A Phase 2 Study of Fedratinib in Myelodysplastic /Myeloproliferative Neoplasms (MDS/MPNs) and Chronic Neutrophilic Leukemia (CNL)

Protocol Identifying Number: MCC 20963 /

FEDR-CL-MF-PI-13910

IND Number: 154485

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IND/IDE Sponsor: Andrew T. Kuykendall/Moffitt Cancer Center

Funded by:

Bristol-Myers Squibb (BMS)

v. 1.7

27 April 2023

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CMML	Chronic Myelomonocytic Leukemia
CMP	Clinical Metabolic Panel
CNL	Chronic Neutrophilic Leukemia
CRF	Case Report Form
CRP	C-reactive protein
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICH E6	International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance
IND	Investigational New Drug Application
IRB	Investigational Review Board
ISO	International Organization for Standardization
IWG-MRT	International Working Group – Myeloproliferative Neoplasms Research and Treatment
JAK2	Janus-associated kinase-2
LDH	Lactate Dehydrogenase
MDS/MPN	Myelodysplastic Syndrome/Myeloproliferative Neoplasm
MF	Myelofibrosis
MPN	Myeloproliferative Neoplasm
OHRP	Office for Human Research Protections
ORR	Overall Response Rate
OS	Overall Survival
PET-MF	Post-Essential Thrombocythemia Myelofibrosis
PFS	Progression Free Survival
PGIC	Patient Global Impression of Change
PI	Principal Investigator
PMF	Primary Myelofibrosis
PPV-MF	Post-Polycythemia Vera Myelofibrosis
RR	Response rate
SAE	Serious Adverse Event
SAF	Symptom Assessment Form
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SVR	Spleen volume reduction
TSS	Total Symptom Score
UP	Unanticipated Problem

US	United States

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Patients (45 CFR Part 46). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed of their obligation to meet the above commitments.

Principal Investigator: Andrew T. Kuykendall
Print/Type Name

Signed: _____ Date: _____

STUDY SUMMARY

Title: A Phase 2 Study of Fedratinib in Myelodysplastic /Myeloproliferative Neoplasms (MDS/MPNs) and Chronic Neutrophilic Leukemia (CNL)

Objectives:

Primary Objective:

1.) To evaluate the efficacy of fedratinib in patients with MDS/MPNs and CNL

Important Secondary Objectives:

1.) To evaluate the safety and tolerability of fedratinib in MDS/MPNs and CNL.
2.) To evaluate the effect of fedratinib in MDS/MPNs and CNL on patient-reported outcomes.

Endpoint

Primary Efficacy Endpoint

1.) Proportion of patients achieving a clinical response from baseline to week 24 as defined as complete remission (CR), partial remission (PR), or clinical benefit (CB) per Modified MDS/MPN IWG Proposed Response Criteria[1]

Safety and Tolerability Endpoints

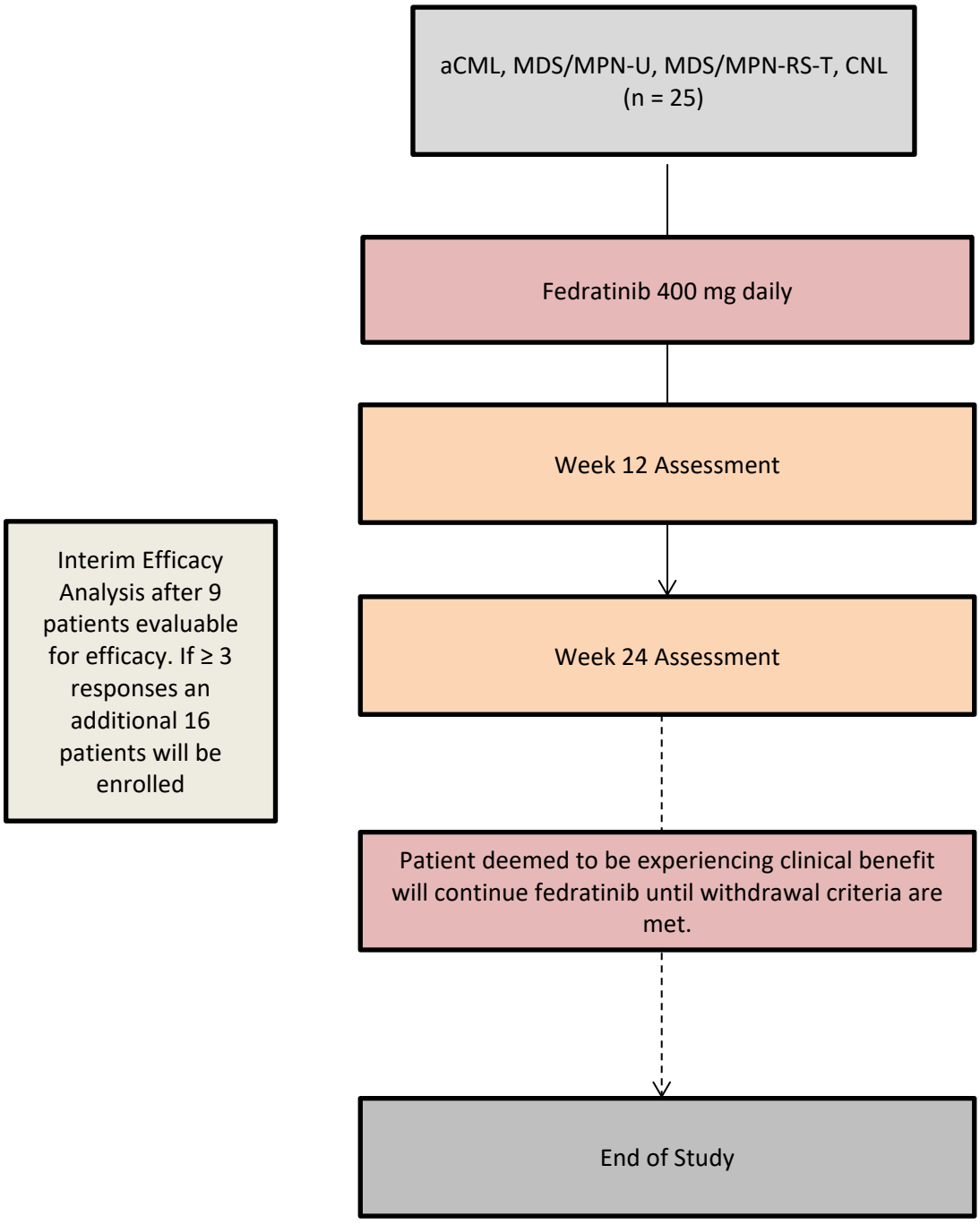
1.) Frequency, duration, and severity of adverse events (AE) will be determined by performing physical exams, and evaluating changes in vital signs, serum chemistry, hematology and urinalysis results using CTCAE version 5.0.
2.) Proportion of patients experiencing grade ≥ 3 AE as defined by CTCAE v.5.0

Important Secondary Efficacy Endpoints:

a. Proportion of patients achieving spleen response at week 12 in patients with baseline splenomegaly.
b. Proportion of patients achieving spleen response at week 24 in patients with baseline splenomegaly.
c. Proportion of patients who have a 50% reduction in MPN-SAF TSS from baseline to week 12 in patients with baseline TSS ≥ 10
d. Proportion of patients who have a 50% reduction in MPN-SAF TSS from baseline to week 24 in patients with baseline TSS ≥ 10
e. Change in TSS from baseline to week 12 in patients with baseline TSS ≥ 10
f. Change in TSS from baseline to week 24 in patients with baseline TSS ≥ 10
g. Change in TSS from baseline to time of best response in patients with baseline TSS ≥ 10
h. Patient's global impression of change (PGIC) at week 12
i. PGIC at week 24

Sample Size:	Total Patient Population: 25
Population:	Patients ≥ 18 years old with MDS/MPNs or CNL.
Phase:	2
Number of Sites enrolling:	4
Description of Study Agent:	Fedratinib 400 mg PO daily
Study Duration:	36 months
Participant Duration:	24 months

SCHEMATIC OF STUDY DESIGN



1 KEY ROLES

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

Disease Background

Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPNs) and chronic neutrophilic leukemia (CNL) are heterogeneous myeloid malignancies that are characterized by proliferative features, bone marrow dysfunction, complex molecular features, and poor outcomes.[2] Clinically and genetically, these diseases have significant overlap and are better viewed as a continuum of disease rather than distinct disease entities.[2] Treatment is typically symptom-directed and based on extrapolation from other, related disease entities. Therapeutic options have traditionally included cytoreductive agents such as hydroxyurea and hypomethylating agents such as azacitidine and decitabine.[3-6] With the exception of azacitidine and decitabine for CMML, there are currently no FDA-approved therapies for these indications. Allogeneic hematopoietic cell transplant (AHCT) offers a curative option for some patients, but the majority of patients are not eligible for this procedure due to age, comorbidities, or lack of a suitable donor.[7-13] Clinical trials represent a preferred option, but these diagnoses are often excluded from clinical trials that specifically enroll myelodysplastic syndrome (MDS) or MPN patients.[14]

Upregulation of the Janus kinase (JAK)/Signal transducer and activator of transcription (STAT) pathway is a hallmark of MPNs. This results in cell proliferation, inhibition of cell death and clonal expansion of myeloproliferative malignant cells.[15] JAK2 inhibitors that downregulate the JAK/STAT pathway can be expected to reduce cell proliferation and induce malignant cell killing in MPN patients. To that end, JAK2 inhibitors have been shown to improve disease-related symptoms and splenomegaly in patients with MF.[16-19]

Preclinical work has shown that MDS/MPNs feature GM-CSF hypersensitivity that can be abrogated with JAK

inhibition.[20] Additionally, driver mutations involving the JAK/STAT pathway are frequently present in MDS/MPNs and CNL.[2] Several small studies assessing JAK inhibition in MDS/MPNs with ruxolitinib have shown activity in this setting.[21-23]

Study Agent Background

Fedratinib, an oral kinase inhibitor with activity against wild type and mutationally activated Janus Associated Kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3), was recently approved in the United States and is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF). The registration of fedratinib was supported by data from Study EFC12153 (JAKARTA), a randomized, placebo-controlled, Phase 3 study in patients with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF with splenomegaly.

JAKARTA met its primary endpoint, with 36.5% of patients in the 400 mg fedratinib arm compared with 1.0% of patients in the placebo arm achieving ≥ 35% SVR at the end of cycle 6 confirmed 4 weeks later ($p < 0.0001$). When response was assessed at the end of cycle 6, as per IWG MRT criteria, 46.9% of patients treated with fedratinib 400 mg achieved ≥ 35% spleen volume reduction (SVR); the rate remained at 1% for patients in the placebo arm ($p < 0.0001$). Kaplan-Meier estimate for median duration of spleen response was 18.2 months for patients in the fedratinib 400 mg arm and suggest durable response. The study also met its key secondary endpoint by demonstrating clinically meaningful and statistically significant superiority of fedratinib 400 mg over placebo for symptom response rate (RR). Symptom RR is defined as ≥ 50% reduction in total symptoms score (TSS) and was 40.4% in the fedratinib 400 mg arm and 8.6% in the placebo arm; the difference was statistically significant ($p < 0.0001$). Further, reductions in all individual symptoms from the modified MF-SAF contributed to the improvement observed in patients treated with fedratinib.

Based on these data, the author believes there is rationale for further study of fedratinib in MDS/MPNs and CNL.

2.2 RATIONALE

MDS/MPNs and CNL comprise a group of molecular complex, heterogenous, myeloid malignancies that have limited treatment options and poor prognoses. Patients frequently exhibit proliferative features of leukocytosis, splenomegaly, and constitutional symptoms that negatively impact quality of life. Moreover, these diseases frequently progress to acute myeloid leukemia and overall survival is estimated between 1-3 years.[24-26] AHCT offers the only curative approach, but is associated with significant morbidity and mortality and most patients are not eligible due to comorbidities, functional status or lack of a suitable donor.

JAK/STAT inhibition offers a promising therapeutic approach for patients with MDS/MPNs and CNL. Preclinical data in MDS/MPNs have shown these cells to exhibit GM-CSF hypersensitivity that signals through the JAK/STAT pathway and can be abrogated by JAK2 inhibition.[20] Moreover, many of these patients harbor driver mutations that signal though the JAK/STAT pathway.[2] Small studies using the JAK1/2 inhibitor ruxolitinib in CMML, aCML and CNL have demonstrated promising activity, and large studies using ruxolitinib and fedratinib in MF have led to regulatory approval based on the ability for these agents to improve disease-related symptoms and reduce spleen size.[16-19,22,27]

Fedratinib is a selective JAK2 inhibitor with a unique kinase inhibition profile. In addition to inhibition JAK2 in its active and mutated form, fedratinib has activity against FLT3 – a protein implicated in proliferative myeloid malignancies. Fedratinib showed significant activity in MF patients who were intolerant or resistant to ruxolitinib – a group of patients known to have molecularly complex disease and extremely poor outcomes.[17,28,29]

Based on this data, we believe that fedratinib will have significant activity in MDS/MPNs and CNL. To further investigate this, we are proposing an open-label, phase 2 study to evaluate the safety and efficacy of fedratinib in this setting. Fedratinib will be given orally at 400 mg daily which is the recommended dose based on its label for patients with higher-risk MF.

