PANOBINOSTAT and RUXOLITINIB In MyElofibrosis
PRIME STUDY
Phase I/II Study of Combination oral JAK2 tyrosine kinase inhibitor (JAK2-TKI) and Histone Deacetylase Inhibitor (HDACI) therapy in patients with Myelofibrosis
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Mount Sinai School of Medicine

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Summary

This is a single-center, single arm, dose finding study to assess safety and tolerability of the oral combination of PANOBINOSTAT and RUXOLITINIB in patients with myelofibrosis (MF) in chronic and accelerated phase.

Study phase: I/II

Study objectives:

- Primary
  - Assess the safety and tolerability of RUXOLITINIB in combination with PANOBINOSTAT in patients with MF
  - Identify a recommended phase II dose of each agent in combination
  - Assess treatment response as defined by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT)

- Secondary
  - Assess changes in spleen size with combination therapy
  - Assess symptom response with a validated MPN tool
- Exploratory
  - Evaluate changes in biomarkers in relation to response to combination treatment with RUXOLITINIB and PANOBINOSTAT
    - Bone marrow histopathology
    - Cytogenetics
    - Acetylation of H2B and H3 histones
    - JAK2V617F peripheral blood mononuclear cell mutational load
    - Peripheral blood CD34+ hematopoietic cell load
    - Peripheral blood CD34+ hematopoietic cells expression of CXCR4
    - Peripheral blood cytokine profile
  - Evaluate a panel of biomarkers as predictors of response and prognosis
    - ASXL1, EZH2, TET2, and others to be determined

Study population:

Adult male or female patients ages 18 or older, who have been diagnosed with intermediate-2 or higher (IWG risk group) chronic and accelerated phase PMF, Post PV MF, or Post ET MF as defined by the World Health Organization. Only patients seen in the Mount Sinai Myeloproliferative Disease Program (MPD) clinic will be enrolled in this protocol. These patients will either be primary patients of this clinic or patients referred by outside hematologists or oncologists. Written informed consent must be obtained prior to any screening procedures. Patients may have received prior therapy for MF, however they must be

willing and able to discontinue all drugs used to treat underlying MF disease, at least 28 days or 5 half-lives (whichever is longer) prior to starting study drug. This trial will allow patients who were treated with either HDACis or JAK2is, as long as these agents were not discontinued due to clinically relevant toxicities as per the investigator's assessment.

Number of patients: 33 to 58

Overview of study design:

Phase I/II open label, single institution, combination therapy trial of induction RUXOLITINIB followed by combination with PANOBINOSTAT in dose escalation cohorts with a primary endpoint of determining the safety and tolerability of combination therapy in patients with myelofibrosis (MF) in chronic and accelerated phase. A 3+3standard dose escalation scheme will be employed and the occurrence of dose limiting toxicities (DLTs) will be captured and the occurrence of such events will determine dose cohort escalation by predetermined and established rules. In addition to establishing the DLTs, maximally tolerated dose (MTD), and recommended phase II dose (RPTD) in the phase I portion of this trial, exploratory biomarkers will be evaluated within phase I as well. Pharmacodynamics and exploratory genetic and epigenetic biomarkers will be explored as predictors of response to therapy. The RPTD cohort will be expanded to incorporate a total of 22 patients, including 6 from phase I, in order to assess clinical response as assessed by International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) as a primary endpoint for the phase II portion of this trial.

Screening for this study will have a window of 56 days and start on day -84 with signing of informed consent. See Figure 4-1 A and B. Eligible patients will begin induction phase therapy on day -28, receiving single agent RUXOLITINIB PO BID daily for 28 days. Patients who maintain a platelet count $\geq$ 50,000/ul at Day 1 will then receive concomitant PANOBINOSTAT PO TIW QOW or PO TIW QW depending on the cohort assignment.

The first 28 days of combination therapy will be the evaluable phase I portion of the study. Patients who do not experience a defined DLT in the evaluable phase I period can remain on study receiving combination drug therapy for a total of 6 cycles (cycles 2-6). See Figure 4-1 A. AEs will continue to be recorded on all patients (phase I and II) receiving combination therapy beyond the first cycle of the study. Dose escalation rules are based on the standard 3+3 design as shown in Figure 4-2.

Phase I patients who complete a total of 6 cycles of combination therapy will be assessed for clinical response by IWG-MRT criteria. Patients who achieve at least Stable Disease (SD) by IWG-MRT (Table 4-2) can remain on therapy indefinitely or until disease progression or drug toxicity as assessed by the investigators. At the discretion of the investigator, phase I patients who have completed 6 cycles of therapy with a minimum of SD can also be dose escalated/deescalated at that time to the RPTD once it is determined. These patients will not be considered for evaluation of response in Phase II.

Once a RPTD is determined from the dose escalation phase I part of this trial, the dose expansion phase-II part of this trial will commence with additional patients added to the original RPTD cohort from phase I to a sample size of 22. See Figure 4-1 B. IWG-MRT response criteria will be applied at the end of cycle 6 and this will include spleen volume

measurement by MRI and bone marrow biopsy to appreciate changes in morphology, degree of reticulin/collagen fibrosis, cytogenetics and molecular markers. Patients who have obtained at least SD by IWG-MRT can remain on study receiving combination therapy in the dose extension stage of Phase II.

In this part of phase II, patients have obtained at least SD by IWG-MRT after 6 cycles of combination therapy and will continue to be treated with dose modifications and stopping rules that are the same as the expansion stage of Phase II. Patients will continue to be followed for signs of response on each monthly visit. After 24 cycles, stable patients may be seen every other month at the discretion of the investigator. Repeat imaging of the spleen and bone marrow biopsy with repeat cytogenetic and molecular testing when appropriate can be performed at the discretion of the investigator for the purpose of assessment of response or disease progression. Additional biomarker assessments can also be made at intervals determined by the clinical course and at the discretion of the investigator.

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List of abbreviated terms

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area under the concentration time curve
BFU-E	Burst forming unit erythroid
BLRM	Bayesian logistic regression dose-escalation model
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of federal regulations
C_{max}	Maximal plasma concentration
eCRF	Electronic Case Report/Record Form
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computer tomography
CV	Coefficient of variation
DACi	Pan-deacetylase inhibitor
DS&E	Drug safety and epidemiology
DLT	Dose limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EPO	Erythropoietin
ET	Essential thrombocythemia
EWOC	Escalation with Overdose Control
FDA	Food and Drug Administration
FT4	Free thyroxine
G-CSF	Granulocyte colony stimulating factor
GCP	Good clinical practice
GI	Gastrointestinal
H3/4	Histone 3 or 4
HDAC	Histone deacetylase
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HL	Hodgkin’s Lymphoma
HPLC	High-performance liquid chromatography
HSCT	Hematopoietic stem cell transplant
HSP90	Heat shock protein 90
Hr	Hour

IB	Investigator's brochure
i.v.	intravenous(ly)
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
INR	International normalized ratio
IRB	Institutional Review Board
IWG	International Working Guidelines
JAK1/JAK2	Janus kinase 1 or 2
LC-MS/MS	liquid chromatography-tandem mass spectrometry method
LFTs	Liver function tests
LLOQ	lower limit of quantification
LMWH	Low molecular weight heparin
LVEF	Left ventricular ejection fraction
LPFV	Last patient first visit
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MedDRA	Medical dictionary for regulatory activities
MDS	Myelodysplastic syndromes
MF	Myelofibrosis
MFSAF	Modified Myelofibrosis Symptom Assessment Form
MPD	Myeloproliferative disorder
MM	Multiple myeloma
MMSAF	Modified Myelofibrosis Symptom Assessment Form
MPL	Myeloproliferative leukemia
MPN	Myeloproliferative neoplasms
MRI	Magnetic resonance imaging
MRM	Multiple reaction monitoring
MTBE	methyl-t-butyl ether
MTD	Maximum tolerated dose
MUGA	Multi Gated Acquisition Scan
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NIH	National Institute of Health
NYHA	New York Heart Association
o.d.	omnia die/once a day
p.o.	per os/by mouth/orally
pan	PANOBINOSTAT
PD	Progressive disease
PD	Pharmcodynamics
PET-MF	Post essential thrombocythemia-myelofibrosis
Ph	Philadelphia chromosome

PHI	Protected health information
PK	Pharmacokinetic
PK-PD	Pharmacokinetic – pharmacodynamic
PMF	Primary myelofibrosis
PPV-MF	Post polycythemia vera-myelofibrosis
PP-MF	post-polycythemia vera-myelofibrosis
PRBC	Packed red blood cells
PT	Prothrombin time
PTT	Partial thromboplastin time
PV	Polycythemia vera
q	Every
QD	Once daily
QOW	Every other week
QW	Every week
pSTAT3/5	Phosphorylated signal-transducer and activator of transcription 3 or 5
RA - need subscript A	Accumulation ratio
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
RBC/HPF	Red blood cells/high power field
REB	Research Ethics Board
RPTD	Recommended Phase 2 Dose
rux	RUXOLITINIB
SAE	Serious Adverse Event
SD	Standard deviation
SEC	Safety event categories
STAT	Signal transducers and activators of transcription
T1/2	Half life
Tmax	Maximum plasma concentration time
TEAE	Treatment emergent adverse event
TIW	Three times a week
TK	Tyrosine kinase
tlast	time zero to the last measurable concentration sampling time
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell count
WBC/HPF	White blood cells/high power field
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (eg: q28 days)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being testing in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient Number (Patient No.)	A unique identifying number assigned to each patient who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures. =
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

1 Background

1.1 Overview of Myelofibrosis

Polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), belong to a group of Philadelphia chromosome negative (Ph-) myeloproliferative neoplasms (MPNs) involving a malignant clonal hematopoetic stem cell population leading to the expansion of myeloid lineage derived cells. (Tefferi 2005) The estimated incidence of PMF is between 0.5-1.5 per 100,000 population with a median age at diagnosis of 65 years (Mesa 1999, Dupriez 1996). PV and ET both have a propensity to transform to a myelofibrotic state, designated Post– PV/ET MF. The three disorders (PMF, Post-PV/ET, collectively termed MF) are related in that progressive bone marrow collagen fibrosis, peripheral cytopenias, extramedullary hematopoesis, and splenomegaly result in debilitating constitutional symptoms, increased risk of infections, thrombotic tendencies, and heightened risk of transformation to acute leukemia (Tefferi 2000).

MF can be risk stratified for survival by multiple scoring systems. The Lille score is based on two prognostic factors: white blood count >30 X 109/ul or < 4 X 109 /ul and hemoglobin <10 g/dL and stratified as low, intermediate or high risk (Dupriez 1996) . Median survival for low risk (0 adverse factors), intermediate risk (1 adverse factor) and high risk disease (2 adverse factors) is 93, 26, 13 months, respectively. Cervantes et al identified age > 65 years, presence of constitutional symptoms, hemoglobin < 10 g/dL, white blood cell count > 25 x 109/ul, and a circulating blast >1% as significant risk factors in multivariate analysis (Cervantes 2009). Patients with no risk factors fell into a low-risk group with a median survival of 135 months, patients with one risk factor fell into an intermediate-1 group with a median survival of 95 months, patients with two risk factors fell within an intermediate-2 group with a median survival of 48 months, and patients with 3 or more risk factors formed a high-risk group with a median survival of 27 months. A dynamic international prognostic scoring system (DIPSS) has recently been developed to predict survival real time (Passamonti 2010). DIPSS predicts a median survival for the low-risk patients (score=0) that has not yet been reached; 14.2 years in intermediate-1 (score=1 or 2) patients; 4 years in the intermediate-2 (score 3 or 4) patients; and 1.5 years in the high-risk (score 5 or 6) patients. Thrombocytopenia is a common hematologic abnormality in MF and holds prognostic significance. The DIPSS Plus incorporates thrombocytopenia into this model to predict survival in a dynamic fashion (Gangat 2011). With this scoring system the median survival for the low-risk patients is 180 months; 80 months for intermediate-1 risk patients; 35 months for intermediate-2 risk patients, and 16 months for the high-risk patients. The most common causes of death in MF are infectious bleeding as a result of bone marrow failure, complications of portal hypertension and transformation to acute myelogenous leukemia (AML) designated MF in blast phase (MF-BP) by the WHO 2008. MF-BP holds a dismal prognosis with a median survival of 3-5 months [1].

Allogeneic stem cell transplantation (ASCT) is the only treatment modality that offers the potential of cure at a significant risk of morbidity and mortality (Rondelli 2005, Kroger 2005). For many patients due to advanced age and/or concurrent medical illness, stem cell transplant is not a valid option, and they must rely on treatments aimed at palliation of symptoms. These treatments include splenic irradiation, splenectomy, melphalan, interferon, corticosteroids, thalidomide, lenalidomide, hydroxyurea, busulfan, danazol, and erythropoietic stimulating agents. Although collectively these therapies have response rates (reduction in splenomegaly and improvement in anemia) of approximately 20-50%, none have definitively been shown to improve survival in MF patients (Mascarenhas 2010).

Activating mutations of the Janus Kinase 2 receptor tyrosine kinase (JAKV617F) and/or the thrombopoetin receptor (MPL W515L/K) have been identified in patients with MPNs in 50-65% of patients with MF carry the JAK2V617F mutation (Baxter 2005; James 2005, Kralovics 2005; Levine 2005,Tefferi 2005). The JAK/STAT signal transduction pathway is believed to be hyperactive in MF patients regardless of the JAK2 mutation status leading to inappropriate cytokine release, and plays a role in the diminished apoptosis of the hematopoietic progenitor cells (Wang 2009). Small molecule inhibitors of JAK2 are currently being evaluated in phase I/II/III trials to treat patients with MF and although there use is associated with dramatic resolution of splenomegaly and constitutional symptoms, these agents as a class do not result in correction of cytopenias or alteration in the JAK2V617F allele burden.

Ruxolitinib (Jakafi; Incyte) is the first FDA-approved (12/2011) therapy for the treatment of patients with intermediate/high risk MF based on the results of 2 pivotal studies (COMFORT 1 and COMFORT 2). These multicenter randomized (placebo controlled in COMFORT1 and versus best available therapy in COMFORT 2) trials achieved their primary endpoint of spleen reduction (>35% of spleen volume by radiographic measurement) as well as significant amelioration of MF related symptoms. The comfort 1 study also was able to show a very modest improvement, but statistically significant difference, in overall survival compared to placebo (Verstovsek et al., NEJM 2012). Although single agent Ruxolitinib appears to improve spleen size and symptoms in patients with MF, it has not been shown to affect the abnormal bone marrow morphology, eliminate JAK2V617F mutation burden, or eliminate karyotypic abnormalities.

1.2 Introduction to PANOBINOSTAT (LBH589)

1.2.1 Overview of PANOBINOSTAT in MF

HDACi's are a class of agents regulating the acetylation of core histones responsible for the epigenetic control of tumor suppressor gene expression, and other genes responsible for cell differentiation and apoptosis in a cell-specific manner (Grozinger 2002). HDACi's also promote the acetylation of other non-histone proteins including heat shock protein 90 (HSP90), a chaperone for various proteins offering protection from ubiquitin directed proteasomal degradation (Bali 2005). Data suggest that malignantly transformed cells are

more sensitive to HDACi induced apoptosis than are normal cells (Zhang 2005). *In vitro* studies investigating the use of DACi in the $JAK2^{V617F}$ mutant HEL cell line and $JAK2^{V617F}$+ cells from PV and ET patients have shown preferential reduction in the mutant JAK2 clone with preservation of the wild type cells (Guerini 2008). In a preclinical experiment by Wang et al, DACis play an important role in the control of cell cycle progression and apoptosis, and have been shown to have increased cytotoxicity in cells bearing mutated $JAK2^{V617F}$ while having relatively minimal effect on normal CD34+ cells (Wang 2009). Also shown in this experiment was a PANOBINOSTAT mediated reduction in JAK2 mRNA by 40%, and hyperacetylation of HSP90 causing a partial disruption of the binding to JAK2. This inhibition of chaperone/client binding resulted in proteasomal degradation of the JAK2 protein. In a separate pre-clinical experiment by Gupta et al (Gupta 2009, poster #925), PANOBINOSTAT was shown to inhibit the STAT proteins by causing STAT3 acetylation in DLBCL cells. Wang et al also reported p-STAT3 and p-STAT5 inhibition following PANOBINOSTAT treatment in HEL cells, with greater reduction being seen in STAT3 levels (Wang 2009). PMF is also characterized by an increased proportion of circulating peripheral blood CD34+ hematopoietic stem cells. *Ex vivo* exposure of PMF CD34+ cells to sequential DNA methyltransferase (DNMT) inhibitor and DACi has been shown to dramatically reduce the burden of malignant progenitor cells as detected by a reduction in $JAK2^{V617F}$ allele burden (Shi 2007).

1.2.2 PANOBINOSTAT non-clinical experience

PANOBINOSTAT (LBH589) is a novel cinnamic hydroxamic pan-DACi that specifically enhances the acetylation of H3, H4, and HSP90 (Glaser 2007). Targeted inhibition of HDAC6, a member of the class IIB HDACs, by PANOBINOSTAT has been shown to enhance acetylation of HSP90 and disrupt its chaperone function leading to the degradation of various client proteins such as BCR-ABL, AKT, c-RAF, FLT-3 (Bali 2005; George 2005). JAK2 is also a client protein of HSP90, and inhibition of this chaperone protein results in the degradation of JAK2 and impairment in cytokine signaling (Shang 2006; Wang 2009). Importantly for patients with MF, DACI's have been shown to down-modulate several soluble cytokines including IL-6, and VEGF (Carta 2006). In a mouse bone marrow transduction/transplantation model of $JAK2^{V617F}$-driven MPN-like disease, PANOBINOSTAT treatment was found to suppress splenomegaly, reticulocyte count, HCT and WBC count. PANOBINOSTAT treatment also reduced circulating GFP-($JAK2^{V617F}$)-positive cells in the blood and the mutant allele burden in bone marrow and spleen, as assessed by FACS and qPCR on genomic DNA, respectively (unpublished, data: Novartis).

1.2.3 PANOBINOSTAT clinical experience

PANOBINOSTAT was tested in a Phase IA/II study [CLH589B2102] in advanced hematologic malignancies including acute myelogenous leukemia, myelodysplasia, multiple myeloma, Hodgkin's lymphoma, Non-Hodgkin's Lymphoma, and myelofibrosis. A total of 176 patients with advanced hematologic malignancies were enrolled in this study, and treated at escalating doses of oral PANOBINOSTAT from 20mg up to 80mg three times a week (TIW). There were two dosing schedules administered: every week (QW) or every other week (QOW). Of these 176 patients, 86 patients received PANOBINOSTAT TIW QW, and 33

patients received PANOBINOSTAT TIW QOW. The remaining 57 patients had indications, including MM, HL, and NHL. A total of 13 MF patients were treated with PANOBINOSTAT, and 4 of these patients saw a clinical improvement lasting≥8 weeks with reduction in palpable spleen size up to 86% (data on file: Novartis). Refer to Table 1-3 for specifics of the treatment schedule for these patients with MF.

The most commonly reported adverse events (AEs) both regardless of causality and suspected to be related to PANOBINOSTAT, were nausea, diarrhea and fatigue. Thrombocytopenia was the most common grade 3 and 4 AE, regardless of causality across doses and indications. Refer to Table 1-4 for further details of AE's, serious adverse events (SAE's) and Grade 3/4 AE's for the patients with hematologic malignancies and MDS across all QOW dosing cohorts. There were no Grade 3 or 4 bleeding events reported in any of the patients with MF treated on this study. In total there were 4 bleeding events seen across the dosing spectrum and diagnostic categories, two of which were suspected to be treatment related. One patient with AML who was treated at 60 mg TIW QW developed Grade 4 pulmonary hemorrhage on Cycle1 Day16 along with a diagnosis of bronchopulmonary aspergillosis. A patient with CML who was treated at 60mg TIW QW developed a Grade 4 cerebral hemorrhage 8 days after the last dose of study medication.

In a Phase I study by Mascarenhas et al, [CLBH589BUS32T], 18 patients with PMF or Post-PV/ET MF were treated with escalating doses of PANOBINOSTAT starting at 20mg TIW QW. Four patients showed clinical improvement as defined by resolution of a palpable spleen and a 2 g/dL increase in hemoglobin, 5 patients had stable disease, and 1 patient had progressive disease. The MTD (maximum tolerated dose) for this trial was 25mg TIW QW, and thrombocytopenia was the main DLT. In a Phase II trial by DeAngelo et al, [CLBH589BUS58], 35 patients with MF were enrolled, and treated with 40mg TIW, QW with dose reductions allowed for toxicities. Thrombocytopenia was the most common Grade 3 or 4 AE occurring in 57% of the patients, however, 45.2% of the patients had a ≥25% reduction in spleen size. See Table 1-5 for more information on the remainder of the AE's for this trial. From this study, the $JAK2^{V617F}$ mutation allele burden was measured pre- and post-treatment from 10 patients. The median percent of mutant JAK2 pre-treatment was 27%, and the median percent post-treatment was 10% indicating a significant median decline in the $JAK2^{V617F}$ allelic burden (DeAngelo 2010).

Table 1-1 CLBH589B2102 MF patients by dosing cohort

Schedule	TIW QW	TIW QOW
Total # of MF patients	12	1
30mg	1	
60mg	11	
80mg		1

Table 1-2 CLBH589B2102 AE and SAE for patients with hematologic malignancies and myelodysplastic syndrome treated across dosing range (30-80mg TIW) on the QOW schedule

Adverse Event	AE	SAE	Grade 3-4
	N = 33	N = 33	N = 33
Nausea	63.6%	0%	0%
Diarrhea	54.5%	3.0%	9.1%
Fatigue	54.5%	6.1%	30.3
Pyrexia	51.5%	21.2%	0%
Thrombocytopenia	42.4%	6.1%	39.4%
Neutropenia	39.4%	6.1%	39.4%
Febrile Neutropenia	27.3%	27.3%	27.3%
Sepsis	12.1%	9.1%	12.1%
Tumor lysis syndrome	9.0%	6.1%	9.1%
Atrial fibrillation	6.1%	3.0%	3.0%
Tachycardia	4.0%	3.0%	0%

Table 1-3 CLBH589BUS58 most common (>15%) AEs in patients with MF, treated with PANOBINOSTAT at 40mg TIW QW (N=35)

	Any Grade N (%)	Grade 3/4 N (%)
Thrombocytopenia	23 (65.7%)	20 (57.1%)
Diarrhea	23 (65.7%)	3 (8.6%)
Nausea	17 (48.5%)	2 (5.7%)
Fatigue	16 (45.7%)	8 (22.9%)
Decreased appetite	15 (42.9%)	1 (2.9%)
Vomiting	12 (34.3%)	1 (2.9%)
Anemia	10 (28.6%)	10 (28.6%)
Dyspnea	8 (22.9%)	4 (11.4%)
Constipation	7 (20.0%)	1 (2.9%)
Abdominal pain	6 (17.4 %)	1 (2.9%)

1.2.3.1 Electrocardiographic experience with PANOBINOSTAT as single agent

In the initial Phase I study utilizing the IV formulation, and where PANOBINOSTAT was dosed on a consecutive day schedule, ECG abnormalities were noted, with one patient experiencing Torsade de pointes. Since then, extensive ECG monitoring has been conducted for patients who are enrolled in clinical studies of PANOBINOSTAT.

