Fostamatinib as a single agent or in combination with ruxolitinib for treatment of patients with myelofibrosis with severe thrombocytopenia

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Protocol Revision History

Initial Approval Version	**day month year**
Amendment #1 Version	**day month year**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
B-HCG	Beta human chorionic gonadotropin
BMT	Bone marrow transplant
CBC	Complete blood count
CFR	Code of Federal Regulations
CNS	Central nervous system
CR	Complete response
CRc	Cytogenetic complete remission
CRi	Complete remission incomplete
CRm	Morphologic complete remission
CRF	Case report form
CST	Central standard time
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose limiting toxicity
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
DSMC	Data Safety Monitoring Committee
ECG (or EKG)	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
FWA	Federal wide assurance
GCP	Good Clinical Practice
HHS	Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
IND	Investigational New Drug
IRB	Institutional Review Board
MDS	Myelodysplastic syndrome
MM	Multiple myeloma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Cancer Center Network

NCI	National Cancer Institute
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer
OHRP	Office of Human Research Protections
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PI	Principal investigator
PR	Partial response
PSA	Prostate-specific antigen
QASMC	Quality Assurance and Safety Monitoring Committee
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RFS	Relapse free survival
RR	Response rate
SAE	Serious adverse event
SCC	Siteman Cancer Center
SCT	Stem cell transplant
SD	Stable disease
TSH	Thyroid stimulating hormone
TTP	Time to progression
UPN	Unique patient number
US	Ultrasound
VEGF	Vascular endothelial growth factor
WBC	White blood cell (count)

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PROTOCOL SUMMARY

Synopsis

Title:	Fostamatinib as a single agent or in combination with ruxolitinib for treatment of patients with myelofibrosis with severe thrombocytopenia
Study Description:	Our hypothesis is that fostamatinib will be safe, tolerable, and effective in patients with myelofibrosis with severe thrombocytopenia (platelet < 50K/microL) as a single agent and in combination with ruxolitinib. Fostamatinib will improve thrombocytopenia in patients with myelofibrosis (MF) with severe thrombocytopenia (platelet < 50K/microL) and allow them to initiate treatment with ruxolitinib. This study will be executed in two parts (Part A and Part B). For Part A, patients with MF with severe thrombocytopenia will initially receive 12 weeks of single agent fostamatinib (by mouth twice daily) until a sustained platelet count of ≥ 50K/microL is achieved (defined as two separate measurements at least two weeks apart). Patients who achieve a sustained platelet count of ≥ 50K/microL will be eligible to continue on to Part B where they will begin treatment with ruxolitinib (dosed as per standard of care) while continuing to take fostamatinib. Patients who do not achieve a sustained platelet count of ≥ 50K/microL by the end of 12 weeks of treatment may continue on fostamatinib monotherapy if they are receiving benefit for up to an additional 36 weeks of treatment, and may be eligible to continue on to Part B of the study if they achieve a sustained platelet count of ≥ 50K/microL at any point before Cycle 10 Day 1. Patients in Part B will continue treatment with fostamatinib and ruxolitinib for up to an additional 36 weeks (total duration of treatment with fostamatinib monotherapy and fostamatinib and ruxolitinib combination therapy will be 48 weeks).
Objectives:	**Part A:** <u>Primary Objective</u>: Evaluate the impact of fostamatinib on platelet counts in patients with myelofibrosis and severe thrombocytopenia (platelets < 50K/microL) <u>Secondary Objectives</u>: 1. Evaluate the safety and tolerability of single agent fostamatinib in patients with MF and thrombocytopenia 2. Evaluate spleen response to fostamatinib

	3. Evaluate anemia response to fostamatinib 4. Evaluate the impact of fostamatinib on transfusion requirements 5. Evaluate the impact of fostamatinib on MF symptoms 6. Evaluate the ability of fostamatinib treatment to enable initiation with ruxolitinib 7. Evaluate the impact of fostamatinib on marrow fibrosis **Part B:** Primary Objective: Evaluate the safety and tolerability of fostamatinib plus ruxolitinib in patients with MF and thrombocytopenia Secondary Objectives: 1. Evaluate spleen response with the combination of fostamatinib and ruxolitinib 2. Evaluate the impact of fostamatinib and ruxolitinib on symptoms 3. Evaluate the ability of fostamatinib to enable sustained treatment with ruxolitinib 4. Evaluate the impact of fostamatinib and ruxolitinib on marrow fibrosis
Endpoints:	**Part A:** Primary Endpoint: Platelet response as defined as an increase in platelet count ≥ 50K/microL with at least one more confirmatory platelet count separated by at least 2 weeks (in the absence of platelet transfusion) within the first 12 weeks of fostamatinib treatment Secondary Endpoints: 1. Platelet response by week 12 and at end of fostamatinib monotherapy treatment 2. Number of patients eligible to initiate therapy with ruxolitinib 3. Adverse events (AEs), serious AEs (SAEs), and laboratory abnormalities on fostamatinib treatment 4. Patients who permanently discontinued fostamatinib due to fostamatinib related AEs 5. Patients who required treatment interruption of fostamatinib due to AEs 6. Patients who were dose escalated who tolerated fostamatinib dose greater than 100 mg BID 7. Patients who achieve 35% or greater reduction in spleen volume as determined by ultrasound at week 12 of fostamatinib treatment and end of fostamatinib monotherapy treatment

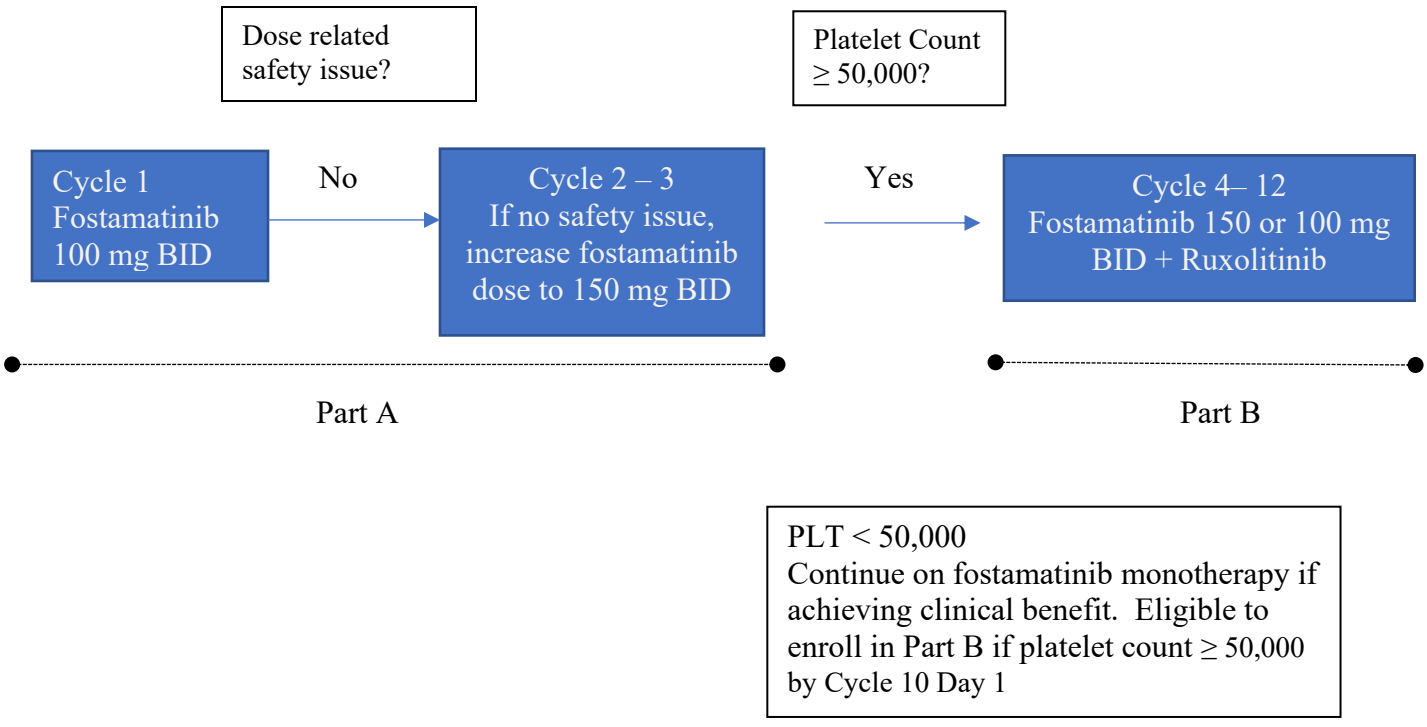
	8. Mean reduction in spleen volume as determined by ultrasound at week 12 of fostamatinib treatment and end of fostamatinib monotherapy treatment 9. Patients with 50% or greater improvement in Total Symptom Score at week 12 of treatment and end of fostamatinib monotherapy treatment 10. Patients who achieve platelet transfusion independence 11. Patients with anemia who achieve RBC transfusion independence 12. Change in marrow fibrosis by WHO grading **Part B:** Primary Endpoint: Incidence, severity, and outcomes of AEs per NCI CTCAE v 5.0, SAEs, AEs of interest (AEIs) and laboratory abnormalities during fostamatinib and ruxolitinib treatment Secondary Endpoints: 1. Patients with 35% or greater reduction in spleen volume as determined by ultrasound after 12 weeks of combination therapy and end of treatment 2. Mean reduction in spleen volume as determined by ultrasound after 12 weeks of combination therapy and end of treatment 3. Patients with a 50% or greater improvement in Total Symptom Score after 12 weeks of combination therapy and at end of treatment 4. Duration of uninterrupted ruxolitinib treatment 5. Change in marrow fibrosis by WHO grading
Study Population:	Twelve adult patients of any race or ethnicity with primary or secondary myelofibrosis with severe thrombocytopenia (platelet count < 50K/microL) with intermediate or high risk disease by IPSS.
Phase:	Pilot Phase II Study
Description of Sites / Facilities Enrolling:	This study will be active at Washington University School of Medicine.
Description of Study Intervention:	Both fostamatinib and ruxolitinib are oral drugs taken twice daily on a continuous basis.
Study Duration:	2 years
Participant Duration:	48 weeks

STUDY SCHEMA

Part A:
The starting dose of fostamatinib is 100 mg twice daily (BID). After the first cycle, if no major dose related safety issue is observed and the platelet count is less than 50K/microL, then the fostamatinib dose will be increased to 150 mg BID for the next 2 cycles; otherwise the dose may be continued at 100 mg BID.