Patients with a diagnosis of MDS/MPN-U, aCML, MDS-MPN-RS-T, and CNL will be enrolled. A modified Simon's minimax 2-stage approach will be used, wherein an interim analysis will be performed after nine patients are evaluable for response to assess for futility. The primary endpoint of the study will be the proportion of patients achieving an objective clinical response at week 24. This endpoint is consistent with typical endpoints for early phase trials in MPN and MDS/MPN and the timeframe is consistent with that which has been utilized in prior studies of JAK inhibitors.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

According to the US fedratinib package insert, fedratinib has been used to treat 608 patients with either MPNs or solid tumors. The safety profile of the drug is consistent across studies with the most common adverse events (AEs) being hematologic and gastrointestinal (GI). The most common hematologic AEs are anemia and thrombocytopenia. These events can be managed by dose modification, including dose interruption and other supportive treatments. The most common GI events are diarrhea, nausea, and vomiting. Gastrointestinal events are generally Grade 1 to 2, but Grade 3 to 4 events have occurred and have led to discontinuation of treatment. These events commonly occur at the highest frequency in the first two cycles. Prophylactic anti-emetic therapy (e.g., 5-HT3 receptor antagonists) during fedratinib treatment should be considered. Diarrhea should be treated with anti-diarrheal medications promptly at the first onset of symptoms. Common laboratory findings include increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased amylase, increased lipase, and creatinine increased. These events are primarily asymptomatic and Grade 1 to 2 in severity. Recommendations for monitoring and dose modifications are included in the protocol.

Serious and fatal encephalopathy, including Wernicke's, was reported in patients taking fedratinib. Serious cases were reported in 1.3% (8/608) of patients treated with fedratinib in clinical trials and 0.16% (1/608) of cases were fatal.

Seven out of the 8 patients were taking fedratinib at 500mg daily prior to the onset of neurologic findings and had predisposing factors such as malnutrition, gastrointestinal adverse events, and other risk factors that could lead to thiamine deficiency. This dose will not be assessed in the current study. Most events resolved with some residual neurological symptoms including memory loss, cognitive impairment, and dizziness. In a solid tumor study, one patient with head and neck cancer, brain metastasis, difficulty eating and weight loss had a fatal outcome.

Despite these potential risks, we believe the investigation of fedratinib in patients with MDS/MPN and CNL is worth pursuing since these diseases have poor prognoses, lack treatment options, and the preclinical and clinical evidence suggests patients have a high potential to benefit.

2.3.2 KNOWN POTENTIAL BENEFITS

Fedratinib was approved in the US in 2019 and is indicated for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF). The registration of fedratinib was supported by data from Study EFC12153 (JAKARTA), a randomized, placebo-controlled, Phase 3 study in patients with intermediate-2 or high-risk PMF, post-PV MF, or post-ET MF with splenomegaly.[16]

In this study, fedratinib was shown to produce spleen responses in 36.5% of the patients treated with a 400 mg daily dose compared to 1% of those patients in the placebo arm. Spleen response lasted for 18.2 months suggesting potential for durable responses. The study also met its key secondary endpoint by producing a symptom response (≥ 50% reduction in total symptoms score) in 40% of patients compared to only 9% of patients who achieved a symptom response on the placebo arm.

In an exploratory analysis of two phase I studies of fedratinib in MF, improvement or stabilization of bone marrow fibrosis was seen in 83% of patients at cycle 6.[30]

Based on the available data, patients treated with fedratinib have the potential to achieve reduction in spleen size, improvement in disease-related symptoms, patient-reported outcomes, and may experience stability or improvement in bone marrow fibrosis.

3 OBJECTIVES AND PURPOSE

The primary objective of this study is to evaluate the efficacy of fedratinib in patients with MDS/MPNs and CNL. Formal response assessment will be performed at week 24 using information from bone marrow biopsy, spleen imaging, hematologic laboratory values and physical exam. Responses will be determined based upon the Modified MDS/MPN IWG Proposed Response Criteria.[1]

We will also evaluate the safety and tolerability of fedratinib in patients with MDS/MPNs and CNL. Safety and tolerability will be assessed in all patients receiving at least one dose of the study drug. CTCAE version 5.0 will be used to detail the scope and severity of AEs.

Secondary objectives will be to evaluate the efficacy of fedratinib in MDS/MPNs and CNL as it pertains to spleen size and patient-reported outcomes (PRO). Patients will have spleen size assessments performed at baseline, week 12, week 24 and every 24 weeks thereafter up to 96 weeks. To evaluate PROs, patients will complete validated questionnaires that assess disease-related symptoms and their global impression of change while on the study agent.

From an exploratory state, we will further assess the efficacy of fedratinib in patients with MDS/MPN and CNL by measuring progression-free survival (PFS),overall survival (OS), and duration of response. Additional exploratory objectives will aim to correlate the presence or lack of a response with the presence and quantity of specific genetic mutations and, when feasible, with matched PDX mouse models. Serial single-cell sequencing will also be used to analyze clonal dynamics at a single-cell level in response to JAK inhibition with fedratinib.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This is an open-label,multi-center, phase 2 study of fedratinib in MDS/MPN and CNL. Approximately 25 patients will be enrolled at 4 US sites. The study will be enrolled via modified Simon's minimax 2-stage approach wherein an interim efficacy analysis will be performed after 9 patients have either completed 24 weeks of treatment or come off study treatmentto assess for futility. This will determine whether the remainder of the planned study population will be enrolled.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINT

- To estimate the response rate of fedratinib in MDS/MPN and CNL, we will measure the proportion of patients achieving a clinical response from baseline to week 24 as defined by CR, PR, or CB by Modified MDS/MPN IWG Proposed Response Criteria.[1] This is a standard endpoint to measure drug activity in phase 2 MPN trials.

4.2.2 SECONDARY ENDPOINTS

- To evaluate the safety and tolerability of fedratinib in MDS/MPNs and CNL we will:
  - Measure the frequency, duration, and severity of AEs per CTCAE v.5.0 using information from physical exams, evaluation of changes in vital signs, serum chemistry, and hematology.
  - Determine the proportion of patients experiencing grade ≥ 3 AE as defined by CTCAE v.5.0
- To evaluate the efficacy of fedratinib on splenomegaly in MDS/MPNs and CNL we will:
  - Determine the proportion of patients who have a spleen response at week 12 as per Modified MDS/MPN IWG Proposed Response Criteria or demonstration of ≥ 35% spleen volume reduction.
  - Determine the proportion of patients who have a spleen response at week 24 as per Modified MDS/MPN IWG Proposed Response Criteria or demonstration of ≥ 35% spleen volume reduction.
- To evaluate the efficacy of fedratinib on patient-reported outcomes in MDS/MPNs and CNL we will:
  - Determine the proportion of patients who have a 50% reduction in MPN-SAF TSS from baseline to week 12 in patients with baseline TSS ≥ 10
  - Determine the proportion of patients who have a 50% reduction in MPN-SAF TSS from baseline to week 24 in patients with baseline TSS ≥ 10
  - Measure the change in TSS from baseline to week 12 in patients with baseline TSS ≥ 10
  - Measure the change in TSS from baseline to week 24 in patients with baseline TSS ≥ 10
  - Measure the change in TSS from baseline to time of best response in patients with baseline TSS ≥ 10
  - Measure patients' global impression of change (PGIC) at week 12
  - Measure PGIC at week 24

4.2.3 EXPLORATORY ENDPOINTS

- OS defined as time from first treatment to death due to any cause. OS of patients with MDS/MPNs and CNL is estimated between 1-3 years. OS is a standard criterion for assessing therapeutic benefit in clinical trials.
- PFS defined by Modified MDS/MPN IWG Proposed Criteria for Disease Progression in adult MDS/MPNs (Appendix H).[1] PFS is a standard criterion for assessing therapeutic benefit in clinical trials and closely correlates with OS.
- Response duration defined as time from initial response to disease progression or death.
- Correlation between the presence of specific genetic mutations as determined by next generation sequencing (NGS) and the presence or lack of a response.
- Correlation between the number of genetic mutations as determined by NGS and the presence or lack of a response.
- Correlation of clinical responses with responses of individually-matched patient-derived xenograft (PDX) mouse models. Each patient will have primary cells transplanted into a matched PDX mouse model that will, in turn, be dosed with fedratinib to assess whether PDX modeling correlates with clinical outcomes on an individual scale.
- Serial analysis of mutations at the single-cell level during treatment with fedratinib and correlation with clinical responses. Correlation of baseline c-myc staining on bone marrow core biopsy and change in c-myc staining on core biopsy and clinical response.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Patients must meet all of the following criteria to be eligible for study entry:

1. Patient must understand and voluntarily sign an ICF prior to any study-related assessments/ procedures being conducted
2. Be ≥ 18 years of age on day of signing informed consent.
3. Morphologically confirmed diagnosis of one of the following in accordance with WHO (2016) diagnostic criteria:
    a. Atypical Chronic Myeloid Leukemia (aCML), BCR-ABL1 negative
    b. Myelodysplastic/Myeloproliferative Neoplasm, Unclassifiable (MDS/MPN-U)
    c. Myelodysplastic Syndrome/Myeloproliferative Neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
    d. Chronic Neutrophilic Leukemia (CNL).
4. Palpable splenomegaly ≥ 5 cm below left costal margin (LCM), spleen volume ≥ 450 cc, AND/OR MPN-SAF TSS > 10.
5. Patient has an Eastern Cooperative Oncology Group (ECOG) Performance Score (PS) of 0, 1 or 2
6. Able to adhere to the study visit schedule and other protocol requirements.
7. Females of childbearing potential (FCBP) must have a negative serum pregnancy test at screening. A FCBP is considered when a sexually mature female: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months.
8. A FCBP must agree to use of two methods of highly effective contraception, be surgically sterile, or abstain from heterosexual activity for the course of the study through 30 days after the last dose of study treatment.

9. Male patients must agree to use an adequate method of contraception starting with the first dose of study therapy through 90 days after the last dose of study therapy. Men must agree to not donate sperm during study therapy and for 30 days after the last dose of study therapy.

5.2 PARTICIPANT EXCLUSION CRITERIA

Any of the following is a criterion for exclusion from the study:

1. Any of the following laboratory abnormalities:
    a. Platelets , < 35 x 10^9/L
    b. Absolute neutrophil count (ANC) < 1.0 x 10^9/L (independent of growth factor for 7 days)
    c. Creatinine clearance < 30 ml/min
    d. Serum amylase and lipase > 1.5 x ULN
    e. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5xULN,
    f. Total bilirubin > 1.5 x ULN, Patients with a total bilirubin between 1.5 –3.0 x ULN are eligible if the direct bilirubin fraction is < 25% of the total bilirubin
2. Accelerated phase or blast phase disease as defined by peripheral or bone marrow blast percentage > 10%
3. Patient is pregnant or lactating female
4. Patient is a woman of childbearing potential as previously defined in inclusion #7, unless using effective contraception while on study treatment
5. Patient is a man who is a partner with of a woman of childbearing potential, unless they agree to use effective contraception while on study treatment as previously defined in inclusion #9.
6. Patient with prior history of encephalopathy, including Wernicke's Encephalopathy (WE)
7. Patient has signs or symptoms of encephalopathy, including Wernicke's Encephalopathy (e.g. severe ataxia, ocular paralysis or cerebellar signs) in which case thiamine deficiency needs to be excluded and a brain MRI might be required to exclude possible Wernicke's encephalopathy
8. Patient has thiamine deficiency if not corrected before enrollment on the study
9. Patient with concomitant treatment with or use of pharmaceutical or herbal agents known to be moderate or strong inducers of CYP3A4 or dual CYP3A4 and CYP2C19 inhibitors. For a list of moderate or strong inhibitors or inducers of CYP3A4, see table 3-2 and 3-3 at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.
10. Patient on any chemotherapy, immunomodulatory drug therapy (e.g., lenalidomide, pomalidomide, thalidomide, interferon-alpha), ruxolitinib, anagrelide, corticosteroids >10 mg/day prednisone or equivalent. Patients may remain on hydroxyurea (e.g., hydrea) if it is being employed to control leukocytosis as long as the patient has been on a stable dose for > 14 days prior to initiation of fedratinib.
11. Prior treatment with fedratinib
12. Patient on treatment with myeloid growth (e.g. G-CSF) factor within 14 days prior to initiation of fedratinib
13. Patient on treatment with aspirin with doses > 150 mg daily.
14. Patient with diagnosis of chronic liver disease (e.g., chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis).
15. Patients with active (uncontrolled, metastatic) second malignancies are excluded.
16. Patient with uncontrolled congestive heart failure (New York Heart Association Classification 3 or 4).
17. Patient with known human immunodeficiency virus (HIV), active infectious Hepatitis B (Hep B), and/or active Hepatitis C (Hep C).

a. Patients with known HIV are eligible if the following criteria are met:
    i. Patient has CD4+ T-cell count ≥ 350 cells/µL
    ii. Patient is on established anti-retroviral therapy (ART) (with medications that are not specifically excluded due to potential interactions within this study) for at least four weeks prior to study enrollment and have an HIV viral load less than 400 copies/mL prior to enrollment.
b. Patients with a history of Hep C infection are eligible if:
    i. Pt has completed curative antiviral treatment and has hepatitis C viral load below the limit of quantification
    ii. Pt has Hep C antibody positive but Hep C RNA negative due to prior treatment or natural resolution.

18. Patient with serious active infection requiring IV anti-microbials.
19. Patient with presence of any significant gastric or other disorder that would inhibit absorption of oral medication.
20. Patient is unable to swallow capsules.
21. Patient with participation in any study of an investigational agent (drug, biologic, device) within 30 days prior to start of fedratinib.
22. Patient has any condition including the presence of laboratory abnormalities, which places the patient at unacceptable risk if he/she were to participate in the study.
23. Patient has any condition that confounds the ability to interpret data from the study.
24. Any major surgery or radiation therapy within four weeks.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment of the 25 participants for this trial will occur from new or established patients treated at one of the participating sites. Screen failure is anticipated to be less than 10%. The target accrual is expected to be reached in 12-18 months. All faculty members in the myeloid sections of participating sites will be trained on the trial design, study agents, and eligibility criteria and will be offered the opportunity to be sub-investigators. This will equip each investigator to discuss the trial with potential participants as appropriate. The trial will be listed on the websites of the participating centers for the availability of local physicians to refer patients who could be eligible for the trial.