As of 31 December 2009, cardiac safety data were available for 532 patients in the TIW QW dose schedule and 70 patients in the TIW QOW dose schedule. All of these patients underwent intensive pre- and post-dose ECG recording to monitor the occurrence of QTc changes as well as to capture other ECG abnormalities. There are mounting evidences that the most common finding is a QTc increase of ≤ 60 msec (CTCAE grade 1) from baseline in both

schedules. The absolute maximal QTc values remain limited to ≤ 480 msec (grade ½). Higher absolute values are infrequent. Of note a QTc increase > 480 msec has been mostly observed at the highest oral dose of 60 mg given TIW QW. There were no cases of torsade de pointes with either schedule for oral PANOBINOSTAT.

1.2.4 PANOBINOSTAT clinical pharmacokinetics

Clinical development of PANOBINOSTAT focuses on the oral administration where PANOBINOSTAT was given TIW (i.e. on days 1, 3, 5), QW or QOW, of a 28-day cycle. To date, the pharmacokinetics (PK) of PANOBINOSTAT have been characterized in over 600 patients with cancer, of which, over 400 patients have used the TIW dosing schedule.

PANOBINOSTAT is rapidly absorbed with a median T_{max} reached within 2 hours after oral administration. PANOBINOSTAT can be administered with or without food as the overall bioavailability and variability in systemic exposure remained unchanged in patients with or without food (Lewis 2009).

The metabolism of PANOBINOSTAT is extensive and several metabolic pathways are involved including reduction, hydrolysis, oxidation, and glucuronidation processes. Oxidation by Cytochrome P450 (CYP) is a minor pathway (f_{mcyp} = 0.4), in comparison to the above non-CYP pathways) where CYP3A4 is the main metabolizing enzyme with minor involvement of CYP2D6 and 2C19. PANOBINOSTAT is an inhibitor of CYP2D6 *in vitro*. It is not an inducer of CYP, UGT1A1, Pgp, MRP2 *in vitro*.

Clinical drug interaction studies showed that a strong CYP3A inhibitor, ketoconazole increased PANOBINOSTAT systemic exposure by 80% in patients (deJonge 2009) which indicated the interaction was weak. PANOBINOSTAT (as a CYP2D6 inhibitor) increased the systemic exposure of a sensitive CYP2D6 substrate, dextromethorphan, by 60% in patients. These two drug interaction studies indicated that PANOBINOSTAT is a weak CYP2D6 inhibitor clinically and is not a sensitive CYP3A substrate.

Based on *in vitro* and *in silico* data, it is also estimated that PANOBINOSTAT may increase a sensitive CYP3A substrate, midazolam, exposure by < 20% and has a low drug interaction risk with a non-sensitive CYP3A substrate.

PANOBINOSTAT and its metabolites are almost equally excreted in the kidney and liver. The median plasma elimination terminal half-life was 15-18 hours. Steady state was achieved by the 3rd dose following days 1, 3, and 5 dosing. On day 5, AUC accumulation ratio (R_A) was ~1.14 times over the single-dose AUC which is consistent with the estimated R_A based on a linear pharmacokinetic process. Doses increased linearly and nearly proportionally with AUC up to 60mg. The inter-individual variability (CV%) in systemic exposure is 60%.

1.3 Introduction to RUXOLITINIB (INC424)

1.3.1 Overview of RUXOLITINIB

RUXOLITINIB is a potent, dual JAK1 and JAK2 inhibitor with excellent selectivity over other kinases (Quintás-Cardama 2010), has been developed to target the constitutive activation of the JAK-STAT pathway for the treatment of MPNs and other hematologic malignancies. It is an important agent in controlling the symptomatology of this disease in

that it is able to inhibit multiple dysregulated JAK pathways; JAK1 plays a major role in the signaling of a number of pro-inflammatory cytokines in MF (Plo 2008) and JAK2 mutations may account for the majority of deregulated oncogenic signaling used primarily by receptors for hematopoietic growth factors (e.g. erythropoietin and thrombopoietin) in MPN patients (Quintás-Cardama 2010). Toxicity (primarily decreased erythropoiesis and thrombocytopoiesis) has been managed by close control of dosing. Based on efficacy and safety data from INC424-251, RUXOLITINIB is a drug that is individually titrated for each patient based on hematologic safety parameters, and that some opportunity for individual titration of dose might offer the best balance of safety and efficacy for any single agent. The dose range of 10-25mg BID for individual dose titration, depending on patient platelet count, is supported by the data from INC424-251.

This study, designed to determine a maximum tolerated dose (MTD) / recommended phase II dose (RPTD) of the combination within a 28 day dose limiting toxicity observation window, will not explore pharmacokinetics.

1.3.2 RUXOLITINIB non-clinical experience

RUXOLITINIB demonstrated potent and selective inhibition of JAK1 and JAK2 (IC_{50} values of 3.3 and 2.8 nM, respectively) *in vitro*. In whole blood assays, RUXOLITINIB inhibited both IL-6- and thrombopoietin-mediated STAT3 phosphorylation, reflecting selective inhibition of JAK1 and JAK2, respectively, in this model system. RUXOLITINIB inhibited $JAK2^{V617F}$-dependent Ba/F3 and IL-6 driven INA-6 cell proliferation with an IC_{50} value of 127 nM and 141 nM, respectively. In Ba/F3 $JAK2^{V617F}$ cells RUXOLITINIB induced apoptosis with an IC_{50} value of 126 nM. Exogenous RUXOLITINIB blocked IL-6-mediated or thrombopoietin-induced STAT3 phosphorylation in human whole blood, with an IC_{50} value of 282 nM or 281 nM, respectively. RUXOLITINIB preferentially suppressed erythroid progenitor colony formation in primary cultures of cells from patients with $JAK2^{V617F}$-positive PV (BFU-E IC_{50} of 223 nM) vs. cells from healthy donors (BFU-E IC_{50} of 407 nM). In a mouse mechanistic model of $JAK2^{V617F}$-positive MPN, oral administration of RUXOLITINIB reduced splenomegaly, tumor burden and circulating levels of inflammatory cytokines (IL-6 and TNF-α), resulting in prolonged survival without causing anemia or lymphopenia (Quintás-Cardama 2010).

1.3.3 RUXOLITINIB clinical experience

In a Phase I/II study [INC424-251] for patients with MF, a total of 154 patients were treated with increasing doses of RUXOLITINIB. 57% of patients treated sustained at least a 50% reduction in palpable splenomegaly below the left costal margin (corresponding to an approximate 35% reduction in volumetric spleen size), and were treated at doses up to 50mg BID, with activity seen at multiple dose levels from 10mg BID (n=30), 15mg BID (n=35), 25mg BID (n=47), and 50mg BID (n=5). This reduction in splenomegaly occurred regardless of presence or absence of the $JAK2^{V617F}$ mutation and independent of the MF disease subtype (PMF, PPV-MF, or PET-MF). The responses seen regardless of the presence or absence of the $JAK2^{V617F}$ mutation are consistent with dysregulated JAK signaling in MF patients. Within 1 month of initiating treatment, levels of pro-inflammatory cytokines and angiogenic growth factors, including CRP, IL-1ra, MIP 1ß, TNFα, and IL -6 were reduced, and patients noted

improvement in night sweats, pruritus, and abdominal pain (Verstovsek 2010). This improvement in symptoms was even seen at the lowest end of the dosing spectrum (10mg BID) even when there was not a clinically noticeable reduction in splenic size. In 34 evaluable patients, treatment with RUXOLITINIB suppressed allelic burden by 13% after 12 cycles (Verstovsek 2010).

The Modified Myelofibrosis Symptom Assessment Form (MMSAF) developed by Mesa et al, and based on an international internet-based survey of over 1000 patients with myeloproliferative diseases (Mesa 2007), was used to probe a range of constitutional symptoms that are related to splenomegaly (including impaired ability to ambulate, abdominal pain and discomfort and early satiety) and elevated cytokines (including fatigue, night sweats and pruritus). Between 45% and 94% of patients report a given symptom at baseline. After 2 or more weeks of RUXOLITINIB therapy, 28% to 61% of patients showed a reduction in individual symptom scores of at least 50% after 6 cycles of therapy when all doses were combined and assessed together.

RUXOLITINIB has been well tolerated by this aged population with advanced disease. Most adverse events were mild to moderate in severity, considered unrelated to study drug administration and not dose dependent. Related adverse events occurring in at least 8 patients (5%) included in the safety database through December 31, 2009 were restricted to thrombocytopenia (66 patients, 43%), anemia (45 patients, 29%), weight increased (11 patients, 7%), diarrhea (10 patients, 6.5%) and fatigue (8 patients, 5%). Both anemia and thrombocytopenia represent JAK2-inhibitor myelosuppression, and are therefore not unexpected for a JAK2 inhibitor. Thrombocytopenia represents the DLT in the population of the [INCB18424-251] study. Forty (40) subjects (26% of study population) had a Grade 3 or Grade 4 decline in platelet count during the study (31 Grade 3 events, 9 Grade 4 events). Subjects with Grade 3 or 4 thrombocytopenia entered the study, in general, with platelet counts less than 200K/μL, although there are exceptions to this trend. Thrombocytopenia occurred rapidly: 20% of Grade 3 and 4 events occurred in the first 4 weeks of dosing, just under half (48%) of Grade 3 and 4 events occurred in the first 16 weeks of dosing. For most subjects, regardless of dose level, thrombocytopenia was rapidly reversible and manageable with RUXOLITINIB dose interruption and/or dose reduction.

The 25mg BID dose group was the largest dose group examined. This dose group included subjects with mean baseline platelet counts of 345 $x10^9$/L and had an overall incidence of Grade 3 + 4 thrombocytopenia of 36% (17 of 47 subjects); 12 subjects had Grade 3 events (26%), and 5 subjects had Grade 4 events (11%). Subjects enrolled in a subsequent cohort were assigned to an initial dose of 15mg BID provided their baseline platelet count was >200 $x10^9$/L; the incidence of Grade 3 thrombocytopenia was markedly reduced (1 of 35 subjects) and there were no Grade 4 events. At a starting dose of 10mg BID, there were 6 of 30 subjects (20%) with Grade 3 thrombocytopenia; there were no Grade 4 events. Importantly, 8 of the 30 subjects at a starting dose of 10mg BID enrolled into the study under a protocol amendment specifying this dose for a baseline platelet count between 100 x 10^9/L to 200 x 10^9/L, inclusive. This is reflected in a lower mean platelet count at baseline for this dose group. Three of these subjects (38%) had baseline platelet counts ranging from 119 $x10^9$/L to 156 x 10^9/L and subsequently developed Grade 3 thrombocytopenia. This accounts, in part, for the higher incidence of Grade 3 and 4 thrombocytopenia in this dose group compared to 15mg

BID. Subjects initially assigned to the 50mg BID dose group had an incidence of Grade 3 thrombocytopenia of 60% (3 of 5 subjects) and of Grade 4 thrombocytopenia of 20% (1 of 5 subjects). From the combined safety and efficacy data of INC424-251, 15mg BID was determined to be the most effective and safe starting dose.

On November 16, 2011, Ruxolitinib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of intermediate/high-risk MF based upon the combined results of the COMFORT-I and COMFORT-II Trials. The *CO*ntrolled *M*yelo*F*ibrosis Study with *O*Ral JAK2 inhibitor *T*reatment (COMFORT-1) study was a randomized (1:1), double-blinded phase III study sponsored by Incyte comparing Ruxolitinib to placebo in patients with intermediate-2 or high risk MF and a baseline platelet count of at least 100 x 10^9/L (25). Oral ruxolitinib was dosed at 15mg BID for patients with platelet counts between 100-200 x 10^9/L and 20mg BID for patients with >200 x10^9/L. A total of 309 patients were randomized (ruxolitinib 155, placebo 154), with a median age of 68 years. The primary endpoint of this study was a reduction in spleen volume of at least 35% by either MRI/CT. The 35% reduction in spleen volume was chosen based on previous studies that established a correlation of 35% reduction in volume by imaging to approximately 50% reduction by manual palpation on physical exam. Secondary endpoints included assessment of duration of spleen reduction and improvement in disease related symptoms as assessed by the MFSAF (myelofibrosis symptom assessment form) (26). Patients were allowed to crossover from placebo if they had a greater than 25% increase in spleen volume by imaging from baseline and all patients were un-blinded and could crossover when every patient had completed week 24 or discontinued the treatment and 50% of remaining patients had completed week 36.

Grade 3/4 anemia was the most frequent hematologic AE observed in 45% vs 19.2%, in the ruxolitinib vs placebo arm, respectively. Grade 3/4 thrombocytopenia was observed in 12.9% vs 1.3% in patients treated with ruxolitinib vs placebo, respectively. Neutropenia that was grade 3/4 was observed in 7.1% vs 2% in the ruxolitinib vs placebo arm, respectively. The most common non-hematologic adverse event seen of any grade in the ruxolitinib treated group was diarrhea 23.2% (compared to 21.2% in placebo group). All in all, this was a well-tolerated drug.

At 24 weeks, 41.9% of patients treated with ruxolitinib experienced a 35% or greater reduction in spleen volume compared to 0.7% of patients receiving placebo ($P < 0.0001$). 45.9% of ruxolitinib treated patients regardless of their JAK2 mutational status experienced a ≥50% improvement in constitutional symptoms as compared to 0.7% in the placebo group.
Survival analysis on extended ruxolitinib therapy with a mean follow up of 52 weeks showed a statistically significant reduction in death with a hazard ratio of 0.499 (0.254, 0.98) and a probability of survival compared to placebo of 0.98 vs 0.90 and 0.84 vs 0.77 in patients with a baseline hemoglobin >10g/dL and <10g/dL, respectively (27). In further subset analysis, patient age ≤ 65 years appeared to have a survival benefit over > 65 years of age with a HR 0.22 (0.06,0.84) with ruxolitinib therapy.

The drug therapy was uniformly ineffective in reversing histopathological abnormalities in the peripheral blood or marrow, eliminating marker cytogenetic abnormalities or reducing the

JAK2V617F allele burden to a degree associated with tyrosine kinase inhibitor therapy of BCR/ABL1 for chronic myeloid leukemia. The other limitation of the agent that has been the rapid return of splenomegaly following discontinuation of the drug and the occasional occurrence of life threatening syndromes attributed to the rapid elevation of cytokines. This "ruxolitinib withdrawal syndrome" has been described in 5 of the 47 MF patients treated at Mayo Clinic that had rapid discontinuation and the authors advise tapering the drug when possible in addition to upfront discussion with the patient regarding this potential drug associated serious adverse event (28).

The *COntrolled MyeloFibrosis Study with ORal JAK2 inhibitor Treatment COMFORT-2* study was a randomized (2:1), Novartis sponsored, open-label phase III clinical trial conducted in nine European countries comparing ruxolitinib to best available therapy (BAT) (29). Hydroxyurea (46.6%), steroids (16.4%) and supportive therapy (32.9%) comprised the BAT arm. At a median age of 66 years, 219 patients with intermediate-2 or high risk MF were randomized (146 ruxolitinib, 73 BAT).

The primary endpoint was met at 48 weeks, when 28.5% of patients treated with ruxolitinib achieved a 35% or greater reduction in spleen volume, compared to 0% of patients in the BAT arm ($P < 0.0001$). The secondary endpoint of spleen reduction at 24 weeks was 31.9% vs 0%, ruxolitinib arm vs BAT, respectively.

As was seen in the COMFORT-1 study, hematologic toxicity of all grades was frequent with ruxolitinib (44.5% and 40.4%, thrombocytopenia and anemia, respectively) and was grade 3/4 thrombocytopenia (7.5% vs 4.1%), and anemia (11% vs 4.1%) in ruxolitinib vs BAT arms, respectively. Diarrhea of all grades was the most frequent non-hematologic adverse event seen in 23% of ruxolitinib treated patients and was grade 3/4 in 1%.

Progression-free survival, leukemia-free survival and overall survival were not statistically significant between the two treatment arms.

1.3.3.1 Electrocardiographic experience with RUXOLITINIB

A thorough QT study [INC18424-138] was performed to assess the heart rate corrected QT interval in healthy subjects dosed with a single dose of 25 mg and 200 mg of RUXOLITINIB, compared to placebo and moxifloxacin. The pharmacokinetic parameters observed in this study were consistent with those reported from previous clinical studies conducted in healthy volunteers. Based on the ICH E14 this study met the requirements for a negative QT study. For RUXOLITINIB dosing, at no time did the upper bound of the 2-sided 90% confidence interval exceed 10 msec. The largest mean change was seen following the 200 mg dose, which was 3.7 beats per minute at 1.5 hours post-dose. This was not considered clinically significant by the expert cardiologist at the central ECG laboratory. There was also no evidence that increasing plasma concentrations of RUXOLITINIB was associated with increases in the change of QTc.

1.3.4 RUXOLITINIB clinical pharmacokinetics

In clinical studies, RUXOLITINIB is completely and rapidly absorbed after oral administration with maximal plasma concentration (C_{max}) achieved approximately 1.5 hours post-dose. Administration with a high-fat meal decreased RUXOLITINIB mean C_{max} by 24% and increased RUXOLITINIB mean AUC by 4%. A linear dose-exposure relationship was observed over a dose range of 5 to 200 mg (single dose). There was minimal accumulation (12%) with multiple dose administration (q12h x 10 days) compared single dose administration. The steady state dose-exposure was linear over the dose range of 15 to 50 mg q12hours. In vitro studies indicate that CYP3A4 is the major enzyme responsible for metabolism of RUXOLITINIB. At clinically relevant concentrations, RUXOLITINIB is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4. RUXOLITINIB is eliminated almost completely by oxidative metabolism with a terminal elimination half-life of approximately 3 h. Following a single oral dose of [^{14}C]-labeled RUXOLITINIB in healthy adult volunteers, 74% of radioactivity excreted in urine and 22% excretion via feces. Unchanged RUXOLITINIB accounted for less than 1% of the excreted total radioactivity.

The pharmacodynamic activity of RUXOLITINIB was characterized by an ex vivo whole blood assay that involves quantitation of pSTAT3 following IL-6 stimulation. Following oral, single or multiple dose administration in healthy subjects, RUXOLITINIB demonstrated dose dependent inhibition of ex vivo cytokine-induced pSTAT3 with maximal inhibition occurring at 1-2 hours after administration for all doses, coincident with maximal RUXOLITINIB levels. The oxidative metabolites of RUXOLITINIB retain pharmacologic activity to varying degrees albeit with 2-5-fold greater IC_{50} compared to the parent compound and represent approximately 20% of overall activity (inhibition of IL-6 stimulated STAT3 phosphorylation in whole blood) observed after a RUXOLITINIB dose.

In vitro metabolism studies strongly suggest that CYP3A4 is the predominant human CYP isozyme responsible for the metabolism of RUXOLITINIB. Co-administration of RUXOLITINIB with ketoconazole, a potent CYP3A4 inhibitor, resulted in an approximate doubling of plasma AUC, whereas co-administration with erythromycin, a moderate CYP3A4 inhibitor, caused approximately 27% increase in exposure. In the presence of rifampin, a potent inducer of CYP3A4, an approximate 70% decrease in plasma AUC of RUXOLITINIB was observed.

In patients with varying degrees of renal impairment, the pharmacokinetics and pharmacodynamics of RUXOLITINIB was similar to the healthy subjects, except in patients with end stage renal disease on hemodialysis who exhibited modestly higher response in the pSTAT3 assay when dosed following dialysis. The recovery of RUXOLITINIB in dialysate was negligible, consistent with the high serum protein binding (97%) of RUXOLITINIB. There was little effect on the plasma C_{max} values of RUXOLITINIB metabolites, whereas the AUC values of RUXOLITINIB metabolites tended to increase with increasing severity of renal impairment, and most markedly in the subjects with end stage renal disease requiring hemodialysis. The metabolites appeared to be dialyzable to varying degrees in a 4-hour hemodialysis procedure.

In patients with hepatic impairment there was no rank order correlation between exposure and degree of hepatic impairment assessed by Child-Pugh scores. RUXOLITINIB AUC increased 88% in mild, 29% in moderate, and 66% in severe disease. The terminal elimination half-life ranged from 4.6 hours in mild, 4.1 hours in moderate and 5.1 hours in severe hepatic impairment compared to 2.8 hours in healthy subjects. No significant differences in pharmacodynamics were observed among subjects with mild or moderate hepatic impairment compared to healthy subjects. In subjects with severe hepatic impairment, the inhibition of IL-6 stimulated pSTAT3 levels appeared to be prolonged. Hepatic impairment, in general, decreased the plasma C_{max} but not the AUC values of RUXOLITINIB metabolites, and no correlation was observed between the change in pharmacokinetic parameters of the metabolites and the degree of hepatic impairment.

Additional details as to the clinical pharmacology of RUXOLITINIB may be found in the IB.

1.4 Risk assessment of the combination of PANOBINOSTAT and RUXOLITINIB

1.4.1 Assessment of drug-interaction potential between PANOBINOSTAT and RUXOLITINIB

Based on *in vitro* metabolic profiling and results from clinical PANOBINOSTAT drug interaction studies ([CLBH589B2110] and [CLBH589B2109]), PANOBINOSTAT was shown to be a non-sensitive CYP3A substrate and a weak CYP2D6 inhibitor in patients. It has also been predicted to have minimal clinical drug interaction risk with a non-sensitive CYP3A substrate.

RUXOLITINIB was also shown to be a non-sensitive CYP3A substrate based on the results from Study [INCB18424-133] (ketoconazole inhibition study) and is not known to be a CYP inhibitor or inducer *in vitro*.

Since CYP3A is the most abundant CYP enzyme in the liver, drugs with shared elimination pathway via CYP3A had not been shown to have compromised elimination. Drug-interaction between PANOBINOSTAT and RUXOLITINIB is therefore not expected by being CYP3A substrates. Based on available in vitro and clinical data, clinical drug interaction between PANOBINOSTAT and RUXOLITINIB is therefore not expected.

PANOBINOSTAT is a weak time-dependent CYP3A inhibitor and predicted to have no clinically relevant consequence on a non-sensitive CYP3A substrate, such as RUXOLITINIB. As PANOBINOSTAT is also administered intermittently, its clinical impact on the chronic RUXOLITINIB administration is deemed even more remote.

1.4.2 Integrative toxicological assessment of PANOBINOSTAT and RUXOLITINIB in combination

When combining both compounds the potential for overlapping toxicities needs to be considered. For PANOBINOSTAT the predominant toxicities seen preclinically consisted of: myelosuppression, lymphoid depletion, degeneration of the intestinal epithelium, variable effects on the thyroid epithelium and thyroid hormones, anabolic effects on bone (manifested

as hyperstosis), atrophy/degeneration of testes, prostate and ovarian follicles and embryo-lethality and fetotoxicity (manifested as decreased fetal body weight). For RUXOLITINIB the predominant toxicities seen preclinically consisted of: myelosuppression, lymphoid depletion resulting in decreased erythropoiesis and lymphopoiesis, immunosuppression resulting in secondary infections in dogs, and embryo-lethality and fetotoxicity (manifested as decreased fetal body weight). For both compounds most of the findings were reversible or showed trends toward reversibility and can be readily monitored in the clinical setting. Preliminary clinical data available from ongoing trials in myelofibrosis with PANOBINOSTAT or RUXOLITINIB as single agents indicate thrombocytopenia as the principal overlapping dose-limiting toxicity. Fatigue, neutropenia and diarrhea are also listed as toxicities for PANOBINOSTAT. Although no combination PANOBINOSTAT and RUXOLITINIB toxicity studies have been conducted, based on clinical data with each. it appears likely that thrombocytopenia will be dose limiting when these agents are combined in the clinical setting.