Part B:
After 3 cycles of fostamatinib monotherapy, all patients with a sustained platelet count ≥ 50K/microL, will continue on the current fostamatinib dose plus ruxolitinib at the recommended dose per standard prescribing guidelines for an additional 9 cycles.

Patients who do not reach platelet count of at least 50K/microL but who achieve clinical benefit per the treating provider may continue on single agent fostamatinib for up to 12 total treatment cycles. If these patients achieve a sustained platelet count of ≥ 50K/microL at any point prior to Cycle 10 Day 1, then they may be eligible to enroll in Part B of the study and continue treatment with fostamatinib and ruxolitinib for the remainder of the study.



SCHEDULE OF ACTIVITIES

	Screening[1]	D1 of each cycle[2]	D15 of each cycle	EOT Part A	C4D1	After 3 cycles Part B	EOT Part B	Follow-up[3]
Informed consent	X							
H&P, ECOG PS, con meds	X	X						
Medical history	X							
CBC	X	X[4]	X[4]					
Select chemistry[5]	X	X	X					
PT/INR, PTT	X							
Lipid Panel[6]	X	X[6]						
Pregnancy test[7]	X	X						
ECG	X							
Abdominal ultrasound for spleen volume[8]	X			X	X	X	X	
Bone marrow biopsy	X[9]			X[8]			X[8]	
MPN symptom assessment form		X						
Fostamatinib		Oral drug taken on a twice daily basis						
Ruxolitinib		As per SOC						
AE assessment		Start of treatment through 30 days after last day of study treatment						
Progression and survival								X

1. Screening evaluations must be conducted within 3 weeks prior to the start of therapy.
2. Each cycle is 28 days. +/- 3 day for Day 1 assessments
3. Every 6 months for up to 2 years.
4. Also on D8 and D22 (weekly) the first cycle of fostamatinib monotherapy and first cycle of fostamatinib + ruxolitinibib combination therapy (+/- 2 days)
5. BUN, creatinine, total bilirubin, AST, ALT, albumin
6. Total Cholesterol, LDL, HDL, non-HDL, Triglycerides, check every 2 cycles after starting ruxolitinib therapy
7. Women of childbearing potential only; test may be a urine test, and if positive, confirm with a serum test.

8. +/- 7 days
9. May be done up to 30 months before signing consent

1.0 INTRODUCTION

1.1 Background

Myelofibrosis (MF) is a clonal stem cell disorder classified within the category of Philadelphia chromosome (Ph)-negative myeloproliferative neoplasms (MPN) that includes polycythemia vera (PV) and essential thrombocythemia (ET) [1]. The disease is characterized by ineffective erythropoiesis and extramedullary hematopoiesis leading to progressive bone marrow failure, severe anemia, constitutional symptoms (e.g., night sweats, fever, fatigue), marked hepatosplenomegaly, thrombosis, and cachexia. MF can arise following a history of PV or ET or can present *de novo* as primary myelofibrosis (PMF).

Among the Ph-negative MPNs, somatic mutations in Janus kinase 2 (JAK2) constitute the most frequent mutation in PV, ET, and PMF [2]. Approximately 50 – 60% of patients with PMF harbor the JAK2 V617F mutation. Mutations in calreticulin (CALR) and myeloproliferative leukemia virus oncogene (MPL) have subsequently been identified in patients with ET and PMF who are negative for the JAK2 mutation [3- 7]. Patients with CALR mutation appear to have a more indolent clinical course than patients with the JAK2 V617F mutation as manifested by lower risk of thrombosis and longer overall survival [3-4]. Several additional molecular mutations have been identified in patients with MF that have also shown to have prognostic impact [8-9]. Mutations in ASXL1, SRSF2, and IDH1/IDH2, for example, are associated with increased risk for leukemic transformation and decreased overall survival.

MF generally affects an older population, with the age at diagnosis around 65 years of age [10]. Median survival can range from months to years depending on the presence or absence of adverse clinical and molecular prognostic factors [11-13], but ultimately survival is significantly reduced in patients with MF compared to the general population and patients with PV and ET [14]. MF can evolve into acute leukemia in about 10 – 20% of patients [15-17] and while current therapies such as JAK2 inhibitors can improve symptoms and have a modest survival benefit [18-21], the only curative treatment remains allogeneic stem cell transplantation.

1.2 JAK2 inhibitors in MF

The JAK-STAT pathway is an important downstream signaling pathway of multiple cytokine and growth receptors. The discovery of the JAK2V617F mutation in 2005 as the most common molecular abnormality in Ph negative MPNs has led to the development of several Janus kinase 2 (JAK2) inhibitors in the treatment of patients with primary myelofibrosis [22]. Ruxolitinib (Jakafi; Incyte, Wilmington, Delaware, USA), a JAK1/JAK2 inhibitor, was the first JAK2 inhibitor approved by the FDA for treatment of patients with intermediate or high-risk myelofibrosis, including PMF, post-PV MF, and post-ET MF.

The FDA approval of ruxolitinib for treatment of patients with MF was based on two phase

III prospective randomized clinical trials (COMFORT-I and COMFORT-II). In these two studies, ruxolitinib demonstrated superiority over placebo and best available therapy (BAT) in reducing spleen size and improving constitutional symptoms in patients with intermediate and high risk primary myelofibrosis [23, 24]. Long term follow up at 3 years of both the COMFORT-I and COMFORT-II trials have also demonstrated a modest survival benefit compared to placebo and BAT, respectively [21, 25, 26].

Targeted inhibitors of JAK2 alleviate clinical symptoms and have demonstrated a modest survival benefit, but they have not been found to improve cytopenias in patients with MF [22]. Their use may also be limited in patients with thrombocytopenia due to their myelosuppresive effects and are generally not recommended for patients with severe thrombocytopenia [27, 28]. Therefore, therapies that can improve platelet counts in MF patients with severe thrombocytopenia are needed.

1.3 Thrombocytopenia in MF and rationale for SYK inhibition

Thrombocytopenia is a hematologic complication of MF resulting from ineffective erythropoiesis as well as hypersplenism in the setting of splenomegaly. There are currently few effective therapies for the treatment of thrombocytopenia in MF. Treatment with ruxolitinib can further lower the platelet count, leading to dose attenuations that may limit the efficacy or prohibit continuation of the medication. Ruxolitinib (as well as Fedratinib) are also not recommended for patients with platelets < 50,000/microL, thereby limiting the treatment options for patients with MF with severe thrombocytopenia.

Fostamatinib is an oral spleen tyrosine kinase (SYK) inhibitor recently approved for the treatment of chronic idiopathic thrombocytopenic purpura (ITP), and may be a potential therapeutic option for patients with MF with severe thrombocytopenia. As hypersplenism from splenomegaly can be a contributing factor to thrombocytopenia in MF, an agent that blocks spleen tyrosine kinase signaling may improve the platelet count in these patients. Additionally, increasing the platelet count >= 50,000/microL would allow patients with severe thrombocytopenia to be treated with ruxolitinib. Another feature of fostamatinib is that there was no reported increased risk of thrombosis in the phase 3 studies [29], which makes it an attractive agent for patients with MF where thrombosis is a concern.