All investigators will be made aware of the emphasis to enroll women and minorities. The design of the trial and eligibility criteria are not restrictive relative to women and minorities.

Potential participants will be assessed prior to screening for any perceived barriers related to the clinical trial process. Referrals will be made to a social worker, supportive care services, financial services, or the research nurse to address barriers prior to consent.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Patients may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur that may jeopardize participant safety. In addition, a patient may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A patient must be discontinued from the trial for any of the following reasons:

- The patient or legal representative (such as a parent or legal guardian) withdraws consent
- Unacceptable adverse events
- Dose delay lasting > 12 consecutive weeks
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the patient
- The patient has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The patient is lost to follow-up
- Administrative reasons
- Disease progression by proposed IWG response criteria for MDS/MPN[1] (Appendix H)
- Lack of response (including clinical benefit, marrow response, partial remission, complete remission) at week 24 assessment as defined by proposed IWG response criteria for MDS/MPN[1]
    a. In cases where the investigator believes a patient is clinically deriving a benefit from fedratinib despite not meeting pre-specified criteria for clinical benefit, continuation of fedratinib will need to be approved by the study PI.
- Requiring a medication/procedure on the prohibited medication/procedure list (refer to section 7.6)
- ≥ 3 dose reductions due to AE suspected to be related to study drug

The End of Treatment and Follow-up visit procedures are listed in the Schedule of Events and Section 7.3 (Visit Requirements). After the end of treatment, each patient will be followed for 30 days for adverse event monitoring. Patients who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status and toxicity up to 30 days. Follow-up rules will apply unless participant initiates a non-study cancer treatment, withdraws consent, or becomes lost to follow-up (unsuccessful attempts to contact for 3 months). After documented disease progression, each patient will be followed 104 weeks for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Every effort will be made to maintain contact with a patient who withdraws early. If the patient remains at MCC for further care, clinic visits may be tracked and the condition of the patient followed. If the patient is not continuing care at MCC, contact information will be updated at the end of treatment visit, including accurate phone numbers, and email address. The importance of the follow-up period for AEs and SAEs will be stressed to the patient.

Replacement of participants is permitted for those who fail to meet the eligibility requirements of the study.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, the IND/IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to patients
4. Plans to modify or discontinue the development of the study drug
5. Determination of futility

In the event Bristol-Myers Squibb decides to no longer supply study drug, ample notification will be provided so that appropriate adjustments to patient treatment can be made.

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

Study agent will be supplied by the manufacturer, Bristol-Myers Squibb to the Moffitt Investigational Pharmacy.

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The dosage form labeled for clinical trials is a hard gelatin capsule Reddish brown, opaque, size 0 capsule, printed with “FEDR 100 mg” in white ink for oral administration. Each capsule contains 100 mg fedratinib (equivalent to 117.30 mg fedratinib dihydrochloride monohydrate) with the following excipients: silicified microcrystalline cellulose and sodium stearyl fumarate.

Bristol-Myers Squibb will supply fedratinib 100 mg capsules for oral administration in high density polyethylene (HDPE) bottles with heat induction seal (tamper-resistant) and polypropylene child-resistant closures, labeled appropriately as Investigational Product.

6.1.3 PRODUCT STORAGE AND STABILITY

Store as directed on the package label: fedratinib must be stored at temperatures below 86°F (30°°C).

6.1.4 PREPARATION

Bristol Myers Squibb will supply fedratinib 100 mg capsules for oral administration in high density polyethylene (HDPE) bottles with heat induction seal (tamper-resistant) and polypropylene child-resistant closures, labeled appropriately as Investigational Product.

6.1.5 DOSING AND ADMINISTRATION

Fedratinib will be given at a dose of 400 mg PO once daily (4-100 mg capsules). Fedratinib can be given at any time during the day, but patients are advised to take the dose at the same approximate time every day. Patients are further advised to take their dose with a high fat meal as this may reduce the incidence of nausea and vomiting.

In patients taking concomitant strong CYP3A4 inhibitors that are deemed necessary by study PI (see section 7.6), fedratinib dose should be reduced to 200 mg once daily. In cases where co-administration with a strong CYP3A4 inhibitor is discontinued, fedratinib dose should be increased to 300 mg once daily during the first two weeks after discontinuation of the CYP3A4 inhibitor, and then to 400 mg once daily thereafter.

If a daily dose of fedratinib is missed, the next scheduled dose should be taken the following day. A dose will be considered “missed” if it is not administered within 8 hours of the typical time of administration. Missed doses do not need to be made up.

6.1.6 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

Patients will be treated at a starting dose of fedratinib 400 mg PO daily, unless they require co-administration with a strong CYP3A4 inhibitor, in which case, fedratinib dose will be reduced to 200 mg PO daily (see section 7.5). There will be no dose escalation above the 400 mg PO daily dose. Dose interruptions and modifications should occur according to the US Package Insert and protocol-defined guidelines and, when feasible, this decision should be after discussion with the study PI. Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose reduction rules. Hematologic AEs that precipitate dose interruptions should be monitored for recovery for at least every 7 days, if feasible.

<u>Guidelines for Management of Gastrointestinal Adverse Events:</u>

Gastrointestinal adverse events, specifically nausea, vomiting and diarrhea, are commonly associated with fedratinib treatment and require multifaceted management using dose adjustment, active treatment or prophylaxis with anti-emetics, and monitoring. GI symptoms generally start in the first treatment cycle but typically improve within 6-8 weeks on fedratinib treatment.

<u>Management of Nausea and Vomiting</u>

Management of nausea and vomiting during treatment with fedratinib will be done according to the following steps:

- Patients will be provided management instructions (including when to contact the study site) before the start of treatment.

- In order to mitigate for nausea and vomiting events, it is recommended to take fedratinib with food during an evening meal. It is highly recommended to use anti-nausea/vomiting treatment prophylactically according to local practice for the first 8 weeks of treatment (eg, ondansetron). If dimenhydrinate or other muscarinic receptor antagonists are used for nausea and vomiting, administer these agents in the evening to minimize drowsiness and other potential neurological AEs.
- Hold / reduce the dose of fedratinib
- Hospitalization may be indicated for Grade 3 or higher nausea or vomiting or events that persist
- For medications that are administered for prophylactic use of nausea and vomiting, if no clinically significant nausea and vomiting occurs during the first 8 weeks of fedratinib treatment, consider weaning the patient off these medications

Management of Diarrhea

Management of diarrhea during treatment with fedratinib will be done according to the following steps:

- Patients should have loperamide available at home and should be provided with diarrhea management instructions (including when to contact the study site) before the start of treatment.
- Loperamide should not be given as prevention in case the patient does not experience diarrhea.
- Treat with loperamide as per local practice at the onset of diarrhea. Consider starting loperamide at a 4 mg loading dose and then 2 mg after each diarrheal bowel movement without exceeding 16 mg/24 hours.
- Dietary modifications including adequate hydration, avoidance of lactose-containing foods and alcohol, small meals with rice, bananas, bread, etc.
- Hold / reduce the dose of fedratinib.
- Hospitalization may be indicated for Grade 3 or higher persisting diarrhea.
- Management of nausea, vomiting and diarrhea will be assessed during the patients visit.

Guidelines for Management of Encephalopathy*:*

A potential case of WE is a medical emergency. Screening for WE and management of potential cases of WE during treatment with fedratinib will be done according the following steps:

Clinical and Cognitive Assessment

Interval history: including a review of the patient's history for confusion, memory problems, vision problems (e.g., double vision) as well as poor nutrition, signs and symptoms of malabsorption, and alcohol use

- Physical examination: including assessment for abnormal eye movements, cerebellar abnormalities and body weight (weight loss compared to previous examination or patient history)

Management of Potential WE

In case of signs or symptoms that may indicate WE:

- Hold fedratinib until WE is ruled out
- Obtain sample for thiamine level
- Empirically start thiamine supplementation
- Report the event as an AESI to the Sponsor
- Obtain a neurological consult

- Perform a brain MRI
- If WE is confirmed, discontinue fedratinib permanently

Thiamine Monitoring and Correction

Thiamine levels (for whole blood) will be monitored and thiamine supplementation will be administered to all patients with thiamine levels below the normal range.

- Thiamine levels are assessed at screening and need to be corrected and retested before starting fedratinib treatment (see inclusion criteria)
- While on treatment with fedratinib, thiamine levels are assessed as clinically indicated
- In case a patient is on thiamine supplementation, thiamine levels should be assessed in a fasting state for thiamine supplementation and thiamine given after the blood draw
- In case a thiamine level result is below normal, the site will contact the patient as soon as possible to start supplementation as described below.
- For thiamine levels below the normal range but ≥ 30 nM/L without signs or symptoms of WE:
- Supplementation with a minimum daily dose of 100 mg of oral thiamine must be started
- In case the results were obtained by a local laboratory, report the event as an Adverse Event of Special Interest (AESI).
- For thiamine level < 30 nM/L with or without signs or symptoms of WE:
- Immediate treatment with thiamine (preferably IV) at therapeutic dosages eg, IV infused over 30 minutes 3 times daily for 2 to 3 days or alternatively IM in equivalent doses according to local standard of care
- This will be followed by 250 mg to 500 mg IV thiamine infused once a day for 3 to 5 days or alternatively IM in equivalent doses according to local standard of care
- And then continue at an oral minimum daily dose of 100 mg thiamine for at least 90 days
- Fedratinib must be held until thiamine levels are restored to normal range.
- Thiamine supplementation should be administered as a thiamine only formulation.
- If thiamine levels are low, ensure that magnesium levels are normal or corrected if low

Guidelines for Interruption and Restarting of Study Drug

Chemistry		
Adverse Event	Trigger	Action Taken

ALT and/or AST elevation	Grade 2	• Continue study drug
		• Monitor LFTs at least weekly until ≤ Grade 1 or baseline
		• If Grade 2 elevation lasts ≤ 14 days, no action required.
		• If Grade 2 elevation lasts > 14 days, interrupt drug, monitor LFTs at least weekly, and:
		  ○ If resolved within 14 days after interruption, resume study drug at the same dose, monitor LFTs at least weekly during the next month and according to the protocol schedule thereafter
		  ○ If LFTs do not resolve to ≤ Grade 1 or baseline within 14 days after interruption lasts, discuss with study PI.

	Grade 3 or 4	• Complete a coagulation profile on the patient. • Interrupt study drug and monitor LFTs at least weekly until ≤ Grade 1 or baseline: ○ If resolved within 14 days after interruption, patient may resume study drug at next lower dose.

		○ If LFTs do not resolve to ≤ Grade 1 or baseline within 14 days after interruption, discuss with study PI. • Carefully examine patient's concomitant medications for those that may contribute to LFT elevations. Hold those medications or switch to an alternative; consult study PI if needed. • In the case of recurrent grade ≥ 3 ALT and/or AST elevation, study drug should be discontinued.
Amylase/Lipase Elevation	Grade 2	• Continue study drug • If Grade 2 elevation lasts > 14 days, interrupt drug, monitor amylase/lipase at least weekly, and: ○ If resolved within 14 days after interruption, resume study drug at the same dose, monitor amylase/lipase at least weekly during the next month and according to the protocol schedule thereafter • If amylase/lipase does not resolve to ≤ Grade 1 or baseline within 14 days after interruption lasts, discuss with study PI.
	Grade 3 or 4	• Interrupt study drug and monitor amylase/lipase at least weekly until ≤ Grade 1 or baseline: ○ If resolved within 14 days after interruption, patient may resume study drug at next lower dose. ○ If amylase/lipase do not resolve to ≤ Grade 1 or baseline within 14 days after interruption, discuss with study PI. • Carefully examine patient's concomitant medications for those that may contribute to amylase/lipase elevations. Hold those medications or switch to an alternative; consult study PI if needed.
Creatinine elevation	Grade 3 or 4	• Interrupt study drug for up to 2 weeks (≤ 14 days) and monitor creatinine at least weekly until ≤ Grade 1 or baseline. • Carefully examine patient's concomitant medications for those that may contribute to creatinine elevation. Hold those medications or switch to an alternative; consult study PI if needed ○ If deemed unrelated to study drug, resume study drug at same dose ○ If assessed as at least possibly related to study drug, resume at next lower dose; monitor as clinically indicated. • If creatinine does not resolve to ≤ grade 1 or baseline within 14 days after interruption, discuss with study PI. Dose reduction to 200 mg daily should be considered in patients with severe renal impairment (creatinine clearance of 15 mL/min to 29 ml/min).

Hematology		
Thrombocytopenia	Grade 4 or Grade 3 with bleeding	• Hold until resolved to > 50 x 10^9/L or baseline, if baseline was lower than 50 x 10^9/L. • Restart dose at 100 mg daily below last given dose. • If grade 4 thrombocytopenia persists for > 14 days, then discontinue study drug.
Neutropenia	Grade 4	• Interrupt dose until ANC > 1.0 x 10^9/L. Restart dose at 100 mg daily below the last given

		dose. • If grade 4 neutropenia persists for > 14 days, discontinue study drug.

Other Toxicities	
Any Grade 1 or Grade 2	Continue study drug treatment and treat the toxicity; monitor as clinically indicated
Any grade 3 toxicity, if clinically significant and not manageable by supportive care	• Interrupt study drug up to 2 weeks (14 days); until toxicity resolves to ≤ Grade 1 or baseline. • Resume study drug at same dose. If assessed as at least possibly related to study drug, resume at next lower dose; monitor as clinically indicated
Any recurrent Grade 3 toxicity at 100 mg daily dose (lowest dose allowed on study) that is at least possibly related to study drug	• Discontinue study drug and follow-up per Protocol. Exceptions require approval of study PI.
Any other non-hematologic Grade 4 toxicity	• Discontinue study drug and follow-up per protocol
New red blood cell (RBC) transfusion requirement	• Dose reduction should be considered in patients who become newly dependent upon RBC transfusions.

