Title: A Single Arm, Open Label, Phase II Study of Ruxolitinib in Sclerotic Chronic Graft-Versus-Host Disease after Failure of Systemic Glucocorticoids

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Abstract

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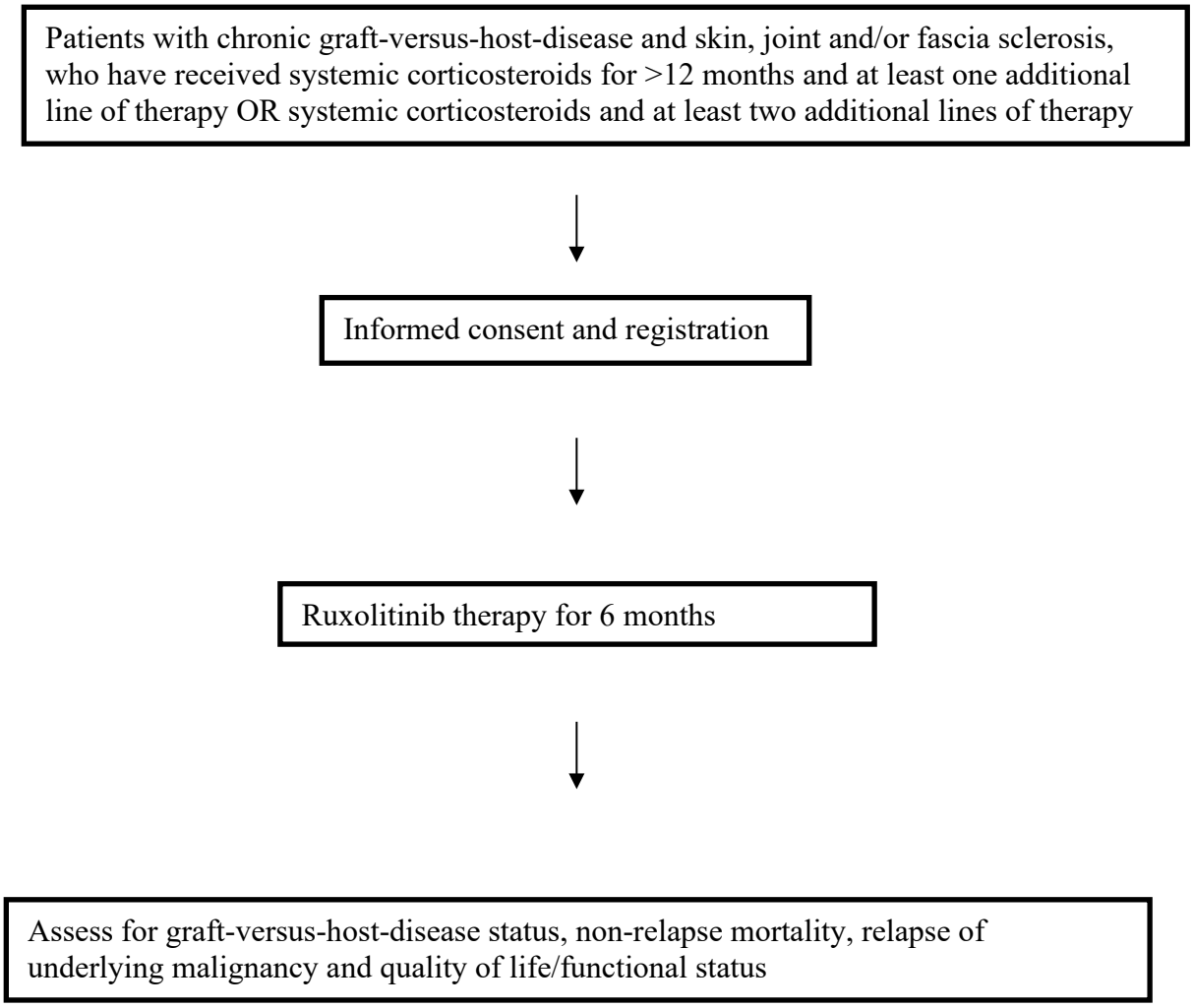
Chronic graft-versus-host-disease (GVHD) is a major complication of allogeneic hematopoietic cell transplant that impairs quality of life, and is associated with significant morbidity and mortality. Management of chronic GVHD with prednisone is associated with an overall response rate of approximately 60%, and a complete response rate of approximately 30% but sclerotic features do not respond as well. Based on the biology of chronic GVHD and available preliminary evidence, we hypothesize that ruxolitinib will be effective in the management of sclerotic chronic GVHD. The study is an open label, phase II multicenter trial designed to evaluate the efficacy of ruxolitinib as a salvage treatment for subjects with sclerotic GVHD (sclerosis or fasciitis). The primary objective is to determine the proportion of subjects with response rate (complete and partial responses) in skin and/or joint, as determined by 2014 NIH consensus criteria, at 6 months of therapy with ruxolitinib. Eligibility criteria includes adult subjects with chronic GVHD and skin, joint and/or fascia sclerosis, who have received systemic corticosteroids for >12 months and at least one additional line of therapy OR systemic corticosteroids and at least two additional lines of therapy for chronic GVHD. A sample size of 47 subjects dosed (42 evaluable subjects and estimated 10% dropout) will allow an α of 0.044 and a power of 84% to test the null hypothesis response rate of 25% compared to an alternative of 45%. Subjects will receive ruxolitinib for 6 months for the treatment of sclerotic chronic GVHD. Subjects will be evaluated for GVHD status as well as non-relapse mortality, relapse of underlying malignancy and quality of life/functional status. Plasma cytokine levels and T/NK cell subset in peripheral blood will be measured at various time points. The response rate will be reported as a proportion and 95% exact confidence interval. If positive, the trial results will support other ongoing studies to establish the role of ruxolitinib in chronic GVHD in general and specifically in sclerotic chronic GVHD.

