zoster. 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, disseminated intravascular coagulation, or multi-organ failure.

- Non-melanoma skin cancer

Non-melanoma 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 Constellation Pharmaceuticals to each investigative site.

The procedures for patient numbering and cohort 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 will be coordinated by the sponsor. During Phase 2, all patients will be assigned to either the Monotherapy Arm (CPI-0610 alone) or the Combination Arm (CPI-0610 plus ruxolitinib).

5.5 Treatment blinding

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

5.6 Phase 1 (Dose Escalation)

NOTE: As of Amendment 6, Phase1 is complete and Phase 2 (MF expansion) is now open. The sections below describe the original dose escalation plan, including having separate dose escalations for MF patients with and without ruxolitinib.

5.6.1 Phase 1 Starting dose for CPI-0610

5.6.1.1 Patients with acute leukemia, MDS and MDS/MPN

The starting dose for this study is based on toxicology studies conducted in dogs and rats and on projections for CPI-0610's human pharmacokinetics.

The toxicology studies evaluated once daily oral dosing of CPI-0610 for 14 consecutive days in both species. The dose severely toxic for approximately 10% of the animals (STD_{10}) in the rat GLP toxicology study was 60 mg/kg/day, which is equivalent to 360 mg/m^2/day. The highest HNSTD in the dog GLP toxicology study was 4 mg/kg/day, which is equivalent to 80 mg/m^2/day. According to Food and Drug Administration (FDA) guidelines the safe starting dose is either 1/10 of the rodent MTD or 1/6 of the dog HNSTD, when doses are normalized to body surface area.[41] The toxicology results in the rat suggest a starting dose of 0.1 × 360 mg/m^2/day x 1.73 m^2 = 62 mg/day. The toxicology results in the dog suggest a starting dose of 1/6 x 80 mg/m^2/day x 1.73 m^2 = 23 mg/day.

However, estimates of CPI-0610's human pharmacokinetics and assessment of PK-efficacy relationships in the MV4-11 xenograft model together suggest that an optimally efficacious dose could be as low as 15 mg/day. Since efficacious and toxic exposures to CPI-0610 are anticipated to be similar, Constellation believes that it is prudent to begin the clinical evaluation of CPI-0610 at a lower dose, specifically at 6 mg/day. If a dose of 15 mg/day is close to the MTD, the starting dose of 6 mg/day will be almost 3-fold lower than the MTD. Moreover, with this starting dose and the use of the modified Fibonacci dose escalation algorithm the MTD will be approached with relatively small dose increments.

Although 6 mg/day is the starting dose for this study in the absence of any preceding experience with CPI-0610 in humans, Phase I studies of CPI-0610 are also planned (or ongoing) in patients with lymphoma and in patients with multiple myeloma using the same starting dose, provisional dose levels (guided by the modified Fibonacci series of dose increments), and schedule of drug administration that are employed in this trial. If data are available from one or both of these studies that demonstrate the safety of the 6 mg/day or a higher dose, that data can be used to

start this study with a dose greater than 6 mg/day. In this case, the starting dose for the current study must be a total daily dose that has completed its evaluation in at least one of the other two Phase 1 studies, has not been associated with any dose-limiting toxicity, and has generated no more than grade 3 hematologic toxicity and no more than grade 2 non-hematologic toxicity.

If the starting dose for this study is chosen on the basis of such clinical experience, then the subsequent maximum increases will be defined by the modified Fibonacci series, as outlined in Table 5-2 (Provisional Dose Levels), as if the preceding dose levels had been evaluated in this study. If, based on previous clinical experience, a decision is made to start this study with a dose other than 6 mg/day, then that decision will be made jointly by the investigators and sponsor, with the supporting data and rationale outlined in an administrative letter distributed to all of the study sites, institutional review boards (IRBs), and the FDA.

5.6.1.2 Patients with MF

In patients with MF the starting dose will be 125 mg QD, using CPI-0610 tablets. The selection of the 125 mg QD tablet starting dose is based on experience with CPI-0610 in the treatment of patients with lymphoma.

In patients with lymphoma there is a relatively linear relationship between the decline in the platelet count and the dose CPI-0610. CPI-0610 capsule doses of 120 and 170 mg QD result in 25% and 50% mean decreases in the platelet count by the end of the 14-day dosing period. Doses of 230 and 300 mg QD are associated more severe thrombocytopenia, with approximately one third of patients requiring delays in the start of the second cycle of treatment in order to allow for adequate recovery of the platelet count. Additionally, single patients at the 230 and 300 mg QD capsule dose levels have developed Grade 4 thrombocytopenia (platelet count < 25K).

The patients with myelofibrosis eligible for this study will have relatively advanced disease, and it is anticipated that they will have low platelet counts at baseline. Therefore the dose of CPI-0610 to be initially evaluated in these patients will need to be lower than the doses currently being evaluated in patients with lymphoma. A dose of 170 mg QD using the capsule formulation would be an appropriate starting dose in patients with myelofibrosis because its suppression of the platelet count is modest (50% decrease relative to baseline) and also because suppression of the BET target gene, *CCR1*, has been observed at this dose in patients with lymphoma.

The capsule formulation of CPI-0610 that has been used to date in clinical studies of CPI-0610 has been replaced with a new tablet formulation. The tablet provides slightly (~34%) greater AUC than the capsule, and hence a tablet dose of 125 mg QD is roughly equivalent to a 170 mg QD capsule dose. The tablets are currently supplied in 25 and 100 mg strengths. Therefore the starting tablet dose for evaluation in patients with myelofibrosis will be 125 mg QD. If the 125 mg QD starting dose is not well tolerated, a 75 mg QD dose may be evaluated.

The 125 mg QD tablet starting dose will be used both for patients with myelofibrosis receiving no other specific treatment for their disease and for patients receiving therapy with ruxolitinib. However, patients receiving CPI-0610 in combination with ruxolitinib will be required to have a higher baseline platelet count of ≥ 75K rather than ≥ 50K.

5.6.2 Phase 1 Dose escalation guidelines

5.6.2.1 General guidelines

In the dose escalation phase of this study sequentially enrolled cohorts of patients will receive increasing doses of CPI-0610 until the MTD is determined. Determination of the MTD of CPI-0610 will be achieved using a standard rule-based algorithm, typically referred to as the "3+3 design", in conjunction with a modified Fibonacci dose escalation scheme.

Cohorts of 3-6 evaluable patients will typically be treated at each dose level. Before a decision is made to increase the dose of CPI-0610 in a new cohort of patients a minimum of three evaluable patients must have been treated at the dose currently under evaluation. Evaluable patients are patients who meet the minimum treatment and safety evaluation requirements of the study and/or who experience a DLT during cycle 1.

With the 14 days on/7 days off schedule the minimum treatment and safety evaluation requirements are met if, in cycle 1, the patient has received $\geq$ 12/14 of the planned doses of CPI-0610, is observed for $\geq$ 21 days following the first daily dose, and is considered by the sponsor and investigators to have sufficient safety data available to conclude that a DLT did not occur.

Patients who do not meet these minimum treatment and safety evaluation requirements and who do not experience DLT will be replaced with new patients if the minimum of 3 evaluable patients per dose level has not been satisfied.

Additional patients may be enrolled to any dose level at or below the MTD, including intermediate dose levels, if doing so is considered appropriate for better defining the safety, PK, or pharmacodynamics of CPI-0610 treatment. The MTD of CPI-0610 is the highest dose that can be given without causing a DLT in 33% or more of the patients treated at that dose. Stated from an operational perspective, it is the highest dose that causes DLT in less than 2/6 evaluable patients. Therefore escalation of the CPI-0610 dose will be terminated when two or more patients at a dose level experience DLT in the first cycle of treatment.

Three patients will be initially enrolled to a new dose level. If 2 or more of these initial 3 patients experiences DLT, then dose escalation will be terminated. If one of the initial 3 patients enrolled to a dose level experiences DLT, then 3 additional patients will be enrolled to this same dose level to further assess its safety. If none of the additional 3 patients experiences DLT, then the next higher dose level may be opened to enrollment. However, if one or more of these additional patients experiences DLT, then dose escalation will be terminated. The operating characteristics of these standard dose escalation rules are found in Appendix 2.

In the case where DLT occurs in 2 of 2 or 2 of 6 patients at a dose level and dose escalation is terminated, the MTD will be the immediately preceding dose. It is also permissible to evaluate an intermediate dose as a possible MTD. Before enrollment is opened to the dose expansion phase of the study a minimum of 6 evaluable patients must be treated at the dose declared to be the MTD.

A modified Fibonacci algorithm will be used to determine the maximum allowable increase in dose from one cohort of patients to the next. The modified Fibonacci algorithm uses the following sequence of relative dose increases from one cohort of patients to the next: 100%, 67%, 50%, 40%, and 35%, with all subsequent increases no greater than 30-35%. The modified Fibonacci algorithm assumes that the initial dose level is 1/10th of the MTD.[42,43] However, based on PK data from the first 8 patients treated with CPI-0610 in a Phase 1 study in lymphoma, the initial dose level, 6 mg PO daily x 14 days, is estimated to be only 1/21st of the MTD. The average elimination half-life of CPI-0610 in these patients was 8.65 hours rather than the 21 hours predicted on the basis of preclinical data, resulting in lower than predicted systemic exposure (AUC). Therefore, in order to minimize the number of patients treated at suboptimal doses of CPI-0610, two additional dose doubling steps have been added to the initial steps of the dose escalation scheme. These two additional dose doubling steps are projected to bring the dose to approximately 40% of the MTD before implementing the successively decreasing dose increments of the modified Fibonacci algorithm. However, if significant CPI-0610-related toxicity is observed before completing these two additional dose doublings then the doubling of doses will be stopped and the dose escalation scheme will use step sizes no greater than those of the modified Fibonacci series, i.e., 67, 50, 40, and 30-35%. Specifically, dose doubling will be stopped if at any given dose level two or more patients experience CTCAE grade 2 CPI-0610-related non-hematologic toxicity or any one patient experiences CTCAE grade 3 or higher CPI-0610-related non-hematologic toxicity during the first cycle of treatment.

In patients with MF dose increments of no more than 33% will be made during dose escalation, since the starting dose (125 mg QD, tablet) is predicted to be close to the MTD.

The dose of CPI-0610 will not be adjusted for body weight or body surface area; all patients treated in the same cohort/at the same dose level will receive the same total milligram dose of CPI-0610 per day.

While the modified Fibonacci algorithm will define the maximum allowable increase in dose, smaller increases in dose may be evaluated if doing so is suggested by review of the clinical safety, PK or pharmacodynamic data, or by comparison to the preclinical toxicology, PK and pharmacodynamic data. Moreover, if needed to better define dose-toxicity relationships, additional patients may be enrolled to the current dose level, to a preceding dose level, or to intermediate dose levels before proceeding with further dose escalation.

5.6.2.2 Additional provisions

Due to the potential for dropouts during the first cycle of treatment (e.g., because of early disease progression), a cohort may initially be expanded to include up to 2 additional patients. However, if these additional patients are to be enrolled they must start treatment ≤14 days after the third patient enrolled in the cohort was first dosed with CPI-0610. The decision to dose escalate may still be made after the third patient enrolled to the dose level in question has completed the first cycle of treatment. However, if under these circumstances the decision is made to enroll patients to a higher dose level, and one of the additional patients treated at the preceding dose level experiences a DLT in the first cycle of treatment, then further enrollment of patients to the higher dose level will be suspended until it can be determined whether the preceding dose level exceeds the MTD. In the meantime, patients enrolled to the higher dose level may continue treatment at

that dose if they are tolerating it well, and if continuing treatment is considered appropriate for the toxicity in question.

As with the selection of a starting dose, the doses evaluated in this study may be subsequently informed by the clinical experience with CPI-0610 in the Phase 1 study being conducted in patients with lymphoma. The information from the lymphoma study may suggest that more conservative dose escalation steps should be taken, or it may provide a rationale for omitting evaluation of one or more of the doses outlined in

Table 5-2 (Provisional Dose Levels). If a decision is made to omit the evaluation of one or more doses in the provisional dose escalation scheme, the next dose level to be evaluated must be a dose that lies below the maximum tolerated dose in the lymphoma study or, if the MTD has not been determined, lies below the highest dose that has been evaluated in the lymphoma study. Further constraints on the dose or doses to be omitted will be derived from a review of all of the existing dosing, PK and safety data from both studies. If a decision to omit the evaluation of one or more doses is made, then an administrative letter will be distributed to all of the study sites, IRBs, and the FDA providing the supporting rationale.

5.6.2.3 Provisional Dose Levels

Table 5-2 depicts provisional dose levels for evaluation in this study, based on the planned starting dose and the maximum increases in dose allowed by the modified Fibonacci algorithm. The dose levels that are actually evaluated in this study may differ from these provisional ones, since the protocol allows for smaller increases in dose and for the evaluation of intermediate and higher doses, if necessary. Doses above 24 mg/day may be rounded so that they can be delivered using 10 and 25 mg capsules, thereby minimizing the number of capsules that patients must take.

The provisional dose levels in

Table 5-2 apply only to CPI-0610 capsules evaluated in patients with acute leukemia, MDS or MDS/MPN.

Comparison of the pharmacokinetics of CPI-0610 tablets and capsules in patients indicates that the tablet is more rapidly absorbed, resulting in an approximately 2-fold higher Cmax, and that it

has approximately 34% greater relative oral bioavailability. Following evaluation of the 400 mg QD capsule dose in patients with acute leukemia, MDS or MDS/MPN, an initial tablet dose of 275 mg QD will be evaluated in a new cohort of 3-6 patients. Dose escalation/de-escalation will thereafter continue with the tablet formulation of CPI-0610.

In patients with MF an initial tablet dose of 125 mg QD will be evaluated, with the provision of evaluating a dose of 75 mg QD if 125 mg QD is not well tolerated. Following evaluation of the initial dose, subsequent increases in the dose of CPI-0610 will be made in no greater than 33% increments. **NOTE:** See Section 1.3.4.2 for the actual dose levels used during Phase 1 (Dose Escalation).