1.4 Fostamatinib

Fostamatinib is an oral spleen tyrosine kinase (SYK) inhibitor that has been developed by Rigel for the treatment of adult patients with persistent or chronic ITP who have had an insufficient response to a previous treatment. Fostamatinib was granted orphan-drug designation for ITP on 25 August 2015. Three Phase 3 studies in ITP provided the basis for the safety and efficacy evaluation of fostamatinib in the treatment of thrombocytopenia in ITP subsequently leading to its FDA approval for the treatment of patients with ITP.
Rigel has also conducted exploratory clinical studies with fostamatinib in patients with B-cell and T-cell lymphomas, and in patients with advanced cancer through a collaboration with the National Cancer Institute (NCI). Syk has been implicated in the pathogenesis of multiple hematologic malignancies including non-Hodgkin's lymphomas (as a component of the B-cell receptor pathway), acute myelogenous leukemia (AML), myelodysplastic

syndrome (MDS), and myelofibrosis (MF). In FMS-like tyrosine kinase-3-internal tandem duplication (FLT3-ITD) positive AML, Syk cooperates with FLT3ITD in promoting the survival and proliferation of AML blasts. Syk has also been implicated as a mediator of venetoclax resistance in chronic lymphocytic leukemia (CLL) and diffuse large B-cell lymphoma cell lines, suggesting inhibition of Syk may be important in mitigating venetoclax resistance during treatment of AML and that Syk inhibition may be beneficial in combination with venetoclax treatment. One of the key mechanisms behind the excessive hematopoietic stem cell death that occurs in MDS is inflammasome activation, which occurs in a Syk-dependent manner. Similar mechanisms have been proposed for MF, and a role for Syk in this disease is supported by the finding that a translocation–Ets–leukemia or ETV6 (TEL) Syk fusion described in MDS patients in mice induces MF-like disease [30]. Many of the symptoms in these mice can be ameliorated by treatment with fostamatinib [31]. These data suggest that Syk is important to the development and progression of these various hematologic malignancies, and that inhibition of Syk, either as a single agent, or in combination with other therapeutic approaches, may be an important new approach to the treatment of these malignancies.

1.4.1 Nonclinical Studies with Fostamatinib

Fostamatinib is the first oral spleen tyrosine kinase (SYK) inhibitor. R406 and its orally administered prodrug (fostamatinib) were effective in rodent models of immune complex activation, arthritis, antibody-mediated glomerulonephritis, immune autoantibody-mediated thrombocytopenia, and non-Hodgkin's lymphoma. In safety pharmacology studies (respiratory, central nervous system [CNS], and cardiovascular including human ether-a-go-go related gene [hERG]), R406 was well tolerated. There was a slight reduction in heart rate at 50 mg/kg and a trend for increased blood pressure (BP) in the monkey cardiovascular study, and there were mild behavioral abnormalities (e.g., hypoactivity) at 50 mg/kg R406 in the rat CNS study.

Nonclinical PK studies demonstrated that fostamatinib was converted to R406 pre-systemically, most likely by phosphatases in the intestinal mucosa, such that little or no R788 could be detected in the plasma. Approximately 40% to 60% of the fostamatinib dose is estimated to be available as R406 in the systemic circulation. In all species tested, R406 exhibits low to moderate clearance, and the elimination half-life of R406 ranges from approximately 0.6 to 3.4 hours. R406 is extensively metabolized by oxidation and conjugation reactions in rats and monkeys. R406 is highly protein bound in plasma (> 97%) and preferentially distributed into blood cells. This distribution is reversible.

Toxicology studies in rats and monkeys (doses ≤ 100 mg/kg/day fostamatinib) for 4 to 26 and 4 to 39 weeks, respectively, identified lymphohematopoietic and liver function test abnormalities (mild and fully reversible), and reproductive and/or developmental liabilities in rats and rabbits. Consistent with bone growth plate effects in rats in the general toxicity studies, similar findings were observed in the rat and mouse carcinogenicity studies and in a 1 month juvenile study in rabbits

(doses of 12.5 to 50 mg/kg/day). A related finding of odontodysplasia was also observed in the rat 2-year carcinogenicity study. There were no adverse effects on any male reproductive parameters in the rat at doses up to 40 mg/kg/day. There was no evidence for mutagenic or clastogenic effects in genotoxicity studies, or any carcinogenic potential in mouse and rat carcinogenicity studies. Fostamatinib promoted no remarkable adverse effects on host response in immunological host resistance models in mice (*Streptococcus*, *Listeria*, and Influenza).

1.4.2 Clinical Studies with Fostamatinib

Clinical studies with fostamatinib have included the following:
Table 1: Summary of Subjects/Patients Treated with Fostamatinib (Rigel Fostamatinib Investigator's Brochure v17. Date of Edition: October 2, 2019)

Population	Number of Studies	Number of Subjects Exposed to Fostamatinib as of 18 April 2019
Completed Studies	**50**	**4585**
Healthy Subjects	26	724[a]
Other Clinical Pharmacology Studies	4	101[b]
ITP	3	119 (Phase 3 studies: N=102 Phase 2 study: N=17)[c]
Rheumatoid Arthritis	13	3,437[d]
Oncology	4	204 (Sponsor studies: N =167 NCI study: N=37)[e]
Ongoing Studies	**3**	**193**
ITP (Study C-935788-049)	1	123[f]
Ongoing Studies (Other Indications)	2	77
IgAN (Study C-935788-050)	1	51
AIHA (Study C-935788-053)	1	26[g]
Total number of subjects exposed to fostamatinib		**4706**

Abbreviations: AIHA = autoimmune hemolytic anemia; IgAN = immunoglobulin A nephropathy; ITP = immune thrombocytopenia; NCI = National Cancer Institute

a. Includes 26 Studies: N = 439 (single dose); N= 183 (multiple dose), N = 183 (drug-drug interaction)
b. Includes clinical pharmacology studies in subjects with renal impairment (N=16), and with hepatic impairment (N = 24), a drug-drug interaction study with methotrexate in RA subjects (N = 16), and a Phase 1 study with R406 the active metabolite of fostamatinib (N =45).
c. Includes one Phase 2 study (N = 17 unique subjects) and 2 Phase 3 Studies (N=102)
d. Includes 9 placebo-controlled studies (N = 2414) and 4 extension studies in rheumatoid arthritis.
e. Includes 3 studies conducted by the sponsor in lymphoma subjects (N=167) and one NCI-sponsored study in subjects with solid tumors (N=37).
f. Includes extension study where 79 subjects received prior fostamatinib and 44 subjects received prior placebo in the placebo-controlled ITP studies.
g. Includes subjects who have completed Stage 1 and Stage 2 of the ongoing study

1.4.3 Pharmacokinetics and Drug Metabolism in Humans

1.4.3.1 Absorption

Oral doses of fostamatinib are converted rapidly and extensively in the gut to the major active metabolite, R406, with a median time to reach maximum concentration following drug administration (T_{max}) of approximately 1.5 hours. Negligible levels of fostamatinib were found in plasma.

Following oral dosing at 150 mg, plasma concentrations of R406 increase rapidly, reaching maximum levels within 1.5 hours. Mean maximum plasma (peak) drug concentration (C_{max}) and area under the plasma concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) estimates are 550 ng/mL and 7080 ng•h/mL, respectively. R406 exposure is approximately dose proportional up to 200 mg twice daily (*bid*). After administration of fostamatinib, the absolute oral bioavailability of R406 was 55%. R406 accumulates approximately 2- to 3-fold upon *bid* dosing at 100 to 200 mg.

1.4.3.2 Effect of Food

Administration of fostamatinib with a high-calorie, high-fat meal (deriving approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively) increased R406 area under the plasma concentration-time curve (AUC) by 23% and C_{max} by 15%, indicating that fostamatinib can be given with or without food.

1.4.3.3 Distribution

The major active metabolite (R406) is 98.3% protein bound in human plasma. The red blood cell to plasma concentration ratio is approximately 2.6:1. The volume of distribution at steady state of R406 is 256 L.

1.4.3.4 Metabolism

Fostamatinib is metabolized in the gut by alkaline phosphatase to the major active metabolite (R406), which is absorbed into the systemic circulation. R406 is extensively metabolized, primarily through pathways of cytochrome P450 (CYP450)-mediated oxidation (by CYP3A4) and glucuronidation (by UGT1A9). R406 is the predominant moiety in the systemic circulation, and there was minimal exposure to any R406 metabolites.

1.4.3.5 Excretion

Following an oral dose of fostamatinib, the majority (~80%) of the

metabolite is excreted in feces with ~20% excreted in the urine. The major component excreted in urine was R406 N-glucuronide. The major components excreted in feces were R406, *O*-desmethyl R406 and a metabolite produced by gut bacteria from the *O*-desmethyl metabolite of R406. The terminal half-life of R406 was approximately 15 hours.

1.4.3.6 Specific Populations

Population pharmacokinetics analyses indicate fostamatinib is not altered based on age, sex, race/ethnicity. The pharmacokinetics of fostamatinib is not altered in subjects with renal impairment (creatinine clearance [CLcr] = 30 to < 50 mL/min, estimated by Cockcroft Gault equation and end stage renal disease requiring dialysis), or hepatic impairment (Child-Pugh Class A, B and C).

1.4.4 Efficacy in Humans

1.4.4.1 ITP Studies

Efficacy results from 2 Phase 3 studies and the long-term extension study demonstrate a rate of stable platelet response of 17.6%–22.7% in patients treated with fostamatinib. The initial signal of a fostamatinib-associated increase in platelets was evident within 2 to 12 weeks of drug exposure. The platelet response was generally robust and durable and prompted most responders to continue on fostamatinib in the extension study. In addition, treatment with fostamatinib resulted in a substantial reduction (~50%) in the incidence of important bleeding-related events compared to placebo. Although the numbers are small, it should be noted that only a single patient (1%) had a severe bleeding-related event in the fostamatinib group, as opposed to 3 (6.1%) in the placebo group.

