Open-label Roll-Over Study to Assess the Long-term Safety and Efficacy of Ruxolitinib in Subjects with Myelofibrosis

Protocol No: 2015-0872

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1. OBJECTIVES

The main objective of this study is to collect long term safety and tolerability data in patients with myelofibrosis previously treated with ruxolitinib on protocol 2007-0169.

2. BACKGROUND

Ruxolitinib (INCB018424 phosphate, JAKAFI™) is an inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs). Ruxolitinib was approved 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. Ruxolitinib was approved in December 2014 for the treatment of patients with polycythemia vera who have an inadequate response to or cannot tolerate hydroxyurea.

JAKs play an important role in signal transduction following cytokine and growth factor binding to their receptors. In addition, JAKs activate a number of downstream pathways implicated in the proliferation and survival of malignant cells including the STATs (signal transducers and activators of transcription), a family of important latent transcription factors. Aberrant activation of JAKs has been associated with increased malignant cell proliferation and survival. In particular, a causal role for JAK2 has recently been suggested for the majority of patients with Philadelphia chromosome negative MPD.

The MPDs are a group of clonal hematologic diseases that include polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF) and post polycythemia vera/essential thrombocythemia myelofibrosis (post-PV/ET MF). MF may occur as a primary disorder or it may follow a preceding disease course with PV or ET. The clinical course in this disease is characterized by bone marrow fibrosis, hepatosplenomegaly, progressive anemia, extra medullary hematopoiesis, leukoerythroblastic peripheral blood findings and constitutional symptoms. Overall median survival is 5 years and causes of premature death include leukemic transformation, infections, thrombosis, cardiac failure, hepatic failure, respiratory failure and portal hypertension. For a small subset of patients who are young, otherwise healthy and have a histocompatible donor, allogeneic stem cell transplantation may provide a curative option, although a risk of significant mortality is associated with the procedure.

Ruxolitinib is the first treatment to increase the survival of patients with MF. A number of therapies may provide temporary symptomatic improvement or improvement in blood cell count, such as drugs (hydroxyurea, thalidomide, lenalidomide, danazol, prednisone), splenectomy, and involved field radiation at a site of extramedullary disease. None of these therapies have been approved as therapy for MF, and do not improve patients survival.

2.1 Rationale

Ruxolitinib is an inhibitor of the Janus kinases (JAKs) and is the only approved therapy for patients with myelofibrosis. Protocol 2007-0169 was a phase 1-2 study of ruxolitinib in these patients; now the therapy is approved and the protocol is closing. However, we plan to continue to monitor patients for long term safety and survival.

2.2 Formulation

Ruxolitinib will be provided by Incyte Corporation, as 5 mg and 25 mg strength tablets. The tablet formulation contains the active ingredient along with commonly used excipients. All excipients are of compendial grade.

2.3 Ruxolitinib Potential Risks

The primary clinical risks with ruxolitinib treatment are the potential sequelae of decreased hematopoiesis, myelopoiesis, thrombopoiesis and decreased levels of circulating cytokines and growth factors, all of which are secondary to the inhibition of growth factor pathways by JAK2 antagonism.

The most frequently reported hematologic adverse reactions (any CTCAE Grade) are anemia, thrombocytopenia, and neutropenia. Increased rates of infection and anemia are potential risks of myelosuppression. Anemia can also lead to increase in number of transfusions. Hematologic parameters will be closely monitored for all subjects during this study, and therapy will be withdrawn or dosing held or reduced until resolution if there are clinically relevant declines.

2.4 Ruxolitinib Benefits

Ruxolitinib has demonstrated marked reduction in spleen size in patients with MF, and without regard to presence of the JAK2 V617F mutation, as well as symptom reduction. Symptoms related to splenomegaly, as well as symptoms related to elevated cytokine levels, all show improvement with ruxolitinib treatment. After an initial small weight loss likely due to resolution of ascites and/or reduction in splenomegaly, there is an increase in total body weight; importantly, there is weight gain in subjects with low body mass index at entry, ie, cachectic subjects. Survival of patients on ruxolitinib is improved.