Table 5-2 Provisional dose levels

Dose Level†	Percent Increase in Dose	CPI-0610 Dose	Schedule
-1*	-	2 mg PO daily	14 consecutive days of treatment, 1-week break
1	-	6 mg PO daily	14 consecutive days of treatment, 1-week break
2	100	12 mg PO daily	14 consecutive days of treatment, 1-week break
3	100	24 mg PO daily	14 consecutive days of treatment, 1-week break
4	100	48 mg PO daily	14 consecutive days of treatment, 1-week break
5	67	80 mg PO daily	14 consecutive days of treatment, 1-week break
6	50	120 mg PO daily	14 consecutive days of treatment, 1-week break
7	40	168 mg PO daily	14 consecutive days of treatment, 1-week break
8	35	226 mg PO daily	14 consecutive days of treatment, 1-week break
9	35	304 mg PO daily	14 consecutive days of treatment, 1-week break
10	35	410 mg PO daily	14 consecutive days of treatment, 1-week break

* The 2 mg daily dose is a dose that may be evaluated if the 6 mg daily dose is not well tolerated
† Doses between and higher than those shown in this table may be evaluated

5.6.2.4 Definitions of dose-limiting toxicity

Dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed by the Investigator as unrelated to disease progression, intercurrent illness, or concomitant medications and that meets any of the criteria listed below in Table 5-3.

For the purpose of making dose-escalation decisions, all DLTs occurring during the first cycle of treatment with CPI-0610 must be included. DLTs occurring in subsequent cycles of treatment may also be considered when making decisions regarding dose escalation, particularly if they suggest that cumulative and/or late-occurring toxicity may limit dosing.

Table 5-3 Definitions of dose-limiting toxicities

Toxicity	**Any of the following:**
Hematology: patients with acute leukemia, MDS, or MDS/MPN	The presence of CTCAE grade 4 neutropenia (ANC < 0.5 x 10^9/L) and/or grade 4 thrombocytopenia (<25 x 10^9/L) in the absence of any morphologic evidence of residual disease (acute leukemia, MDS or MDS/MPN), 21 or more days after suspending dosing with CPI-0610
Hematology: patients with MF	CTCAE grade 4 neutropenia (ANC < 0.5 x 10^9/L) occurring during CPI-0610 dosing and resulting in the omission of more than 1, 2 or 3 of the planned 7, 14 or 21 days of dosing CTCAE grade 4 neutropenia lasting for more than 7 days Platelets < 10 x 10^9/L of any duration ≥ CTCAE grade 3 thrombocytopenia (platelets < 50 x 10^9/L) with bleeding or any requirement for platelet transfusion
Renal	≥ CTCAE grade 3 serum creatinine (> 3.0 x baseline or > 3 x ULN)
Hepatic	≥ CTCAE grade 3 total bilirubin (> 3 x ULN)
	≥ CTCAE grade 3 ALT
Cardiac	≥ CTCAE grade 3
Other adverse events	≥ CTCAE grade 3 vomiting or CTCAE grade 3 nausea despite optimal anti-emetic therapy
	≥ CTCAE grade 3 diarrhea despite optimal anti-diarrhea treatment
	≥ CTCAE grade 3, except for the exclusions noted below[a]
	Other CPI-0610-related non-hematologic toxicities ≥ CTCAE grade 2 that, in the opinion of the investigator, require dose reduction or discontinuation of treatment with CPI-0610

Toxicity	**Any of the following:**
Treatment interruption	Treatment interruption caused by CPI-0610-related toxicity and resulting in the delivery of less than 6, 12 or 18 of the planned 7, 14 or 21 days of dosing in a cycle of treatment
Treatment delay	Treatment delay of more than 1 week (i.e., interval between the beginning of one CPI-0610 treatment cycle and the next by > 28 days for the 14 days on/7 days off schedule or the continuous daily dosing schedule; or by > 21 days for the 7 days on/7 days off schedule) because of inadequate recovery from the toxicity of the previous cycle of treatment (see Section 5.6 for retreatment criteria). In patients with acute leukemia, MDS or MDS/MPN treatment delays incurred because of hematologic toxicity are not dose-limiting unless there has been an absence of recovery of marrow function 21 or more days following the morphologic elimination of all disease from the bone marrow and peripheral blood.
Exceptions to DLT criteria[a]	CTCAE grade 3-4 elevations in alkaline phosphatase CTCAE grade 3-4 increases in serum uric acid without other associated physiologically significant effects
	CTCAE grade 3 increases in amylase and/or lipase in the absence of symptoms consistent with pancreatitis
	< 72 hours of CTCAE grade 3 fatigue

Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03 will be used for all toxicity grading.

Patients may receive supportive care (e.g., transfusion with packed red blood cells [PRBCs]0 and platelets) as per local institutional guidelines. The use of erythropoietin is permitted according to the American Society of Clinical Oncology (or other institutional) Guidelines.

Optimal therapy for nausea, vomiting and diarrhea will be based in institutional guidelines, with consideration of medications that are prohibited in this study.

When laboratory abnormalities form the basis for a DLT they should be confirmed by repeated testing with a new sample or assessment.

5.6.3 Phase 1 Criteria for continuing CPI-0610 during a cycle of treatment

During a cycle of treatment CPI-0610 should continue to be administered as planned unless a dose-limiting toxicity has occurred, as defined in Table 5-3.

If dosing with CPI-0610 has been interrupted because of treatment-related toxicity and this interruption has resulted in the omission of more than 2 of the planned 14 days of therapy, then the associated treatment-related toxicity is considered to be dose-limiting. If treatment is to be resumed following resolution of the dose-limiting toxicity, then it should be resumed only with a new cycle of treatment, following the criteria outlined below in Section 5.6.2.1. Conversely, if only 1 or 2 days of dosing has been omitted because of a treatment-related toxicity and it is possible to resume dosing within the planned 14 days of treatment, no attempt should be made to make up the missed doses of CPI-0610.

PATIENTS WITH ACUTE LEUKEMIA, MDS OR MDS/MPN

Once a cycle of therapy has begun the planned 14 days of treatment should not in general be interrupted for hematologic toxicity, since dose-limiting hematologic toxicity is defined by the presence of CTCAE grade 4 neutropenia (ANC < 0.5 x 10^9/L) and/or grade 4 thrombocytopenia (<25 x 10^9/L) in the absence of any morphologic evidence of residual disease (acute leukemia, MDS or MDS/MPN), 21 or more days after suspending dosing with CPI-0610. This definition of hematologic DLT allows patients to continue to receive CPI-0610 in the face of severe peripheral cytopenias as long as the underlying disease is improving or at least is not worsening.

PATIENTS WITH MF

In the case of CPI-0610-related neutropenia and/or thrombocytopenia, dosing as planned should continue as long as the ANC remains ≥ 0.5 x 10^9/L and the platelet count remains ≥ 10 x 10^9/L. If either the ANC or platelet count fall below these values, dosing with CPI-0610 should be interrupted. CPI-0610 dosing within the planned 14 days of treatment should not be resumed until the ANC is ≥ 0.75 x 10^9/L and the platelet count is ≥ 25 x 10^9/L. In addition, dosing within the cycle of treatment should not be resumed if the interruption has resulted in the omission of more than 2 of the planned 14 days of dosing. If more than 2 of the planned 14 days of therapy have been omitted, then treatment should be resumed only with a new cycle of treatment, following the criteria outlined below in Section 5.6.2.1. If it is possible to resume dosing within the planned 14 days of treatment, no attempt should be made to make up the missed doses of CPI-0610.

5.6.4 Phase 1 Criteria for beginning a new cycle of treatment

In order for a new cycle of therapy to begin all non-hematologic toxicity considered to be related to CPI-0610 must have resolved to CTCAE grade 1 or baseline. If the patient fails to meet the above-cited criteria for retreatment, then initiation of the next cycle of treatment should be delayed. Should treatment need to be delayed for more than 7 days (if there are more than 28 days between the start of one cycle and the start of the next) because of inadequate recovery from non-hematologic toxicity related to CPI-0610, this will be considered a dose-limiting event.

PATIENTS WITH ACUTE LEUKEMIA, MDS OR MDS/MPN

Because acute leukemias, MDS and MDS/MPN cause marked impairment of normal hematopoiesis, treatment may continue in the face of severe peripheral cytopenias until all disease has been cleared from the peripheral blood and bone marrow. If all disease has been cleared from the marrow, then treatment with CPI-0610 should be held until the platelet count and absolute neutrophil count have had the opportunity to recover. It is anticipated that even with the morphologic elimination of all disease from the marrow peripheral blood counts may not return to normal levels, reflecting stem cell depletion from the disease and its prior treatment. Re-treatment with CPI-0610 may be considered once there is evidence that improvements in the platelet count and absolute neutrophil count have plateaued.

PATIENTS WITH MF

In order for a new cycle of therapy to begin following the scheduled 7-day break from therapy the patient's ANC must be $\geq 1.0 \times 10^9$/L and the platelet count must be $\geq 50 \times 10^9$/L. If the patient fails to meet these criteria for retreatment, then initiation of the next cycle of treatment should be delayed by one week. If treatment needs to be delayed for more than 7 days (if there are more than 28 days between the start of one cycle and the start of the next) because of inadequate recovery from CPI-0610-related hematologic toxicity, this will be considered a dose-limiting event.

5.6.5 Phase 1 Dose modification guidelines

5.6.5.1 Dose reduction

Patients should not have planned dosing with CPI-0610 reduced unless a dose-limiting toxicity has occurred, as outlined in Table 5-3. If a DLT occurs, then the patient may be withdrawn from the study after appropriate follow-up has been completed. However, if the patient's disease is at least stable and the investigator believes that it is in the patient's best interest to continue therapy with CPI-0610, then consideration may be given to resuming treatment at a previously evaluated lower dose. Note that resumption of treatment at a lower dose will not be allowed in the case of CTCAE grade 4 non-hematologic toxicities. Moreover, when a dose reduction of CPI-0610 is required, no re-escalation of dose will be permitted.

The lower dose to be used cannot be specified *a priori*, since the actual doses evaluated and the dose-toxicity relationships will not be known until there is clinical experience with CPI-0610. Hence the choice of the lower dose at which to resume treatment will require discussion between the investigator and sponsor following review of the relevant clinical data.

5.6.5.2 Intra-patient dose escalation

Individual patients may be considered for treatment with a dose of CPI-0610 that is higher than the dose to which they were originally assigned. In order for a patient to be treated at a higher dose of CPI-0610, the patient must have tolerated the lower dose for at least two cycles of therapy, i.e., no CPI-0610-related toxicity > CTCAE grade 1 was observed with the patient's treatment at the lower dose. Moreover, the new, higher dose with which the patient is to be treated must be a dose that has completed evaluation and does not exceed the MTD.

There is no limit to the number of times the dose of CPI-0610 may be increased for each patient. However, for any instance of intra-patient dose escalation the rules remain the same: the patient must not have experienced CPI-0610-related non-hematologic toxicity > CTCAE grade 1 for at least two cycles of therapy at the lower dose, and the higher dose being considered must have been well tolerated (i.e., is below or equal to the MTD).

Consultation with Constellation must occur prior to any intra-patient dose escalation.

5.6.6 Phase 1 Management of DLTs and other adverse events

5.6.6.1 Assessment of potential cardiac toxicity

Because this study includes serial measurements of serum cardiac troponin (cTn) levels, it is anticipated that there may be patients in whom a measurement is found to be increased and therefore requires further evaluation. Cardiac troponin (cTn) levels ≥ 99% percentile of the upper reference limit (URL) should be considered abnormal. The significance of the increased cTn should be further investigated with repeated cTn measurements and ECGs, in consultation with a cardiologist. Constellation will retain a cardiologist to assist it and the investigators in the interpretation of cTn measurements and other cardiac data. The study investigators are expected to consult with their own local cardiologists, but will also have access to the cardiology consultant retained by Constellation.

5.6.6.2 Follow-up for dose-limiting toxicities

Patients whose treatment is interrupted or permanently discontinued because of dose-limiting toxicity must be followed until the toxicity resolves or stabilizes. Table 5-4 provides specific guidelines for follow-up of some of the more common hematologic, renal, hepatic and cardiovascular dose-limiting toxicities encountered in Phase 1 oncology clinical trials.

Table 5-4 Follow-up evaluations for dose-limiting toxicities

Toxicity	Follow-up evaluation
Hematology: patients with acute leukemia, MDS or MDS/MPN	In patients who have CTCAE grade 4 neutropenia (ANC < 0.5 x 10^9/L) and/or grade 4 thrombocytopenia (<25 x 10^9/L) in the absence of any morphologic evidence of residual disease (acute leukemia, MDS or MDS/MPN), a CBC with differential should be obtained twice weekly until the ANC is ≥ 0.5 x 10^9/L and the platelet counts is ≥ 25 x 10^9. Bone marrow aspiration and biopsy should be repeated at least once monthly until there is evidence of marrow recovery or disease relapse.
Hematology: patients with MF	If the platelet count falls below 10 x 10^9/L, the CBC must be repeated at least twice a week until it is ≥ 25 x 10^9/L, as determined on at least 2 consecutive days. Thereafter the CBC should be repeated at least once a week until the platelet count is ≥ 50 x 10^9/L. If CTCAE grade 4 neutropenia occurs, the CBC must be repeated at least once a week.
Renal	If the serum creatinine is > 3 x baseline or > 3 x ULN, then it must be re-determined at least twice a week until it resolves to CTCAE grade 2, and then at least once a week until it resolves to ≤ CTCAE grade 1 or stabilizes.
Hepatic	If the total bilirubin > 3 x ULN or the ALT is > 5.0 x ULN, these parameters must be repeated at least twice a week until resolution to CTCAE grade 2, and then at least once a week until resolved to CTCAE grade 1 or stabilized. Patients with total bilirubin > ULN (any duration) should have fractionation of bilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by these results.
Cardiac	If a QTcF > 500 msec has been demonstrated:

Toxicity	Follow-up evaluation
	For all patients with a new QTcF greater than 500 msec, occurring at any time during the study, as identified by the investigator, an immediate evaluation of that ECG by the central laboratory will be obtained and confirmed. The subject will be monitored by the investigator with hourly ECGs until the QTcF is < 500 msec and the QTcF has returned to < 30 msec from baseline. Immediate attention to potassium and magnesium and other clinical factors such as oxygenation and ischemia will be addressed. A plasma sample will be drawn to assess the concentrations of CPI-0610, magnesium and potassium at the time when the absolute QTcF is first noted to be > 500 msec. Once QTcF prolongation has resolved, patients may be re-treated at a lower dose with ECG monitoring frequency as in cycle 1. Subjects who experience absolute QTcF > 500 msec after dose reduction will be discontinued from study. Cardiac troponin (cTn) levels ≥ 99% percentile of the upper reference limit (URL) should be considered abnormal. The significance of the abnormality should be further investigated with repeated cTn measurements, ECGs, and potentially with other studies (e.g., echocardiography), in consultation with a cardiologist.
Non-laboratory	Patients who experience non-laboratory DLTs must be evaluated at least once a week following the initial identification of the toxicity until its resolution or stabilization.