Study Schema



Section 1.0 Objectives

1.1 Primary Objective

The primary objective of the study is to examine the efficacy of ruxolitinib in subjects with sclerotic chronic graft-versus-host disease (GVHD).

Efficacy will be assessed by:

- Determining the proportion of subjects with complete and partial responses in skin and/or joint, as determined by 2014 NIH Criteria (1), at 6 months of therapy.

1.2 Secondary Objective

To determine the proportion of subjects with complete or partial responses overall, as determined by 2014 NIH Criteria (1), at 6 months of therapy.

1.3 Exploratory Objectives

The exploratory objectives are to assess the following:

1. Treatment failure (treatment failure defined as: administration of additional systemic therapy for chronic GVHD, malignancy relapse or mortality) by 6 months from study enrollment
2. Non-relapse mortality by 6 months
3. Change in patient-reported outcomes: skin subscale and summary score of the Lee Chronic GVHD Symptom Scale, and Scleroderma Health Assessment Questionnaire between enrollment and 6 months
4. Response rate in skin/joint and overall at 12 months, for subjects treated on the extension study
5. Proportion who reduce prednisone (or prednisone equivalent) dose by 50% from baseline to 6 months

1.4 Correlative Objectives

1. Determine the association between responses at 6 months and the changes in the plasma levels of various proteins and cytokines (ST2, SPON1, CXCR3, CXCL10, IFN gamma, soluble IL-2R, IL-2, IL-4, IL-5, IL-6, IL-12, TNF-α, TRAIL/TNSFSF10/7; profibrotic cytokines such as IL-1β and TGF-β) from baseline to 3 and 6 months.
2. Determine the correlation between responses at 6 months and changes in the percentage of peripheral blood T/NK-cell population (CD3-CD56+) [Treg(FoxP3+), effector T cell (CD8+T cell, CD4+ T_H1, T_H2 and T_H17 cells), CD3+, CD4-CD25+, Gr-1, Ter-119, and Antigen presenting cells (APC) APC-CD80+] from baseline to 3 and 6 months.

Section 2.0 Introduction

Chronic graft versus host disease

Chronic graft-versus-host disease (GVHD) is a major late complication of allogeneic hematopoietic cell transplantation (HCT) that affects up to 70% of HCT survivors. The syndrome is associated with major transplant-related morbidity, mortality, infectious complications, prolonged duration of immune suppression, and impaired patient-reported quality of life (2-9). Thus, it represents a major obstacle to recovery and survival following HCT, and its prevention and treatment are of significant importance. The syndrome is characterized by diverse clinical manifestations, but the most commonly affected organs are the skin, eyes, mouth, and liver.