In addition to identifying common target organ toxicities understanding the metabolism and elimination of each compound and how the presence of one compound might impact systemic drug concentrations of the other can further inform the potential for additive or synergistic toxicities. Based on in vitro metabolic profiling and results from clinical PANOBINOSTAT drug interaction studies, PANOBINOSTAT has shown to be a non-sensitive CYP3A substrate and a weak CYP2D6 inhibitor in patients. It has also been predicted to have minimal clinical risk with a non sensitive CYP3A substrate. RUXOLITINIB is also a non-sensitive CYP3A substrate and is not known to be a CYP inhibitor or inducer. Since CYP3A is the most abundant CYP enzyme, drugs with shared elimination pathway via CYP3A have not been shown to have compromised elimination. Therefore drug-interaction between PANOBINOSTAT and RUXOLITINIB is not expected by being CYP3A substrates. PANOBINOSTAT is a weak time-dependent CYP3A inhibitor and predicted to have no consequence on a non-sensitive CYP3A substrate, such as RUXOLITINIB. Since PANOBINOSTAT is also administered intermittently, its clinical impact on the chronic RUXOLITINIB administration is deemed even more remote. Based on available in vitro and clinical data, clinical drug interaction between PANOBINOSTAT and RUXOLITINIB is not expected. Based on preclinical data a summary of the integrative assessment for potential for additive and/or synergistic toxicity of combining PANOBINOSTAT with RUXOLITINIB is presented below.

Table 1-4 Integrative toxicological assessment of PANOBINOSTAT (LBH589) / RUXOLITINIB (INC424) combination

Target Organ	LBH589	INC424	Potential Impact of Combination
Genotoxicity	Positive in Ames and Chromosomal Aberration Assays	Not genotoxic	None predicted
Cardiovascular	QT prolongation (dog, human)	↓ in blood pressure, ↑ heart rate (dog), ↓ respiratory minute volume (rat) minimal heart fibrosis (rat)	None predicted[a]
Hematopoietic	Myelosuppression, lymphoid atrophy and/or depletion (↓ erythrocytes, granulocytes and platelets). Rat, dog) Thrombocytopenia, most common adverse event seen in patients	Myelosuppression, lymphoid atrophy, ↓ erythropoiesis and lymphopoiesis (rat, mouse, dog). Infections/infestations due to immunosuppression (dog) Thrombocytopenia, most common adverse event seen in patients, not observed in non clinical studies	Potential for additive or synergistic hematopoietic toxicity (thrombocytopenia most likely in patients)
Gastrointestinal	Degeneration/necrosis - epithelium of the small intestine, diarrhea (dog), atrophy of parotid gland (rat)	Inflammation and/or erosion of the small intestine (dog), Hyperplasia of non-glandular stomach (mouse)	Potential for additive gastrointestinal toxicity
Thyroid	Follicular epithelial hypertrophy, cytoplasmic vacuolation, reduced follicular colloid, variable changes in T3, T4 and TSH (rat, dog)	No change	None predicted
Reproductive	♂ Atrophy/degeneration of prostate and testes (oligospermia), ♀ atretic ovarian follicles and uterine atrophy (rat, dog), Embryo-lethal and fetotoxic, but not teratogenic (rat, rabbit)	Embryo-lethal and fetotoxic, but not teratogenic (rat, rabbit)	Embryo-fetal warning and highly effective birth control required clinically
Bone	Endosteal Hyperstosis (rat)	No change	None predicted

[a] INC424 cardiovascular effects in dogs and rats were seen at maximal plasma concentrations (Cmax) and exposures (AUC) that were 10 -50-fold greater than those seen in patients at the MTD of 25 mg bid.

2 Rationale

2.1 Study rationale and purpose

Histone deacetylase inhibitors (HDACi) are a class of agents regulating the acetylation of core histones responsible for the epigenetic control of tumor suppressor gene expression and other genes responsible for cell differentiation and apoptosis (Schreiber 2002). Acetylated histones remain in a relaxed state allowing for the transcription of genes. HDACi block the action of

histone deacetylases (HDAC) from removing these moieties and repressing transcription. HDACi also promote the acetylation of other non-histone proteins including heat shock protein, HSP90, a chaperone for various proteins offering protection from ubiquitin directed proteasomal degradation (Bali 2005). HDACi promote cell cycle growth arrest and accumulation in G1 or G2-M and apoptosis involving both mitochondrial and receptor ligand-mediated pathways. Previous in vitro studies investigating the use of HDACi in the HEL cell line and JAK2V617F+ cells from PV and ET patients have shown selective reduction in the mutant JAK2 clone with preservation of the wild type cells (Guerini 2007). These studies also make the point that not only are direct targets of the mutated JA2 pathway such as signal transducers and activators 3 and 5 (STAT3/5) down-modulated, but so are downstream target genes such as PRV-1. JAK2V617F specific attenuation was only seen at the protein level as JAK2 mRNA levels remained unaffected and may reflect either preferential mutant directed proteosomal degradation, selective acetylation of the mutant form or acetylation of other stabilizing proteins. PMF is also characterized by an increased proportion of circulating peripheral blood CD34+ hematopoietic stem cells and ex vivo exposure of PMF CD34+ cells to sequential DNA methyltransferase (DNMT) inhibitor and HDACi has been shown previously to dramatically reduce the burden of malignant progenitor cells as detected by a reduction in JAK2V617F allele burden (Shi 2007).

PANOBINOSTAT is a novel cinnamic hydroxamic HDACi and a very potent pan-HDAC inhibitor specifically enhancing acetylation on H3 and H4 and HSP90 (Glaser 2007). Targeted inhibiton of HDAC6, a member of the class IIB HDACs, by PANOBINOSTAT has been shown to enhance acetylation of HSP90 and disrupt its chaperone function leading to the degradation of various client proteins such as BCR/ABL, AKT, c-RAF, and FLT-3(Bali 2005; George 2005). JAK2 is also a client protein of HSP90 and inhibition of this chaperone protein results in the degradation of JAK2 and impairment in cytokine signaling (Shang 2006). The use of PANOBINOSTAT in MF patients would be an additional or alternative mechanism of down-regulating the JAK2V617F mutant clone by direct inhibition of JAK2V617F and suppression of the various downstream targets and effectors responsible for cell growth, differentiation and survival with the ultimate goal of modifying the disease phenotype. PANOBINOSTAT has shown activity in patients with MF as described in the previous section. PANOBINOSTAT will be provided in the oral formulation for ease of administration in the outpatient setting and due to the fact that PK/PD studies have already been completed in previous studies using oral PANOBINOSTAT [CPANOBINOSTATB 2101] and both bioavailability and histone acetylation data as mentioned previously favor oral dosing on a TIW schedule in this patient population.

Due to the encouraging, but limited results of RUXOLITINIB alone in patients with MF, we propose a phase I/II study of PANOBINOSTAT in combination with RUXOLITINIB in patients with MF. A standard 3+3 dose escalation schema with RUXOLITINIB at a starting dose of 10mg PO BID given continuously will be combined with PANOBINOSTAT given QOW on 28 day cycle with continuous RUXOLITINIB at 10mg PO BID. This schedule will allow for determination of both the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of both drugs as well as evidence of clinical response as defined by the International Working Group (IWG) criteria. Based on our previous work with PANOBINOSTAT (not yet

published), we hypothesize that prolonged administration at low doses is required to effect changes in the peripheral blood and ultimately in the bone marrow that reflect disease modification and potential improvement in outcome.

At this time there still exists no standard medical treatment for myelofibrosis and of the many drugs that have been used in the past (hydroxyurea, melphalan, danazol, interferon-alfa, thalidomide, lenalidomide) and presently being investigated (JAK2-TKI, HDACI, mTORi pomalidomide) have not been shown to affect the natural history and progression of disease. These drugs have individually shown the ability to induce response rates as measured in spleen reduction, amelioration of constitutional symptoms and to some degree modulation of hematologic profile and reduction in JAK2V617F allele burden. We believe that the combination of the RUXOLITINIB and PANOBINOSTAT is a novel and rational approach to the treatment of MF based on both pre-clinical science and clinical data as single agents in MF.

To further the benefit seen with RUXOLITINIB in patients with MF, PANOBINOSTAT will be added to the treatment regimen to act synergistically in the blockade of the dysregulated pathway driving this disease. See Section 2.4 for more information on the preclinical study demonstrating the synergistic activity exerted by the combination of PANOBINOSTAT and the JAK inhibitor TG101209 against $CD34^{+}$ primary MPN cells and JAK2V617F-expressing cell lines. This synergy will hopefully provide enhanced anti-proliferative activity in patients and reduce overall treatment related toxicity by using lower than single agent maximum tolerated dose levels. This clinical trial will be a single arm, safety and dose-finding phase I/II study, with a primary endpoint within the phase II portion of IWG-MRT treatment response and secondary endpoints of spleen volume response and changes in exploratory biomarkers

2.2 Rationale for the study design

This is a Phase I/II single arm, dose escalation study with expansion at the RPTD to assess efficacy and exploratory endpoints and further define safety and toxicity. This dose escalation process will be based on the toxicity profile. Following the determination of the MTD and/or potential RPTD, a dose expansion phase will be conducted at that dose to further define the safety and tolerability of the combination. See Section 10.4.2.1 for further details of the dose expansion cohort. Also during the dose expansion phase, biomarker data will be collected.

2.3 Rationale for dose and regimen selection

Since thrombocytopenia has been established as the DLT of PANOBINOSTAT, a dosing schedule of QOW will first be attempted in the early dose escalation cohorts since data from [CLBH589B2102] suggests QOW dosing decreased the incidence and time to severe treatment related thrombocytopenia as well as the duration of thrombocytopenia. Refer to Table 2-1 for more detailed information.

Table 2-1 Comparison of dose reductions, duration of exposure, relative dose intensity and thrombocytopenia between QW and QOW schedule with oral PANOBINOSTAT in patients with HL in study CLBH589B2102

	Every Week Schedule (QW)				Every Other Week Schedule (QOW)		
Parameters Analyzed	**30 mg TIW**	**40 mg TIW**	**60 mg TIW**	**All**	**45 mg TIW**	**60 mg TIW**	**All**
	N=2	**N=15**	**N=5**	**N=22**	**N=3**	**N=7**	**N=10**
Dose Reductions (%)							
None	100	40	60	50	100	71	80
1 dose reduction	0	27	40	27	0	29	20
≥2 dose reductions	0	33	0	23	0	0	0
Thrombocytopenia							
Time to grade 3/4 (median, days)	86.5	12	8	12	N/A (>376)	64	N/A (>208)
Duration (median, days)	4.5	8	5	7	N/A	7	7
Maximum duration (days)	6	26	29	29	N/A	8	8
Exposure (median, days)	392.5	115	176	136	348	131	260
Relative dose intensity	91.0 %	62.1%	47.3%	57.3%	92.9%	96.7%	94.5%
Abbreviation: N/A = not applicable (median not reached because Grade 3/4 thrombocytopenia has not yet occurred)							

From study [INC424-251], anemia and thrombocytopenia were the most frequently reported grade 3 or 4 events. While thrombocytopenia was the most frequently reported treatment emergent adverse event (TEAE) leading to study drug interruption (18.8%), only 3.2% of the patients required discontinuation of study medication. The only other TEAEs leading to discontinuation that occurred in more than one patient were anemia (2.6%), multi-organ failure (1.3%), and acute myeloid leukemia (1.3%). Analysis of grade 3 and 4 thrombocytopenia by initial treatment group also showed a clear dose response. Patients who began therapy at lower doses (10-15mg BID) were less likely to have grade 3 thrombocytopenia, and no patient receiving these doses had grade 4 thrombocytopenia or worsening anemia (data on file: Novartis). Refer to Section 1.3.3 for more detailed information on these events.

2.4 Rationale for choice of combination drugs

In a preclinical study (Wang 2009), it was demonstrated that compared with either agent alone, combined treatment with PANOBINOSTAT and TG101209 (a JAK2 TK inhibitor) is more effective in attenuating not only p-STAT3 and p-STAT5, but also the mutant JAK2V617F. This effect was more pronounced when PANOBINOSTAT was combined with lower concentrations of TG101209. Preclinically this combination also showed a synergistic increase in cytotoxicity for cells expressing the JAK mutation (Wang 2009). HEL cells treated with PANOBINOSTAT showed an approximately 40% depletion of the mRNA expression of JAK2 (Wang 2009). PANOBINOSTAT has also been shown to induce hyperacetylation and

inhibition of the chaperone function of HSP90, resulting in proteasomal degradation of HSP90 client proteins which includes JAK2. The distinct mechanisms of action of PANOBINOSTAT in addition to the blockade of the JAK/STAT pathway provided by RUXOLITINIB, may allow for greater disease control at lower doses of each of these agents to avoid toxicities. There is no predicted pharmacokinetic interaction between these two drugs, and synergistic toxicities are not anticipated. See Section 1.4.1 and Section 1.4.2 for further details.

From this study, the JAK2V617F mutation allele burden was measured pre- and post-treatment from 10 patients. The median percent of mutant JAK2 pre-treatment was 27%, and the median percent post-treatment was 10% indicating a significant median decline in the JAK2V617F allelic burden (DeAngelo 2010).

From study INC424-251, in the 34 patients for whom data were available the mean maximal suppression of 13% from baseline was seen after 12 cycles of therapy (Verstovsek 2010).

As both of these agents modify the overall JAK2V617F allele burden, given sufficient follow up this may prove to have meaningful clinical benefit.

3 Objectives and endpoints

Objectives:

- Evaluate the tolerability and safety of combination RUXOLITINIB and PANOBINOSTAT in patients with MF in chronic and accelerated phase.
- Assess clinicopathologic response of MF patients treated with RUXOLITINIB and PANOBINOSTAT.
- Assess changes in biomarkers of disease in relation to response to combination treatment with oral PANOBINOSTAT and RUXOLITINIB.
- Explore genetic and epigenetic predictors of disease response to combination therapy in MF.

Endpoints:

- Determine the Dose Limiting Toxicities (DLTs) of each agent in combination.
- Characterize the adverse events (AEs) and serious adverse events (SAEs) of combination therapy.
- Establish the Maximally Tolerated Doses (MTDs) and the Recommended Phase Two Doses (RPTDs) for each agent in combination.
- Assessing clinical response by International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) consensus criteria.
    - Spleen reduction by palpation on exam.
    - Peripheral blood count and morphology normalization.
    - Bone marrow histopathology and fibrosis.
- Evaluate reduction in spleen volume by MRI/CT.
- Evaluation bone marrow response in terms of cellularity, histopathology and fibrosis in patients treated with RUXOLITINIB and PANOBINOSTAT.

- Evaluation of histone H3/H4 acetylation, JAK2V617F mononuclear allele burden, degree of circulating CD34+ hematopoietic cells in the peripheral blood; CXCR4 expression in CD34+ hematopoietic cells; changes in cytokine and other plasma protein levels from baseline.
- Assess if the presence of JAK2V617F, TET2, ASXL1, EZH2 and other MPN markers can predict clinical response to combination therapy

4 Study design

4.1 Description of study design

Phase I/II open label, single institution, study of induction RUXOLITINIB followed by concurrent administration of RUXOLITINIB and PANOBINOSTAT in a 3+3 cohort dose escalation schema in eligible patients with MF (see Figure 4-2). Screening for this study will have a window of 56 days and start on day -84 with signing of informed consent. See Figure 4-1 A and B. Eligible patients will begin induction phase therapy on day -28, receiving single agent RUXOLITINIB PO BID daily for 28 days. The dose of RUXOLITINIB in the induction cycle days -28 to 0 will be the same dose that the patient will receive in the assigned combination cycles. Patients who maintain a platelet count≥ 50,000/ul at Day 1 will then receive concomitant PANOBINOSTAT PO TIW QOW or PO TIW QW depending on the cohort assignment. The induction phase of the Phase I study is not the evaluable phase I component and AEs that are noted in the induction phase will not constitute a dose limiting toxicity (DLT) and patients who do not maintain a platelet count >50 x 10^9/L will be removed and will not be able to continue onto the combination drug evaluable phase I period of 28 days and will not be counted in the evaluable phase I cohort for the purposes of dose escalation.

Phase I

The first 28 days of combination therapy will be the evaluable phase I portion of the study. Patients who do not experience a defined DLT in the dose evaluation stage of phase I can remain on study receiving combination drug therapy for a total of 6 cycles (cycles 2-6). See Figure 4-1 A. AEs will continue to be recorded on all patients (phase I and II) receiving combination therapy beyond the first cycle of the study. Dose escalation rules are based on the standard 3+3 design as shown in Figure 4-2.

Note that in this Phase I study, the initial cohort(s) will fix the dose of RUXOLITINIB and escalate the dose of PANOBINOSTAT. Thus, the first endpoint will be to find the MTD of PANOBINOSTAT associated with a fixed dose of 10 mg of RUXOLITINIB. At that point, the dose of PANOBINOSTAT will be fixed at the MTD just mentioned, and RUXOLITINIB will be escalated to 15 mg. The rules of the 3+3 design will govern whether 15 mg is an acceptable dose for RUXOLITINIB in combination with the MTD of PANOBINOSTAT. The rules of the 3+3 design will again be employed to decide on the frequency of administration of PANOBINOSTAT.

Phase I patients who complete a total of 6 cycles of combination therapy will be assessed for clinical response by IWG-MRT criteria. Patients who achieve at least Stable Disease (SD) by IWG-MRT (Table 4-1) can remain on therapy indefinitely or until disease progression or drug toxicity as assessed by the investigators in the Phase I extension stage. After 24 cycles, stable patients may be seen every other month at the discretion of the investigator. At the discretion of the investigator, phase I patients who have completed 6 cycles of therapy with a minimum of SD can also be dose escalated at that time to the RPTD once it is determined. These patients will not be considered for evaluation of response in Phase II.

Myelosuppression is expected and anticipated given the known toxicity profiles of these drugs in single agent therapy for MF. During the dose evaluation stage, Days 1-28, while both drugs are administered in combination, platelet transfusions will not be allowed to avoid the predetermined DLT of platelet count $<10 \times 10^9$/L or any platelet count with grade 3 bleeding. If a platelet transfusion is indicated by best clinical practice guidelines and the PI feels it is necessary to transfuse a patient in these 28 days of the phase I study even at a platelet count $>10 \times 10^9$/L, then the patient will be transfused and will come off study and this will be considered a DLT. Platelet transfusions are allowed and should be given when clinically indicated and at the discretion of the investigator in Phase I continuation stage and extension stage. This would not necessarily require discontinuation from the study.

Phase II

Expansion stage [Cycles 1-6]

Once a RPTD is determined from the dose escalation phase I part of this trial, the dose expansion of the phase-II part of this trial will commence with 16 additional patients added to the 6 original RPTD cohort from phase I to total 22 patients. See Figure 4-1 B. IWG-MRT response criteria will be applied at the end of cycle 6 and this will include spleen volume measurement by MRI/CT and bone marrow biopsy to appreciate changes in morphology, degree of reticulin/collagen fibrosis, cytogenetics and molecular markers. Patients who have obtained at least SD by IWG-MRT can remain on study receiving combination therapy in the phase II extension stage.

Extension stage [Cycles 7+]

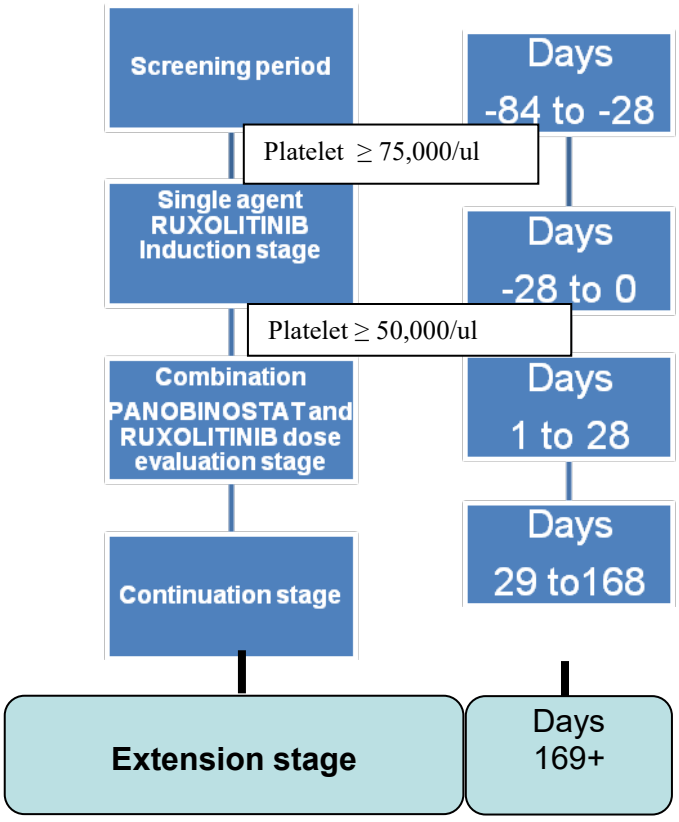
In this part of phase II, patients have obtained at least SD by IWG-MRT after 6 cycles of combination therapy and will continue to be treated with dose modifications and stopping rules that are the same as the expansion stage. Patients will continue to be followed for signs of response on each monthly visit. After 24 cycles, stable patients may be seen every other month at the discretion of the investigator. Repeat imaging of the spleen and bone marrow biopsy with repeat cytogenetic and molecular testing when appropriate can be performed at the discretion of the investigator for the purpose of assessment of response or disease progression. Additional biomarker assessments can also be made at intervals determined by the clinical course and at the discretion of the investigator.

Platelet transfusions are allowed in the Phase II portion of this trial and should be given when clinically indicated. Specific instructions are provided for dose modifications and holding of study drugs as outlined in Table 6.2.3. Red blood cell transfusion are allowed and anemia does not require dose holding or modification until after cycle 6 if the PI believes the study

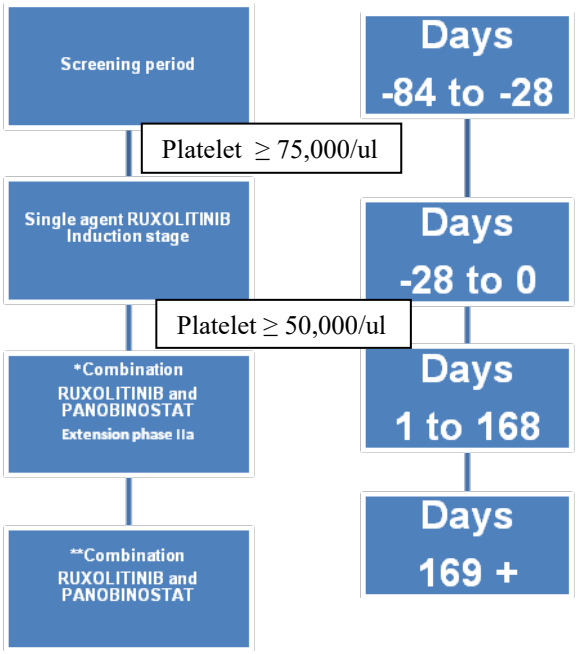
drugs are primarily the cause of worsening anemia and in these cases the instructions for dose holding and modification can be followed as outlined in Table 6.2.3.