5.7 Phase 2 (MF Expansion)

Following completion of Phase 1 (dose escalation), and after evaluation of 3 Phase 1 trials, the MTD of single agent CPI-0610 across all hematological malignancies was defined as 225 mg QD (tablet formulation). The expansion phase of the study will evaluate CPI-0610 in two separate groups of patients:

Monotherapy Arm (MF patients treated with CPI-0610 alone)

- Open to patients with MF who have previously been treated with a JAK inhibitor and are intolerant, resistant, refractory or lost response to the JAK inhibitor. The initial dose of CPI-0610 will be 125 mg QD (tablet formulation). Upward titration (see Section 5.7.1) of CPI-0610 is allowed (up to a maximum dose of 225 mg QD) based on platelet count, hemoglobin levels and safety evaluation. Dose modification using downward titration will be utilized for patients who meet the dose adjustment criteria as outlined in Section 5.7.2.1. CPI-0610 may be re-escalated after dose reduction provided the criteria in Section 5.7.2.2 are met.

Combination Arm (MF patients treated with CPI-0610 in combination with ruxolitinib)

- Open to patients with MF who are currently taking ruxolitinib but have disease that is not being adequately controlled by ruxolitinib. The initial dose of CPI-0610 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 CPI-0610 only up to a maximum dose of 225 mg QD based on platelet count, hemoglobin levels and safety evaluation; see Section 5.7.1) and downward titration (for either CPI-0610 or for ruxolitinib; see Section 5.7.2.1) will be utilized for patients who meet the dose adjustment criteria. **NOTE:** no dose above the original dose of ruxolitinib is allowed. CPI-0610 may be re-escalated after dose reduction provided the criteria in Section 5.7.2.2 are met.

5.7.1 NOTE: Patients in the Combination Arm are required to have been on a stable dose of ruxolitinib for ≥ 8 weeks prior to start of study drug. Therefore, 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. Upward Titration Criteria for CPI-0610

The starting dose of CPI-1205 for all patients in Phase 2 will be 125 mg QD. Upward titration of CPI-0610 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) or Cycle 3 Day 1 (Combination Arm).

The following criteria must be met in order for the dose of CPI-0610 to be upward titrated by 50 mg (Monotherapy Arm) or 25 mg (Combination Arm) on Day 1 of a cycle:

- No dose reduction of CPI-0610 has been required for toxicity as per Section 5.7.2.1, Table 5-5*.
- No safety concerns requiring CPI-0610 interruption, dose reduction or discontinuation on the day the dose increase is under consideration
- For Monotherapy Arm patients, platelet count has been > 75 x 10^9/L over the course of the prior 1 cycle
- For Combination Arm patients, platelet count has been >100 x 10^9/L over the course of the prior 2 cycles (**NOTE:** both cycles do not have to be at the same dose)

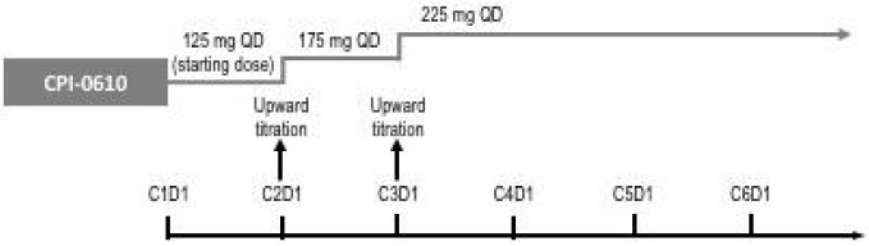
*If a dose reduction of CPI-0610 is required for toxicity, re-escalation back to the original dose is allowed, provided the patient meets the criteria as described in Section 5.7.2.2. Once the patient is back on their original dose, further upward titration of their dose may be possible only after consultation with the CPI Medical Monitor.

For Combination Arm patients, the dose of ruxolitinib should remain the same during the treatment, unless a dose modification is required for toxicity (see Section5.7.2.1).

Figure 5-1 and Figure 5-2 below provide 2 examples of how upward titration of CPI-0610 may work for the Monotherapy Arm depending on the patient's clinical scenario. Figure 5-3 and

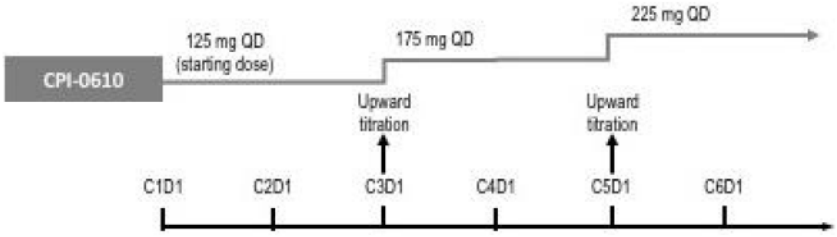
Figure 5-4 provide 2 examples of how upward titration of CPI-0610 may work for the Combination Arm.

Figure 5-1 Example 1: Upward Titration of CPI-0610 for Monotherapy Arm Patients



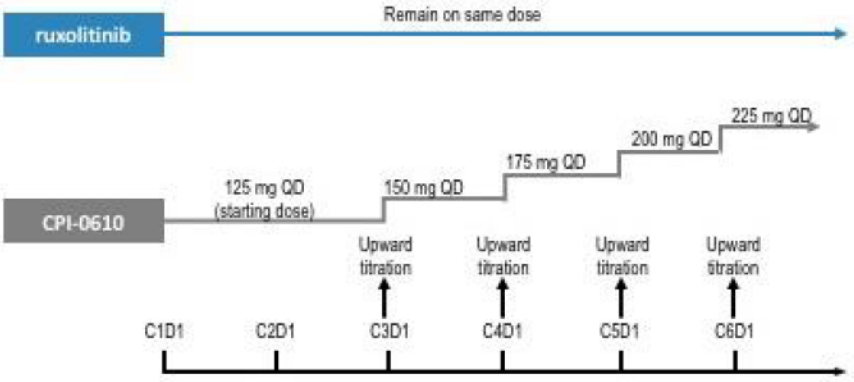
Criteria for upward titration are met on C2D1 as per Section 5.7.1, CPI-0610 can be increased to 175 mg QD
Criteria for upward titration are met on C3D1 as per Section 5.7.1, CPI-0610 can be increased to 225 mg QD

Figure 5-2 Example 2: Upward Titration of CPI-0610 for Monotherapy Arm Patients



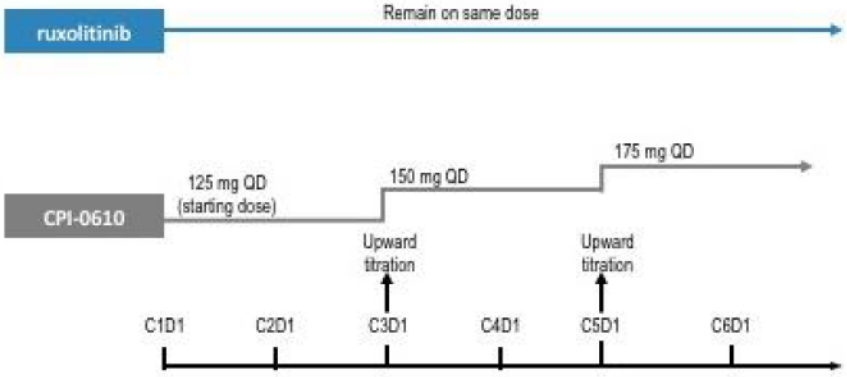
Criteria for upward titration are NOT met on C2D1 as per Section 5.7.1, and no dose reduction required as per Section 5.7.2; CPI-0610 dose remains at 125 mg QD
Criteria for upward titration are met on C3D1 as per Section 5.7.1, CPI-0610 can be increased to 175 mg QD
Criteria for upward titration are NOT met on C4D1 as per Section 5.7.1, and no dose reduction required as per Section 5.7.2; CPI-0610 dose remains at 175 mg QD
Criteria for upward titration are met on C5D1 as per Section 5.7.1, CPI-0610 can be increased to 225 mg QD

Figure 5-3 Example 1: Upward Titration of CPI-0610 for Combination Arm Patients



Criteria for upward titration are met on C3D1 as per Section 5.7.1, CPI-0610 can be increased to 150 mg QD
Criteria for upward titration are met on C4D1 as per Section 5.7.1, CPI-0610 can be increased to 175 mg QD
Criteria for upward titration are met on C5D1 as per Section 5.7.1, CPI-0610 can be increased to 200 mg QD
Criteria for upward titration are met on C6D1 as per Section 5.7.1, CPI-0610 can be increased to 225 mg QD

Figure 5-4 Example 2: Upward Titration of CPI-0610 for Combination Arm Patients



Criteria for upward titration are met on C3D1 as per Section 5.7.1, CPI-0610 can be increased to 150 mg QD
Criteria for upward titration are NOT met on C4D1 as per Section 5.7.1, and no dose reduction required as per Section 5.7.2; CPI-0610 dose remains at 150 mg QD
Criteria for upward titration are met on C5D1 as per Section 5.7.1, CPI-0610 can be increased to 175 mg QD
Criteria for upward titration are NOT met on C6D1 as per Section 5.7.1, and no dose reduction required as per Section 5.7.2; CPI-0610 dose remains at 175 mg QD

5.7.2 Phase 2 Dose Modifications Rules

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 6-2). Toxicity will be assessed according to the NCI CTCAE, v4.03. The investigator should carefully assess all treatment-associated toxicities and in the Combination Arm, whenever possible, determine if they can be attributed to CPI-0610 alone, ruxolitinib alone or to the combination of CPI-0610 plus ruxolitininb.

If patients experience CPI-0610 drug toxicity as specified in Table 5-5 below, follow the actions required. If Combination Arm patients experience ruxolitinib drug toxicity as specified in Table 5-5 below, follow the actions required.

Monotherapy Arm (CPI-0610 alone):

- For CPI-0610 dose reduction, the dose will be downwards titrated by 25 mg/day (minimum dose level 125 mg QD**).

Combination Arm (CPI-0610 plus ruxolitinib):

- For CPI-0610 dose reduction, the dose will be downwards titrated by 25 mg/day (minimum dose level 125 mg QD**).

- For ruxolitinib dose reduction, the dose will be downwards titrated by 5 mg/day (minimum dose level 5 mg BID).

**Dose reductions of CPI-0610 below 125 mg QD should be discussed with the CPI Medical Monitor on a case-by-case basis. If it is deemed that a dose reduction below 125 mg QD is not appropriate, CPI-0610 will be permanently discontinued and the patient followed-up per protocol.

If CPI-0610 must be held for >28 days due to toxicities (i.e., if a break of >35 days is required), CPI-0610 must be permanently discontinued (unless patient has evidence of clinical benefit) and the patient follow-up per protocol. If CPI-0610 is permanently discontinued in patients in the Combination Arm, ruxolitinib may be continued as monotherapy at the discretion of the investigator, but this will be considered off protocol treatment. 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. The patient may be allowed to continue on CPI-0610 monotherapy after discussion and approval of the CPI Medical Monitor provided patient has evidence of clinical benefit.

Cycles are defined throughout the trial as every 3 weeks. In the event that dosing with CPI-0610 (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 CPI-0610 for Days 15-21 (the prescribed 7-day off period).

5.7.2.1 Phase 2 Dose Modification for Toxicities for Both Arms

Table 5-5 provides rules on holding and/or dose modifying CPI-0610 (Monotherapy Arm and Combination Arm) and ruxolitinib (Combination Arm only) for drug-related toxicities. See Section 5.7.2.2 for possible re-escalation of CPI-0610 after any dose reduction required for toxicity.

Table 5-5 Dose Modification Table for Toxicities in Phase 2 (Both Arms)

Toxicity	Actions Required
Hematology	
Grade 4 neutropenia (ANC < 0.5 x 10^9/L)	• Hold CPI-0610 for up to 28 days. Repeat CBC at least twice weekly until resolution to ≤ Grade 3 • Once resolved to ≤ Grade 3, restart CPI-0610 reduced by one dose level. • In the Combination Arm, if Grade 4 recurs despite CPI-0610 dose reduction, then hold CPI-0610 and ruxolitinib for up to 28 days. • Repeat CBC at least twice weekly until resolution to ≤ Grade 3 • Once resolved to ≤ Grade 3, restart CPI-0610 at the same dose and ruxolitinib reduced by one dose level.
Grade 2 thrombocytopenia (platelets 50 to <75 x 10^9/L)	• Repeat CBC at least twice weekly until resolution to ≤ Grade 1
≥ Grade 3 thrombocytopenia (platelets < 50 x 10^9/L)	• Contact the CPI Medical Monitor for decisions regarding dose reductions and restarting rules
Hepatic	
≥ Grade 3 direct bilirubin (>3 x ULN)	• Hold CPI-0610 up to 28 days • Repeat direct bilirubin at least weekly until resolution to ≤ Grade 1 • Once resolves to ≤ Grade 1, restart CPI-0610 reduced by one dose level. • In the Combination Arm, if ≥ Grade 3 recurs despite CPI-0610 reduction, continue CPI-0610 at the reduced dose and hold ruxolitinib for up to 28 days. • Repeat direct bilirubin at least weekly until resolution to ≤ Grade 1 • Once resolves to ≤ Grade 1, restart ruxolitinib reduced by one dose level.
≥ Grade 3 ALT (>5 x ULN) in patients who enroll with ≤ Grade 1 ALT **OR** Tripling of ALT in patients who enroll with Grade 2 ALT	• Hold CPI-0610 up to 28 days • Repeat serum transaminases at least weekly until resolved to ≤ Grade 1 or baseline • Once resolves to ≤ Grade 1or baseline, restart CPI-0610 reduced by one dose level • In the Combination Arm, if toxicity recurs despite CPI-0610 reduction, continue CPI-0610 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 resolves to ≤ Grade 1or baseline, restart ruxolitinib reduced by one dose level
	• Hold CPI-0610 up to 28 days • Hold ruxolitinib up to 28 days

Toxicity	Actions Required
≥ Grade 2 direct bilirubin (>1.5 x ULN) **AND** ≥ Grade 2 ALT (>3 x ULN) in patients who enroll with ≤ Grade 1 ALT **OR** ≥ Grade 2 direct bilirubin (>1.5 x ULN) **AND** tripling of ALT in patients who enroll with Grade 2 ALT	• Once resolved to ≤ Grade 1 or baseline, if another cause is identified, restart CPI-0610 and ruxolitinib at same dose • Permanently discontinue CPI-0610 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 institutional guidelines (see Section 5.8.1 and 5.8.2) until resolution to ≤ Grade 1 • Hold CPI-0610 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 (e.g., hospitalization). • Resume CPI-0610 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, if ≥ Grade 3 persists >72 hours despite holding CPI-0610 dose, then also hold ruxolitinib for up to 28 days. • Resume ruxolitinib at same dose once recovers to ≤ Grade 1 and resume CPI-0610 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, and a hold of ruxolitinib was previously required because the duration was >72 hours, hold both CPI-0610 and ruxolitinib for up to 28 days
Other Non-specified	
≥ Grade 2 that, in the opinion of the investigator, requires dose reduction	• 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
Any toxicity caused by CPI-0610 that requires >28 days hold	• Permanently discontinue CPI-0610 if a break of >35 days off is required unless clear evidence of clinical benefit.
Any toxicity caused by ruxolitinib that requires >28 days hold	• Discontinue ruxolitinib

5.7.2.2 Re-escalation of CPI-0610 after Dose Reduction for Toxicity

If a dose of CPI-0610 has been reduced for a given patient and the toxicity resolves (with exceptions noted below) as indicated in Table 5-5 for at least 1 cycle, the dose level may be upward titrated one dose level higher per cycle at the discretion of the Investigator. This can be repeated until the original dose level (defined as the dose level before receiving the downwards

titration) is reached. **Exceptions:** Upward titration of the CPI-0610 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 judgment. 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 at the discretion of the Investigator. However, if Grade 4 neutropenia recurs, no subsequent upward dose titration will be permitted, even after the toxicity resolves. If a patient experiences ≥ Grade 3 thrombocytopenia, all re-escalation decisions must be made in consultation with the CPI Medical Monitor.

