Protocol for

Official Title of Study

A PHASE 3B, MULTICENTER, SINGLE-ARM, OPENLABEL EFFICACY AND SAFETY STUDY OF FEDRATINIB IN SUBJECTS WITH DIPSSINTERMEDIATE OR HIGH-RISK PRIMARY MYELOFIBROSIS, POST-POLYCYTHEMIA VERA MYELOFIBROSIS, OR POST-ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS AND PREVIOUSLY TREATED WITH RUXOLITINIB

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A PHASE 3B, MULTICENTER, SINGLE-ARM, OPEN-LABEL EFFICACY AND SAFETY STUDY OF FEDRATINIB IN SUBJECTS WITH DIPSS-INTERMEDIATE OR HIGH-RISK PRIMARY MYELOFIBROSIS, POST-POLYCYTHEMIA VERA MYELOFIBROSIS, OR POST-ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS AND PREVIOUSLY TREATED WITH RUXOLITINIB

The "FREEDOM" Trial

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Printed Name of Site Principal Investigator

Institution Name: _____

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PROTOCOL SUMMARY

Study Title

A Phase 3b, Multicenter, Single-Arm, Open-Label Efficacy and Safety Study of Fedratinib in Subjects with DIPSS (Dynamic International Prognostic Scoring System)-Intermediate or High-Risk Primary Myelofibrosis (PMF), Post-Polycythemia Vera Myelofibrosis (post-PV MF), or Post-Essential Thrombocythemia Myelofibrosis (post-ET MF) and Previously Treated with Ruxolitinib.

Objectives

The primary objective of the study is to evaluate the percentage of subjects with at least a 35% spleen volume reduction with fedratinib.

The secondary objectives are:

- To evaluate the safety of fedratinib
- To evaluate the reduction of spleen size by palpation
- To evaluate the symptom response rate in myelofibrosis (MF)-associated symptoms as measured by the Myelofibrosis Symptom Assessment Form (MFSAF)
- To evaluate durability of spleen response by MRI (magnetic resonance imaging)/CT (computed tomography) and by palpation
- To evaluate the durability of symptoms response
- To assess the effectiveness of the risk mitigation strategy for gastrointestinal (GI) events
- To assess the effectiveness of the risk mitigation strategy for encephalopathy including Wernicke's

Study Design

The study will consist of the following 3 periods:

- A 28-day Screening Period
- Fedratinib Treatment Period including a 30-Day Follow-up after last dose visit

- A 12 month Survival Follow-up Period

This study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

The study will enroll approximately 110 subjects internationally.

Study population consists of subjects with intermediate or high-risk primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), or post-essential thrombocythemia myelofibrosis (post-ET MF).

Length of Study

The expected duration of the study is approximately 4 years, which includes approximately 18 months to fully enroll, and 24 months for treatment and follow-up. Actual duration of the trial will be dependent upon the median treatment duration for subjects.

The End of Trial is defined as either the date of the last visit of the last subject to complete the Survival Follow-up (or Long-term Follow-up), or the date of receipt of the last data point from the last subject that is required for primary, secondary, [redacted] analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

Fedratinib will be orally self-administered on an outpatient basis, once daily preferably together with food during an evening meal at the same time each day in consecutive 4-week (28-day) cycles. However, fedratinib may be taken with or without regard to food.

The fedratinib dose in this study is 400 mg/day. If a subject experiences a drug toxicity as specified in the Fedratinib Dose Modification Schedule table (Table 4), the dosing should be interrupted and the dose may need to be modified (Section 7).

If a subject does not tolerate fedratinib therapy after 2 dose level reductions from the starting dose, he/she must be withdrawn from the study treatment. If the toxicity does not resolve in the time period as specified in the Fedratinib Dose Modification Schedule table (Table 4), subjects must be withdrawn from the study treatment. Reescalation of doses is possible in certain cases as defined in the Fedratinib Dose Modification Schedule table (Table 4). The daily dose of fedratinib cannot exceed 400 mg/day.

Subjects may continue treatment with fedratinib until unacceptable toxicity, lack of therapeutic effect, progression of disease, or until a subject is not compliant with treatment or withdraws consent.

Overview of Key Efficacy Assessments

Assessment of Spleen Size

Spleen volume will be assessed (MRI or CT Scan if MRI is contraindicated) during screening and at the end of Cycle 3, 6, 12, 18, 24, and End of Treatment (EOT). The same method (MRI or CT scan) should be used throughout the study. An MRI or CT scan (if MRI is contraindicated) needs to be performed within 5 days of starting study treatment and after previous treatments

have been discontinued for ≥ 14 days according to exclusion criteria #9 and #10 (Section 4.3). The MRI/CT scans will be reviewed centrally.

Spleen size will also be assessed by palpation at screening and on Day 1 of each treatment cycle, at the end of treatment visit and at the 30-Day Follow-up visit after last dose of fedratinib.

Assessment of MF-associated symptoms

The MF-related symptoms evaluation will be performed using the MFSAF version 4.0 using a 7-day recall period (Gwaltney, 2017).

Overview of Key Safety Assessments

Safety of fedratinib is evaluated based on the incidence of treatment-emergent adverse events (TEAEs) and changes in clinical laboratory parameters, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), electrocardiogram (ECG), and vital signs.

Safety assessments will be comprised of:

- Record of adverse events (AEs) and serious adverse events (SAEs) at each study visit
- Physical examination including assessment of abnormal eye movements, cerebellar abnormalities, body weight
- Vital signs
- Cognitive assessment: Mini-Mental State Examination (MMSE)
- Laboratory assessments: hematology, serum chemistry, lipid profile, thiamine level, coagulation, urinalysis, serum/urine pregnancy tests
- Electrocardiogram (ECG)
- Risk mitigation strategies for gastrointestinal events and encephalopathy including Wernicke's

[redacted]

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1. INTRODUCTION

1.1. Disease Background

1.1.1. Myeloproliferative Neoplasm (MPN) Associated Myelofibrosis

Myeloproliferative neoplasm-associated myelofibrosis (MF) is a serious and life-threatening disease that can present as a de novo or primary myelofibrosis (PMF) or evolve from previous polycythemia vera (post-PV MF) or essential thrombocythemia (post-ET MF) (Swerdlow, 2008). The disease is characterized by clonal myeloproliferation, ineffective erythropoiesis, bone marrow stromal changes, hepatosplenic extramedullary hematopoiesis, and aberrant cytokine expression [redacted] Patients typically present with splenomegaly, constitutional symptoms, moderate to severe anemia, thrombocytopenia, and leukocytosis.

Primary myelofibrosis is a member of a group of Philadelphia chromosome (Ph1)-negative myeloproliferative neoplasm (MPN) which also includes PV and ET (Tefferi, 2007). Almost all patients with PV and about one-half of patients with ET and PMF have a Janus kinase 2 (JAK2) mutation, typically JAK2V617F. Other mutations in patients with PMF include calreticulin (CALR) and myeloproliferative leukemia virus (MPL). About 20% of patients with PMF have no detectable mutation in JAK2, CALR, or MPL and are termed triple negative [redacted]. Mutations in JAK2, CALR, and MPL result in activation of the JAK/ signal transducers and activators of transcription (STAT) signaling pathway resulting in cell proliferation and inhibiting cell death. The result is clonal expansion (Ihle, 2007). Thus, a JAK2 inhibitor that can down regulate the JAK/STAT pathway is expected to be helpful in reducing cell proliferation.

Polycythemia vera (PV) and essential thrombocythemia (ET) are characterized by increased levels of red blood cells (RBCs) and platelets. However, about 10% of affected patients develop bone marrow fibrosis morphologically indistinguishable from PMF. These conditions are termed post-PV MF and post-ET MF (Campbell, 2005), and are clinically named MPN-associated myelofibrosis. Patients with MPN-associated myelofibrosis have similar survival prognoses to that of the PMF and about a 10% cumulative risk of transformation to acute myeloid leukemia (AML).

There are several prognostic scoring systems predicting survival of patients with PMF. The International Prognostic Scoring System (IPSS) is used to predict survival at diagnosis and the Dynamic International Prognostic Scoring System (DIPSS) at any time in the disease course (Cervantes, 2009; Passamonti, 2010). Variables included in the IPSS are age > 65 years, constitutional symptoms, hemoglobin level < 10 g/dL, and white blood cell (WBC) counts. Additional recent prognostic scoring systems include the Dynamic International Prognostic Scoring System Plus (DIPSS Plus) and scoring systems incorporating data from mutation analyses. There is a strong association between overall survival for MF patients and the DIPSS risk category for patients with low, intermediate risk 1, intermediate risk 2, or high risk with median survival of 15.4, 6.5, 2.9, and 1.3 years, respectively (Tefferi, 2016).

Approximately 70% of individuals with MF are in the intermediate-2 or high-risk categories (Gangat, 2011), representing the greatest unmet medical need. Symptomatic enlargement of the spleen and liver, the necessity for RBC transfusions, cachexia, and the other

MF-associated symptoms result in greatly compromised quality of life in these patients (Mesa, 2007).

1.1.2. Treatment Options for MPN-Associated Myelofibrosis

Allogeneic stem-cell transplantation (SCT) is the only treatment that can induce long-term remission in patients with MF. The average age at diagnosis of MF is 65 years; thus, the majority of patients are not eligible for SCT. Therefore, the treatment options are primarily symptom-oriented, to help mitigate the clinical presentation of anemia, splenomegaly, constitutional symptoms and less commonly increased levels of platelets, and WBCs. So far, none of these symptom-oriented treatments has shown an anti-clonal effect, although alleviation in spleen size and splenic discomfort, symptoms, and anemia have been shown (Vannucchi, 2017).

Fortunately, the understanding of MPNs and the molecular mechanisms of the disease have been expanding. In 2005, the JAK2V617F mutation was discovered and observed in approximately 50% to 60% of patients with PMF or ET and 90% to 95% of patients with PV. This discovery, along with the observation of other mutations in patients with MPNs found to activate the JAK/STAT pathway (JAK2 exon 12, myeloproliferative leukemia, and adaptor protein LNK) (Oh, 2010; Pikman, 2006; [redacted]), has established dysregulation of the JAK signaling pathway as the major contributor to the pathogenesis of MPNs. It has also translated into the development of small-molecule JAK inhibitors.

Until recently, the JAK1/2 inhibitor ruxolitinib was the only approved therapy for MPN-associated MF in the United States (US). On 16 Aug 2019, fedratinib (INREBIC®) was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis. Ruxolitinib is indicated for treatment of patients with intermediate or high-risk MPN-associated MF, including primary MF, post-polycythemia vera MF and post-essential thrombocythemia MF. The registration of ruxolitinib was based on 2 randomized, controlled studies (COMFORT-I and COMFORT-II) that compared ruxolitinib to placebo and to the best available therapy (BAT), respectively (Harrison, 2012; Verstovsek, 2012). The studies demonstrated benefit, with a higher proportion of subjects in the ruxolitinib arms exhibiting a ≥ 35% reduction in spleen volume as measured by magnetic resonance imaging (MRI) at 24 weeks in COMFORT-I (41.9% ruxolitinib versus (vs) 0.7% placebo) and at 48 weeks in COMFORT-II (28.5% ruxolitinib versus 0% BAT). In COMFORT-I, there was a > 50% improvement in the Myelofibrosis Symptom Assessment Form (MFSAF) Total Symptom Score (TSS) at 24 weeks in 45.9% of subjects on ruxolitinib compared with 5.3% of subjects on placebo. Improvement of survival in the ruxolitinib arm as compared with BAT was also demonstrated based on the recent 3-year follow-up data from the COMFORT-II study. The Kaplan-Meier estimated probability of survival at 144 weeks was 81% in the ruxolitinib arm and 61% in the BAT arm (Cervantes, 2012). Improvement in bone marrow fibrosis was observed in 15% of subjects receiving ruxolitinib at 24 months compared with 5% of subjects who received BAT; however, the improvements declined by 48 months in the small number of subjects who were available for follow-up. It is unclear if any of the subjects who were included in this study achieved clinical resolution of their spleen and symptoms (Kvasnicka, 2013).

1.1.3. Approved Therapies

Ruxolitinib is approved in the United States (US) and in the European Union (EU) for the treatment of MPN-associated myelofibrosis.

In the US ruxolitinib (Jakafi™[1]) has been approved by the Food and Drug Administration (FDA) in November 2011 for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

In the EU ruxolitinib (Jakavi™[2]) has been approved by the European Medicines Agency (EMA) in August 2012 for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

In Canada, ruxolitinib is approved for the treatment of splenomegaly and/or its associated symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

On 16 Aug 2019, INREBIC (fedratinib) was approved by the US FDA for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis.

1.1.4. Medical Need

MPN-associated myelofibrosis, particularly intermediate or high-risk disease, is a serious and fatal condition. Until recently, ruxolitinib, a JAK1/2 inhibitor, was the only drug approved for the treatment of patients with intermediate or high-risk MF in the US. While the benefits of ruxolitinib therapy in terms of spleen response and improvement of constitutional symptoms are significant, ruxolitinib is also associated with the risks of treatment-associated anemia (40.4% vs 12.3% for BAT) and thrombocytopenia (44.5% vs 9.65% for BAT) (Harrison, 2012). The 1-, 2-, and 3-year discontinuation rates are 49, 71 and 86%, respectively. Major reasons for ruxolitinib treatment discontinuation are loss of therapeutic effect, lack of response and drug-induced cytopenias [redacted]. Additionally, responses to ruxolitinib are typically observed within the first 3–6 months after therapy initiation (Harrison, 2012; Verstovsek, 2012) and it has been suggested that for patients who have not had a reduction in spleen size or improvement in symptoms after that period, alternative therapies should be considered (Harrison, 2018; Keohane, 2013). The effect of ruxolitinib on overall survival (OS) continues to be debated and the unclear limited effects on bone marrow fibrosis and driver mutation allele burden suggest that the disease-modifying activity of the drug is likely to be minor.

Therefore, the unmet medical need for frontline MF patients remains high, despite the availability of ruxolitinib, especially for patients who have low baseline platelet counts and are susceptible to myelosuppression/thrombocytopenia.

[1] Jakafi is a registered trademark of Incyte Corporation.

[2] Jakavi is a registered trademark of Novartis AG in countries outside of the US.

For patients who have been previously treated with a JAK2 inhibitor, there is no approved therapy and the prognosis is very poor. Mechanisms of resistance to ruxolitinib remain unclear. It has been shown preclinically that MF is intrinsically more resistant to JAK2 inhibition than PV or ET and there continues to be a major unmet need for a JAK2 inhibitor that is effective after ruxolitinib treatment failure. Moreover, the median survival of relapsed and refractory patients who discontinued ruxolitinib has been reported to be 6 months (Jabbour, 2013). Notably, after a median follow-up of 10 months from stopping ruxolitinib, only 34% of patients remained alive (Kantarjian, 2013). Only 27% of patients remained on therapy after 5 years in the COMFORT-I trial. Outcomes for patients who discontinue ruxolitinib in this situation are poor.

Therefore, there remains an unmet need for the patients who have been previously treated with a JAK2 inhibitor due to the low life expectancy, notably high discontinuation rate with ruxolitinib and the myelosuppression.

1.2. Fedratinib

Fedratinib is an oral kinase inhibitor with activity against wild type and mutationally activated Janus Kinase 2 (JAK2) and fibromyalgia syndrome (FMS)-like tyrosine kinase 3 (FLT3). Fedratinib is a JAK2-selective inhibitor with higher potency for JAK2 over family members JAK1, JAK3 and tyrosine kinase 2 (TYK2). In cell models expressing mutationally active JAK2 or FLT3, fedratinib reduced phosphorylation of signal transducer and activator of transcription (STAT3/5) proteins, inhibited cell proliferation, and induced apoptotic cell death. In mouse models of JAK2V617F-driven myeloproliferative disease, fedratinib blocked phosphorylation of STAT3/5, increased survival and improved disease-associated symptoms, including reduction of white blood cells, hematocrit, splenomegaly, and fibrosis.

Eighteen clinical studies were conducted with fedratinib. Fedratinib has been studied extensively in the treatment of patients with MPN-associated myelofibrosis.

Fedratinib demonstrated clinical efficacy in a randomized, placebo-controlled, Phase 3 study (JAKARTA [EFC12153]) in patients with intermediate-2 or high-risk MF who were previously untreated. The primary endpoint was response rate, defined as the proportion of subjects who had a ≥ 35% reduction in spleen volume from baseline to the End of Cycle 6 and confirmed 4 weeks later by MRI. Analyses for spleen response were also performed at the end of Cycle 6 (eg regardless of confirmation), as recommended by the International Working Group – Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Criteria. Symptom response rate (SRR), based on a patient-reported outcome (PRO) tool, the modified MFSAF that assessed 6 key MF-associated symptoms (night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, and bone or muscle pain) was a key secondary endpoint. The SRR was defined as the proportion of subjects with a ≥ 50% reduction in the Total Symptom Score (TSS) of the modified MFSAF diary from baseline to the end of Cycle 6. Both endpoints are measures for demonstrating clinical benefit in the proposed population. The response rate per primary endpoint was 36.5% and 40.2% at the 400 mg (proposed dose for this study) and 500 mg daily dose respectively vs 1% on the placebo arm. The response rate at Cycle 6 as recommended by IWG-MRT was of 46.9% and 49.5% in patients treated with the 400 mg and 500 mg daily doses respectively. A total of 36.3% and 34.1% of subjects at the dose of 400 mg and 500 mg doses respectively achieved a ≥ 50% reduction in TSS compared with 7.1% of subjects receiving placebo. Median duration of response (≥35% reduction in spleen volume) was 10.4 months for

responders from both active groups (400-mg and 500-mg groups). The most common treatment-emergent adverse events (TEAEs) of all grades reported in the fedratinib 400-mg daily dose group were diarrhea 65.6%, nausea 63.5%, anemia (Grade 3 and Grade 4) 42.7%, vomiting 41.7%, fatigue 15.6%, and peripheral edema 15.6%. The 400-mg dose was confirmed to be better tolerated than the 500-mg dose, in particular with fewer subjects reporting Grade 3 or 4 TEAEs (54.2% and 70.1%, respectively), treatment-emergent serious adverse events (SAEs) (27.1 % and 30.9%, respectively) and TEAEs leading to permanent treatment discontinuation (13.5% and 24.7%, respectively) [redacted]

The single-arm Phase 2 JAKARTA2 study (ARD12181) enrolled patients with intermediate-1 with symptoms, intermediate-2 or high-risk MPN-associated myelofibrosis who have been previously treated with ruxolitinib. The primary endpoint was response rate, which was defined as the proportion of subjects who have a ≥ 35% reduction from baseline in spleen volume to the End of Cycle 6 in the per protocol defined population.