3. PATIENT ELIGIBILITY

3.1 Inclusion Criteria:

- Currently enrolled in study 2007-0169 and benefiting from therapy as determined by treating physician,

- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 at enrollment of this study,
- Ability and agreement to attend protocol-specified visits at the study site,
- Able to comprehend and willing to sign the informed consent form.
- Negative pregnancy test in females of childbearing potential. Male patients with female partners of child-bearing potential and female patients of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the study and for 30 days following last dose. Acceptable forms of contraception include 1 highly effective method such as an intrauterine device (IUD), hormonal (birth control pills, injections, or implants), tubal ligation, or partner's vasectomy and at least 1 additional approved barrier method such as a latex condom, diaphragm, or cervical cap. Female patients of childbearing potential must not be breast-feeding or planning to breast feed and must have a negative pregnancy test ≤7 days before first study treatment.
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3.2 Exclusion Criteria:

- none

4. TREATMENT PLAN

4.1 Starting Dose of Ruxolitinib and Treatment Cycle

Ruxolitinib has been developed for oral administration, a route of administration that is widely used and helps promote subject compliance to medication dosing. Both BID and QD regimens are permitted. Because of the short plasma half-life of ruxolitinib, there is little accumulation of ruxolitinib or active metabolites. The treatment period consists of multiple 28-day cycles, with subjects continuing in the study indefinitely as long as provided withdrawal criteria is not met, and there is continuing evidence of clinical benefit. Patients will continue therapy with ruxolitinib at the same dose and schedule as they have been receiving on study 2007-0169.

4.2 Administration of Ruxolitinib

Subjects will self-administer the study medication, orally, in an outpatient setting every day in only one dose on daily schedule, and every 12 hours on twice a day schedule.

4.3 Duration of Therapy

Subjects may continue on therapy indefinitely as long as they are receiving clinical benefit based per investigator's criteria, and if they do not meet any of the withdrawal criteria (see section 5.5) and do not have disease progression.

4.4 Dosing Delays/Dose Modifications/Dose Interruptions

The course of management of the subject is at discretion of the investigator as determined in the best interest of the subject. For subjects who do not require dose interruption but have thrombocytopenia or neutropenia and no other serious safety concerns, strategy may vary case-by-case situation, to include one or more aspects of dosing schedule (ex. daily dose regimen, dosing interval, and frequency of dose or overall duration of administration of the therapy) as well as concomitant treatments to manage any untoward symptoms.

Mandatory dose decreases for safety reasons are dictated by platelet count levels. Dose modification strategies will be applied to all ongoing subjects enrolled in the study as per ruxolitinib's label (guidelines provided by FDA). When a decision is made to discontinue the subject or interrupt the therapy, then the recommendation is to consider instituting a tapering strategy based on the investigator's clinical judgment.

Utilization of a tapering strategy is based on condition of the subject, the current dosing regimen and the investigator's clinical judgment, and maintains a dose that has been shown to provide benefit to the subject or to increase the dose to a dose previously shown to provide benefit to the subject.

In any case, the following rules will ALWAYS apply:

1. The maximum dose must never exceed 25 mg BID, or if once-daily doses are used, dose may never exceed 100 mg QD.
2. Dosing must be interrupted with observation of a platelet count $<25 \times 10^9$/L.Dosing may be resumed with recovery of platelet count to a confirmed value of 35×10^9/L or higher. Doses should be restarted at 5 mg BID, and may be increased by 5 mg BID every 2 weeks provided platelet count remains stable and exceeds 35×10^9/L.
3. Dosing should be decreased by at least 5 mg BID increments with confirmed platelet count values of 25×10^9/L to 35×10^9/L. Dose increases may be instituted with recovery of platelets above 50×10^9/L.

Drug may be held up to 2 months for platelet or ANC abnormalities but if counts do not return to the level for reinstituting drug by that time, the subject will be discontinued from the study. Similarly, if drug is held for a non-hematologic toxicity for greater than two months, then the subject must be discontinued from the study.