5.8 Supportive Care

5.8.1 Management of nausea and/or vomiting

As nausea and vomiting were not noted to be dose-limiting in Phase 1 (dose escalation), prophylactic anti-emetic therapy will not be administered. However, patients who develop severe or acute nausea and vomiting deemed related to CPI-0610 should be treated with anti-emetic therapy as per institutional standards. Subsequently, the prophylactic use of anti-emetics is allowed for those patients as needed.

5.8.2 Management of diarrhea

As diarrhea was not noted to be dose limiting in Phase 1 (dose escalation), prophylactic use of anti-diarrheal medicines will not be administered. Patients who develop diarrhea should be treated with anti-diarrhea medications as per 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 CPI-0610 must be contacted by the investigator or study nurse daily until it is clear that the problem has resolved or requires additional support (e.g., hospitalization). Subsequently, the prophylactic use of anti-diarrheal medication is allowed for those patients as needed.

5.9 Concomitant medications

5.9.1 Anti-neoplastic therapy

During Phase 1, patients with acute leukemia are allowed to receive therapy with oral hydroxyurea during the first 14 days of treatment with CPI-0610, if required for control of the peripheral blast count. If it is not possible to adequately control the peripheral blast count without hydroxyurea after the first 14 days of treatment with CPI-0610 have been completed, then the patient should be considered to have progressive disease and therapy with CPI-0610 should be discontinued. During Phase 2, patients are prohibited from receiving concomitant treatment with hydroxyurea and should discontinue treatment within 24 hours of starting CPI-0610.

Apart from the limited use of hydroxyurea noted above, and from the use of ruxolitinib in patients enrolled in the Phase 2 Combination Arm, patients are prohibited from receiving any

anti-neoplastic therapy other than CPI-0610 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 at enrollment. During the trial, doses > 10 mg of oral prednisone or equivalent are allowed if only required for ≤ 5 days. Topical, nasal and inhaled corticosteroids are also allowed.

5.9.3 Hematopoietic Growth Factors

Patients who have received a myeloid, erythroid or thrombopoietin growth factor within 4 weeks of the first dose of study drug will not be eligible for Phase 2 (MF expansion). During Phase 2, use of any of these growth factors are 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, 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 Combination Arm. 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 Arm; see Appendix 4. **NOTE:** Patients who require fluconazole at the time of screening will not be eligible for the Phase 2 Combination Arm of this trial. Patients 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. However, **initiation of treatment** of a strong CYP3A4 inhibitor or inducer (listed in Appendix 4) during study treatment with ruxolitinib in Combination Arm patients is prohibited.

CCI [redacted]

CCI [redacted]

CCI [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 QTdrugs on this website by risk category (i.e., 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.

5.10 Withdrawal of patients from protocol-mandated treatment

CPI-0610 treatment is to be permanently discontinued for patients meeting any of the following criteria:

- Development of progressive disease
- Occurrence of an unacceptable treatment-related AE
- Female patient becomes pregnant

An End of Treatment (EOT) visit is required for all patients within 7 days of the last dose of study 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 CPI-0610. 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, but this will be considered off protocol treatment. For patients who discontinue treatment for reasons other than documented disease progression should receive follow-up visits every 12 weeks to document response by imaging, palpation and transfusion requirements until initiation of another anti-cancer therapy, progression, death or cutoff date, whichever comes first.

5.11 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
- Alternative therapy or medication
- Administrative reasons

- Intercurrent illness
- Adverse event
- 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.

Following withdrawal of consent to participate in this trial 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.

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 IRB or independent ethics committee (IEC). Any other arrangements will be described in the study manual.

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 6-1. A separate schedule of events is presented for patients with MF in Phase 2 (MF expansion) in Table 6-2.

The screening period includes the 28 days before the first dose of CPI-0610.

In Phase 1, for logistical reasons (such as holidays) changes to the scheduled start day of new cycles and to scheduled visits following the first cycle of treatment (± 3 days) are permitted; however, patients must meet the criteria outlined in Section 5.6.2 to begin a new cycle of treatment. When applicable, specific visit windows for assessments (e.g., 6 hours [±1 hr]) are provided in the footnotes to the study schedules.

In Phase 1, for patients with acute leukemia, MDS or MDS/MPN, the approximate volume of blood collected from each patient will be 225 mL in Cycle 1 and 40 mL in each subsequent cycle.

In Phase 2, for logistical reasons (such as holidays), 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 CPI-0610 (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 CPI-0610 for Days 15-21 (the prescribed 7-day break). Because CPI-0610 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 CPI-0610. If a (+) window is utilized, missed doses cannot be made up.

For patients in Phase 2, the approximate volume of blood collected from each patient will be 10 mL (about 2 teaspoons) during screening, 140 mL (about 29 teaspoons) in Cycle 1, 10 mL (about 2 teaspoons) in Cycle 2, 65 mL (about 13 teaspoons) in Cycle 3, and approximately 10-100 mL (about 2-20 teaspoons) in all other cycles.

Table 6-1 Phase 1 (Dose Escalation) Schedule of Events: Patients with Acute Leukemia, MDS, MDS/MPN: 14 days of daily dosing, 7-day break (21-day cycle)

	Screening	Cycle 1						Cycle 2 and Beyond						
Assessment	**Days -28 to -1**	**Day 1**	**Days 2-7**	**Day 8**	**Days 9-13**	**Day 14**	**Days 15-19**	**Day 1**	**Days 2-7**	**Day 8**	**Days 9-14**	**Day 15**	**EOT[q]**	**EOS[q]**
Informed consent	X													
Study entry criteria	X													
Demographics	X													
Medical history	X													
Signs & symptoms/Physical Examination	X[a,b]	X[a,b]						X[b]					X	X
ECOG performance status	X	X[c]						X[c]					X	X
Vital signs	X	X[d]						X[c]						
ECG	X	X[d]		X[d]		X[d]		X[c]						
ECHO	X											X[e]		
ACTH stimulation test	X											X[e]		
Coagulation	X													
Hematology	X	X[f]		X[f]		X[f]		X[c]		X[f]		X[f]	X	X
Clinical chemistry	X	X[f]		X[f]		X[f]		X[c]		X[f]		X[f]	X	X
Pregnancy testing	X	X						X[c]					X	X
PK sampling		X[g]		X[h]		X[i]	X[j]	X[k]						
Peripheral blood pharmacodynamic sampling (leukocyte gene expression)		X[l]												
Bone marrow aspirate and biopsy	X[m]			X[n]								X[o]	X[p]	X[p]
Pharmacogenetic sample	X													
CPI-0610 administration		X	X	X	X	X		X	X	X	X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. The screening signs and symptoms assessment and physical examination may be used for the baseline evaluations if they are conducted ≤ 72 hours before the first dose of CPI-0610.
b. Physical examination, including weight, will be performed within 72 hours prior to the start of each cycle.
c. Performed ≤ 72 hours before the start of each cycle
d. ECGs and vital signs will be obtained prior to dosing and 1 hr (± 15 mins), 2 hrs (± 30 mins), 4 hrs (± 1 hr) and 6 hrs (± 2 hrs) after dosing
e. ECHO and ACTH stimulation test to be obtained after every 2 cycles of treatment for the first 6 cycles, and thereafter following every 4 cycles of treatment
f. These clinical chemistry and hematology tests will be assessed at least once each week during each cycle.
g. A PK blood sample will be collected prior to the first dose of CPI-0610 and at the following time points after the first dose: 30 mins (± 10 min), 1 hr (± 15 min), 1.5 hrs (± 15 min), 2 hrs (± 30 min), 3 hrs (± 30 min), 4 hrs (± 30 min), 6 hrs (± 1 hr), 8 hrs (± 1 hr), and 24 hrs (± 3 hrs).
h. A single PK blood sample will be collected prior to dosing on Day 8.

i. An additional PK sample will also be collected on the day during Cycle 1 that bone marrow biopsy and aspiration is conducted (between Days 8 and 13). This additional blood PK sample will be collected 0-2 hours before the bone marrow aspirate and biopsy are obtained. A PK blood sample will be collected prior to dosing on Day 14, and at the following time points after that dose: 30 min (± 10 min), 1 hr (± 15 min), 1.5 hrs (± 15 min), 2 hrs (± 30 min), 3 hrs (± 30 min), 4 hrs (± 30 min), 6 hrs (± 1 hr), and 8 hrs (± 1 hr).
j. A single PK blood sample will be collected on each study day.
k. A single PK blood sample will be collected prior to dosing on Cycle 2, Day 1 only.
l. A peripheral blood pharmacodynamic sample will be collected prior to dosing on Day 1 at the following time points after dosing: 2 hrs (± 30 min), 6 hrs (± 1 hr), and 8 hrs (± 1 hr).
m. The bone marrow biopsy and aspiration performed during screening will be used for both response assessment and for pharmacodynamic assessments.
n. The bone marrow biopsy and aspiration performed for pharmacodynamic assessments between Days 8 and 13 of Cycle 1 should be obtained 2-6 hours after that day's dose of CPI-0610.
o. Bone marrow biopsy and aspiration will be performed for response assessment between Days 15-21 of every second cycle of treatment for the first 6 cycles, thereafter once after every 4 cycles of treatment.
p. Bone marrow biopsy and aspiration performed for response assessment only if progressive disease has not been previously documented or, in the absence of documented progressive disease, if they have not been performed within the previous three weeks.
q. The EOT visit will be the same as the EOS for patients who will not be followed off study treatment.

Table 6-2 Phase 2 (MF Expansion) Schedule of Events: Patients with MF: 14 days of daily dosing, 7-day break (21-day cycle)

	Screening	Cycle 1				Cycle 2 & beyond	EOT	EOS[p]
Assessment (+/- days)	**Days** (-28 to Prior to Dosing)	**Day 1**	**Day 2[g]**	**Day 8**	**Day 14**	**Day 1** Each cycle (+/- 3)	(within 7 days of last dose of CPI-0610)	(within 30 days of last dose of CPI-0610 [+ 7 days])
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographics	X							
Medical history	X							
Physical examination	X[a,b]	X[a,b]				X[b]	X[b]	
MFSAF v4.0	Completed every day for 7 days prior to Day 1 of each cycle[r]							
PGIC		X[s]				X[s]	X[s]	
ECOG performance status	X	X[c]				X[c]	X	
Vital signs	X	X[c,d]				X[c,d]	X[d]	
ECG	X	X[c]				X[c]	X	
Transfusion documentation	X[e]	X[e]				X[e]	X[e]	
Coagulation	X[f]							
Hematology	X[a,f]	X[a,f]		X[f]	X[f]	X[c,f]	X[f]	
Clinical chemistry	X[a,f]	X[a,f]		X[f]	X[f]	X[c,f]	X[f]	
Pregnancy testing	X[f]	X[c,f]				X[c,f]	X[f]	
PK sampling		X[g]	X[g]	X[g]	X[g]	See footnote g		
Leukocyte gene expression (peripheral blood sample)		X[h]				See footnote h		
Cytokine assessment (peripheral blood sample)	X[i]				X[i]	See footnote i	X[i]	
Viable cells (peripheral blood sample)	X[j]					See footnote j	X[j]	
Mutated allele burden (peripheral blood sample)	X[k]					See footnote k	X[k]	
Bone marrow biopsy	X[l]					See footnote m	X[n]	
CT (or MRI) scan	X					See footnote o	X[n]	
CPI-0610 administration		Administered on Days 1-14 of each cycle						
Ruxolitinib administration (Combination Arm only)		Administered daily BID						
Adverse events	X	Collected continuously while the patient is on study[q]						X
Concomitant medications	X	Collected continuously while the patient is on study[q]						X