Dose reductions will be made in increments of 100 mg with 100 mg daily being the lowest dose to be administered on study. Any toxicity that occurs at a dose level of 100 mg daily that would require a dose reduction will result in discontinuation of study drug unless otherwise approved by the study PI.

Dose increases can occur after a dose reduction if toxicity has remained ≤ 1 or at baseline for ≥ 28 days. Dose increases will be made in increments of 100 mg daily may only occur once per cycle. Dose levels can only be tried on three occasions.

6.1.7 DURATION OF THERAPY

All patients receiving at least 1 dose of study drug will evaluable for safety and efficacy. Patients may continue on study drug until withdrawal criteria are met (section 5.4.1). Treatment duration will vary significantly between patients but is expected to average approximately 12-24 months.

6.1.8 TRACKING OF DOSE

All patients will be given a study drug diary to document compliance with daily dosing schedule. This diary will also provide an opportunity for the patient to document missed/skipped doses, new or discontinued concomitant medications and adverse events.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

The study drugs will be stored in the Moffitt Investigational Pharmacy Department. There will be an accountability log for the drug. Any unused study drug will be destroyed on site per Investigational Pharmacy

standard procedures.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY-SPECIFIC PROCEDURES

The Schedule of Events - Section 7.3.7 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the PI and/or Bristol-Myers Squibb for reasons related to patient safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional consent be obtained from the patient. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

The majority of procedures and laboratory tests on this trial will be performed per standard of care for MDS/MPNs and CNL. Standard of care screening testing will include CBC with differential, serum chemistry, amylase, lipase, thiamine level, vital signs, physical exam, bone marrow biopsy/aspirate, serum pregnancy test (in women of childbearing age).

During routine follow-up, CBC with differential, serum chemistry, vital signs, and supportive care measures will be following standard of care for any other MDS/MPN or CNL patient.

7.1.3 Informed Consent

Prior to any study procedure, informed consent must be obtained and documented by the patient's dated signature or by the patient's legally acceptable representative's dated signature on a consent form. The dated signature of the person conducting the consent discussion must also appear on the consent form.

7.1.4 Inclusion/Exclusion Criteria

Prior to any trial treatment, all inclusion and exclusion criteria will be reviewed and signed by the PI or Sub-Investigator to ensure the patient qualifies for the trial. For collaborating sites, eligibility will be reviewed by study PI prior to enrollment.

7.1.5 Demographics and Medical History

Demographical information collected will include birth date, age, sex, race, and ethnicity. A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions and any condition diagnosed that is considered to be clinically significant by the Investigator. Details regarding the disease for which the patient has enrolled in this study will be recorded separately and not listed as medical history.

7.1.6 Baseline Symptoms

Baseline symptoms are defined as those present at the closest time before the start of study drug administration.

7.1.7 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG status (see Appendix) as specified in the Schedule of Events.

7.1.8 Concomitant Medications Review

The investigator or qualified designee will record medication, if any, taken by the patient starting at the screening visit until the last dose of study drug. All medications related to reportable SAEs should be recorded as defined in the SAE section of the protocol.

7.1.9 Adverse Event Review

The investigator or qualified designee will assess each patient to evaluate for potential new or worsening AEs as specified in the Schedule of Events and more frequently if clinically indicated. Adverse events will be collected from the time of consent until 30 days after last dose.

7.1.10 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Physical exam must include assessment of spleen size on Cycle 4 Day 1 and Cycle 7 Day 1. Problem-focused physical exams will suffice for other time points.

7.1.11 Vital Signs

The investigator or qualified designee will take vital signs at screening andon day 1 of cycles 1-6. Vital signs should include temperature, pulse, respiratory rate, and blood pressure. Weight is required to be measured on cycle 1 day 1.

7.1.12 Laboratory Procedures

At screening, laboratory procedures will include a CBC with differential, CMP (albumin, BUN, creatinine, alkaline phosphatase, ALT, AST, CO2, calcium, chloride, glucose, potassium, sodium, total bilirubin, total protein), LDH, uric acid, magnesium, phosphorous, thiamine (vitamin B1) level, vitamin B12 level, folic acid, C-reactive protein (CRP), amylase and lipase. Standard follow-up visits (Day 1, 8,15, and 22 of cycle 1, Day 1 and 15 of Cycle 2 and Day 1 of 3,5,6,8+) will include CBC with differential, CMP, LDH, amylase, and lipase. Disease assessment visits on day 1 of cycle 4 and 7 will include CBC with differential, CMP, LDH, thiamine level, and CRP. Thiamine level will also be checked on Day 1 of Cycle 2.

7.1.13 Bone Marrow Biopsy

A bone marrow biopsy will be performed during screening and after cycle 6 (day 168 +/- 14 days). If a

patient discontinues treatment early or progression of disease is suspected, a bone marrow biopsy will be done at the discretion of the investigator. During follow-up, bone marrow biopsies will be performed per investigator discretion.

7.1.14 Correlative Studies

Next-generation sequencing (NGS) will be performed on a bone marrow aspirate or peripheral blood sample during screening and after cycle 6. NGS will be performed per institutional standards. Acceptable NGS platforms must include testing for the following genes with sensitivity of at least 5%: JAK2, MPL, CALR, TET2, DNMT3A, ASXL1, EZH2, SRSF2, U2AF1, ZRSR2, SF3B1, RUNX1, CSF3R, KRAS, NRAS, CBL, PTPN11, TP53, PHF6, IDH1, IDH2, ETV6, SETBP1. If NGS has been performed within 12 months of screening, this may be used as baseline NGS if approved by PI.

Mononuclear cells from bone marrow aspirate will be collected at screening and used to develop PDX mouse models for each enrolled patient. Samples will be under the care of Dr. Eric Padron's lab.

To determine whether PDX models recapitulate responses to study drug in patients with MDS/MPN and CNL, we will obtain purified hCD34+ cells from each primary pre-treatment patient sample. These cells will be sent to the lab of Dr. Eric Padron at Moffitt Cancer Center where they will be xenografted into 6 NSGS vehicle- and 6 fedratinib-treated mice. After 7 days of transplantation and peripheral blood analysis to assess for hCD45 cell engraftment, we will treat NSGS mice with fedratinib at pharmacologically comparable doses to that exposed to the patient on clinical study. Treatment would occur until the animal becomes moribund. PDX response assessment would be measured in three categories compared to vehicle: 1.) Reduction in splenomegaly as measured by spleen weight at necropsy and MRI at baseline and at the time that the first mouse becomes moribund. MRI experiments will be done on a 7T horizontal magnet (Agilent Technologies) using a 35 mm 1H birdcage coil (Doty Scientific). 2) Improvement in hematologic parameters (to include anemia, thrombocytopenia, WBC count, monocyte count). 3) Improvement in BM pathology to include decreases in bone marrow myeloblasts (hCD34+) and resolution of dysplasia/fibrosis. We will also measure survival of each treatment cohort of mice. These responses will then be compared to those seen in the clinical trial to determine the ability for the NSGS PDX to recapitulate drug response.

Patients enrolled after the interim analysis of nine patients will have purified hCD34+ cells from primary pre-treatment samples xenografted into an additional 6 NSGS mice that will be treated with ruxolitinib. These mice will be subjected to the same procedures as the vehicle- and fedratinib-treated mice in an effort to directly compare the efficacy of ruxolitinib and fedratinib in PDX mouse models of MDS/MPN and CNL.

7.1.15 Spleen Imaging

Spleen imaging will be performed during screening (day -30 – 0), at week 12 assessment (day 84 +/- 7 days), at week 24 assessment (day 168 +/- 14 days) and every 24 weeks thereafter (+/- 28 days) while on study drug up to week 96. Preferred spleen imaging is ultrasound; however, CT without contrast or MRI without contrast can be used in patients whom ultrasound is not feasible/sufficient per the discretion of the investigator. Spleen length on three axes (anteroposterior [AP] length, craniocaudal [CC] height, transverse [TR] width at the hilum) should be documented with emphasis to the spleen length in longest dimension. The imaging modality for each patient should be kept consistent throughout the study (i.e. always use ultrasounds for patients with screening ultrasound and always use CT for patients with screening CT). When possible, spleen volume should be calculated using the following formula:

AP x TR (at the hilum) x CC x 0.524 = Spleen Volume (cc)

If spleen imaging has been performed within 90 days of fedratinib initiation, this can be substituted for a screening spleen imaging as long as, in the opinion of the treating physician, the spleen has not undergone substantial change in size during that period of time and required spleen measurements have been performed. If any treatment-directed medications (i.e. ruxolitinib, hydroxyurea, interferon, lenalidomide, thalidomide, pomalidomide, corticosteroids, azacitidine, decitabine) have been started, stopped, or had dose modifications since the last spleen imaging test, then new spleen imaging must be obtained during the screening period.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

- **Hematology**: hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.
    - To be performed at screening and at each protocol-defined follow-up visit.
- **Metabolic Panel**: albumin, BUN, alkaline phosphatase, CO2, calcium, chloride, glucose, potassium, sodium, total proteincreatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST).
    - To be performed at screening and at each protocol-defined follow-up visit.
- Additional electrolytes/labs: lactate dehydrogenase (LDH), uric acid, magnesium, phosphorous, amylase, lipase
    - Uric acid, magnesium, and phosphorous are to be drawn during screening and as clinically indicated afterward.
    - LDH is to be drawn during screening and on day 1 of cycle 1-7 and every 3 cycles thereafter.
    - Amylase and lipase are to be drawn during screening, day 1, 8, 15, 22 of cycle 1, day 1 of cycle 2-4 and day 1 of cycle 7.

- **Nutritional Labs:** Vitamin B12, vitamin B1 (thiamine), folic acid
    - To be performed during screening period. Thiamine level to be assessed on day 1 of cycle 1, 2, 4 and 7.
- **Inflammatory Labs:** CRP
    - To be performed on day 1 of cycles 1, 4, and 7 and at disease assessment visits thereafter.

Laboratory testing to be performed as stated above or at the discretion of the treating physician. Laboratory tests will be performed at the respective treating institution.

7.2.2 SPECIMEN PREPARATION, HANDLING, AND STORAGE

At screening (day -30 to 0), week 12 assessment, week 24 assessment peripheral blood will be collected. Designated study personnel will collect the sample from the laboratory draw area. Peripheral blood will be

collected in six green top (heparinized) 10 ml tubes and one red top (clot activator or no additive) 10 ml tube for a total of seven tubes and 70 cc of peripheral blood. At screening and week 24 assessment (see study calendar), bone marrow aspirate will be collected in three lavender (EDTA) 10 ml tubes or a 60 ml heparinized syringe for a total of 30 cc. These will be shipped to the H. Lee Moffitt Cancer Center laboratory as directed in section 7.2.4 and will be processed first by centrifugation (530 rcf for 20 minutes) with density gradient medium to collect the mononuclear cellular layer, followed by the addition of RBC lysis buffer to remove RBCs and debris. The mononuclear cells will be cryopreserved as previously described and stored in liquid nitrogen for later use labeled with a unique identifier that corresponds to each patient known only to the investigator and study personnel. The plasma and serum will be cryopreserved for later use and labeled with a unique identifier that corresponds to each patient known only to the investigator and study personnel.

7.2.3 SPECIMEN SHIPMENT

Contact Information:

For general shipping concerns:

Eric Padron, MD
e-mail: eric.padron@moffitt.org,
Phone: 8137458264 (office)

Maria Balasis
e-mail: Maria.Balasis@moffitt.org
Phone: 813-745-6458

For detailed specimen processing concerns:

Maria Balasis
e-mail: Maria.Balasis@moffitt.org
Phone: 813-745-6458

Site Requirements:

- Green Top (heparinized) Vacutainer (6 per peripheral blood sample shipment)
- Red Top Vacutainer (1 per peripheral blood sample shipment)
- Lavender Top (EDTA) Vacutainer (3 per bone marrow sample shipment) or 60 ml heparinized syringe
- Biohazard bags, coolers
- Bio-mailer boxes, IATA placards, etc.

Collection Procedures:

- Peripheral Blood.
  - Peripheral blood will be collected at time points as described in study protocol.
  - At time of phlebotomy, 6 green tops (10 ml each) and 1 red top (10 ml) will be collected for a total of 70 cc.
  - Please label each vacutainer as follows:
    - ***Abbreviate site name –Subject ID #-PB-mm/dd/yyyy***
    - Please fill out accompanying correlative worksheet (see below)

Bone Marrow.

- The bone marrow aspirate will be collected at time points as described in study protocol.
- At time of aspirate, 3 lavender tops (10 ml) or one 60 ml heparinized syringe will be collected for a total of 30 cc.
- Please label each vacutainer as follows:
  - ***Abbreviate site name –Subject ID #-BM-mm/dd/yyyy***
  - Please fill out accompanying worksheet (see below)

Packaging and Shipment

- Shipping Timelines and General Guidelines
  - **Ship samples overnight on Monday through Thursday ONLY.** Do not ship samples to arrive on weekends or holidays.
  - All samples are to be sent at room temperature in biohazard bags, bio mailer boxes.
  - Ensure all tubes are tightly capped when packaging.
  - Shipments should be performed by personnel who have completed IATA 1.5 training for transportation of dangerous goods.
  - Notify the Cancer Center at least 24 hours prior to arrival of shipment.
  - Email the details along with the patient # and courier tracking # to:
    - Maria Balasis: maria.balasis@moffitt.org and
    - Eric Padron: eric.padron@moffitt.org
    - Andrew Kuykendall: Andrew.Kuykendall@moffitt.org
- Sample Packaging
  - All samples from one patient should have been able to fit in one bio mailer box.
  - Be sure to fill the internal cooler with ambient packing to keep all samples near room temperature during transit.
  - Ship samples to:

    Maria Balasis
    12902 Magnolia Drive
    Stabile Research Building (SRB) Room #23234
    Tampa, FL 33612
    813-745-6458
  - Label appropriately as in section 4
  - Use FedEx mailing 3rd party billing as the billing option on the label and include this account number: 156056111
- Transportation and Record Keeping
  - Schedule the samples for pickup and next day delivery with FedEx.
  - Retain a copy of the shipment's waybill with the photocopy of the patient's correlative worksheet sampling document. The original should be sent with the sample.