As in the Phase 3 JAKARTA study, one of the key secondary endpoints was symptom response rate (SRR), defined as the proportion of subjects with a ≥ 50% reduction in the TSS using the modified MFSAF diary from baseline to the end of Cycle 6.

Resistance to ruxolitinib was defined as any one of the following: a) Lack of response: absence of response; b) disease progression: spleen size increase during ruxolitinib treatment; or c) loss of response at any time during ruxolitinib treatment. Intolerance to ruxolitinib was defined as any one of the following: a) hematologic toxicity (anemia, thrombocytopenia, others); b) non-hematologic toxicity.

The overall spleen response rate (proportion of patients with ≥ 35% reduction from baseline in spleen volume to the End of Cycle 6) was 55.4%. A total of 25.6% of subjects achieved a ≥ 50% reduction in TSS.

All 97 patients had at least 1 TEAE (all grades); Grade 3 or 4 TEAEs were reported by 62.9% patients. The most common nonhematologic TEAEs (reported by ≥ 10% of patients) (all grades) were gastrointestinal disorders including diarrhea (61.9%), nausea (55.7%), and vomiting (41.2%). The most common hematologic TEAEs (reported by > 10 patients) (all grades) were anemia (48.5%) and thrombocytopenia (26.8%). Thirty-eight and one-tenth percent experienced Grade 3 or 4 anemia and 21.6% experienced Grade 3 or 4 thrombocytopenia. No Grade 5 hematologic TEAEs were reported. Anti-infectives for systemic use were given to 55.7% patients in the study (Harrison, 2017).

On 16 Aug 2019, INREBIC (fedratinib) was approved by the US FDA for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis.

Please refer to the Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of fedratinib.

1.2.1. Encephalopathy including Wernicke's in Patients Treated with Fedratinib

Following the submission of cases with potential events of Wernicke's encephalopathy (WE) in subjects treated with fedratinib across the fedratinib clinical development program, the Food and

Drug Administration (FDA) placed the fedratinib Investigational New Drug (IND) application (IND 078286) on full clinical hold on 15 Nov 2013.

Consequently, Sanofi terminated the development of fedratinib on 18 Nov 2013. All subjects worldwide were permanently discontinued from fedratinib treatment, offered thiamine supplementation for ≥ 90 days, and followed for safety. The FDA removed the clinical hold on 18 Aug 2017, following additional data being provided to the FDA by a new sponsor.

Eight subjects with potential Wernicke's encephalopathy (WE) were identified in 608 patients treated with multiple doses of fedratinib in the clinical program. One subject was determined to have hepatic encephalopathy. Of the remaining 7 subjects, all were taking fedratinib 500 mg daily prior to the onset of neurological symptoms. One of these subjects had a confirmed diagnosis of WE based upon review by 5 independent experts. These subjects had predisposing factors (including baseline malnutrition and/or treatment emergent GI AEs) that are known to lead to thiamine deficiency and increase the risk of WE in any population. Preclinical studies in rats have demonstrated that, under clinically relevant doses, fedratinib does not inhibit thiamine transport in the gastrointestinal tract or the brain.

Recommendations for the use of fedratinib with adequate supportive treatment of nausea, vomiting, and diarrhea, as well as for increased clinical awareness of the signs and symptoms of encephalopathy, including Wernicke's and routine thiamine monitoring with thiamine supplementation, are included in this study protocol.

1.3. Rationale

1.3.1. Study Rationale and Purpose

Myeloproliferative neoplasm-associated MF is a serious and life-threatening disease. The only approved therapy currently available worldwide is the JAK1/2 inhibitor ruxolitinib.

While many JAK1/2 inhibitors are in development, only ruxolitinib was approved in the US and EU for the treatment of MPN-associated myelofibrosis. Recently, fedratinib was approved on 16 Aug 2019 in the US for the treatment of MPN-associated myelofibrosis.

For patients who have been previously treated with ruxolitinib and who failed first-line treatment, there is no approved therapy and prognosis for these patients is poor.

The Phase 3 JAKARTA study of fedratinib enrolled patients with intermediate-2 or high risk MPN -associated myelofibrosis. Fedratinib was given at 400 mg daily or 500 mg daily versus placebo evaluating the proportion who had ≥ 35% reduction in spleen volume determined by CT/MRI at the end of Cycle 6 with a confirmation 4 weeks later. The proportion of patients with this reduction were 1.0% in placebo, 36.5% in fedratinib 400 mg and 40.2% in fedratinib 500 mg.

The single-arm Phase 2 JAKARTA2 study of fedratinib enrolled patients with intermediate-1 with symptoms, intermediate-2 or high-risk MPN-associated myelofibrosis who were previously treated with ruxolitinib. In that study, fedratinib at a starting dose of 400 mg daily, resulted in a reduction in splenomegaly at the end of Cycle 6 (last observation carried forward) (response rate 55.4%) and improvement in symptom burden (response rate: 25.6%).

The studies were affected by the clinical hold mandated by the US FDA of the fedratinib development program in November 2013 due to reports of potential Wernicke's encephalopathy (WE) and all subjects on treatment with fedratinib were discontinued from treatment.

Based on the presentation of further analyses of the potential WE cases, the US FDA removed the clinical hold in August 2017 and required that steps be implemented to mitigate the risk for encephalopathy including Wernicke's for future clinical studies.

The present study is a multicenter, single-arm, open-label, Phase 3b study designed with the purpose to assess the efficacy of fedratinib administered at the dose of 400 mg daily orally in successive 28-day cycles and implement mitigation strategies to address US FDA request and to further evaluate the safety of fedratinib in subjects with DIPSS-intermediate or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis.

To mitigate the risk for encephalopathies including Wernicke's, routine thiamine monitoring and supplementation, monitoring for signs and symptoms of encephalopathy including Wernicke's, and proactive management of nausea, vomiting, and diarrhea to prevent thiamine deficiency have all been implemented in the present study.

The study will also provide additional data for Patient Reported Outcomes.

1.3.2. Rationale for the Study Design

This is a multicenter, single-arm, Phase 3b study with spleen volume reduction at the end of Cycle 6 as the primary objective.

The secondary objectives of the study are to further evaluate the safety and to assess and implement mitigation strategies for encephalopathy including Wernicke's and for gastrointestinal (GI) adverse events.

The study will be at multiple centers to provide access to a broad population and have assurance the results are likely to have general applicability.

This is also conducted as an open-label study to collect efficacy and safety data with fedratinib use, no randomization or stratification will occur.

The sample size of approximately 110 subjects and accounting for approximately 10 subjects that are not evaluable for evaluation will approximately yield 90% power to detect a lower bound of the 95% confidence interval for primary endpoint response rate excludes 20% under the assumption of a 35% response rate (Refer to Section 9.3).

The primary endpoint is the proportion of subjects who have a $\geq$ 35% reduction in spleen volume (measured by MRI or CT scan and assessed by central review) at the end of Cycle 6.

Safety will be assessed by evaluating adverse events and laboratory data. Adverse events and abnormal laboratory value severity will be graded using Version 5.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Efficacy data will be assessed using symptoms response assessment and palpation as well as MRI/CT imaging collected for the first year.

1.3.3. Rationale for Dose, Schedule and Regimen Selection in the Study

Fedratinib capsules will be administered orally, once-daily at a dose of 400 mg.

Dose finding (study TED12037) and dose ranging (study ARD11936) studies with fedratinib were performed, with the maximum tolerated dose (MTD) being 680 mg for patients with MPN-associated myelofibrosis.

In the JAKARTA study, doses of 400 mg and 500 mg were used in separate study arms, and while the efficacy in terms of spleen response was similar, the 400-mg dose was better tolerated than the 500-mg dose, in particular with fewer subjects reporting Grade 3 or 4 TEAEs (70.8% and 78.4%, respectively) and TEAEs leading to permanent treatment discontinuation (27.1% and 36.1%, respectively).

Fedratinib dose modifications will be allowed based on observed toxicity to a 300 mg or 200 mg daily dose in this study. Provisions are in place to allow further dose reduction for subjects with co-medication with moderate or strong Cytochrome P450 3A4 (CYP3A4) inhibitors.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is: • To evaluate the percentage of subjects with at least 35% spleen volume reduction with fedratinib
Secondary Objective(s)
The secondary objectives are: • To evaluate the safety of fedratinib • To evaluate the reduction of spleen size by palpation • To evaluate the symptom response rate in myelofibrosis (MF)-associated symptoms as measured by the Myelofibrosis Symptom Assessment Form (MFSAF) (Appendix B) • To evaluate the durability of spleen response by magnetic resonance imaging (MRI)/computer tomography (CT)-scan and by palpation • To evaluate the durability of symptoms response • To assess the effectiveness of the risk mitigation strategy for gastrointestinal events • To assess the effectiveness of the risk mitigation strategy for encephalopathy including Wernicke's
[redacted]

Table 2: Study Endpoints

Endpoint	Name	Description	Assessment Timeframe
Primary	Spleen volume response rate (RR)	Proportion of subjects who have a ≥ 35% SVR at end of Cycle 6	From screening to the end of Cycle 6
Secondary	Safety profile of fedratinib	Incidence and severity of all Grade AEs per NCI CTCAE (Appendix E) Incidence and severity of Grade 3-4 AEs as per the NCI CTCAE (Appendix E), including laboratory parameters	From ICF signature up until 30 days post last dose For fedratinib related AEs, anytime until the last study visit
	Spleen response rate by palpation (RRP)	Proportion of subjects who have ≥ 50% reduction in spleen size by palpation	From C1D1 to the end of Cycle 6
	Symptom response rate (SRR)	Proportion of subjects with ≥ 50% reduction in total symptom scores measured by MFSAF	From C1D1 to the end of Cycle 6
	Durability of spleen volume response (DR)	Duration of ≥ 35 % SVR	From screening to the End of Treatment visit
	Durability of spleen response by palpation (DRP)	Duration of ≥ 50 % reduction in spleen size by palpation for subjects with a palpable spleen at least 5 cm below the left costal margin (LCM) at C1D1	From C1D1 until the 30-Day Follow-up after last dose visit
	Durability of symptoms response (DSR)	Duration of ≥ 50% reduction in total symptom scores measured by MFSAF	From C1D1 until the 30-Day Follow-up after last dose visit
	Assessment of the effectiveness of the risk mitigation strategy for gastrointestinal adverse events and encephalopathy including Wernicke's	Incidence of subjects with a CTCAE Grade ≥3 of nausea, diarrhea, or vomiting, or occurrence of encephalopathy including Wernicke's (confirmed by brain MRI or autopsy). Assessment of thiamine levels at screening, on Day 1 of the first 3 cycles and every third cycle thereafter, and at the End of Treatment visit	From ICF signature to the 30-Day Follow-up after last dose visit

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Assessment Timeframe
[redacted]			

AEs = adverse events; C1D1 = Cycle 1 Day 1; CTC = Common Terminology Criteria for Adverse Events; ICF = informed consent form; MFSAF = Myelofibrosis Symptom Assessment Form; MRI = magnetic resonance imaging; NCI = National Cancer Institute; [redacted]; SVR = spleen volume reduction.

3. OVERALL STUDY DESIGN

3.1. Study Design

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

This is a Phase 3b, multicenter, single-arm, open-label study in subjects with Dynamic International Prognostic Scoring System (DIPSS) (Appendix F) intermediate or high-risk PMF (Appendix G, Appendix H), post-PV or post-ET MF (Appendix I).

The study will consist of 3 periods: a Screening Period, a Treatment Period including a 30-Day Follow-up after last dose visit and a Survival Follow-up Period. Further details are provided in Section 3.1.1.

The overall study design is described in Figure 1, with more detail for each phase of the study design found in Section 6.

3.1.1. Study Periods

Screening Period

All enrolled subjects will undergo screening procedures during the screening period which must be completed within 28 days prior to the start of study treatment. This will serve to determine subject eligibility based on all inclusion and exclusion criteria defined in the protocol. For subjects that are receiving ruxolitinib during the screening period or that have potentially reversible laboratory abnormalities (or other criteria that excludes the subject from enrollment) detected during screening, the screening period may be extended to 35 days (additional 7 days).

If needed, enrollment will be preceded by a taper-off period for previous treatment according to the prescribing information and a washout period for previous treatment in line with the inclusion and exclusion criteria for the study which is to be started at least 14 days before enrollment. Specifically, ruxolitinib should be gradually tapered before the 14-day washout and supportive care provided to mitigate potential ruxolitinib withdrawal syndrome with close physician supervision. When screening a subject, it is necessary to account for the required duration of the ruxolitinib washout period of 14 days and the need to perform the MRI or CT scan within 5 days prior to enrollment.

Treatment Period

Upon confirmation of eligibility, subjects will be enrolled and receive treatment with fedratinib at a dose of 400 mg once daily orally continuously. Cycles are defined for administrative purposes as 4-week (28-day) periods. Unless otherwise noted, visit windows are ± 3 days except for MRI/CT scan procedures which have a visit window of ± 7 days.

For the first 3 cycles, site visits will be performed on Day 1 and Day 15 and thereafter on Day 1 for the subsequent cycles. At Cycle 1 Day 8 the site will contact the subject by telephone to assess occurrence and discuss management of nausea, vomiting and diarrhea.

Subjects may continue treatment with fedratinib until unacceptable toxicity, lack of therapeutic effect, progression of disease, or until consent is withdrawn.

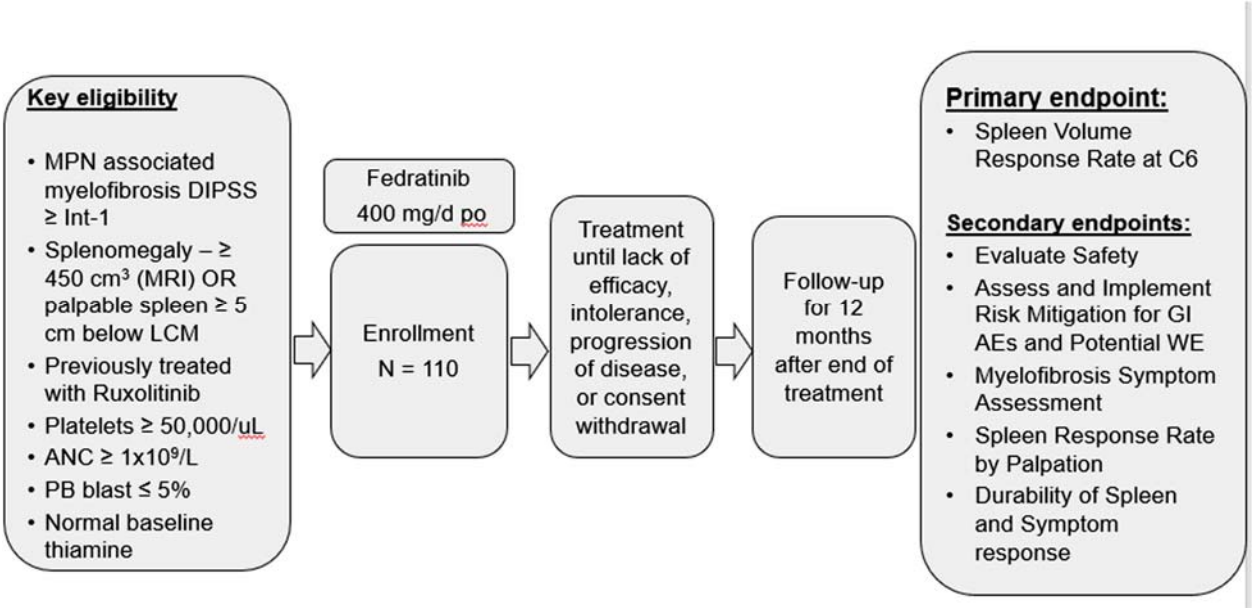
All subjects will be monitored for adverse events during the study.

All subjects discontinued from protocol-prescribed therapy for any reason will be followed for at least a period of 30 days following the last dose of fedratinib.

Survival Follow-up Period

All subjects discontinued from protocol-prescribed therapy for any reason will be followed for survival, subsequent therapies, new malignancy and progression of myelofibrosis to acute myeloid leukemia (AML) every 3 months until death or up to 12 months after End of Treatment (EOT), lost to follow-up, withdrawal of consent for further data collection, or study closure whichever comes first.

Figure 1: Overall Study Design



AE = adverse events; ANC = absolute neutrophil count; DIPSS = Dynamic International Prognostic Scoring System; GI = gastrointestinal; Int = intermediate; LCM = left costal margin; MPN = myeloproliferative neoplasm; MRI = magnetic resonance imaging; PB = peripheral blood; po = orally; [redacted]; WE = Wernicke's encephalopathy.

3.2. Study Duration for Subjects

The average treatment period for each subject enrolled in the Study is expected to be approximately 12 months. The Survival Follow-up period will last up to 12 months. The total expected study duration for enrolled subjects, including the Survival Follow-up period, will be approximately 2 years. Actual study duration will be dependent upon actual treatment duration for individual subjects.

3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the Survival follow-up (or Long-term Follow-up), or the date of receipt of the last data point from

the last subject that is required for primary, secondary, [redacted] analysis, as prespecified in the protocol, whichever is the later date.

The End of Trial is expected approximately 2 years after last patient has enrolled.

The trial completes when the endpoints and objectives of the study have been analyzed. The subjects who remain on active treatment and are continuing to derive benefit may have available to them either a roll-over protocol, or alternative means for providing study drug to them after study closure.

4. STUDY POPULATION

4.1. Number of Subjects

The study will enroll a maximum of 110 subjects previously treated with ruxolitinib (as per the definition below) and with DIPSS-intermediate or high-risk PMF, post-PV MF or post-ET MF.