Table 6-2 Footnotes

a. The screening physical examination, hematology and clinical chemistry results do not need to be repeated on Cycle 1, Day1 if they are conducted ≤ 72 hours before the first dose of CPI-0610.
b. Complete physical examination at screening, including height, weight, clinical signs and symptoms, and palpable spleen and liver length, measured with a ruler. The complete physical exam will include assessment of splenomegaly and hepatomegaly. Subsequent physical exams (within 72 hours prior to the start of each 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 and liver length by palpation.
c. Performed ≤ 72 hours before the start of each cycle
d. Vital signs must include: temperature, pulse, respiratory rate, and blood pressure
e. A complete transfusion history will be taken during screening to include the date, type (e.g., whole blood, platelets, packed cells), number of units of the transfusion as well as the hemoglobin 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.
f. Coagulation parameters must include PT (INR) and aPTT. PT (INR) and aPTT will be determined during screening for all patients, thereafter coagulation parameters will be repeated only if clinically indicated.
   Hematology parameters must include a CBC with differential (i.e., RBC, hemoglobin, hematocrit, reticulocyte count, platelet count, total WBC count, differential WBC count, neutrophils, Bands/stabs, eosinophils, basophils, lymphocytes, monocytes, and % blasts) and a peripheral blood smear (i.e., total cell count, blast cells, nucleated erythrocytes, myelocytes, metamyelocytes, and promyelocytes). Hematology will be obtained at screening, weekly during Cycle 1, ≤ 72 hours before the start of each subsequent cycle of treatment, and at the EOT visit.
   Chemistry parameters must include sodium, potassium, carbon dioxide, chloride, serum glucose, blood urea nitrogen (BUN), serum creatinine, total and direct bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), lactate dehydrogenase (LDH), uric acid, calcium phosphate, hepcidin*, iron*, iron binding capacity*, ferritin* and transferrin saturation*. The chemistry parameters will be obtained at screening, weekly during Cycle 1, ≤ 72 hours before the start of each subsequent cycle of treatment and at the EOT visit. *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.
   Pregnancy test is only required in women of child bearing potential
g. PK sampling should follow the detailed tables outlined in Section 6.3.12.2. A visit on Cycle 1, Day 2 is required for patients in the Combination Arm only. PK samples are collected on Cycle 1, Day 8 in the Monotherapy Arm only. Additional PK sampling should be collected on Day 1 and Day 14 (when feasible) of the cycle when upward dose titration occurs as outlined in Section 6.3.12.2.
h. A peripheral blood sample for leukocyte gene expression will be collected prior to dosing on Cycle 1, Day 1 and at 4 hours after CPI-0610 dosing on Cycle 1, Day 1. In addition, samples will be collected on Day 1 of any cycle where the dose of CPI-0610 is changed (pre-dose and 4 hours after CPI-0610).
i. A peripheral blood sample for measurement of plasma cytokine concentrations will be collected prior to dosing on Cycle 1, Day 1 (may be collected anytime during screening), and then anytime on Cycle 1, Day 14, Day 1 of every third cycle of treatment (C3, C6, C9, etc.), and at the EOT visit.

j. A peripheral blood sample for collection of viable cells will be collected prior to dosing on Cycle 1, Day 1 (may be collected anytime during screening), and then anytime on Day 1 of every third cycle of treatment (C3, C6, C9, etc.) and at the EOT visit.
k. A peripheral blood sample for the assessment of mutated allele burden will be collected prior to dosing on Cycle 1, Day 1 (may be collected anytime during screening), after 24 weeks of treatment (Cycle 9, Day 1) and then every 24 weeks (8 cycles) thereafter and at the EOT visit.
l. The bone marrow biopsy sample will be accepted as the screening sample if obtained within 3 months of Cycle 1, Day 1.
m. 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 -7 days applies to these assessments.
n. The EOT bone marrow biopsy does not need to be collected if a biopsy has been performed within the previous 12 weeks. A CT (or MRI) scan will be performed at the EOT visit only if progressive disease has not been previously documented or, in the absence of documented progressive disease, if imaging has not been performed within the previous three weeks.
o. A CT (or MRI) scan to measure spleen (and liver) size will be performed 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 -7 days applies to these assessments.
p. The EOS visit should occur within 30 days from the last dose of CPI-0610 or for patients initiating a new anti-cancer therapy, EOS visit should occur just prior to initiation of new therapy. This visit may be conducted by telephone. For patients who discontinue treatment for reasons other than documented disease progression should receive follow-up visits every 12 weeks to document response by imaging, palpation and transfusion requirements until initiation of another anti-cancer therapy, progression, death or cutoff date, whichever comes first.
q. This information will be collected during clinic visits and during telephone calls (contact weekly) by study staff.
r. Symptom assessment via MFSAF v.4.0 by completion of a paper diary. 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 (i.e., Days 15-21 of the previous cycle).
s. 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 every cycle and at the EOT visit.

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.

6.3.2 Clinic visits

Patients should be seen in the clinic by the investigator during Screening, on Day 1 of Cycle 1, and then weekly during Cycle 1. Subsequently, patients should be seen in the clinic by the investigator on Day 1 of each new cycle of treatment, and they should be contacted weekly (in person or by phone) by study personnel to assess their well-being and compliance with the study.

During Phase 1, patients will have weekly safety labs collected and evaluated, as indicated in the Schedule of Events (Table 6-1).

During Phase 2, patients will have safety labs collected and evaluated weekly during Cycle 1, ≤ 72 hours before the start of each subsequent cycle of treatment and at the EOT visit. Additional visits for PK and biomarker assessments are outlined in the Schedule of Events (Table 6-2).

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 CPI-0610). 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 completed enrollment form has been sent to the study's clinical CRO, signed by the appropriate representative, and returned to the investigational site.

Procedures for completion of enrollment information will be described in the study manual.

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 Transfusions (Phase 2)

During Phase 2, a complete transfusion history will be taken during screening to include the date, type (e.g., whole blood, platelets, packed cells), number of units of the transfusion as well as the hemoglobin or platelet value at the time of the transfusion. An assessment of transfusion events will also be collected on Day 1 of every cycle and at the EOT visit.

6.3.7 CPI-0610 administration (All Patients)

Patients will receive CPI-0610 during the treatment period as outlined in Section 5. The first day of study treatment will be considered Day 1 of Cycle 1. CPI-0610 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.

During Phase 1, criteria for continuing treatment during a cycle of therapy and for beginning a new cycle of treatment are provided in Section 5.6.3 and Section 5.6.4.

During Phase 2, dose modification rules are provided in Section 5.7.2 and upward titration rules are provided in Section 5.7.1.

6.3.8 Ruxolitinib administration (Phase 2 Combination Arm)

Patients in the Phase 2 Combination Arm 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. See Section 5.7.2 for dose modification rules.

6.3.9 Phase 2 Patient Reported Outcomes (PROs)

6.3.9.1 Myelofibrosis Symptom Assessment Form Version 4.0 (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. The MFSAF uses a 24-hour recall (daily paper diary) 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 seven items on a 0 (Absent) to 10 (Worst Imaginable) numeric rating scale (see Appendix 5).

6.3.9.2 Patient Global Impression of Change (PGIC)

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 every cycle and at the EOT visit. The PGIC is a single question to assess the patient's impression of change in their myelofibrosis symptoms since the start of study treatment. The PGIC has been widely used to evaluate a patient's overall sense of whether a treatment has been beneficial. The patient will answer the following question: "Since

the start of the treatment you've received in this study, your myelofibrosis symptoms are (1) Very much improved, (2) Much improved, (3) Minimally improved, (4) No change, (5) Minimally worse, (6) Much worse, (7) Very much worse."

6.3.10 Safety assessments

6.3.10.1 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 CPI-0610. 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.

6.3.10.2 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed during screening, ≤ 72 hours before the start of each new cycle of treatment, at the End of Treatment (EOT) visit and at the EOS visit (Phase 1 only).

6.3.10.3 Signs and symptoms/Physical examination

Phase 1:

An assessment of signs and symptoms and a complete physical examination will be conducted during screening. The screening physical examination will record the patient's height and weight. The screening signs and symptoms assessment and physical examination may be used as the baseline assessments if they are conducted ≤ 72 hours before the first dose of CPI-0610.

An assessment of signs and symptoms and physical examination, including weight, will be conducted ≤ 72 hours before the beginning of each new cycle of treatment.

A signs and symptoms assessment and physical examination will be conducted at the EOT and EOS visits.

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 exam will include assessment of splenomegaly and hepatomegaly. If the screening physical examination is conducted ≤ 72 hours before the first dose of CPI-0610, it does not need to be repeated on Cycle 1, Day 1.

Subsequent physical exams (within 72 hours prior to the start of each cycle and at the EOT visit) may be targeted to areas of known disease and potential areas of MF involvement. The targeted physical examination must include weight and examination of the abdomen to assess the spleen and liver length by palpation.

6.3.10.4 Vital signs

Phase 1:

Vital signs (blood pressure, heart rate, and oral temperature) will be taken during screening; prior to dosing and1 hr (± 15 mins), 2 hrs (± 30 mins), 4 hrs (± 1 hr) and 6 hrs (± 2 hrs) after dosing on Cycle 1 Day 1; and ≤ 72 hours before the start of each new cycle of treatment.

Phase 2:Vital signs (temperature, pulse, respiratory rate, and blood pressure) will be taken at screening, ≤ 72 hours before the start of each new cycle of treatment and at the EOT visit.

6.3.10.5 Electrocardiograms

Phase 1:

A 12-lead ECG will be obtained as part of the screening evaluation.

On Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 14 a 12-lead ECG will be performed prior to dosing with CPI-0610, and ECGs will be repeated at 1 hr (± 15 min), 2 hrs (± 30 min), 4 hrs (± 1 hr), and 6 hrs (± 2hrs) hours post-dosing.

An ECG will be performed ≤ 72 hours before the start of each new cycle of treatment.

Phase 2:

A 12-lead ECG will be obtained as part of the screening evaluation, then performed ≤ 72 hours before the start of each new cycle of treatment and at the EOT visit.

6.3.10.6 Left ventricular ejection fraction by echocardiography (Phase 1 only)

An echocardiographic assessment of LVEF will be made during the screening evaluation. In patients with acute leukemia, MDS or MDS/MPN repeated echocardiographic assessment of LVEF will be made after the completion of every 2 cycles of therapy for the first 6 cycles, and thereafter following the completion of every 4 cycles of treatment.

Although LVEF can be assessed with a nuclear medicine scan, in this study echocardiography is the preferred technique because of the additional information that it can provide (e.g., detection of focal wall motion abnormalities).

6.3.10.7 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.

6.3.10.8 Clinical laboratory evaluations

COAGULATION PARAMETERS

Prothrombin time (PT) (INR) and activated partial thromboplastin time (aPTT) will be determined during screening for all patients. Thereafter the PT (INR) and aPTT will be repeated only if clinically indicated.

HEMATOLOGY

Phase 1:

A CBC with differential white blood cell (WBC) count ("CBC with differential") will be obtained during screening, baseline, at least once weekly during each cycle of treatment with CPI-0610, and at the EOT and EOS visits.

Phase 2:

A CBC with differential and a peripheral blood smear will be obtained at screening, weekly during Cycle 1, ≤ 72 hours before the start of each subsequent cycle of treatment, and at the EOT visit. If the screening assessment is conducted ≤ 72 hours before the first dose of CPI-0610, it does not need to be repeated on Cycle 1, Day 1.

The CBC with differential consists of the following: RBC, hemoglobin, hematocrit, reticulocyte count, platelet count, total WBC count, differential WBC count, neutrophils, Bands/stabs, eosinophils, basophils, lymphocytes, monocytes, and % blasts.

Peripheral blood smear consists of the following: total cell count, blast cells, nucleated erythrocytes, myelocytes, metamyelocytes, and promyelocytes.

CLINICAL CHEMISTRY

Phase 1:

A clinical chemistry panel will be obtained during screening, baseline, once weekly during each cycle of treatment with CPI-0610, and at the EOT and EOS visits.

Phase 2:

A clinical chemistry panel will be obtained at screening, weekly during Cycle 1, ≤ 72 hours before the start of each subsequent cycle of treatment and at the EOT visit. If the screening assessment is conducted ≤ 72 hours before the first dose of CPI-0610, it does not need to be repeated on Cycle 1, Day 1.

The clinical chemistry panel consists of the following: sodium, potassium, 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 (cTn; Phase 1 only), uric acid, calcium phosphate, hepcidin*, 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.

PREGNANCY TESTING

A serum beta-human chorionic gonadotropin (β-hCG) pregnancy test will be performed for women of childbearing potential during screening and at baseline. Both results must be negative before the first dose of CPI-0610 is given. In women of childbearing potential, the serum pregnancy test will be repeated ≤ 72 hours before the start of each new cycle of treatment. The pregnancy test will be repeated at the EOT visit.In Phase 2, females with β-hCG values that are within the range for pregnancy but are not pregnant (false-positives) may be enrolled with written consent of the Constellation Pharmaceuticals medical monitor, after pregnancy has been excluded.

If a female patient or a male patient's partner becomes pregnant or suspects pregnancy while participating in this study, the investigator must be informed immediately.

ACTH STIMULATION TESTING (PHASE 1 ONLY)

An adrenocorticotropic hormone (ACTH) stimulation test will be performed before the patient receives his or her first dose of CPI-0610. In patients with acute leukemia, MDS or MDS/MPN, this test will then be repeated after the completion of every 2 cycles of treatment for the first 6 cycles, and thereafter following the completion of every 4 cycles of treatment.

The ACTH stimulation test consists of drawing blood for the measurement of serum cortisol concentrations before and then 30 and 60 minutes after the intravenous injection of 250 mcg of cosyntropin. The current criteria used to indicate normal adrenal function are a minimum serum cortisol concentration ≥18 to 20 mcg/dL (500 to 550 nmol/L) before ***or*** after ACTH injection.

Because different glucocorticoids interfere with the measurement of serum cortisol, patients who are taking glucocorticoids on an ongoing basis should be switched to an equivalent dose of dexamethasone, which does not interfere with this measurement.

6.3.11 Efficacy measurements

6.3.11.1 Disease response assessment

PATIENTS WITH ACUTE LEUKEMIA, MDS OR MDS/MPN (PHASE 1)

Disease response assessment will be performed by the investigator, following the 2013 NCCN criteria for ALL, the 2003 Cheson criteria for AML, and the 2006 modification of the IWG response criteria for MDS and MDS/MPN.[44-46] These response criteria are provided in Section 7.2.1.

During the screening period patients will have bone marrow aspiration and biopsy performed, accompanied by a CBC with differential on the same day, to establish baseline disease status. A portion of the aspirate sample will be sent for cytogenetic and molecular analyses, which may be helpful in later assessing the depth of responses. Patients suspected of having extramedullary

disease or with a history of extramedullary disease may also require the conduct of additional studies (spinal fluid cytology, radiographic imaging) to delineate the extent of their disease.

Re-assessment of the patient's disease status, mainly via assessment of peripheral blood counts and of the bone marrow aspirate and biopsy, will be repeated after the completion of every 2 cycles of treatment. Re-assessment of disease status will generally be conducted at the end of the relevant cycle of treatment, in order to help determine whether beginning a new cycle of treatment is appropriate.

Patients who achieve morphologic disappearance of all blasts from the bone marrow and peripheral blood will have therapy with CPI-0610 held until the outcome (evidence of hematologic recovery) of the leukemic blast clearance can be determined. During this time the CBC will be performed at least once a week and bone marrow aspiration and biopsy will be performed at least once every 4 weeks. Cytogenetic and molecular re-evaluation of the marrow should be repeated in patients achieving a CR.

