UNIVERSITY OF MICHIGAN COMPREHENSIVE CANCER CENTER

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STUDY TITLE: ***A Pilot Study of Ruxolitinib in Secondary Hemophagocytic Syndrome (Version November 7, 2019)***

PRINCIPAL INVESTIGATOR:

PI: Ryan Wilcox, MD, PhD
University of Michigan Comprehensive Cancer Center
[redacted]

CO-PI: Asra Ahmed, MD
University of Michigan Comprehensive Cancer Center
[redacted]

CO- INVESTIGATOR:

Paula Bockenstedt, MD
University of Michigan Comprehensive Cancer Center
[redacted]

Erica Campagnaro, MD
University of Michigan Comprehensive Cancer Center
[redacted]

Sumana Devata, MD
University of Michigan Comprehensive Cancer Center
[redacted]

Scott Gitlin, MD
University of Michigan Comprehensive Cancer Center
[redacted]

Mark Kaminski, MD
University of Michigan Comprehensive Cancer Center
[redacted]

Alice Marie Garry McCoy, MD
University of Michigan Comprehensive Cancer Center
[redacted]

Tycel Phillips, MD
University of Michigan Comprehensive Cancer Center
[redacted]

Suman Sood, MD
University of Michigan Comprehensive Cancer Center
[redacted]

Moshe Talpaz, MD
University of Michigan Comprehensive Cancer Center
[redacted]

Albert Quiery, MD
University of Michigan Comprehensive Cancer Center
[redacted]

STATISTICIAN:
Philip S. Boonstra, Ph.D.
University of Michigan, Department of Biostatistics
[redacted]

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SCHEMA

Pilot study to determine the efficacy of Ruxolitinib in secondary hemophagocytic syndrome.

STUDY SYNOPSIS

Disease : Secondary Hemophagocytic Syndrome (HPS)

Primary objective: To assess the efficacy of ruxolitinib 15 mg PO twice daily in patients with HPS.

Primary endpoint: Overall survival at 2 months.

Secondary objectives:

1) To assess the safety and tolerability of ruxolitinib in patients with HPS.

2) To determine the response rate, duration of response, progression-free survival, and overall survival in ruxolitinib treated subjects.

Exploratory objectives:

To assess inflammatory cytokines and markers of T-cell/macrophage activation (i.e. cytokines, sIL-2R, sCD163) as predictive biomarkers.

Inclusion Criteria:

1) Patients, or their legally authorized representative, must voluntarily provide written IRB-approved informed consent.

2) Males and females, 18 years of age or older at the time of enrollment.

3) Patients must meet the diagnostic criteria for HPS (at least 5 of the following):

-fever

-splenomegaly

-cytopenia involving ≥2 cell lines (Hemoglobin <9 g/dL; platelets <100,000/µL; absolute neutrophil count <1000/µL)

-hypertriglyceridemia or hypofibrinogenemia

-tissue demonstration of hemophagocytosis

-low or absent NK cell activity

-serum ferritin ≥3000 ug/L

-soluble IL-2 receptor (CD25) >2400 U/mL.

4) In the investigator's opinion, the patient has the ability to participate fully in the study and comply with all its requirements.

Exclusion criteria:

1) CNS involvement

2) Malabsorption

3) Pregnant or lactating female: all females of child-bearing potential must have a negative serum pregnancy test within 7 days of treatment

4) Has received any prior systemic therapy, excluding corticosteroids, within 7 days of treatment.

5) Estimated creatinine clearance <15mL/min

6) No active malignancy at the time of enrollment, except nonmelanoma skin cancers or carcinoma in situ. Patients with a prior history of malignancy are eligible if their malignancy has been definitely treated or is in remission and does not require ongoing adjuvant or cancer-directed therapies.

7) Active hepatitis B or hepatitis C or known HIV infection.

8) Known (and biopsy-confirmed) liver cirrhosis; or, a reported history of liver cirrhosis with a model for end-stage liver disease (MELD) score >20.

1. INTRODUCTION

1.1 Hemophagocytic Syndrome

Hemophagocytic Syndrome (HPS) is a disorder characterized by pathological activation of the immune system resulting in a systemic disorder characterized by excessive cytokine production and macrophage activation, culminating in cytopenias and evidence of hemophagocytosis on tissue specimens. The disorder can be sporadic or familial due to one of several mutations and is primarily seen in the pediatric population, with a reported incidence of 1 case per 3000 admissions[1]. The actual incidence in adults is unknown and can be rarely sporadic, or secondary to viral infections, malignancy, or autoimmune disease.

HPS is a universally fatal disease if untreated. In adults, the median survival has been reported to be less than 2 months if diagnosis and treatment is delayed[2]**.** Adult patients are treated with pediatric protocols with early institution of etoposide and steroids and consolidation with allogeneic stem cell transplant in appropriately selected patients if a familial form is identified [3]. Other treatment strategies have been attempted, including rituximab[4], infliximab[5], **e**ntaracept[6], tocilizumab[7], and alemtuzumab[8]. These anecdotal reports highlight the therapeutic potential of cytokine-targeted therapies in this disorder.

1.2 Ruxolitinib

1.2.1 Preclinical Data

Ruxolitinib (INCB018424 phosphate, INC424, ruxolitinib phosphate) represents a novel, potent, and selective inhibitor of JAK1 (Janus kinase 1) (inhibition concentration 50% [IC50]=3.3 ± 1.2 nM) and JAK2 (IC50=2.8 ± 1.2 nM) with modest to marked selectivity against TYK2 (tyrosine kinase 2) (IC50=19 ± 3.2 nM) and JAK3 (IC50=428 ± 243 nM), respectively. Ruxolitinib interferes with the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function[9-11].

JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK-STAT pathway has been associated with several types of cancer and increased proliferation and survival of malignant cells[12-23]. In particular, this pathway may be dysregulated in the majority of

patients with Philadelphia chromosome negative myeloproliferative neoplasms (MPNs, including myelofibrosis [MF] and polycythemia vera [PV]), suggesting that JAK inhibition may be efficacious in these diseases.

During the Phase I and Phase II development program, ruxolitinib was assessed in healthy volunteers, subjects with various degrees of renal or hepatic impairment, in patients with rheumatoid arthritis, prostate cancer, multiple myeloma (MM), MF, PV and essential thrombocythemia (ET). Ruxolitinib is currently approved for the treatment of MF/ PV/ET, and is currently under development for the treatment of other hematologic malignancies, and solid tumors. Two pivotal Phase III trials in MF patients have been completed and one in PV patients is ongoing.