4.5 Concomitant, Prohibited or Restricted Medications

Ruxolitinib is predominantly metabolized by CYP3A4. When administering Jakafi with strong CYP3A4 inhibitors a dose reduction is recommended. Patients should be closely monitored and the dose titrated based on safety and efficacy.

Erythropoietin or danazol may be used for patients who meet ALL of the following criteria:

- Patients with symptomatic anemia OR who are unable to maintain a Hb above 8.0 without transfusion.
- Patients for whom a dose reduction would be required to a dose < 10 mg BID OR to a dose that was previously shown to be ineffective in order to manage anemia OR patients whose current dose is sub optimally effective and cannot be dose escalated because of anemia.

Patients for whom the addition of danazol or erythropoietin is used to escalate from their current dose to gain additional efficacy may not escalate the dose of ruxolitinib until after at least 8 weeks of erythropoietin or danazol treatment and demonstration of improvement in Hb or transfusion requirements.

- Granulocyte growth factors are not allowed while study medication is being administered but may be used for severe neutropenia at the Investigator's discretion while study medication is being held.
- Anagrelide and hydroxyurea are not allowed.
- Steroid doses greater than the equivalent of 10 mg prednisone per day, unless part of a dose tapering regimen for a discontinuing subject.
- Any investigational medication other than the study medications. Use of such medications within 14 days or 6 half-lives, whichever is longer, prior to the first dose of study medication and during the study through the Follow-up Visit is prohibited.
- In emergency situations, the Investigator may use any treatment, including prohibited treatments, to manage life-threatening events including events which may be secondary to discontinuation, interruption or reduction of administration of ruxolitinib. These concomitant treatments must be documented in the subject's medical records. The treatment(s) will not be considered a protocol violation in this circumstance.

- Drugs that are classified as CYP3A4 inhibitors and/or inducers are restricted (ie: fluconazole) and should only be used with Investigator approval.

4.6 Compliance:

Study medication compliance will be ascertained by tablet count of study medication at each protocol required clinic visit. Missed doses will not be considered a protocol violation unless a subject takes < 75% of the prescribed dose in a 6-month period. 6 months medication diary will be provided in every site visit.

5. STUDY PROCEDURES

5.1 Cycles:

Cycles will be 28 consecutive days, on a daily or twice a day schedule. Subjects will have an every 6 cycle site visit with +/- 30 days window.

The following observations will be carried out at **site study visits every 6 cycles (± 30 days):**

- Targeted physical examination,
- Vital signs,
- Overall response assessment (IWG-MRT),
- EORTC QLQ-C30 questionnaire must be completed by the subject consistent with the EORTC guideline or standard guideline for completion of QOL questionnaires (see Appendix section),
- MFSAF questionnaire must be completed by the subject consistent with the standard guideline for completion of QOL questionnaires (see Appendix section)
- Blood draws for:
  - Serum chemistries (see Appendix section)
  - Hematology (CBC with differential and platelets)
- Adverse event assessment,
- Concomitant medication assessment,
- Dispense ruxolitinib, conduct study medication compliance: medication diary review, providing new one in every site visit.

Between study visits, subjects will have hematology (CBC with differential) and serum chemistry on day 1 of every 3 cycles, with +/- 14 days window (see Appendix section).

Every 3 cycles, in between site visits, subjects will be contacted for follow-up to assess well-being, any new or worsening signs and/or symptoms, compliance with study medication and dosing instructions, compliance with the local laboratory schedule and to answer any questions that the subject might have.