Bone marrow biopsy and aspiration for disease response assessment should be repeated at the EOT/EOS visit, only if progressive disease has not been previously documented or, in the absence of documented progressive disease, if they have not been performed within the previous three weeks.

PATIENTS WITH MF (PHASE 2)

Disease response including splenic response, change in PROs, RBC transfusion status and response as assessed by the investigator following the 2013 revised IWG-MRT criteria[47] will be evaluated. These response criteria are provided in Section 7.2.4.

The patient's disease status will be evaluated with measurement of peripheral blood counts (see Section 6.3.10.8), history/documentation of transfusion requirements (see Section 6.3.6), MF-associated symptoms (see Section 6.3.9), spleen and liver size by palpation (see Section 6.3.10.3) and by CT or MRI (see below), extent of marrow fibrosis (with bone marrow biopsy; see Section 6.3.15.5), and mutant allele burden (in peripheral blood; see Section 6.3.15.4).

A CT or MRI scan will be done 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 -7 days applies to these assessments. A CT or MRI scan should be repeated at the EOT visit only if progressive disease has not been previously documented or, in the absence of documented progressive disease, if imaging has not been performed within the previous three weeks.

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

6.3.12 Pharmacokinetic measurements

6.3.12.1 Overview of the pharmacokinetic sampling strategy

Serial peripheral blood samples (approximately 4 mL each) will be drawn before and after dosing with CPI-0610 in the first cycle of treatment in order to determine circulating concentrations of CPI-0610, and in the Phase 2 Combination Arm, to evaluate the PK profile of

ruxolitinib when given in combination with CPI-0610. See the specific time points for sampling outlined in Section 6.3.12.2. The sampling following the last dose is designed to assess steady-state concentrations of CPI-0610 and to provide an assessment of its elimination half-life. A pre-dose PK sample will be collected on Day 8 to permit an assessment of the extent to which steady-state concentrations have been achieved after one week of dosing. In Phase 2, serial blood samples will also be collected before and after dosing with CPI-0610 when upward dose titration occurs.

In patients with acute leukemia, MDS, or MDS/MPN (Phase 1), one additional blood sample for determining the circulating concentration of CPI-0610 will be collected during Cycle 1 on the day that bone marrow aspiration and biopsy are performed. This additional PK sample serves to facilitate an assessment of the relationship between circulating concentrations of CPI-0610 and its pharmacodynamic effects in leukemic cells.

6.3.12.2 Specific time points for pharmacokinetic sampling

The PK sampling time points for patients enrolled in Phase 1 are shown in Table 6-3. In patients with acute leukemia, MDS, or MDS/MPN, a total of approximately 108 mL of blood will be taken for pharmacokinetic samples; in patients with MF the total will be approximately 104 mL. The PK sampling time points for patients with MF enrolled in the Phase 2 Monotherapy Arm are shown in Table 6-4. The total volume of blood drawn in the Monotherapy Arm will be approximately 36 mLs during Cycle 1 and 56 mLs in cycles where upward titration occurs. The PK sampling time points for newly enrolled patients with MF in the Phase 2 Combination Arm are shown in Table 6-5. The total volume of blood drawn in the Combination Arm will be approximately 76 mLs in Cycle 1 and 72 mLs in cycles where upward titration occurs.

Table 6-3 Phase 1 pharmacokinetic sampling schedule

Cycle Day	Time point	Total approximate amount of blood per study day
C1D1	Prior to dosing 30 minutes (±10 min) after dosing 1 hour (±15 min) after dosing 1.5 hours (±15 min) after dosing 2 hours (±30 min) after dosing 3 hours (±30 min) after dosing 4 hours (±30 min) after dosing 6 hours (± 1 hr) after dosing 8 hours (± 1 hr) after dosing 24 hours (± 3 hr) after dosing	40 mL
C1D8	Prior to dosing	4 mL
C1D8-13*	0-2 hours before bone marrow aspirate and biopsy	4 mL
C1D14	Prior to dosing 30 minutes (±10 min) after dosing 1 hour (±15 min) after dosing 1.5 hours (±15 min) after dosing 2 hours (±30 min) after dosing 3 hours (±30 min) after dosing 4 hours (±30 min) after dosing 6 hours (± 1 hr) after dosing 8 hours (± 1 hr) after dosing	36 mL

C1D15	Prior to dosing	4 mL
C1D16	Anytime	4 mL
C1D17	Anytime	4 mL
C1D18	Anytime	4 mL
C1D19	Anytime	4 mL
C2D1	Prior to dosing	4 mL

* sample collected only in patients with acute leukemia, MDS, or MDS/MPN

Table 6-4 Pharmacokinetic sampling schedule: Phase 2 Monotherapy Arm

Cycle Day	Time point	Total approximate amount of blood per study day
C1D1	Prior to dosing	4 mL
C1D8	Prior to dosing	4 mL
C1D14	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
CXD1 (X = cycle when upward dose titration 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
CXD14 (X = cycle when upward dose titration occurs if feasible)	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

Table 6-5 Pharmacokinetic sampling schedule: Phase 2 Combination Arm

Cycle Day	Time point	Total approximate amount of blood per study day
C1D1	Prior to dosing* 30 minutes (±10 min) after dosing 1 hour (±15 min) after dosing 1.5 hours (±15 min) after dosing 2 hours (±30 min) after dosing 3 hours (±30 min) after dosing 4 hours (±30 min) after dosing 6 hours (± 1 hr) after dosing 8 hours (± 1 hr) after dosing	36 mL
C1D2	Prior to dosing* (24 hours after C1D1 dosing [±3 hours])	4 mL
C1D14	Prior to dosing* 30 minutes (±10 min) after dosing 1 hour (±15 min) after dosing 1.5 hours (±15 min) after dosing 2 hours (±30 min) after dosing 3 hours (±30 min) after dosing 4 hours (±30 min) after dosing 6 hours (± 1 hr) after dosing 8 hours (± 1 hr) after dosing	36 mL
CXD1 (X = cycle when upward dose titration occurs)	Prior to dosing* 30 minutes (±10 min) after dosing 1 hour (±15 min) after dosing 1.5 hours (±15 min) after dosing 2 hours (±30 min) after dosing 3 hours (±30 min) after dosing 4 hours (±30 min) after dosing 6 hours (± 1 hr) after dosing 8 hours (± 1 hr) after dosing	36 mL
CXD14 (X = cycle when upward dose titration occurs if feasible)	Prior to dosing* 30 minutes (±10 min) after dosing 1 hour (±15 min) after dosing 1.5 hours (±15 min) after dosing 2 hours (±30 min) after dosing 3 hours (±30 min) after dosing 4 hours (±30 min) after dosing 6 hours (± 1 hr) after dosing 8 hours (± 1 hr) after dosing	36 mL

*Times are prior to dosing with CPI-0610 (which is to be ingested immediately prior to ruxolitinib)

The timing, but not the number (unless fewer) of blood samples drawn for CPI-0610 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 CPI-0610's and/or ruxolitinib's PK.

CCI [redacted]

CCI [redacted]

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

6.3.13 Phase 1: Pharmacodynamic biomarker measurements in patients with acute leukemia, MDS or MDS/MPN

6.3.13.1 Peripheral blood samples for assessment of gene expression changes in circulating leukocytes

Patients will have peripheral blood samples (approximately 5 mL of whole blood each) collected at selected time points that coincide with PK sampling and with the collection of bone marrow aspirates and biopsies. The blood samples will be collected into PAXgene blood RNA tubes, and RNA will be subsequently isolated. These RNA samples will be assessed by qPCR for changes in the expression of genes predicted to be sensitive to exposure to CPI-0610. Gene expression in these samples may also be assessed in a global, unbiased manner using RNA Seq.

Table 6-6 Peripheral blood pharmacodynamic sampling schedule

Cycle Day	Time point
C1D1	Pre-dose, 2 (± 30 mins), 6 (± 1 hr) and 8 (± 1 hr) hours post-dose

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

6.3.13.2 Bone marrow biopsies and aspirates for pharmacodynamic analyses

All patients with acute leukemia, MDS or MDS/MPN will have a bone marrow biopsy and a bone marrow aspirate performed before the first dose of CPI-0610 is given, in order to establish the status of their disease prior to treatment and to provide baseline measurements of pharmacodynamic markers. A second bone marrow biopsy and aspirate will be obtained during the first cycle of treatment (between Days 8 and 13), for comparison to the pre-treatment sample, in order to assess potential changes in pharmacodynamic markers.

Slides prepared from the baseline and Cycle 1 bone marrow biopsy and aspirate will be assessed by IHC and *in situ* hybridization (ISH) for changes in the expression of selected genes predicted to be sensitive to BET protein bromodomain inhibition.

Table 6-7outlines the schedule of bone marrow biopsies and aspirates that are performed for pharmacodynamic assessments. Note that additional bone marrow biopsies and aspirates are performed after Cycle 1 for assessment of the clinical status of the patient's disease and are not used for pharmacodynamic assessments.

Table 6-7 Bone marrow biopsy and aspirate for pharmacodynamic assessments

Cycle Day	Time point

Screening	Any time
C1, once between Days 8 and 13	2-6 hours after dosing

All bone marrow biopsies and aspirates should be accompanied by a CBC with differential.

In addition, 0-2 hours before the marrow aspirate and biopsy are performed four additional peripheral blood samples will be obtained; one for PK; two for pharmacodynamics (changes in gene expression in circulating leukocytes) and one for the isolation of leukemic cells from peripheral blood for the assessment of potential predictive biomarkers (see Section 6.3.14).

The timing of the Cycle 1 bone marrow biopsy and aspirate may be changed if the emerging data indicate that an adjustment in the timing of the procedure is needed to better characterize the pharmacodynamic effects of CPI-0610 in leukemic/dysplastic cells.

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

6.3.14 Phase 1: Predictive biomarker measurements in patients with acute leukemia, MDS or MDS/MPN

As described Section 6.3.12.2 (Specific time points for pharmacokinetic sampling), a peripheral blood sample (approximately 8.5 mL CCI [redacted] In patients with acute leukemia, MDS, or MDS/MPN this sample may also be used for the isolation of DNA and identification of mutations in circulating leukemic cells that may correlate with response or resistance to treatment with CPI-0610.

In patients with acute leukemia, MDS, or MDS/MPN leukemic cells will be isolated from the bone marrow aspirates and accompanying samples of peripheral blood using antibodies against leukemia-specific cell surface markers (e.g., CD33 for myeloid leukemias), and both DNA and RNA will be harvested from these cells. DNA sequencing may be performed to identify mutations that could be associated with response or resistance to CPI-0610 treatment. RNA Seq may be used to identify patterns of gene expression that could be associated with response or resistance to CPI-0610 treatment.

Samples will be sent to a contract laboratory for analysis. Details regarding sample handling and shipping will be provided in the study manual.

6.3.15 Phase 2: Pharmacodynamic biomarker measurements in patients with MF

6.3.15.1 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 pre-dose and 4 hours after administration of CPI-0610 on Cycle 1 Day 1 (see Table

6-8). In addition, these samples will be collected on Day 1 of any cycle where the dose of CPI-0610 is changed. 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 CPI-0610.

Table 6-8 Peripheral blood circulating leukocytes sampling schedule

Cycle Day	Time point
C1D1	Pre-dose 4 hours
CXD1 (upon any dose change)	Pre-dose 4 hours

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

6.3.15.2 Peripheral blood samples for cytokine 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. Samples will be collected prior to the administration of CPI-0610 on Cycle 1, Day 1, on Cyc1e 1, Day 14, then on Day 1 of every third cycle of treatment (Day 1 of Cycle 3, 6, 9, etc.) and at the EOT visit (see Table 6-9).

Table 6-9 Peripheral blood cytokine sampling schedule

Cycle Day	Time point
C1D1	Pre-dose*
C1D14	Anytime
CXD1 (X = every 3 cycles, i.e., C3, C6, C9, etc.)	Anytime
EOT	Anytime

* Can be collected anytime during the screening period

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.

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

6.3.15.3 Peripheral blood samples for collection of viable cells

Peripheral blood samples (approximately 30 mL of whole blood at each time point) will be collected for cryopreservation of viable mononuclear cells for assessment of changes in genes associated with myelofibrosis 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 CPI-0610 on Cycle 1, Day 1, on Day 1 of every third cycle of treatment (Day 1 of Cycle 3, 6, 9, etc.) and at the EOT visit (see Table 6-10).

Table 6-10 Peripheral blood viable cell sampling schedule

Cycle Day	Time point
C1D1	Pre-dose*
CXD1 (X = every 3 cycles, i.e., C3, C6, C9, etc.)	Anytime
EOT	Anytime

* Can be collected anytime during the screening period

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

6.3.15.4 Peripheral blood samples for allele burden assessment

Peripheral blood samples (approximately 10 mL of whole blood at each time point) will be collected for the measurement of mutant allele burden of selected genes (e.g., *JAK2*, *CALR*) using a focused NGS assay. Samples will be collected 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 6-11). CCI [redacted] Additionally, changes in allelic burden of specific mutations in patients treated with CPI-0610 may identify hypersensitivity of certain mutational contexts to CPI-0610.

Table 6-11 Peripheral blood mutant allele sampling schedule

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

* Can be collected anytime during the screening period

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

6.3.15.5 Bone marrow biopsies for grading of fibrosis

Bone marrow biopsy samples will be collected and assessed by a local hematopathologist for grading of bone marrow fibrosis following the European classification[48] during screening, after 24 weeks of treatment (Cycle 9, Day 1), every 24 weeks (8 cycles) thereafter and at the EOT visit (see Table 6-12). The EOT bone marrow biopsy does not need to be collected if a biopsy has been performed within the previous 12 weeks. Slides should be sent to the central lab. 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]

Table 6-12 Bone marrow sampling schedule

Cycle Day	Time point
Screening	Anytime*
CXD1 (X = every 8 cycles, i.e., C9, C17, etc)	Anytime
EOT**	Anytime

* 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 study manual.

6.3.16 CCI [redacted]

All blood and bone marrow samples collected as detailed in Section 6.3.15 may be used for additional exploratory analysis CCI [redacted]

6.3.17 Patient contact

Patients who complete an EOS visit less than 30 days after the last CPI-0610 dose should be contacted by telephone on Day 30 post-treatment to assess new or ongoing adverse events (AEs) or serious adverse events (SAEs) that may have occurred since the last visit.