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is at least 18 years of age at the time of signing the informed consent form (ICF)
2. Subject has an Eastern Cooperative Oncology Group (ECOG) (Appendix J) Performance Score (PS) of 0, 1 or 2
3. Subject has diagnosis of primary myelofibrosis (PMF) according to the 2016 World Health Organization (WHO) criteria (Appendix G, Appendix H), or diagnosis of post-ET or post-PV myelofibrosis according to the IWG-MRT 2007 criteria (Appendix I), confirmed by the most recent local pathology report
4. Subject has a DIPSS Risk score of Intermediate or High (Appendix F)
5. Subject has a measurable splenomegaly during the screening period as demonstrated by spleen volume of ≥ 450 cm^3 by MRI or CT-scan assessment or by palpable spleen measuring ≥ 5 cm below the left costal margin
6. Subject has been previously exposed to ruxolitinib while diagnosed with MF (PMF, post-ET MF or post-PV MF), and must meet at least one of the following criteria (a or b)
    a. Treatment with ruxolitinib for ≥ 3 months
    b. Treatment with ruxolitinib for ≥ 28 days complicated by any of the following:
        – Development of a red blood cell transfusion requirement (at least 2 units/month for 2 months) or
        – Grade ≥ 3 AEs of thrombocytopenia, anemia, hematoma, and/or hemorrhage while on treatment with ruxolitinib
7. Subject must have treatment-related toxicities from prior therapy resolved to Grade 1 or pretreatment baseline before start of last therapy prior to fedratinib treatment.
8. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted
9. Subject is willing and able to adhere to the study visit schedule and other protocol requirements
10. A female of childbearing potential (FCBP) must:
    a. Have two negative pregnancy tests as verified by the Investigator prior to starting study therapy. She must agree to ongoing pregnancy testing during the course of the study, and after end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.

b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with highly effective contraception** without interruption, –14 days prior to starting investigational product, during the study therapy (including dose interruptions), and for 30 days after discontinuation of study therapy.

Note: A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

11. Male subjects must:

a. Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 30 days following investigational product discontinuation, or longer if required for each compound and/or by local regulations, even if he has undergone a successful vasectomy.

* True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].

** Agreement to use highly effective methods of contraception that alone or in combination result in a failure rate of a Pearl index of less than 1% per year when used consistently and correctly throughout the course of the study. Such methods include: Combined (estrogen and progestogen containing) hormonal contraception: Oral; Intravaginal; Transdermal; Progestogen-only hormonal contraception associated with inhibition of ovulation: Oral; Injectable hormonal contraception; Implantable hormonal contraception; Placement of an intrauterine device; Placement of an intrauterine hormone-releasing system; Bilateral tubal occlusion; Vasectomized partner.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Any of the following laboratory abnormalities:

a. Platelets < 50,000/μL
b. Absolute neutrophil count (ANC) < 1.0 x 10^9/L
c. White blood count (WBC) > 100 x 10^9/L
d. Myeloblasts > 5 % in peripheral blood
e. Estimated glomerular filtration rate < 30 mL/min/1.73 m^2 (as per the Modification of Diet in Renal Disease [MDRD] formula) (Appendix K)
f. Serum amylase or lipase > 1.5 x ULN (upper limit of normal)
g. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x ULN
h. Total bilirubin > 1.5 x ULN, subject's total bilirubin between 1.5 – 3.0 x ULN are eligible if the direct bilirubin fraction is < 25% of the total bilirubin

2. Subject is pregnant or lactating female
3. Subject with previous splenectomy
4. Subject with previous or planned hematopoietic cell transplant
5. Subject with prior history of encephalopathy, including Wernicke's

6. Subject with signs or symptoms of encephalopathy including Wernicke's (eg, severe ataxia, ocular paralysis or cerebellar signs)
7. Subject with thiamine deficiency, defined as thiamine levels in whole blood below normal range according to institutional standard and not corrected prior to enrollment on the study
8. Subject with concomitant treatment with or use of pharmaceutical, herbal agents or food known to be strong or moderate inducers of Cytochrome P450 3A4 (CYP3A4), or dual CYP2C19 and CYP3A4 inhibitors (refer to Section 8 and Appendix L)
9. Subject on any chemotherapy, immunomodulatory drug therapy (eg, thalidomide, interferon-alpha), anagrelide, immunosuppressive therapy, systemic corticosteroids > 10 mg/day prednisone or equivalent. Subjects who have had prior exposure to hydroxyurea (eg, Hydrea) in the past may be enrolled into the study as long as it has not been administered within 14 days prior to the start of fedratinib treatment
10. Subject has received ruxolitinib within 14 days prior to the start of fedratinib
11. Subject on treatment with myeloid growth factor (eg, granulocyte-colony stimulating factor [G-CSF]) within 14 days prior to the start of fedratinib treatment
12. Subject with previous exposure to Janus kinase (JAK) inhibitor(s) for more than 1 cycle other than ruxolitinib treatment
13. Subject on treatment with aspirin with doses > 150 mg daily
14. Subject with major surgery within 28 days before starting fedratinib treatment
15. Subject with diagnosis of chronic liver disease (eg, chronic alcoholic liver disease, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis, non-alcoholic steatohepatitis)
16. Subject with prior malignancy other than the disease under study unless the subject has not required treatment for the malignancy for at least 3 years prior to enrollment. However, subject with the following history/concurrent conditions provided successfully treated may enroll: non-invasive skin cancer, in situ cervical cancer, carcinoma in situ of the breast, incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system), or is free of disease and on hormonal treatment only
17. Subject with uncontrolled congestive heart failure (New York Heart Association Classification 3 or 4) (Appendix M)
18. Subject with known human immunodeficiency virus (HIV), known active infectious Hepatitis B (HepB), and/or known active infectious Hepatitis C (HepC)
19. Subject with serious active infection
20. Subject with presence of any significant gastric or other disorder that would inhibit absorption of oral medication
21. Subject is unable to swallow capsule

22. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
23. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
24. Subject has any condition that confounds the ability to interpret data from the study
25. Subject with participation in any study of an investigational agent (drug, biologic, device) within 30 days prior to start of fedratinib treatment
26. Subject with life expectancy of less than 6 months.

5. TABLE OF EVENTS

5.1. Table of Events

Table 3: Study Table of Events

Visits	Screening [d]	Treatment Period [a]													30-Day Follow-up after last dose Visit (+ 7 days)	Survival Follow-up every 3 months (± 14 days)
		Cycle 1			Cycle 2		Cycle 3 [b]		Cycle 4	Cycle 5	Cycle 6 [b]	Cycle ≥ 7	Response Assessment [c]	End of Treatment (EOT)		
Days	-28 to -1	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	End of C3, 6, 12, 18, 24 (±7 Days)	-		
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inclusion / Exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical History	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Myelofibrosis disease history (local confirmation)	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Prior therapies for disease under study	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IRT subject registration	X	X	-	-	-	-	-	-	-	-	-	-	-	X	-	-
Height	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Treatment																
Fedratinib dispensing to subject	-	X	-	-	X	-	X	-	X	X	X	X	-	-	-	-
Fedratinib accountability	-	-	-	-	X	-	X	-	X	X	X	X	-	X	-	-
Fedratinib administration	-	Once daily with an evening meal including daily dose of thiamine												-	-	-
Safety assessments																
Pregnancy test for FCBP only	X	X	-	-	X	-	X	-	X	X	X	X	-	X	X	-

Table 3: Study Table of Events (Continued)

Visits	Screening [d]	Treatment Period [a]													30-Day Follow-up after last dose Visit (+ 7 days)	Survival Follow-up every 3 months (± 14 days)
		Cycle 1			Cycle 2		Cycle 3 [b]		Cycle 4	Cycle 5	Cycle 6 [b]	Cycle ≥ 7	Response Assessment [c]	End of Treatment (EOT)		
Days	-28 to -1	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	End of C3, 6, 12, 18, 24 (±7 Days)	-		
Adverse events	From ICF signature until 30 days after last dose of fedratinib taken by subject															-
Risk mitigation for GI & encephalopathy including Wernicke's	From ICF signature until 30 days after last dose of fedratinib taken by subject															-
Prior/concomitant medications	From 28 days prior to C1D1 until 30 days after last dose of fedratinib taken by subject															-
Prior/concomitant procedures	From 28 days prior to C1D1 until 30 days after last dose of fedratinib taken by subject															-
Phone call for management of nausea, vomiting, diarrhea	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Vital signs including weight	X	X	-	-	X	-	X	-	X	X	X	X	-	X	X	-
Physical exam	X	X	-	-	X	-	X	-	X	X	X	X	-	X	X	-
Transfusion burden assessment	From 84 days prior to C1D1 until 30 days after last dose of fedratinib taken by subject															-
Local 12-lead ECG	X	At any time if clinically indicated														-
Hematology	X	X	-	X	X	X	X	X	X	X	X	X	-	X	X	-
Serum Chemistry	X	X	-	X	X	X	X	X	X	X	X	X	-	X	X	-
Lipid Panel	X						X				X (every 3rd cycle)			X		
Urinalysis & Coagulation	X	At any time if clinically indicated														
Thiamine (whole blood sample) [e]	X	X	-	-	X	-	X	-	-	-	X (every 3rd cycle)	-	-	X	-	-
Cognitive assessments (MMSE) [e]	X	-	-	-	X	-	X	-	-	-	X (every 3rd cycle)	-	-	X	-	-

Table 3: Study Table of Events (Continued)

Visits	Screening [d]	Treatment Period [a]													30-Day Follow-up after last dose Visit (+ 7 days)	Survival Follow-up every 3 months (± 14 days)
		Cycle 1			Cycle 2		Cycle 3 [b]		Cycle 4	Cycle 5	Cycle 6 [b]	Cycle ≥ 7	Response Assessment [c]	End of Treatment (EOT)		
Days	-28 to -1	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 1	Day 1	Day 1	End of C3, 6, 12, 18, 24 (±7 Days)	-		
Survival Follow-up	-	-	-	-		-	-	-	-	-	-	-	-	-	X	X
Assessment of progression of MF to AML	After signing ICF and until death, lost to follow-up, withdrawal of consent for further data collection, or study closure															
Subsequent therapies for disease under study	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X
ECOG PS	X	X	-	-	X	-	X	-	X	X	X	X	-	X	X	-
Efficacy Assessments																
MRI measurements (or CT-Scan if MRI contraindicated) [f]	X	-	-	-	-	-	-	-	-	-	-	-	X	X	-	-
Spleen size by palpation	X	X	-	-	X	-	X	-	X	X	X	X	X	X	X	-
MFSAF v.4.0	X	X	-	-	X	-	X	-	X	X	X	X	X	X	X	-
[redacted]																

AML = acute myeloid leukemia; C1D1 = Cycle 1 Day 1; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; FCBP = female of childbearing potential: GI = gastrointestinal; ICF = informed consent form; IRT = Interactive Response Technology; MF = myelofibrosis; MFSAF = Myelofibrosis Symptom Assessment Form; MMSE = Mini-mental state examination; MRI = magnetic resonance imaging; [redacted]; PS = Performance Status.

[a] A visit window of ± 3 days is allowed.

[b] Subjects that discontinue study treatment prior to Cycle 4 or prior to Cycle 7 will complete the response assessments in the End of Treatment visit.

[c] Response assessments can be done at the same time as the Day 1 of the following Cycle.

[d] For subjects that are on ruxolitinib during the screening period or that have potentially reversible laboratory abnormalities (or other criteria that excludes the subject from enrollment) detected during screening, the screening period may be extended to 35 days (additional 7 days).

[e] And at any time if clinically indicated.

[f] A window of ± 7 days is allowed for MRI/CT scan procedures. The screening MRI needs to be performed within 5 days before the start of study treatment and after previous treatments have been discontinued for ≥ 14 days according to exclusion criteria #9 and #10. MRI/CT scans may be performed at any time during the study if clinical progression of splenomegaly is suspected.

[redacted]

6. PROCEDURES

Any questions regarding the protocol should be directed to the Celgene-Impact Medical Monitor or designee.

All data obtained from these assessments must be recorded in the subject's source documentation. Refer to the eCRF (electronic Case Report Form) completion guidelines for additional information related to data entry requirements.

Procedures will be performed as stated in the sections below. Detailed instructions for sample collection, processing, storage, shipping and handling will be contained in a separate laboratory manual provided to the sites.

Waivers or deviations to the protocol will not be granted during the conduct of this trial, under any circumstances.

Procedures and assessments are described in detail below. The timing of all the below Study assessments / procedures is specified in Sections 6.1, 6.2, 6.3.

6.1. Screening Period

All screening procedures and assessments are performed during a subject's screening period in order to establish eligibility and to document relevant medical and demographic data (eg, medical history and prior/concomitant medications). The written informed consent form must be signed before any study-specific procedures are performed and any samples are collected for study-specific analysis. Subject eligibility is established by the Investigator by confirming all inclusion and exclusion criteria are satisfied. Documentation used to establish eligibility should be forwarded to the sponsor to ensure documentation is sufficient from a regulatory and quality perspective. The sponsor may contact the study site for additional information if there is any deficiency in the documentation provided. Failure to satisfy any entry criterion will preclude a subject from receiving the first study treatment dose.

The following will be performed during the 28-day Screening Period as specified in the Table of Events (Table 3) after informed consent has been obtained:

- **Interactive Response Technology (IRT) Subject Registration**:

  Registration of the subject into the IRT system.

- **Assessment of inclusion/exclusion criteria for study eligibility:**

  Screening evaluations will be performed for all subjects to determine eligibility. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window, if necessary.

- **Demographics:**

  Information about the subject's demographics (if allowed per local country regulations; including, but not limited to: initials, date of birth, sex, race, and ethnicity).

- **Medical history (including Disease history):**

  Relevant medical history, including potential alcohol abuse, and current medical conditions, including MF signs and symptoms, must be recorded on the appropriate Case Report Form (CRF) pages at screening. History of myelofibrosis disease including its prior treatments, response to prior therapy with ruxolitinib and current DIPSS (Dynamic International Prognostic Scoring System) Score, other prior malignancies will also be recorded on the appropriate eCRF pages. This should include relevant information related to original MF diagnosis and/or other past malignancies as applicable.

  Review of historical bone marrow biopsy information will be used to confirm MPN-associated myelofibrosis diagnosis. The report should come from the most recent local bone marrow biopsy performed and should contain the mutational status of the disease (eg, *JAK2*, *MPL*, and *CALR*).

- **Transfusion history:**

  Transfusion history for at least 84 days prior to C1D1 including pretransfusion hemoglobin (Hgb) or platelet levels, number of units transfused and dates of transfusions, will be collected and reported in the appropriate eCRF. Any transfusions given at outside institutions must also be collected.

- **Pregnancy testing:**

  Pregnancy testing is required for all female subjects of childbearing potential. The Investigator will appraise a female subject as a FCBP according to the definition included in Eligibility criteria (Section 4.2). Justification must be recorded in the eCRF and the source document. Pregnancy testing is not required for non-FCBP subjects.

  Two urine (or serum) pregnancy tests will be performed to assess subject eligibility during screening with one pregnancy test occurring within 72 hours prior to the first administration of investigational product (IP) (negative results required for IP administration).

- **Adverse events:**

  All subjects will be monitored for AEs including Adverse Events of Special Interest (AESIs) during the study as described in Section 10.

  Information about common side effects already known about fedratinib will be included in the subject informed consent form and should be discussed with the subject as needed during the study. This information can also be found in the IB or will be communicated between IB updates in the form of Investigator notifications.

- **Risk mitigation for Gastrointestinal toxicity & Encephalopathy including Wernicke's:**

  Refer to Section 7.3 and Section 7.4.

- **Height:**

  Height will be measured only during the screening period.

- **Prior/concomitant medications:**

  Information relating to prior/concomitant medications (including those taken ≤28 days before screening) are to be reported on the appropriate eCRF pages. Refer to Section 8 for more information. The details of prior treatment by ruxolitinib with outcomes will be recorded in the subject's eCRF.

- **Prior/concomitant procedures:**

  Information relating to prior/concomitant procedures (including all procedures occurring ≤ 28 days before screening) to be reported on the appropriate eCRF pages. Refer to Section 8 for more information.

- **Physical exam:**

  Information about the physical examination for clinically significant findings including assessment of abnormal eye movements, assessment for cerebellar abnormalities, spleen palpation, as well as spleen size assessment are to be captured in the eCRF.

- **Vital signs including weight:**

  Information regarding vital signs including, seated blood pressure (systolic and diastolic), body temperature, heart rate and weight are measured and reported on the appropriate eCRF.

- **Electrocardiogram (ECG):**

  A 12-lead ECG is to be performed locally at site. The following ECG parameters will be recorded on the respective eCRF(s): Heart rate, PR interval, QRS duration, QT, QTc. The Investigator will review the results and assess as normal, abnormal – not clinically significant, or abnormal – clinically significant, and report the abnormal finding(s) on the appropriate eCRF. If the ECG is abnormal, the Investigator should consult a cardiologist if deemed appropriate. ECG will be performed at screening and if clinically indicated thereafter.

- **Hematology:**

  This assessment may include the following: red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, white blood cell (WBC) count, RBC morphology, and differential cell count including myeloblasts. Detailed instructions for sample collection, processing, storage, shipping and handling will be contained in a separate laboratory manual provided to the sites.

- **Serum Chemistry:**

  This assessment may include the following: total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bicarbonate, alkaline phosphatase (AP), lactate dehydrogenase (LDH) amylase, lipase, total protein, albumin, globulin, sodium, potassium, chloride, calcium, phosphate, magnesium, glucose, blood urea nitrogen or urea, creatinine and creatinine clearance as per the Modification of Diet in Renal

Disease (MDRD) formula, blood urea nitrogen (BUN) and uric acid. Detailed instructions for sample collection, processing, storage, shipping and handling will be contained in a separate laboratory manual provided to the sites.

- **Lipid Panel:**

  This assessment may include the following: cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL) and triglycerides. Lipid testing will be performed at screening and at every 3 cycles starting with Cycle 3 Day 1 (then C6D1, C9D1, etc).

- **Coagulation:**

  This assessment may include the following: prothrombin time/international normalized ratio and activated partial thromboplastin time. Coagulation testing will be performed at screening and if clinically indicated thereafter.

- **Urinalysis:**

  This assessment may include the following: macroscopic (eg, color, bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity and urobilirubin), microscopic (eg, RBC, WBC, casts, crystals, bacteria and epithelial cells). Urinalysis testing will be performed at screening and if clinically indicated thereafter.