5.2 End of Study or Early Termination Visit

End of Study or Early Termination visits are part of the study protocol. However, if the subject has been contacted and cannot/chooses not to return for this visit, this will not be reported as a protocol deviation. This subject decision will be documented on the CRF. Subjects must return any remaining medication to the study site for final drug reconciliation. The following procedures will be performed:

- EORTC QLQ-C30 questionnaire must be completed by the subject consistent with the EORTC guideline or standard guideline for completion of QOL questionnaires (see Appendix section).
- MFSAF questionnaire must be completed by the subject consistent with the standard guideline for completion of QOL questionnaires (see Appendix section).
- Where feasible the EORTC QLQ-C30 and MFSAF questionnaire should be administered prior to any study-specific procedures.
- Review of medical history and concomitant medication,
- Review of any adverse events,
- Complete physical examination and vital signs,
- ECOG performance status,
- Blood draws for:
  - Serum chemistries (see Appendix section)
  - Hematology (CBC with differential),
- Overall response assessment (IWG-MRT),
- A study medication tablet count will be done to assess compliance: medication diary review.

5.3. Duration of Participation and Number of Subjects:

Subjects may continue on therapy indefinitely if they do not meet any of the withdrawal criteria, do not have disease progression, and are receiving clinical benefit as per treating physician.

5.4. Outside Physician Participation During Treatment

MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.

A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care (Appendix VI).

Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.

Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.

A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician.

Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.

Patients will return to MDACC every 6 cycles as long as they are enrolled in the study.

5.5 Criteria for Removal from the Study

Treatment with study drug is to be discontinued when any of the following occurs:

- Loss of therapeutic effect in the judgment of the Investigator
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.
- Withdrawal of consent
- Lost to follow up
- Death
- Suspected pregnancy

6. RESPONSE DEFINITIONS

Overall response assessment will be graded according to the International Working Group (IWG) consensus criteria for treatment response in PMF and Post-PV/ET MF:

1. **Complete remission (CR):** Requires <u>all</u> of the following in the absence of both transfusion and growth factor support:

   i) Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly.

   ii) Peripheral blood count remission defined as hemoglobin > 11 g/dL, platelet count ≥ 100 x 10^9/L, and absolute neutrophil count ≥ 1.0 x 10^9/L.

   iii) Normal leukocyte differential including disappearance of nucleated red blood cells and immature myeloid cells in the peripheral smear, in the absence of splenectomy.

iv) Bone marrow histological remission defined as the presence of age-adjusted normocellularity, < 5% myeloblasts, and an osteomyelofibrosis grade of ≤ 1.

2. **Partial remission (PR):** Requires all of the above criteria for CR except the requirement for bone marrow histological remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.

3. **Clinical improvement (CI):** Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment *(CI response is validated only if it lasts for ≥ 8 weeks).*

i) A ≥ 2 g/dL increase in hemoglobin level or becoming transfusion independent (applicable only for subjects with baseline hemoglobin level of < 10 g/dL).

ii) Either a ≥ 50% reduction in palpable splenomegaly of a spleen that is ≥ 10 cm at baseline or a spleen that is palpable at > 5 cm at baseline becomes not palpable.

iii) A ≥ 100% increase in platelet count and an absolute platelet count of ≥ 50,000 x 10^9/L. (applicable only for subjects with baseline platelet count of < 50 x 10^9/L).

iv) A ≥ 100% increase in ANC and an ANC of ≥ 0.5 x 10^9/L (applicable only for subjects with baseline absolute neutrophil count of < 1 x 10^9/L).

4. **Progressive disease:** Requires one of the following:

i) Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at > 5 cm below the left costal margin or a ≥ 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a ≥ 50% increase in palpable distance for baseline splenomegaly of > 10 cm.

ii) Leukemic transformation confirmed by a bone marrow blast count of ≥ 20%. iii) An increase in peripheral blood blast percentage to ≥ 20% that lasts for ≥ 8 weeks.

5. **Stable disease:** None of the above.

6. **Relapse:** Loss CR, PR, and CI. In other words, a patient with CR or PR is considered to have undergone relapse when he or she no longer fulfils the criteria for even CI.

Footnotes

- *In patients with CR, a complete cytogenetic response is defined as failure to detect a cytogenetic abnormality in cases with a pre-existing abnormality. A partial cytogenetic response is defined as 50% or greater reduction in abnormal metaphases. In both cases, at least 20 bone marrow- or peripheral blood-derived metaphases should be analyzed.*

A major molecular response is defined as the absence of a specific disease-associated mutation in peripheral blood granulocytes of previously positive cases. In the absence of a cytogenetic/molecular marker, monitoring for treatment-induced inhibition of endogenous myeloid colony formation is encouraged. Finally, baseline and post- treatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process.