Correlative worksheet (see Appendix G)

Site name: _____ Patient's Initials:_____ Pt. Study ID #:_____

Blood or Bone Marrow (circle) Collections – all times must be recorded in military time

Cycle/Day	**Date of Collection (mm-dd-yyyy)**	Collection Time
Comments		

Please photocopy this for your records and maintain with a copy of the shipping waybill. Return the original to Moffitt with the specimens. This source document stands as a custodial record.

Ship all the above samples to:
Maria Balasis
12902 Magnolia Drive
Stabile Research Building (SRB) Room #23234
Tampa, FL 33612
813-745-6458
*Please email (*maria.balasis@moffitt.org, eric.padron@moffitt.org, Andrew.Kuykendall@moffitt.org*) on the day of shipment with courier tracking information.*

Ship Monday through Thursday ONLY!

Do not write below this line

Condition received: _____ Initials: _____

Comments: _____ Initials: _____

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Screening Visit (Day -30 to 0)

- Obtain and review medical history to determine eligibility based on inclusion/exclusion criteria.
- Written informed consent to be obtained prior to any screening procedures

- Review medications history (including over-the-counter drugs, vitamins, herbs, alcohol) to determine eligibility based on inclusion/exclusion criteria.
- Perform physical examination needed to determine eligibility based on inclusion/exclusion criteria
- Vital signs measurements
- Evaluation of ECOG performance status
- Spleen imaging needed to determine eligibility based on inclusion/exclusion criteria
- Symptom assessment needed to determine eligibility based on inclusion/exclusion criteria
- Serum beta-human chorionic gonadotropin (β-hCG) pregnancy test for women of childbearing potential
- Clinical laboratory testing including serum chemistry, hematology, thiamine level, folic acid, vitamin B12,amylase, lipase, magnesium, phosphorous, uric acid, LDH. Clinical assessments (laboratory tests, spleen imaging) performed as part of the subject's routine clinical evaluation and not specifically for this study need not be repeated after signed informed consent has been obtained provided the assessments fulfill the study requirements and are performed within 30 days of starting study treatment.
- Bone marrow biopsy and aspirate and peripheral blood sample will be performed in order to collect correlative samples. Biopsy must include reticulin stain.
- Cytogenetics
- Next-generation sequencing to assess for mutation involving the following genes: *JAK2, MPL, CALR, TET2, DNMT3A, ASXL1, EZH2, SRSF2, U2AF1, ZRSR2, SF3B1, RUNX1, CSF3R, KRAS, NRAS, CBL, PTPN11, TP53, PHF6, IDH1, IDH2, ETV6, SETBP1*

7.3.2 Cycle 1 Day 1 (Cycle length = 28 days)

7.3.2.1 Baseline Visit (Cycle 1; Day 1)

- Verify patient still meets inclusion/exclusion criteria
- Review results of serum pregnancy test, if applicable
- Assess and record baseline symptoms prior to study drug administration
- Administer MPN symptom assessment form (SAF). This will serve as baseline symptom score.
- Physical exam with documentation of spleen size measured as extent below the left costal margin (LCM) at the mid-clavicular line (measured in centimeters) (e.g. 10 cm below the LCM).
- ECOG performance status assessment
- Record vitals
- Weight
- CBC with differential
- Chemistry profile (sodium, potassium, chloride, creatinine, BUN, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, calcium, CO2)
- LDH, amylase, lipase
- Thiamine level
- C-reactive protein (CRP)
- Administer study treatment and provide medication supply sufficient to reach next protocol-defined visit.
- Provide patient pill and adverse event diary

7.3.3 ON-TREATMENT VISITS

7.3.3.1 Cycle 1; Day 8, 15, 22 and Cycle 2, Day 15)

- Focused physical exam
- Assess and record symptoms
- CBC with differential
- Chemistry profile (sodium, potassium, chloride, creatinine, BUN, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, calcium, CO2)
- LDH, amylase, lipase

7.3.3.2 Cycle 2-3; Day 1

- Record vitals
- Focused physical exam
- Assess and record symptoms
- CBC with differential
- Chemistry profile (sodium, potassium, chloride, creatinine, BUN, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, calcium, CO2)
- LDH, amylase, lipase
- Thiamine level to be checked on Cycle 2, Day 1
- Assess TSS with MPN SAF
- Assess PGIC

7.3.3.3 Week 12 Assessment – Performed at day 84 +/- 7 days

- Record vitals
- Physical exam with documentation of spleen size measured as extent below the left costal margin (LCM) at the mid-clavicular line (measured in centimeters) (e.g. 10 cm below the LCM)Assess and record symptoms
- Peripheral blood drawn for correlatives
- CBC with differential
- Chemistry profile (sodium, potassium, chloride, creatinine, BUN, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, calcium, CO2)
- LDH, amylase, lipase
- Thiamine level
- CRP
- Assess TSS with MPN SAF
- Assess PGIC
- Spleen imaging with documentation of spleen length on three axes (length, height, width at the hilum) and volume (when feasible).
- MDS/MPN Response Assessment

7.3.3.4 Cycle 4-6; Day 1 (Assessments here can contribute to week 12 assessment)

- Record vitals
- Focused physical exam

- Assess and record symptoms
- CBC with differential
- Chemistry profile (sodium, potassium, chloride, creatinine, BUN, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, calcium, CO2)
- LDH
- Assess TSS with MPN SAF
- Assess PGIC

7.3.3.5 Week 24 Assessment – Performed at day 168 +/- 14 days

- Record vitals
- Physical exam with documentation of spleen size measured as extent below the left costal margin (LCM) at the mid-clavicular line (measured in centimeters) (e.g. 10 cm below the LCM)Assess and record symptomsBone marrow biopsy and aspirate (with correlative samples sent from aspirate)
- Peripheral blood drawn for correlatives
- CBC with differential
- Chemistry profile (sodium, potassium, chloride, creatinine, BUN, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, calcium, CO2)
- LDH, amylase, lipase
- Thiamine level
- CRP
- Assess TSS with MPN SAF
- Assess PGIC
- Spleen imaging with documentation of spleen length on three axes (length, height, width at the hilum) and volume (when feasible).Bone marrow biopsy and/aspirate with reticulin stain
- MDS/MPN Response Assessment

7.3.3.6 Cycle 7; Day 1 (Assessments here can contribute to week 24 assessment)

- Record vitals
- Focused physical exam
- Assess and record symptoms
- CBC with differential
- Chemistry profile (sodium, potassium, chloride, creatinine, BUN, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, calcium, CO2)
- LDH
- Assess TSS with MPN SAF
- Assess PGIC

7.3.3.7 Post-Week 24 On Treatment Visits (To occur every 3 cycles while on study drug)

- Record vitals
- Focused physical exam
- Assess and record symptoms
- CBC with differential
- Chemistry profile (sodium, potassium, chloride, creatinine, BUN, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, calcium, CO2)

- LDH
- Assess TSS with MPN SAF
- Assess PGIC

7.3.3.8 Post-Week 24 Disease Assessment(s) (To occur on day 336 +/- 14 days and every 168 +/- 14 days thereafter while on study drug)

- Record vitals
- Physical exam with documentation of spleen size measured as extent below the left costal margin (LCM) at the mid-clavicular line (measured in centimeters) (e.g. 10 cm below the LCM)Assess and record symptoms
- CBC with differential
- Chemistry profile (sodium, potassium, chloride, creatinine, BUN, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, calcium, CO2)
- LDH
- Thiamine level
- CRP
- Assess TSS with MPN SAF
- Assess PGIC
- Spleen imaging with documentation of spleen length on three axes (length, height, width at the hilum) and volume (when feasible).MDS/MPN Response Assessment
- MDS/MPN Response Assessment

7.3.4 FINAL STUDY VISIT

7.3.4.1 End of Treatment Visit (28 +/- 7 days from study drug completion)

- Record vitals
- Peripheral blood drawn for correlativesPhysical exam
- Assess and record symptoms
- CBC with differential
- Chemistry profile (sodium, potassium, chloride, creatinine, BUN, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, calcium, CO2)
- LDH

Final instructions will be provided to the patient and the patient will be informed if results will be available or any planned presentation or publication of the study data.

7.3.5 EARLY TERMINATION VISIT

If a patient terminates study participation for any reason prior to completion of the protocol treatment plan, any subsequent procedures or evaluation will be per physician discretion as part of standard of care. Evaluation of AEs will continue as outlined in Section 7.1.9.

7.3.6 UNSCHEDULED VISIT

Any visit not include on the Schedule of Events Table that includes examination in the Moffitt hematology clinic, inpatient hospitalization, or any unexpected extended hospitalization, laboratory evaluation or management of adverse events, will be considered an Unscheduled Visit. It will be documented in the subject's medical record and included on the adverse event log. Adverse event or serious adverse event data will be collected in OnCore. No separate OnCore form for an unscheduled visit will be used to collect additional data.

7.3.7 SCHEDULE OF EVENTS TABLE

Procedures	Screening	Enrollment/Baseline Cycle 1, Day 1	Cycle 1*, Day 8,15 , 22 (+/- 5 days)	Cycle 2, Day 1 (+/- 7 days)	Cycle 2, Day 15 (+/- 5 days)	Cycle 3, Day 1 ((+/- 7 days)	Cycle 4, Day 1 Week 12 Assessment (+/- 7 days)	Cycle 5, Day 1 (+/- 7 days)	Cycle 6, Day 1 (+/- 7 days)	Cycle 7, Day 1 Week 24 Assessment (+/- 14 days)	Subsequent Visits (Every 3 cycles) (+/- 14 days)	End of Treatment Visit (+/- 7 days from study drug completion)[e]
Informed consent	X											
Demographics	X											
Medical history	X											
Concurrent meds	X		X ----------									X
Fedratinib dispensed[d]		X	X	X	X	X	X	X	X	X	X	
Investigational Drug Diary Provided		X		X		X	X	X	X	X	X	
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X										
Performance status (ECOG)	X	X										
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X	X	X
Metabolic panel [a]	X	X	X	X	X	X	X	X	X	X	X	X
Uric acid, magnesium, phosphorous	X											
Amylase, lipase	X	X	X	X		X	X			X		
LDH	X	X		X		X	X	X	X	X	X	X
Folic acid, Vitamin B12	X											
Thiamine	X	X		X			X			X	X	
CRP		X					X			X	X	
Serum Pregnancy test [b]	X											
Adverse event evaluation			X ----------									X
Spleen Imaging	X						X			X	X[c]	
MPN SAF TSS	X	X		X	X	X	X	X	X	X	X	
PGIC				X	X	X	X	X	X	X	X	
MDS/MPN Response Assessment							X			X	X[c]	
Bone Marrow Biopsy/Aspirate	X									X		
Bone marrow aspirate for correlatives	X									X		

Peripheral Blood Draw for correlatives	X						X			X		
Cytogenetics	X											
Next Generation Sequencing	X											

a: Albumin, alkaline phosphatase, total bilirubin, CO2, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, AST,ALT, sodium,
b: Serum pregnancy test (women of childbearing potential).
c: Spleen imaging and MDS/MPN response criteria to be performed every 24 weeks +/- 28 days (6 cycles) after week 24
d. See section 7.2.3 and 7.2.4 for details regarding specimen preparation, handling, and storage
* Cycle length = 28 days

7.4 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications taken during study participation will be reviewed in the electronic medical record. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

7.5 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Treatment with the following drugs will not be permitted unless discussed with, and approved by, the primary investigator:

- Moderate and strong CYP3A4 Inducers (should be avoided in all cases)
  - Phenytoin
  - Rifampicin
  - Enzalutamide
  - Apalutamide
  - Carbamazepine
  - Bosentan
  - Efavirenz
  - Phenobarbital
  - Primidone
  - St. John's Wort

Treatment with the following drugs is cautioned against; however, if absolutely necessary, necessitates dose reduction.

- CYP3A4 Inhibitors
  - Diltiazem
  - Erythromycin
  - Clarithromycin
  - Ketoconazole
  - Itraconazole
  - Voriconazole
  - Posaconazole
  - Fluconazole
  - Ritonavir
  - Aprepitant
  - Ciprofloxacin

- Cyclosporine
- Dronedarone
- Fluconazole
- Imatinib
- Fluovaxaomine
- Verapamil

7.6 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Prophylactic anti-emetics (e.g. ondansetron) are highly recommended during the first 8 weeks of treatment with fedratinib. See section 6.1.6 for detailed guidance.

7.7 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

- In the setting of leukocytosis > 50,000/µL, hydroxyurea can be provided up to a dose of 2,000 mg per day per the discretion of the treating physician. For hydroxyurea use outside of these parameters, use will be determined after discussion with the PI.
- In the setting of anemia (Hgb < 11 g/dL) and EPO level < 500, erythropoiesis-stimulating agent (ESA) can be provided at the discretion of the treating physician. Patients who start ESA within 2 months of study enrollment or while on study will not be eligible for anemia response.
- Growth factor support with granulocyte stimulating factor may be administered for patients with an absolute neutrophil count (ANC) < 500/µL per the discretion of the treating physician.
- The use of transfusion support (RBCs and platelets) will be according to standard of care as rescue therapy for anemia or thrombocytopenia.
- Corticosteroids and antihistamines may be administered per institutional protocol for the treatment of hypersensitivity reactions should they emerge.
- Loperamide should be available at home for each patient enrolled on the study. Treatment with loperamide should be directed by the treating physician based on local practices. Consider starting loperamide at a 4 mg loading dose at the onset of diarrhea and giving 2 mg after each diarrheal bowel movement without exceeding 16 mg/24 hours.
- See section 6.1.6 for detailed guidance on management of expected toxicities.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A

diagnosis or syndrome should be recorded rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. An overdose, accidental or intentional, whether or not it is associated with an AE, should be reported. Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and as an AE.