Sclerotic GVHD is a distinctive phenotype of chronic GVHD that usually begins in superficial layers of the skin and then extends to deeper layers. Sclerotic GVHD can severely affect patients' mobility and quality of life, and it is often refractory to standard and secondary therapies. The presence of sclerosis after allogeneic HCT is considered diagnostic for chronic GVHD (10). Progressive or poorly controlled sclerotic GVHD results in joint contractures, chronic skin ulcers and pulmonary restriction causing major disability. In a large study from Fred Hutchinson Cancer Research Center and Seattle Cancer Care Alliance, the cumulative incidence of sclerosis was 20% at 3 years. Of the patients who developed sclerosis, 13% had only skin sclerosis, 33% had only joint contracture or fasciitis, and 53% had both clinical manifestations. The development of sclerosis was associated with a reduced rate of withdrawal of immunosuppressive treatment (11). These findings as well as our own experience indicate that patients with sclerotic chronic GVHD have poor quality of life, often require multiple sequential therapies and frequently exhaust available treatment options (12-15).

Diagnosis and staging of chronic GVHD

Diagnosis, classification and staging of chronic GVHD are based on the 2014 NIH Consensus Conference on Chronic GVHD (10). According to the historical classification, acute and chronic GVHD were distinguished by the occurrence of manifestations before or following day 100 post-HCT. According to the 2014 NIH Consensus definitions, the diagnosis of chronic GVHD is based on the presence of diagnostic manifestations of the syndrome, rather than the time of onset following HCT. Two subtypes of chronic GVHD exist, namely classic chronic GVHD and overlap syndrome. Classic chronic GVHD is defined by the definitive manifestations of the syndrome in the absence of concurrent acute GVHD manifestations (Appendix A). Presence of both chronic and acute GVHD manifestations defines the overlap subtype of chronic GVHD (10). Chronic GVHD severity is scored according to objective criteria for each organ involved (Appendix B), which is summarized for an overall global severity score of mild, moderate, or severe (Appendix C) (10).

Therapy of established chronic GVHD

Accepted standard primary therapy for chronic GVHD includes 1 mg/kg or greater of prednisone (or prednisone equivalent) with or without a calcineurin inhibitor (3, 16). The addition of other systemic immune-suppressive agents to initial therapy has not provided benefit, as evidenced by trials adding azathioprine, thalidomide, hydroxychloroquine or mycophenolate mofetil to initial treatment with steroids(17). Published primary chronic GVHD therapy trials demonstrate that on

average 30% will achieve complete response, and 60% will achieve overall response (complete + partial response) by 6-9 months after starting initial therapy(16-21). However, sclerotic features do not respond as well. Consequently, most patients with chronic GVHD require salvage therapies, which are frequently ineffective in sclerotic chronic GVHD (12-15).

Based on insufficient response to primary therapy or a flare of chronic GVHD after tapering of initial therapy, many will go on to require additional immune-suppressive agents for chronic GVHD control.

Steroid-refractory chronic GVHD (22) is defined when:

"Manifestations progress despite the use of a regimen containing prednisone at ≥1 mg/kg/day for at least 1 week or persist without improvement despite continued treatment with prednisone

at ≥0.5 mg/kg/day or 1 mg/kg every other day for at least 4 weeks."

Such a definition is less relevant to eligibility criteria for trials beyond second-line treatment, because the decision to start second-line treatment has already been made (22).

In addition to steroid-refractoriness, other clinical indications for additional lines of systemic immune suppressive therapy include steroid dependence and steroid intolerance. Patients with steroid-dependent chronic GVHD cannot tolerate tapering prednisone due to recurrent chronic GVHD manifestations. **Steroid-dependent chronic GVHD** (22) is defined when:

"Prednisone doses >0.25 mg/kg/day or >0.5 mg/kg every other day are needed to prevent recurrence or progression of manifestations as demonstrated by unsuccessful attempts to taper the dose to lower levels on at least 2 occasions, separated by at least 8 weeks."