- *Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the last month for hemoglobin of < 8.5 g/dL that was not associated with clinically overt bleeding. Similarly, during protocol therapy, transfusions for hemoglobin of ≥ 8.5 g/dL is discouraged unless it is clinically indicated.*

- *It is acknowledged that worsening cytopenia might represent progressive disease but its inclusion as a formal criterion was avoided because of the difficulty distinguishing disease-associated from drug-induced myelosuppression. However, a decrease in hemoglobin of ≥ 2 g/dL, a 100% increase in transfusion requirement, and new development of transfusion dependency, each lasting for more than 3 months after the discontinuation of protocol therapy can be considered disease progression.*

7. REGULATORY AND REPORTING REQUIREMENTS:

Adverse event reporting will be as per the current NCI criteria and the MDACC Leukemia-specific Adverse Event Recording Reporting Guidelines. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html).*

Serious Adverse Event Reporting (SAE)

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization, unless for planned, elective procedure
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**
- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**
- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Leukemia Guidelines for AE reporting will be followed.

Adverse Events and Protocol specific data will be entered into PDMS/CORe. PDMS will be used as the electronic case report form.

7.1. Expedited Adverse Event Reporting

Leukemia associated symptoms are not to be reported as adverse events on this protocol. Myelosuppression and associated complication are expected events during leukemia therapy and are part of the treatment success (marrow emptying of leukemia cells). Therefore, myelosuppression and associated complications such as fever, infections, bleeding, and related hospitalization will be reported in the study summary.

For this protocol, the following adverse events are specifically excluded from expedited AE reporting:

CTCAE Category	**Adverse Event**	**Grade**	**Hospitalization/ Prolongation of Hospitalization**	**Comments**
Blood/ Bone marrow/ Infection	Hemoglobin, leukocytes (total WBC), lymphopenia, Neutrophils/ granulocytes (ANC/AGC), Platelets, fever, sepsis	1-4	Yes	Do not require expedited reporting
Gastro-intestinal	Diarrhea, nausea, vomiting, stomatitis	1-3	Yes	Hospitalization for grade 3 AEs does not require expedited reporting
Metabolic/ laboratory	↓K,↓Mg, ↓Na, ↓glucose, ↑K, ↑Mg, ↑glucose, ↑uric acid,↑LDH Or other metoablic indeces	1-4	Yes	Do not require expedited reporting unless hospitalized for

				management

8. STATISTICS

8.1 Study Population

All subjects who received at least one dose of study medication with at least one follow up assessment for safety will be included in the safety and tolerability analyses.

8.2 Safety Analysis

The clinical safety data (vital signs, routine laboratory tests and adverse events) will be analyzed using summary statistics (e.g., mean, frequency).

8.3 Adverse Events

Severity of adverse events will be based on the NCI–CTCAE v3.0 (NCI Common Terminology Criteria for Adverse Events, Publ. Aug 9, 2006). The subset of adverse events that are considered by the Investigator to have a possible or probable relationship to study medication will be considered to be treatment-related adverse events. If the Investigator does not specify the relationship of the adverse event to study medication, the adverse event will be considered to be treatment-related. The incidence of adverse events and treatment-related adverse events will be tabulated.

8.4 Clinical Laboratory Tests and Vital Signs

Laboratory test values outside the normal range will be assessed for drug association based on screening and baseline values and for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, heart rate, respiratory rate and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities and patients exhibiting clinically notable vital sign abnormalities that were not present at screening or baseline will be listed.

9. REGULATORY CONSIDERATIONS

9.1 Institutional Review Board/Ethics Committee approvals

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

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

9.2 Informed consent

The PI must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form, signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the medical records.

9.3 Subject Confidentiality

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

9.4 Study records requirements

The PI must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of eCRF and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The PI agrees to adhere to the document/records retention procedures by signing the protocol. All data will be entered in PDMS/CORE.