1.2.2 Clinical Data

Ruxolitinib is a potent, selective ATP-competitive inhibitor of JAK1 and JAK2 kinases, with an IC50 of 3.3nM and 2.8nM, respectively. Ruxolitinib inhibits JAK signaling by targeting the cytokines that support transformed cells and are responsible for constitutional symptoms. It arrests growth factor signaling by inhibiting downstream STAT phosphorylation. Ruxolitinib has been administered to over 180 healthy volunteers as single, repeat single, or multiple doses of up to 10 days duration. Ruxolitinib has been administered to approximately 450 subjects with MF for periods of up to > 24 months, and over 100 subjects with prostate cancer, multiple myeloma, polycythemia vera or essential thrombocythemia for periods of up to > 24 months. In healthy volunteer studies, a transient, reversible decrease in neutrophil count has frequently been seen following dosing, which reverses after 12 to 24 hours off drug, suggestive that the neutropenia may reflect an effect of ruxolitinib blocking IL-6 signaling and causing neutrophil margination on blood vessel walls. In a repeat dose healthy volunteer study, neutropenia of any severity grade was seen in 22% of placebo subjects, 11% of subjects receiving 50 mg qd, 67% of subjects receiving 100 mg qd, 13% of subjects receiving 15 mg bid, 33% of subjects receiving 25 mg bid and 67% of subjects receiving 50 mg bid. Importantly, these neutropenia events were of Grade 1 or Grade 2 severity with a single instance of severe Grade 4 neutropenia that led to discontinuation of study drug in 1 subject receiving ruxolitinib at 50 mg bid (highest dose). The maximum tolerated dose in healthy volunteers was determined to be 25 mg bid and no dose limiting toxicities (DLT) were seen at 100 mg qd. A definitive QT study was carried out in 50 healthy volunteers, evaluating the effects of single doses of 25 mg or 200 mg ruxolitinib compared with placebo and 400 mg moxifloxacin (positive control). The overall conclusion was that there appeared to be no adverse impact on ventricular repolarization (no increase in QTcF) and little change in heart rate, QRS duration, and a slight, non-clinically significant, increase in PR interval with the administration of ruxolitinib. This agent is currently FDA approved for the treatment of patients with intermediate to high-risk myelofibrosis, including primary myelofibrosis, post-Polycythemia Vera myelofibrosis and Post-Essential Thrombocytopenia myelofibrosis based on pre-clinical activity in cellular assays driven by *JAK2*V617F and on the results of the phase III studies COMFORT-1 and COMFORT-2 [24,25]. In those trials, the agent was continuously dosed at 15-20mg PO twice daily (BID); currently, depending on platelet count, ruxolitinib is FDA approved from 5 mg BID to a maximum dose of 25mg BID. To further demonstrate the tolerability of this agent in other disease settings; pilot studies have

demonstrated , ruxolitinib was well tolerated in patients with psoriasis and rheumatoid arthritis studies [26]. Ruxolitinib use has been associated with myelosuppression, thrombocytopenia, and anemia in patients with myelofibrosis. Other documented side effects include dizziness, headaches, bruising and tranaminitis.

1.2.3 Clinical Pharmacokinetics

Twelve Phase I , five Phase II, and two Phase III clinical studies were conducted to explore the clinical pharmacology of ruxolitinib in healthy volunteers and in patients with MF, ET, PV, subjects with renal or hepatic impairment, prostate cancer, MM or rheumatoid arthritis (RA).

- Oral absorption of ruxolitinib is rapid and nearly complete, with ≥95% absorption indicating high in vivo permeability in the human gastrointestinal tract, consistent with a Biopharmaceutical Classification System (BCS) Class I compound. Mean peak plasma concentrations (Cmax) is achieved 1-2 h post-dose.
- The effect of food on ruxolitinib exposure is minimal and is not expected to be clinically significant; as a result, the drug may be administered either with or without food.
- Dose proportional exposure is observed between 5 and 200 mg dose range with linear pharmacokinetics (PK).
- Plasma protein binding is approximately 97% in vitro. There is moderate distribution to organs and tissues with no long-term retention of drug-related material in preclinical species and limited drug penetration into the central nervous system (CNS) or across the blood-brain barrier.
- There is >95% [14C] drug recovery in a mass balance study with 74% and 22% of the dose excreted in urine and feces of healthy subjects, respectively. Less than 1% of the administered dose is recovered in urine and feces as unchanged parent drug.
- The mean terminal elimination half-life is ~3 h with no appreciable accumulation of either parent or metabolites with twice daily dosing.
- Metabolism is predominantly via the cytochrome P450 isozyme CYP3A4 to yield oxygenated and subsequent conjugated metabolites.
- Oxidative metabolites of ruxolitinib retain pharmacological activity albeit with one half to one fifth of the activity of the parent compound. Ex vivo pharmacokinetic/pharmacodynamic (PK/PD) analysis indicates that the sum total of 8 active metabolites contribute to 18% of the overall PD activity of ruxolitinib.
- When administering ruxolitinib with strong CYP3A4 inhibitors, the total daily dose should be reduced by approximately 50%.
- No dose adjustment is necessary when co-administering ruxolitinib with strong CYP3A4 inducers.
- In patients with severe [creatinine clearance (Clcr) < 30 mL/min] and moderate renal impairment (Clcr = 30 - 49 mL/min), the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice a day. Patients on hemodialysis should initiate ruxolitinib with a single dose of 15 mg or 20 mg based on platelet counts with subsequent single doses only on hemodialysis days and following each hemodialysis session. Ruxolitinib doses should be titrated based on individual safety and efficacy.
- In patients with mild, moderate or severe hepatic impairment, the recommended starting dose based on platelet count should be reduced by approximately 50% with subsequent dose titration based on individual safety and efficacy.

- Baseline elevations in inflammatory markers such as tumor necrosis factor alpha (TNFα), interleukin (IL)-6, and C-reactive protein (CRP) noted in subjects with MF were associated with constitutional symptoms such as fatigue, pruritus, and night sweats. Decreases were observed in these markers over the 24 weeks of treatment with ruxolitinib, with no evidence that subjects became refractory to the effects of ruxolitinib treatment.

1.3 Background and Rationale

Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome (HPS) is an inflammatory disorder associated with the activation and expansion of reactive (i.e. non-clonal) macrophages. Primary HPS is associated with mutations (e.g. ≈50% of familial cases are caused by perforin gene mutations) that culminate in defective natural killer (NK) cell and cytotoxic T-lymphocyte (CTL) degranulation and impaired killing of target cells. In these patients, a triggering event (e.g. viral infection) is associated with immune dysregulation that is characterized by the overproduction of proinflammatory cytokines (e.g. IL-12 and IFN-γ) and tissue accumulation of activated T-cells and macrophages. [27-31] These immunologic changes are associated with protean clinicopathologic manifestations, including: fever, hepatosplenomegaly, hyperferritinemia (due to macrophage activation), cytopenias (caused by phagocytosis - "hemophagocytosis"- of hematopoietic cells), hypofibrinogenemia, and multi-organ failure.[32] Predominantly observed in children, primary HPS is initially managed with supportive care and chemotherapy, but is only curable in approximately 60% of children with allogeneic stem cell transplantation.[3,33] In contrast to primary HPS, secondary HPS is more common in adults and is associated with a variety of triggers, including infection (often viral), autoimmunity, or hematologic malignancies (commonly non-Hodgkin lymphomas).[32] For many patients, a precipitating cause cannot be identified. Apart from disease-specific therapies for patients in which a precipitating cause can be identified (e.g. non-Hodgkin lymphoma directed therapies for those with an underlying lymphoma), no HPS-specific therapies are currently available for the majority of adults with HPS. Therefore, these patients are frequently treated with a regimen originally developed for use in children with primary HPS that includes combinations of steroids, immunuosuppressive agents (i.e. cyclosporine A), and etoposide. Not surprisingly, secondary HPS in adults is associated with high morbidity and mortality. In one of the largest single center studies, the overall mortality was 67%, with a median time from diagnosis to death of 35 (range: 5-160) days.[2] Therefore, improved therapeutic strategies for adults with secondary HPS are greatly needed.