- **Thiamine level:**

  Information regarding thiamine level in whole blood will be tested according to the Table of Events (Section 5.1) which is every cycle for the first 3 cycles, then every 3rd cycle thereafter or as clinically indicated.

- **Cognitive assessment - Mini-Mental State Examination:**

  Information regarding the cognitive status will be performed using the Mini-Mental State Examination (MMSE): to objectively assess for signs/symptoms of encephalopathy.

  If the MMSE-2 Standard Version (SV) questionnaire (Appendix N) is unavailable at the time of study start, the original version of the MMSE questionnaire may be used. This is questionnaire is to be completed as specified in the Table of Events (Table 3).

- **Spleen volume by MRI/CT scan:**

  Spleen volume will be assessed at the study site (MRI or CT Scan if MRI is contraindicated) during screening. The screening MRI/CT scan needs to be performed within 5 days before the start of treatment and after previous treatments have been discontinued for ≥ 14 days according to exclusion criteria #9 and #10 (see Section 4.3). The locally assessed spleen volume will be recorded in the appropriate eCRF pages. The same method MRI or CT scan should be used consistently throughout the study. The MRI/CTs will be reviewed centrally.

- **Spleen size by palpation:**

  Spleen size palpation in cm below left costal margin (LCM) will be assessed at the study site.

- **Eastern Cooperative Oncology Group (ECOG) performance status:**

  Performance status will be assessed by the Investigator using the ECOG criteria provided in Appendix J.

- **Symptoms response assessment:** Myelofibrosis Symptom Assessment Form (MFSAF) Refer to Section 6.7.1

- **Progression of myelofibrosis to AML assessment**: Refer to Section 10.7

Specified screening assessments must take place within 28 days after the date of the informed consent form signature. For subjects that are on ruxolitinib at the start of the screening period, the dose of ruxolitinib should be gradually tapered (refer to prescribing information) before the 14-day washout and supportive care provided to mitigate potential ruxolitinib withdrawal syndrome with close physician supervision. In some cases, restarting of ruxolitinib may be indicated and the subject should be screen failed. Future rescreening may occur after resolution of ruxolitinib withdrawal syndrome. In addition, for subjects that are on ruxolitinib at the start of the screening period or who have a laboratory abnormality detected during screening, the screening period may be extended to 35 days to allow for retesting to demonstrate resolution of the laboratory abnormality. In case a subject has a laboratory parameter related to an exclusion criterion that was under the influence of a treatment or medication (eg platelet transfusion in the last 7 days, G-CSF in last 14 days) retesting needs to be performed before enrollment after an appropriate washout period (refer to Section 4.3).

Subjects who screen fail for study entry may be rescreened if it is reasonable to believe they will meet eligibility criteria during rescreening. If screening assessments are not within the allowed screening period, the rescreened subject must reconsent to participation in the study by signing a new and current informed consent form.

6.1.1. Enrollment of a Subject in the Study

All the screening evaluations must be completed, and eligibility criteria must be verified by the responsible Investigator. The appropriate documentation may be reviewed by the sponsor prior to a subject receiving the first study treatment dose. Enrollment of the subject (inclusion in the Treatment Period) will occur via Interactive Response Technology (IRT) to enable automated tracking and replenishment of study treatment. Specific contact information and instructions will be provided to each study site.

The IRT enrollment should be performed as close as possible to the planned first dose of study treatment to avoid enrolling a subject who ultimately does not receive study treatment for any reason. The first dose of study treatment should be administered at the site on the day of enrollment, but may be delayed for up to 3 days if necessary, for logistical reasons.

If screening assessments are performed within 7 days of the C1D1 date, safety laboratory and physical examinations will not need to be repeated during the C1D1 except for hematology

laboratory. Note: A negative pregnancy result is required for FCBP within 72 hours of the first dose of study treatment.

6.2. Treatment Period

The following procedures/evaluations will be performed at the frequency specified in the Table of Events (Table 3) during Treatment Period.

Study visits during the Treatment Period must occur within ± 3 days of the scheduled day except for MRI/CT scan procedures which have a visit window of ±7 days. For the first 3 cycles, site visits will be performed on Day 1 and Day 15 and thereafter on Day 1 for the subsequent cycles. At Cycle 1 Day 8 the site will contact the subject by telephone to assess management of nausea, vomiting and diarrhea.

The procedures/evaluations should be performed prior to dosing on the visit day, unless otherwise specified. The following will be performed at treatment visits as specified in the Table of Events (Section 5.1):

- **IRT subject registration** (at Cycle 1 Day 1)
- **Pregnancy testing:** As detailed in Section 6.1
- **Prior/concomitant medications and procedures:** As detailed in Section 6.1
- **Vital signs, Physical exam and weight:** As detailed in Section 6.1
- **Electrocardiogram (ECG):** As clinically indicated (detailed in Section 6.1)
- **Hematology:** As detailed in Section 6.1

  Before starting each treatment cycle, local hematology lab results including ANC, platelet (PLT) and RBC must be available
- **Serum Chemistry:** As detailed in Section 6.1
- **Lipid Panel:** Every 3rd cycle thereafter (starting from C3D1) (detailed in Section 6.1)
- **Coagulation:** As clinically indicated (detailed in Section 6.1)
- **Urinalysis:** As clinically indicated (detailed in Section 6.1)
- **Thiamine level:** As detailed in Section 6.1

  As clinically indicated and at C1D1, C2D1, C3D1, C6D1 and every 3rd cycle thereafter
- **Transfusion burden assessment:**

  Information regarding RBC and PLT transfusions including pretransfusion Hgb or PLT levels, number of units transfused and dates of transfusions, will be collected and reported in the appropriate eCRF. Any transfusions given at outside institutions must also be collected.
- **Cognitive assessment - Mini-Mental State Examination:** As detailed in Section 6.1

  As clinically indicated and at C2D1, C3D1, C6D1 and every 3rd cycle thereafter

- **Response assessments:** As detailed in Section 6.5
- **Spleen volume by MRI/CT scan:** As detailed in Section 6.5
- **Spleen size by palpation:** As detailed in Section 6.1
- **Eastern Cooperative Oncology Group (ECOG) performance status:** As detailed in Section 6.1

[redacted]

- **Administration/accountability of fedratinib:** Refer to Section 7 for details
- **Adverse events:** Refer to Section 6.1
- **Risk mitigation for Gastrointestinal toxicity & Encephalopathy including Wernicke's:** Refer to Section 7.3 and Section 7.4
- **Symptoms response assessment:** Myelofibrosis Symptom Assessment Form (MFSAF) Refer to Section 6.7.1
- [redacted]
- **Progression of myelofibrosis to AML assessment**: Refer to Section 10.7

6.2.1. End of Treatment Visit

The treatment period will be concluded by an End of Treatment (EOT) visit performed for subjects who are withdrawn from treatment for any reason as soon as possible after the decision to permanently discontinue treatment has been made.

End of Treatment Visit procedures/assessments may not need to be repeated if previously performed within ±7 days of EOT visit. If a subject is discontinued during a regular scheduled visit, all EOT procedures should be completed at that visit.

The following assessments will be performed at the EOT visit as specified in the Table of Events (Section 5.1):

- **IRT subject registration for treatment discontinuation**
- **Pregnancy testing:** As detailed in Section 6.1
- **Concomitant medications and procedures:** As detailed in Section 6.1
- **Vital signs, Physical exam and weight:** As detailed in Section 6.1
- **Electrocardiogram (ECG):** As clinically indicated (detailed in Section 6.1)
- **Hematology:** As detailed in Section 6.1
- **Serum Chemistry:** As detailed in Section 6.1
- **Lipid Panel:** As detailed in Section 6.1

- **Coagulation:** As clinically indicated (detailed in Section 6.1)
- **Urinalysis:** As clinically indicated (detailed in Section 6.1)
- **Thiamine level:** As detailed in Section 6.1
- **Transfusion burden assessment:** As detailed in Section 6.2
- **Cognitive assessment - Mini-Mental State Examination:** As detailed in Section 6.1
- **Spleen volume by MRI/CT scan:** As detailed in Section 6.5
- **Spleen size by palpation:** As detailed in Section 6.1
- **Eastern Cooperative Oncology Group (ECOG) performance status:** As detailed in Section 6.1
- [redacted]
- **Adverse events:** Refer to Section 6.1
- **Accountability of fedratinib treatment**
- **Risk mitigation for Gastrointestinal toxicity & Encephalopathy including Wernicke's:** Refer to Section 7.3 and Section 7.4.
- **Symptoms response assessment:** as detailed in Section 6.7.1
- [redacted]
- **Progression of myelofibrosis to AML assessment**: Refer to Section 10.7

6.3. Follow-up Period

6.3.1. 30-Day Follow-up After Last Dose Visit (+ 7 days)

All subjects will be followed for 30 days after the last dose of study treatment for AE reporting, as well as any SAEs made known to the Investigator at any time thereafter that are suspected of being related to study treatment, as described in Section 10.1.

The following will be performed as specified in the Table of Events (Section 5.1, Table 3):

- **Concomitant medications and procedures:** As detailed in Section 6.1
- **Vital signs, Physical exam and weight:** As detailed in Section 6.1
- **Electrocardiogram (ECG):** As clinically indicated (detailed in Section 6.1)
- **Pregnancy testing:** As detailed in Section 6.1
- **Hematology:** As detailed in Section 6.1
- **Serum Chemistry:** As detailed in Section 6.1
- **Coagulation:** As clinically indicated (detailed in Section 6.1)
- **Urinalysis:** As clinically indicated (detailed in Section 6.1)

- **Thiamine level:** As clinically indicated (detailed in Section 6.1)
- **Transfusion burden assessment:** As detailed in Section 6.2
- **Cognitive assessment - Mini-Mental State Examination:** As clinically indicated (detailed in Section 6.1)
- **Survival:** Refer to Section 6.3.2
- **Progression of myelofibrosis to acute myeloid leukemia (AML) assessment:** Refer to Section 6.3.2 and Section 10.7
- **Subsequent therapies for disease under study:** Refer to Section 6.3.2
- **Spleen size by palpation:** As detailed in Section 6.1
- **Eastern Cooperative Oncology Group (ECOG) performance status:** As detailed in Section 6.1
- **Adverse events:** Refer to Section 6.1
- **Risk mitigation for Gastrointestinal toxicity & Encephalopathy including Wernicke:** Refer to Section 7.3 and Section 7.4.
- **Symptoms response assessment:** as detailed in Section 6.7.1
- [redacted]

6.3.2. Survival Follow-up

All subjects discontinued from protocol-prescribed therapy for any reason will be followed for survival, subsequent therapies, new malignancy and progression of myelofibrosis to acute myeloid leukemia (AML) every 3 months until death, up to 12 months after EOT, lost to follow-up, withdrawal of consent for further data collection, or study closure whichever comes first. See Section 10.7 for additional details on reporting.

A window of ± 14 days is allowed for post treatment Survival Follow-up assessments; the visits should be performed every 3 months ± 14 days and can be done by a documented telephone contact between site and subject.

6.4. Unscheduled Assessments or Visits

Should it become necessary to repeat an evaluation (eg, laboratory tests, vital signs, etc.) outside of scheduled study visits, or to perform additional evaluations than the ones described in the current protocol, the results of these additional evaluations should be recorded in an unscheduled visit eCRF pages(s). These evaluations should also appear in the subject's chart and/or other source documentation.

In the event that immediate hematology/biochemistry/urinalysis/coagulation/thiamine/lipid values are needed for clinical decisions, local laboratory results may be used pending the outcome of the central laboratory assessment. However, matching samples must always be sent to the central laboratory and clinical decisions and assessments must be reconciled with the

results of the central laboratory. The results of these additional analyses will be recorded in the subjects' eCRF as applicable as described in Section 10.

6.5. Response Assessment

Response assessments should occur at the end of C3, C6, C12, C18, C24, and EOT (and at the end of every 6th cycle [24 weeks]) as applicable afterwards. The response assessment can be combined with the Day 1 visit of the subsequent cycle or End of Treatment visit. The following assessments will be performed:

- **Symptoms response assessment:** Refer to Section 6.7.1
- **Spleen volume by MRI/CT scan:** Refer to Section 6.1
- **Spleen size by palpation:** Refer to Section 6.1

If a bone marrow assessment is performed as per standard of care, in addition to the assessments described above, the Investigator will assess response, for example, in terms of CR, PR, relapse, cytogenic and molecular response as per IWG-MRT 2013 (Tefferi, 2013).

- [redacted]

[redacted]

6.7. Subject Reported Outcomes

All PRO evaluations will be performed on an electronic tablet at the site. These assessments should be performed before any other assessments are performed by the Investigator or designee during the visit.

6.7.1. Symptoms Response Assessment

The MF-related symptoms evaluation will be performed using the MFSAF v.4.0 version using a 7-day recall period (Gwaltney, 2017).

This questionnaire assesses 7 key MF-associated symptoms (night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, bone or muscle pain, and fatigue). Due to the number of different questionnaires used in clinical trials for patient-reported MF symptoms, this version was developed following harmonization work conducted in collaboration with industry and the FDA with the aim to create a publicly available, consensus -based and

harmonized version of MF symptoms questionnaire (Gwaltney, 2017). The MFSAF version 4.0. was validated and recommended to be used in clinical trials to assess MF symptoms.

The Total Symptom Score is a composite score defined as the sum of each of the 7 symptom scores. To allow indirect comparison with previous MF studies, a modified Total Symptom Score (Mesa, 2013) will also be derived from the 6 symptoms considered (night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, bone or muscle pain).

The MF-related symptoms evaluation will be performed at the site at screening, on Day 1 of each treatment cycle (and for Response Assessments), at the EOT and the 30-Day Follow-up after last dose visit. If exceptional circumstances preclude the continued administration of measures using planned modalities, then alternate administration methods may be required.

A copy of the questionnaire is presented in Appendix B.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Products

7.1.1. Fedratinib

The Sponsor will supply fedratinib 100 mg capsules in high density polyethylene (HDPE) bottles for oral administration and will be labeled appropriately as investigational product for this study.

The study drug must be kept at the temperature condition as specified on the label. Fedratinib must be stored at temperatures below 30°C.

Other recommended/required concomitant medications per the protocol will be provided by the site. Celgene will not provide these medications.

7.2. Treatment Administration and Schedule

Fedratinib

Fedratinib will be dispensed to subjects using the IRT system. The fedratinib dose is 400 mg/day PO (4 x 100 mg capsules) to be self-administered orally once daily continuously on an outpatient basis, preferably together with an evening meal, the same time each day. However, fedratinib may be taken with or without regard to food. In case a dose is missed, the next dose should be taken the following day at the same time of day as previously taken before the dose was missed.

A flexible dose modification regimen may be employed to minimize drug toxicity for individual subjects, with possible daily doses of 100 mg, 200 mg, 300 mg, or 400 mg. For subjects with severe impairment of renal function and co-administration of strong or moderate CYP3A4 inhibitors the fedratinib dose is adjusted (Refer to Section 7.2.2 and Section 7.2.3).

For administrative purposes cycles are defined as 4-week (28-day) periods. Subjects may continue treatment with fedratinib until one of the conditions described in the "Treatment Period" section of Section 3.1 occurs.

All study subjects will receive thiamine supplementation (Refer to Section 7.4.3).

7.2.1. Fedratinib Dose Modification for Toxicity

The most common adverse events associated with fedratinib are hematological and gastrointestinal events. Hematological adverse events associated with JAK2 inhibitors are dose dependent, mechanism-based and are managed through dose reductions, dose interruptions and transfusions.

The Fedratinib Dose Modification table (Table 4) should only be used for events attributed to fedratinib treatment or if the AE cannot be attributed by the investigator to an identifiable cause such as underlying illness or disease progression, other concurrent illness, or concomitant medication.

If a subject experiences a drug toxicity as specified in the table below, the dosing must be interrupted; in some cases (ie, when it is not a liver function test (LFT) abnormality) the dose can be titrated by a 100 mg/day decrement during the study, depending upon the Investigator's judgment, down to a minimum dose of 200 mg/day. For subjects with severe impairment of renal

function and co-administration of strong or moderate CYP3A4 inhibitors the fedratinib dose is adjusted (Refer to Section 7.2.2 and Section 7.2.3). In addition, if a subject experiences a dose interruption of fedratinib for more than 28 consecutive days, consultation with the Medical Monitor is required to determine if study treatment may resume.

If a subject does not tolerate fedratinib therapy after 2 dose level reductions from the starting dose, he/she must be withdrawn from the study treatment. If the toxicity does not resolve in the time period as specified in the table below the subject must be withdrawn from the study treatment. Reescalation of doses is possible in certain cases. The daily dose of fedratinib cannot exceed 400 mg/day.

Table 4: Fedratinib Dose Modification Schedule

Adverse Event	Fedratinib Management	Recovery	Fedratinib Dose After Recovery
Hematological			
Grade 4 or Grade 3 thrombocytopenia with major bleeding	Hold fedratinib up to 28 days	Grade ≤ 3 thrombocytopenia without bleeding	Dose decrement by 1 dose level: 100 mg/daily decrease
Grade 4 neutropenia	Hold fedratinib up to 28 days	Grade ≤ 2 neutropenia	Dose decrement by 1 dose level: 100 mg/daily decrease
Grade 4 hematological toxicity with dose reduction in subsequent cycle	-	Toxicity resolves for at least 1 cycle	Subsequent upward dose titration possible of 1 dose level (100 mg daily) per cycle as per the Investigator's discretion
Recurrence of a Grade 4 hematological toxicity	-	-	Subsequent upward dose titration not permitted Fedratinib discontinuation as per the Investigator's discretion
Non-hematological			
Non-hematological Grade 4 or unmanageable Grade 3 toxicity after already dose reducing in the previous cycle	-	-	Subsequent upward dose titration not permitted Consider fedratinib discontinuation as per the Investigator's discretion

Table 4: Fedratinib Dose Modification Schedule (Continued)

Adverse Event	Fedratinib Management	Recovery	Fedratinib Dose After Recovery
Hepatic (LFT abnormalities)			
Grade ≥ 3 AST or ALT or total bilirubin	Hold fedratinib Weekly monitoring of LFTs, until resolution, After fedratinib resumed, LFT monitoring every 2 weeks for the 3 subsequent cycles at a minimum	Grade ≤ 1	**Fedratinib Hold ≤ 14 days:** Dose decrement by 1 dose level: 100 mg daily decrease, Subsequent upward dose titration not permitted **Fedratinib Hold > 14 days** (AE did not return to Grade ≤ 1): Fedratinib permanently discontinued Grade 4 in the absence of demonstrable cause: permanently discontinue fedratinib
Recurrence of LFT abnormality (ie, ≥ Grade 3 toxicity) after dose reduction	Discontinue fedratinib permanently	-	-
Gastrointestinal			
Grade 2 nausea, vomiting, diarrhea, or constipation that does not respond to adequate therapeutic or supportive measures within 48 hours	Hold fedratinib up to 14 days	Toxicity resolves to Grade ≤ 1	Consider resuming the dose at the same level after resolution of adverse event (see section on management of GI toxicity)
Grade ≥ 3 or recurrence of Grade 2 nausea, vomiting, diarrhea, or constipation that does not respond to adequate therapeutic or supportive measures within 48 hours	Hold fedratinib up to 14 days	Toxicity resolves to Grade ≤ 1	Consider reducing one dose level after resolution of adverse event (see section on management of GI toxicity below)
Other Adverse Events Not Described Above			
Grade ≥ 3 non-hematological toxicity, non-gastrointestinal toxicity or Grade ≥ 2 peripheral neuropathies	Hold fedratinib up to 14 days	Toxicity resolved to Grade ≤ 1	Dose decrement by 1 dose level: 100 mg daily decrease
In case of a potential case of encephalopathy including Wernicke's refer to Section 7.4, Management of encephalopathy, including Wernicke's.			