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Events and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

Toxicities will be characterized in terms regarding seriousness, causality, severity, duration, action taken, and outcome with regard to trial treatment.

Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- Results in discontinuation from the study;
- Requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- Is judged to be of significant clinical importance, e.g., one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity of grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g. record thrombocytopenia rather than decreased platelets).

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A qualified Investigator will evaluate all adverse events as to their seriousness. A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);

- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied Indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS

Unanticipated problems (UPs) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm

(including physical, psychological, economic, or social harm) than was previously known or recognized.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

8.2.2 RELATIONSHIP TO STUDY AGENT

For all collected AEs, the investigator will evaluate the participant and will determine the AE's causality based on temporal relationship and his/her clinical judgment. Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal

laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Unrelated** – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3 EXPECTEDNESS/DURATION/ACTION TAKEN/OUTCOME

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

The Investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews with study participants presenting for medical care, or upon review by a study

monitor. All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of event. All AEs occurring during the study must be documented appropriately, regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of AEs will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as "intermittent" require documentation of onset and duration of each episode in the medical record.

Adverse events for the purpose of this study will be reported from the time period beginning when patient has received first dose of study drug until 30 days after study drug discontinuation up to 3 years. Events will be followed for outcome information until resolution or stabilization is achieved. Any AE present at the time of final study closure will be considered ongoing.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.
All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the event's outcome, including lab abnormalities. AEs will be recorded in the patient's source documents.

The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the event's outcome or lab abnormality.

Adverse event documentation will be performed by entry into the Moffitt OnCore electronic database. Reporting of adverse events to the FDA for IND renewal will occur annually by a report obtained from the AEs collected in OnCore.

All AEs will be documented on a paper log with columns for the replication of the fields in the OnCore AE data form. The treating physician/investigator will review the log for accuracy and assign CTCAE grade and the attribution of a study agent to the AE.

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8.4.2 SERIOUS ADVERSE EVENT REPORTING

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed. For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome. All SAEs made known to the investigator at any time after treatment that are suspected of being related to the IP must be record by the Investigator. All SAEs must be must be recorded in the patient's source documents and reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by Bristol-Myers Squibb and should be provided as soon as possible.

Investigator Reporting to the FDA

Serious adverse events (SAEs) that are unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Moffitt as the study sponsor will be responsible for notifying FDA of any unexpected fatal or life threatening SAEs that meet the criteria for reporting to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

SAE Reporting From External Sites

Information about all serious adverse events will be collected and recorded. To ensure patient safety, each SAE must be reported to the PI and to the sponsor expeditiously. Moffitt Cancer Center and all participating sites will report SAEs by completing an SAE report in OnCore, the electronic data capture system. The SAE Report from OnCore must be signed and reported by email (ESC_Partnerships@moffitt.org) to the External Site Coordination (ESC) office within 2 working days. If applicable, the site should also follow protocol guidelines for additional reporting to Financial Sponsors and government agencies.

8.4.3 UNANTICIPATED PROBLEM REPORTING

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to Bristol-Myers Squibb. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor within 2 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures) and the supporting agency head (or designee), within 7 days of the IRB's receipt of the report of the problem from the investigator.

8.4.4 EVENTS OF SPECIAL INTEREST

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring of patients and rapid communication by the investigator to the study PI. AESIs will additionally be reported back to Celgene/BMS. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product

The following are considered to be Adverse Events of Special Interest (AESIs):
- Wernicke encephalopathy (WE) or suspected cases of WE associated with thiamine levels below normal range.
- Thiamine levels below normal range with or without signs or symptoms of WE
- Cardiac failure or cardiomegaly

8.4.5 REPORTING OF PREGNANCY

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 4 months, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene/BMS Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify Celgene/BMS Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any

of the serious criteria, it must be reported as an SAE to Celgene/BMS Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene/BMS Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects
If a female partner of a male subject taking investigational product becomes pregnant while the male subject is on study treatment or within 4 months of the male subject's last study treatment, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

8.5 STUDY HALTING RULES

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry parameters and regular physical examinations. Adverse events will be evaluated continuously throughout the study. Safety and tolerability will be assessed according to the NIH/NCI Common Terminology Criteria for Adverse Events version (CTCAE v5.0) that is available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

The Protocol Monitoring Committee (PMC) at Moffitt monitors its assigned ongoing research protocols for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC, upon review of any agenda item, may approve the study for continuation, require revisions, suspend or close a protocol. The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.

Investigators of studies which are designated to be reviewed by the PMC for data and safety monitoring, shall provide a statistical report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable. The PI will be notified for recommendations or notifications after the PMC review in regards of continuation or stopping the clinical trial.

8.6 SAFETY OVERSIGHT

Serious Adverse Events: Serious Adverse Events (SAEs) from this protocol will be reported concurrently to the IRB (per IRB guidelines) and Bristol-Myers Squibb within 24 hours of staff awareness of the event. The Protocol Monitoring Committee (PMC) will review these SAEs in accordance with their policy. The data and safety plan will define dose limiting toxicities and criteria for stopping the trial according to rules set forth by this protocol. This trial will be continuously monitored by the PI and the research team. A final safety and monitoring report will be submitted to the PMC. This protocol will be subject to periodic internal audits based on risk or as recommended by the PMC.

9 CLINICAL MONITORING

Data will be captured in OnCore, Moffitt's electronic Clinical Trials Database. For each participant enrolled, the electronic CRF must be completed by the assigned data manager or other authorized study staff. Any paper forms should be typed or filled out indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate. This also applies to records for those patients who fail to complete the study. If a patient stops dosing or terminates from the study, the dates and reasons must be noted on the CRF. If a patient terminates from the study because of a DLT, thorough efforts should be made to clearly document the outcome.

Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification of data entry, validation of appropriate informed consent process, reporting of SAEs, adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

External Site Monitoring

Compliance to the Protocol and Adherence to Moffitt External Site Coordination Handbook
Moffitt is responsible for monitoring each sites compliance to adherence to applicable Moffitt External Site Coordination Handbook. In coordination with the Monitoring office, the ESC Office assists to monitor compliance to the protocol.

External Site Access to Clinical Trial Database
To obtain access to OnCore, the External Site Coordinator will supply forms required to be completed by the site staff. Once the completed forms are received, the site coordinator will receive VPN access, logon/password, and information on how to access OnCore. The ESC office will provide OnCore training to the site once initial access is granted and on an ongoing basis, as needed.

Registration Procedures for External Sites
All external enrolled subjects must be registered with the External Site Coordination (ESC) office to be able to participate in a trial. The participating site must email the completed current eligibility checklist, registration form, all supporting documents, and signed, unredacted informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the ESC Coordinator will review them to confirm eligibility and complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.

Upon completion of registration, the ESC Coordinator will provide the participating site with the study sequence number and, when applicable, randomization information. Within 48 hours after registration, it is the site's responsibility to enter the on-study patient information into the OnCore database and order investigational agent(s), if indicated per protocol.

It is the responsibility of the participating Investigator or designee to inform the subject of the research treatment plan and to conduct the study in compliance with the protocol as agreed upon with Moffitt Cancer Center and approved by the site's IRB.
To register a patient send the completed signed eligibility checklist along with the patient registration form and supporting documentation to the ESC via email at ESC_Partnerships@Moffitt.org, Monday through Friday between 8:00AM and 5:00PM (EST). If a short turnaround time is required between registration and first treatment, please consider discussing this with you ESC Coordinator and, if possible, submit a partial submission.

Required Documentation for External Sites
Before the study can be initiated at any site, the site will be required to provide regulatory documentation to the External Site Coordination (ESC) office at Moffitt Cancer Center. Sites must provide a copy of their informed consent to the ESC office for review and approval prior to submission of any documents to the site's IRB. Any changes requested by the site's IRB must be provided to the ESC staff for review and approval prior to resubmission to the IRB.

The ESC office must receive the following trial specific documents either by hardcopy or email before a site can be activated for any trial. All corresponding updates to these documents are required to be submitted to the ESC office throughout the trial:

- IRB Approval Letter that includes the protocol version and date
- FDA Form 1572Protocol Signature Page
- Investigator Brochure (or Package Insert) Signature Page(s)
- IRB Approved Consent Form
- Site Delegation of Authority Log
- Signed Financial Interest Disclosure Forms (For all individuals listed on the 1572)
- Investigator/Personnel documents (CVs, licenses, GCP and HSP training certificates, etc.) as needed
- Laboratory Documents (certifications, normal ranges, etc.) as needed
- Signed Clinical Trial Agreement
- Protocol specific documentation as needed

A study initiation teleconference will be held prior to the start of any study related activity at the site. Attendance is required for:

- The site PI and appropriate research staff
- Moffitt PI and ESC Coordinator

The requirements of the protocol and all associated procedures and processes will be reviewed and agreed upon prior to the activation of the study. The ESC utilizes the EDC system, OnCore. OnCore training will be scheduled, if indicated, with the appropriate staff from the site. External sites are required to send updated documentation to the ESC Office at ESC_Partnerships@Moffitt.org within 10 business days of updating.

External Site Monitoring and Reporting
The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures

reporting, pharmacy records, response assessments, and data management. All monitoring efforts will occur based on the protocol specific monitoring plan.

Following each monitoring visit, a monitoring follow-up report will be provided to the Participating Site (i.e. Site PI and Coordinator). The monitoring report will summarize any issued queries or data clarification requests, identify any reportable events or required follow-up on prior events and will specify details of any non-compliance. Participating Sites are requested to respond to all queries and data clarifications requests within 20 business days. The Moffitt Cancer Center Protocol Monitoring Committee will review all monitoring reports and issue resolution. This Committee reserves the right to close accrual for non-compliance to monitoring.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

The following study is a phase 2 trial. Analysis of response rate and safety are planned. Exploratory analyses of progression free survival, overall survival, and duration of response are planned.

10.2 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  - Overall response rate will serve as the primary endpoint
- Secondary Efficacy Endpoint(s):
  - Proportion of patients achieving spleen response at week 12 in patients with baseline splenomegaly.
  - Proportion of patients achieving spleen response at week 24 in patients with baseline splenomegaly.
  - Proportion of patients who have a 50% reduction in MPN-SAF TSS from baseline to week 12 in patients with baseline TSS ≥ 10
  - Proportion of patients who have a 50% reduction in MPN-SAF TSS from baseline to week 24 in patients with baseline TSS ≥ 10
  - Change in TSS from baseline to week 12 in patients with baseline TSS ≥ 10
  - Change in TSS from baseline to week 24 in patients with baseline TSS ≥ 10
  - Change in TSS from baseline to time of best response in patients with baseline TSS ≥ 10
  - Patient's global impression of change (PGIC) at week 12
  - PGIC at week 24

10.3 ANALYSIS DATASETS

- All patients receiving at least one dose of fedratinib will be evaluable for safety and efficacy. Patients who do not complete at least 28 days of therapy will be considered non-responders.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

This will be a phase 2 trial to assess the efficacy of fedratinib in MDS/MPN and CNL. Patients with a

diagnosis of MDS/MPN-U, aCML, MDS-MPN-RS-T, or CNL will be enrolled using modified Simon's minimax 2-stage approach.[31] The primary endpoint of the study is the proportion of patients achieving an objective clinical response at week 24 which is determined based upon the Modified MDS/MPN IWG Proposed Response Criteria.

An interim analysis will be performed after 9 patients have completed their week 24 disease assessment or have discontinued study treatment prior to week 24 to assess for futility. If there are ≥ 3 responses among these 9 patients, an additional 16 patients will be enrolled for a total of 25. This will be sufficient to test our hypothesis that fedratinib will increase the ORR from a historical standard of 30% to 55% using a power of 80% and a one-sided type 1 error rate of 0.05. The null hypothesis will be rejected if 12 or more responses are observed.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint is overall response rate. This is defined as the proportion of patients achieving a clinical response from baseline to week 24. Clinical response is defined as those achieving complete response, partial response or clinical benefit per Modified MDS/MPN IWG Proposed Response Criteria. Formal response assessments will be performed after cycle 3, cycle 6 and every 6 cycles thereafter. If a patient does not complete 3 cycles (does not undergo formal response assessment), the patient will be considered a non-responder. A patient who completes at least 3, but not 6 cycles, will have week 24 response assessment carried forward from week 12.

Patients lacking evidence of response, whether this is due to failure to meet response criteria or unavailable information to determine response, will be considered non-responders.

The p-value and confidence interval will be computed by using conditional distribution in order to reflect the nature of two-stage design.[32]

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

- Proportion of patients achieving spleen response at week 12 in patients with baseline splenomegaly.
    - This will be measured by comparing spleen measurement at day 84 assessment with baseline spleen measurement. Spleen response is defined as 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline, a spleen that is palpable at more than 5 cm at baseline becoming non-palpable, or, in cases where volumetric evaluation is feasible, a ≥ 35% reduction in spleen volume in patients with a baseline spleen volume > 450 cc. Spleen responses by palpation will need to correlate with a 50% reduction in longest diameter of the spleen by imaging.
    - Only patients with a palpable spleen or spleen volume > 450 cc will be eligible for spleen response
    - Patients with baseline splenomegaly who do not have spleen size assessment performed at day 84 assessment or who have discontinued study drug prior to day 84 assessment will be considered not to have had a spleen response.
- Proportion of patients achieving spleen response at week 24 in patients with palpable spleen at baseline.