Both pre-clinical and clinical data highlight the central role of proinflammatory cytokines, particularly IFN-γ, that are dependent upon the JAK/STAT signaling in HPS pathogenesis. [27-31] The disease biology and clinical manifestations associated with HPS are driven by this underlying "cytokine storm", culminating in T-cell accumulation and macrophage activation. Therefore, inhibition of JAK/STAT signaling may represent a novel therapeutic approach. As ruxolitinib inhibits upstream Janus kinases (JAK) at nanomolar concentrations, and is well tolerated in myelofibrosis patients (and alleviates signs/symptoms associated with hypercytokinemia), we sought to determine whether it inhibits STAT1 phosphorylation in IFN-γ treated macrophages. Not surprisingly, ruxolitinib (1 μM) was able to inhibit STAT1 phosphorylation in treated macrophages. Therefore, ruxolitinib represents a novel therapeutic

approach for secondary HPS that has the potential to dramatically change the standard of care (and improve outcomes) for these patients. Cytopenias (including thrombocytopenia) observed in HPS are secondary to consumption ("hemophagocytosis") and cytokine-mediated suppression, and are not secondary to underlying bone marrow "failure". Therefore, treatment will be initiated at 15 mg po twice daily.

2. OBJECTIVES

2.1 Primary Objective

To assess the efficacy of ruxolitinib 15 mg PO twice daily in patients with HPS.

2.1.1 Primary Endpoint

Overall survival at two months.

2.2 Secondary Objective(s)

To assess the safety and tolerability of ruxolitinib in patients with HPS.

To determine the response rate, duration of response, progression-free survival, and overall survival in ruxolitinib treated subjects.

2.3 Exploratory Objectives

To assess inflammatory cytokines and markers of T-cell/macrophage activation (i.e. cytokines, sIL-2R, sCD163) as predictive biomarkers.

3. STUDY DESIGN

3.1 Study design including dose escalation / cohorts

Pilot study to determine the efficacy of Ruxolitinib in secondary hemophagocytic syndrome.

3.2 Number of Subjects

Up to 10 patients meeting the inclusion and exclusion criteria will be enrolled into this pilot study.

3.3 Replacement of Subjects

Subjects who do not receive the first dose of study drug will be replaced.

3.4 Expected Duration of Subject Participation

3.4.1 Duration of Therapy

In the absence of treatment delays or cessation due to adverse events, treatment may continue indefinitely or until one of the following criteria applies:

- Disease progression.
- Intercurrent illness that prevents further administration of treatment.
- The investigator considers it, for safety reasons, to be in the best interest of the patient. The investigator may recommend gradual discontinuation (i.e. ruxolitinib taper) in patients achieving a prolonged response (defined as a PR or CR ≥6 months in duration). The rate of a ruxolitinib taper, and decisions to dose escalate in the setting of recurrent signs/symptoms, are not specified in this protocol, and are at the discretion of the investigator.
- Unacceptable adverse events such as any toxicity or other issue that causes a delay of study drug administration by more than 4 weeks.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Patient decision to withdraw from treatment (partial consent) or from the study (full consent.

- Death.
- Sponsor reserves the right to temporarily suspend or prematurely discontinue this study.

The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

3.4.2 Duration of Follow Up

Patients will be followed for efficacy and toxicity for 30 days after treatment has been discontinued. Thirty days after treatment discontinuation, progression-free and overall survival will be collected every 6-12 months by a review of the clinical notes from the treating investigator or other provider. Patients will be followed for up to five years or until the end of the study or death, whichever occurs first.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately per IRB & FDA reporting guidelines.

4. PATIENT SELECTION

A checklist will be used to confirm a patient's eligibility. The check list will include the inclusion and exclusion criteria listed below, and must be completed for each patient and must be signed and dated by the treating physician.

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment:

1. Patients, or their legally authorized representative, must voluntarily provide written IRB-approved informed consent.

2. Males and females, 18 years of age or older at the time of enrollment.

3. Patients must meet the diagnostic criteria for HPS (at least 5 of the following):
   -fever
   -splenomegaly
   -cytopenia involving ≥2 cell lines (Hemoglobin <9 g/dL; platelets <100,000/μL; absolute neutrophil count <1000/μL)
   -hypertriglyceridemia or hypofibrinogenemia
   -tissue demonstration of hemophagocytosis
   -low or absent NK cell activity
   -serum ferritin ≥3000 ug/L
   -soluble IL-2 receptor (CD25) >2400 U/mL.

4. In the investigator's opinion, the patient has the ability to participate fully in the study and comply with all its requirements.

4.2 Exclusion Criteria

The presence of any of the following will exclude a patient from study enrollment.

1. CNS involvement

2. Malabsorption

3. Known secondary HPS that is otherwise treatable (e.g. non-Hodgkin's lymphoma).

4. Pregnant or lactating female: all females of child-bearing potential must have a negative serum pregnancy test within 7 days of treatment; lactating females must discontinue breast feeding.

5. Has received any prior systemic therapy, excluding corticosteroids, within 7 days (or 5 half-lives) of treatment.

6. Estimated creatinine clearance <15 mL/min

7. No active malignancy at the time of enrollment, except nonmelanoma skin cancers or carcinoma in situ. Patients with a prior history of malignancy are eligible if their malignancy has been definitely treated or is in remission and does not require ongoing adjuvant or cancer-directed therapies.
8. Active hepatitis B or hepatitis C or known HIV infection.

9. Known (and biopsy-confirmed) liver cirrhosis; or, a reported history of liver cirrhosis with a model for end-stage liver disease (MELD) score >20.

4.3 Inclusion of Women and Minorities

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

5. REGISTRATION

All subjects who have been consented are to be registered in an online Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

6. TREATMENT PLAN

6.1 Study Drug Administration

Appropriate dose modifications for Ruxolitinib are described in Section 7.0

Reported adverse events and potential risks of Ruxolitinib are described in Section 8.0.

TREATMENT REGIMEN DESCRIPTION					
Agent	**Pre-medicate / Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Ruxolitinib	None	15 (mg)	PO in twice daily	Days 1-28	28 days

6.1.1 Ruxolitinib Administration

Patients will receive Ruxolitinib at 15 mg twice daily orally either on an empty stomach or with food for 4 weeks (28 days) in a 4 week (28 day) cycle. Ruxolitinib will be administered in continuous 28-day cycles. For patients unable to ingest tablets, ruxolitinib suspended in water may be administered through a nasogastric (NG) or percutaneous endoscopy gastrostomy (PEG) tube. Tablets should be suspended (1 tablet in ~40 mL water) in water and stirred for 10 minutes and administered within 6 hours of dispersion with an appropriate syringe. The NG or PEG tube should be rinsed with ~75 mL water following administration.