Steroid intolerant patients have medical complications of steroid therapy (e.g., hyperglycemia, psychosis, osteoporosis), and thus require additional immune-suppressive agents to control GVHD and facilitate taper of prednisone. Multiple immune-suppressive therapies, including pharmacologic agents, monoclonal antibodies, and strategies such as extracorporeal photopheresis have demonstrated moderate activity in this setting, both ameliorating objective chronic GVHD manifestations, as well as facilitating taper of systemic steroids (reviewed in detail in the report of the Consensus Conference on Clinical Practice in Chronic GVHD) (23). Their effectiveness is suboptimal, however, and many patients will require multiple agents to achieve disease control or stabilization. For example, imatinib and rituximab are two commonly utilized therapies for sclerotic chronic GVHD. A randomized phase II trial of imatinib versus rituximab for steroid refractory cutaneous sclerosis conducted at 11 institutions within the Chronic GVHD Consortium demonstrated a significant clinical response rate of 26-27% (15). The overall burden of chronic GVHD despite routine pharmacologic GVHD prophylaxis, limited response to primary and secondary therapies, and the attendant morbidity and mortality all support the need for novel approaches in chronic GVHD treatment.

In August 2017, the Food and Drug Administration approved ibrutinib for management of chronic GVHD after failure of one or more treatments. Ibrutinib is the first therapy to receive FDA approval for the treatment of chronic GVHD. The approval was based on a multicenter single-arm trial of 42 patients with chronic GVHD with inadequate response to corticosteroid (24). The best overall response was 67% at a median follow-up of 13.9 months. A total of 34

patients had skin involvement, and 88% of these patients had a response. Details regarding the number of patients with skin sclerosis, fasciitis or joint contractures, and responses in these patients are unavailable. Adverse events including infectious complications (69%, grade ≥3 events 36%) were common and led to treatment discontinuation in 33% of patients. No major hemorrhage event was observed, and grade 3 atrial fibrillation was reported in 1 patient in this study (24). Nonetheless, the use of ibrutinib can be associated with a significant risk of complications in some patients including but not limited to those with cardiac arrhythmias, history of major bleeding, or those requiring anticoagulation or antiplatelet agents (25). Hence, the use of ibrutinib may not be appropriate in some patients.

Patient-Reported Outcomes

Chronic GVHD can severely affect patients' quality of life (1). Progressive or poorly controlled sclerotic GVHD can also result in joint contractures, chronic skin ulcers and pulmonary restriction causing major disability (11). Sclerotic GVHD is difficult to assess; responses are slow, and potentially reversible active sclerotic manifestations are not easily distinguished from fixed, irreversible deficits. Hence, patient-reported quality of life measures can provide valuable insight regarding the impact of chronic GVHD, and changes in quality of life in response to therapy. Such patient-reported outcome measures can augment but not replace objective changes in chronic GVHD activity (1).

Lee Chronic GVHD Symptom Scale (26) (Appendix D), recommended by the 2014 NIH Consensus conference (1), will be utilized as measures of patient-reported outcomes in this study. The Lee Chronic GVHD Symptom Scale (26) provides a global assessment of the burden of a symptom resulting from varying intensity of the symptom, its frequency, and its emotional and functional impact. Additionally, Scleroderma Health Assessment Questionnaire (Appendix E) will be used (27, 28). There are no validated functional or quality of life measures specifically for patients with sclerotic GVHD. The Scleroderma Health Assessment Questionnaire, a validated self-reported functional status measure in scleroderma, will therefore be utilized given the similarity between sclerotic GVHD and scleroderma. An improvement (decrease) in the SHAQ score by ≥0.2 is considered clinically meaningful (15, 27, 29).

Biomarkers in chronic GVHD

The 2014 NIH Biomarker Working Group Report states that the development of diagnostic and predictive biomarkers is critically necessary and represents the areas of high priority in chronic GVHD (30). In this study, we will measure the percentage of peripheral blood T/NK-cell population and the plasma levels of various proteins and cytokines (ST2, SPON1, CXCL10, IFN gamma, soluble IL-2R, IL-2, IL-6, TNF-α; profibrotic cytokines such as IL-1β and TGF-β) at various time points. Such assessments may allow identification of predictive biomarkers and provide insights into the biology of sclerotic chronic GVHD, and the pharmacodynamic effect of ruxolitinib in sclerotic chronic GVHD.