1.4.4.2 RA Studies

In the Phase 2 and Phase 3 randomized, placebo-controlled trials evaluating fostamatinib in RA patients with active disease despite treatment with oral disease modifying anti-rheumatic drugs (DMARDs), a statistically significant improvement in signs and symptoms was established for fostamatinib doses of 150 mg once daily (*qd*) or greater (100 mg *bid*, 100 mg *bid* followed by 150 mg *qd*, 150 mg *qd*, and 150 mg *bid*). However, in both Phase 3 trials assessing prevention of progression of structural joint damage (oral SYK inhibition in RA [OSKIRA-1 and OSKIRA-3]), no statistically significant difference in modified total Sharp score (mTSS) compared to placebo was observed. The RA indication is no longer being pursued by Rigel but is briefly mentioned in this IB for completeness.

1.4.4.3 Other Indications

In the Phase 2 study in IgAN, a reduction in the primary endpoint of spot urine protein/creatinine ratio (sPCR) was observed for all 3 treatment groups (fostamatinib 150 mg *bid*, fostamatinib 100 mg *bid*, placebo) at 24 weeks. The differences between the fostamatinib groups (combined or by individual dose groups) were not statistically significant; thus, the primary endpoint was not achieved. In the Phase 2 study in AIHA, 8 of 17 patients (47%) treated with fostamatinib 150 mg *bid* who were evaluable for efficacy achieved the efficacy endpoint of hemoglobin response in Stage 1 of the study. Hence, the criteria were met for continuing treatment in Stage 2. Hemoglobin response was defined as hemoglobin > 10 g/dL and ≥ 2 g/dL higher than baseline.

1.4.5 Safety in Humans

1.4.5.1 ITP Studies

The safety profile of fostamatinib in patients with ITP comes primarily from the analyses of the 3 Phase 3 studies. Table 1 presents the incidence of common adverse drug reactions from the 2 ITP placebo-controlled Phase 3 studies. In these studies, serious adverse drug reactions were febrile neutropenia, diarrhea, pneumonia, and hypertensive crisis, which each occurred in 1% of patients receiving fostamatinib. In addition, severe adverse reactions observed in patients receiving fostamatinib included dyspnea and hypertension (both 2%); and neutropenia, arthralgia, chest pain, diarrhea, dizziness, nephrolithiasis, pain in extremity, toothache, syncope and hypoxia (all 1%). Serious adverse events (SAEs) were reported in 13 patients (12.7%) receiving fostamatinib and 10 patients (20.8%) receiving placebo. The SAEs were deemed related to study drug by the investigator in 4 patients (3.9%) receiving fostamatinib (febrile neutropenia, diarrhea, pneumonia, hypertensive crisis) and 1 patient (2.1%) receiving placebo (menorrhagia). All adverse reactions were reversible and manageable with appropriate monitoring, dose modifications or interruptions, and standard therapeutic approaches.

Table 1: Incidence of Common (≥ 5%) Adverse Reactions from Double-Blind Clinical Studies (C788-047 and C788-048)

	Fostamatinib (N=102)				**Placebo (N=48)**			
Adverse Reaction	**Mild %**	**Moderate %**	**Severe %**	**TOTAL %**	**Mild %**	**Moderate %**	**Severe %**	**TOTAL %**
Diarrhea[a]	21	10	1	31	13	2	0	15
Hypertension[b]	17	9	2	28	10	0	2	13
Nausea	16	3	0	19	8	0	0	8
Dizziness	8	2	1	11	6	2	0	8

ALT increased	5	6	0	11	0	0	0	0
AST increased	5	4	0	9	0	0	0	0
Respiratory infection[c]	7	4	0	11	6	0	0	6
Rash[d]	8	1	0	9	2	0	0	2
Abdominal pain[e]	5	1	0	6	2	0	0	2
Fatigue	4	2	0	6	0	2	0	2
Chest pain	2	3	1	6	2	0	0	2
Neutropenia[f]	3	2	1	6	0	0	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase

Note: Common adverse reactions were defined as all adverse reactions occurring at a rate of ≥ 5% of patients in the fostamatinib group and greater than placebo rate.

a. Includes diarrhea and frequent bowel movement.
b. Includes hypertension, blood pressure (BP) increased, BP diastolic abnormal, and BP diastolic increased.
c. Includes upper respiratory tract infection, respiratory tract infection, lower respiratory tract infection, and viral upper respiratory tract infection.
d. Includes rash, rash erythematous, and rash macular.
e. Includes abdominal pain and abdominal pain upper.
f. Includes neutropenia and neutrophil count decreased.

1.4.5.2 RA Studies

Overall, fostamatinib was well tolerated at doses up to 300 mg per day given for extended periods of time to patients with RA. The most commonly occurring adverse reactions —diarrhea, hypertension, neutropenia, and liver function test elevations were the same as those observed in the ITP program—were generally mild to moderate, predictable, easily managed, and reversible, allowing patients to receive long-term fostamatinib for multiple years. In general, these adverse events (AEs) did not worsen over time or resolved during continued treatment.

1.4.5.3 AIHA Study

The safety profile of fostamatinib in the Phase 2 AIHA study was consistent with the overall safety profile of fostamatinib. The most commonly reported AEs were diarrhea, fatigue, hypertension; dizziness, insomnia and nausea. The most commonly reported treatment-related AEs were diarrhea, hypertension, fatigue and neutrophil count decreased. The majority of AEs were mild or moderate and SAEs were reported in 7 patients, none which were considered treatment-related. Two fatal AEs were reported; however, they were attributed to underlying conditions.

1.4.5.4 Other Indications

Safety data in lymphoma patients showed that fostamatinib was well tolerated at all doses administered to patients with various lymphoma histologies that had received multiple prior therapies for their malignancy. Fostamatinib was administered at doses higher than those intended for the

market indication of ITP. The most common AEs, i.e., fatigue, diarrhea, nausea, pyrexia, and cytopenias were generally mild to moderate in severity, manageable and reversible, allowing most patients to receive their full dose of fostamatinib for the intended duration. In patients with solid tumors, cytopenias, hypertension and fatigue were commonly reported. Treatment-related elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin were also noted. Differences between patients with solid tumors and those with lymphomas were felt to be due to underlying disease in the different patient populations. Fostamatinib was not well tolerated in patients with colorectal cancer—particularly those with liver involvement—but was well tolerated in the other tumor types. The AEs reported in IgAN and AIHA studies are consistent with the safety profile established to date for fostamatinib.

1.4.5.5 Safety Conclusions

Nearly 4700 subjects/patients have received fostamatinib as part of clinical studies in a variety of indications, including 163 patients with ITP, more than 3400 RA patients at doses of 100 to 300 mg/day, and more than 160 oncology patients at doses of 200 to 500 mg/day. The safety profile of fostamatinib in these studies shows a consistent pattern of adverse reactions across indications with diarrhea, hypertension, nausea, and increased transaminases being the most frequent adverse reactions reported from these populations.

1.5 Study Rationale

Thrombocytopenia is a common hematologic complication of MF and can limit a patient's ability to be treated with a JAK2 inhibitor if their thrombocytopenia is severe (<50,000/microL). Approximately 16 to 26% of MF patients will have a platelet count of < 100,000/microL and 11 to 16% will have a platelet count of < 50,000/microL at diagnosis. And given the progressive nature of the disease, an additional 20% of patients will develop thrombocytopenia at some point during their disease course [32]. Additionally, severe thrombocytopenia may lead to serious complications such as bleeding.

There are currently few effective therapies for the treatment of thrombocytopenia in patients with MF and this is an area of unmet need. Fostamatinib may be effective in improving platelet counts in MF through its inhibition of spleen tyrosine kinase signaling, as hypersplenism can be a contributing factor to thrombocytopenia in these patients. Furthermore, preclinical studies suggest a possible therapeutic benefit of fostamatinib in a MF mouse model, further supporting its evaluation in the treatment of MF patients. Fostamatinib at dosages of 100 mg BID and 150 mg BID have been shown to be effective and well tolerated for the treatment of thrombocytopenia in patients with ITP, and these dosages will be used in this study.

In summary, fostamatinib may improve thrombocytopenia in MF patients with severe

thrombocytopenia (platelet <50,000/microL) and allow them to initiate treatment with a JAK2 inhibitor, ruxolitinib. Additionally, fostmatinib monotherapy may also improve MF related symptoms and splenomegaly.