Ruxolitinib administration must be at least 1 hour before or after any other medications.

6.2 General Concomitant Medications and Supportive Care Guidelines

Because there is a potential for interaction of Ruxolitinib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect CYP3A4. In patients who concurrently take strong CYP3A4 inhibitors and a platelet count of at least 50,000 the dose of ruxolitinib should be capped at 10 mg twice daily due to the concern for increased serum concentrations of ruxolitinib's active metabolites. Strong CYP3A4 inhibitors, including grapefruit juice, should be avoided whenever possible.

Patients should receive full supportive care, including transfusions of blood and blood products, cytokines, antibiotics, anti-emetics, etc when appropriate.

6.3 Duration of Follow Up

Patients will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first. Patients will be followed for survival for up to five years or until the end of the study or death, whichever occurs first.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause for a maximum of 6 months.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately per IRB and FDA reporting guidelines.

7. DOSING DELAYS / DOSE MODIFICATIONS

Ruxolitinib will be dosed twice daily throughout the study. In the event a dose is missed, the subject should be instructed to take the next scheduled dose.

Dose Level	**Ruxolitinib (BID schedule)**	
	CrCl ≥60	**CrCl 15-59**
Level 1 (starting dose)	15 mg	10 mg
Level -1 (reduction)	10 mg	5 mg
Level -2 (reduction)	5 mg	Hold

Event Name	**Nausea**
Grade of Event	**Management/Next Dose for Ruxolitinib**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold * until < Grade 2. Resume at one dose level lower, if indicated. **
Grade 4	Off protocol therapy
*Patients requiring a delay of >4 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: antiemetics.	

Event Name	**Vomiting**
Grade of Event	**Management/Next Dose for Ruxolitinib**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated. **
Grade 4	Off protocol therapy
*Patients requiring a delay of >4 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: antiemetics; in the event a dose of ruxolitinib is vomited, it is recommended that subjects resume ruxolitinib with the next scheduled dose.	

Event Name	Diarrhea
Grade of Event	**Management/Next Dose for Ruxolitinib**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated. **
Grade 4	Off protocol therapy
*Patients requiring a delay of >4 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

Event Name	Thrombocytopenia
Platelet Count	**Management/Next Dose for Ruxolitinib**
50,000-100,000	Level 1 Ruxolitinib
35,000-49,999	Level -1 (reduction) if determined to be secondary to Ruxolitinib per the discretion of the investigator or PI.
20,000-34,999	Level -2 (reduction)
Less than 20,000	Hold* until platelet count is at least 50,000 then resume at one dose level lower if determined to be secondary to Ruxolitinib per the discretion of the investigator or PI. Transfuse as needed for bleeds.
*Patients requiring a delay of >4 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

Treatment will be discontinued for any patient that experiences a Grade 4 non-hematologic toxicity that is possibly related to ruxolitinib.

Dose adjustments for grades 1-3 non-hematologic toxicity that is possibly related to ruxolitinib will be at the discretion of the investigator or PI.

With the exception of thrombocytopenia (see table above), dose adjustments for grades 1-4 hematologic toxicity that is possibly related to ruxolitinib will be at the discretion of the investigator or PI.

8. ADVERSE EVENTS

The clinical database (safety set based on cut-off for COMFORT-II: 04-Jan-2011; cut-off for COMFORT-I: 02-Nov-2010) in solid tumor and hematologic malignancies consists of 787 patients treated in 6 studies evaluating patients with MF (n=679), prostate cancer (n=22), MM (n=13), ET and PV (n=73), of whom 617 patients received ruxolitinib:

- Hematologic events are the most frequently reported adverse events (AEs) and include thrombocytopenia and anemia. The majority of these AEs are of Grades 1-2, seldom led to study drug discontinuation (<1% of patients), and can be usually managed through dose reduction or interruption.
- Increased rates of anemia resulted in an increase in packed red blood cell (PRBC) transfusion requirements for some ruxolitinib-treated patients. Platelet transfusions while on ruxolitinib were rare.
- Biochemistry laboratory abnormalities of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and cholesterol were reported. The majority of these increases were Grade 1 or 2. No Grade 4 events were reported.
- The Phase III safety dataset in MF patients (COMFORT-I, COMFORT-II) shows that it is appropriate to individually adjust doses for patients according to their tolerability and efficacy. However, 124 patients (41.2%) required no dose reduction, indicating the starting dose was appropriate for these individuals. Of the 177 patients who had dose reduction, 91 patients (51%) had only one reduction in dose. Interruptions of dosing were less frequent than dose reductions, with 215 patients (71.4%) requiring no dose interruption. Of the 86 patients who had dose interruptions, 59 patients (19.6%) had only one dose interruption.
- The Phase III data in MF patients (COMFORT-I, COMFORT-II) indicate that the only notable imbalances (ruxolitinib versus placebo or best available therapy [BAT]) in AEs related to hemorrhagic events were in Grade 1-2 skin and soft tissue bruising which did not lead to dose reduction or discontinuation. Similarly, the only notable imbalances (ruxolitinib versus placebo or BAT) in AEs related to infections were urinary tract infections and herpes zoster infections. Finally, an imbalance between ruxolitinib and BAT was noted in systolic blood pressure with an increase of 20 mmHg or more from baseline in COMFORT-II (31.5% of patients on at least one visit compared with 19.5% of the control-treated patients).
- Cases of tuberculosis have been reported. In addition, one case of progressive multifocal leukoencephalopathy has been reported in one patient with myelofibrosis.

The AE profile of the compound has been assessed in 198 healthy volunteers, subjects with various degrees of renal (n=32) or hepatic (n=24) impairment, and in patients with RA (n=59) receiving ruxolitinib:

- AEs were, in general, mild and resolved without interventions.

A thorough QT study was conducted in 50 healthy subjects. There was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supra-therapeutic dose of 200 mg indicating that ruxolitinib has no effect on cardiac repolarization.

The following is a list of AEs (Section 8.1) and the reporting requirements associated with observed AEs (Sections 8.3 and 8.4).

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs within 30 days after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.1 Adverse Events and Potential Risks

In a phase III population, the comparison of the control groups to the ruxolitinib patients showed that headache was more frequent in ruxolitinib-treated patients (13.6% vs. 6.0% on placebo and 5.5% on BAT). Most AEs of headache were Grade 1 or 2. Similarly, dizziness (12.0% vs. 6.6% on placebo and 6.8% on BAT) was more frequent in ruxolitinib-treated patients, again mostly Grade 1 or 2. When adjusted for patient-year exposure, the differences are still present for headache and dizziness.

Weight increase was also more frequent in ruxolitinib-treated patients than in the control groups (9.6% vs. 1.3% on placebo and 1.4% on BAT). Although some of these patients had co-reported AEs of edema, many had a past medical history of weight loss and the weight gain usually gradually accumulated over the course of one year of treatment. The majority of weight gain AEs were Grade 1 and 2. It is worth noting that weight gain may be a beneficial effect in patients with MF, given the catabolic nature of the disease and the frequency of weight loss reported as a constitutional symptom.