- This will be measured by comparing spleen measurement at day 168 assessment visit with baseline spleen measurement. Spleen response is defined as 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline, a spleen that is palpable at more than 5 cm at baseline becoming non-palpable, or, in cases where volumetric evaluation is feasible, a ≥ 35% reduction in spleen volume in patients with a baseline spleen volume > 450 cc. Spleen responses by palpation will need to correlate with a 50% reduction in longest diameter of the spleen by imaging.
- Only patients with a palpable spleen or spleen volume > 450 cc will be eligible for spleen response
- Patients with baseline splenomegaly who do not have spleen size assessment performed at day 168 assessment or who have discontinued study drug prior to day 168 assessment will be considered not to have had a spleen response.

- Proportion of patients who have a 50% reduction in MPN-SAF TSS from baseline to week 12 in patients with baseline TSS ≥ 10
  - Reduction in MPN-SAF TSS score will be measured by comparing TSS score at day 84 assessment to TSS score on cycle 1 day 1.
  - Only patients with baseline TSS ≥ 10 will be eligible for symptom response.
  - Patients who do not have a TSS score performed at day 84 assessment or who have discontinued study drug prior to day 84 assessment will be considered to not have 50% reduction in TSS.
- Proportion of patients who have a 50% reduction in MPN-SAF TSS from baseline to week 24 in patients with baseline TSS ≥ 10
  - Reduction in MPN-SAF TSS score will be measured by comparing TSS score at day 168 assessment to TSS score on cycle 1 day 1.
  - Only patients with baseline TSS ≥ 10 will be eligible for symptom response.
  - Patients who do not have a TSS score performed at day 168 assessment or who have discontinued study drug prior to day 168 assessment will be considered to not have 50% reduction in TSS.
- Change in TSS from baseline to week 12 in patients with baseline TSS ≥ 10
  - These will be reported as a nominal value calculated by subtracting the TSS on cycle 1 day 1 from the TSS at day 84 assessment. Improvements in TSS will be represented with values less than zero, while progression of symptoms will be represented with values greater than zero.
  - All enrolled patients' baseline TSS ≥ 10 and documented day 84 TSS will be included in this analysis.
  - Patients who do not have a TSS score performed at day 84 assessment or who have discontinued study drug prior to day 84 assessment will not be included in this analysis.
- Change in TSS from baseline to week 24 in patients with baseline TSS ≥ 10
  - These will be reported as a nominal value calculated by subtracting the TSS on cycle 1 day 1 from the TSS at day 168 assessment. Improvements in TSS will be represented with values less than zero, while progression of symptoms will be represented with values greater than zero.
  - All enrolled patients' baseline TSS ≥ 10 and documented day 168 TSS will be included in this analysis.
  - Patients who do not have a TSS score performed at day 168 assessment or who have discontinued study drug prior to day 168 assessment will not be

included in this analysis.

- Change in TSS from baseline to time of best response in patients with baseline TSS ≥ 10
    - These will be reported as a percent change from the baseline value by subtracting the TSS on cycle 1 day 1 from the lowest TSS score documented for the patient between cycle 2 day 1 and cycle 7 day 1 and dividing the difference by the baseline TSS score. Improvements in TSS will be represented with values less than zero, while progression of symptoms will be represented with values greater than zero.
    - All enrolled patients' baseline TSS ≥ 10 and at least one other documented TSS score after cycle 1 will be included in this analysis.
    - Patients who do not have a TSS score documented at or beyond cycle 2 day 1 will not be included in this analysis.
- Patient's global impression of change (PGIC) at week 12
    - This will be measured using the validated questionnaire wherein patients are asked about the change in their myelofibrosis symptoms since starting on the study. Patients can choose from one of seven potential answers: Very much improved, Much improved, Minimally improved, No change, Minimally worse, Much worse, Very much worse.
    - This will be reportedly qualitatively wherein the number of patients choosing particular answers will be tabulated and frequencies will be reported.
- PGIC at week 24
    - This will be measured using the validated questionnaire wherein patients are asked about the change in their myelofibrosis symptoms since starting on the study. Patients can choose from one of seven potential answers: Very much improved, Much improved, Minimally improved, No change, Minimally worse, Much worse, Very much worse.
    - This will be reportedly qualitatively wherein the number of patients choosing particular answers will be tabulated and frequencies will be reported.

The analysis of binary endpoint including spleen response will be analyzed by the exact binomial distribution. The change of baseline to week 12 or 24 of the continuous variables including patient-reported outcomes (PROs) will be examined by paired-t test or Wilcoxon signed-rank test, as appropriate.

10.4.4 SAFETY ANALYSES

Using summary statistics, safety data will be coded using CTCAE 5.0 criteria, with each AE being counted only once for a given participant. The severity, frequency, duration, outcome and relationship of AEs to the study agent, as defined by the treating investigator, will be presented by System Organ Class (SOC) and preferred term groupings. Adverse events leading to premature discontinuation from the study drug, adverse events of special interest, and serious treatment-emergent AEs will be presented in a table.

The proportion of patients experiencing grade ≥ 3 AEs will be calculated and presented separately in a table. Hematologic grade ≥ 3 AEs will be included if not present at baseline.

Hematologic values (hemoglobin, WBC, platelet count) will be calculated at the beginning of each cycle with median values being presented as a function of time while receiving treatment with study drug.

10.4.5 ADHERENCE AND RETENTION ANALYSES

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to patients enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol. To document compliance with the treatment regimen, patients will be instructed to return all fedratinib bottles (empty, partially filled or full), to the study site personnel prior to each visit and at the treatment completion visit. The site staff will document the bottles returned and the number of capsules per bottle on the appropriate form. Compliance below 80% require counseling of the patient by study site personnel.

Reason for treatment discontinuation will be documented in the treatment completion visit. This will be reported descriptively.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Planned baseline demographic and clinical information will include age, gender, specific disease-associated mutations, cytogenetics, prior therapies, spleen size, hematologic laboratory parameters (hemoglobin, WBC, immature myeloid cell percentage, platelet, peripheral blast percentage), LDH, bone marrow/aspirate parameters (blast percentage, fibrosis grade, ring sideroblast percentage, cellularity).

Demographics will be presented using summary statistics.

10.4.7 PLANNED INTERIM ANALYSES

The interim efficacy review will take place after 9 patients are evaluable for efficacy (i.e., completed week 24 disease assessment or discontinued study treatment prior to week 24). Enrollment will be halted if there are ≤ 2 responses among the first 9 patients. Enrollment will not be stopped while waiting for the first 9 patients to become evaluable for efficacy. If ≥ 3 responses are seen in the first 9 patients, an additional 16 patients will be enrolled for a total enrollment of 25 patients.

Overall response data will be presented in aggregate.

Individual patient TSS, PGIC will be measured at week 12 and week 24 assessment and presented as a function of time.

10.4.11 EXPLORATORY ANALYSES

- Overall Survival: OS will be measured for each patient on the study. OS will be defined as time from first treatment to death due to any cause or censored at last follow-up. OS will be measured by Kaplan-Meier method. Median OS, as well as OS rate at 1-year and 2-year will be reported

descriptively. The confidence interval will be computed by log-log transformation.

- Progression free survival: Progression will be measured for each patent as defined by Modified MDS/MPN IWG Proposed Criteria for Disease Progression in adult MDS/MPNs (Appendix H). PFS will be defined as time from first treatment to progression or censored at last follow-up. PFS will be measured by Kaplan-Meier method. Median PFS, as well as PFS at 1-year and 2-year will be reported descriptively. The confidence interval will be computed by log-log transformation.
- Duration of response: Response duration will be measured for each responding patient. Response and progression will be defined by Modified MDS/MPN IWG Proposed Criteria.[1] Duration of response is defined as the amount of time from the date of initial response to the date of disease progression or death.
- Correlation between mutations detected from NGS at baseline and response will be assessed using contingency tables and Mantel-Haenszel test to calculate relative risk and p-values.
- Correlation between the number of mutations detected from NGS at baseline and response will be assessed using cut-points of 2 and 3 mutations with relative risk and p-values calculated using contingency tables and Mantel-Haenszel test.
- For correlative study, the primary endpoint is the response. The difference between vehicle and fedratinib will be examined by Mantel-Haenszel test. The difference in survival between arms will be evaluated by the log-rank test. In addition, the agreement between PDX mouse response and patients' response will be measured by Kappa index.

10.5 SAMPLE SIZE

MDS/MPNs and CNL are rare diseases with few FDA approved treatment options. Cases are often referred to academic, tertiary care centers for evaluation. As stated in section 10.4.1 25 patients will be enrolled to test our hypothesis that fedratinib will increase the ORR from a historical standard of 30% to 55% with 80% power and a one-sided type 1 error rate of 0.05.

An interim efficacy analysis will be conducted after 9 patients have completed week 24 disease assessment or discontinued study treatment prior to week 24. If ≥ 3 responses are observed among these 9 patients, this will support continued investigation and an additional 16 patients will be enrolled for a total of 25.

The lead site for this study, Moffitt Cancer Center, is a high-volume center for myeloid malignancies, with approximately 150 new cases of MDS/MPN or CNL seen annually. Based on the current inclusion/exclusion criteria, we estimate 25 cases of MDS/MPN-U, CNL, aCML, or MDS/MPN-RS-T would meet eligibility criteria for study enrollment on an annual basis. Historical enrollment patterns support a 30% rate of enrolling eligible patients, a screen failure rate of < 10% and a dropout rate of < 10%. Accordingly, we anticipate annual accrual of 8 patients. In order to expedite full accrual, three additional high-volume centers with expertise in myeloid malignancies will participate. Conservatively, each additional site will be expected to enroll 3-4 patients annually. Allowing for 4 months of lag time for additional sites to open the study, we expect full enrollment at 18 months from when the study is opened at the lead site.

10.6 MEASURES TO MINIMIZE BIAS

As this study is a single-arm study randomization is not considered.

10.6.1 ENROLLMENT

Patients with morphologically confirmed diagnosis of aCML, MDS/MPN-U, MDS/MPN-RS-T, or CNL will be enrolled from the Malignant Hematology clinic at the Moffitt Cancer Center and other participating sites. Patients will not be blinded to therapy. Patients who fail to meet the eligibility requirements (i.e screen fail) may be replaced.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The PI and other appropriate study staff are responsible for maintaining appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Representatives of Bristol-Myers Squibb and federal regulatory agencies may examine records for the purpose of quality assurance reviews, evaluation of the study safety, progress of the trial, and data validity.

Source documentation in both electronic and paper form shall be retained for at least two years after the final closure of the trial. These include hospital records, clinical research subject charts (with paper AE logs), research laboratory notes, electronic CRFs, and pharmacy dispensing records.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control procedures will be implemented beginning with the OnCore data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the staff for clarification/resolution.

Following written SOPs, the Moffitt internal monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., good laboratory practices (GLP), good manufacturing practices (GMP)).

The investigational site will provide direct access to source data/documents, and reports for the purpose of monitoring and auditing, and inspection by local and regulatory authorities.

All staff will be trained by the PI through a site initiation presentation, power point training for training on the initial protocol for those staff unable to attend the initiation presentation, and ongoing self-study as protocol amendments are approved. Training will be documented on a signature log that will be filed in the electronic regulatory binder.

13 ETHICS/PROTECTION OF HUMAN PATIENTS

13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the 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. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks will be given to the participant and written documentation of informed consent will be required prior to starting intervention/administering study product.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The Moffitt study monitor, other authorized representatives of Moffitt, representatives of the IRB or pharmaceutical companies supplying study products may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Moffitt. This will not include the participants' contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Moffitt research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Moffitt.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS, OR DATA

- Intended Use: Samples and data collected under this protocol may be used to study myelodysplastic and myeloproliferative neoplasms.
- Storage: Samples and data will be stored using codes assigned by the investigators and only known to investigators and authorized study personnel. Data will be kept in password-protected computers
- Patients are free at any time in the future to decide not to provide specimens or to withdraw his/her specimens from further scientific research. Such a decision will have no impact on his/her treatment or other aspects of participation in this study.

13.5 FUTURE USE OF STORED SPECIMENS

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored in Dr. Eric Padron's lab at Moffitt Cancer Center. These samples could be used for research into the causes of myeloid malignancies, their complications and other conditions for which individuals with myeloid malignancies are at increased risk, and to improve treatment. The lab of Dr. Eric Padron will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the lab of Dr. Eric Padron.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. All paper source documents will be scanned into the electronic medical record of each subject for storage. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into OnCore, a 21 CFR Part 11-compliant data capture system provided by Moffitt. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 10 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 10 years have elapsed since the formal discontinuation of clinical development of the drug combination studied in this protocol. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when there is no longer a need for these documents to be retained. Permission must be acquired from the State of Florida for document destruction after the 10-year minimum record-retention period described above has elapsed.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations as defined by the Moffitt Clinical Trials Office standard. All deviations must be addressed in study source documents. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

14.4 PUBLICATION AND DATA SHARING POLICY

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine.

The PI will provide to the Protocol Information Specialist at Moffitt Cancer Center, details as requested for registering and reporting results for this clinical trial on ClinicalTrials.gov. At the conclusion of the trial, the PI will make study results available to the research community and the public-at-large.

Authorship in publications will be determined by the PI depending on participation, enrollment, and significant contribution during the trial process and manuscript elaboration.

15 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership and the Moffitt Cancer Center have established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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APPENDIX

APPENDIX A. Patient Global Impression of Change (PGIC)

Instructions: Circle the answer that is most appropriate.