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APPENDIX I: CLINICAL LABORATORY TESTS AT SITE VISITS

APPENDIX II: CLINICAL LABORATORY TESTS AT INTERIM VISITS

APPENDIX III: EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

APPENDIX IV: EORTC QLQ-C30 (VERSION 3)

APPENDIX V: MODIFIED MYELOFIBROSIS SYMPTOM ASSESSMENT FORM (MFSAF)

APPENDIX I - CLINICAL LABORATORY TESTS AT SITE VISITS

Serum Chemistry	**Hematology:**
Albumin	Complete Blood Count (CBC), with differential
Alkaline phosphatase	
ALT *or* AST	
Bicarbonate	
BUN	
Calcium	
Chloride	
Creatinine	
Glucose	
LDH	
Potassium	
Sodium	
Total bilirubin	
Total protein	

APPENDIX II - CLINICAL LABORATORY TESTS AT INTERIM VISITS

Serum Chemistry	**Hematology**
Albumin	Complete Blood Count (CBC), with differential
Alkaline phosphatase	
ALT *or* AST	
Bicarbonate	
BUN	
Calcium	
Chloride	
Creatinine	
Glucose	
Potassium	
Sodium	
Total bilirubin	
Total protein	

APPENDIX III - EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

APPENDIX IV – EORTC QLQ-C30 (VERSION 3)

EORTC QLQ-C30 version 3 is a validated quality of life questionnaire (QLQ) for assessing the health-related quality of life (QOL) of cancer patients participating in clinical trials (Aaronson et al, 1993). *The QLQ-C30 is a set of core questionnaire that includes a range of physical, emotional, and social health issues commonly experienced by cancer patients. The QLQ comprises distinct scales, each of which represents a different aspect of QOL. The response to questionnaire is assessed by using scoring procedures provided in the EORTC QLQ-C30 user manual. Version 3 is currently the standard version of the QLQ-C30*

- Subjects enrolled in Part 3 will be asked to use EORTC QLQ-C30v3 questionnaires to answer some health related questions on Cycle 1 Days 1 and 15, and then on Day 1 of each clinic visit, at End-of-Study and at Follow-up visits in accordance with Part 3 Schedule of Observations.

- EORTC QLQ-C30 must be administered and completed by the subject, preferably prior to any study specific procedure. The completed, signed and dated EORTC QLQ-C30 will be given to the study site staff before MFSAF is administered to the subject for completion.

- In all instances, the EORTC QLQ-C30 questionnaire is completed prior to the subject's appointment with the Investigator.

- The questionnaire asks subjects to rate the level of activity or symptom experienced during the preceding 7 days.

- The questionnaire comprises of both multi-item scales and single–item measures. EORTC QLQ-C30v3 has four-point rating scale of 1 to 4 for the first 28 questions and four response categories ranging from 1 = Not at all, 2 = A Little, 3 = Quite a bit and 4 = very much. Last two questions relating to overall health and quality of life provide have 7 categories for response ranging from 1= Poor to 7 = Excellent.

- Questionnaire should be administered to subjects consistent with guideline from European Organisation for Research and Treatment of Cancer, also referred to as EORTC QLQ-C30 or standard guideline for QOL questionnaires.

- Subjects must complete the questionnaire without assistance from any study staff by circling the number that best applies to them. Subjects must be asked to respond to all questions.

- Study Staff should be available to provide clarification but must not take an active role (verbal or written) in completion of the forms

- Subjects must be notified that there is no right or wrong answer. Additionally, it should be emphasized that the subject **is required to respond to all questions in the EORTC QLQ-C30 questionnaire** and that the information provided by them will stay confidential.

- EORTC QLQ-C30 serves as the source documents and original form must be completed and dated by the subject.

- The questionnaires must be completed by each subject enrolled in Part 3 on Cycle 1 Day 1 visit unless screening visit is within -3 to -1 days of Cycle 1 Day 1. Study staff must ensure that the subject knows that that their response is required to all questions.