2.0 OBJECTIVES AND ENDPOINTS

2.1 Part A Objectives and Endpoints

Objectives	Endpoints	Justification for Endpoints
Primary		
To evaluate the impact of fostamatinib on platelet counts in patients with myelofibrosis and severe thrombocytopenia	Platelet response as detailed in Section 11.2.2, platelet response by week 12 and end of fostamatinib monotherapy treatment, and number of patients eligible to initiate treatment with a JAK2 inhibitor (ruxolitinib)	The efficacy of fostmatinib on thrombocytopenia in MF patients is unknown
Secondary		
To evaluate the safety and tolerability of single agent fostamatinib in patients with MF and thrombocytopenia	Incidence, severity, frequency, and outcomes of AEs and SAEs as defined by CTCAE v5.0 criteria, AEIs, laboratory abnormalities, and number of patients who permanently discontinue fostamatinib due to fostamatinib-related AEs, number of patients who require treatment interruptions due to fostamatinib-related AEs	The safety and tolerability of fostamatinib in MF patients is unknown.
To evaluate spleen response in patients with MF receiving fostamatinib	Spleen response as detailed in Section 11.4 at week 12 and end of fostamatinib monotherapy treatment, mean reduction in spleen volume as determined by ultrasound at week 12 and end of fostamatinib monotherapy treatment	The efficacy of fostamatinib on reducing spleen size in MF patients is unknown
To evaluate anemia response in patients with MF receiving fostamatinib	Anemia response as detailed in Section 11.2.1	The impact of fostamatinib on anemia in MF patients is unknown

To evaluate the impact of fostamatinib on constitutional symptoms in patients with MF	Constitutional symptoms as detailed in Section 11.3 at week 12 and end of fostamatinib monotherapy treatment	The efficacy of fostamatinib on improving symptoms in MF patients is unknown
To evaluate the impact of fostamatinib on transfusion requirements	Number of patients who achieve platelet and RBC transfusion independence who were previously requiring transfusions	The impact of fostamatinib on transfusion burden in MF patients is unknown
To evaluate the impact of fostamatinib on marrow fibrosis	Change in marrow fibrosis per WHO grading on bone marrow biopsy performed at the end of fostamatinib monotherapy	The impact of fostamatinib on marrow fibrosis is unknown

2.2 Part B Objectives and Endpoints

Objectives	**Endpoints**	**Justification for Endpoints**
Primary		
To evaluate the safety and tolerability of the combination of fostamatinib and ruxolitinib in MF patients	Incidence, severity, frequency, and outcomes of AEs and SAEs as defined by CTCAE v5.0 criteria and AEs of interest (AEIs) as defined in section 5.5	The safety of this combination therapy in MF patients is not known.
Secondary		
To evaluate the spleen response in patients with MF receiving fostamatinib in combination with ruxolitinib	Spleen response as detailed in Section 11.4 after 12 weeks of combination therapy, mean reduction in spleen volume as determined by ultrasound after 12 weeks of combination therapy and at the end of treatment	The efficacy of fostamatinib in combination with a JAK inhibitor on reducing spleen size in patients with MF is unknown
To evaluate the impact of fostamatinib in combination with ruxolitinib on constitutional symptoms in patients with MF	Constitutional symptoms as detailed in Section 11.3 after 12 weeks of combination therapy and at the end of treatment	The efficacy of fostamatinib in combination with a JAK inhibitor on symptoms in MF is unknown
Evaluate the ability of fostamatinib to enable sustained treatment with ruxolitinib	Duration of uninterrupted JAK inhibitor (ruxolitinib) therapy	The ability of fostamatinib to maintain an adequate platelet count for patients

		to remain on JAK inhibitor therapy is unknown
To evaluate the impact of fostamatinib and ruxolitinib on marrow fibrosis	Change in marrow fibrosis per WHO grading on bone marrow biopsy performed at the end of fostamatinib and ruxolitinib therapy	The impact of fostamatinib and ruxolitinib combination therapy on marrow fibrosis is unknown

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Confirmed diagnosis of primary myelofibrosis or post-polycythemia vera/essential thrombocythemia myelofibrosis classified as high risk, intermediate-2 risk, or intermediate 1 risk by IPSS.

2. Severe thrombocytopenia defined as platelet count < 50,000/microL (confirmed on at least two measurements over an 8-week period prior to date of consent).

3. At least 18 years of age.

4. ECOG performance status ≤ 2 (see Appendix A)

5. Able to swallow pills

6. Adequate bone marrow and organ function as defined below:
   a. ANC ≥ 1000/microL
   b. Peripheral blood blasts ≤ 10%
   c. Albumin > 2.7 g/dL
   d. Total bilirubin ≤ 1.5 x IULN; patients with Gilbert's syndrome may enroll if direct bilirubin ≤ 1.5 x IULN
   e. AST(SGOT)/ALT(SGPT) ≤ 1.5 x IULN
   f. Creatinine clearance > 30 mL/min by Cockcroft-Gault

7. Female subjects must be either post-menopausal for at least 1 year or surgically sterile; or, if of childbearing potential, must not be pregnant or lactating and must agree to use a highly effective method of birth control throughout the duration of the trial and for 30 days following the last dose. Acceptable methods of birth control are defined as: hormonal contraception (pill, injection or implant) used consistently for at least 30 days prior to screening, an intrauterine device (IUD), or intrauterine hormone-releasing system (IUS), or true abstinence (i.e. abstinence is in line with the preferred and usual lifestyle of the subject.). Male subjects do not need to use contraception for fostamatinib because human studies showed minimal R406 in sperm.

8. Ability to understand and willingness to sign an IRB approved written informed

consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. History of allogeneic stem cell transplant.

2. Any solid tumor or hematologic malignancy (other than myelofibrosis) requiring active treatment at the time of study entry

3. Currently receiving any other investigational agents.

4. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to fostamatinib, ruxolitinib, or other agents used in the study.

5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

6. Subject has uncontrolled or poorly controlled hypertension, defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg, whether or not the subject is receiving anti-hypertensive treatment.

7. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative pregnancy test within 14 days of study entry and prior to the first dose of fostamatinib.

8. Known positive status for human immunodeficiency virus (HIV)

9. Chronic, active, or acute viral hepatitis A, B, or C infection, or hepatitis B or C carrier.

10. Treatment with strong CYP3A inhibitors or inducers within 14 days before the first dose of study drug. Strong CYP3A inhibitors and CYP3A inducers are not permitted during the study.

11. Ongoing gastrointestinal medical condition such as Crohn's disease, inflammatory bowel disease, or chronic diarrhea that is not well controlled and could interfere with absorption of oral medication or be exacerbated by study medication

12. Known hepatic cirrhosis or severe pre-existing hepatic impairment.

13. Uncontrolled coagulopathy or bleeding disorder.

14. Female patients who intend to donate eggs and male patients who intend to donate sperm during the course of this study or for 4 months after receiving the last dose of study treatment.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

4.5 Strategies for Recruitment and Retention

The study will enroll 12 patients who are over 18 years of age of all genders, races, and ethnicities. The anticipated accrual rate will be approximately 1 patient per month. This pilot study will be a single center study and participants will be screened in the outpatient clinics of the PI and sub-investigators. Potential participants will be identified by the PI or sub-investigators and approached by the study coordinator(s) for the study. Financial compensation in the form of parking vouchers or reimbursement for travel expenses (ie gas, mileage, etc.) may be provided depending on the distance the participant may live from the study site.

5.0 TREATMENT PLAN

5.1 Premedication Administration

No pre-medications are required for either fostamatinib or ruxolitinib.

5.2 Study Intervention Description

Fostamatinib is a kinase inhibitor indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia. It is considered investigational in this study.

Ruxolitinib is a kinase inhibitor indicated for the treatment of intermediate or high risk myelofibroisis, polycythemia vera, and steroid-refractory acute GVHD. Because it is being given in combination with fostamatinib, it is considered investigational in this study.

5.3 Study Intervention Administration

In Part A of the study, patients will initially receive fostamatinib single agent at a starting dose of 100 mg PO twice daily (BID) for three cycles (12 weeks). Each cycle is 28 days (4 weeks).

Patients who tolerate single agent fostamatinib and achieve a sustained platelet count of $\geq$ 50,000/microL on at least two separate measurements taken at least two weeks apart at any point before Cycle 10 Day 1 will be eligible to proceed to Part B of the study and initiate treatment with ruxolitinib (starting dose will be determined by platelet count as per package insert).

For patients who do not achieve a sustained platelet count of $\geq$ 50,000/microL following the first cycle (4 weeks) of fostamatinib 100 mg BID and no AEIs (see Section 5.5) are reported, then the dose of fostamatinib may be increased to 150 mg BID and continued for subsequent cycles. If a platelet count of $\geq$ 50,000/microL is not achieved after three cycles of fostamatinib, but the patient is achieving clinical benefit, then the patient may continue on fostamatinib monotherapy for up to a total of 12 cycles of treatment and may continue

on to Part B of the study if they achieve a sustained platelet count of ≥ 50,000/microL by Cycle 10 Day 1. If the patient is not achieving clinical benefit or has evidence of disease progression, then the patient will be taken off study.

For Part B of the study, patients will continue on treatment with fostamatinib for up to an additional nine cycles (36 weeks) to complete a total treatment duration of 48 weeks. Ruxolitinib will be initiated in combination with fostamatinib at the start of Part unless the patient is experiencing progressive MF symptoms and is eligible to initiate ruxolitinib, in which case ruxolitinib may be initiated sooner at the discretion of the PI. If the platelet count decreases to < 50,000/microL following initiation of ruxolitinib, then the dose of fostamatinib may be increased to 150 mg BID if the patient is on the 100 mg BID dose.