Figure 4-1 **Study Design**

A. Phase I Study design



B. Phase II study design



*Phase II expansion stage is Days 1 to 168 (end of cycle 6)

**Phase II extension stage is days 169 and beyond (cycle 7+)

Figure 4-2 Dose escalation rules for 3+3 phase I study design

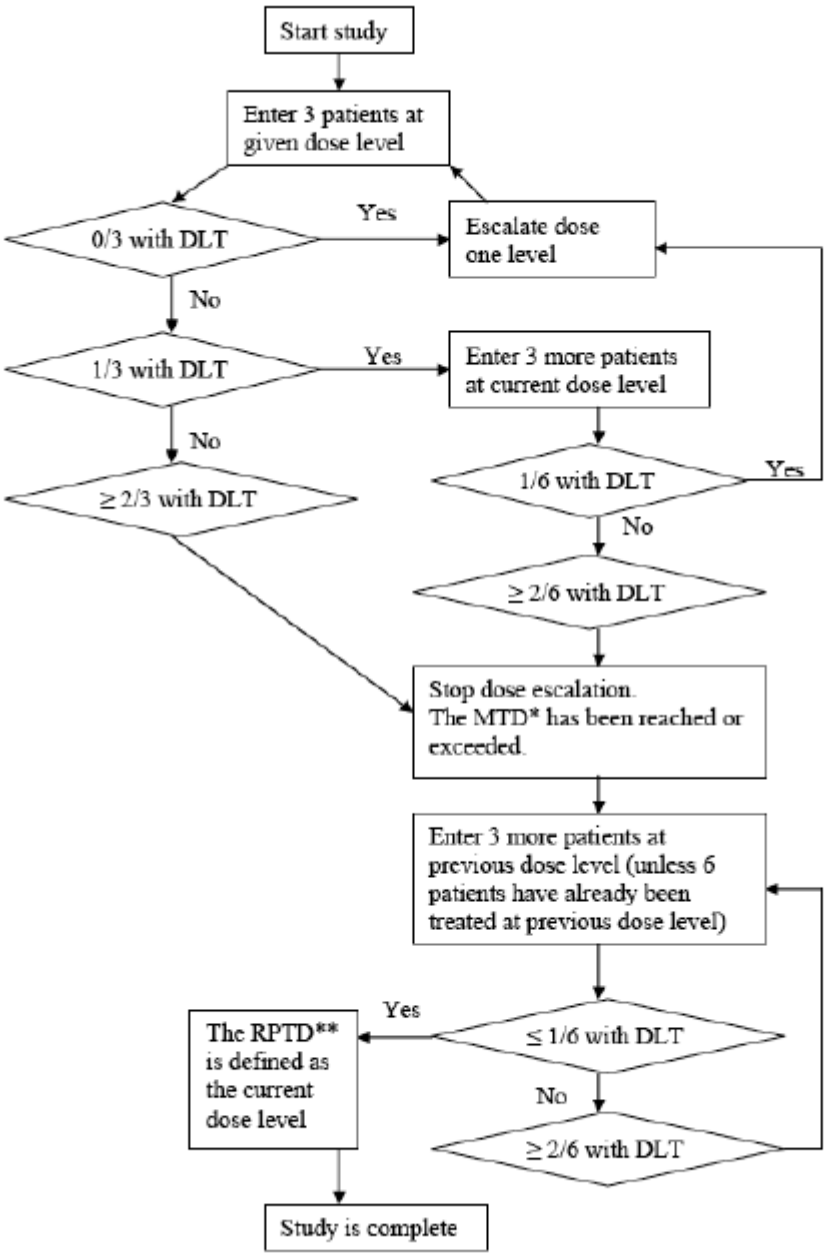


TABLE 4-1 International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia

1. Complete remission (CR)	i. Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly.
	ii. Peripheral blood count remission defined as hemoglobin level at least 110 g/L, platelet count at least 100 × 10^9/L, and absolute neutrophil count at least 1.0 × 10^9/L. In addition, all 3 blood counts should be no higher than the upper normal limit.
	iii. Normal leukocyte differential including disappearance of nucleated red blood cells, blasts, and immature myeloid cells in the peripheral smear, in the absence of splenectomy.*
	iv. Bone marrow histologic remission defined as the presence of age-adjusted normocellularity, no more than 5% myeloblasts, and an osteomyelofibrosis grade no higher than 1.†
2. Partial remission (PR)	Requires all of the above criteria for CR except the requirement for bone marrow histologic remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.
3. Clinical improvement (CI)	Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment (CI response is validated only if it lasts for no fewer than 8 weeks)
	i. A minimum 20-g/L increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of less than 100 g/L).‡
	ii. Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable.§
	iii. A minimum 100% increase in platelet count and an absolute platelet count of at least 50 000 × 10^9/L (applicable only for patients with baseline platelet count below 50 × 10^9/L).
	iv. A minimum 100% increase in ANC and an ANC of at least 0.5 × 10^9/L (applicable only for patients with baseline absolute neutrophil count below 1 × 10^9/L).
4. Progressive disease (PD)	Requires one of the following:‖
	i. Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at greater than 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of greater than 10 cm.
	ii. Leukemic transformation confirmed by a bone marrow blast count of at least 20%.
	iii. An increase in peripheral blood blast percentage of at least 20% that lasts for at least 8 weeks.
5. Stable disease (SD)	None of the above.
6. Relapse	Loss of CR, PR, or CI. In other words, a patient with CR or PR is considered to have undergone relapse when he or she no longer fulfills the criteria for even CI. However, changes from either CR to PR or CR/PR to CI should be documented and reported.

4.2 Definition of end of the study

Patients may continue treatment until they progress, withdraw consent, experience unacceptable toxicity, start new MF therapy, and/or it is believed by the investigator to be in the best interest of the patient to discontinue. The study will continue until the last patient completes all required safety evaluations per extension phase of protocol. Data on patients will continue to be collected on all patients who remain on study.

4.3 Timing of interim analyses and design adaptations

No interim analyses are planned for this study.

4.4 Early study termination

The sponsor/investigator has the right to terminate the study at any time. Should this be necessary, the patient should be informed, and seen as soon as possible to perform a final visit. At this visit, the same assessments should be performed as End of Treatment, see Appendix A. The investigator will be responsible for informing the patients and the IRBs and/or ECs and FDA, as well as other relevant committees at MSSM of the early termination of the trial.

5 Population

5.1 Patient population

Adult male or female patients ages 18 or older, who have been diagnosed with Primary myelofibrosis (PMF), Post-polycythemia vera related myelofibrosis (Post PV MF) or Post Essential Thrombocythemia related Myelofibrosis (Post ET MF) as defined by the World Health Organization (WHO 2008), will be included in this study. These patients will be seen at the Mount Sinai School of Medicine Myeloproliferative Disorders Program.

Patients must be classified by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) (Passamonti, 2010) and be either Intermediate-2: 3-4 points; or High Risk: 5 or more points. Patients can have either chronic phase (MF-CP), or accelerated phase (MF-AP) disease.

Patients may have received prior therapy for MF, but must discontinue chemotherapy for 3 weeks (except for hydroxyurea which can be discontinued 24 hours before starting RUXOLITINIB), and targeted therapy for 2 weeks prior to screening. Anagrelide can be continued up until 24 hours of starting the RUXOLITINIB. An exception are patients currently on at least 10mg BID of RUXOLITINIB for greater than 3 months and who have not shown an optimal response (i.e. without 50% reduction in palpable splenomegaly or 50% reduction in symptom burden). With a reduction of RUXOLITINIB to 10mg BID these patients may enter onto the study without stopping RUXOLITINIB. This trial will allow

patients who were treated with either HDACi's or JAK2 inhibitors, as long as these agents were not discontinued due to clinically relevant toxicities per the investigator.

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are allowed to enter study treatment in this study. Written informed consent must be obtained prior to any screening procedures.

5.2 Inclusion criteria

1 Male or female patients aged ≥ 18 years old
2 Ability to provide written informed consent obtained prior to participation in the study and any related procedures being performed
3 Intermediate-2 and higher by IWG-MRT Post PV/ET MF and PMF patients either in
   a. Chronic Phase (MF-CP)
   b. Accelerated Phase (MF-AP)
4 Patients must meet the following laboratory criteria:
   a. ANC ≥ .750 x 10^9/L
   b. Platelets ≥ 75 x 10^9/L
   c. Creatinine ≤ 1.5 x ULN,
   d. AST and ALT ≤ 2.5 x ULN
   e. Serum bilirubin ≤ 1.5 x ULN (unless Gilbert's syndrome and evidence of hemolysis)
   f. Serum potassium ≥ LLN
   g. Total serum calcium [corrected for serum albumin] or ionized calcium ≥LLN,
   h. Serum magnesium ≥ LLN
   i. Serum phosphorus ≥ LLN
   j. Free T4 within normal limits
5 ECOG Performance Status of ≤ 3
6 Any prior therapy with JAK2-TKI, hypomethylating agents, HDACI, mTORi, or iMiDs is allowed as long as it is greater than 3 weeks since last dose of administration and in the case of a JAK2-TKI or HDACI that discontinuation was not due to non-hematologic drug toxicity. An exception to this criteria are patients currently on at least 10mg BID of ruxolitinib for greater than 3 months and who have not shown an optimal response (i.e. without 50% reduction in palpable splenomegaly or 50% reduction in symptom burden). With a reduction of ruxolitinib to 10mg BID these patients may enter onto the study without stopping ruxolitinib.

Exclusion criteria

1. Patients who will need valproic acid for any medical condition during the study or within 5 days prior to first PANOBINOSTAT treatment.
2. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
   a. With permanent cardiac pacemaker

b. Resting bradycardia defined as <50 beats per minute
c. QTcF >480 msec on screening ECG
d. Complete Left bundle branch block, bifascicular block
e. Any clinically significant ST segment and/or T-wave abnormalities
f. Presence of unstable atrial fibrillation (ventricular response rate >100 bpm). Patients with stable atrial fibrillation can be enrolled provided they do not meet other cardiac exclusion criteria.
g. Symptomatic congestive heart failure (NYHA class III-IV)

3. Impairment of GI function or GI disease that may significantly alter the absorption of PANOBINOSTAT or RUXOLITINIB
4. Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes or active or uncontrolled infection) including abnormal laboratory values, that could cause unacceptable safety risks or compromise compliance with the protocol
5. Patients using medications that have a relative risk of prolonging the QT interval or inducing torsade de pointes if treatment cannot be discontinued or switched to a different medication prior to starting study drug
6. Concomitant use of strong CYP3A4 inhibitors
7. Patients who have received targeted agents within 2 weeks or within 5 half-lives of the agent and active metabolites (whichever is longer) and who have not recovered from side effects of those therapies.
8. Chemotherapy witihin 3 weeks prior to screening are excluded (other than hydroxyurea at stable doses and will be discontinued 24 hours prior to starting study drug).
9. Patients with an active bleeding tendency or are receiving any treatment with therapeutic doses of sodium warfarin (Coumadin®) or coumadin derivatives. Patients will be allowed to enter study on aspirin at doses of 81mg/d.
10. Patients who have undergone major surgery≤ 4 weeks prior to starting study drug or who have not recovered from side effects of such therapy
11. Women who are pregnant or breast-feeding or women of childbearing potential (WOCBP) not using an effective method of birth control. WOCBP are defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months). Women of childbearing potential must have a negative serum pregnancy test within 24hrs of receiving the first dose of study medication.
12. Male patients whose sexual partners are WOCBP not using effective birth control
13. Patients with a prior malignancy within the last 5 years (except for basal or squamous cell carcinoma, or *in situ* cancer of the cervix)
14. Disease associated with secondary MF such as metastatic carcinoma, lymphoma, myelodysplasia, hairy cell leukemia, mast cell disease or acute leukemia (including M7 disease or acute panmyelosis with MF)

6 Treatment

6.1 Investigational treatment

The terms "investigational study drug(s)" or "study drug(s)" will refer to oral RUXOLITINIB (also known as INCB18424) tablets and oral PANOBINOSTAT (also known as LBH589) capsules and both drugs will be supplied by Incyte and Novartis, respectively, at no cost to the subjects.

6.1.1 Dosing administration

RUXOLITINIB is administered orally BID everyday in a 28-day treatment cycle (Q4wk). Induction phase dose is 10 mg PO BID. In the combination phase, the starting dose of RUXOLITINIB is 10 mg and may be increased to 15mg PO BID. See Table 6-1, Table 6-2 for dose and treatment schedules.

PANOBINOSTAT is administered orally TIW, QOW, or QW in a 28-day cycle depending on the assigned cohort. Starting dose of PANOBINOSTAT is 10mg TIW QOW and may be increased to 20mg TIW QW depending on the assigned cohort. See Table 6-1 for dose and treatment schedules.

Patients may take RUXOLITINIB and PANOBINOSTAT without regard to food. However, once the patient has made a choice (e.g., take drug after breakfast or at fasting), it is recommended that patient will follow the election choice consistently throughout the protocol.

On Day -28, the first dose of RUXOLITINIB only will be administered at the clinical site. First dose of PANOBINOSTAT will start on Cycle 1 Day 1 administered with the RUXOLITINIB morning dose at the clinical site. See Table 6-2 for provisional escalating dose levels.

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Escalating Doses	Frequency and/or Regimen
RUXOLITINIB	Oral	10,15 mg	Twice daily, 28-day cycles
PANOBINOSTAT	Oral	10, 15 mg	Three times a week, every other week, 28-day cycles OR Three times a week, every week, 28 day cycle To be taken with the AM dose of RUXOLITINIB

Patients will self-administer RUXOLITINIB and PANOBINOSTAT as instructed as follows:

- RUXOLITINIB will be orally administered BID (approximately 12 hours apart: morning and evening)
- PANOBINOSTAT should be taken orally TIW (e.g. day 1, 3, and 5) at the same time on each day with the AM dose of RUXOLITINIB. Doses should be separated by a minimum of 30 hours within the week of dosing

- Dose may be taken with or without food
- Each dose of study drug should be taken with a glass of non-carbonated water (approximately 8 ounces/240ml). Patients should be instructed to swallow the capsules/tablets whole and not chew them.
- Patients must avoid grapefruits, grapefruit juice, pomegranate, starfruit, starfruit juice, Seville oranges and Seville orange juice during the entire study treatment period
- The timing of the clinic visit for ECG monitoring (7-1) should be considered when determining the initial time of dosing, as the dose time on the day of ECG performance should be consistent, as much as possible, throughout the study.
- If the patient forgets to take a dose of RUXOLITINIB, then he/she should take study drug within 3 hours after the missed dose. If more than 3 hours have passed, then that missed dose should be omitted and the patients should continue treatment with the next scheduled dose.
- If the patient forgets to take a dose of PANOBINOSTAT, then he/she should take study drug within 12 hours after the missed dose. If more than 12 hours have passed, then that missed dose should be omitted and the patients should continue treatment with the next scheduled dose.
- If a patient vomits study drug within one hour of study drug administration, the dose will not be re-administered. The patient will resume therapy at the next schedule dose. On all other days corresponding to study visits, the patients may take the morning dose of study drug prior to their scheduled clinic visit.
- If vomiting occurs on non-study visit days, re-dosing of the patient is not allowed before the next scheduled dose, and the event should be noted in the appropriate eCRFs.

6.1.2 Ancillary treatments

Not applicable

6.1.3 Rescue medication

Not applicable

6.1.4 Guidelines for continuation of treatment

Patients may continue treatment until they progress, withdraw consent, experience unacceptable toxicity, start new MF therapy, and/or it is believed by the investigator to be in the best interest of the patient to discontinue (in consultation between the sponsor and investigator).

6.1.5 Study duration

The study will continue until the last patient completes all required safety evaluations per protocol per extension stage of Phase II protocol.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

In [CLBH589BUS32T], the established MTD of PANOBINOSTAT in patients with MF, was 25mg PO TIW QW. PANOBINOSTAT has been tolerated up to a dose of 80mg TIW QW, but the majority of these patients will dose reduce due to toxicities [CLBH589B2102]. RUXOLITINIB has been tolerated up to doses of 50mg BID, but a minimum of 25% reduction in splenomegaly was seen in the majority of patients treated at 10mg BID, 15mg BID, and 25mg BID (Verstovsek 2010). From [INCB018424-251], 15mg BID was established as the most effective and safest starting dose, followed by individualized dose titration (Verstovsek 2010).

As described in Section 2.4, there was synergistic anti-proliferative activity seen in a preclinical *in vitro* experiment (Wang 2009) when combining the JAK2 inhibitor TG101209 and PANOBINOSTAT. This combination of agents was effective in attenuating mutant JAK2V617F, p-STAT3 and p-STAT5, especially when PANOBINOSTAT was combined with lower concentrations of TG101209.

In the interest of patient safety, both of these compounds will start at dose levels below 50% of the respective maximum tolerated doses due to the potential overlapping toxicity with respect to thrombocytopenia, anemia and neutropenia. This was also determined to be an appropriate way to assess if a more biologically effective dose could be found prior to determining the MTD for this combination. As such the provisional doses are shown in Table 6-2.

6.2.2 Provisional dose levels

The provisional dose escalation levels for RUXOLITINIB and PANOBINOSTAT are described in Table 6-2. Deviation from this provisional dose escalation plan is allowed if emerging data on toxicities and signals for activity are observed and are felt to be important to warrant modification of the provisional dose levels by the Investigators. It will be the responsibility of the Investigators to provide appropriate rationale and study data to justify deviation. Any planned deviation from the provisional dose escalation levels shown in Table 6.2 will have to first be approved by the local IRB, FDA and Novartis.

Table 6-2 Dose escalation cohorts for combination therapy evaluable phase I study

	Cohorts							
	1	**2**	**3**	**4a**	**4b**	**5**	**6**	**7**
RUXOLITINIB	10mg PO BID	10mg PO BID	10mg PO BID	15mg PO BID	15mg PO BID	15mg PO BID	15mg PO BID	15mg PO BID
PANOBINOSTAT	10mg PO TIW QOW	15mg PO TIW QOW	20mg PO TIW QOW	15mg* PO TIW QOW	20 mg PO TIW QOW	10mg PO TIW QW	15mg PO TIW QW	20mg PO TIW QW
Cumulative dose/cycle	60mg	90mg	120mg	90mg*	120mg	120mg	180mg	240mg

*DOSE WILL DEPEND ON PREVIOUS COHORT AND WILL EITHER BE PANOBINOSTAT 10MG, 15MG OR 20MG PO TIW QOW FOR A CUMULATIVE DOSE/CYCLE OF EITHER 60MG, 90MG, OR 120MG

6.2.3 Criteria for dose escalation and determination of MTD and/or RPTD

A patient will be considered evaluable for the dose-determining set if he or she experiences a DLT during the combination phase days 1 to 28, or is observed for at least 28 days in the combination phase and is fully evaluated for any toxicities and has completed all study required tests. Patients who do not experience a DLT in the 28 days of the combination phase are considered evaluable if they have taken at least 50% of the RUXOLITINIB doses and not missed more than 1 dose of PANOBINOSTAT in the QOW dosing cohorts and no more than 2 doses in the QW dosing cohorts.

All available safety information (including DLTs, adverse events that are not DLTs, vital signs, and ECGs will be reviewed by the investigators in each cohort to decide if the next dose cohort will begin. Drug administration at the next dose level may not proceed until the investigators have documented it is safe to proceed to a higher dose level. Dose escalation will continue until identification of the MTD and/or RPTD is made.

The initial 3 cohorts will have RUXOLITINIB administered at a fixed dose of 10mg PO BID and cohort 1 will combine PANOBINOSTAT at a dose of 10mg PO TIW QOW, cohort 2 will be PANOBINOSTAT 15mg PO TIW QOW and cohort 3 will be PANOBINOSTAT 20mg PO TIW QOW for cumulative cycle doses of 60mg, 90mg and 120mg, respectively. If an MTD of PANOBINOSTAT is not established by cohort 3, then cohort 4a will test RUXOLITINIB at 15mg PO BID in combination with PANOBINOSTAT 15mg PO TIW QOW and 20mg PO TIW QOW in 4b. If an MTD of PANOBINOSTAT is established in the first 3 cohorts, then the cohort 4a will test RUXOLITINIB at 15mg PO BID in combination with PANOBINOSTAT at the dose level preceding the MTD dose level of PANOBINOSTAT.

If the dose escalation of RUXOLITINIB continues to cohort 4b and this cohort does not define the MTD of RUXOLITINIB, then cohort 5 will allow patients to be treated at a dose of PANOBINOSTAT of 10mg PO TIW QW for a cumulative dose/cycle of 120mg. Cohorts 6 and 7 will be pursued if the previous cohorts don't reach MTD and will include 15mg PO BID of RUXOLITINIB and 15mg PO TIW QW and 20mg PO TIW QW, respectively.

The RPTD of each agent will be determined by the MTD and the dose limiting toxicities observed in Phase I. The RPTD will not necessarily be the MTD doses reached in the Phase I dose escalation part of this study. However, the RPTD will not exceed the estimated MTD dose of either drug as determined from the drugs given in combination in Phase I. The decision to define the RPTD will ultimately be made by the PI and will be based on the toxicity profiles and in part any and all data on tolerability and efficacy of the combination therapy in the Phase I patients who remain on study drugs beyond the first cycle.

6.2.3.1 Definition of MTD

The MTD is defined as the highest drug dosage not causing in the first cycle of treatment medically unacceptable, dose-limiting toxicity in more than 33% of the treated patients.

6.2.3.2 Definition of RPTD

If the evolving safety profile (long term or overall) along with other assessments suggest that further increases in dose will result in excessive toxicity, without substantial benefit in exposure/activity, the dose escalation phase of the study will be halted. The potential RPTD will be determined by a combination of the MTD determination in the Phase I and the tolerability and efficacy of PANOBINOSTAT and RUXOLITINIB in combination over multiple cycles in patients who remain receiving therapy beyond cycle 1. The rationale for this approach is based on the fact that although higher doses of PANOBINOSTAT may be tolerated, lower doses (or alterations in the treatment schedule) may be equally effective or even more effective in inducing chromatin modifying effects in the malignant cells while limiting both heme and non-heme toxicities. It is the hypothesis of the investigators based on the previous studies of PANOBINOSTAT in MF that lower doses of drug delivered over extended periods of time are most effective and most well tolerated.