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GI = gastrointestinal; LFT = liver function test.

7.2.2. Fedratinib Dose Adjustment for Co-administration with Strong CYP3A4 Inhibitors

Concomitant administration of fedratinib with strong CYP3A4 inhibitors increases fedratinib exposure. Increased fedratinib exposure may increase the risk of AEs. In place of strong

CYP3A4 inhibitors, consider alternative therapies that do not strongly inhibit CYP3A4 activity. If strong CYP3A4 inhibitors cannot be replaced, reduce fedratinib dose to 200 mg when administering with strong CYP3A4 inhibitors, (eg, ketoconazole, ritonavir; refer to Appendix L). Additional dose adjustments (decrease or increase of the daily dose) should be made with monitoring of fedratinib-related safety (Section 7.3) and efficacy.

In cases where co-administration with a strong CYP3A4 inhibitor is discontinued, the fedratinib dose should be increased to 300 mg daily during the first 2 weeks after discontinuation of the CYP3A4 inhibitor, and then to 400 mg daily thereafter as tolerated. Additional dose adjustments should be made as needed based upon frequent monitoring of safety.

In all the situations above, please contact the sponsor Medical Monitor for any question or guidance.

7.2.3. Fedratinib Dose Adjustment for Renal Impairment

No modification of the starting dose is recommended for patients with mild to moderate renal impairment. Due to potential increase of fedratinib exposure, patients with pre-existing moderate renal impairment require more intensive safety monitoring, and if necessary, dose modifications based on adverse reactions.

In subjects that develop severe renal impairment during the study the fedratinib dose should be adjusted by 2 dose decrement levels (eg, from 400 mg to 200 mg once a day [QD]).

Clinical signs and symptoms for efficacy and fedratinib-related AEs should be monitored and the dose of fedratinib should be further adjusted as necessary.

7.2.4. Overdose

Overdose, as defined in this protocol, refers to fedratinib dosing only. On a per dose basis, an overdose is defined as any amount over the protocol-specified dose of fedratinib, regardless of any associated adverse events or sequelae.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. See Section 10.1 for the reporting of adverse events associated with overdose.

7.3. Overview on Management of Gastrointestinal Adverse Events (Fedratinib)

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 to 8 weeks on fedratinib treatment.

7.3.1. Management of Nausea and Vomiting

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

- Subjects 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 according to Table 4
- 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 subject off these medications

7.3.2. Management of Diarrhea

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

- Subjects 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 subject 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 according to Table 4
- Hospitalization may be indicated for Grade 3 or higher persisting diarrhea.
- Management of nausea, vomiting and diarrhea will be assessed during the subject's visit in the study on Day 1 of every following 28-day cycle, at Day 15 of the first 3 cycles and by a mandatory telephone contact at Day 8 of the first cycle.

7.4. Management of Encephalopathy, including Wernicke's

A potential case of encephalopathy including Wernicke's is a medical emergency. Screening for encephalopathy, including Wernicke's and management of potential cases during treatment with fedratinib will be done according the following steps:

7.4.1. Clinical and Cognitive Assessment

Interval history: including a review of the subject's history for confusion, memory problems, vision problems (eg, 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 subject history) during screening and Day 1 of every treatment cycle, at the End of Treatment (EOT), and the 30-Day Follow-up visit during the study.
- Mini-Mental State Examination (MMSE): to objectively assess for signs/symptoms of encephalopathy during screening, on Day 1 of Cycles 2 and 3 and every third cycle thereafter, and at the EOT visit for the study.

7.4.2. Management of Encephalopathy Including Wernicke's

In case of signs or symptoms that may indicate encephalopathy including Wernicke's:

- Hold fedratinib until Encephalopathy, including WE is ruled out
- Obtain sample for thiamine level
- Start parenteral thiamine supplementation, as described in Section 7.4.3 for subjects with thiamine levels < 30 nM/L regardless of thiamine level
- Report the event as an AESI to the Sponsor
- Obtain a neurological consult
- Perform a brain MRI
- If WE is confirmed, discontinue fedratinib permanently
- If WE is ruled out, assess for other causes of encephalopathy and treat accordingly. Once resolved, consider restarting treatment with fedratinib after discussion with Medical Monitor.

7.4.3. Thiamine Supplementation, Monitoring, and Correction

All subjects receiving study medication will receive thiamine supplementation. Start oral thiamine supplementation at a minimum daily dose of 100 mg (or equivalent) at Cycle 1 Day 1. Continue supplementation throughout the Treatment Period until study medication is discontinued, and through the 30-Day Follow-up visits.

Thiamine levels (for whole blood) will be monitored in all subjects.

- Thiamine levels are assessed at screening and need to be corrected and retested before starting fedratinib treatment (see inclusion criteria)

- While on treatment with study medication, thiamine levels are assessed in a fasting state at start of Cycles 1, 2, 3 and every third cycle thereafter, at the End of Treatment Visit and as clinically indicated
- In case of documented thiamine deficiency and a subject is receiving thiamine supplementation, while on study:
  - Thiamine levels should be assessed in a fasting state and thiamine supplementation should be given after the blood draw
  - If the subject develops signs or symptoms suggestive of encephalopathy including Wernicke's, please follow instruction in Section 7.4.2
  - For thiamine levels below normal range but > 30 nM/L without signs or symptoms of WE while receiving thiamine supplementation:
    - The site should contact the Medical Monitor regarding the low thiamine level as soon as possible
    - Report the event as an Adverse Event of Special Interest (AESI) to the Sponsor.
    - Consider increasing the dose of oral thiamine supplementation to twice the daily dose (if the subject is taking 100 mg, increase to 200 mg)
    - Monitor thiamine level closely (monthly at least) and adjust dose as needed
  - For thiamine level < 30 nM/L **without signs or symptoms** of WE while receiving thiamine supplementation:
    - The site should contact the Medical Monitor regarding the low thiamine level as soon as possible
    - Report the event as an Adverse Event of Special Interest (AESI) to the Sponsor.
    - Study medication must be held until thiamine levels are restored to normal range.
    - Immediate treatment with IV thiamine (stop oral thiamine), at therapeutic dosages eg, 500 mg 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 consider increasing the dose of oral thiamine supplementation to twice the previous daily dose (for example if the subject is taking 100 mg, increase the dose to 200 mg)
    - Monitor thiamine levels closely (at least monthly) and adjust the dose as needed
  - 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

7.5. Method of Treatment Assignment

The treatment assignment will occur at the end of the Screening Period, once all the required screening procedures have been completed, the investigator has verified the subject meets all eligibility criteria, and all required data have been submitted to the Sponsor or its authorized representative. Upon receiving acknowledgment of subject's eligibility review from the Sponsor or its authorized representative, the subject can be assigned fedratinib treatment using an IRT built for this study.

Designated research personnel at each investigational site will be assigned unique, password-protected user accounts which give them the authorization to utilize the IRT to enroll subjects.

7.6. Packaging and Labeling

The label(s) for fedratinib will include Sponsor name, address and telephone number, the protocol number, fedratinib, dosage form and strength (where applicable), amount of fedratinib per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.7. Investigational Product Accountability and Disposal

Sponsor (or designee) will review with the Investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction including responsibilities for the site versus Sponsor (or designee).

7.8. Investigational Product Compliance

Subjects will self-administer all fedratinib doses in the treatment phase. Study site personnel will review the dosing information with the subject (or legally authorized representative) on scheduled clinic visit days. Subjects (or legally authorized representative) will be asked to bring all unused capsules with them to scheduled clinic visits (ie, prior to the start of the next treatment Cycle). Study site personnel will perform a fedratinib administration compliance check and record this information in the subject's source documentation.

Administration of all fedratinib will be recorded including dispensing, dosing and any changes in dosage administration such as interruption or reduction in dosing due to an AE.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression. Supportive care, such as anti-emetic medications, may be administered at the discretion of the Investigator.

All prior/concomitant medications including, prescription, over-the-counter, and herbal preparations taken for any indication used from 28 days prior to enrollment until 30 days after the last dose of fedratinib must be reported on the eCRF. The type, dose route, start and end date of administration must be documented on the appropriate pages of the eCRF.

The details of the prior treatment with ruxolitinib and its outcomes will also be recorded in the subject's eCRF regardless of treatment discontinuation/procedure date.

Information regarding transfusion history (at least 84 days prior to and including the enrollment date), including pretransfusion hemoglobin (Hgb) levels, number of units transfused and dates of transfusions, will be collected and reported in the appropriate eCRF.

For information regarding other drugs that may interact with fedratinib and affect its metabolism, pharmacokinetics, or excretion, please also see the Investigator's Brochure.

8.1. Permitted Concomitant Medications and Procedures

Prophylaxis and/or treatment of gastrointestinal adverse events, specifically nausea, vomiting and diarrhea (eg, loperamide) is an essential part of management of potential fedratinib toxicity. (Refer to Section 7.3)

Subjects are required to take daily thiamine supplementation (Refer to Section 7.4)

Blood product support (RBCs and platelets transfusions) may be administered according to institutional standards.

Subjects may be administered supportive and palliative care (eg, pain control) as clinically indicated throughout the study.

Prior anticancer treatments should be recorded on the appropriate eCRF(s) regardless of treatment discontinuation/procedure date.

The details of the prior treatment and its outcomes will also be recorded in the subject's eCRF regardless of treatment discontinuation/procedure date.

For information regarding clinically relevant P450 inducers, inhibitors, substrates, and Transporter Substrates refer to Section 8.3.

8.2. Prohibited Concomitant Medications

The following concomitant medications are specifically excluded during the course of the study:

- Cytotoxic, chemotherapeutic, targeted or investigational agents/therapies
- Immunomodulatory drug therapy (eg, thalidomide)
- Immunosuppressive therapy

- Systemic corticosteroids >10 mg/day prednisone or equivalent
- Hydroxyurea
- Interferon-alpha
- Anagrelide
- JAK inhibitors other than fedratinib
- Aspirin at doses of > 150 mg daily
- Any investigational agent

For information regarding clinically relevant P450 inducers, inhibitors, substrates, and Transporter Substrates refer to Section 8.3.

If a subject requires treatment with any new medications that are specifically excluded, the subject may need to be discontinued from treatment. The Investigator should consult the Medical Monitor regarding any questions about whether a new medication or dosage of existing medication would require the subject to discontinue from the study.

8.3. Clinically Relevant Cytochrome P450 Inducers, Inhibitors, Substrates, and Transporter Substrates

Fedratinib is metabolized by multiple cytochrome P450 enzymes (CYPs) in vitro, with prominent contribution from CYP3A4 and with a lesser contribution from CYP2C19.

8.3.1. CYP3A4 Inducers and Inhibitors

Strong and moderate CYP3A4 inducers (Appendix L) that may decrease fedratinib plasma concentrations are not permitted while receiving fedratinib.

Strong CYP3A4 inhibitors (Appendix L) increase fedratinib plasma concentrations. In place of strong CYP3A4 inhibitors, alternative therapies that do not inhibit CYP3A4 need to be considered. If strong CYP3A4 inhibitors cannot be replaced, the strong CYP3A4 inhibitor needs to be used with caution and the fedratinib dose needs to be adjusted (refer to Section 7.2.2).

8.3.2. Dual CYP2C19 and CYP3A4 Inhibitors

Dual inhibitors of CYP2C19 and CYP3A4 (eg, fluconazole, fluvoxamine) that may increase fedratinib plasma concentrations are not permitted while receiving fedratinib.

8.3.3. Sensitive Substrates: Effect of Fedratinib on Plasma Levels of Other Co-administered Drugs (Drugs Metabolized by CYP3A4, CYP2C19, and CYP2D6):

Co-administration of fedratinib with drugs that are CYP3A4 substrates (eg, midazolam), CYP2C19 substrates (eg, omeprazole), or CYP2D6 substrates (eg, metoprolol) increase the area under the plasma concentration curve from time zero to infinity (AUC_{inf}) of these drugs by 4-, 3-, and 2-fold, respectively, which may increase the risk of adverse reactions of these drugs. Monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates (Appendix L) as necessary when co-administering with fedratinib.

8.3.4. Transporters: Effect of Fedratinib on Plasma Levels of Other Co-administered Drugs (Drugs Transported by P-gp, BCRP, MATE1, MATE2-K, OATP1B1/1B3, and OCT1/2):

Fedratinib inhibits transporters P-gp, BCRP, MATE1, MATE2-K, OATP1B1/1B3, and OCT2, which may increase the concentration of drugs that are substrates of these transporters. Monitor for adverse reactions and adjust the dose of drugs that are substrates of these transporters (Appendix L) as necessary when coadministered with fedratinib.

A list of clinically relevant P450 inducers and inhibitors as well as substrates, and transporter substrates can be found in Appendix L.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a multicenter, single-arm, open-label efficacy and safety study of fedratinib in subjects previously treated with ruxolitinib and with DIPSS-intermediate or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis.

The sections below provide an overview of the proposed statistical considerations and analyses. The final statistical analysis methods will be documented in detail in the statistical analysis plan (SAP).

General Considerations

Descriptive summary for continuous data will include the number of non-missing observations (n), mean, standard deviation, median, minimum and maximum. In addition, 25% percentile and 75% percentile may be provided if needed.

Categorical data will be summarized using counts (n) and percentages (%). The number of subjects with missing data may be displayed but will not be included in the denominator for the calculation of percentages unless otherwise specified.

Unless otherwise specified, baseline value is defined as the last value or measurement taken prior to the first dose in the study.

9.2. Study Population Definitions

Enrolled Population: this population includes all subjects enrolled into the study.

Safety population: this population will consist of all subjects who were administered at least one dose of fedratinib.

Efficacy evaluable population: this population includes subjects treated with fedratinib with evaluable spleen volume measurements based on MRI/CT scan at baseline and at least one post baseline response assessment by MRI/CT scan. This population will be used for analyses of spleen volume changes.

MFSAF population: For symptoms response (MFSAF version 4.0), fedratinib treated subjects with a Total Symptom Score (TSS) at baseline (eg, symptom score) > 0 and at least 1 post baseline TSS assessment will be included in the analysis.

9.3. Sample Size Consideration

Assuming the primary endpoint response rate is 35%, 100 evaluable subjects will approximately yield 90% power to detect the lower bound of 95% confidence interval (calculated by Pearson-Klopper method) for primary endpoint response rate excludes 20%.

The study will enroll approximately 110 subjects by accounting for a 10% drop-out rate.

9.4. Background and Demographic Characteristics

9.4.1. Demographic and Baseline Characteristics

Standard demographic and baseline characteristics (including age and race), medical history, cancer diagnosis and prior anti-cancer therapy will be collected at screening as a baseline. Baseline efficacy variables and other prognostic variables will be assessed as well. The details of previous ruxolitinib treatment (eg, dose, best response, duration of response) will be summarized.

For quantitative variables, the summary using descriptive statistics will be provided, while frequency tabulations will be given for categorical variables.

9.4.2. Prior or Concomitant Medications

The prior and concomitant medications will be presented for the safety population.

Medications will be summarized according to the World Health Organization (WHO) drug dictionary, considering the first digit of the anatomical therapeutic chemical (ATC) class (anatomic category) and the first three digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized. Subjects will be counted for each of the ATC categories (anatomic or therapeutic) linked to the medication.

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percentage for the study.

9.6. Efficacy Analysis

Unless otherwise specified, analysis of spleen volume response will be performed on the efficacy evaluable population, myelofibrosis symptom response analyses will be performed on the MFSAF population and spleen size response analyses will be performed on the safety population.

9.6.1. Spleen Volume Response Rate (RR) by MRI/CT:

Response rate of reduction in spleen volume is defined as proportion of subjects who have a ≥ 35% reduction in spleen volume at the end of Cycle 6 as compared to baseline. The response rate and 95% confidence interval will be provided. In addition, a descriptive summary of spleen volumes measurements and percentage change from baseline will be provided. Subjects with a missing MRI/CT spleen volume at the end of Cycle 6 including those who meet the criteria for progression of splenomegaly before the end of Cycle 6 will be considered non-responders.

A sensitivity analysis will be conducted for response rate of subjects who have a ≥ 25% reduction in spleen volume at the end of Cycle 6 as compared to baseline.

9.6.2. Spleen Response Rate by Palpation (RRP)

Spleen response rate by palpation is the proportion of subjects with a spleen response according to the IWG-MRT 2013 (Appendix D) at the end of Cycle 6 as compared to baseline. This will be

calculated for subjects that have an enlarged spleen (≥ 5 cm below LCM) at baseline. Subjects with a missing spleen size assessment at the end of Cycle 6 including those who meet the criteria for progression of splenomegaly before the end of Cycle 6 will be considered not to be responders. The response rate and 95% confidence interval will be provided.