Other preferred terms with increased frequency in the ruxolitinib arms included bruising (2.6% vs. 1.3% on placebo in COMFORT-I only), contusion (8.6% vs. 5.3% on placebo and 1.4% on BAT), urinary tract infection (7.3% vs. 4.6% on placebo and 2.7% on BAT), herpes zoster (4.0% vs. 0.7% on placebo and 0% on BAT) and flatulence (3.3% vs. 1.3% on placebo and 0% on BAT).

Abdominal pain was more frequent in the control groups than in the ruxolitinib group (43% on placebo and 13.7% on BAT vs. 12% on ruxolitinib), as were weight decrease (8.6% on placebo and 8.2% on BAT vs. 1% on ruxolitinib), early satiety (8.6% on placebo and 0% on BAT vs. 0.3% on ruxolitinib) and splenic infarction (6.0% on placebo and 0% on BAT vs. 1.0% on ruxolitinib).

For COMFORT-I at the Week 144 interim analysis, for subjects initially randomized to ruxolitinib, although the frequency of AEs reported increased as expected with increased

duration of exposure and follow-up, the types of TEAEs reported remained consistent with what was reported in the initial analysis. Thrombocytopenia/platelet count decrease remained the most frequently reported AE (58.1%). Anemia/Hgb decreased was reported in 84 subjects (54.2%), which was also an expected effect of ruxolitinib. Among the non-hematologic TEAEs, the most frequently reported TEAE was fatigue (44.5%) followed by diarrhea (35.5%), and peripheral edema (31.0%).

In the ruxolitinib-treated Phase III population, the overall frequency of AEs requiring dose reduction or interruption was 59.8%. This frequency was higher than in the control groups (placebo: 27.2%, BAT: 15.1%). The most frequently reported AEs requiring dose reduction or interruption in ruxolitinib-treated patients were thrombocytopenia (36.9%), platelet count decreased (7.6%) and anemia (5.6%). The high frequency for thrombocytopenia is due to protocol-mandated dose reductions and interruptions. Although there were no protocol-specified guidelines for dose reductions secondary to anemia, some investigators chose to reduce a patient's dose in the setting of anemia to minimize this particular effect of ruxolitinib. The frequency of these AEs was higher than in the control groups. All other AEs requiring dose reduction or interruption occurred with a frequency of 1.3% or less in the ruxolitinib-treated patients. For COMFORT-I at the Week 144 analysis for patients initially randomized to ruxolitinib 70 patients (45.2%) had at least 1 AE leading to interruption or discontinuation of study drug and 82 (52.9%) had at least 1 AE leading to dose reduction. Thrombocytopenia/platelet count decrease was the most common reason for dose reduction or discontinuation.

In the Phase III population, at the initial analysis, there were 34 deaths in total, 27 of which were on-treatment deaths: 20 deaths in study COMFORT-I (9 in the ruxolitinib group, 11 in the placebo group) and 7 deaths in study COMFORT-II (4 in the ruxolitinib group, 3 in the BAT group). The reasons for death (infections, intestinal perforation, disease progression and events probably due to disease progression, bleedings events) were similar in the ruxolitinib and the placebo groups.

8.1.1 Ruxolitinib-related Adverse Effects

The following Ruxolitinib side effects are common (occurring in greater than 10%):

- Cardiovascular: Peripheral edema (22%), elevation in systolic blood pressure
- Central nervous system: Dizziness (15% to 18%), headache (10% to 15%), insomnia (12%)
- Dermatologic: Bruising (19% to 23%)
- Endocrine & metabolic: Cholesterol increased (17%; grade 2: <1%)
- Gastrointestinal: Diarrhea (23%), constipation (13%), nausea (13%), vomiting (12%)

- Hematologic: Anemia (96%; grade 3: 34%; grade 4: 11%), thrombocytopenia due to bone marrow suppression (70%; grade 3: 9%; grade 4: 4%), neutropenia (19%; grade 3: 5%; grade 4: 2%)
- Hepatic: ALT increased (25%; grades 2/3: 2%), AST increased (17%; grade 2: <1%)

The following Ruxolitinib side effects are less common (occurring in less than 10%):

- Respiratory: Dyspnea (16%), nasopharyngitis (16%)
- Gastrointestinal: Flatulence (5%)
- Genitourinary: Urinary tract infection (9%)
- Miscellaneous: Herpes zoster infection (2%)

The following Ruxolitinib side effects are rare:

- Cardiac murmur
- peripheral neuropathy
- weight gain
- progressive multifocal leukoencephalopathy (PML)
- Tuberculosis reactivation

9. DEFINITIONS

9.1 Adverse Events

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject. In general, adverse events that

are at least partially the result of the interventions and interactions used in the research or the collection of identifiable private information in the research;would be considered related to the research, whereas adverse events solely related to an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject would be considered unrelated to the research.

The significance of an adverse event is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe or life threatening). Based on the National Cancer Institute Guidelines for the Cancer Therapy Evaluation Program, severity can be defined by the following grades of events:

Grades 1 are mild adverse events. (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)

Grades 2 are moderate adverse events (e.g., minimal intervention; local intervention; non-invasive intervention.

Grades 3 are severe and undesirable adverse events (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 4 are life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life–threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

Grades 5 are fatal adverse event resulting in death.

9.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 12 hours OR

- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) OR
- The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse 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 disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.3 Expectedness

Adverse Events can be Expected or Unexpected.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the package insert, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

9.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

9.5 Reporting Procedures for All Adverse Events

All participating investigators will assess the occurrence of AEs throughout the subject's participation in the study. Subjects will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject which occur after the subject has been started on the investigational agent are fully recorded in the subject's case report form, subject's medical records, and/or any other institutional requirement. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study), requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event.

The investigator will provide the following for all adverse events:

- Description of the event
- Date of onset and resolution
- Grade of toxicity
- Attribution of relatedness to the investigational agent
- Action taken as a result of the event
- Outcome of event

In this study, descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm will be utilized for AE reporting.

9.5.1 Serious Adverse Event Reporting Procedures

Serious adverse events that occur beginning after the subject has been started on the investigational agent or within 30 days of the last dose of treatment must be reported to the Sponsor Investigator. Serious adverse events will be reported to the IRBMED according to their reporting guidelines and to the FDA as detailed in Section 9.5.3.