6.2.4 Dose cohort modification

Provisional dose level cohorts are listed in Table 6-2. Possible changes in dose administration include but are not limited to:

- Expansion of the current dose group to further assess safety
- Administration of an intermediate dose between the current and preceding dose
- Administration of an intermediate dose between the current and the next planned dose
- Termination of any further escalation of study drug

If there is less than the required number of evaluable patients, then additional patients will be enrolled until at least the minimum number of evaluable patients is available for assessment.

6.2.5 Definitions of dose limiting toxicities (DLTs)

DLTs are listed in Table 6-3, and will be defined as all AEs of the specified grade occurring within Days 1-28 of the combination phase, unless clearly and incontrovertibly due to extraneous causes.. Table 6-3 was created using Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

For the purpose of dose-escalation decisions, only DLTs occurring during the first 28 days of treatment with RUXOLITINIB and PANOBINOSTAT will considered and included in dose escalation decisions. However, all safety information including adverse events, ECG monitoring data, and vital sign abnormalities, will be included in the final decision for dose escalation and determination of how many patients should be evaluated at a given dose level.

Thrombocytopenia will only be considered a DLT in the combination phase (Day 1-28) if the platelet count is recorded below 10,000/ul by manual count or≥10,000/ul and associated with a grade 3 bleed. Phase I patients who require platelet transfusions within Days 1-28 will have to be removed from study. Patients are allowed to receive platelet transfusions after day 28 if clinically warranted, and this does not necessitate removal from study. Transfusional support of red blood cells (RBC) is permissible at any point in the study and is not considered a DLT.

In the event that an AE begins during the first 28 days of combination therapy, but does not qualify for the definition of a DLT at the time of the dose-escalation decision, due to a specific length requirement until Cycle 2; it will be provisionally considered a DLT during the decision-making process. Adverse events occurring after treatment day 28 will not be considered DLTs, however, they will guide the decision of dose escalation and how many patients will be evaluated at a given dose level. All AE's, vital signs, and ECG data will be included in the final analysis to determine the MTD and/or RPTD.

Table 6-3 Criteria for Defining Dose Limiting Toxicity (DLT)

TOXICITY	Any of the following criteria:
Hematologic	
Febrile Neutropenia	≥Grade 3 (ANC < 1.0 x 10^9/L + Fever single reading >38.3°C or ≥38°C sustained >1 hr)
Thrombocytopenia	<10 x 10^6/ul or ≥10 x$10^{6/}$ul associated with grade 3 bleeding
Non-Hematologic	
Gastrointestinal	
Vomiting	≥Grade 3
Nausea	≥Grade 3 nausea uncontrolled despite use of standard anti-emetics
Diarrhea	≥Grade 3 Diarrhea
Constitutional symptoms	
Fatigue	Grade 4 Fatigue
Hepatobiliary	
Bilirubin	≥Grade 3, Coincident Direct Bilirubin ≥0.5mg/dl
AST/SGOT and/or ALT/SGPT	≥ Grade 3
	≥Grade 4
Other	Any Grade 3 non-hematologic toxicity : With the exception of: ≥Grade 3 QTc prolongation (QTc > 500 ms), which is a DLT at any incidence
	Any Grade 4 non-hematologic toxicity

Any of the following AEs, which when assessed as treatment related, will require patients to be permanently discontinued from study:

- any grade ≥ 3 hemorrhagic event
- 2nd episode of grade ≥3 febrile neutropenia
- grade 3 renal toxicity
- grade ≥ 3 QTc prolongation (QTc > 500 ms)
- grade 4 renal toxicity
- grade 4 serum bilirubin with direct bilirubin ≥ 0.5 mg/dL
- grade 4 non-hematologic toxicity

6.2.6 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed at least once a week for 4 weeks up to day 28. Patients whose treatment is interrupted or permanently discontinued due to an SAE, must be followed at least once a week for 4 weeks up to day 28, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. If a patient requires a dose delay for either drug for longer than 90 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. Hematology labs (CBC) and pertinent non-hematology labs will be part of the follow up procedures. ECG will also be part of the follow up procedures if the AE/SAE was cardiac related.

All patients will be followed for AE's and SAE's for 30 days following the last dose of study treatment, with the exception of prolonged QTc.

6.2.7 Dose modification and dose delay

Transfusional support as clinically indicated is also permissible at the discretion of the investigators.

Dose modification rules in Phase I cycles 2-6 (Day 29 - 168) and beyond cycle 7 (Day 169+) or any time in phase II are shown in Table 6.2.3 below. These are to be followed for patients in Phase I as well as Phase II expansion and extension stages. Dose reductions (for PANOBINOSTAT) based on platelet count will be allowed and the dose of PANOBINOSTAT will not go below 5mg PO TIW QOW. See Table 6.2.1/6.2.2 for PANOBINOSTAT and RUXOLITINIB dose levels. The dose of RUXOLITINIB will not be reduced below 5mg PO BID.

Based on the expected occurrence of thrombocytopenia in this patient population with the combination of these agents, we intend to submit a request for agency feedback form to update the safety data in terms of thrombocytopenia after 10 patients have been enrolled on this study. If the safety profile with the combination of PANOBINOSTAT and RUXOLITINIB is acceptable in terms of incidence of platelet count below 20 x 10^9/L and grade 3 or higher bleeding events, then we will continue the study with a threshold of 20 x 10^9/L for dose holding/modification. If there is a single incidence of grade 3 or higher bleeding in association with a platelet count of <35 x 10^9/L, then this threshold will be modified accordingly. This determination will be made after review by the FDA.

Table 6.2.1 RUXOLITINIB dose levels for dose modifications in Cycles 2+ (day 29+)

Dose level	RUXOLITINIB	Comment
-1	5mg PO BID	Lowest dose allowed in the study
0	10mg PO BID	Starting dose in induction phase for all patients on study
1	15mg PO BID	Starting dose for cohort 4a, 4b

Table 6.2.2 PANOBINOSTAT dose levels for dose modifications in Cycles 2+ (day 29+)

Dose level	PANOBINOSTAT	Cumulative dose (per cycle)	Comment
-1	5mg PO TIW QOW	30mg	Lowest allowable dose on the study
0	10mg PO TIW QOW	60mg	Starting dose of cohort 1
1	15mg PO TIW QOW	90mg	Starting dose for cohort 2, 4a
2	20mg PO TIW QOW	120mg	Starting dose for cohort 3, 4b
3	10mg PO TIW QW	120mg	Starting dose for cohort 5
4	15mg PO TIW QW	180mg	Starting dose for cohort 6
5	20mg PO TIW QW	240mg	Maximum dose allowed in study

Dose modifications or interruptions for adverse events occurring during the DLT-definition period (Cycle 1 Day 1 through Cycle 1 Day 28 of Phase I), and considered as treatment-related will not be allowed. This would require removal of a patient with a DLT within Day 1-28 of Phase I.

Beginning in cycle 2 (day 29), patients who do not tolerate the protocol-specified dosing schedule are permitted to dose adjust in order to allow the patient to continue the study treatment. Tables 6.2.1 and 6.2.2 outline the possible dose level reductions permitted depending on the current dose of each drug at the time of the AE. Patients who experience toxicity at either a dose of RUXOLOTINIB at 5mg PO BID or PANOBINOSTAT at 5mg PO TIW QOW cannot be dose reduced further and will be removed from study. Table 6.2.3 and Table 6-4 provide instruction on management per toxicity. All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.0). Patients who require dose hold of RUXOLITINIB are allowed to receive steroids (prednisone, dexamthesone, etc) as per the Investigators discretion to avoid or blunt potential RUXOLITINIB-withdrawal syndrome.

All adverse events should be treated as per the local standard of care and referred to a specialist if clinically indicated. Investigators can use their discretion when making dose-reduction decisions unless otherwise specified in the guidelines below.

If at any time during the study period the use of a strong CYP3A4 inhibitor becomes necessary to treat the patient, a dose modification for RUXOLITINIB is necessary. See Section 6.3 for permitted or prohibited concomitant medications for this study. Also see Section 6.3.4 for dose modification schema for RUXOLITINIB.

Table 6.2.3 Criteria for dose modifications of RUXOLITINIB and PANOBINOSTAT due to study drug-related toxicity from Day 29 and beyond in Phase I or anytime in Phase II (see Table 6-6 for QT prolongation dose management)

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
HEMATOLOGICAL TOXICITIES		
Thrombocytopenia	< 20 x 10^9/L	Interrupt study treatment dosing until resolved to ≥ 20 x 10^9/L, then restart study treatment at reduced level as per Table 6.2.1/6.2.2.
	> 20 x 10^9/L + grade 3 bleed	Interrupt study treatment dosing until bleeding is resolved and platelet count is at level before bleed was noted, then resume study treatment at reduced level as per Table 6.2.1/6.2.2
Neutropenia (ANC)	Grade 4 (ANC < 0.5 x 10^9/L)	Interrupt study treatment dosing until resolved to ≤ grade 2, or baseline, then: • If resolved within 7 days restart study treatment at an unchanged dose level • If resolved in more than 7 days then restart study treatment at reduced level as per Table 6.2.1/6.2.2.
	Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Interrupt study treatment dosing until fever resolved and ANC ≤ grade 2, then restart study treatment at reduced level as per Table 6.2.1/6.2.2
Anemia[#] only requires dose reductions after cycle 6 (day 169+)	Doubling of transfusion frequency from baseline or hemoglobin 2g/dL below baseline (screening period)	Hold PANOBONISTAT only and continue RUXOLITINIB, if hemoglobin (or transfusion frequency) returns to baseline within 28 days restart PANOBINOSTAT at same dose, if this recurs again then reduce dose as pre TABLE 6.2.1/6.2.2
NON-HEMATOLOGICAL TOXICITIES		
CARDIAC		
Cardiac - Prolonged QT interval**		Please refer to Table 6-6, Section 6.2.8 and Section 7.2.7.

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
GASTROINTESTINAL		
Diarrhea	Grade 2 (4-6 stools/day over baseline, etc) despite the use of optimal anti-diarrheal medications	Hold PANOBINOSTAT dosing until resolved to ≤ grade 1, or baseline, then restart at unchanged dose level
	Grade 3 (≥ 7 stools/day over baseline, etc) despite the use of optimal antidiarrheal medications	Hold PANOBINOSTAT dosing until resolved to ≤ grade 1, or baseline, then restart study treatment at reduced level as per Table 6.2.2
	Grade 4 (life-threatening consequences, hemodynamic collapse, etc) despite the use of optimal antidiarrheal medications	Permanently discontinue study treatment dosing
Vomiting/Nausea* **	Grade 1 & 2 not requiring treatment **or** controlled using standard anti-emetics	Maintain dose level
	Grade 3 or 4 vomiting or Grade 3 nausea that cannot be controlled despite the use of standard anti-emetics	Interrupt study treatment dosing until resolved to ≤ grade 1, or baseline, then restart study treatment at reduced level as per Table 6.2.1/6.2.2
Fatigue		
Fatigue	Grade 3	Hold PANOBINOSTAT dosing until resolved to ≤ grade 2, or baseline, then: • If resolved within 7 days after suspending study treatment, then restart at unchanged dose level • If resolved in more than 7 days after suspending study treatment, then restart study treatment at reduced level as per Table 6.2.1/6.2.2
HEPATIC		
Total Bilirubin	Grade 3 or 4	Interrupt study treatment dosing until resolved to ≤ grade 2, or baseline, then restart study treatment at reduced level as per Table 6.2.1/6.2.2
Note: If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then reduction of one dose level and continuation of treatment is at the discretion of the Investigator.		

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)**
AST/SGOT, ALT/SGPT	> 5-10 x ULN	Interrupt study treatment dosing until resolved to ≤ grade 1 (or ≤ grade 2 if liver infiltration with tumor is present), or baseline, then: • If resolved within 7 days, then: • restart study treatment at unchanged dose level • If resolved in more than 7 days, then restart study treatment at reduced level as per Table 6.2.1/6.2.2.
	> 10 x ULN	Interrupt study treatment dosing until resolved to ≤ grade 1, or baseline, then: • restart study treatment at reduced level as per Table 6.2.1/6.2.2.
All dose modifications should be based on the worst preceding toxicity.		
* Common Terminology Criteria for Adverse Events (CTCAE Version 4.0)		
** It is critical that electrolyte abnormalities be followed closely and corrected prior to dosing		
*** See also concomitant medication Section 6.3.		
#Management of anemia Prior experience with RUXOLITINIB and PANOBINOSTAT as single agents in patients with myelofibrosis suggest that worsening anemia can be treated with PRBC transfusions, and will eventually resolve within 4-6 months without other interventions (LBH589BUS58, LBH589BUS32T). Interestingly, the decrease in spleen size observed in the PANOBINOSTAT responders was accompanied by increases in hemoglobin by at least 2 g/dL (LBH589BUS58). Dose modifications specifically for anemia should be implemented after cycle 6 if the rate of transfusion has significantly increased, and continues without improvement as compared to baseline. Following day 168, patients can be placed in dose hold of the PANOBINOSTAT (up to 28 days) to allow for hemoglobin to return to baseline, after which the study treatment should then be resumed at the same level. If after resumption of PANOBINOSTAT, worsening anemia recurs, then dose modifications according to Table 6.2.1/6.2.2 will be followed. If after holding PANOBINOSTAT for 28 days the patient's hemoglobin has not returned to baseline, but attained a clinically acceptable hemoglobin level, dose modifications according to Tables 6.2.1/6.2.2 can be followed. If after a dose hold of study treatment for 28 days a clinically acceptable hemoglobin value has not been reached the patient must be discontinued from study treatment.		

If a patient experiences new (or treatment emergent) grade 2 non-hematologic adverse event(s) considered at least possibly related to study treatment, and which the patient finds intolerable or in the Investigator's judgment is/are not acceptable, treatment should be held

until the adverse event(s) resolves to ≤ CTCAE grade 1. Study treatment may then be restarted at the same dose and schedule. If the same intolerable grade 2 adverse event(s) occurs again, study treatment should again be temporarily discontinued until the toxicity resolves to ≤ CTCAE grade 1. Study treatment should then be restarted at a reduced dose level as per Tables 6.2.1/6.2.2. At the discretion of the Investigator, patients with grade ≥ 2 adverse events of major organs (e.g., heart, lungs, CNS) may be discontinued from further study therapy without being retreated with a dose reduction.

6.2.7.1 Dose modifications for Grade 3 or 4 non-hematologic toxicity

Patients experiencing new (or treatment emergent) CTCAE grade 3 or 4 non-hematologic AEs not listed in Table 6.2.3, should have their treatment temporarily discontinued until the adverse event resolves to≤ CTCAE grade 1 or baseline. If the AE was considered related to study treatment, the drug should then be restarted at reduced level according to Table 6.2.1/.2.2. If the AE was considered not related to study treatment, then therapy may be restarted (when the AE resolves to ≤ grade 1 or baseline) at the current dose.

6.2.8 Dose modifications for prolonged QTc interval

All cardiac events should be treated as per the local standard of care and referred to a specialist if clinically indicated. Any final decision concerning dose modifications or permanent discontinuation of the patient from study drug due to QTc prolongation will be based on the assessment of the Investigator. If a patient cannot be dosed due to prolonged QTc for more than 7 days since last dose, the patient should be discontinued from study. See Table 6-4 for further details on criteria for dose delays, dose reductions, and re-initiation of study treatment for drug related QTc abnormalities.

Table 6-4 Criteria for dose delays, dose reductions, and re-initiation of treatment due to study drug related QTc abnormalities*

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Pre-Dose Combination phase day 1 (triplicate ECGs only)		
Pre-dose in cycle 1, Day 1 : 3 ECGs separated by 5-10 minutes, obtained prior to dosing	One of the three ECGs obtained shows QTc > 500 msec	Check and correct the patient's serum potassium, magnesium and calcium immediately, as well as evaluate con-meds.. Delay PANOBINOSTAT dose at least 3 days and repeat ECGs in triplicate. If the 3 ECGs: QTc > 500 msec, discontinue patient from study.
Post-Dose Combination phase day 1 and Subsequent Cycles (triplicate ECG only)		
3 hr Post-Dose: triplicate ECGs Cycle 1, Day 1, 5, 8, 15, 22 Cycle 2 Day 1 (Day 29) and beyond	One of the three ECGs obtained shows QTc > 500 msec OR QTc increased > 60 msec compared to baseline.	Check and correct the patient's serum potassium, magnesium and calcium immediately, as well as evaluate con-meds. Monitor ECG hourly or by telemetry until at least 2 consecutive hourly ECGs performed at least 3 hours post dose are <500. If any ECG has QTc > 500 msec. discontinue patient from study.
* If there are no additional procedures to be carried out on the day, arrangements may be made such that the ECGs may be performed at their local physician's office near the patient's home and transmitted to the site investigator or responsible delegate in a timely manner. ECGs done outside the MSSM MPD clinic are only permitted day 29 and beyond.		

6.2.9 Dose escalation

Dose escalation post-toxicity after cycle 2 (Day 29)

Patients who have experienced treatment-related ≥ grade 3 toxicity of any nature aside from thrombocytopenia, or grade 4 thrombocytopenia may not dose re-escalate nor return to the dose level for which this toxicity was encountered.

At the discretion of the Investigator, a patient may undergo dose re-escalation if it is felt to be in the best interest of the patient, and they have met the criteria as outlined in Section 6.2.6, 6.2.7, or 6.2.8 depending on the toxicity. For patients who undergo dose re-escalation, platelet counts must be obtained at least weekly for 4 weeks, and then at least every second week for the next 4 weeks. Thereafter, they may resume monthly evaluations.

Patients may continue treatment with RUXOLITINIB and PANOBINOSTAT until they experience unacceptable toxicity that precludes any further treatment, disease progression, and/or at the discretion of the Investigator. Patients will be discontinued from the study if they withdraw consent, or if the treating physician judges that further therapy with RUXOLITINIB and PANOBINOSTAT is no longer in the patient's best interest.

6.2.9.1 Intra-patient dose escalation Post MTD and/or RPTD determination (non-toxicity related)

Intra-patient dose escalation may be permitted by the Investigator following 13 patients treated for at least 2 cycles at the RPTD. During the course of study treatment, patients can be dose-escalated to the next higher dose level only once every two cycles, provided that ALL of the following criteria are met:

- Inadequate efficacy is seen with the current dose level, as defined by the observation of one or both of the following:
  - Not achieving at least a 50% reduction in palpable spleen length compared to baseline
  - Lack of meaningful improvement in disease symptoms based on the Investigator's expert judgment
- No treatment related toxicity has occurred with the current dose level, resulting in treatment reduction or interruption or discontinuation in the previous 56 days
- The higher dose with which the patient is to be treated does not exceed the MTD and/or RPTD
- Platelet counts must be obtained at least weekly for 4 weeks, and then at least every second week for the next 4 weeks after escalation. Thereafter, they may resume monthly evaluations.

There is no limit to the number of times the study drug may be increased for each patient, provided the above rules are followed for each subsequent dose escalation. The same rules for dose reductions as outlined in Section 6.2.7 apply to these patients.

The rules for intra-patient dose escalation described above apply only to those patients who have undergone one and only one dose reduction. Once a patient undergoes a dose reduction due to treatment-related toxicity, the patient may not have a dose increase unless they have been on a stable dose for at least 28 days with no dose interruptions.

6.2.10 Optional dose tapering strategy for RUXOLITINIB in the event of discontinuation

When RUXOLITINIB therapy is stopped, the return of constitutional symptoms associated with elevated cytokines (e.g. night sweats, fever, fatigue) that had been suppressed while on therapy is expected. When a decision is made to permanently discontinue RUXOLITINIB therapy for reasons other than hematologic safety, a dose tapering strategy may be considered, based on evaluation of the condition of the patient, current dosing regimen and the clinical judgment of the Investigator, so that symptoms may return to pre-treatment condition more slowly. If considered to be medically necessary, the Investigator may use any treatment to manage withdrawal from RUXOLITINIB including gradual tapering of the study drug dosage or use of other medications to manage events occurring after discontinuation. Short-term course of corticosteroids at doses > 10mg/day have been used in patients with MF and may be considered as part of a tapering strategy. Corticosteroids may be started prior to, or concurrent with, RUXOLITINIB tapering. When a decision has been made to discontinue the patient utilizing a tapering strategy, regardless of the use of concomitant medications, safety data will

continue to be assessed in accordance with the protocol for a period of times at least through the continued administration of RUXOLITINIB and 30 days after for AEs.

6.2.11 Management of diarrhea

Patients should be instructed to contact their physician at the onset of diarrhea. Each patient should be instructed to have loperamide readily available and to begin treatment for diarrhea at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient.

Loperamide 4 mg should be taken at the first loose stool or more frequent than usual bowel movements, followed by 2 mg as needed, no more frequently than every 4 hours, not to exceed a total of 16 mg in 24 hours. Patients with diarrhea ≥ grade 2 despite this loperamide regimen should interrupt study treatment as described in Table 6.2.3. If the above regimen is inadequate then additional evaluation and treatment should be pursued as medically indicated. Replacement i.v. fluids and electrolytes may be used as appropriate. Additional treatment should be provided in accordance with institutional standard of care and/or local guidelines.

Premedication with loperamide is not recommended.

The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

6.3 Concomitant medications

6.3.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered during the study must be recorded in source documents and eCRFs.

6.3.2 Permitted concomitant therapy requiring caution and/or action

The following medications have restrictions on use or doses or required changes to the way in which RUXOLITINIB and/or PANOBINOSTAT is administered during the study:

- Systemic corticosteroid doses greater than the equivalent of 10 mg of prednisolone per day are not permitted, unless use is part of a RUXOLITINIB dose tapering strategy (Section 6.2.10) as this may impact splenic size and cytokine reduction and interfere with the ability to assess the clinical activity of this combination of agents in this patient population.
- In patients for whom low molecular weight heparin use will be initiated, the degree of thrombocytopenia should be considered, coagulation parameters monitored, and dose of anti-coagulant adjusted accordingly.
- During the study, concomitant use of strong CYP3A4/5 inhibitors is strongly discouraged. However, when such a concomitant administration of a strong systemic CYP3A4 inhibitor (see Appendix 1 for a listing of these medications) is required for patient management, the

dose of RUXOLITINIB must be adjusted as described in Section 6.3.4. However, there is no dose adjustment of PANOBINOSTAT proposed.

- During the study, the use of moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin, ritonavir, talviraline, tipranavir) is discouraged, and investigators should seek alternatives where possible. No dose adjustments are needed when moderate CYP3A4 inducers are co-administered with study treatment. However, any concomitant use of moderate CYP3A4 inducers must be documented. See Appendix 1 for a listing of these medications.
- During the study, concomitant use of medications which are known CYP2D6 substrates are to be used with caution. See Appendix 1 for a list of these medications.
- Granulocyte growth factors (G-CSF) are not allowed while study medication is being administered but may be used for severe neutropenia at the Investigator's discretion while study medication is being withheld.