5.3.1 Dosing of Fostamatinib

Fostamatinib is an oral drug which will be given at a starting dose of 100 mg BID each day of a 28-day cycle. The dose of fostamatinib can be increased to 150 mg BID after Cycle 1 if the platelet count remains < 50,000/microL. Fostamatinib should be taken at approximately the same times each day, with or without food. In case of a missed dose, patients should be instructed to resume dosing at the next scheduled dose. Patients will be instructed to bring all unused drug and their medication diary (Appendix B) to each study visit for assessment of compliance.

5.3.2 Dosing of Ruxolitinib

Ruxolitinib is an oral drug which will be taken twice daily each day of a 28-day cycle. The starting dose of ruxolitinib given will depend on the patient's baseline platelet count. If platelets are > 200,000/microL, patients should take 20 mg BID. If platelets are between 100,000/microL and 200,000/microL, patients should take 15 mg BID. If platelets are between 50,000/microL and 100,000/microL, patients should take 5 mg BID. Ruxolitinib should be taken at approximately the same times each day, with or without food. In case of a missed dose, patients should be instructed to resume dosing at the next scheduled dose. Patients will be instructed to bring their medication diary (Appendix C) to each study visit for assessment of compliance.

5.4 Toxicity Monitoring (Stopping Rules)

A Bayesian sequential monitoring rule will be used to protect patients from excessive toxicities (see Section12.2 for technique details), and the table below shows the boundaries of early stopping rule. That is, an early stopping of the study due to excessive toxicities will be recommended if we observe 3 patients who experienced AEs of interest (as defined in Section 5.5) out of the first 5 patients or 4 patients who experience AEs of interest out of first 9 patients.

# Patients treated	1	2	3	4	5	6	7	8	9	10	11	12
Stop if the # AEIs ≥	N/A	N/A	N/A	N/A	3	3	3	3	4	4	4	4

5.5 Adverse Events of Interest (AEIs)

Adverse events of interest (AEIs) are defined as clinically relevant grade 3 or 4 adverse events considered possibly, probably, or definitely related to either fostamatinib or ruxolitinib as defined by CTCAE v5.0 criteria and are not related to the underlying disease.

5.6 Definitions of Evaluability

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients are evaluable for disease response unless they discontinue treatment prior to completion of Cycle 1 and have not had any disease assessment.

5.7 Concomitant Therapy and Supportive Care Guidelines

General supportive care measures, including blood and platelet transfusions, antiemetics, administration of granulocyte colony-stimulating growth factors, corticosteroids, and use of antibiotics and antivirals are permitted at the discretion of the treating physician.

It is recommended that nausea, vomiting, diarrhea, or blood pressure elevation be medically managed according to the investigator's discretion.

5.8 Prohibited Concurrent Therapy

Patients should not receive treatment with any potent CYP3A4 inhibitors for one week prior to the start of and for the duration of study treatment.

Other chemotherapeutic or investigational agents are not permitted while the patient is receiving active treatment on protocol.

The use of thrombopoietin (TPO) stimulating agents are not permitted while the patient is receiving active treatment on protocol.

Patients cannot receive radiotherapy within 14 days prior to study enrollment or while on study.

5.9 Women of Childbearing Potential

Female subjects must be either post-menopausal for at least 1 year or surgically sterile; or,

if of childbearing potential, must not be pregnant or lactating and must agree to use a highly effective method of birth control throughout the duration of the trial and for 30 days following the last dose. Acceptable methods of birth control are defined as: hormonal contraception (pill, injection or implant) used consistently for at least 30 days prior to screening, an intrauterine device (IUD), or intrauterine hormone-releasing system (IUS), or true abstinence (i.e. abstinence is in line with the preferred and usual lifestyle of the subject.). Male subjects do not need to use contraception for fostamatinib because human studies showed minimal R406 in sperm.

If a patient is suspected to be pregnant, study treatment should be immediately discontinued. In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

5.10 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for up to 48 weeks or until one of the following criteria applies:

- Documented and confirmed progression of underlying myelofibrosis
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- Dose interruptions due to fostamatinib-related AE lasting > 4 weeks (dose interruptions due to other reasons would not warrant permanent discontinuation)
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar.

5.11 Duration of Follow-up

Following the end of treatment, patients will be followed every 6 months for up to 2 years or until the patient is lost to follow up or death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization

of the adverse event. Decisions regarding future therapy for both responding and refractory patients will be made at the discretion of the treating physician.

5.12 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study team.

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

- The study team will attempt to contact the participant and reschedule the missed visit within 14 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

Besides the modifications described below, other dose holds and modifications will be made at the discretion of the PI.

6.1 Dose Modifications for Fostamatinib

For each individual patient, if no AEIs are observed following Cycle 1 of fostamatinib at the starting dose of 100 mg BID, but their platelet count remains < 50,000/microL, then the dose of fostamatinib may be increased to 150 mg BID for all subsequent cycles in the absence of toxicity. Additionally, for each patient whose platelet count improves to ≥50,000/microL on 100 mg BID of fostamatinib, but then decreases to <50,000/microL after starting ruxolitinib (for at least two platelet measurements at least 2 weeks apart), the dose of fostamatinib may be increased to 150 mg BID for all subsequent cycles.
Dose reductions for fostamatinib will be performed as per the US package insert.

For dose interruptions due to a fostamatinib related AE lasting > 4 weeks, treatment will be permanently discontinued, and the patient will be taken off study.

Recommended Dose Modifications and Management for Specific Adverse Reactions

Adverse Reaction	Recommended Action
Hypertension	
Stage 1: systolic between 130-139 or diastolic between 80-89 mmHg	• Initiate or increase dosage of antihypertensive medication for patients with increased cardiovascular risk, and adjust as needed until BP is controlled. • If the BP target is not met after 8 weeks, reduce fostamatinib to next lower daily dose.
Stage 2: systolic at least 140 or diastolic at least 90 mmHg	• Initiate or increase dosage of antihypertensive medication, and adjust as needed until BP is controlled. • If BP remains 140/90 mmHg or higher for more than 8 weeks, reduce fostamatinib to next lower daily dose. • If BP remains 160/100 mmHg or higher for more than 4 weeks despite aggressive antihypertensive therapy, interrupt or discontinue fostamatinib.
Hypertensive crisis: systolic over 180 and/or diastolic over 120 mmHg	• Interrupt or discontinue fostamatinib. • Initiate or increase dosage of antihypertensive medication, and adjust as needed until BP is controlled. If BP returns to less than the target BP, resume fostamatinib at same daily dose. • If repeat BP is 160/100 mmHg or higher for more than 4 weeks despite aggressive antihypertensive treatment, discontinue fostamatinib.
Hepatotoxicity	
AST/ALT is 3 x ULN or higher and less than 5 x ULN	If patient is symptomatic (e.g., nausea, vomiting, abdominal pain): • Interrupt fostamatinib. • Recheck LFTs every 72 hours until ALT/AST values are no longer elevated (below 1.5 x ULN) and total BL remains less than 2 x ULN. • Resume fostamatinib at next lower daily dose.
	If patient is asymptomatic: • Recheck LFTs every 72 hours until ALT/AST are below 1.5 x ULN) and total BL remains less than 2 x ULN. • Consider interruption or dose reduction of fostamatinib if ALT/AST and TBL remain in this category (AST/ALT is 3 to 5 x ULN; and total BL remains less than 2 x ULN) • If interrupted, resume fostamatinib at next lower daily dose) when ALT/AST are no longer elevated (below 1.5 x ULN) and total BL remains less than 2 x ULN.

AST/ALT is 5 x ULN or higher and total BL is less than 2 x ULN	• Interrupt fostamatinib. • Recheck LFTs every 72 hours: • If AST and ALT decrease, recheck until ALT and AST are no longer elevated (below 1.5 x ULN) and total BL remains less than 2 x ULN; resume fostamatinib at next lower daily dose. • If AST/ALT persist at 5 x ULN or higher for 2 weeks or more, discontinue fostamatinib.
AST/ALT is 3 x ULN or higher and total BL is greater than 2 x ULN	• Discontinue fostamatinib.
Elevated unconjugated (indirect) BL in absence of other LFT abnormalities	• Continue fostamatinib with frequent monitoring since isolated increase in unconjugated (indirect) BL may be due to UGT1A1 inhibition
Diarrhea	
Diarrhea	• Manage diarrhea using supportive measures (e.g., dietary changes, hydration and/or antidiarrheal medication) early after the onset until symptom(s) have resolved. • If symptom(s) become severe (Grade 3 or above), temporarily interrupt fostamatinib. • If diarrhea improves to mild (Grade 1), resume fostamatinib at the next lower daily dose.
Neutropenia	
Neutropenia	• If absolute neutrophil count decreases (ANC less than 1.0 x 10^9/L) and remains low after 72 hours, temporarily interrupt fostamatinib until resolved (ANC greater than 1.5 x 10^9/L). • Resume fostamatinib at the next lower daily dose.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BL = bilirubin; ULN = upper limit of normal; LFT = liver function tests (AST, ALT, total BL with fractionation if elevated, alkaline phosphatase); AST/ALT = AST or ALT

6.2 Dose Modifications for Ruxolitinib

Ruxolitinib dose modifications will be performed as per standard of care. Refer to the package insert for guidance.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix D for definitions and Appendix E for a grid of reporting timelines.