9.5.2 Incyte Reporting

If the SAE is not previously documented in the package insert for the study drug (new occurrence) and is thought to be related to the study drug, a manufacturer's associate may urgently require further information from the Investigator or Sponsor for reporting to Health Authorities. Incyte will be notified within 24hrs of any IND safety event and will receive a copy of the initial and follow up IND Adverse Event reports within 48hrs of submission to regulatory authorities. This will be submitted to the following email address: IncytePhVOpsIST@incyte.com

9.5.3 FDA Reporting

The University of Michigan Sponsor Investigator, Ryan Wilcox, as holder of the IND, will be responsible for all communication with the FDA. In accordance with 21 CFR 312.32, The University of Michigan Sponsor Investigator, Ryan Wilcox is responsible for notifying the FDA of SAEs that are serious, unexpected (not listed in the package insert) and judged to be related (i.e., possible, probable, definite) to the study drug. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

7 Calendar Day IND Safety Report
Any unexpected fatal or life-threatening suspected adverse event represent especially important safety information and, therefore, must be reported more rapidly to FDA (21 CFR 312.32(c)(2)). Any unexpected fatal or life-threatening suspected adverse event must be reported to FDA no later than 7 calendar days after the University of Michigan Sponsor Investigator, Ryan Wilcox, obtains initial receipt of the information (21 CFR 312.32(c)(2)). The University of Michigan Sponsor Investigator, Ryan Wilcox, will complete a Medwatch Form FDA 3500A and notify the FDA by telephone or facsimile transmission with the assistance of the Michigan IND/IDE Assistance Program (MIAP).

15 Calendar Day IND Safety Report
The timeframe for submitting an IND safety report to FDA is no later than 15 calendar days after the University of Michigan Sponsor Investigator determines that the suspected adverse event or other information qualifies for reporting (21 CFR 312.32(c)(1)). This includes any serious, unexpected adverse events considered reasonably or possibly related to the investigational agent. The University of Michigan Sponsor Investigator, Ryan Wilcox will complete a CTO standard SAE Form and notify the FDA by telephone or facsimile transmission with the assistance of MIAP. If FDA requests any additional data or information, the University of Michigan Sposor Investigator must submit it to FDA as soon as possible, but no later than 15 calendar days after receiving the request (21 CFR 312.32(c)(1)(v)).

Follow-up IND Safety Report
Any relevant additional information that the University of Michigan Sponsor Investigator obtains that pertains to a previously submitted IND safety report must be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)). The University of Michigan Sponsor Investigator, Ryan Wilcox, will maintain records of its efforts to obtain additional information.

Reporting Serious Problems to FDA
Medwatch Form FDA 3500A:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
Telephone: 1-800-332-1088
Fax: 1-800-FDA-0178

IND Annual Reports

A summary of all IND safety reports submitting during the previous year will be reported to the FDA in the annual report by The University of Michigan Sponsor Investigator, Ryan Wilcox, as holder of the IND.

10. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.

10.1 Investigational Agent

Agents are listed in <u>alphabetical</u> order.

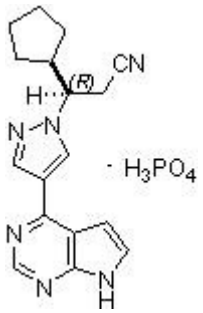
10.1.1 Ruxolitinib

Chemical Name: (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate

Other Names: Ruxolitinib

Classification: selective JAK1 and JAK2 inhibitor

Molecular Formula:



Mode of Action: Inhibits Janus Associated Kinases (JAKs) JAK1 and JAK2 which mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function

Metabolism: *In vitro* studies suggest that CYP3A4 is the major enzyme responsible for metabolism of ruxolitinib. Ruxolitinib is the predominant entity in humans representing approximately 60% of the drug-related material in circulation. Two major and active metabolites were identified in plasma of healthy subjects representing 25% and 11% of parent AUC. These two metabolites have one-fifth and one-half of ruxolitinib's pharmacological activity, respectively. The sum total of all active metabolites contributes 18% of the overall pharmacodynamics of ruxolitinib.

Product description: Ruxolitinib (ruxolitinib) Tablets are for oral administration. The tablet contains ruxolitinib phosphate equivalent to 5 mg of ruxolitinib free base together with Microcrystalline cellulose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxypropyl cellulose.

Solution preparation: Not applicable

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

Stability: Not applicable

Route of administration: Ruxolitinib is dosed orally and can be administered with or without food.

Drug Procurement: Ruxolitinib will be supplied for this study by Incyte. Once notified by Incyte of IST support, Principal Investigator or study staff will contact Incyte's Medical Affairs Operations and Program Manager or Medical Science Liaison to inform them of the amount of study drug needed to conduct the study. The Medical Affairs Operations and Program Manager at Incyte will generate a requisition for Investigational Product (IP) supplies and manage shipments through a third party vendor.

Drug Accountability: The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol. Drug storage, drug dispensing, and drug accountability will be performed by the UM Research Pharmacy. Final drug accountability will be made to Incyte. **Drug Destruction*:*** At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files. Final drug accountability certificate will be provided to Incyte at the end of the study.

11. CORRELATIVE / SPECIAL STUDIES

11.1 Background

Hemophagocytic syndrome is driven by inflammatory cytokines, including interferon-γ, that culminate in STAT1 phosphorylation, activated T-cell accumulation, and macrophage activation.

11.2 Rationale for Analysis

We will utilize immunofluorescent staining (by flow cytometry) to test the hypothesis that ruxolitinib inhibits Stat1 activation in HPS. We will evaluate the expression of Stat1 and pStat1 in peripheral blood T-cells and monocytes pre- and post-treatment. The post-treatment analysis will be conducted 7 (+/- 3) days following treatment initiation. T-cell (sIL-2R) and macrophage (soluble CD163) activation markers will be serially analyzed by ELISA in patient plasma. Plasma samples will by obtained weekly and cryopreserved for analysis of relevant cytokines (including interferon-γ) by ELISA. We will test the hypothesis that ruxolitinib decreases inflammatory markers (e.g. soluble CD163) associated with macrophage activation.

11.3 Collection of Specimens

Research blood samples (≈20 mL) will be obtained prior to treatment, and every 7 days (+/-2 days) thereafter.

Handling of Specimens

All specimens are to be shipped to the Wilcox laboratory at the address below. Lab personnel will re-label the specimen using a code specific for this trial. Peripheral blood mononuclear cells will be isolated by density centrifugation and viably frozen using laboratory standard operating procedures. Platelet-poor plasma will be isolated using laboratory standard operating procedures and cryopreserved.

Wilcox laboratory
1400 E. Medical Center Drive
4431 Cancer Center
Ann Arbor, MI 48109

12. STUDY PARAMETERS AND CALENDAR

12.1 Study Parameters

12.1.1 Screening Evaluation

Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion. All evaluations must be completed no longer than 14 days prior to administration of protocol therapy.