6.3.3 Prohibited concomitant therapy

The following medications are prohibited during the study:

- Any investigational medication (other than PANOBINOSTAT) that is not approved for any indication. Use of such medications within 30 days, prior to the first dose of study drug and during the study through the Safety Follow-up Visit is prohibited.
- Use of strong inducers of CYP3A4 (e.g. avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort) is not permitted at any time during the study. (See Appendix 1 for further details)
- Patients who are currently receiving treatment with any of the medications which have a relative risk of prolonging the QT interval or inducing Torsades de Pointes and cannot either discontinue this treatment or switch to a different medication prior to study enrollment, will be excluded from the study. Patients may not begin treatment with any of the medications while receiving study treatment unless approval is given by the Investigators to temporarily discontinue study treatment during administration with these drugs. Should a patient already enrolled on this study require short-term (i.e. approximately $\leq$ 2 weeks) treatment with these drugs, study treatment must be interrupted for at least 72 hours prior to starting these drugs and should not resume until at least 72 hours after the last dose of such a drug or longer (i.e. 5 half-lives) as listed.
- Any use of drugs that interferes with coagulation or inhibits platelet function (including non-steroidal anti-inflammatory drugs), with the exception of:
  - Aspirin $\leq$ 81 mg/day
  - LMWH, direct thrombin inhibitors, anti-10a inhibitors as long as INR remains less than 1.5
- Any other medication for the treatment of myelofibrosis, including but not limited to:
  - Hydroxyurea
  - Busulfan
  - Interferon
  - Lenalidomide

- Thalidomide
- Anagrelide

- Any hematopoietic growth factor receptor agonists (including but not limited to: erythropoietin, romiplostim, or eltrombopag). The use of G-CSF can be used as discussed in Section 6.3.2.

6.3.4 Dose reduction of RUXOLITINIB for concomitant strong CYP3A inhibitor usage

RUXOLITINIB is metabolized in the liver by the cytochrome (CYP) P450 metabolizing enzyme system, predominantly by the 3A4 isozyme. With concomitant dosing of strong CYP3A4 inhibitors such as systemic ketoconazole clarithromycin, itraconazole, nefazodone and telithromycin (Appendix 1), plasma exposure of RUXOLITINIB increases approximately 2-fold. Patients under therapy with a strong CYP3A4 inhibitor cannot be enrolled in the study. Use of strong CYP3A4 inhibitors during Cycle 1 of the study is prohibited. Use of strong CYP3A4 inhibitors after Cycle 1 Day 28 is strongly discouraged, and investigators should consider alternative therapies wherever possible. However, if the use of a strong CYP3A4 inhibitor is necessary for the sake of patient's safety, then a dose reduction of ~ 50% for RUXOLITINIB is mandatory. The following dose-reduction rules must be followed:

- If dose is 5 mg bid., change dose to 5 mg qday
- If dose is 10 mg bid., change dose to 10 mg qday
- If dose is 15 mg bid., change dose to 15 mg qday

NOTE: once the course of therapy using a CYP3A4 inhibitor has been completed, the patient may resume his/her prior dose level of RUXOLITINIB beginning the next day.

6.4 Patient numbering, treatment assignment and randomization

6.4.1 Patient numbering

Each patient is uniquely identified in the study by a unique patient number (001, 002, etc), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. Upon signing the informed consent form, the patient is assigned to the next available sequential patient number. Once a number is assigned, it cannot be reused for any other patient and the patient number for that individual must not be changed, even if the patient is re-screened.

If patient signed informed consent but fails to start the study treatment, the reason will be entered into the Screening Log eCRF page.

6.4.2 Treatment assignment and randomization

The assignment of a patient to a particular cohort will be coordinated by the investigator.

6.4.3 Treatment blinding and Randomization

Not applicable

6.5 Study drug supply

6.5.1 Study drug preparation and dispensation

Both RUXOLITINIB and PANOBINOSTAT capsules including instructions for administration, will be dispensed by site study personnel on an outpatient basis. Patients will be provided with adequate supply of study drug for self-administration at home until at least their next scheduled study visit.

6.5.2 Study drug packaging and labeling

The investigators at MSSM will be supplied with oral PANOBINOSTAT and oral RUXOLITINIB by Novartis. The packaging will contain a 2-part label. Immediately before dispensing study drug to the patient, authorized clinical site staff member will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) containing the patient's unique patient number. Medication labels will comply with the legal requirements of the United States. The storage conditions for study drug will be described on the medication label.

As with all anti-cancer drugs, their preparation and administration should be closely supervised by a qualified physician (Study Investigator) experienced in the use of cancer chemotherapeutic agents.

RUXOLITINIB

RUXOLITINIB tablets will be provided in bottles. Medication labels will be in the local language and comply with the legal requirements of each country. They will also include storage conditions for the drug.

PANOBINOSTAT

Oral PANOBINOSTAT will be supplied as 5-mg, 10-mg (when available), or 20-mg hard gelatin capsules and will be given on a flat scale of mg on a given day. The capsules are packaged in HDPE bottles with plastic child resistant closures.

Store in very tight packaging (water permeation <0-5ng/day/L) at 15^0C to 30^0C (room temperature) and protect from light.

6.5.3 Drug supply and storage

Study treatments must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels.

6.5.4 Study drug compliance and accountability

6.5.4.1 Study drug compliance

Dosing frequency and compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.5.4.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability ledger. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability ledger to the the Pharmacy at MSSM.

6.5.5 Disposal and destruction

The drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

7 Visit schedule and assessments

7.1 Visit schedule

Appendix 2 lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation and data will be captured in the e-CRF.

7.1.1 Pre-screening assessments

Not applicable

7.1.2 Screening

Below is a brief description of the screening tests/procedures for this protocol. The screening window is 56 days. The informed consent must be signed prior to any screening procedure. For details of assessments, refer to Appendix 2.

- Inclusion/Exclusion
- Demographics
- Relevant medical history / Current Medical Conditions
- Myelofibrosis (MF) disease history
- Diagnosis of PMF, PPV MF and PET-MF
- Prior and current concomitant medications and Significant non-drug therapies
- Transfusion history
- Physical Examination
- Vital signs, Weight and Height
- ECOG
- 12-Lead ECG
- ECHO or MUGA
- Chest X Ray PA/Lat
- Biomarkers (blood for genomic, epigenomic and cellular studies)
- Buccal swab
- Cytokine profile
- Measurement of spleen by palpation in craniocaudal length
- MRI/CT of spleen
- Laboratory Safety Tests including the following: Hematology, Biochemistry, Coagulation, Thyroid, Urinalysis and serum Pregnancy, quantitative JAK2V617F and/or MPL, cytogenetics
- Bone Marrow biopsy/aspirate (should be done at screening but if a specimen is available within 3 months of screening and the patient has not had any MF-directed therapy during this period, a biopsy during the screening period can be omitted)
- MPN-SAF

7.1.2.1 Eligibility screening

Patients must meet all inclusion and exclusion criteria at Screening in order to be eligible for the study. Patient eligibility will be confirmed by the investigative staff and captured within the source documents maintained at the site. Only when eligibility is confirmed will the patient be assigned to a dose level. The Primary Investigator/co-investigators must approve eligibility and will assign the patient to the appropriate dose level.

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log. The demographic information must also be completed for Screen Failure patients. No other data will be entered into the clinical database for patients who are screen failures. If a patient experiences a Serious Adverse Event during the Screening Phase it will be captured in the source documents and eCRF but the patient will not be considered as evaluable within the dose cohort level and this data will not contribute to dose escalation decisions.

7.1.2.3 Patient demographics and other baseline characteristics

At the screening visit, the following data should be collected/evaluated and recorded on the appropriate eCRF:

- Complete demographic information (age, gender, race, body weight, and height)
- Complete medical (including MF) history
- Medication history (prior and concomitant, including those used to treat MF)
- Prior JAK2V617F mutational status (if available before the signature of the Informed Consent Form) or any other MPN molecular marker
- Review of Packed Red Blood Cells (PRBC) transfusion history (for the last 12 weeks prior to Screening).
- Adverse Events
- Eastern Cooperative Oncology Group (ECOG) status
- Pregnancy test performed and prevention methods will be discussed
- Spleen length below the left costal margin by palpation
- Vital signs (blood pressure, pulse, respiratory rate and body temperature)
- 12-lead electrocardiogram (ECG)
- Complete physical examination
- Buccal swab for germline DNA banking
- Clinical laboratory tests (Biochemistry panel, hematology, and coagulation tests, urinalysis, TSH and fT4)
- Cytokine profile sample
- Chest X ray
- MPN-SAF

All medications and significant non-drug therapies (e.g. herbs) taken within 14 days before the first dose is administered must be recorded updated on a continual basis if there are any new changes to the medications. Medications include physician prescribed and over-the-counter medications, as well as vitamins and herbal and alternative therapies. Information to be collected on concomitant medications/significant non-drug therapies will include the following:

- Medication/Non-drug therapy trade name

- Reason for medication
- Start date and end date or continuing at time of exam

In addition to the general demographic and relevant medical history information, study specific information will be collected during the screening period as indicated in the assessment schedule (Appendix 2) in order to determine eligibility of the patient.

7.1.3 Run-in period

Not applicable

7.1.4 Treatment period

7.1.4.1 Cycles 1-6 [core study period]

Patients may continue study treatment through the first 6 cycles, unless they progress, withdraw consent, experience intolerable toxicity, start new MF therapy, and/or based on investigator discretion, it is believed to be in the best interest of the patient to discontinue. Cycle 1 will be the dose evaluation period for those patients enrolled in the phase I portion of the study and can continue on to complete the 6 cycles of therapy if they did not experience a DLT.

7.1.4.2 Cycle 7+ (Day 169+) [extension phase]

Following the completion of the first 6 cycles, the patient may continue study onto if they are continuing to receive clinical benefit and the investigator believes it is in the best interest of the patient. After 24 cycles, stable patients may be seen every other month at the discretion of the investigator. Assessment by IWG-MRT response criteria will be applied to determine the patient has achieved at least Stable Disease (SD) and therefore is eligible for continued therapy. Refer to Table 4-1.

7.1.5 End of treatment visit, including premature withdrawal and study discontinuation visit

Patients who discontinue study treatment should be scheduled for an end of treatment visit, at least 30 days post-last dose of treatment. 30 day post last dose, end of study visit will include: history, physical exam, Hematology, Biochemistry, and ECG. An End of Treatment Phase Disposition eCRF page should be completed, giving the date and reason for stopping the study treatment. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

For criteria for premature withdrawal refer to Section 7.1.5.1.

7.1.5.1 Criteria for premature patient withdrawal

Patients may voluntarily withdraw from the study or be removed at the discretion of the investigator at any time. If such withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from

the study and record this information on the appropriate eCRF. Patients may be withdrawn from the study prematurely for one of the following reasons:

- Adverse event(s)
- Abnormal laboratory value(s)
- Abnormal test procedure result(s)
- Protocol deviation
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Death
- Initiation of new cancer therapy
- Disease progression
- The investigator determines that further therapy is not in the patient's best interest (e.g., due to non-compliance, toxicity etc.).

Patients who experience disease progression, start of new anti-cancer therapy, or withdraw consent, must be permanently discontinued from the study.

For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Patients must be followed for 30-days post-last treatment of study drug.

7.1.5.2 Replacement policy

Patients prematurely withdrawn from the study will not be replaced, however in the phase I portion of this study, from Cycle 1 Day 1 through Day 28, a patient misses more than 11 oral administrations of RUXOLITINIB or more than 1 dose of PANOBINOSTAT in QOW dosing or 2 doses in the QW dosing, the patient can continue in the study without being evaluable for DLTs. Consequently an additional patient may be added to the same dose level in order to reach the required number of patients in the cohort. See Section 10.4.3 for specific details.

7.1.6 Follow up period

All patients must have safety evaluations for 30 days after the last dose of study treatment. In addition, all patients must be followed for the occurrence of Adverse Events and Serious Adverse Events for 30 days after the last dose of study drug. Once an Adverse Event or a Serious Adverse Event is detected, it should be followed until its resolution or until it is judged to be permanent.

Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

7.2 Assessment types

7.2.1 Disease progression

Disease progression will be documented by a > 25% increase in spleen length by palpation compared to the on-study nadir **or** by disease symptoms progression based on the Investigator's expert judgment **or** by a significant increase in blood or bone marrow blasts consistently for at least 2 weeks that in the expert opinion of the Investigators indicates progression of disease. Bone marrow biopsies are not required to document progression, however may be performed as clinically indicated and at the discretion of the investigator. If performed, findings should be documented in the eCRF.

7.2.2 Efficacy assessments

Efficacy, beyond clinical response assessment by IWG-MRT, is an exploratory endpoint in this study.

7.2.2.1 Splenic palpation

This assessment will consist of measurement of the spleen length by manual palpation at the end of Cycle 6 (Study Day 169) in comparison to the Cycle1 Day 1 measurement or by change in volume by MRI/CT (see section 7.2.2.3). Patients who have a≥ 50% reduction in spleen length by palpation compared to the initial measurement at Cycle 1 Day 1 will be considered as responders, otherwise they will be considered non-responders by IWG-MRT criteria. Spleen length measurements will be conducted at the start of every cycle in order to exclude disease progression, which is a criterion for premature patient withdrawal (see Section 7.1.5.1).

The edge of the spleen shall be determined by palpation, and measured in centimeters, from the costal margin to the point of greatest splenic protrusion.

7.2.2.2 Disease symptom assessments/MPN-SAF

Evaluation of constitutional symptoms (weight loss >10% of the baseline value in the year preceding C1D1, unexplained fever, or excessive night sweats persisting for more than 1 month) should be performed at baseline, and the start of every cycle. The MPN-SAF validated symptom assessment tool questionnaire will be used to gauge baseline MF symptoms and changes in symptoms with treatment. See Appendix 3.

7.2.2.3 MRI/CT

MRI or CT will be performed for the purpose of measuring spleen volume. This will be performed at baseline (screening), C4D1 +/- 1 week, and C6D29/C7D1 +/- 1 week, or when possible when the patient permanently discontinues study treatment, whichever comes first. Patients achieving a 35% reduction in splenic volume will be considered responders, otherwise they will be considered non-responders. These patients will also continue to be assessed by physician palpation of splenic length at the start of each cycle. MRI is the preferred method for obtaining spleen volume data, however, CT scans may be performed at the visits where MRI would be conducted if the subject is not a candidate for MRI, or if MRI

is unavailable. The imaging modality used at baseline (MRI or CT) to assess spleen volume should be kept constant throughout the trial period for a given patient, unless a new contraindication to the use of MRI occurs.

7.2.2.4 Bone marrow biopsy

The bone marrow biopsy and aspirate should be collected, processed, stained, and assessed by an experienced hematopathologist using his/her Institutional standards. Bone marrow fibrosis should be graded using the European consensus grading system (Tefferi 2006).

The bone marrow biopsy and/or aspirate will be collected at screening and C6D29 (+/- 1 week). The screening bone marrow biopsy and/or aspirate can be omitted if a sample was collected within the previous 3 months from study treatment, and the subject has not been on any therapy for MF during the intervening period, and all data from this collection can be entered into the eCRF for this study, with explanation as to the origin of the data. In the extension phase of the study the bone marrow biopsy and aspiration will be performed when clinically indicated and not more frequent than every 6 months.

7.2.3 Safety assessments

Safety will be monitored by assessing and collecting the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.4 Physical examination

A complete physical examination will be performed, as noted in Appendix 2 (+/- 3 days up until the end of cycle 6 and then +/- 7 days for C7 and beyond), and must include at a minimum measurement of spleen length, assessed by palpation and measured in centimeters using a soft ruler, from the costal margin to the point of greatest splenic protrusion at every visit.

Significant findings that were present prior to the signing of informed consent must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent is signed must be recorded on the Adverse Event within the eCRF.

7.2.4.1 Vital signs

Vital signs (blood pressure, pulse, respiratory rate and body temperature) will be collected at every visit (+/- 3 days up until the end of cycle 6 and then +/- 7 days for C7 and beyond). Vital signs should be taken with the patient in the sitting position after 5 minutes of rest. Body temperature may be measured orally or via ear.

7.2.4.2 Height and weight

Height in centimeters (cm) should be measured at screening only. Body weight in kilograms (to the nearest 0.1 kilogram [kg], without shoes) should be measured at every visit (+/- 3 days up until the end of cycle 6 and then +/- 7 days for C7 and beyond).

7.2.4.3 Performance status

The performance status will be assessed according to the ECOG performance status scale (Table 7-3), at time points specified in Appendix 2 (+/- 3 days up until the end of cycle 6 and then +/- 7 days for C7 and beyond).

Table 7-3 ECOG performance status

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

7.2.5 Laboratory evaluations

The laboratory evaluations will be performed by a local lab according to the visit schedule in Appendix 2 (+/- 3 days up until the end of cycle 6 and then +/- 7 days for C7 and beyond).

Abnormal laboratory values or test results constitute as an AE only if they induce clinical signs or symptoms, and are considered clinically significant (i.e., require dose modification and/or interruption of study drug, lead to clinical symptoms, cause study discontinuation or constitute in and of itself an SAE) or require therapy. These events should be recorded on the eCRF. If the administration of PANOBINOSTAT and/or RUXOLITINIB is delayed/modified due to unacceptable toxicities (see Section 6.2.7), re-evaluation should be performed prior to the next study treatment at a minimum.

All available labs should be performed and results of Hematology reviewed prior to administration of study drug. More frequent examinations may be performed at the Investigator's discretion if medically indicated; results should be recorded on the Unscheduled Visit eCRF.

Baseline labs may be repeated, if needed, to obtain acceptable values before the patient would screen fail. Laboratory tests should be collected and analyzed on the scheduled day appendix 2, or +/- 3 days up until the end of cycle 6 and then +/- 7 days for C7 and beyond.

7.2.5.1 Hematology

Hematology tests include the following parameters:

- Complete blood count (CBC) consisting of total white blood cell count (WBC) with differential (total neutrophil including bands, lymphocyte, monocyte, eosinophil, basophils counts, and blasts)
- Hemoglobin
- Hematocrit

- Platelet count

7.2.5.2 Biochemistry

Biochemistry includes the following parameters:

- Urea or blood urea nitrogen (BUN), creatinine, sodium, potassium, glucose, total calcium (corrected for serum albumin) or ionized calcium, albumin, total protein, total bilirubin (direct and indirect if total bilirubin is > ULN), lactate dehydrogenase (LDH), alkaline phosphatase, AST/SGOT, ALT/SGPT, phosphorous, magnesium, and uric acid.

Potassium, calcium, magnesium, and/or sodium supplements may be given to correct values that are <LLN. Post-correction values must not be deemed to be a clinically significant abnormality prior to patients being dosed.

7.2.5.3 Coagulation

The coagulation profile includes a prothrombin time (PT)/International Normalized Ratio (INR), and partial thromboplastin time (PTT).

The coagulation profile should be repeated as clinically indicated and these results should be recorded on the Unscheduled Visit eCRF.

7.2.5.4 Thyroid function tests

TSH and free thyroxine (FT4) will be evaluated at time points specified in Appendix 2.

7.2.5.5 Urinalysis

Urinalysis tests include a macroscopic exam, including assessment of protein, glucose, blood, and specific gravity at timepoints specified in Appendix 2. Should an abnormality be noted in the macroscopic exam, a microscopic examination should also be performed, including assessment of WBC/HPF, RBC/HPF, and documentation of any additional findings.

If the administration of oral PANOBINOSTAT is delayed/modified due to unacceptable renal toxicities, re-evaluation should be performed prior to the next study treatment at a minimum.

7.2.5.6 Pregnancy test

All WOCBP should complete a serum pregnancy test within 7 days prior to the first dose of study drug on Cycle 1 Day 1. The serum pregnancy test is only required to be repeated on Cycle 1 Day 1 if the baseline test was performed > 7 days prior to the first dose of PANOBINOSTAT. A urine pregnancy test will be repeated on day 1 of each 28-day cycle that a patient continues to receive study therapy, and at end of treatment. Evaluations may be repeated while the patient is on study, where clinically indicated.

Post-menopausal women must have been amenorrheic for ≥ 12 months in order to be considered “of non-childbearing potential.”

7.2.6 Radiological examinations

Once the MTD/RPTD has been established, patients who are ongoing active study treatment and enrolled in this dosing level will have MRIs/CT performed at scheduled time points. See Section 7.2.2.3 for further details.

7.2.7 Cardiac assessments

7.2.7.1 Electrocradiogram (ECG)

12-Lead ECG evaluation will be performed per Table 7-1 and Appendix 2. For phase I patients only, cycle 1 day 1 ECG tracings will be done in triplicates to obtain the mean, and should be separated by 5-10 minutes each. On treatment days when ECGs are to be performed, the patient should take their study medication in the clinic.

The mean of the 3 ECGs obtained pre-dose on cycle 1 day 1 will be calculated by the Investigators and will be used as the baseline value to compare to throughout the study. If a prolonged QTc interval is noted at any time, additional days of QTc monitoring may be required (see Table 6.4).

Treatment decisions should be based on the real-time assessment of QTc values at the clinical center, as determined by the automated machine reading or as measured and calculated by trained personnel at the site. All cardiac events should be treated as per the local standard of care and referred to a specialist, if clinically indicated (see Section 6.2.8 for required dose modifications for prolonged QTc). Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to QTc prolongation will be based on the assessment performed by the Investigator.

Table 7-1 12-Lead ECG schedule time points:

Screen/Cycle	DAY	Pre-dose	Post dose
		0-hour	3-hour
Screening	Baseline	x	
Cycle 1	1	x	x
	4, 8, 15, 22	x	
Cycle 2	1, 8, 15, 22	x	
Cycle 3+subsequent cycles	1, 15	x	
Cycle 6	29	x	
Cycle 6-12	1	x	
Cycle 12+	1*		

- After cycle 12 ECG is no longer required prior to dosing and can be performed at any time during the visit

ECGs will be performed at the scheduled time points, at a minimum, as indicated above as well as in Appendix 2. If there are no additional procedures to be carried out on that day, arrangements may be made such that the ECGs may be performed at a local office of a

physician near the patient's home and transmitted to the site investigator or responsible delegate in a timely manner. ECGs should be performed on the day of dose administration and, therefore, should there be a delay in dose administration, the corresponding pre-and/or post-dose ECGs should be delayed accordingly.

7.2.7.2 Holter monitoing

There will be no holter monitor used in this study.

7.2.7.3 Cardiac imaging -- MUGA (multiple gated acquisition) scan or echocardiogram

A baseline MUGA scan or ECHO to assess left ventricular ejection fraction (LVEF) will be performed within the screening period prior to the first administration of study drug treatment and may be repeated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity.

7.2.8 Tolerability

Not applicable

7.2.9 Biomarkers

All biomarker sample collection and analysis will be done as per Appendix 2 study schedule .

Biomarker analysis will be done to assess changes in JAK2V617F allele burden, plasma cytokine level, and genetic and epigenetic mutations impacting the molecular pathogenesis of MF other than JAK2V617F upon treatment with the combination of drugs.