Adverse events will be tracked from start of treatment through 30 days after last day of study treatment. All adverse events must be recorded on the toxicity tracking case report form (CRF)

with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF

Refer to the data submission schedule in Section 9 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 Sponsor-Investigator Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Sponsor-Investigator (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.1.3 Reporting to Rigel Pharmaceuticals

7.1.3.1 Expedited Reporting Requirements for Serious Adverse Events
An investigator should report all SAEs as soon as possible after his/her awareness of the event via a MedWatch form to Rigel's authorized safety representative.

The MedWatch form should be sent to the following email or fax:

Email: clinsafety@rigel.com
Fax: +1.650.745.0971

The site may contact Rigel Drug Safety at the above fax/e-mail with questions regarding reporting of SAEs.

7.1.3.2 Pregnancy

Although pregnancy itself is not regarded as an AE, the initial notification and outcome of any pregnancy that occurs during the study must be documented. The pregnancy in a female study participant and the pregnancy outcome must be reported to Rigel Drug Safety within 24 hours of awareness. Partners that become pregnant by a male subject do not need to report pregnancy.

Prior to screening, females of childbearing potential must agree in the ICF to take appropriate measures to avoid pregnancy at all times during the study, commencing from the time of consent to 30 days after the last dose of study drug, and, if pregnancy occurs, they must agree to report the pregnancy and cooperate with the investigator as set forth below.

Should a pregnancy occur, the female study participant must immediately inform the investigator and must immediately discontinue study drug. The investigator should counsel the study participant on any risks of continuing the pregnancy and any possible effects on the fetus in view of the subject's participation in the study. The study participant must agree to follow-up by the investigator regarding the outcome of any pregnancy that occurs during the study. Outcome is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Any congenital anomaly/birth defect noted in the infant must be reported as an SAE.

7.1.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Sponsor-Investigator to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix D for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix D) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix D) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
  - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
  - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug

    - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 8.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

8.0 PHARMACEUTICAL INFORMATION

8.1 Fostamatinib

8.1.1 Fostamatinib Description

Fostamatinib is a tyrosine kinase inhibitor. Fostamatinib is formulated with the disodium hexahydrate salt of fostamatinib, a phosphate prodrug that converts to its pharmacologically active metabolite, R406, in vivo.

The chemical name for fostamatinib disodium hexahydrate is disodium (6-[[5-fluoro-2-(3,4,5trimethoxyanilino) pyrimidin-4-yl]amino]-2,2-dimethyl-3-oxo-pyrido[3,2-b][1,4]oxazin-4-yl)methylphosphate hexahydrate. The molecular formula is $C_{23}H_{24}FN_6Na_2O_9P \cdot 6H_2O$, and the molecular weight is 732.52.

8.1.2 Clinical Pharmacology

Fostamatinib is a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase (SYK). The major metabolite of fostamatinib, R406, inhibits signal transduction of Fc-activating receptors and B-cell receptor. The fostamatinib metabolite R406 reduces antibody-mediated destruction of platelets.

8.1.3 Pharmacokinetics and Drug Metabolism

Fostamatinib is a prodrug that is converted in the gut to the major active metabolite, R406. Mean (± standard deviation [SD]) exposure estimates of R406 are 550 (± 270) ng/mL for Cmax and 7080 (± 2670) ng•h/mL for AUC. R406 exposure is approximately dose proportional up to 200 mg twice daily (1.3 times the 150 mg dosage). R406 accumulates approximately 2-to 3-fold upon twice daily dosing at 100–160 mg (0.67 to 1.06 times the 150 mg dosage). R406 is extensively metabolized, primarily through pathways of CYP450-mediated oxidation (by CYP3A4) and glucuronidation (by UDP glucuronosyltransferase [UGT]1A9). R406 is the predominant moiety in the systemic circulation, and there was minimal exposure to any R406 metabolites. Refer to the prescribing information of TAVALISSE™ (fostamatinib) for details on drug-drug interaction potential.

8.1.4 Supplier

Fostamatinib will be supplied by Rigel Pharmaceuticals.

8.1.5 Dosage Form and Preparation

Fostamatinib is available as a 100 mg or 150 mg tablet.

8.1.6 Storage and Stability

Store at room temperature, 20ºC to 25ºC (68ºF to 77ºF); excursions permitted between 15ºC to 30ºC (59ºF to 86ºF). Do not remove desiccants.

8.1.7 Administration

Please refer to Section 6.3.

8.2 Ruxolitinib

8.2.1 Ruxolitinib Description

Ruxolitinib phosphate is a kinase inhibitor with the chemical name (R)-3-(4-(7H-pyrrolo[2,3d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate and a molecular weight of 404.36.

8.2.2 Clinical Pharmacology

Ruxolitinib, a kinase inhibitor, inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation and subsequent localization of STATs to the nucleus leading to modulation of gene expression.

MF and PV are myeloproliferative neoplasms (MPN) known to be associated with dysregulated JAK1 and JAK2 signaling. In a mouse model of JAK2V617F-positive MPN, oral administration of ruxolitinib prevented splenomegaly, preferentially decreased JAK2V617F mutant cells in the spleen and decreased circulating inflammatory cytokines (e.g., TNF-α, IL-6).

JAK-STAT signaling pathways play a role in regulating the development, proliferation, and activation of several immune cell types important for GVHD pathogenesis. In a mouse model of acute GVHD, oral administration of ruxolitinib was associated with decreased expression of inflammatory cytokines in colon homogenates and reduced immune-cell infiltration in the colon.

8.2.3 Pharmacokinetics and Drug Metabolism

Mean ruxolitinib maximal plasma concentration (Cmax) and AUC increased proportionally over a single dose range of 5 mg to 200 mg. Mean ruxolitinib Cmax ranged from 205 nM to 7100 nM and AUC ranged from 862 nM*hr to 30700 nM*hr over a single dose range of 5 mg to 200 mg.

Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C9. Refer to

the prescribing information of JAKAFI™ (ruxolitinib) for details on drug-drug interaction potential.

8.2.4 Supplier

Ruxolitinib is commercially available.

8.2.5 Dosage Form and Preparation

Ruxolitinib is available at 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg tablets.

8.2.6 Storage and Stability

Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)

8.2.7 Administration

Refer to Section 6.3.

9.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to starting treatment
CBC Form	Baseline, C1D1, C1D8, C1D15, C1D22, Weekly the first cycle of combination therapy and Day 1 & Day 15 of all other cycles
Treatment Form	Every cycle
Toxicity Form Transfusion Form	Continuous
Treatment Summary Form	Completion of treatment
Follow Up Form	Every 6 months for 2 years
Progression Form	Time of progression
Death Form	Time of death
Spleen Response Form	Baseline, end of Part A treatment, Cycle 4 Day 1, after 3 cycles in Part B, end of Part B treatment
MPN TSS Form	Day 1 of each cycle
MedWatch Form	See Section 8.0 for reporting requirements

9.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 8.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

10.0 MEASUREMENT OF EFFECT

10.1 IWG-MRT Response Criteria

Objective response is defined as CR (complete remission/response) + PR (partial remission/response) + CI (clinical improvement). Responses are defined by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) consensus [59]:

Complete Response (CR):

- Bone marrow: Age-adjusted normocellularity; <5% blasts; ≤ grade 1 MF
  AND
- Peripheral blood: Hemoglobin ≥ 10 g/dL; neutrophil count ≥ 1 x 10^9/L; platelet count ≥ 100 x 10^9/L and < UNL; <2% immature myeloid cells
  AND
- Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of extramedullary hematopoiesis (EMH)

Partial Response (PR):

- Peripheral blood: Hemoglobin ≥ 10 g/dL; neutrophil count ≥ 1 x 10^9/L; platelet count ≥ 100 x 10^9/L and < UNL; <2% immature myeloid cells
  AND
- Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of extramedullary hematopoiesis (EMH)

  OR
- Bone marrow: Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF
  AND
- Peripheral blood: Hemoglobin ≥ 8.5but < 10 g/dL and <UNL; neutrophil count ≥ 1 x 10^9/L and <UNL; platelet count ≥ 50 x 10^9/L, but < 100 x 10^9/L and <UNL; <2% immature myeloid cells
  AND
- Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH

Clinical Improvement (CI):

- The achievement of anemia (10.2.1), spleen (10.4) or symptoms response (10.3) without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia

Stable Disease (SD):
- Not meeting the definition of CR, PR, CI or PD

Progressive Disease (PD):
- Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM
  OR
- A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm
  OR
- A ≥ 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm
  OR
- Leukemic transformation confirmed by a bone marrow blast count of ≥ 20%
  OR
- A peripheral blood blast content of ≥ 20% with an absolute blast count of ≥ 1 x 10^9/L for at least 2 weeks

10.2 Hematologic Response

10.2.1 Anemia Response

Anemia response is only applicable for patients with a baseline hemoglobin level less than 10 g/dL for 8 weeks or more, and requires:
- ≥ 2 g/dL increase in hemoglobin level
  OR
- becoming transfusion-independent (no RBC transfusions in past 1 month)

10.2.2 Platelet Response

Platelet response is only applicable for patients with a baseline platelet count of less than 50 x 10^9/L for 8 weeks or more, and requires:
- An absolute platelet count of at least 50 x 10^9/L on two separate measurements at least 2 weeks apart

10.3 Symptoms Response

A ≥ 50% reduction in the myeloproliferative neoplasm symptom assessment total symptom score (see Appendix F)

10.4 Spleen Response

- A baseline splenomegaly that is palpable at 5-10 cm below the left costal margin becomes not palpable
  OR
- A baseline splenomegaly that is palpable > 10 cm below the left costal margin decreases by ≥50%
  OR
- A baseline splenomegaly that is palpable < 5 cm below the left costal margin is not eligible for spleen response
  OR
- Ultrasound shows ≥35% spleen volume reduction (calculated)

11.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

12.0 STATISTICAL CONSIDERATIONS

12.1 Hypothesis

Our primary hypothesis is that fostamatinib alone and in combination with ruxolitinib will provide a safe and tolerable treatment in patients with myelofibrosis with severe thrombocytopenia (platelet < 50K/microL). Treatment with fostamatinib will improve thrombocytopenia in patients with myelofibrosis with severe thrombocytopenia (platelet < 50K/microL) and allow them to initiate treatment with ruxolitinib.