In a murine model, ruxolitinib reduced proliferation of effector T cells and suppression of proinflammatory cytokine production (such as TNF-alpha and IL-12p70). Further, differentiation of CD4+T cells into IFN-gamma and IL17A-producing T-cells (implicated in GVHD) was impaired (31). In patients with steroid refractory acute and chronic GVHD, responses correlated with an increase in FoxP3+ regulatory T cells, as well as a reduction in the serum levels of IL-6 and soluble IL-2 receptor (31). Zeiser et al demonstrated a decline in CD3+HLA-DR+ cells, IL-6

and soluble IL-2R in peripheral blood after ruxolitinib treatment (32). In myelofibrosis, the use of ruxolitinib was associated with suppression of proinflammatory cytokines such as IL-6, and TNF-alpha (33). Hence, the changes in T-cell subsets and cytokine levels correlate with GVHD activity and are associated with responses to ruxolitinib.

Although the pathogenesis of chronic GVHD is complex and still incompletely understood, various T/NK-cell subsets play an important role in various phases of the development of chronic GVHD (34). T/NK-cell subsets such as CD8+T cells and NK-cells are the main effector populations in the adaptive immune system responsible for chronic GVHD. Regulatory populations such as Tregs provide compensatory inhibition to limit chronic inflammation and tissue injury. The relative predominance of effector or regulatory cells determine whether chronic GVHD is active or absent. Other T-cell subsets such as T_H2 and T_H17 cells are considered pro-fibrotic and may contribute to fibrosis (34). Whereas many cytokines are implicated in sclerosis and dampened by ruxolitinib (31), two-protein biomarkers (Spondin-1, ST2) may correlate with longitudinal changes in sclerosis (35). CXCL10 is elevated in sclerosis, and levels may correlate with clinical worsening or responses (36). This molecular underpinning provides the rationale for the proposed tests in this trial.

Ruxolitinib

Detailed information is available in the attached investigator brochure.

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.

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. 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.

Ruxolitinib is currently under development for the treatment of MF, PV, essential thrombocytopenia (ET), GVHD and other hematologic malignancies and has been granted Marketing Authorization Approval for the treatment of MF and PV.

Summary of clinical efficacy data

The results from two Phase III studies in myelofibrosis (COMFORT-I, COMFORT-II) demonstrate the effectiveness of ruxolitinib in patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET-MF). The results of these two studies were consistent, demonstrating statistically significant ($p<0.0001$) improvement in rates of ≥35% spleen volume reduction compared with

either placebo or an investigator's selection of best available therapy (BAT). Ruxolitinib was associated with prolonged survival compared with placebo (COMFORT-I) and best available therapy (COMFORT-II).

Consistent with its activity in myelofibrosis, ruxolitinib demonstrated efficacy in a related myeloproliferative neoplasm, polycythemia vera in the RESPONSE and RESPONSE-2 studies. A significantly greater proportion of patients who were randomized to ruxolitinib met the primary endpoint of the RESPONSE study, which was a composite endpoint of hematocrit control in the absence of phlebotomy and spleen volume reduction ≥35% when compared to patients randomized to BAT (22.7% vs. 0.9%, $p<0.0001$). Of the patients meeting the primary endpoint at Week 32, 88% maintained their response at Week 48, and 80% maintained their response for at least 48 weeks from initial response. The efficacy analyses at Week 80 data cutoff (03-Sept 2014) for the RESPONSE study confirmed the durability of the responses in the patients randomized to ruxolitinib arm. The RESPONSE-2 study met its primary endpoint and the findings of this study indicate that ruxolitinib could be considered a standard of care for second-line therapy in this post-hydroxyurea patient population.

Summary of clinical safety data

In the randomized period of the two pivotal studies in MF, COMFORT-I and COMFORT-II (cut-off 01-Mar-2011, median duration of exposure = 10.8 months) discontinuation due to adverse events, regardless of causality was observed in 11.3% of patients. The most frequently reported adverse drug reactions were thrombocytopenia and anemia. Hematological adverse reactions (any CTCAE Grade) included anemia (82.4%), thrombocytopenia (69.8%) and neutropenia (16.6%). Anemia, thrombocytopenia and neutropenia are dose-related effects. The three most frequent non-hematological adverse reactions were bruising (21.6%), dizziness (15.3%) and headache (14.0%). The three most frequent non-hematological laboratory abnormalities were raised alanine aminotransferase (ALT) (27.2%), raised aspartate aminotransferase (AST) (18.6%) and hypercholesterolemia (16.9%).

Long-term follow-up in patients with MF (including 615 patients treated with ruxolitinib during the controlled and extension phases of studies INCB 18424-251: cut-off 01-Oct-2012.