Peripheral blood (PB) and bone marrow (BM) aspirate samples when obtained as indicated in the protocol or when indicated for standard of care, will also be processed and stored in a secure freezer in the laboratory of Dr Ronald Hoffman at Mount Sinai School of Medicine. The samples will be stored in freezer vials that are labeled with the study patient identification number only in a box that will only be used for samples obtained from this study. These samples will be stored for no longer than 10 years from time of initial storage. Only the study investigators and those individuals under the assurance of the study will have access to the linked study identification numbers. The de-identified samples will be available to other research collaborators for the purpose of analyzing samples. The samples will be used for research purposes only and results will not be provided to the individual nor will they influence the direct care of that individual. At any time, a patient's stored BM or PB research sample can be destroyed if the patient requests that these samples no longer be used in the context of this research study. The samples will be batched and at a later date may be analyzed for cytokine profile, histone acetylation, DNA methylation status, and the mutational status of genes that have been implicated in the pathogenesis of MPNs (e.g. EZH2, ASXL1, TET2, IDH1/2 and others that may not yet be identified). Due to the rapidly evolving understanding of this disease process, additional tests may be performed on these stored samples that cannot yet be determined.

7.2.9.1 Blood sample for allele burden analysis

JAK2V617F allele burden analysis in the subset of subjects with evidence of a JAK2V617F mutation will be monitored. Subsequent samples need only to be collected from patients with the mutant allele present.

Approximately 5.0 mL of blood for JAK2V617F allele burden quantitation will be collected at as indicated in the study schedule.

7.2.9.2 Blood sample for plasma cytokine assays

A panel of cytokine and other plasma protein markers, including but not limited to, IL-1 beta, IL-6, and IL-8 will be analyzed and correlated with response and symptom measures.

Approximately 5.0 mL of blood for cytokine and other plasma protein markers will be collected at the following time points as shown in the study schedule.

7.2.9.3 Genetic mutations impacting the molecular pathogenesis of MF other than JAK2V617F

Genotyping of subjects will be performed on Cycle 1 Day 1 pre-dose to assess the mutational status at diagnosis. This assessment will require approximately 5mLs of blood and analysis will be performed by a collaborating laboratory. Samples will be collected at specified time points as shown in the study schedule and the specimens will be de-identified and processed in the research laboratory of Dr Ronald Hoffman. Blood will be centrifuged with ficoll and mononuclear cells will be separated from polymorphonuclear cells and aliqouted into microtubes and stored at -80’C freezer. The serum/plasma will also be collected and aliqouted. The samples will be analyzed for genetic and epigenetic markers by a collaborating laboratory at a time to be determined in the future when the investigators believe an adequate number of samples and time points have been obtained. The exact mutational studies will be determined at a later time as emerging understanding of the pathogenetic mechanisms of MF are elucidated.

7.2.9.4 Other biomarker assessments/ Buccal swab

Buccal swab will be performed at screening for germline DNA reference. This will only be done at screening.

Remaining blood samples may be used for additional biomarker assessments related to drug action and effect and/or cancer.

7.2.10 Transfusion dependence

During the Screening Visit the patients will provide a review of PRBC transfusion history for the last 12 weeks prior to screening. During the Study Visits on D1 of each cycle the patients will provide updates on PRBC transfusion history status.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occurs after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
   or
   Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution, it is judged as no longer clinically significant by the investigator, stable or until it is judged to be permanent. Assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of disease (including fatal outcomes), if documented by use of appropriate method should not be reported as a serious adverse event.

Adverse events separate from the progression of disease (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities constitute an Adverse event if they are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment, and should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event or laboratory abnormality (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol and is still, by definition, an adverse event.

Laboratory abnormalities will only be captured as adverse events if they are considered clinically significant by the investigator. Laboratory abnormalities are considered clinically significant if they:

- Require clinical intervention (medication and/or procedure)
- Trigger additional investigation
- Require study drug dose medication
- Cause discontinuation of study treatment
- Require more frequent follow-up assessments
- Result in the alteration of the patient's well-being

- Are life-threatening
- Are considered clinically significant according to the investigator's judgment

8.1.3 Adverse events of special interest

Due to the overlapping toxicity for both study drugs, special attention should be given to the occurrence of hematologic adverse events, especially thrombocytopenia, hemorrhagic events as well as anemia and leukopenia and their clinical consequences (i.e. infections and increased blood transfusion requirements as well as worsening of ischemic heart disease in the presence of new onset anemia and/or cardiac failure/edema after blood transfusion). Thromboembolic events, infection, syncope with prolonged QTc, syncope without QTc, TIA, LVEF abnormalities, Pneumonia, Colitis, fatigue are also AEs of special interest.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Protocol exempt SAEs: Progression of disease (including fatal outcomes), if documented by use of appropriate method (for example, as per IWG criteria for treatment response in myelofibrosis with myeloid metaplasia (Tefferi 2006)), should not be reported as a serious adverse event. However, other adverse events associated with disease progression (PD) but not a typical component of PD such as thrombosis, must be reported as appropriate, per AE/SAE criteria.

8.2.2 Reporting

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 working hours of learning of its

occurrence. Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 working hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 working hours to FDA as well as fulfill the appropriate reporting requirements for the PPHS at MSSM.

8.3 Emergency unblinding of treatment assignment

Not Applicable, as this study is open label.

8.4 Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the PPHS of MSSM and the FDA. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Instances of pregnancies and positive pregnancy tests should be collected for all patients who have conceived after receiving study medication. Pregnancies that are noted prior to administration of study medication but after signing informed consent may require reporting if they are considered to be associated to the conduct of the study by the investigator. Pregnancy data should be submitted to the Local Safety Helpdesk at the CPO via the clinical trial pregnancy form within 24 hours of the site becoming aware of the information. If the pregnancy has resulted in a Serious Adverse Event (SAE), a SAE form should be completed irrespective of whether or not the patient has received the study medication.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Since PANOBINOSTAT is associated with potential genotoxicity per the current labeling information (current Investigator's Brochure), as such this protocol includes highly effective contraception per the Novartis pregnancy prevention guidelines document. Where applicable and able the female pregnant partner of the male study participant may also be informed of this information as appropriate and feasible.

Principal Investigator Responsibilities for pregnancy reporting:

- Report all pregnancies for all female trial participants, including outcome, and adverse events during pregnancy.

- Report all pregnancies for pregnant partners of male clinical trial participants.
- Report all outcomes and any adverse events experienced by the pregnant partner during pregnancy
- Obtain follow-up for outcome and other data as requested by CTSO/CPO.
- Adhere to general SAE reporting timelines and guidelines.

8.5 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator's Brochure (IB). Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

A Data Monitoring Committee will not be used in this study.

8.7 Steering Committee

A steering committee will not be used in this study.

9 Data collection and management

9.1 Site monitoring

There is no site monitoring for this investigator-initiated study. However, the Investigators can choose to have internal audits performed.

9.2 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eRAP system at MSSM will be used for this study.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.2.1 Biomarker data collection

Designated investigator staff must enter the information required by the protocol onto the biomarker sample collection eCRFs.

9.3 Database management and quality control

This will be maintained by the investigators and the research staff in accordance with all the rules of MSSM.

10 Statistical methods and data analysis

10.1 Analysis sets

10.1.1 Full Analysis Set

Patients who took at least one dose of study medication will define the full analysis set which will be the primary analysis set for the safety and efficacy assessments

10.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication. For this study, the safety set and the full analysis set are identical.

10.1.3 Per-Protocol Set

Since the sample size for this study is relatively small, no per-protocol set will be defined, although protocol compliance will be reported by listing and summarizing protocol deviations.

10.1.4 Dose-determining set

The dose escalation analysis and the determination of the MTD and/or RPTD will be based on the set of evaluable patients in every dose cohort where evaluability is defined in Section 6.2.3.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be listed by patient and/or summarized descriptively by initial doses of study treatment and by study phase for the safety set. Categorical data will be presented as frequencies and percentages. For continuous data, summary statistics such as mean, standard deviation, median, 25^{th} and 75^{th} percentiles, minimum, and maximum will be presented. This will include baseline JAK2V617F mutational status and review of Packed Red Blood Cell (PRBC) transfusion history for the last 12 weeks prior to screening; this information will be recorded in the appropriate eCRF.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The dose and duration in days of PANOBINOSTAT and RUXOLITINIB will be listed and summarized by dose level using descriptive statistics. Data may be presented by cycle in addition to over the entire study duration. The daily dose will be summarized using descriptive statistics by dose level and will be listed by patient.

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized for the safety set.

Compliance to the study protocol will be assessed by reporting the number and type of protocol deviations. These will be identified prior to database lock and will be listed and summarized.

In this trial, the days of each cycle will continue to be counted even if study drugs are being held. It will be the responsibility of the investigators to monitor the actual cumulative doses each patient is receiving per cycle.

10.4 Primary objective

The primary objective of the phase I trial is to establish safety and tolerability of the combination of PANOBINOSTAT and RUXOLITINIB as we'll as the MTD and/or RPTD in patients with MF. The primary objective of phase II is to determine the proportion of patients that achieve at least SD by IWG-MRT treatment response. The target IWG-MRT treatment response rate of >40% in the phase II part of this study will signify a positive result.

10.4.1 Variable

The quantities of primary interest are rates of dose limiting toxicities (DLTs) at the different dose levels, and the MTD and/or RPTD for the desired patient population.

10.4.2 Statistical hypothesis, model, and method of analysis

10.4.2.1 Dose escalation

The initial 3 cohorts will have RUXOLITINIB administered at a fixed dose of 10mg PO BID and cohort 1 will combine PANOBINOSTAT at a dose of 10mg PO TIW QOW, cohort 2 will be PANOBINOSTAT 15mg PO TIW QOW and cohort 3 will be PANOBINOSTAT 20mg PO TIW for cumulative cycle doses of 60mg, 90mg and 120mg, respectively. If an MTD of Panobinostat is not established by cohort 3, then cohort 4a will test RUXOLITINIB at 15mg PO BID in combination with PANOBINOSTAT 15mg PO TIW QOW. Cohort 4b will test RUXOLITINIB at 15mg PO BID in combination with PANOBINOSTAT 20mg PO TIW QOW. If an MTD of Panobinostat is established in the first 3 cohorts, then the cohort 4a will test RUXOLITINIB at 15mg PO BID in combination with PANOBINOSTAT at the dose level preceding the MTD dose level of PANOBINOSTAT.

If the dose escalation of Ruxolitinib continues to cohort 4b and this cohort does not define the MTD of Ruxolitinib, then cohort 5 will allow patients to be treated at a dose of PANOBINOSTAT of 10mg PO TIW QW for a cumulative dose/cycle of 120mg. Cohorts 6 and 7 will be pursued if the previous cohorts don't reach MTD and will include 15mg PO BID of RUXOLITINIB and PANOBINOSTAT at 15mg PO TIW QW and 20mg PO TIW QW, respectively.

The RPTD of each agent will be determined by the MTD and the dose limiting toxicities observed in Phase I. Subjects can start single agent ruxolitinib as long as the dose evaluation period of the previous cohort is complete before combination therapy begins. The RPTD will not necessarily be the MTD doses reached in the Phase I dose escalation part of this study. However, the RPTD will not exceed the estimated MTD dose of either drug as determined from the drugs given in combination in Phase I.
Initially, 3 subjects will be entered into a cohort with a specified dose level for each drug.

- If 2 or more of the initial subjects experience DLT, then the Maximally Tolerated Dose (MTD) of the drug being escalated has been exceeded.

- If none of the 3 subjects initially enrolled into this cohort experiences DLT, then subsequent subjects will be enrolled into the next higher dose level of the drug being escalated.
- If 1 of the initial subjects experiences DLT, then 3 additional subjects (to a total of 6 subjects) will be enrolled into the cohort.
    - If it is found that 1 of the 6 subjects in the cohort encounters DLT, then subsequent subjects will be enrolled into the next cohort.
    - If it is found that 2 or more of the 6 subjects in a cohort encounter DLT, then the MTD of the drug being escalated has been exceeded and the next lower dose level for that drug (or frequency at which the drug is administered, as in Cohorts 5, 6, and 7) will be evaluated with a maximum of 6 patients.
- The MTD for the drug being escalated will be defined as the dose level of that drug immediately below that at which 2 or more patients out of 6 experience a DLT.
- If the final cohort under consideration in the escalation of either drug in Phase I has enrolled only 3 patients and none of these 3 patients experiences a DLT, then the cohort will be expanded to 6 patients before deciding on a MTD for that drug (or frequency of drug administration).

10.4.2.2 Dose expansion

The cohort of 6 patients at the MTD and/or RPTD will be expanded by an additional 16 patients in order to further assess safety and tolerability. Thus the number of patients treated at the MTD and/or RPTD will be 22, which ensures that there is a 90% chance to detect any AE with a 10% incidence rate among patients treated at the MTD and/or RPTD. During this phase of the study, further defining of the biological activity of this combination will be explored. The primary endpoint of this portion of the trial is response rate by IWG-MRT criteria. We hypothesize a response rate of >40% in treated patients at C6D28 will constitute a positive primary endpoint. A positive response by IWG-MRT criteria includes SD, CI, PR, or CR. Since preclinical studies suggest a synergistic effect of the two agents in combination, we would expect a spleen response rate (>35% reduction in spleen volume by MRI or >50% reduction in palpable spleen) of >30% as was assumed in the COMFORT study. Since the proportion of patients obtaining this efficacy endpoint was 42%, we will have a target response for this secondary endpoint of >50%, and this will be reported in a descriptive manner.

10.4.3 Handling of missing values/censoring/discontinuations

During the dose-finding part of the trial, one additional patient may be enrolled in each cohort, for each patient who does not meet the criteria necessary for inclusion in the dose-determining set. During the dose expansion part of the trial, one additional patient may be enrolled for each patient who does not meet the criteria necessary for inclusion in the safety set. At the time of the writing of the study report, patients will have continuing events (e.g., adverse events) summarized using the data cut-off date as the date of completion, with an indication within the listings that the event is continuing.

10.4.4 Supportive analyses

Additional supportive analyses may be conducted if appropriate.

10.5 Secondary objectives

The secondary objectives of this study are:

10.5.1 To evaluate the safety of the oral co-administration of RUXOLITINIB and PANOBINOSTAT to patients with MF

All adverse events recorded during the study will be listed and summarized. All serious adverse events will be listed by patients and tabulated by type of adverse event and initial dose level. Any other safety information will be listed and tabulated as appropriate. This includes analysis of all AE, SAE, labs, vital signs, and ECG data to include dose level and cycle.

10.5.2 Safety objectives

10.5.2.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used, except for summaries of DLTs, for which the dose determining set will be used in addition to the safety set. All listings will be presented by dose levels and all tables will be presented by dose level or groups of dose levels, as appropriate, based on the number of dose levels used and number of patients treated.

The overall observation period will be divided into three mutually exclusive segments:

- Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
- On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
- Post-treatment period: starting at day 31 after last dose of study medication.

10.5.2.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the **treatment-emergent** AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class, preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment, and dose level. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and dose level.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific

clinical interest in connection with the study treatment(s). For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

DLTs will be listed and their incidence summarized by primary system organ class, worst grade, type, and dose level. The dose determining set will be used for these summaries.

10.5.2.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (NCI 2009), the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges. The following by-treatment summaries will be generated separately for hematology and biochemistry laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4 (see below for details)
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges. Time to onset of grade 3 or higher SECs will be summarized by dose level.

10.5.2.4 Other safety data

Data from other tests (e.g., electrocardiogram or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate by study phase. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

10.5.2.5 Supportive analyses for secondary objectives

No supportive analyses for secondary objectives are planned.

10.5.2.6 Tolerability

Not applicable

10.5.3 Biomarkers

See Section 7.2.10.

10.5.4 Resource utilization

Not applicable

10.5.5 Patient-reported outcomes

Not applicable

10.6 Exploratory objectives

The following exploratory efficacy objectives will be included on the study:

10.6.1 To assess preliminary efficacy of the combination of RUXOLITINIB and PANOBINOSTAT by physician palpation in all dosing cohorts

Spleen measurements by palpation will be obtained with a primary emphasis on the change in measurements from baseline to Week 12. Descriptive statistics will be provided for the spleen length and percent change from baseline over time. The proportions of patients with at least a 50% reduction in palpable spleen length at any time point, at week 12 and at week 24 will be summarized. This analysis will be done separately on patients in every dosing cohort, as well as, on the pooled patients, in the escalation phase.

10.6.2 To assess the preliminary efficacy at the MTD and/or RPTD by the use of MRI/CT

The endpoint for this objective will be the volumetric reduction in spleen size from baseline to Week 12 (or end of study, whichever comes early), as assessed by MRI/CT. The analysis will be restricted to patients in the expansion phase, who are dosed at the MTD and/or RPTD. Responders (defined as those achieving at least 35% reduction in splenic volume (compared to baseline), at week 12 or end of study, whichever comes first), will be summarized in terms of percentage rates of response, along with 95% confidence intervals. An **exact binomial confidence interval** (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper 1934). Descriptive statistics for the volumetric reduction in spleen size and percent change (from baseline) at the end of week 24 will also be provided. Since preclinical studies suggest a synergistic effect of the two agents in combination, we would expect a spleen response rate (>35% reduction in spleen volume by MRI) of >30% as was assumed in the COMFORT study. Since the proportion of patients obtaining this efficacy endpoint was 42% in COMFORT-1, we will have a target response for this secondary endpoint of >50%, and this will be reported in a descriptive manner.

10.6.3 To assess (preliminary) efficacy of the combination of RUXOLITINIB and PANOBINOSTAT by bone marrow biopsy in all dosing cohorts

The endpoint for this objective will be the change in bone marrow histomorphology from aspirate and/or biopsy samples collected at baseline as compared to Cycle 6 (+/- 1 week), and any subsequent biopsies. The change in fibrosis will be assessed, and graded according to the International Working Group (IWG) consensus criteria for treatment response (Tefferi 2006).

10.6.4 To explore biomarkers at the MTD and/or RPTD (including but not limited to: JAK2V617F allele burden, genetic mutations impacting the molecular pathogenesis of MF other than JAK2V617F , and cytokine measures)

Exploratory biomarker analysis include (but are not limited to) the following, JAK2V617F allele burden, genetic mutations impacting the molecular pathogenesis of MF other than JAK2V617F, and cytokine measurement (all done pre and post treatment).

Unless otherwise specified, all statistical analyses of biomarker data will be performed on the FAS with the related measures. Data transformations, such as base 2 logarithms, may be used prior to summarizing and analyzing the data.

Although analyses are described herein, data synergies may be realized through correlation of biomarker data with other biomarker and/or clinical response variables. In addition, other post-hoc exploratory assessments are expected and may be performed.

Summary statistics in absolute values at each visit and absolute and percentage change from baseline at each visit will be provided for JAK2V617F allele burden, and cytokine measurement.

Exploratory correlation of the biomarker levels at baseline or their post-treatment changes with clinical response variables will be performed depending on trial outcome.

10.6.5 To evaluate changes in packed red blood cell transfusion dependence

The proportion of patients who are transfusion dependent, as well as, the proportion of patients whose transfusion status (dependent or independent) changed (from dependent to independent or vice versa - (Gale 2011)) at each cycle will be tabulated with summary statistics.

- A patient will be defined as transfusion dependent at baseline if he or she received 2 or more units of red blood cell products during the 12 weeks prior to first study treatment administration
- New onset of transfusion dependence will be defined as the use of 2 or more units of red blood cell products during the last 12 weeks prior to end of study for patients who were not transfusion dependent at Baseline
- New transfusion independence will be defined as no use of red blood cell products during the last 12 weeks prior to the end of study for patients who met the definition of transfusion dependence at baseline.

10.7 Interim analysis

There is no plan for an interim analysis.

10.8 Sample size calculation

For a cohort size of 3-6 patients, and assuming that escalation happens all the way up to and including cohort 7, and all patients are evaluable, the maximum total sample size will be 58 patients. The minimum sample size will be 33, which will occur if DLT is observed in the

first 2 patients in cohort 4a. In such a case, cohort 3 would add another 3 patients to bring its total to 6. An additional 16 patients for Phase II would bring the total to 12 + 2 + 3 + 16 = 33. If MTD and/or RPTD is achieved earlier, the sample size will be smaller. This is a Phase I study with a 3 + 3 dose-escalation scheme, first escalating Panobinostat followed by escalation of Ruxolitinib and finally an escalation of the frequency of administration of Panobinostat, as described above. In each escalation, the probabilities of escalating to the next dose after only 3 patients, and of escalating to the next dose after 3 or 6 patients, as a function of the probability of a Dose Limiting Toxicity (DLT) for a given dose, are shown in the table below [Rubinstein and Simon, 2003] :

Probability of DLT for given dose level	.05	.10	.20	.30	.40	.50	.60
Probability of continuing escalation after only 3 pts	.86	.73	.51	.34	.22	.13	.06
Probability of continuing escalation after 3 or 6 pts	.97	.91	.71	.49	.31	.17	.08

Since this is an adaptive design, it is not know exactly how many patients will be required in the trial. If all proposed doses of both drugs, as well as both proposed frequencies of administration for Panobinostat, are such that the trial does not terminate due to DLTs, it is possible that a maximum of 42 patients will be enrolled in Phase I, given the history of enrollment up through cohort 3. Since only 12 patients have been enrolled up through cohort 3, if 6 patients are required for each cohort up through cohort 7, a total of 42 patients will have contributed to Phase I. An additional 16 patients for Phase II would bring the maximum number of patients to 42 + 16 = 58.

In the Phase II expansion study, 22 patients treated at the MTD and/or RPTD, ensuring that there is a 90% power, at an alpha level of 5%, to detect any AE with a 10% incidence rate among patients treated at the MTD and/or RPTD. However few or many patients are enrolled in Phase I, the 6 patients at the RPTD will be carried forward as the initial 6 patients in the Phase II study (Messer et al., 2010).

All inferential statistical analyses for secondary variables will be based on an estimation approach. There will be no formal testing of hypotheses for these variables, and no power analysis has been done.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research

Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their eCRFs.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

The investigators assure that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.6 Study documentation, record keeping and retention of documents

The investigators will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and

complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study eCRF is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. Any change or correction to an eCRF should be explained (if necessary) and should not obscure the original entry. An audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who is directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

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14 Appendices

Appendix 1: Co-medications which are known to prolong the QT interval and/or induce Torsades de Pointes, are strong CYP3A4/5 inhibitors and inducers, moderate CYP3A4 inducers, CYP2D6 substrates, or otherwise prohibited for use

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A. Medication prohibited during the treatment period and 30 day follow-up for Study CLBH589x2106

The following medications are prohibited during this study:

1. Systemic steroids greater than 10 mg daily, unless use is part of a RUXOLITINIB dose tapering strategy (Section 6.2.10)
2. Systemic anticoagulation, or drugs that inhibit platelet function, with the exception of:
   - Aspirin ≤ 150 mg/day
   - Low molecular weight heparin (LMWH)
3. Any other investigational medication
4. Any other medication used for the treatment of myelofibrosis, including but not limited to the following:
   - Anagrelide
   - Busulfan
   - Hydroxyurea
   - Interferon
   - Lenalidomide
   - Thalidomide
5. Any medication which is known to be a strong CYP3A4 inducer* (e.g. avasimibe, carbamazepine, Phenobarbital, phenytoin, rifabutin, or St. John's wort)

*This list of strong CYP3A4 inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; from the University of Washington's Drug Interaction Database; and from Pursche et al (2008).

6. Any use of hematopoietic growth factor receptor agonists (including but not limited to:erythropoietin, romiplostim, or eltrombopag). The use of G-CSF may be used after consultation with the sponsor. See Section 6.3.2 for further details.