- Completed questionnaire will be used for data entry and will be retained in the subject file after data entry.

EORTC QLQ-C30 <version 3>

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in *your* initials:
Your birthdate (Day, Month, Year):
Today's date *(Day,* Month, Year):

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2 Do you have any trouble taking a long walk?	1	2	3	4
3Do *you* have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A little	Quite a bit	Very much
6. Were you limited in doing either *your* work or other daily activities?	1	*2*	3	*4*
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	*4*
6Were you short of breath	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	*2*	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	*2*	3	4
15. Have you vomited?	1	*2*	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty In concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX V– MODIFIED MYELOFIBROSIS SYMPTOM ASSESSMENT FORM (MFSAF)

This is a newly developed tool for assessment of symptoms experienced by patient with myelofibrosis (Mesa et al, personal communication). The modified form is designed to capture patient's assessment of symptoms on a scale of 1 to 10.

Note: Study staff must enter subject ID before giving the form to subject for completion. This questionnaire is administered to the subject after the EORTC QLQ-C30 questionnaire has been completed and given to the study site staff.

For Completion by Subject:

- Subjects enrolled in Part 3 will be asked to use MFSAF questionnaires (see attached sample form) to answer some health related questions on Cycle 1 Day 1 and Day 15 and then on Day 1 of each clinic visit, at End-of-Study and at Follow-up visits in accordance with Part 3 Schedule of Observations.

- MFSAF questionnaire asks the subjects to rate the symptoms they are experiencing at the time or day of the visit.

- The questionnaire asks subjects to rank the symptom on scale of 1 to 10 with "0" being "Not Present" and "1" being most favorable and "10" being the "Worst" or least favorable. Use NA when "Not applicable" and UNK when "Unknown"

- The questionnaire comprises fifteen common signs or symptoms experienced by subjects with Myelofibrosis.

- Questionnaire should be administered to subjects consistent with standard guideline for administration of QOL questionnaires.

- Subjects must complete the questionnaire without assistance from any study staff by ranking the sign or symptom on a scale of 1 to10 or 0 that best applies to them. Rating of number 1 is most favorable and 10 being least favorable. Subjects must be asked to respond to all questions.

- Study Staff should be available to provide clarification but must not take an active role (verbal or written) in completion of the forms

- Subjects must be notified that there is no right or wrong answer and that the information provided by them will stay confidential.

- The questionnaires must be completed by each subject enrolled in Part 3 on Cycle 1 Day 1 visit unless screening visit is within -3 to -1 days of Cycle 1 Day 1. Study staff must ensure that subject knows that they are required to respond to all questions.

- o MFSAF serves as the source document and original form for subject's reported experience must be completed, and dated by the subject and handed to the study site staff.

- o Subject completed MFSAF form remains in the subject file until data entry. The original form is a source document and must be retained in the subject file after data entry.

Patient ID#
Visit Day: Cycle# Day#

Modified Myelofibrosis Symptom Assessment Form (MFSAF)

The form is to be completed by the patient according to standard instructions on clinic visit days per Schedule of Observations *(refer to publication Mesa et al.).*
Patient's assessments must be done independent of the Investigator assessments.

Please fill in your initials:

Your date of birth (Day-Month-Year):

Today's date: (Day-Month-Year):

Symptom	1 to 10 (0 if absent) ranking* 1 is most favor able and 10 least favorable
General fatigue	
Night Sweats	
Itching	
Muscle or Bone Pain	
Fever or uncomfortable feeling of warmth	
Cough	
Ability to move and walk around including exercise	
Swelling of extremities (hands and legs)	
Ability to bend down including to tie shoes	
Abdominal discomfort/bloating/pain	
Altered bowel movement and/or difficult or painful urination	
Appetite (include weight gained or lost)	
Difficulty sleeping	
Body image and hindrance to perform daily activities	
Patient's perception on overall quality of life	

*As reported by patient

**National Cancer Institute Common Terminology Criteria for Adverse Events

Use NA when "Not applicable" and UNK when "Unknown"