COMFORT-I: 15-Oct-2015; COMFORT-II: 20-Apr-2015) has shown that as expected, the numbers and proportions of AEs and SAEs has increased. However, no new safety signals have emerged (median duration of exposure for this population is 28.78 months, with 1578.45 patient-years of exposure).

Study INCB 18424-258 established 5 mg b.i.d. as a safe starting dose in patients with PMF,

PPVMF, and PET-MF, with a platelet count between 50 and 100 × 109/L.

Study INCB 18424-261 showed that 10 mg b.i.d was an effective starting dose by providing symptomatic benefit and reducing palpable spleen length in the majority of subjects while having less of an impact on hematologic parameters than seen in the pivotal Phase III studies.

Up to Week 32 of the randomized phase in the RESPONSE trial (median duration of exposure was 7.8 months), ruxolitinib was generally well tolerated in patients with PV and only a small proportion of patients discontinued ruxolitinib due to AEs (6.4%). Most of the AEs have been

managed by dose adjustments and/or supportive care. Hematological toxicities were less frequent and less severe in patients with PV as compared to those observed in patients with MF. Analysis of Week 80 data did not identify any new safety findings.

The AE profile of the compound has been assessed in more than 370 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.

Rationale for using ruxolitinib in graft-versus-host disease

A study in MHC-mismatched mouse transplant model has demonstrated that interferon (IFN)-gamma receptor signaling via induction of chemokine receptor CXCR3 alters alloreactive T-cell trafficking to GVHD target organs and reduces GVHD (37). The same study also highlighted that pharmacologic inhibition of IFN-gamma receptor signaling with ruxolitinib reduces GVHD and improves survival after allogeneic HCT (37). Subsequent studies in murine models confirmed that the use of ruxolitinib mitigated GVHD (31, 38, 39) while preserving graft-versus-leukemia effect (38, 39). In a murine model, ruxolitinib also reduced proliferation of effector T cells and suppression of proinflammatory cytokine production (such as TNF-alpha and IL-12p70). Further, differentiation of CD4+T cells into IFN-gamma and IL17A-producing T-cells (implicated in GVHD) was impaired (31).

Subsequent studies have provided evidence of clinical efficacy and safety of ruxolitinib in patients with steroid refractory acute and chronic GVHD including patients with cutaneous and musculoskeletal chronic GVHD (31, 32, 40). Spoerl et al. demonstrated responses in 6 patients with steroid refractory acute and chronic GVHD (31). In a retrospective multicenter study (n=95) (32), ruxolitinib at a dose of 5–10 mg orally twice daily was studied as a salvage therapy for steroid refractory grade III/IV acute (n=54) or moderate or severe chronic (n=41) GVHD. Patients with chronic GVHD were heavily pre-treated with a median of 3 (range 1-10) prior therapies. Patients were followed for a median of 22 (3–135) weeks. Ruxolitinib resulted in an overall response rate of 85% with a rate of GVHD-relapse of 5.7% in responding patients, and 6-month survival of 97%. The median time from initiation of ruxolitinib to response was 3 (1–25) weeks. Cytopenia and CMV reactivation was observed in 17% and 15% of patients. Cytopenias preceded the use of ruxolitinib in most of the patients (15%). CMV reactivation responded to antiviral therapy. Relapse of underlying malignancy was reported in 2.4% of patients (32). Additional follow-up of these patients have demonstrated a one-year survival of 92.7%. Approximately, 24% of patients have an ongoing response and are free of any immunosuppression, whereas 86% of patients (n=13) with GVHD relapse or progression responded to retreatment with ruxolitinib or any immunosuppressive therapy (41). These results provide preliminary evidence of the safety and efficacy of ruxolitinib in chronic GVHD patients.

Study Design and Rationale

The study is an open label, phase II multicenter trial designed to evaluate ruxolitinib as a salvage treatment for patients with sclerotic GVHD (sclerosis or fasciitis). Previous trials (12-15) and our own experiences have demonstrated that patients with sclerotic chronic GVHD have poor quality

of life, often require multiple sequential therapies and are among the most likely group of patients to be enrolled in clinical trials because they have exhausted other treatment options. Preliminary evidence indicates that ruxolitinib may be effective in previously treated patients with sclerotic chronic GVHD (31, 32). In this context, the overarching goal of the study is to assess the role of ruxolitinib in the management of steroid refractory sclerotic chronic GVHD.