B. Medications which are known to prolong the QT interval and/or induce Torsades de pointes ventricular arrhythmia should be avoided

Patients, who are currently receiving treatment of the medications listed in Table 2-1 and cannot either discontinue from this treatment or switch to an alternative medication prior to enrollment in a PANOBINOSTAT clinical study, will be excluded from the study. Patients enrolled in a PANOBINOSTAT clinical study may not begin treatment with any of the medications listed in Table 2-1 unless discussed with the Sponsor and approval is granted by the Sponsor. The Sponsor may agree to temporarily discontinue PANOBINOSTAT treatment (e.g., for 72 hours) during administration with these drugs or withheld medications in Table 2-1 for at least 72 hours when PANOBINOSTAT is to be administered.

NOTE: It is of great importance to avoid combining drugs listed below in Table 2-1 and Table 3-1 (CYP3A inhibitors) in combination with PANOBINOSTAT especially in the presence of electrolyte abnormalities, notably decreased potassium or magnesium levels commonly associated with diuretic usage.

In general, medications listed in Table 2-1 should be avoided. Medications listed in Table 3-1 and Table 4-1 are to be used with caution when co-administered with PANOBINOSTAT. The use of any of the drugs in Table 2-1, Table 3-1, and Table 4-1 in combination with PANOBINOSTAT must be discussed with the Sponsor.

Table 2-1 Medications which are known to prolong the QT interval and/or induce Torsades de pointes to be avoided

All Class IA antiarrhythmics • quinidine • procainamide • disopyramide • any other class IA antiarrhythmic drug
All Class III antiarrhythmics • amiodarone • sotalol • dofetilide • ibutilide • any other class III antiarrhythmic drug

Anti-infectives **Macrolide antibiotics*** • erythromycin • clarithromycin **Quinolone antibiotics*** • sparfloxacin **Antifungals** • pentamidine **Antimalarials** • halofantrine • chloroquine
Antihistamines • astemizole • terfenadine
Antinausea • chlorpromazine • domperidone • droperidol • dolasetron (intravenous and oral)^
Antipsychotics • thioridazine • mesoridazine • chlorpromazine • pimozide
Miscellaneous drugs • arsenic trioxide • bepridil • cisapride • levomethadyl • methadone
*Note: azithromycin, ciprofloxacin, levofloxacin, pefloxacin, ofloxacin, tosufloxacin, difloxacin, temafloxacin, fleroxacin, acrosoxacin, nalidixic acid and enoxacin are allowed. ^Intravenous dolasetron is contraindicated for preventing nausea and vomiting associated with chemotherapy based on FDA drug safety communication dated December 17, 2010. Based on this finding, both intravenous and oral dolasetron are prohibited to be taken with PANOBINOSTAT.

This is not a comprehensive list of medications which may prolong the QT interval and/or induce Torsades de pointes. This list of medications was developed in collaboration with an external cardiology consultant, and represents those medications which are deemed to have an unacceptable risk of co-administration with PANOBINOSTAT.

The following website may be referenced as a supplemental guide for drugs which have been associated with Torsades de pointes or prolonging the QT interval but at this point lack substantial evidence for causing Torsades de pointes:

http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm (Version 3/25/2008).

Medications listed on the website which do not appear in Table 2-1 above may be used with caution at the discretion of the investigators.

Ondansetron (a known CYP2D6 substrate, see Table 4-1) has been associated with Torsades de points and QT prolongation but has not been shown to cause Torsades de pointes. Therefore, ondansetron is not per se prohibited to be combined with PANOBINOSTAT but caution is to be exercised and close monitoring for signs and symptoms of QT prolongation is recommended.

C. Medications which are known strong CYP3A4/5 inhibitors to be used with caution

The use of these drugs is prohibited during the first cycle of study treatment

PANOBINOSTAT is a substrate of CYP3A4 with minor involvement of CYP2D6, and CYP2C19 in *in vitro* evaluation of its metabolism. Thus, a clinical drug-drug interaction study was conducted using ketoconazole, a strong CYP3A inhibitor, in combination with PANOBINOSTAT in study [CLBH589B2110].

Multiple ketoconazole doses at 400 mg increased C_{max} and AUC of PANOBINOSTAT by 1.6- and 1.8-fold, respectively, but with no change in T_{max} or half-lives in 14 cancer patients. The less than 2-fold increase in PANOBINOSTAT AUC upon co-administration of a strong CYP3A inhibitor is considered a weak drug inhibition and not clinically relevant, as PANOBINOSTAT doses at least 2-fold greater than the evaluated 20 mg dose (i.e., 40 mg and 60 mg) have been safely administered in patients. Thus, co-administration of PANOBINOSTAT with a moderate or weak CYP3A inhibitor is allowed. However, clinical monitoring of signs and symptoms of PANOBINOSTAT treatment related adverse events is recommended when long-term (≥ 1 week) concomitant administration of any strong CYP3A inhibitors and PANOBINOSTAT is medically indicated or investigated in a clinical study.

RUXOLITINIB is metabolized in the liver predominantly by the CYP3A4 isozyme. With concomitant dosing of potent CYP3A4 inhibitors such as those medications listed in Table 3-1, plasma exposure of RUXOLITINIB increases approximately 2-fold. Use of those medications listed in Table 3-1 is strongly discouraged, and investigators should consider alternative therapies wherever possible. However, if the use of a potent CYP3A4 inhibitor is necessary for the sake of the patient's safety, then a dose reduction of ~50% of RUXOLITINIB is mandatory. See Section 6.3.4 for further details of this dose reduction schema.

Based on the low overall bioavailability of topical ketoconazole, with very low systemic levels seen following topical administration, no dose adjustment of RUXOLITINIB is needed for use with topical ketoconazole. No dose adjustments are necessary when RUXOLITINIB is co-administered with erythromycin, or by extension, with other moderate or weak inhibitors of CYP3A4, including grapefruit juice.

Patients with impaired liver function (as defined by NCI CTEP criteria)[1] are recommended not to receive PANOBINOSTAT concomitantly with strong CYP3A inhibitors because potential interaction has not been established in this population.

Table 3-1 Medications which are known strong CYP3A4/5 inhibitors to be used with caution

Macrolide antibiotics*
• telithromycin • troleandomycin
Antifungals (azoles)
• ketoconazole • itraconazole • posaconazole • voriconazole
Antidepressants
• nefazodone
HIV protease inhibitors:
• indinavir • nelfinavir • ritonavir • saquinavir • lopinavir
Miscellaneous drugs or products
• [2]Star fruit and pomegranate product and juice • conivaptan
* azithromycin and regular orange juice are allowed. Although clarithromycin is a known strong CYP3A inhibitor, it is also known to prolong QT intervals which is listed in Table 2-1 and is prohibited to be taken with PANOBINOSTAT. This drug is thus not listed again in Table 4-1.

This is not a comprehensive list of medications which may inhibit CYP3A4/5. The above list was compiled by using information listed under "draft guidance for industry, drug interaction studies, CDER 2006", Indiana University School of Medicine drug interaction tables at http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp, and "drug interaction database" from University of Washington. Additional updated versions with moderate and weak CYP3A inhibitors, which are meant to be used as a guide, may be found at the following website: http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp.

D. Medications which are known CYP2D6 substrates to be used with caution

PANOBINOSTAT was also shown to be a CYP2D6 inhibitor (K_i 0.17 μM) *in vitro*. Thus, clinical drug-drug interaction study with PANOBINOSTAT as CYP2D6 inhibitor and dextromethorphan as CYP2D6 substrate was recently conducted in study [CLBH589B2109].

Multiple PANOBINOSTAT doses increased C_{max} and AUC of dextromethorphan by a mean of 1.8- and 1.6-fold respectively, but with no change in T_{max} in 17 cancer patients. An approximately 2-fold increase in dextromethorphan AUC upon co-administration with PANOBINOSTAT indicated that *in vivo* CYP2D6 inhibition of PANOBINOSTAT is weak.

As the study was conducted using a sensitive CYP2D6 substrate which resulted in a weak inhibition, drugs with a large therapeutic index such as anti-emetics, anti-hypertensives, and anti-depressants are generally safe to be co-administered with PANOBINOSTAT.

Patients should be carefully monitored for potential signs and symptoms of toxicity and may require dose titration or dose reduction of a sensitive CYP2D6 substrate which also have a narrow therapeutic window (e.g., the ratio of toxicity exposure is ≥2 -fold higher than the efficacious or therapeutic exposure).

Table 4-1 Medications which are known CYP2D6 substrates to be used with caution

Beta blockers (listed below):	**Antipsychotics** (listed below):
S-metoprolol	aripiprazole
propafenone	haloperidol
timolol	risperidone
Antidepressants (listed below):	thioridazine
amitriptyline	**Antiarrhythmics** (listed below):
clomipramine	mexilletine
desipramine	flecainide
imipramine	**Others** (listed below):
fluoxetine	codeine
paroxetine	dextromethorphan
venlafaxine	tamoxifen
duloxetine	tramadol
Antiemetics (listed below):	
ondansetron^	
^Intravenous dolasetron is a CYP2D6 substrate and contraindicated for preventing nausea and vomiting associated with chemotherapy based on FDA drug safety communication dated December 17, 2010. Please see Table 2-1.	

This is not a comprehensive list of CYP2D6 substrates. Additional updated versions of this list, which are meant to be used as a guide, may be found at the following website: http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp

E. Medications which are known to be moderate inducers of CYP3A4 are to be used with caution

During the study, the use of moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin, ritonavir, talviraline, tipranavir) is discouraged, and investigators should seek alternatives where possible. No dose adjustment will be used when moderate CYP3A4 inducers are co-administered with RUXOLITINIB. However, any concomitant use of moderate CYP3A4 inducers must be documented.

This is not a comprehensive list of medications which may induce CYP3A4/5. The above list was compiled by using information listed under "draft guidance for industry, drug interaction studies, CDER 2006", Indiana University School of Medicine drug interaction tables at http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.asp, and "drug interaction database" from University of Washington.

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Appendix 2: Study Schedules (Phase 1 and Phase 2)

STUDY: Phase I		CORE STUDY PERIOD																					
		Single agent RUXOLITINIB		COMBINATION THERAPY RUXOLITINIB and PANOBINOSTAT																			
		INDUCTION PHASE		dose evaluation period					dose continuation period													Ext	End of Study Follow Up
	Screen	Cycle -1		Cycle 1					Cycle 2				Cycle 3		Cycle 4		Cycle 5		Cycle 6			C7+	
		D 1	D 15	D 1	D 4	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 29	D 1	D 30+
	-84	-28	-14	1	4	8	15	22	29	36	43	50	57	71	85	99	113	127	141	155	169*		
IC	X																						
H&P	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CXR	X																						
MRI[1]	X														X						X		
ECHO/MUGA	X																						
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochem	X	X	X	X	X	X	X	X	X				X		X		X		X		X	X	X
PT/PTT	X																						
TFT	X																						
Urinalysis	X																						
sHCG	X			X																			
Urine Preg									X				X		X		X		X			X	
V617F/MPL	X								X						X						X	X***	
Buccal swab	X																						
Histone-acetyl	X			X		X							X								X		
CD34+ Burden	X			X		X							X								X		
CXCR4	X[2]																				X		
BMBX	X																				X	X***	
Cytogenetics	X																				X	X***	
Biomarkers	X								X												X	x	
Cytokine Profile	X	X	X	X					X				X		X		X		X		X	X	
MPN-SAF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[1] MRI is preferred but can be substituted by CT if patient is unable or unwilling to get MRI

[2] BM biopsy and aspirate at baseline can be ommitted if an adequate specimen had been obtained no greater than 3 months prior to screening (no MF-directed therapy during this

* C6D29 may also be C7D1 for patients that will continue on the extension stage of the study

** Each study visit from cycle -1 to EOS has a +/- 3 day window and for cycle 7 and beyond, each study visit has a +/- 7 day window, End of study visit should be at least 30 days after patient stops study medication

*** these tests will be performed when clinically indicated and not on each visit and not more frequently then every 6 months

RESEARCH RELATED

STANDARD OF CARE

STUDY: Phase 2		CORE STUDY PERIOD																					
		Single agent RUXOLITINIB		COMBINATION THERAPY RUXOLITINIB and PANOBINOSTAT																			
				Expansion stage																		Ext	
	Screen	Cycle -1		Cycle 1					Cycle 2				Cycle 3		Cycle 4		Cycle 5		Cycle 6			Cycle 7+	End of Study/ Follow Up
		D 1	D 15	D 1	D 4	D 8	D 15	D 22	D 1	D 8	D 15	D 22	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 29	D 1	D 30+
	‡	-28	-14	1	4	8	15	22	29	36	43	50	57	71	85	99	113	127	141	155	169*		
IC	X																						
H&P	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CXR	X																						
MRI[1]	X														X						X		
ECHO/MUGA	X																						
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochem	X	X	X	X	X	X	X	X	X				X		X		X		X		X	X	X
PT/PTT	X																						
TFT	X																						
Urinalysis	X																						
sHCG	X			X																			
Urine Preg									X				X		X		X		X			X	
Buccal swab	X																						
V617F/MPL	X								X						X						X	X***	
BMBX	X[2]																				X	X***	
Cytogenetics	X																				X	X***	
Biomarkers	X								X												X	X	
Cytokine Profile	X	X	X	X					X				X		X		X		X		X	X	
MPN-SAF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[1] MRI is preferred but can be substiuted by CT if patient is unable or unwilling to get MRI

[2] BM biopsy and aspirate at baseline can be ommitted if an adequate specimen had been obtained no greater than 3 months prior to screening (no MF-directed therapy during this period) and the pathology has been confirmed by the local pathologist and results appropriately entered in the eCRF.

* C6D29 may also be C7D1 for patients that will continue on the extension stage of the study

** Each study visit from cycle -1 to EOS has a +/- 3 day window and cycle 7 and beyond, each study visit has a +/- 7 day window, End of study visit should be at least 30 days after patient stops taking study medication.

*** these tests will be performed when clinically indicated and not on each visit and not more frequently then every 6 months

RESEARCH RELATED

STANDARD OF CARE

Appendix 3 MPN-SAF Symptom Assessment PAckage

Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)

Instructions: Please fill out all questions, as best able, reflecting how these symptoms affected you over the **LAST WEEK** unless directed otherwise. Complete forms until the STOP instruction toward the end of the packet.

Symptom	**1 to 10 (0 if absent) ranking* 1 is most favorable and 10 least favorable**
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL Level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your	
• General Activity	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Mood	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Walking ability	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Normal Work (includes work both outside the home and daily chores)	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Relations with other people	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)
• Enjoyment of life	(Does not Interfere) 0 1 2 3 4 5 6 7 8 9 10 (Completely Interferes)

Circle the one number that describes how, during the past Week how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early Satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal pain	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with Headaches	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with Concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Dizziness/ Vertigo/ Lightheadedness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/ Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Difficulty sleeping	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Depression or sad mood	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with Sexual Desire or Function	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Cough	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night Sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone Pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
What is your Overall Quality of Life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As Bad as it can be)

Appendix 4: Dynamic International Prognostic Scoring System (DIPSS)

The DIPSS is calculated as follows:

- Age >65 years: 1 point
- Leukocyte count >25,000/microL: 1 point
- Hemoglobin <10 g/dL: 2 points
- Circulating blast cells ≥1 percent: 1 point
- Presence of constitutional symptoms: 1 point

Subjects with zero, one to two, three to four, or 5 to 6 points were considered low, intermediate-1, intermediate-2, or high risk, respectively

Prognostic Variable	**Value**		
	0 Points	**1 Point**	**2 Points**
Hemoglobin	≥ 10 g/dL		< 10 g/dL
Age, years	< 65	≥ 65	
White blood cell count	≤ 25 x 10^3/uL	> 25 x 10^3/uL	
Peripheral blood blasts	< 1%	≥ 1%	
Constitutional symptoms	No	Yes	

Appendix 5: Subject Study Pill Diaries

PRIME: 12-1225
Subject Dosing Diary (Ruxolitinib)

Patient ID #	
Study Doctor Name:	
Study Doctor Phone Number:	

- Take RUXOLITINIB twice daily approximately 12 hours apart (morning and evening). Swallow the pills and do not chew them.
- All doses may be taken with or without food. Each dose should be taken with a glass of water. Avoid grapefruit juice and Seville (sour) oranges during the entire study.
- If you forget to take a dose of RUXOLITINIB, take your dose within 3 hours after the missed dose. After 3 hours, that dose should not be taken.
- If you vomit any doses of study drug DO NOT take another dose.
- Do not start any new medication including over-the-counter medications. All medications must be approved by your physician.
- Be sure to bring your diary, pill bottles and all leftover pills with you for all of your return appointments. Thank you.

RUXOLITINIB: You should take the following pills by mouth, with water, 12 hours apart

_____ pills in the morning _____ pills in the evening

Cycle_____ DAY	Date (DD/MM/YYYY)	Time Morning Dose	Time Evening Dose	Number of Pills	Side Effect or Question I Have	Time Noticed Side Effect
1	___/___/___	_____	_____			_____:_____ AM / PM
2	___/___/___	_____	_____			_____:_____ AM / PM
3	___/___/___	_____	_____			_____:_____ AM / PM
4	___/___/___	_____	_____			_____:_____ AM / PM
5	___/___/___	_____	_____			_____:_____ AM / PM
6	___/___/___	_____	_____			_____:_____ AM / PM
7	___/___/___	_____	_____			_____:_____ AM / PM
8	___/___/___	_____	_____			_____:_____ AM / PM
9	___/___/___	_____	_____			_____:_____ AM / PM
10	___/___/___	_____	_____			_____:_____ AM / PM
11	___/___/___	_____	_____			_____:_____ AM / PM
12	___/___/___	_____	_____			_____:_____ AM / PM
13	___/___/___	_____	_____			_____:_____ AM / PM

PRIME: 12-1225
Patient Dosing Diary (Calendar Combo-Weekly)

Patient ID #	
Study Doctor Name:	
Study Doctor Phone Number:	

- Take RUXOLITINIB twice daily approximately 12 hours apart (morning and evening). Swallow the pills and do not chew them.
- Take PANOBINOSTAT three times per week each week at the same time on each day **with the morning dose** of RUXOLITINIB. Swallow the capsules and do not chew them.
- All doses may be taken with or without food. Each dose should be taken with a glass of water. Avoid grapefruit juice and Seville (sour) oranges during the entire study.
- If you forget to take a dose of RUXOLITINIB, take your dose within 3 hours after the missed dose. After 3 hours, that dose should not be taken
- If you forget to take a dose of PANOBINOSTAT, take your dose within 12 hours after the missed dose. After 12 hours, that day's dose should not be taken.
- If you vomit any doses of study drug DO NOT take another dose.
- Do not start any new medication including over-the-counter medications. All medications must be approved by your physician.
- Have Loperamide (Imodium) readily available in case you develop diarrhea. Contact Dr. Mascarenhas at onset of diarrhea. If the diarrhea does not improve on Loperamide or if you're having more than 4 stools per day (soft to watery in large amounts), contact **Dr. Mascarenhas at 646-812-8444.**
- Be sure to bring your diary, pill bottles and all leftover pills with you for all of your return appointments. Thank you.

RUXOLITINIB: You should take the following pills by mouth, 12 hours apart

_____ pills in the morning _____ pills in the evening

PANOBINOSTAT: You should take the following capsules by mouth, 3 times per week, every week

_____ capsules in the morning

Cycle_____ DAY	Date (DD/MM/YYYY)	Time Morning Dose	Time Evening Dose	Number of Pills/ Capsules	Side Effect or Question I Have	Time Noticed Side Effect
1 Ruxolitinib & Panobinostat	___/___/___	_____	_____	Rux:____ Pan:____		_____:_____ AM / PM
2 Ruxolitinib	___/___/___	_____	_____	Rux:____		_____:_____ AM / PM
3 Ruxolitinib & Panobinostat	___/___/___	_____	_____	Rux:____ Pan:____		_____:_____ AM / PM
4 Ruxolitinib	___/___/___	_____	_____	Rux:____		_____:_____ AM / PM
5 Ruxolitinib & Panobinostat	___/___/___	_____	_____	Rux:____ Pan:____		_____:_____ AM / PM
6 Ruxolitinib	___/___/___	_____	_____	Rux:____		_____:_____ AM / PM
7 Ruxolitinib	___/___/___	_____	_____	Rux:____		_____:_____ AM / PM
8 Ruxolitinib & Panobinostat	___/___/___	_____	_____	Rux:____ Pan:____		_____:_____ AM / PM

PRIME: 12-1225
Patient Dosing Diary (Calendar Combo-QOW)

Patient ID #	
Study Doctor Name:	
Study Doctor Phone Number:	

- Take RUXOLITINIB twice daily approximately 12 hours apart (morning and evening). Swallow the capsules and do not chew them.
- Take PANOBINOSTAT three times per week every other week at the same time on each day **with the morning dose** of RUXOLITINIB. Swallow the capsules and do not chew them.
- All doses may be taken with or without food. Each dose should be taken with a glass of water. Avoid grapefruit juice and Seville (sour) oranges during the entire study.
- If you forget to take a dose of RUXOLITINIB, take your dose within 3 hours after the missed dose. After 3 hours, that dose should not be taken
- If you forget to take a dose of PANOBINOSTAT, take your dose within 12 hours after the missed dose. After 12 hours, that day's dose should not be taken.
- If you vomit any doses of study drug DO NOT take another dose.
- Do not start any new medication including over-the-counter medications. All medications must be approved by your physician.
- Have Loperamide (Imodium) readily available in case you develop diarrhea. Contact Dr. Mascarenhas at onset of diarrhea. If the diarrhea does not improve on Loperamide or if you're having more than 4 stools per day (soft to watery in large amounts), contact **Dr. Mascarenhas at 646-812-8444.**
- Be sure to bring your diary, pill bottles and all leftover pills with you for all of your return appointments. Thank you.

RUXOLITINIB: You should take the following pills by mouth, 12 hours apart

_____ pills in the morning _____pills in the evening

PANOBINOSTAT: You should take the following capsules by mouth, 3 times per week, every other week

_____ capsules in the morning

Cycle_____ DAY	Date (DD/MM/YYYY)	Time Morning Dose	Time Evening Dose	Number of Pills/ Capsules	Side Effect or Question I Have	Time Noticed Side Effect
1 Ruxolitinib & Panobinostat	___/___/___	_____	_____	Rux:____ Pan:____		_____:_____ AM / PM
2 Ruxolitinib	___/___/___	_____	_____	Rux:____		_____:_____ AM / PM
3 Ruxolitinib & Panobinostat	___/___/___	_____	_____	Rux:____ Pan:____		_____:_____ AM / PM
4 Ruxolitinib	___/___/___	_____	_____	Rux:____		_____:_____ AM / PM
5 Ruxolitinib & Panobinostat	___/___/___	_____	_____	Rux:____ Pan:____		_____:_____ AM / PM
6 Ruxolitinib	___/___/___	_____	_____	Rux:____		_____:_____ AM / PM
7 Ruxolitinib	___/___/___	_____	_____	Rux:____		_____:_____ AM / PM