Since the start of the treatment you've received in this study, your myelofibrosis symptoms are:

1. Very much improved
2. Much improved
3. Minimally improved
4. No change
5. Minimally worse
6. Much worse
7. Very much worse

APPENDIX B. ECOG Performance Status[33]

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

APPENDIX C. Myeloproliferative Neoplasm Symptoms Assessment Form Total Symptom Score (MPN-SAF TSS)[34]

Symptom	1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours*	**(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)**
Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early satiety)	**(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)**
Abdominal discomfort	**(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)**
Inactivity	**(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)**
Problems with concentration - Compared to prior to my MPD	**(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)**
Night sweats	**(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)**
Itching (pruritus)	**(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)**
Bone pain (diffuse not joint pain or arthritis)	**(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)**
Fever (>100 F)	**(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)**
Unintentional weight loss last 6 months	**(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)**

*** Question used with permission from the MD Anderson Cancer Center Brief Fatigue Inventory**

APPENDIX D. Moderate/strong inhibitors/inducers of CYP3A4

	Strong inhibitors	**Moderate inhibitors**
CYP3A4	boceprevir, cobicistat[h], danoprevir and ritonavir[j], elvitegravir and ritonavir[j], grapefruit juice[k], indinavir and ritonavir[j], itraconazole[h], ketoconazole, lopinavir and ritonavir[h,j], paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[j], posaconazole, ritonavir(h,j), saquinavir and ritonavir[h,j], telaprevir[h], tipranavir and ritonavir[h,j], telithromycin, troleandomycin, voriconazole	aprepitant, ciprofloxacin, conivaptan[l], crizotinib, cyclosporine, diltiazem[m], dronedarone[h], erythromycin, fluconazole[f], fluvoxamine[a], imatinib, tofisopam, verapamil[h]

	Strong inducers	**Moderate inducers**
CYP3A	apalutamide, carbamazepine[e], enzalutamide[g], mitotane, phenytoin[b], rifampin[a], St. John's wort[h]	bosentan, efavirenz[f], etravirine, phenobarbital, primidone

APPENDIX E. Diagnostic Criteria[35]

Chronic Neutrophilic Leukemia (CNL)

CNL diagnostic criteria
1. PB WBC $\geq 25 \times 10^9$/L
Segmented neutrophils plus band forms ≥80% of WBCs
Neutrophil precursors (promyelocytes, myelocytes, and metamyelocytes) <10% of WBC
Myeloblasts rarely observed
Monocyte count $< 1 \times 10^9$/L
No dysgranulopoiesis
2. Hypercellular BM
Neutrophil granulocytes increased in percentage and number
Neutrophil maturation appears normal
Myeloblasts <5% of nucleated cells
3. Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PV, ET, or PMF
4. No rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or *PCM1-JAK2*
5. Presence of *CSF3R* T618I or other activating *CSF3R* mutation
or
In the absence of a *CSFR3R* mutation, persistent neutrophilia (at least 3 mo), splenomegaly and no identifiable cause of reactive neutrophilia including absence of a plasma cell neoplasm or, if present, demonstration of clonality of myeloid cells by cytogenetic or molecular studies

CMML diagnostic criteria
• Persistent PB monocytosis ≥1 × 10^9/L, with monocytes accounting for ≥10% of the WBC count
• Not meeting WHO criteria for *BCR-ABL1*$^+$ CML, PMF, PV, or ET*
• No evidence of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement or *PCM1-JAK2* (should be specifically excluded in cases with eosinophilia)
• <20% blasts in the blood and BM†
• Dysplasia in 1 or more myeloid lineages. If myelodysplasia is absent or minimal, the diagnosis of CMML may still be made if the other requirements are met and
• An acquired clonal cytogenetic or molecular genetic abnormality is present in hemopoietic cells‡
or
• The monocytosis (as previously defined) has persisted for at least 3 mo and
• All other causes of monocytosis have been excluded

*Cases of MPN can be associated with monocytosis or they can develop it during the course of the disease. These cases may simulate CMML. In these rare instances, a previous documented history of MPN excludes CMML, whereas the presence of MPN features in the BM and/or of MPN-associated mutations (*JAK2*, *CALR*, or *MPL*) tend to support MPN with monocytosis rather than CMML.

†Blasts and blast equivalents include myeloblasts, monoblasts, and promonocytes. Promonocytes are monocytic precursors with abundant light gray or slightly basophilic cytoplasm with a few scattered, fine lilac-colored granules, finely distributed, stippled nuclear chromatin, variably prominent nucleoli, and delicate nuclear folding or creasing. Abnormal monocytes, which can be present both in the PB and BM, are excluded from the blast count.

‡The presence of mutations in genes often associated with CMML (eg, *TET2*, *SRSF2*, *ASXL1*, *SETBP1*) in the proper clinical contest can be used to support a diagnosis. It should be noted however, that many of these mutations can be age-related or be present in subclones. Therefore, caution would have to be used in the interpretation of these genetic results.

Atypical Chronic Myeloid Leukemia (aCML)

aCML diagnostic criteria
• PB leukocytosis due to increased numbers of neutrophils and their precursors (promyelocytes, myelocytes, metamyelocytes) comprising ≥10% of leukocytes)
• Dysgranulopoiesis, which may include abnormal chromatin clumping
• No or minimal absolute basophilia; basophils usually <2% of leukocytes
• No or minimal absolute monocytosis; monocytes <10% of leukocytes
• Hypercellular BM with granulocytic proliferation and granulocytic dysplasia, with or without dysplasia in the erythroid and megakaryocytic lineages
• <20% blasts in the blood and BM
• No evidence of *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangement, or *PCM1-JAK2*
• Not meeting WHO criteria for *BCR-ABL1*$^{+}$ CML, PMF, PV, or ET*

*Cases of MPN, particularly those in accelerated phase and/or in post-polycythemic or post-essential thrombocythemic myelofibrosis, if neutrophilic, may simulate aCML. A previous history of MPN, the presence of MPN features in the BM and/or MPN-associated mutations (in *JAK2*, *CALR*, or *MPL*) tend to exclude a diagnosis of aCML. Conversely, a diagnosis of aCML is supported by the presence of *SETBP1* and/or *ETNK1* mutations. The presence of a *CSF3R* mutation is uncommon in aCML and if detected should prompt a careful morphologic review to exclude an alternative diagnosis of CNL or other myeloid neoplasm.

Myelodysplastic/Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis (MDS/MPN-RS-T)

MDS/MPN diagnostic criteria
• Anemia associated with erythroid lineage dysplasia with or without multilineage dysplasia, ≥15% ring sideroblasts,* <1% blasts in PB and <5% blasts in the BM
• Persistent thrombocytosis with platelet count ≥450 × 10^9/L
• Presence of a *SF3B1* mutation or, in the absence of *SF3B1* mutation, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features†
• No *BCR-ABL1* fusion gene, no rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*; or *PCM1-JAK2*; no (3;3)(q21;q26), inv(3)(q21q26) or del(5q)‡
• No preceding history of MPN, MDS (except MDS-RS), or other type of MDS/MPN

*At least 15% ring sideroblasts required even if *SF3B1* mutation is detected.

†A diagnosis of MDS/MPN-RS-T is strongly supported by the presence of *SF3B1* mutation together with a mutation in *JAK2* V617F, *CALR*, or *MPL* genes.

‡In a case which otherwise fulfills the diagnostic criteria for MDS with isolated del (5q)-no or minimal absolute basophilia; basophils usually <2% of leukocytes.

APPENDIX F. MDS/MPN Response Criteria[1]

CR (presence of all of the following improvements)*
Bone marrow: ≤5% myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity*
Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤grade 1 fibrosis)†
Peripheral blood‡
WBC ≤10 × 10^9 cells/L
Hgb ≥11 g/dL
Platelets ≥100 × 10^9/L; ≤450 × 10^9/L
Neutrophils ≥1.0 × 10^9/L
Blasts 0%
Neutrophil precursors reduced to ≤ 2%
Monocytes ≤1 × 10^9/L
Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly
Provisional category of CR with resolution of symptoms:‡ CR as described above, and complete resolution of disease-related symptoms as noted by the MPN-SAF TSS
Persistent low-level dysplasia is permitted given subjectivity of assignment of dysplasia*
Complete cytogenetic remission
Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic, syndrome myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal of 20 metaphases or FISH§
Partial remission
Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity *except* in cases of MDS/MPN with ≤5% bone marrow blasts at baseline
Marrow response
Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above.
Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity, *or* reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 mo apart
Clinical benefit
Requires 1 of the following in the absence of progression or CR/partial response and independent of marrow response (cord blood response must be verified at ≥8 wk) to be considered a clinical benefit
Erythroid response
Hgb increase by ≥2.0 g/dL
TI for ≥ 8 wk for patients requiring at least 4 packed red blood cell transfusions in the previous 8 wk
Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤8.5 g/dL will count in the red blood cell TI response evaluation‖
Platelet response
Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 wk
Pretreatment ≤20 × 10^9/L: increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100%
Pretreatment >20 × 10^9/L but ≤ 100 × 10^9/L: absolute increase of ≥30 × 10^9/L‖
Neutrophil response
Pretreatment ≤0.5 × 10^9/L at least 100% increase and an absolute increase ≥0.5 × 10^9/L
Pretreatment, >0.5 × 10^9/L and ≤1.0 × 10^9/L At least 50% increase and an absolute increase ≥0.5 × 10^9/L‖
Spleen response
Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable
Symptom response
Improvement in symptoms as noted by decrease of ≥50% as per the MPN-SAF TSS scoring <20 were not considered eligible for measuring clinical benefit.¶

*Presence of dysplastic changes, which may be interpreted within the scope of normal range of dysplastic changes, may still exist in the presence of CR as allowed in MDS IWG. Marrow should exhibit age-adjusted normocellularity in CR.

†If there is no significant fibrosis present on the initial bone marrow biopsy, a second biopsy is not required to prove resolution of fibrosis. Grading of fibrosis in measurement of treatment response should be according to the European Consensus System.[67]

‡Given the current lack of a validated tool to assess complete resolution of symptoms in MDS/MPN, "CR with resolution of symptoms" (a complete resolution of disease-related symptoms as noted by the MPN-SAF TSS in presence of CR) will be a provisional category of disease response.

§Loss of cytogenetic burden of disease by (via FISH or classic karyotyping) known to adversely affect prognosis is required to reach complete cytogenetic remission. Decrease in the cytogenetic burden of disease must be by ≥50% (via FISH or classic karyotyping) to be indicative of a partial cytogenetic response. Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on the performance characteristics of the specific probes used.

‖Resolution of abnormal peripheral blood counts must persist for at least 2 separate analyses over at least 8 wk. In the case of proliferative MDS/MPN, CR will include resolution of thrombocytosis to a normal platelet count (150-450 × 10^9/L) and resolution of leukocytosis to WBC ≤10 × 10^9 cells/L but ≥1.5 × 10^9/L. Hgb should be maintained >11 g/dL and platelets ≥100 × 10^9/L without the support of transfusions. Clinical benefit may occur when these changes occur in absence of other changes required for CR or marrow response. Platelet and packed red blood cell TI would be considered for clinical benefit, and duration of TI should be monitored. Reduction in myeloid precursors (promyelocytes, myelocytes, metamyelocytes, nucleated red blood cells) to less than appreciable levels (≤2-3%) and/or 1 × 10^9/L monocytosis in the absence of infection, cytokine treatment, or other reactive causes.

APPENDIX G. Correlative Worksheet

Site name: _____ Patient's Initials:_____ Pt. Study ID #:_____

Blood or Bone Marrow (circle) Collections – all times must be recorded in military time

Cycle/Day	**Date of Collection (mm-dd-yyyy)**	Collection Time
Comments		

Please photocopy this for your records and maintain with a copy of the shipping waybill. Return the original to Moffitt with the specimens. This source document stands as a custodial record.

Ship all the above samples to:
Maria Balasis
12902 Magnolia Drive
Stabile Research Building (SRB) Room #23234
Tampa, FL 33612
813-745-6458
*Please email (*maria.balasis@moffitt.org**,** eric.padron@moffitt.org, Andrew.Kuykendall@moffitt.org*) on the day of shipment with courier tracking information.*

Ship Monday through Thursday ONLY!

Do not write below this line

Condition received: _____ Initials: _____

Comments: _____ Initials: _____

APPENDIX H[1] Proposed Progression Criteria for MDS/MPN

Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from list
Major criteria
Increase in blast count*
<5% blasts: ≥50% increase and to >5% blasts
5-10% blasts: ≥50% increase and to >10% blasts
10-20% blasts: ≥50% increase and to >20% blasts
20-30% blasts: ≥50% increase and to >30% blasts†
Evidence of cytogenetic evolution‡
Appearance of a previously present or new cytogenetic abnormality in complete cytogenetic remission via FISH or classic karyotyping
Increase in cytogenetic burden of disease by ≥50% in partial cytogenetic remission via FISH or classic karyotyping
New extramedullary disease
Worsening splenomegaly
Progressive splenomegaly that is defined by IWG-MRT: the appearance of a previously absent splenomegaly that is palpable at >5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of >10 cm
Extramedullary disease outside of the spleen
To include new/worsening hepatomegaly, granulocytic sarcoma, skin lesions, etc.
Minor criteria
Transfusion dependence§
Significant loss of maximal response on cytopenias ≥50% decrement from maximum remission/response in granulocytes or platelets
Reduction in Hgb by ≥1.5g/dL from best response or from baseline as noted on complete blood count
Increasing symptoms as noted by increase in ≥50% as per the MPN-SAF TSS‖
Evidence of clonal evolution (molecular)¶

*Blasts as measured from the bone marrow.

†Patients with development of acute myeloid leukemia from MDS/MPN; 20-30% blasts may be allowed on some clinical trials for patients with MDS/MPN.

‡Increase in cytogenetic burden of disease by ≥50% (via FISH or classic karyotyping). Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on specific probes used.

§Transfusion dependency is defined by a history of at least 2 U of red blood cell transfusions in the past month for a hemoglobin level <8.5 g/dL that was not associated with clinically overt bleeding. Cytopenias resulting from therapy should not be considered in assessment of progression.

‖MPN-SAF TSS validation among patients with MDS/MPN is currently under way (R.A. Mesa, personal communication, 2014).

¶The identification of new abnormalities using single nucleotide polymorphism arrays or sequencing or a clearly significant increase in mutational burden of a previously detected abnormality. Precise criteria for defining new abnormalities and what exactly constitutes a significant increase in mutational burden are open to interpretation; we suggest that this criterion should be used conservatively based on current evidence.