- Informed Consent
- Medical History
- Complete physical examination
- Vital signs including: blood pressure, pulse, respiratory rate, weight and temperature
- Concomitant Medications Assessment including prescription and herbal supplements
- Laboratory Studies:
    - Complete Blood Count (CBC) with differential and platelets.
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
    - ß-HCG for women of childbearing potential at time of study entry
    - Ferritin
    - Lipids (Triglycerides)
    - Fibrinogen
    - Soluble IL-2 receptor
    - NK cell activity

12.2 Calendar

	Enrollment (within 14 days of treatment)	**Pre-treatment** (within 48 hours of treatment)	**Weekly (weeks 1-5)[4]** (beginning day 7, +/- 2 days)	**q14 days +/- 3 days (weeks 6-12)[4]**	**q28 days +/- 3 days (>12 weeks)[4]**
Informed consent	X				
H&P (including medication review)	X	X	X	X	X
CBC[1]	X	X	X	X	X
Serum Chemistries (including AST/ALT)	X	X	X	X	X
Pregnancy test[5]	X				
Ferritin	X	X	X	X	X
Lipids	X	X	X	X	
Fibrinogen	X	X	X	X	
sIL-2 Receptor	X	X	X	X	
NK cell activity[2]	X	X	X		
Research blood draw[3]		X	X		
Collect Adverse Events	X	X	X	X	X

[1]Performed at least every 72 hours for weeks 1-5 of treatment. [2]May be performed every 7-14 days. If total lymphocytes are insufficient to measure NK cell activity during enrollment, repeat testing is not required. [3]Four heparin tubes (≈20 mL total volume) will be collected. Peripheral blood mononuclear cells and platelet-poor plasma will be obtained and cryopreserved for ancillary studies. Research blood draws will cease 14 days after a CR is achieved or after 5 weeks of treatment, whichever comes first. [4]Study procedures required for response assessments and toxicity monitoring will be performed every two weeks (Bi-weekly) for patients who remain on treatment >6 weeks. For patients who remain on treatment >12 weeks, the following procedures will be performed monthly: H&P, CBC, serum chemistries, ferritin, and adverse events. [5]Pregnancy testing will be performed every 6 weeks (+/- 7 days) in women of child-bearing potential.

13. MEASUREMENT OF EFFECT

13.1 Response evaluation

13.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Ruxolitinib**.**

Evaluable for objective response. Only those patients who received at least 7 days of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

13.1.2 Disease Parameters

- Fever
- Splenomegaly (by physical examination or radiographic imaging).
- Cytopenias involving ≥2 cell lines
- Ferritin
- Triglycerides
- Fibrinogen
- Soluble IL-2 receptor
- NK cell activity

13.1.3 Response Criteria

Evaluation of Response

Response	Evaluation of Target Lesions
Complete Response (CR)	Complete normalization of all quantifiable signs and laboratory abnormalities included in the diagnostic criteria for HPS.
Partial Response (PR)	At least a 25% improvement in two or more quantifiable signs/laboratory markers.
Progressive Disease (PD)	At least a 50% worsening in two or more quantifiable signs/laboratory markers.
Stable Disease (SD)	Neither sufficient improvement to qualify for CR/PR, nor sufficient worsening to qualify for PD.

13.1.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented. The duration of overall CR is measured from the time criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met.

14. RECORDS TO BE KEPT / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

14.1 Data Reporting

The Velos Database will be utilized, as required by the UNIVERSITY OF MICHIGAN COMPREHENSIVE CANCER CENTER, to provide data collection for both accrual entry and trial data management. Velos is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the Velos database. A calendar of events and required forms are available in Velos.

14.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

14.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject.

14.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the manufacturer and/or allow the manufacturer, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

14.2.3 Accessing Electronic Medical Records for University of Michigan Hospital and Health Systems

This study will access electronic medical records systems to obtain medical information for the subjects enrolled to this study.

In order to insure patient safety, investigators and study personnel must have up-to-the-minute health information for subjects enrolled to this study. Therefore, electronic medical records must be utilized to obtain medical information in a timely manner.

The following electronic systems will be used: MiChart to access scheduling information; MiChart and Careweb to access lab results and physician notes; MiChart and Careweb as necessary to locate archived medical records; PACS to access radiological imaging results.

Access to these systems is required for the life of this research study.

Information obtained from electronic systems will be copied into the University of Michigan Cancer Center Clinical Trials Unit research chart and/or printed (lab results, physician notes, etc.) and stored in the research chart. Research charts are kept secure and destroyed according to UH policy.

Study data will be obtained by the PI, co-investigators, study coordinator, and/or data manager for this study via password-protected login. All study personnel involved in this research will adhere to the UH policies regarding confidentiality and Protected Health Information.

14.2.4 Retention of records

The Principal Investigator of The UNIVERSITY OF MICHIGAN COMPREHENSIVE CANCER CENTER supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

14.2.5 Audits and inspections

Authorized representatives of the manufacturer, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the Center to perform audits

or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), and any applicable regulatory requirements.

14.2.6 Data Safety and Monitoring Plan

This protocol will adhere to the policies of the UNIVERSITY OF MICHIGAN COMPREHENSIVE CANCER CENTER Data and Safety Monitoring Plan in accordance with NCI regulations.

This trial will be monitored in accordance with the NCI approved University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Plan. The study specific Data and Safety Monitoring Committee (DSMC), consisting of the protocol investigators, data manager or designee, and other members of the study team involved with the conduct of the trial, will meet quarterly or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness. At the regular DSMC meetings, the protocol specific Data and Safety Monitoring Report form will be completed. The report will be signed by the Principal Investigator or by one of the co-investigators. Data and Safety Monitoring Reports will be submitted to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Board (DSMB) on a quarterly basis for independent review.

15. STATISTICAL CONSIDERATIONS

15.1 Sample Size

We will accrue and treat 10 patients on this pilot trial. We expect a 2-month survival rate approximating 15% in patients meeting the inclusion criteria with current standard of care. As we believe ruxolitinib may be highly active in this disease and change the current treatment paradigm, we believe the majority of treated patients will be alive at 2 months. Therefore, if 4 or more patients are alive 2 months following diagnosis, this would provide sufficient evidence to pursue ruxolitinib in an expanded cohort of patients in a future study. This design has 80% power to detect a survival rate of 60% versus an estimated survival rate of 15% using a 2-sided test, with 5% type 1error. The operating characteristics for design are given in the table below for a range of true values for the probability of survival at 2 months, with at least 4 responders the critical value.

Probability of survival at 2 months following diagnosis	Probability therapy is deemed effective
0.05	0.010
0.15	0.050
0.25	0.228
0.35	0.488
0.45	0.738
0.55	0.901
0.65	0.978

15.2 Analyses

Primary:

The primary analysis is the count of patients alive after 2 months since study entry. If 4 or more patients are alive at the 2 months assessment, the null hypothesis of a 15% survival probability at 2 months will be rejected in favor or our alternative hypothesis of a 60% survival probability. Ninety-five percent confidence intervals will be constructed based upon the exact binomial confidence interval. No loss-to-follow-up or censoring is expected prior to the study's primary endpoint assessment.

Secondary:

There are no formal response criteria for secondary HPS. Therefore, efficacy assessments (including appropriate laboratory studies) will be performed weekly (weeks 1-5), and every two weeks (weeks 6-12), and monthly (after 12 weeks), and responses determined as previously reported in a retrospective study.[8] Briefly, a complete response is defined as

complete normalization of all quantifiable symptoms and laboratory abnormalities (described in the diagnostic criteria for HPS, above). A partial response is defined as at least a 25% improvement in two or more quantifiable symptoms/laboratory markers following the initiation of treatment. The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence

Follow-up time will be calculated from the first administration of ruxolitinib, until death for OS or until disease-progression or death for PFS. Patients lost to follow-up will be censored on the date of their last known clinical assessment. Specifically for DOR, only patients having at least a PR to therapy are evaluable. Duration will be calculated from the date of the determination of partial response or better until the date of progression, death, or additional non-protocol therapy. Again, for patients lost to follow-up, duration will be censored at the time of last clinical assessment. The count and percentage of the number having an objective response (CR, CRu, or PR) will be reported along with confidence intervals. Product-limit estimates of Kaplan and Meier will be used to estimate OS, PFS, and DOR. The likelihood of loss to follow-up is expected to be extremely low.