9.6.3. Symptom Response Rate (SRR)

Symptom response rate (SRR) is defined as the proportion of subjects with ≥ 50% reduction from baseline to the end of Cycle 6 in total symptom score (TSS) measured by MFSAF version 4.0. The SRR and 95% confidence interval will be provided. The TSS will be defined as the sum of each of the 7 symptom scores (Gwaltney, 2017). To allow indirect comparison with previous MF studies, a modified TSS (Mesa, 2013) will also be derived from the 6 symptoms considered (night sweats, pruritus, abdominal discomfort, early satiety, pain under ribs on left side, bone or muscle pain) and analysis of SRR will be also performed.

At each timepoint, the TSS (based on 7 symptoms) and the modified TSS will be calculated. Descriptive summary statistics (size, mean, standard deviation, median, range) will be provided for baseline scores, postbaseline scores and change from baseline for TSS, modified TSS and symptom scores.

Subjects without a baseline TSS > 0 will be considered non-evaluable (due to no place for symptom reduction) for the SRR analysis. Subjects with a missing TSS at the end of Cycle 6 or who had disease progression before the end of the Cycle 6 will be considered non-responders.

Details of the statistical analysis will be provided in a separate Health-related Quality of Life (HRQoL) SAP and will be reported under a separate cover.

9.6.4. Durability of Spleen Volume Response by MRI/CT (DR)

Durability of spleen volume response (DR) by MRI/CT is defined as time from the first documented spleen response (ie, ≥ 35% reduction in spleen volume) to the date of subsequent progressive disease (PD) (ie, ≥ 25% increase in spleen volume from baseline) or death, whichever is earlier. In the absence an event (ie, subsequent spleen volume reduction < 35% before the analysis is performed), the DR will be censored at the date of the last valid assessment performed before the analysis performed date.

Durability of spleen volume response by MRI/CT scan will be analyzed using Kaplan-Meier method. The K-M estimates of the 25th, 50th, and 75th percentiles and the 95% confidence interval of median will be provided, and the K-M curves will be plotted.

9.6.5. Durability of Spleen Response by Palpation (DRP)

Durability of spleen response by palpation (DRP) is defined as time from the date of first documented palpable spleen response, according to the IWG-MRT 2013 (Appendix D) to the date of subsequent PD according to the IWG-MRT 2013 or death, whichever is earlier. Durability of spleen response by palpation according to the IWG-MRT 2013 criteria will be calculated for subjects that have an enlarged spleen at baseline (≥ 5 cm below LCM), and that have a spleen response by palpation. In the absence of an event (ie, no loss of spleen response by palpation) before the analysis is performed, the DRP will be censored at the date of the last valid assessment performed before the analysis performed date.

Durability of spleen response by palpation will be analyzed using Kaplan-Meier (K-M) method. The K-M estimates of the 25th, 50th, and 75th percentiles and the 95% confidence interval of median will be provided, and K-M curves will be plotted.

9.6.6. Durability of Symptoms Response (DSR)

Durability of symptoms response is defined as time from the first documented response in TSS (ie, reduction in TSS ≥ 50%) measured by MFSAF version 4.0 to the first documented TSS reduction < 50%. In the absence of TSS reduction < 50% before the analysis performed, the DSR will be censored at the date of the last valid assessment performed before the analysis performed date. The DSR will be analyzed using K-M method. The K-M estimates of the 25th, 50th, and 75th percentiles and the 95% confidence intervals of median will be provided, and K-M curves will be plotted.

9.7. Safety Analysis

All safety analyses will be conducted based on the safety population for the study.

Literature "book" values and normal ranges from local laboratory results will be utilized for this study.

9.7.1. Extent of Study Treatment Exposure and Compliance

Extent of exposure will be assessed within the safety population for the study.

Dose information will be assessed by the following variables:

- Duration of treatment exposure is defined as: last dose date - first dose date regardless of unplanned intermittent discontinuations
- The cumulative dose is the sum of all doses from Cycle 1 to the last dose
- The actual dose intensity is defined as the cumulative dose divided by the duration of treatment exposure in terms of the number of weeks on study
- The relative dose intensity is defined as the ratio of the actual dose intensity to the planned dose intensity. The planned dose intensity is defined as the planned dose for each cycle divided by planned cycle length in weeks
- Dose reduction and reason for dose reduction
- Dose interruption/delays

The number of subjects treated, number of cycles administered, duration of dosing (weeks), cumulative dose (mg), dose intensity (mg/week), and relative dose intensity (%) will be summarized for fedratinib in the study.

Dose interruption, delays and dose reductions will also be analyzed for study IPs within the study.

9.7.2. Adverse Events

The endpoints of this study are type, frequency, seriousness and severity of AEs, and relationship of AEs to study treatment. The safety population, which includes all enrolled subjects who received at least 1 dose of fedratinib, will be the analysis population for all safety analyses.

Adverse events will be analyzed in terms of TEAEs that are defined to be any event that begins or worsens in grade after the start of fedratinib through 30 days after the last dose. AEs will be summarized by severity/grade based on the NCI CTCAE. If a subject experiences the same AE multiple times during the treatment, the event will be counted only once by the worst grade / greatest severity.

Treatment-emergent adverse events, Grade 3 or higher TEAEs, serious AEs, TEAEs leading to dose reduction, and dose interruption, TEAEs leading to treatment discontinuation, and TEAEs with an outcome of death will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. Adverse events of special interest of fedratinib identified in previous trials in a similar population will be summarized in the same manner. If data warranted, additional analyses on fedratinib safety profile may be performed (eg, incidence of nausea, vomiting and diarrhea in relationship to prophylaxis and treatment, etc.) and will be specified in the statistical analysis plan.

9.7.3. Assessment of Risk Mitigation Strategy for Gastrointestinal Adverse Events and Potential Encephalopathy including Wernicke's

Assessment of risk mitigation strategy will include an analysis of incidence of subjects with a CTCAE Grade ≥3 of nausea, diarrhea, or vomiting, or occurrence of encephalopathy including Wernicke's (confirmed by brain MRI or autopsy). Analysis of thiamine levels will be at screening, on Day 1 of the first 3 cycles, every third cycle and at the EOT during the study.

9.7.4. Laboratory Results

Analysis of laboratory data will be descriptive and conducted on the safety population. Summary of laboratory data (including thiamine levels) and change from baseline will also be performed by subject and by cycle. For each of the parameters, a baseline value is defined as the last value or measurement taken up to the first dose of fedratinib.

Hematological toxicities will be assessed from laboratory parameters. Worst NCI CTCAE grades of leukopenia, neutropenia, thrombocytopenia, and anemia will be calculated according to the NCI common terminology criteria.

Qualitative and quantitative results will be summarized for hematological toxicities. Qualitative data (worst NCI CTCAE grade) will be summarized by cycle and by subject.

9.7.5. Electrocardiogram (ECG)

All ECG data will be provided in a listing.

9.7.6. Vital Signs

Vital signs will be summarized based on the number of subjects with at least one potentially clinically significant abnormality (PCSA) occurring during the observation period according to baseline status. The PCSA criteria are provided in Table 5.

Table 5: PCSA Criteria for Vital Signs and Weight

Parameter	PCSA
Heart (bpm)	≤ 50 bpm and decrease from baseline ≥ 20 bpm ≥ 120 bpm and increase from baseline ≥ 20 bpm
SBP (mmHg)	≤ 95 mmHg and decrease from baseline ≥ 20 mmHg ≥ 160 mmHg and increase from baseline ≥ 20 mmHg
DBP (mmHg)	≤ 45 mmHg and decrease from baseline ≥ 10 mmHg ≥ 110 mmHg and increase from baseline ≥ 10 mmHg
Weight (kg)	≥ 5 % increase from baseline ≥ 5 % decrease from baseline

DBP = diastolic blood pressure; kg = kilograms; mmHg = millimeters of mercury; PCSA = potentially clinically significant abnormalities; SBP = systolic blood pressure.

[redacted]

9.9. Interim Analysis

A formal interim analysis is not planned in this study.

9.10. Steering Committee

The conduct of this trial will be overseen by a steering committee (SC), presided over by a coordinating Principal Investigator, and if possible, the representative Regional Investigators from countries participating in this study.

The SC will serve in an advisory capacity to the Sponsor. Operational details for the SC will be detailed in a separate SC charter.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An 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 (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, 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 on the AE page of the CRF 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. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 7.2.4 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product which meets the definition of an adverse event should be reported as an AE on the CRF. If the sequela of an overdose meets serious criteria, then it must be marked as serious on the CRF. The overdose itself should not be reported as an SAE.

[redacted] Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for fedratinib overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

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 AEs will be recorded by the Investigator from the time the subject signs informed consent until 30 days after the last dose of fedratinib, as well as those SAEs made known to the investigator at any time thereafter that are suspected of being related to fedratinib AE and SAEs. All adverse events (serious/non-serious) will be recorded on the CRF and in the subject's source documents. Refer to Section 10.5 for instructions on how to report SAEs to Drug Safety.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;

- Is life-threatening (ie, 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** to be 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 (eg, 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 (ie, planned prior to start 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, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

For each AE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2. Severity/Intensity

For each AE, 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);

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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.

10.2.3. Causality

The Investigator must determine the relationship between the administration of fedratinib and the occurrence of an AE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to fedratinib administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of fedratinib caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between fedratinib and the adverse event.

Causality should be assessed and provided for each AE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene-Impact, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For each AE, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with fedratinib as a result of each AE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for each AE.

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).

10.3. 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 fedratinib dose administration, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity 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 as the AE. 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 (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject of childbearing potential or partner of childbearing potential of a male subject are immediately reportable events.

10.4.1. Females of Childbearing Potential

Pregnancies and suspected pregnancies (including elevated β-subunit of human chorionic gonadotropin [β-hCG] or positive pregnancy test in a female subject of childbearing potential

regardless of disease state) occurring while the subject is on fedratinib treatment, or within 30 days of the subject's last dose of fedratinib, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the fedratinib to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or 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 or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy and must notify Celgene 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 (eg, spontaneous 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 Drug Safety within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as an SAE. In addition, any infant death after 30 days that the Investigator suspects is related to the in-utero exposure to the fedratinib should also be reported as an SAE to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

10.4.2. Male Subjects

If a female partner of a male subject taking fedratinib becomes pregnant, the male subject taking fedratinib should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Males will be advised to use a latex condom during any sexual contact with FCBP prior to study entry and continue for 30 days following the last dose of fedratinib, even if he has undergone a successful vasectomy.

10.5. Reporting of Serious Adverse Events

Any AE that meets any serious criterion requires reporting as an SAE within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 30 days after the last dose of IP) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) are to be recorded within the CRF, but do not require reporting to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE source documents and all correspondence with the IRB/EC.

The SAE is recorded within the CRF, and the data is transmitted electronically to Celgene Drug Safety. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to Celgene Drug Safety, ensuring the event is recorded on the CRF as well.

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via electronic data capture (EDC) or other appropriate method.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to fedratinib based on the Investigator Brochure.

In the United States, expedited reports sent to the FDA by the sponsor based on the reasonable possibility threshold are known as "IND safety reports" and will be reported in accordance with 21 CFR 312.32.

For reporting to the FDA, events that are not suspected to be causally related to fedratinib by the sponsor will not be considered adverse reactions. As per FDA regulations, events that are anticipated in the study population, listed in the IB, will not be considered adverse reactions on individual assessment and will be reviewed on an aggregate basis for assessment of frequency.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information

- Any AE suspected of being related to the use of fedratinib in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 14.3 for record retention information).

10.7. Adverse 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 and rapid communication by the Investigator to the sponsor. All AESI (serious and non-serious) are to be recorded within the CRF and the data transmitted electronically to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event. In the event electronic transmission is not available, a paper SAE Report Form will be completed and sent directly to Celgene Drug Safety,

ensuring the event is recorded on the CRF as well. The rapid reporting of AESIs allows ongoing surveillance of these events to characterize and understand them in association with the use of this investigational product. Events of special interest may be referred to external experts for review as needed.

10.7.1. Fedratinib AESI

The following are considered to be Adverse Events of Special Interest (AESIs) for Fedratinib:

- Encephalopathy, including Wernicke's 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
- New malignancy after start of study treatment
- Progression of myelofibrosis to acute myeloid leukemia (AML)
- Cardiac failure or cardiomyopathy
- Grade 3 or 4 hyperlipasemia, or Grade 3 or 4 hyperamylasemia; according to CTCAE criteria, v 5.0 or events of pancreatitis
- Grade 3 or 4 alanine transaminase (ALT), aspartate transaminase (AST), or total bilirubin elevation or events of hepatotoxicity

11. DISCONTINUATIONS

11.1. Study Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from fedratinib

- Lack of Efficacy
- Adverse Event
- Progression of Disease according to the IWG-MRT 2013 criteria
- Withdrawal by subject
- Death
- Lost to follow-up
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Treatment discontinuation guidance related to the Dose Modification Schedule table (Table 4)
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

Subjects who discontinue from treatment for any reason will be followed via telephone contact by the site for collection of data on survival including: cause(s) of death, disease progression, and posttreatment therapies for MPN-associated MF; until death, lost to follow up, or withdrawal of consent from the study.

Every attempt should be made to contact subjects during follow up unless subjects discontinue from the study. Every attempt should be made to collect all data on discontinued subjects.

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
  - The following information is to be captured in the subject's source documents and eCRF page(s): the date the informed consent forms (ICFs) were signed, demographics, prior ruxolitinib history, the reason a subject did not qualify for the

study, and the investigator's signature for the eCRF pages. Any adverse events experienced by a screen failure subject will be collected from the date of signing the ICF to the day the subject is confirmed as a screen failure. Serious adverse events occurring prior to treatment (after signing the ICF) are to be recorded within the eCRF, but do not require reporting to Celgene Drug Safety. Relevant information will also be recorded on the Screening Log.

- Withdrawal by subject
- Death
- Lost to follow-up
- Protocol deviation
- Study terminated by Sponsor
- Other (to be specified on the CRF)

The reason for study discontinuation should be recorded in the CRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene-Impact/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, fedratinib will be identified on the package labeling.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene-Impact, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene-Impact staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene-Impact information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene-Impact on public registry websites) is considered Celgene-Impact confidential information. Only information that is previously disclosed by Celgene-Impact on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene-Impact protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene-Impact. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene-Impact for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene-Impact will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

Celgene-Impact affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene-Impact requires the Investigator to permit Celgene-Impact's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene-Impact Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Fedratinib can only be supplied to an Investigator by Celgene-Impact or its authorized representative after documentation on all ethical and legal requirements for starting the study has

been received by Celgene-Impact or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene-Impact and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Celgene-Impact reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene-Impact has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene Standard Operating Procedures (SOPs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene-Impact, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- Fedratinib accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene-Impact if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene-Impact prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene-Impact for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene-Impact or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene-Impact ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene-Impact representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene-Impact representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene-Impact. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene-Impact immediately.

15.3. Product Quality Complaint

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene-Impact after it is released for distribution. Product Quality Complaints may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the patient. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing [redacted] or by contacting the Celgene Customer Care Center [redacted]

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene-Impact on public registry websites, is considered Celgene-Impact confidential information and is not to be used in any publications. Celgene-Impact protocol-related information proposed for use in a publication must be submitted to Celgene-Impact for review and approval, and should not be utilized in a publication without express written approval from Celgene-Impact, or as described in the Clinical Trial Agreement.

Celgene-Impact will ensure Celgene-Impact -sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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18. APPENDICES

APPENDIX A. TABLE OF ABBREVIATIONS

Table 6: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ActRIIB	Human activin receptor type IIB
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
β-hCG	β-subunit of human chorionic gonadotropin
BAT	Best available therapy
BM	Bone marrow
BUN	Blood urea nitrogen
CALR	Calreticulin
CRF	Case report form
CRP	C-reactive Protein
CSR	Clinical Study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP2C19	Cytochrome P450 2C19
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DIPSS	Dynamic International Prognostic Scoring System
DR	Durability of spleen volume response
DRP	Durability of spleen response by palpation
DSR	Durability of symptoms response
EC	Ethics Committee

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
ECD	Extracellular domain
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EMA	European Medicine Agency
EOT	End of treatment
EPO	Erythropoietin
ESA	Erythropoietin-stimulating agent
ET	Essential Thrombocythemia
EU	European Union
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FLT3	Fibromyalgia syndrome (FMS)-like tyrosine kinase 3
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GDF	Growth differentiation factor
GI	Gastrointestinal
HDPE	High density polyethylene
Hgb	Haemoglobin
HI-E	Hematological Improvement – Erythroid
HIV	Human immunodeficiency virus
HRQoL	Health-related Quality of Life
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IM	Intramuscular
IND	Investigational new drug
IP	Investigational product

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	Intravenous
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
K-M	Kaplan-Meier
LCM	Left costal margin
LFT	Liver function test
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis (in terms of this protocol, myeloproliferative neoplasm associated myelofibrosis)
MFSAF	Myelofibrosis Symptom Assessment Form
MMSE	Mini-Mental State Examination
MPL	Myeloproliferative leukemia virus
MPN	Myeloproliferative neoplasms
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NTD	Non-transfusion dependent
OS	Overall survival
PB	Peripheral blood
PBPK	Physiologically based pharmacokinetics
PCSA	Potentially clinically significant abnormality
PK	Pharmacokinetics

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PLT	Platelet
PMF	Primary myelofibrosis
PQC	Product Quality Complaint
PRO	Patient-reported outcomes
[redacted]	
PS	Performance Status
PV	Polycythemia vera
QD	Once a day
[redacted]	
RBC	Red blood cell
RR	Spleen volume response rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Stem-cell transplantation
SOP	Standard Operating Procedure
SRR	Symptom response rate
STAT	Signal transducers and activators of transcription
SUSAR	Suspected unexpected serious adverse reaction
SV	Standard version
SVR	Spleen volume reduction
TD	Transfusion dependent
TEAE	Treatment emergent adverse event
TGF-β	Transforming growth factor - beta
TNF	Tumor necrosis factor
TSS	Total Symptom Score
ULN	Upper limit of normal
US	United States
vs	Versus
WBC	White blood cell

Table 6: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
WE	Wernicke's encephalopathy
WHO	World Health Organization

APPENDIX B. MYELOFIBROSIS SYMPTOM ASSESSMENT FORM (MFSAF) VERSION 4.0

Myelofibrosis Symptom Assessment Form version 4.0 7-Day Recall
(MFSAF v4.0 7-Day Recall)

Instructions (to be modified based on data collection mode): The following questions refer to symptoms that you may experience as a result of your myelofibrosis. Please read through and complete the questions on the following screens. There are no right or wrong answers. Please select the answer that best applies to you.