6.4 Study compliance

CPI-0610 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 CPI-0610 (and if applicable ruxolitinib), including that CPI-0610 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. Detailed instructions for completion and review of the diaries will be provided in the study manual.

Patients will receive a sufficient quantity of CPI-0610 for each treatment cycle at the beginning of the treatment cycle. The study center staff will check the patient's diary versus the patient's supply of remaining CPI-0610 tablets at the Day 1 visit of each new treatment cycle 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 the MFSAF v4.0 diary to be completed as detailed in Section 6.3.9.1.

6.5 Post-end of trial

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 CPI-0610 and CPI-0610 plus ruxolitinib in this study are outlined below.

7.1 Safety

Assessment of the safety of CPI-0610 and CPI-0610 plus ruxolitinib treatment will rely on the continuous evaluation of AEs and SAEs 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, liver function tests [LFTs], and renal function), on monitoring of vital signs and physical examination, and on the evaluation of serial ECGs and ECHOs (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 1 patients with acute leukemia, MDS or MDS/MPN disease response to treatment with CPI-0610 will be assessed through the evaluation of bone marrow aspirates and biopsies, along with CBCs and examination of peripheral blood films. In some cases additional studies, e.g., examination of the CSF, may be needed to assess possible extramedullary disease. Response will be categorized by the investigator using the 2013 NCCN criteria for ALL[44], the 2003 Cheson criteria for AML,[45] and the 2006 modified IWG criteria for MDS and MDS/MPN.[46]

In Phase 2 patients with MF, disease response to treatment with CPI-0610 and CPI-0610 plus ruxolitinib will be assessed through the evaluation of peripheral blood counts, transfusion requirements, symptom scores, spleen and liver size (by palpation and CT/MRI), mutated allele burden and extent of marrow fibrosis. Response will include splenic response, change in PROs, RBC transfusion status, and response as categorized by the investigator using the 2013 revised IWG criteria for myelofibrosis.[47]

7.2.1 Acute lymphoblastic leukemia (Phase 1)

National Comprehensive Cancer Network (NCCN) Guidelines, Version 1.2013, 03/25/2013:

Response Criteria for Blood and Bone Marrow:

Complete remission (CR)

- No circulating blasts or extramedullary disease
- No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement
- Trilineage hematopoiesis (TLH) and <5% blasts
- Absolute neutrophil count (ANC) >1000/μL
- Platelets >100,000/microL

- No recurrence for 4 weeks

CR with incomplete blood count recovery (CRi)
- Recovery of platelets but <100,000 or ANC is <1000/µL

Overall response rate (ORR = CR + CRi)

Refractory disease
- Failure to achieve CR at the end of induction

Progressive disease (PD)
- Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease

Relapsed disease
- Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR

Response Criteria for CNS Disease:
- CNS remission: Achievement of CNS-1 status in a patient with CNS-2 or CNS-3 at diagnosis.
- CNS relapse: New development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome.

Classification of CNS status:
- CNS-1: No lymphoblasts in CSF, regardless of WBC count
- CNS-2: WBC <5/mcL in CSF with presence of lymphoblasts
- CNS-3: WBC ≥ 5/mcL in CSF with presence of lymphoblasts
- If the patient has leukemic cells in the peripheral blood and the LP is traumatic and WBC ≥5/mcL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.

Response Criteria for Mediastinal Disease:
- CR: Complete resolution of mediastinal enlargement by computed tomography (CT).
- CR unconfirmed (CRu): Residual mediastinal enlargement that has regressed by 75% in the sum of the product of the greatest perpendicular diameters (SPD).
- PR: >50% decrease in the SPD of the mediastinal enlargement.
- PD: >25% increases in the SPD of the mediastinal enlargement.
- No response (NR): Failure to qualify for PR or PD.

Relapse: Recurrence of mediastinal enlargement after achieving CR or CRu.

7.2.2 Acute myelogenous leukemia (Phase 1)

Cheson criteria, 2003:

Complete Remission (CR)

The designation of CR requires that the patient achieve less than 5% blasts in a bone marrow aspirate sample that contains marrow spicules, with a count of at least 200 nucleated cells. There

should be no blasts with Auer rods or persistence of extramedullary disease. A biopsy allows more bone marrow tissue to be examined and should be performed if spicules are absent from the aspirate sample. There is no requirement that the bone marrow achieve a certain degree of cellularity. A CR designation also requires that the patient have an ANC ≥ 1.0K/μL and a platelet count ≥ 100K/ μL. Neither the hemoglobin concentration nor the hematocrit has any bearing on remission status, although the patient must be independent of transfusions.

Complete Remission with Incomplete Blood Count Recovery (CRi)

The designation of complete remission with incomplete blood count recovery (CRi) requires that all of the criteria for CR are met, but there is either residual thrombocytopenia (< 100K/ μL) or residual neutropenia (<1.0K/μL).

Partial Remission (PR)

The designation of partial remission (PR) requires all of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts, to between 5% and 25% of the nucleated cells in the bone marrow. Therefore, if the pre-treatment bone marrow blast percentage was 50% to 100%, the percentage of blasts must decrease to a value between 5% and 25%. If the pre-treatment blast percentage was 20% to 49%, it must decrease by at least half to a value of more than 5%. A value of ≤ 5% blasts may also be considered a PR if Auer rods are present.

Relapse (Rel)

Relapse after CR is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause (e.g., bone marrow regeneration after therapy). The appearance of new dysplastic changes should also be considered relapse. In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5% to 20% blasts, a repeat bone marrow performed at least 1 week later is necessary to distinguish relapse from bone marrow regeneration. In such instances the date of relapse is defined as the first date that more than 5% blasts were observed in the marrow. The reappearance or development of cytologically proven extramedullary disease also indicates relapse.

7.2.3 Myelodysplastic syndrome (Phase 1)

Table 7-1 and Table 7-2 describe the response criteria for altering the natural history of MDS and hematologic improvement, respectively.

Table 7-1 Proposed modified International Working Group response criteria for altering natural history of MDS[44]

Category	Response criteria (responses must last at least 4 wks)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines* Persistent dysplasia will be noted*† Peripheral blood‡ Hgb ≥ 11 g/dL Platelets ≥ 100 × 10^9/L Neutrophils ≥1.0 × 10^9/L† Blasts = 0%
Partial remission	All CR criteria if abnormal before treatment except:

	Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment† Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete Disappearance of the chromosomal abnormality without appearance of new ones Partial At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts 5%-10% blasts: ≥ 50% increase to > 10% blasts 10%-20% blasts: ≥ 50% increase to > 20% blasts 20%-30% blasts: ≥ 50% increase to > 30% blasts Any of the following: At least 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥ 2 g/dL Transfusion dependence
Survival	Endpoints: Overall: death from any cause Event free: failure or death from any cause PFS: disease progression or death from MDS DFS: time to relapse Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.
To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.
*Dysplastic changes should consider the normal range of dysplastic changes (modification).
†Modification to IWG response criteria.
‡In some circumstances, protocol therapy may require the initiation of further treatment (e.g., consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Table 7-2 Proposed modified International Working Group response criteria for hematologic improvement[44]

Hematologic improvement*	Response criteria (responses must last at least 8 wks)†
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wks compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, < 100 × 10^9/L)	Absolute increase of ≥ 30 × 10^9/L for patients starting with > 20 × 10^9/L platelets Increase from < 20 × 109/L to > 20 × 10^9/L and by at least 100%†
Neutrophil response (pretreatment, < 1.0 × 10^9/L)	At least 100% increase and an absolute increase > 0.5 × 109/L†

Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by > 1.5 g/dL Transfusion dependence

Deletions to the IWG response criteria are not shown.
To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.
*Pretreatment count averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).
†Modification to IWG response criteria.
‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

7.2.4 Myelofibrosis (Phase 2)

7.2.4.1 Splenic response

A primary endpoint for Phase 2 is splenic response by imaging after 24 weeks of treatment. The percent change in spleen size by MRI or CT from baseline will be documented for each patient.

For the purpose of response for the Simon's two-stage design, a splenic response will be a ≥35% reduction from baseline spleen size by imaging (MRI or CT). This is the reduction in spleen volume used to define splenic response in several trials including COMFORT-I[39] and SIMPLIFY-2.[50]

Splenic response will also be evaluated by palpation after 24 weeks of treatment. The percent change in spleen size by palpation from baseline will be documented for each patient.

Duration of each type of splenic response will also be evaluated. For splenic response via imaging, duration of the spleen response is defined as the time when splenic response criteria are first met (a ≥ 35% reduction from baseline spleen size) until the time at which an increase of ≥ 25% in spleen volume by imaging compared to baseline is documented. For splenic response via palpation, duration of the spleen response is defined as the time when the splenic response criteria are first met (≥ 50% reduction from baseline spleen size) until the time at which an increase of ≥ 50% in spleen length by palpation compared to baseline is documented.

7.2.4.2 PROs

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

Changes in total symptom scores via the MFSAF and in patients' impressions of change in MF symptoms via the PGIC will be described for each patient over time.

7.2.4.3 RBC transfusion status

A primary endpoint for Phase 2 is the transfusion independence rate for patients who are transfusion dependent. Any RBC units given to each patient will be documented in order to calculate the average number of RBC units per subject-month. The RBC transfusion independence rate and dependence rate will also be determined (i.e., the proportion of patients who are RBC transfusion independent and the proportion of patients who are RBC transfusion dependent).

RBC transfusion independence is defined as: absence of RBC transfusion and no hemoglobin level below 8 g/dL in the prior 12 weeks.

RBC transfusion dependence is defined as: at least 4 units of RBC transfusions, or a hemoglobin level below 8 g/dL in the prior 8 weeks.

NOTE: These definitions are from the SIMPLIFY-1 trial.[49]

For the purpose of response for the Simon's two-stage design, a response based on RBC transfusion status will be conversion from RBC transfusion dependent to RBC transfusion independent.

7.2.4.4 Response via revised IWG-MRT response criteria

Table 7-3 describes the revised IWG-MRT response criteria for MF. The rate of response categories such as CR, PR, CI, SD, PD and relapse will be calculated at the end of 24 weeks of treatment and every 6 months thereafter.

Table 7-3 Revised IWG-MRT and ELN response criteria for MF[47]

Response categories	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)
CR	Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF† and
	Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥ 1 × 10^9/L and <UNL;
	Platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
PR	Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥100 × 109/L and <UNL; <2% immature myeloid cells‡ and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or
	Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF†, and peripheral blood: Hemoglobin ≥85 but <100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥50, but <100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and

Response categories	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement (CI)	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia§
Anemia response	Transfusion-independent patients: a ≥20 g/L increase in hemoglobin level‖
	Transfusion-dependent patients: becoming transfusion-independent¶
Spleen response#	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable** or
	A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50%** http://www.bloodjournal.org/content/122/8/1395.figures-only?sso-checked=true - fn-11
	A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response
	A spleen response requires confirmation by MRI or computed tomography showing ≥35% spleen volume reduction
Symptoms response	A ≥50% reduction in the MPN-SAF TSS††
Progressive disease‡‡	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or
	A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or
	A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or
	Leukemic transformation confirmed by a bone marrow blast count of ≥20% or
	A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 × 10^9/L that lasts for at least 2 weeks
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or
	Loss of anemia response persisting for at least 1 month or
	Loss of spleen response persisting for at least 1 month
	Recommendations for assessing treatment-induced cytogenetic and molecular changes
Cytogenetic remission	At least 10 metaphases must be analyzed for cytogenetic response evaluation and
	requires confirmation by repeat testing within 6 months window
	CR: eradication of a preexisting abnormality
	PR: ≥50% reduction in abnormal metaphases
	(partial response applies only to patients with at least ten abnormal metaphases at baseline)

Response categories	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)
Molecular remission	Molecular response evaluation must be analyzed in peripheral blood granulocytes and
	requires confirmation by repeat testing within 6 months window
	CR: Eradication of a pre-existing abnormality
	PR: ≥50% decrease in allele burden
	(partial response applies only to patients with at least 20% mutant allele burden at baseline)
Cytogenetic/molecular relapse	Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing

EMH, extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhepatosplenic EMH); LCM, left costal margin; UNL, upper normal limit.

* Baseline and posttreatment bone marrow slides are to be interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

† Grading of MF is according to the European classification

Thiele et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. *Haematologica*. 2005;90:1128.

It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.

‡ Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, <5% immature myeloid cells is allowed.

§ See above for definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥25 000 × 10(9)/L and absolute neutrophil count of ≥0.5 × 10(9)/L.

‖ Applicable only to patients with baseline hemoglobin of <100 g/L. In patients not meeting the strict criteria for transfusion dependency at the time of study enrollment (see as follows), but have received transfusions within the previous month, the pretransfusion hemoglobin level should be used as the baseline.

¶ Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBC), in the 12 weeks prior to study enrollment, for a hemoglobin level of <85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥85 g/L.

In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy.

** Spleen or liver responses must be confirmed by imaging studies where a ≥35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

†† Symptoms are evaluated by the MPN-SAF TSS.17 The MPN-SAF TSS is assessed by the patients themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). Symptoms response requires ≥50% reduction in the MPN-SAF TSS.

‡‡ Progressive disease assignment for splenomegaly requires confirmation my MRI or computed tomography showing a ≥25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to posttreatment measurements.

7.2.4.5 Transformation to AML

Peripheral blood will also be used to monitor for conversion to AML throughout the study.

7.3 Pharmacokinetic measurements

Blood samples for determination of the plasma concentration of CPI-0610, and in the Phase 2 Combination Arm to evaluate the PK profile of ruxolitinib when given in combination with CPI-0610, will be obtained before at pre-specified time points during dosing with in the first cycle of treatment. In Phase 2, serial blood samples will also be collected before and after dosing with CPI-0610 when upward dose titration occurs. Some of the PK parameters to be estimated are $AUC_{0-\tau}$, C_{max}, T_{max}, C_{trough}, elimination half-life, peak-to-trough ratio, and accumulation ratio.

7.4 Phase 1: Pharmacodynamic biomarker measurements in patients with acute leukemia, MDS or MDS/MPN

Before the start of CPI-0610 administration and at selected time points during the first cycle of treatment peripheral blood, bone marrow aspirates and bone marrow biopsies will be collected in order to assess the effects of CPI-0610 on gene expression in leukemic cells and to detect corresponding phenotypic effects, such as inhibition of cellular proliferation and induction of apoptosis. Peripheral blood for these pharmacodynamic assessments will be collected at selected PK sampling time points during the first cycle of treatment, for comparison to a pre-treatment sample. A bone marrow biopsy and aspirate for pharmacodynamic assessments will be collected between Days 8 and 14 of the first cycle of treatment, for comparison with pharmacodynamic assessments made in the pre-treatment bone marrow biopsy and aspirate.