12.2 Study Design

This is a hypothesis generating limited pilot phase II study evaluating the efficacy and safety of the use of fostamatinib as a single agent and when given in combination with ruxolitinib in patients with intermediate to high risk myelofibrosis. Previous studies with fostamatinib and ruxolitinib monotherapy indicate that toxicity will be low grade and reversible with standard treatment.

This study consists of two parts. For Part A, patients with MF and severe thrombocytopenia will initially receive 12 weeks of single agent fostamatinib and the primary endpoint will be platelet response (defined as platelet count of ≥ 50K/microL as two separate measurements at least two weeks apart) at the end of the 12 week treatment period. Patients who achieve a sustained platelet response will then be eligible to proceed to Part B of the study and begin treatment with ruxolitinib while continuing to take fostamatinib. For Part B, patients will continue treatment with fostamatinib and ruxolitinib for up to an additional 36 weeks and the primary endpoint will be safety as assessed by NCI CTCAE v 5.0. Patients who do not have a sustained platelet response after 12 weeks of treatment but are clinically benefiting from fostamatinib may remain on Part A of the study and be eligible to enroll in Part B if they achieve a sustained platelet response prior to Day 1 Cycle 10 of treatment.

A maximum of 12 patients will be enrolled. A Bayesian sequential monitoring rule will be implemented for safety.

Safety monitoring (Part B): The stopping rule is defined as $Pr(\theta > \theta_T | data) > 0.8$, where θ denotes the proportion of AEs of interest as defined in Section 5.5 and θ_T denotes the rate of AEs of interest under the null hypotheses (i.e., 20% AEs of interest). That is, an early termination of the study due to excessive toxicities will be recommended whenever, given the accumulated observed data, there is high chance (i.e., >80% probability) for the "true" AEs of interest rate >20%. The stopping boundaries were obtained using Multc99 version 2.1, a free-download software from M.D. Anderson Cancer Center. Specifically, we assume that the parameter θ follows a prior distribution of beta (0.2, 0.8), i.e., θ with mean = 0.2 but with relatively large variability (non-informative prior). Early stopping will be recommended if we observe 3 patients who experience AEs of interest out of first 5 patients

or 4 patients who experience AEs of interest out of first 9 patients. A simulation study was also performed to assess the operating characteristics for the above stopping rule (all scenarios are based on 10,000 simulated trials). If the "true" AEs of interest rate is 10%, there will be only 4% chance to stop. In contrast, we will have 76% chance to stop if the "true" rate is 40%.

# Patients treated	1	2	3	4	5	6	7	8	9	10	11	12
Stop if the # AEIs ≥	N/A	N/A	N/A	N/A	3	3	3	3	4	4	4	4

12.3 Analysis Plan

All data analyses will be descriptive in nature. Demographic and clinical characteristics of the sample, as well as response to treatment, and loss to follow up will be summarized using descriptive statistics. Rate of AEs, overall response rate, hematologic response rate, symptom response rate, and spleen response rate will be documented with exact 95% confidence intervals.

12.4 Sample Size and Study Power

A total of 12 patients will be enrolled. As a pilot phase II study for hypothesis generating, formal power calculations to determine sample size were not performed. Based on simulation studies regarding the sample size for translational studies, however, Piantadosi recommends that a sample size of 10 to 20 patients be adequate to provide preliminary information [33]. For efficacy, for example, the probability of observing at most 1 platelet response out of 12 patients is 27% given that the true rate is 20%. However, the probability of observing at least 2 platelet responses is 98% given that the true is 40%. For safety, if the "true" AEs of interest rate is 20% or higher, there will be more than 93% chance to observe at least 1 patient with AE of interest out of 12 patients. Conversely, there is less than 2% chance to observe 3 or more patients with AE of interests if the "true" rate is 5% or less.

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: PATIENT'S MEDICATION DIARY

Today's Date: _____ Agent: fostamatinib Cycle: _____ Study ID#: _____

1. Complete one form for each month. Take _____mg (___capsules) of fostamatinib twice daily with or without food at approximately the same time each day.
2. Record the date, the number of capsules taken, and when you took them.
3. If you forgot to take your dose, do not make up that dose, but restart taking it with your next scheduled dose.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	What time was dose taken?		# of tablets taken		Comments
		AM	PM	AM	PM	
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APPENDIX C: PATIENT'S MEDICATION DIARY

Today's Date: _____ Agent: ruxolitinib Cycle: _____ Study ID#: _____

1. Complete one form for each month. Take _____mg (___capsules) of ruxolitinib twice daily with or without food at approximately the same time each day.
2. Record the date, the number of capsules taken, and when you took them.
3. If you forgot to take your dose, do not make up that dose, but restart taking it with your next scheduled dose.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment.

Day	Date	What time was dose taken?		# of tablets taken		Comments
		AM	PM	AM	PM	
1						
2						
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APPENDIX D: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE. "Serious" is a regulatory definition.

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening. (With regards to determining if an AE is serious, "life-threatening" is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the Sponsor believes that an AE meets the definition of life threatening, it will be considered life-threatening);
- Requires in-patient hospitalization or prolongation of an existing hospitalization;
- Results in persistent or significant disability/incapacity (e.g., the AE results in substantial disruption of the subject's ability to conduct normal life functions); or
- Is a congenital anomaly/birth defect;
- Is considered an important medical event (or medically significant) that may not result in any of the above outcomes but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed

Medical and scientific judgment should be exercised in deciding whether other situations, such as important medical events, should also be considered serious. Some examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Given that the investigator's perspective may be informed by having actually observed the event and Rigel is likely to have broader knowledge of the study drug and its effects to inform its evaluation of the significance of the event, if either Rigel or the investigator believes that the event is serious, the event will be considered an important medical event.

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents

including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX E: Reporting Timelines

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Rigel**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	
Serious adverse events				Report as soon as possible after awareness to Rigel.
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information	
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment		
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.			
Pregnancy				Notify Rigel within 24 hours of awareness.
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.			
Protocol exception	Approval must be obtained prior to implementing the change			
Clinically important increase in the rate of a serious suspected adverse reaction of			Report no later than 15 calendar days after it is determined that the information qualifies for reporting	

Expedited Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Rigel**
that list in the protocol or IB				
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Breach of confidentiality	Within 10 working days.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Rigel**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.	
Minor deviation	Report summary information at the time of continuing review.			
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant			

Routine Reporting Timelines				
Event	**HRPO**	**QASMC**	**FDA**	**Rigel**
	enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.			
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.			

APPENDIX F: Symptom Assessment Form

Fostamatinib + Ruxolitinib

Today's Date: _____ Visit: _____

Patient ID: _____

Myeloproliferative Neoplasm – Symptom Assessment Form
Total Symptom Score (MPN-SAF-TSS)

Rate your WORST level of fatigue during the **past 24 hours**	(absent) 0 1 2 3 4 5 6 7 8 9 10 (worst imaginable)

Circle the number that describes in the PAST WEEK, how much difficulty you have had with each of the following symptoms	
1. Filling up quickly when you eat	(absent) 0 1 2 3 4 5 6 7 8 9 10 (worst imaginable)
2. Abdominal discomfort	(absent) 0 1 2 3 4 5 6 7 8 9 10 (worst imaginable)
3. Inactivity	(absent) 0 1 2 3 4 5 6 7 8 9 10 (worst imaginable)
4. Problems with concentration	(absent) 0 1 2 3 4 5 6 7 8 9 10 (worst imaginable)
5. Night sweats	(absent) 0 1 2 3 4 5 6 7 8 9 10 (worst imaginable)
6. Itching	(absent) 0 1 2 3 4 5 6 7 8 9 10 (worst imaginable)
7. Bone pain (not joint pain or arthritis)	(absent) 0 1 2 3 4 5 6 7 8 9 10 (worst imaginable)
8. Fever (greater than 100º F)	(absent) 0 1 2 3 4 5 6 7 8 9 10 (daily)
9. Unintentional weight loss in the last 6 months	(absent) 0 1 2 3 4 5 6 7 8 9 10 (worst imaginable)

Office use only below	
Add up Total Symptom Score from questions 1-9 above	TSS =
Site Signature	