Items:

1. During the past 7 days, how severe was your worst fatigue (weariness, tiredness)?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

2. During the past 7 days, how severe were your worst night sweats (or feeling hot or flushed)?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

3. During the past 7 days, how severe was your worst itching?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

4. During the past 7 days, how severe was your worst abdominal discomfort (feeling pressure or bloating)?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

5. During the past 7 days, how severe was the worst pain under your ribs on your left side?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

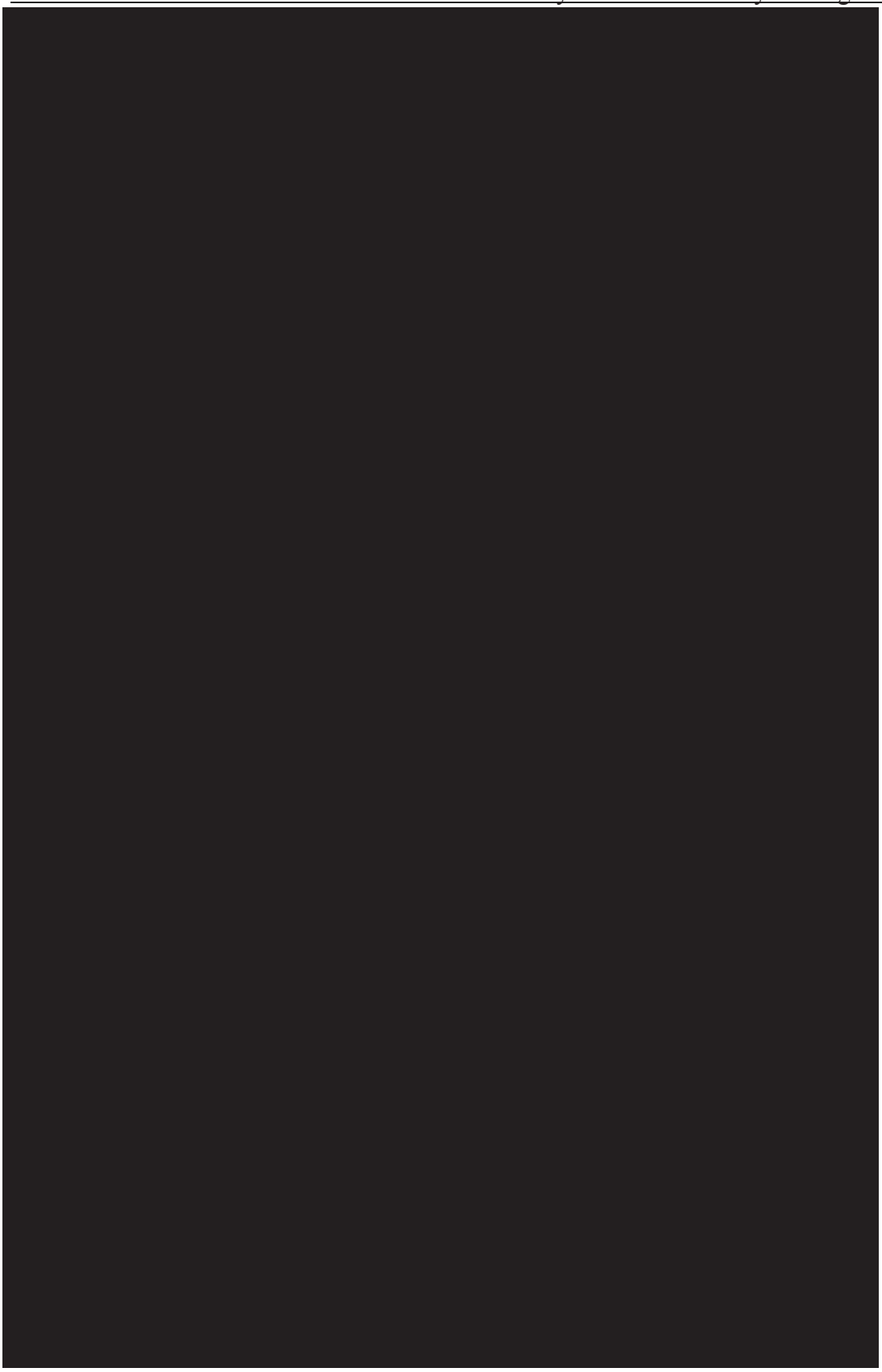
6. During the past 7 days, what was the worst feeling of fullness you had after beginning to eat?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

7. During the past 7 days, how severe was your worst bone pain (not joint or arthritis pain)?

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst Imaginable

Source: (Gwaltney, 2017).



APPENDIX D. REVISED RESPONSE CRITERIA FOR MYELOFIBROSIS: INTERNATIONAL WORKING GROUP-MYELOPROLIFERATIVE NEOPLASMS RESEARCH AND TREATMENT (IWG-MRT) AND EUROPEAN LEUKEMIANET (ELN) CONSENSUS REPORT (2013)

Response categories	Required criteria (for all response categories, benefit must last for ≥ 12 weeks to qualify as a response)
CR	Bone marrow:* Age-adjusted normocellularity; < 5% blasts; ≤ grade 1 MF† and Peripheral blood: Hemoglobin ≥ 100 g/L and < UNL; neutrophil count ≥ 1 x 10^9/L and < UNL; Platelet count ≥ 100 x 10^9/L and < UNL; < 2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
PR	Peripheral blood: Hemoglobin ≥ 100 g/L and < UNL; neutrophil count ≥ 1 x 10^9/L and < UNL; platelet count ≥ 100 x 10^9/L and < UNL; < 2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or Bone marrow:* Age-adjusted normocellularity; < 5% blasts; ≤ grade 1 MF†, and peripheral blood: Hemoglobin ≥ 85 but < 100 g/L and < UNL; neutrophil count ≥ 1 x 10^9/L and < UNL; platelet count ≥ 50, but < 100 x 10^9/L and < UNL; < 2% immature myeloid cells‡ and Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement (CI)	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia§
Anemia response	Transfusion-independent patients: a ≥ 20 g/L increase in hemoglobin level‖ Transfusion-dependent patients: becoming transfusion-independent {
Spleen response	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable** or A baseline splenomegaly that is palpable at > 10 cm, below the LCM, decreases by ≥ 50%** A baseline splenomegaly that is palpable at < 5 cm, below the LCM, is not eligible for spleen response A spleen response requires confirmation by MRI or computed tomography showing ≥ 35% spleen volume reduction
Symptoms response#	A ≥ 50% reduction in the MPN-SAF TSS††
Progressive disease‡‡	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or A 50% increase in palpable distance, below LCM, for baseline splenomegaly of > 10 cm or Leukemic transformation confirmed by a bone marrow blast count of ≥ 20% or A peripheral blood blast content of ≥ 20% associated with an absolute blast count of ≥ 1 x 10^9/L that lasts for at least 2 weeks
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or Loss of anemia response persisting for at least 1 month or Loss of spleen response persisting for at least 1 month

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

* Baseline and posttreatment bone marrow slides are to be interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.
† Grading of MF is according to the European classification
Thiele et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica. 2005;90:1128.
‡ Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells . In splenectomized patients, < 5% immature myeloid cells is allowed.
§ Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥ 20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the CTCAE version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥ 25 000 x 10(9)/L and absolute neutrophil count of ≥ 0.5 x 109/L.
|| Applicable only to patients with baseline hemoglobin of < 100 g/L. In patients not meeting the strict criteria for transfusion dependency at the time of study enrollment, but have received transfusions within the previous month, the pretransfusion hemoglobin level should be used as the baseline.
{ Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBC), in the 12 weeks prior to study enrollment, for a hemoglobin level of < 85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥ 85 g/L.
In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy.
** Spleen or liver responses must be confirmed by imaging studies where a ≥ 35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥ 35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.
†† Symptoms are evaluated by the MPN-SAF TSS.17 The MPN-SAF TSS is assessed by the patients themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). Symptoms response requires ≥ 50% reduction in the MPN-SAF TSS.
‡‡ Progressive disease assignment for splenomegaly requires confirmation by MRI or computed tomography showing a ≥ 25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to posttreatment measurements.

Source: (Tefferi, 2013).

APPENDIX E. NATIONAL CANCER INSTITUTE (NCI) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) VERSION 5.0

Currently active version of NCI CTCAE, Version 5.0:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

APPENDIX F. DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM (DIPSS)

DIPSS Risk Score

Prognostic variables	Value		
	0	**1**	**2**
Age, years	≤ 65	> 65	
White blood cell count, $x10^9/L$	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional symptoms, Y/N	N	Y	

The risk category is obtained adding up the values of each prognostic variable.

Risk categories are defined as low: 0; intermediate-1: 1 or 2; intermediate-2: 3 or 4; and high: 5 or 6.

Constitutional symptoms are defined as >10% weight loss in 6 months, night sweats, unexplained fever higher than 37.5°C.

Sources: (Passamonti, 2010).

APPENDIX G. IWG-MRT: INTERNATIONAL WORKING GROUP-MYELOPROLIFERATIVE NEOPLASMS RESEARCH AND TREATMENT (IWG-MRT)

Proposed nomenclature by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT)

de novo presenting disease
Primary myelofibrosis (PMF)
Myelofibrosis transformation from prior polycythemia vera
(PV) or essential thrombocythemia (ET)
Post PV myelofibrosis (post-PV MF)
Post ET myelofibrosis (post-ET MF)
Transformation to acute leukemia
Primary myelofibrosis in blast phase (PMF-BP)
Post PV/ET MF in blast phase

Source: (Mesa, 2007).

APPENDIX H. 2016 WORLD HEALTH ORGANIZATION (WHO) DIAGNOSTIC CRITERIA FOR PRIMARY MYELOFIBROSIS (PMF)

2016 WHO diagnostic criteria for prePMF and overt PMF

PrePMF[a]	Overt PMF[b]
Major criteria	
1. Megakaryocytic proliferation and atypia, without reticulin fibrosis > grade 1*, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis	1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3*
2. Not meeting the WHO criteria for BCR-ABL1$^+$ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms	2. Not meeting WHO criteria for ET, PV, BCR-ABL1$^+$ CML, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker[c], or absence of minor reactive BM reticulin fibrosis[d]	3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker[c], or absence of reactive myelofibrosis[d]
Minor criteria	
Presence of at least 1 of the following, confirmed in 2 consecutive determinations:	Presence of at least 1 of the following, confirmed in 2 consecutive determinations:
a. Anemia not attributed to a comorbid condition	a. Anemia not attributed to a comorbid condition
b. Leukocytosis ≥ 11 x 10^9/L	b. Leukocytosis ≥ 11 x 10^9/L
c. Palpable splenomegaly	c. Palpable splenomegaly
d. LDH increased to above upper normal limit of institutional reference range	d. LDH increased to above upper normal limit of institutional reference range
	e. Leukoerythroblastosis

* More than 25% above mean normal predicted value.

[a] Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion

[b] Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion.

[c] In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1) are of help in determining the clonal nature of the disease.

[d] Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Grading of myelofibrosis

Myelofibrosis grading	
MF-0	Scattered linear reticulin with no intersections (crossovers) corresponding to normal BM
MF-1	Loose network of reticulin with many intersections, especially in perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis*
MF-3	Diffuse and dense increase in reticulin with extensive intersections and coarse bundles of thick fibers consistent with collagen, usually associated with osteosclerosis*

Semiquantitative grading of BM fibrosis (MF) with minor modifications concerning collagen and osteosclerosis. Fiber density should be assessed only in hematopoietic areas.
*In grades MF-2 or MF-3 an additional trichrome stain is recommended.

Source: (Arber, 2016).

APPENDIX I. PROPOSED CRITERIA FOR THE DIAGNOSIS OF POST-POLYCYTHEMIA VERA AND POST-ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS

International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) recommended criteria for post-PV MF and post-ET MF

Criteria for post-polycythemia vera myelofibrosis	Criteria for post-essential thrombocythemia myelofibrosis
Required criteria:	
1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria	1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria
2. Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale) [a]	2. Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale) [a]
Additional criteria (two are required):	
1. Anemia[b] or sustained loss of requirement of either phlebotomy (in absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis	1. Anemia[b] and a ≥ 2 $mgml^{-1}$ decrease from baseline hemoglobin level
2. A leukoerythroblastic peripheral blood picture	2. A leukoerythroblastic peripheral blood picture
3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly	3. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4. Development of ≥ 1 of three constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5°C)	4. Increased LDH (above reference level)
	5. Development of ≥ 1 of three constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5°C)

[a] Grade 2–3 according to the European classification:[3] diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3–4 according to the standard classification:[4] diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

[b] Below the reference range for appropriate age, sex, gender and altitude considerations.

Source: (Barosi, 2008).

APPENDIX J. ECOG PERFORMANCE STATUS SCALE

The ECOG Performance Status Scale is used to score a subject's quality of life through evaluation, by a health professional, of daily activities and how those activities are affected by the disease of the subject.

Score	Description
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, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: (Oken, 1982).

APPENDIX K. ESTIMATION OF THE GLOMERULAR FILTRATION RATE BY THE MDRD FORMULA

GFR Estimation

GFR is estimated using the MDRD formula below:

GFR (mL/min/1.73 m^2) = 175 x $Scr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if African American) x 0.742 (if female)

Where Scr (standardized serum creatinine) = mg/dL; age = years

Source: (Levey, 2006).

APPENDIX L. CLINICALLY RELEVANT P450 INDUCERS, INHIBITORS, SUBSTRATES, AND TRANSPORTER SUBSTRATES

A list of clinically relevant P450 inducers and inhibitors as well as substrates, and transporter substrates can be found in this appendix This is not an exhaustive list. It is periodically updated at the following link:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Examples of clinical inducers for P450-mediated metabolisms

Strong CYP3A inducers	Moderate CYP3A inducers
carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	bosentan, efavirenz, etravirine, modafinil

Examples of clinical inhibitors for P450-mediated metabolisms

Strong CYP3A inhibitors	Dual CYP2C19 and CYP3A4 inhibitors
boceprevir, cobicistat, conivaptan, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole	fluconazole, fluvoxamine
clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir	

Examples of clinical substrates for P450-mediated metabolism

	Sensitive substrates	Substrates with narrow therapeutic range
CYP2C19	S-mephenytoin, omeprazole	S-mephenytoin
CYP2D6	atomoxetine, dextromethorphan, eliglustat, nebivolol, nortriptyline, perphenazine, tolterodine, venlafaxine	desipramine
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil	Alfentanil, cyclosporin, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus
	budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	

Examples of clinical substrates for transporters

Transporter	Substrate
P-gp	dabigatran, digoxin, fexofenadine
BCRP	rosuvastatin, sulfasalazine
OATP1B1 OATP1B3	asunaprevir, atorvastatin, bosentan, cerivastatin, danoprevir, docetaxel, fexofenadine, glyburide, nateglinide, paclitaxel, pitavastatin, pravastatin, repaglinide, rosuvastatin, simvastatin acid
MATE1, MATE-2K, OCT2	dofetilide, metformin

APPENDIX M. NEW YORK HEART ASSOCIATION CLASSIFICATION FOR CONGESTIVE HEART FAILURE

Classification of Heart Failure

Class	Functional Capacity
Class I	Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Source: (AHA Medical/Scientific Statement. (1994)).

APPENDIX N. MINI-MENTAL STATE EXAMINATION (MMSE)

MMSE-2™

Standard Version

Blue Form

Date of examination ___/___/___ Examiner ___

Name ___ Age ___ Sex ___

Years of school completed ___ Purpose of exam ___

Assessment of level of consciousness

Alert/ Responsive | Drowsy | Stuporous | Comatose/ Unresponsive

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Unless otherwise specified, circle 0 if the response is incorrect or 1 if the response is correct. Begin by introducing the test:

Now I'd like to ask you some questions about your memory.

	RESPONSE	SCORE (circle one)
REGISTRATION		
Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are... MILK [*pause*], **SENSIBLE** [*pause*], **BEFORE** [*pause*]. **Now repeat those words back to me.** [*Repeat up to 3 times, but score only the first trial.*]		
MILK		0 1
SENSIBLE		0 1
BEFORE		0 1
Now keep those words in mind. I am going to ask you to say them again in a few minutes.		
ORIENTATION TO TIME		
What day is today? What is the...		
year?		0 1
season?		0 1
month of the year?		0 1
day of the week?		0 1
date?		0 1
ORIENTATION TO PLACE*		
Where are we now? What is the...		
state (or province)?		0 1
county (or city/town)?		0 1
city/town (or part of city/neighborhood)?		0 1
building (name or type)?		0 1
floor of the building (room number or address)?		0 1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

RECALL

What were those three words I asked you to remember? [*Do not offer any hints.*]

MILK		0 1
SENSIBLE		0 1
BEFORE		0 1

If administering the MMSE-2:SV, copy the MMSE-2:BV total raw score to the space provided at the top of page 2 and continue with administration.

MMSE-2:BV total raw score ☐ (16 max. points)

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MMSE-2:BV total raw score ☐ (16 max. points)

ATTENTION AND CALCULATION [*Serial 7s*]

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]	_____	0	1
If needed, say: **Keep going.**	[86]	_____	0	1
If needed, say: **Keep going.**	[79]	_____	0	1
If needed, say: **Keep going.**	[72]	_____	0	1
If needed, say: **Keep going.**	[65]	_____	0	1

Score 1 point for each correct answer. An answer is considered correct if it is 7 less than the previous answer, even if the previous answer was incorrect.

NAMING

What is this? [*Point to eye.*]	_____	0	1
What is this? [*Point to ear.*]	_____	0	1

REPETITION

Now I am going to ask you to repeat what I say. Ready? IT IS A LOVELY, SUNNY DAY BUT TOO WARM. Now you say that. [*Wait for examinee response and record response verbatim. Repeat up to one time.*]

IT IS A LOVELY, SUNNY DAY BUT TOO WARM.	_____	0	1

Detach the last page of this form. Tear the detached page in half along the horizontal perforation line. Use the upper half of the detached page, which has three shapes on it, as a stimulus form for the Comprehension task. Use the bottom half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") task. Use the upper back half of the detached page as a stimulus and response form for the Drawing (intersecting pentagons) task and the bottom half of the page (blank) as a response form for the Writing task.