Based on studies of leukemic cell lines and freshly isolated human leukemic blasts, there are approximately 100 genes, such as *MYC* and *HEXIM1*, whose expression is expected to be

affected by BET protein bromodomain inhibition. The expression of a subset of these genes in leukemic cells will be assessed using slides prepared from the bone marrow biopsies and aspirates, employing IHC for proteins and ISH for mRNA. These same slides may be assessed by IHC for evidence of changes in leukemic cell proliferation (Ki67) and/or apoptosis (cleaved caspase 3).

Serial peripheral blood samples will be collected into PAXgene RNA tubes for the isolation of leukocyte-derived RNA. This will provide an alternative approach to the assessment of changes in gene expression with BET protein bromodomain inhibition. Gene expression in these samples will be assessed by qPCR. In patients without circulating leukemic cells the expression of 7 genes known to be sensitive to BET protein bromodomain inhibition in peripheral blood mononuclear cells will be measured. In patients with circulating leukemic cells the qPCR assessment will be expanded to the broader set of approximately 100 genes predicted to be sensitive to BET protein bromodomain inhibition. And in this latter case gene expression may also be assessed in a global, unbiased manner using RNA Seq.

7.5 Phase 1: Predictive biomarker measurements in patients with acute leukemia, MDS or MDS/MPN

The bone marrow aspirates and accompanying peripheral blood samples obtained from patients with acute leukemia, MDS or MDS/MPN before the start of treatment and between Days 8 and 13 of the first cycle of treatment will be processed to isolate leukemic cells and to extract from those cells both DNA and RNA. Leukemic cells will be isolated from the marrow aspirates and peripheral blood using antibodies directed against specific surface antigens (e.g., CD33 in myeloid leukemia) coupled to magnetic particles. The DNA and RNA will then potentially be sequenced in order to provide initial hypotheses regarding mutations or patterns of gene expression associated with response or resistance to CPI-0610.

In patients with circulating malignant leukocytes peripheral blood samples may also be collected for the isolation of DNA and identification of mutations that could correlate with response or resistance to treatment with CPI-0610.

7.6 Phase 2: Pharmacodynamic biomarker measurements in patients with MF

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. 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 (e.g., *JAK2*, *CALR*) using a focused NGS assay. CCI [redacted]

CCI [redacted] Additionally, changes in allelic burden of specific mutations in patients treated with CPI-0610 may identify hypersensitivity of certain mutational contexts to CPI-0610.

Bone marrow biopsy samples will be collected and assessed by a local hematopathologist for grading of bone marrow fibrosis. 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]

7.7 CCI [redacted]

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

During Phase 1, dose escalation and determination of the MTD was originally planned in three separate groups of patients: (1) patients with acute leukemia, MDS or MDS/MPN; (2) patients with MF receiving no other specific treatment for their disease; and (3) patients with MF receiving treatment with ruxolitinib. As of Amendment 6, dose escalation in group (1) is completed.

These three separate groups were suggested because although all of these diseases are hematologic malignancies arising in the bone marrow, hematologic toxicity is managed differently in patients with MF than in patients with acute leukemia, MDS or MDS/MPN. After a review of the safety data on CPI-0610 as monotherapy across 3 Phase 1 trials in hematological malignancies (described in Section 1.3.4.1), 225 mg QD (tablet formulation) was determined to be the MTD of CPI-0610 as monotherapy for all hematological indications. Therefore, as of Amendment 6, rather than dose escalation within cohorts, all MF patients enrolled to either the Monotherapy Arm or the Combination Arm of Phase 2 will start CPI-0610 at a dose of 125 mg QD with upward titration of their CPI-0610 dose allowed (up to a maximum dose of 225 mg QD) based on platelet count, hemoglobin levels and safety evaluation.

In Phase 2 (MF expansion), two separate groups of patients will be evaluated: Monotherapy Arm (MF patients treated with CPI-0610 alone) and Combination Arm (MF patients treated with CPI-0610 in combination with ruxolitinib). The primary endpoint is splenic response via imaging after 24 weeks of treatment or for patients who are transfusion dependent, the transfusion independence rate. Since the appropriate reduction in spleen volume to define splenic response or the approximate transfusion independence rate is not clear for the patient population being enrolled in this study, the analysis of splenic response and transfusion independence will be primarily descriptive. However, a Simon's two-stage design will be used for each arm to allow the possibility of early stopping for futility. For the purpose of the two-stage design, a response will be defined as a ≥35% reduction from baseline spleen size by imaging (MRI or CT) or conversion from RBC transfusion dependent to independent (see definitions in Section 7.2.4.3) . A ≥35% reduction from baseline spleen size is the reduction in spleen volume used to define splenic response in several trials including COMFORT-I[39] and SIMPLIFY-2.[50] The null hypothesis that the true response rate is 6% will be tested against a one-sided alternative. The null rate is based on the best available therapy (BAT) arm in the SIMPLIFY-2[50] trial, where the splenic response rate was 5.8%. In this trial, patients had previously been treated with ruxolitinib and the BAT was ruxolitinib for most patients, making this a reasonable comparator for the current study.

In the first stage, 17 patients will be accrued in each arm. If there are 1 or fewer responses in these 17 patients, that arm will be stopped. Otherwise, 18 additional patients will be accrued for a total of 35 in each arm. The null hypothesis will be rejected for a given arm if 5 or more responses are observed in 35 patients. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 20%. If an arm is stopped after Stage 1, the sample size

(n=17) is still adequate for descriptive analyses of splenic response. This data will be used to design subsequent trials.

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. 44 patients with acute leukemia, MDS or MDS/MPN were enrolled in Phase 1. Up to 35 patients will be enrolled in each arm during Phase 2. Therefore, it is estimated that up to 114 patients will be enrolled into this study.

8.1.2 NOTE: All patients with MF enrolled under Amendment 5 will be included in Stage 1 of Phase 2.Randomization and stratification

No randomization or stratification will be used in this trial.

The heterogeneity of the patient population enrolled in this study, the variability in the dose of CPI-0610 with which patients are treated, and the small size of this study all preclude the use of any meaningful stratification.

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 any amount of study drug.

8.1.3.2 Population evaluable for dose-limiting toxicity

The population of patients evaluable for DLT during Phase 1 is defined as all patients who receive at least 85% of their planned dose of CPI-0610, unless interrupted by a DLT, and who have sufficient follow-up data to allow the investigators and sponsor to determine whether DLT occurred. Eighty-five percent of the planned dose is 12 of 14 doses with the 14 days on/7 days off schedule.

Patients who discontinue from the study for reasons other than DLT (e.g., disease progression) before completing the treatment and evaluations needed to be evaluable for DLT will be replaced. Patients will be analyzed by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower or higher dose level.

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 of splenic response via imaging after 24 weeks of treatment is defined as all patients who have imaging results available on Cycle 9, Day 1.

8.1.3.4 Population evaluable for pharmacokinetics

The population of patients evaluable for CPI-0610's PK is defined as all patients for whom there are sufficient dosing and CPI-0610 concentration-time data to reliably estimate the drug's PK. This population will be used for analyses of CPI-0610 PK parameters. For the Phase 2 Combination Arm, the population of patients evaluable for ruxolitinib's PK is defined as all patients for whom there are sufficient dosing and ruxolitinib concentration-time data to reliably estimate the drug's PK. This population will be used for analyses of ruxolitinib PK parameters.

8.1.3.5 Populations evaluable for pharmacodynamic assessments (Phase 1)

Pharmacodynamic markers will consist of measurements of gene expression in a variety of tissues, (peripheral blood, bone marrow biopsies and bone marrow aspirates), using a variety of techniques, e.g., IHC, ISH, qPCR, and RNA Seq. 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 CPI-0610, the samples must have been processed according to study procedures, and a sufficient number of cells (or associated DNA and RNA) must have been present in the sample to permit the performance of the assay.

8.1.3.6 Populations evaluable CCI

CCI

[redacted].

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 CPI-0610

(and ruxolitinib in the Combination Arm), 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 Populations evaluable 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

The statistical methods employed in this protocol will be primarily descriptive and graphical in nature. Determination of the MTD of CPI-0610 with this schedule of administration will be achieved using a standard deterministic algorithm, typically referred to as the "3+3 design," in conjunction with a modified Fibonacci dose escalation scheme, as described in Section 5.6.2 and in Appendix 2. Statistical hypothesis testing is neither intended nor appropriate during Phase 1 due to the small sample size of the study. See Section 8.1.1 for a description of the Simon's two-stage design being used in Phase 2.

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 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

For Phase 1, analysis of efficacy measures will be descriptive. A number of the variables described in Section 7.2 that may characterize the efficacy of CPI-0610, primarily the disease response category based on the IWG MDS guidelines and the duration of response, will be summarized.

For Phase 2, the primary endpoint is splenic response via imaging after 24 weeks of treatment. The % change from baseline will be calculated for each patient and will be presented using a waterfall plot. This approach will also be used for splenic response via palpation. Changes in PROs will also be analyzed using descriptive and graphical methods. Binary variables (i.e., response rates) will be estimated and reported along with exact 95% confidence intervals for each arm. Duration of splenic response 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 in Phase 2 and, where appropriate, for the entire population. PK parameters will include (but are not limited to) C_{max}, time to maximum concentration (T_{max}), AUC, and elimination half-life. 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 CCI [redacted]

CCI [redacted]

8.1.11 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 CPI-0610 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 adverse events 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
- SAEs

The most commonly reported treatment-emergent AEs (i.e., 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.

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

All concomitant medications collected from screening through the study period will be classified to preferred terms according to the World Health Organization (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 CPI-0610 and CPI-0610 plus ruxolitinib.

8.1.12 Interim analysis

No formal interim analysis is planned during Phase 1. Data will be evaluated on a continuous basis.

During Phase 2, an interim analysis will occur after 17 evaluable patients are accrued in each arm (after Stage 1 of the Simon's two-stage design). If 2 responses (either spleen response or conversion from RBC transfusion dependence to independence) are not seen in the first 17 patients enrolled in each arm, additional patients may be enrolled if all 17 patients are not evaluable for response (e.g., do not have imaging data available) if needed in order to make a decision about moving to Stage 2.

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 (e.g., 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 (i.e., 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).
- 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 result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient 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 adverse events 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 (CRO), PAREXEL International, following instructions provided in the Study Manual, within 1 working day 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 PAREXEL International within 1 working day 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. A sample of the SAE Form may be found in the study manual. Follow-up information on the SAE may be requested by Constellation or PAREXEL International.

Table 9-1 SAE reporting contact information

PAREXEL International	
Fax Number:	781-434-5957

In accordance with local guidelines, Constellation 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 (e.g., surgery was performed earlier or later than planned).

For both SAEs and non-serious 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 National Cancer Institute

(NCI) CTCAE, Version 4.03, as a guideline, wherever possible. The criteria are provided in the study manual and also 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 9-2 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 ruxolitiib 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 adverse events 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 adverse event 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, CML currently in blast crisis, MDS, MDS/MPN, MF or to the treatment of these diseases are listed below and should not be reported as suspected unexpected serious adverse reactions (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 CNS 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, 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 Constellation and an expedited report will be submitted if an aggregate analysis indicates that the events are occurring more frequently than in historical control groups.

9.3 Monitoring of adverse events and period of observation

Monitoring of AEs and SAEs will be conducted throughout the study. AEs, both serious and non-serious, 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 PAREXEL International.

9.4 Procedures for reporting drug exposure during pregnancy and birth events

If a patient or a patient's partner becomes pregnant or suspects she is pregnant while participating in this study, the treating physician must be informed immediately and the patient must permanently discontinue study drug. PAREXEL International must also be contacted immediately by faxing a completed Pregnancy Form, in accordance with the instructions provided in the Study Manual. The pregnancy must be followed through the final pregnancy outcome 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 Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). 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 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. Constellation 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 completion

Constellation 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.

Constellation will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc (CD) 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 Constellation 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 Constellation or its designee. Monitoring will be done 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, e-mail, and fax).

All unused study drug is to be returned to Constellation 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 Constellation or its designee.

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 Constellation 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 Constellation, 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 Constellation. 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. Constellation 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 Constellation, 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 Constellation'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 Constellation (or disposal of the drug, if approved by Constellation) 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 Constellation. 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 Constellation 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 the study

Study participation by individual sites or the entire study may be prematurely terminated, if in the opinion of the investigator or Constellation, there is sufficient reasonable cause.

Written notification documenting the reason for study termination will be provided to the investigator or Constellation 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
- Plans to modify, suspend, or discontinue the development of the study drug

Should the study be closed prematurely, all study materials (study medication, etc.) must be returned to Constellation. 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, Constellation 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 Constellation or its designee.

11 USE OF INFORMATION

All information regarding CPI-0610 supplied by Constellation 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 Constellation. It is understood that there is an obligation to provide Constellation with complete data obtained during the study. The information obtained from the clinical trial will be used towards the development of CPI-0610 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 Constellation, 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 Constellation 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 Constellation.

A prepublication manuscript or abstract is to be provided to Constellation 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 Constellation of the notification, Constellation 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 Constellation's 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 Constellation's request.

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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 two months of stable blood counts, ≤30 percent bone marrow blasts and ≤19 percent 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 five groups with the following estimated overall survival and progression to AML.

Risk group	IPSS-R score	Median overall survival (years)	Median time to 25 percent 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; 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.

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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

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

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 x 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 13-1 Strong CYP3A4 Inhibitors and Inducers

Strong CYP3A4 Inhibitors	Strong CYP3A4 Inducers
amprenavir	carbamazepine
atazanavir	enzalutamide
boceprevir	mitotane
clarithromycin	phenobarbital
cobicistat	phenytoin
conivaptan	rifabutin
diltiazem	rifampin
foasmprenavir	rifapentine
grapefruit (fruit or juice)[1]	St. john's wort[2]
idelalisib	
indinavir	
itraconazole	
ketoconazole	
lopinavir	
nefazodone	
nelfinavir	
posaconazole	
ritonavir	
saquinavir	
starfruit (fruit or juice)	
suboxone	
telaprevir	
telithromycin	
troleandomycin	
voriconazole	

[1]The effect of grapefruit juices varies widely among brands and is concentration, dose, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A4 inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A4 inhibitor" when another preparation was used (e.g., low does, single strength).
[2]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)?