Exploratory:

Plasma will be obtained before treatment and weekly thereafter, and cryopreserved for future corollary studies (e.g. cytokine[27,28] and soluble CD163 determination[34]). We will compare cytokine, soluble IL-2R and soluble CD163 levels pre-treatment and post treatment. We seek to correlate change in expression (decrease) with positive response (complete vs. partial vs. stable) to therapy via regression models that appropriately account for the serial correlation of repeated measures within a patient. Inference from these models would be hypothesis generating.

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17. APPENDIX A

POTENTIAL CYP3A4 INTERACTIONS

CYP3A4 Substrates

Albuterol	Dihydroergotamine	Isosorbide	Progesterone
Alfentanil	Diltiazem	Isosorbide, dinitrate	Quetiapine
Alprazolam	Disopyramide	Isosorbide mononitrate	Quinidine
Amiodarone	Docetaxel	Isradipine	Rabeprazole
Amlodipine	Doxepin	Itraconazole	Ranolazine
Amprenavir	Doxorubicin	Ketamine	Repaglinide
Aprepitant	Doxycycline	Ketoconazole	Rifabutin
Aripiprazole	Efavirenz	Lansoprazole	Ritonavir
Atazanavir	Eletriptan	Letrozole	Salmetrol
Atorvastatin	Enalapril	Levonorgestrel	Saquinavir
Benzphetamine	Eplerenone	Lidocaine	Sibutramine
Bisoprolol	Ergoloid mesylates	Losartan	Sildenafil
Bortezomib	Ergonovine	Lovastatin	Simvastatin
Bosentan	Ergotamine	Medroxyprogesterone	Sirolimus
Bromazepam	Erythromycin	Mefloquine	Spiramycin
Bromocriptine	Escitalopram	Mestranol	Sufentanil
Budesonide	Estradiol	Methadone	Sunitinib
Buprenorphine	Estrogens, conj., synthetic	Methylergonovine	Tacrolimus
Buspirone	Estrogens, conj., equine	Methysergide	Tamoxifen
Busulfan	Estrogens, conj., esterified	Miconazole	Tamsulosin
Carbamazepine	Estrone	Midazolam	Telithromycin
Cerivastatin	Estropipate	Miglustat	Teniposide
Chlordiazepoxide	Ethinyl estradiol	Mirtazapine	Tetracycline
Chloroquine	Ethosuximide	Modafinil	Theophylline
Chlorpheniramine	Etoposide	Montelukast	Tiagabine
Cilostazol	Exemastane	Moricizine	Ticlopidine
Cisapride	Felbamate	Nateglinide	Tipranavir
Citalopram	Felodipine	Nefazodone	Tolterodine
Clarithromycin	Fentanyl	Nelfinavir	Toremifene
Clobazam	Flurazepam	Nevirapine	Trazodone
Clonazepam	Flutamide	Nicardipine	Triazolam
Clorazepate	Fluticasone	Nifedipine	Trimethoprim
Cocaine	Fosamprenavir	Nimodipine	Trimipramine
Colchicine	Gefitinib	Nisoldipine	Troleandomycin
Conivaptan	Haloperidol	Norethindrone	Vardenafil
Cyclophosphamide	Ifosfamide	Norgestrel	Venlafaxine
Cyclosporine	Imatinib	Ondansetron	Verapamil
Dantrolene	Indinavair	Paclitaxel	Vinblastine
Dapsone	Irinotecan	Pergolide	Vincristine
Dasatinib (1)		Phencyclidine	Vinorelbine
Delvirdine		Pimozide	Zolpidem
Diazepam		Pipotiazine	Zonisamide
		Primaquine	Zopiclone

APPENDIX A (continued)

POTENTIAL CYP3A4 INTERACTIONS

CYP3A4 Inhibitors

Acetaminophen	Diclofenac	Lomustine	Primaquine
Acetazolamide	Dihydroergotamine	Losartan	Progesterone
Amiodarone	Diltiazem	Lovastatin	Propofol
Amlodipine	Disulfiram	Mefloquine	Propoxyphene
Amprenavir	Docetaxel	Mestranol	Quinidine
Anastrozole	Doxorubicin	Methadone	Quinine
Aprepitant	Doxycycline	Methimazole	Quinupristin
Atazanavir	Drospirenone	Methoxsalen	Rabeprazole
Atorvastatin	Efavirenz	Methylprednisolone	Ranolazine
Azelastine	Enoxacin	Metronidazole	Risperidone
Azithromycin	Entacapone	Miconazole	Ritonavir
Betamethasone	Ergotamine	Midazolam	Saquinavir
Bortezomib	Erythromycin	Mifepristone	Selegiline
Bromocriptine	Ethinyl estradiol	Mirtazapine	Sertraline
Caffeine	Etoposide	Mitoxantrone	Sildenafil
Cerivastatin	Felodipine	Modafinil	Sirolimus
Chloramphenicol	Fentanyl	Nefazodone	Sulconazole
Chlorzoxazone	Fluconazole	Nelfinavir	Tacrolimus
Cimetidine	Fluoxetine	Nevirapine	Tamoxifen
Ciprofloxacin	Fluvastatin	Nicardipine	Telithromycin
Cisapride	Fluvoxamine	Nifedipine	Teniposide
Clarithromycin	Fosamprenavir	Nisoldipine	Testosterone
Clemastine	Glyburide	Nizatidine	Tetracycline
Clofazimine	Grapefruit Juice(2)	Norfloxacin	Ticlopidine
Clotrimazole	Haloperidol	Olanzapine	Tranylcypromine
Clozapine	Hydralazine	Omeprazole	Trazodone
Cocaine	Ifosfamide	Orphenadrine	Troleandomycin
Conivaptan	Imatinib	Oxybutynin	Valproic Acid
Cyclophosphamide	Indinavair	Paroxetine	Venlafaxine
Cyclosporine	Irbesartan	Pentamidine	Verapamil
Danazol	Isoniazid	Pergolide	Vinblastine
Dasatinib (1)	Isradipine	Phencyclidine	Vincristine
Delvirdine	Itraconazole	Pilocarapine	Vinorelbine
Desipramine	Ketoconazole	Pimozide	Voriconazole
Dexmedetomidine	Lansoprazole	Pravastatin	Zafirlukast
Diazepam	Lidocaine	Prednisolone	Ziprasidone

APPENDIX A (continued)

POTENTIAL CYP3A4 INTERACTIONS

CYP3A4 Inducers

Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Oxcarbazepine	Primidone	St. John's Wort (3)
Fosphenytoin	Pentobarbital	Rifabutin	
Nafcillin	Phenobarbital	Rifampin	

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.
Only major substrates and effective inducers are listed.
Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

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