COMPREHENSION

Listen carefully because I am going to ask you to do something. [*Show examinee the geometric figures stimulus page.*] **Look at these pictures and point to the circle, then point to the square, and then point to the triangle.**

Correct response	Observed response		
○		0	1
□		0	1
△		0	1

READING

[*Show examinee the word stimulus page.*] **Please do what this says to do.**

CLOSE YOUR EYES	_____	0	1

WRITING

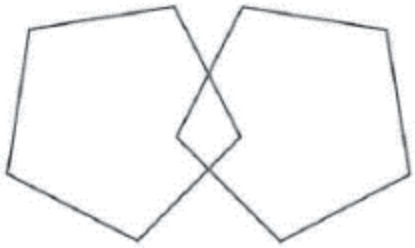
[*Place the blank piece of paper in front of the examinee and provide a pen or pencil.*] 0 1
Please write a sentence. [*If examinee does not respond, say:* **Write about where you live.**]
Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

DRAWING

[*Display the intersecting pentagons on the stimulus form and provide a pen or pencil.*] **Please copy this design.** Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure. 0 1

MMSE-2:SV total raw score ☐ (30 max. points)

CLOSE YOUR EYES



Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: Monday, 03 May 2021, 03:50 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

As of 12 Nov 2020, BMS – Celgene has made the decision to not implement the sub-study due to the coronavirus disease 2019 (COVID-19) pandemic's impact on the sub-study start-up activities.

In the ongoing clinical program, BMS has observed events of low thiamine and one case of Wernicke's encephalopathy which was discussed with the Scientific Steering Committee. The Steering Committee made the recommendation to implement prophylactic thiamine supplementation for all study subjects.

This amendment will therefore include updated language to reflect the mandatory thiamine supplementation and updated guidelines for thiamine deficiency as well as the removal of all sub-study language.

The protocol has been revised to remove this optional sub-study throughout the protocol from the Cover page through Sections 11, including figures and tables. The subsections added in Protocol Amendment 1; which separated sections referred to as the "Main Study" and "Sub-Study" have been amended to only reflect the original protocol design.

The following changes were made to the protocol with the removal of the sub-study:

- Title updated to remove the sub-study – Cover page and Protocol Summary
- The following sections, tables, and figures from Protocol Amendment 1 were deleted and subsequent sections have therefore been renumbered, as applicable: Sections 1.1.5, 1.3, 1.3.1, 1.4.5, 1.4.5.2-1.4.5.4, 2.1, 3.1.2, 4.4-4.4.3, 5.2, 6.8-6.8.5, 7.1.2, 7.2.4-7.2.4.3, 8.4-8.4.2, 9.2.1, 9.3.2, 9.6.7-9.6.7.2, 10.7.2-10.7.2.2, and 11.3. Tables 3, 4, 6, and 8-10. Figures 1 and 3.
- The following sections and figure have been updated to remove all references to the sub-study: Protocol Summary, Sections 3.1-3.3, 4.1, 6.5, 7.2, 7.2.4, 7.4.3, 7.5-7.6, 7.8, 9.1, 9.5, 9.7-9.7.2, [redacted] 10.1, 10.2.3, 10.2.5, 10.3, and 10.4.1-10.6. Figure 2.
- References to "Main study" have been removed or revised to "study" throughout.

1.1. Additional Clarifications and Corrections

Other changes included in this amendment are summarized below. These changes are based on recommendations received from internal discussions and expert opinions.

- Updated language in Section 6.7.1. Symptoms Response Assessment
  - To ensure every possible attempt to collect symptom response information is made, wording has been updated to include alternate modalities.

- Updated language in Section 6.5 Response Assessment
  - Revised language regarding the time point frequency and assessments to be completed. Aligned frequency of all "response assessments" to occur every six (6) cycles after Cycle 24 which includes spleen imaging (in addition to spleen size by palpation and Myelofibrosis Symptom Assessment Form [MFSAF])
- Updated language in Sections 7.4.2 Management of Encephalopathy Including Wernicke's
  - Updated Section 7.4.3- Management of Encephalopathy including Wernicke's language to empirically start parenteral thiamine supplementation for subjects with thiamine levels < 30 nM/L
- Updated language in Section 7.4.2 Thiamine Supplementation, Monitoring, and Correction
  - Updated Section 7.4.3 title from "Thiamine Monitoring and Correction" to "Thiamine Supplementation, Monitoring, and Correction" to reflect updated language for required thiamine supplementation
  - Revised language to state that oral thiamine supplementation of 100 mg or equivalent is mandatory for all subjects throughout the treatment period until study medication is discontinued and though the 30-Day Follow-Up visit
  - Revised language to reflect thiamine level monitoring to be taken in a fasting state at the start of Cycles 1, 2, 3 and every third cycle thereafter, including end of treatment (EOT) visits
  - Revised language to include new monitoring parameters and thiamine level thresholds for encephalopathy including Werneck's Encephalopathy (WE) monitoring
    - Updated guidance to site if subject develops signs or symptoms suggestive of WE, to follow instructions updated in Section 7.4.2
    - For thiamine levels below normal range but > 30 nM/L without signs or symptoms of WE – updated language to increase thiamine supplementation to twice the daily dose (100 mg to 200 mg)
    - Updated guidance to site to contact Medical Monitor regarding low thiamine level
    - For thiamine levels < 30 nM/L without signs or symptoms of WE – updated language to stop oral thiamine supplementation and start intravenous (IV) thiamine at therapeutic dosages
      - Updated guidance to follow IV thiamine therapy with 250 mg to 500 mg IV thiamine infused once daily for 3 to 5 days (or via intramuscular [IM] injection)
      - Updated guidance to increase subjects daily dose to twice the previous daily dose post event

- Updated guidance to monitor thiamine levels monthly
- Updated guidance to hold study medication until thiamine levels are restored

▪ Updated Table 3 – Table of events to include daily dose of thiamine

▪ Updated language in Section 8.1 to reflect the mandatory thiamine supplementation

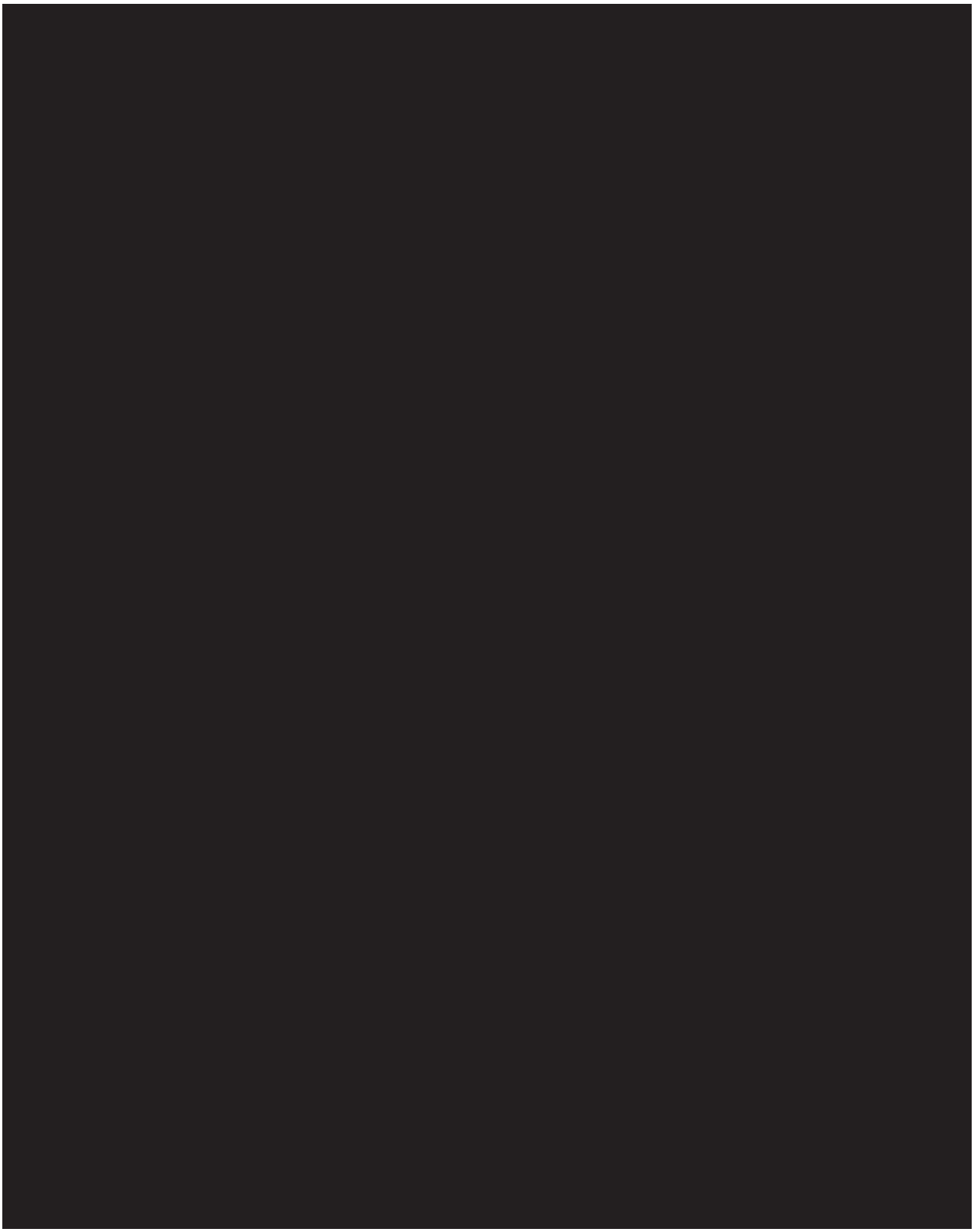
- Updated safety language in Section 10.6 to reflect changes in the heritage Celgene (hCelgene) protocol template to alleviate the confusion resulting from reporting pre-treatment events

1.2. Minor Corrections, Clarifications and Administrative Changes

- Other clarifications, corrections of minor typographical errors and incidental formatting changes were made throughout the document
- Clarified Section 11.1 Study Treatment Discontinuation to include International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) 2013 criteria
- New Medical Monitor on "Medical Monitor / Contact Information" page

1. JUSTIFICATION FOR AMENDMENT

As of 12 Feb 2020, approximately 20 subjects have been enrolled into the main study of FEDR-MF-001 of which ~2 have completed at least 8 cycles of treatment with fedratinib.



[redacted]

Other significant changes included in this amendment are summarized below. These changes are based on recommendations received from the [redacted] expert opinion, and internal discussions.

- Modifications to the eligibility criteria
  - To ensure subjects are evaluable for the primary and key secondary endpoints in the study, an additional exclusion criterion is added requiring subjects to have a minimum life expectancy of 6 months. Subjects with a white blood cell count > 100 x 10^9/L are not eligible to participate in the study.
    Revised section: Section 4.3;
- Surveillance of suspected encephalopathy, including Wernicke's encephalopathy, in patients receiving or who have received fedratinib from any source [redacted]
  - The objective, endpoint, and further reference in the protocol to assess the effectiveness of the risk mitigation strategy for Wernicke encephalopathy is updated to include Encephalopathy, including Wernicke's.
    Revised sections: Protocol Summary, Section 1.2.1, Section 1.4.1, Section 1.4.2, Section 4.3, Table 5, Section 6, Section 7.4, Section 9.7.3 and Section 10.7.1;
  - Language is revised to clarify that platelet and red blood cell transfusion history will be collected 84 days prior to enrollment. This will establish the subject's baseline transfusion status information.
    Revised sections: Table 5, Section 6.1 and Section 8;
- Lipid testing is included in the study [redacted]
  - Lipid profile monitoring is added [redacted] since lipid profile changes have been observed in patients treated with ruxolitinib. This request is to better understand if the lipid profile changes are specific to ruxolitinib or if changes could possibly be a Janus kinase inhibitor class effect.
    Revised sections: Table 5, Section 6.1, Section 6.2, Section 6.2.1, and Section 6.4;
- The language is updated throughout the protocol for concomitant administration of fedratinib with clinically relevant cytochrome P450 inducers, inhibitors, substrates, and transporter substrates to align with the information included in the Inrebic® label recently approved by the FDA
  - The eligibility criteria are updated to exclude subjects receiving concomitant treatment with or use of pharmaceutical, herbal agents or food known to be strong

or moderate inducers of Cytochrome P450 3A4 (CYP3A4) or dual CYP2C19 and CYP3A4 inhibitors.
Revised section: Section 4.3;

- Clarifying language is added for the recommended dose adjustment for co-administration of fedratinib with CYP3A4 inhibitors and for subjects with renal impairment.
Revised section: Section 7.2.2 and 7.2.3;
- Clarification is made to the cytochrome P450 inducers, inhibitors, substrates, and transporter substrates section and associated appendix information for consistency with the previously stated updates.
Revised section: Section 8.3 and Appendix L;

- Statistical sections were updated to ensure accurate population and durability of response definitions.
  - Addition of an "Enrolled population" added for the main study – Section 9.2;
  - Durability of spleen volume response revised from loss of response to disease progression or death – Section 9.6.4;
  - Durability of spleen response by palpation revised from loss of response to disease progression or death – Section 9.6.5;
- A Steering Committee was formed during study start-up but language was missing from the protocol.
  - Provided details on the study Steering Committee – Section 9.10;
- Extended the duration of response assessment capture during the main study and provided clarity on assessment timeframe beyond End of Cycle 24
  - Revised the Response Assessment duration to include End of Cycles 18 and 24 to align with FEDR-MF-002. In addition, adding language on every 6 cycles thereafter for spleen size by palpation and symptom response – Protocol Summary, Section 6.5;
- [redacted]
- Language and sections related to fedratinib dose modification were aligned and clarified to avoid potential confusion and duplication
  - Provided clarification regarding the Fedratinib Dose Modification table is for related events. Also added details on the duration for fedratinib treatment interruption – Section 7.2.1;
  - Updated table to clarify repeating toxicities and "Other AE" definition - Table 7;
  - Updated definition changing cardiomegaly to cardiomyopathy – Section 10.7.1;

1.1. Additional Clarifications and Corrections

This amendment also includes the following clarifications and corrections:

- Language is added to the key secondary objective to evaluate MF-associated symptoms by the Myelofibrosis Symptom Assessment Form (MFSAF) version 4.0 to further describe the secondary objective to evaluate the percentage of subjects with at least 50% reduction in MF-associated symptoms as measured by the MFSAF – Protocol Summary and Table 1 in Section 2;
- Added clarification regarding ruxolitinib washout timing during screening – Section 3.1.1;
- Clarified previous exposure with ruxolitinib must be when the subject is diagnosed with primary MF (PMF), post-essential thrombocythemia MF (post-ET MF) or post-polycythemia MF (post-PV MF) – Section 4.2;
- Added clarification on prior JAK inhibitor excluding ruxolitinib – Section 4.3;
- Added criteria to ensure subjects have a life expectancy of at least 6 months – Section 4.3
- Clarification that all patient reported outcomes (PRO) evaluations will be performed on an electronic tablet – Section 6.7;
- Language is added to provide more detail for the mechanism of action of fedratinib and to provide additional background as to how resistance and intolerance to ruxolitinib was defined for subjects in previous clinical studies – Section 1.2;
- Modified the units of measure for the hematology laboratory key eligibility criteria for platelets to maintain consistency throughout the protocol – Figure 2;
- Modified language to accurately describe the units of measure for results reporting and the formula to calculate the estimated glomerular filtration rate using the Modification of Diet in Renal Disease Study (MDRD) formula – Section 4.3 and Appendix K;
- Language is revised to include reference to the recent new drug approval of fedratinib by US FDA – Section 1.1.2, Section 1.1.3 and Section 1.4.1;
- Added an additional timepoint for pregnancy testing at End of Treatment to align with program standards – Section 6.2.1 and Table 5;
- Language is added providing high level guidance for when fedratinib retreatment may be considered after encephalopathy is resolved – Section 7.4.2;
- Language is added providing high level guidance for when thiamine supplementation may be discontinued – Section 7.4.3;
- Language is removed to record dose reduction or titration in the Interactive Response Technology (IRT) system as titration data will not be included in the IRT system functionality – Section 7.5;

- Moved and clarified the definition of Study Treatment Overdose – Section 7.2.5 and Section 10.1;
- The requirements for monitoring, recording and reporting adverse events and serious adverse events are clarified– Section 10.1, Section 10.2.1, Section 10.2.2, Section 10.2.3, Section 10.2.4, Section 10.2.5, Section 10.2.6, Section 10.3, Section 10.4.1, Section 10.5, Section 10.6 and Section 10.7;
- Added collection of prior ruxolitinib history for screen failures – Section 11.2;

1.2. Minor Corrections, Clarifications and Administrative Changes

- Added clarification on the trademark and availability of ruxolitinib – Section 1.1.3 and Section 1.4.1;
- Revised JAKARTA adverse event percentages to align with the citation – Section 1.2;
- The Table of Events screening range is clarified to -28 to -1 days. The visit description in the Table of Events for *Risk mitigation for GI & WE* is updated to *Risk mitigation for GI & Encephalopathy including Wernicke's* – Table 5;
- Described the physical exam requirements further to include clinically significant findings – Section 6.1;
- Clarified sections of management of gastrointestinal (GI) AEs and Encephalopathy including Wernicke's is for fedratinib – Section 7.3 and Section 7.4;
- Added language for clinical guidance on the minimum required thiamine dosing for treating subjects with thiamine levels below normal to maintain a consistent treatment approach as was used in the JAKARTA Phase 3 study – Section 7.4.3;
- Included a recent change to the standard protocol template language stating that literature "book" values and normal ranges will be utilized for local laboratory results – Section 9.7;
- Updated details on Study discontinuation and SAE reporting to align with other sections – Section 11.2;
- Added a clarifying note to ensure reference to the author's definition of constitutional symptoms for Dynamic International Prognostic Scoring System (DIPSS) calculation – Appendix F;
- Corrected typo in the Progressive disease criteria and added response categories for stable disease and relapse – Appendix O;
- Other clarifications, corrections of minor typographical errors and incidental formatting changes were made throughout the document;
- References were updated based on updated details throughout the document – Section 17.