Section 3.0 Eligibility Criteria

3.1 Inclusion Criteria

1. Sclerotic chronic GVHD (classic chronic or overlap syndrome) that meets 2014 NIH Consensus Criteria. Eligible patients will have superficial or deep skin sclerosis, fasciitis or joint contractures.
2. The subject must have received the following therapy for chronic GVHD (not necessarily for sclerotic manifestations):
    a) Systemic corticosteroids for >12 months and at least one additional line of systemic therapy **OR**
    b) Systemic corticosteroids and at least two additional lines of systemic therapy.

For the purpose of this study, intra-oral narrow-band UVB phototherapy and "FAM" (fluticasone, azithromycin and montelukast) therapy for lung GVHD will be considered a topical therapy. Investigators are encouraged but not mandated to use ibrutinib for appropriate patients prior to enrollment in this trial.

3. Adults, Age ≥18 years (state of Nebraska, Age ≥19 years)
4. Karnofsky performance status ≥60% at the time of enrollment
5. All allogeneic donor sources and all conditioning regimens are allowed.
6. Absolute neutrophil count (ANC) greater than 1000/μL, and platelet count ≥50,000/μL without the use of growth factors or platelet transfusion.
7. Able to take orally-administered medication.
8. Female patient of reproductive potential must have a negative serum or urine pregnancy test ≤7 days prior to starting the study drug. Women are considered NOT to have reproductive potential if they have had 12 months of amenorrhea with an appropriate clinical profile (i.e. ≥51 years, history of vasomotor symptoms, OR supportive hormone levels such as low estrogen and high follicle-stimulating hormone levels), OR surgical sterilization.
9. Male and female subjects of reproductive potential must be willing to avoid pregnancy or fathering children from enrollment to one month after the end of study treatment. This will require either a total abstinence, OR exclusively non-heterosexual activity (when this is in line with the preferred and usual lifestyle of the subject), OR two methods of contraception (male or female condom with or without a spermicidal agent, diaphragm or cervical cap with spermicide, or hormonal based contraception including intrauterine device).
10. Life expectancy greater than 6 months
11. Written informed consent to participate in the study.

3.2 Exclusion Criteria

1. Fibrosis of internal organs such as gut, liver or lung as the sole manifestation of sclerosis.
2. Fluconazole at a dose more than 200 mg daily. Subjects should stop fluconazole or lower dose to less than or equal to 200 mg daily before starting ruxolitinib.
3. Current evidence of malignancy after allogeneic transplant.
4. History of progressive multifocal leuko-encephalopathy (PML)
5. Active uncontrolled bacterial, fungal, parasitic, or viral infection. Infections are considered controlled if appropriate therapy has been instituted and, at the time of screening, no signs of infection progression are present. Progression of infection is defined as hemodynamic instability attributable to sepsis, new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection
6. Presence of known HIV infection, active hepatitis B or C infection.
7. Active tuberculosis infection that developed after allogeneic HCT
8. Total bilirubin 1.5 × the upper limit of the normal range
9. Creatinine clearance <30 mL/min
10. Presence of uncontrolled cardiopulmonary conditions such as ongoing cardiac arrhythmias, unstable angina or myocardial infarction, uncontrolled hypertension (e.g. blood pressure higher than 150/90), New York Heart Association class III/IV congestive heart failure, or requirement of supplemental oxygen at rest or having a resting O2 saturation <90% by pulse oximetry
11. Any other condition that is judged by the physician to potentially interfere with compliance to the study protocol or pose a significant risk to the patient.
12. Pregnancy, breastfeeding or planning to be pregnant.
13. Exposure to JAK inhibitor therapy for any indication after allogeneic transplant
14. Initiation of a new systemic immunosuppressant for management of chronic GVHD within 8 weeks prior to enrollment. However, subjects who develop disease progression can enroll as early as 4 weeks after initiation of a new systemic immunosuppressant. Also, subjects who are unable to tolerate current therapy can enroll any time after initiation of a new systemic immunosuppressant, as long as the "new" immunosuppressant is stopped in these cases prior to initiation of ruxolitinib. Initiation of any new topical therapy (including FAM or intra-oral narrow-band UVB phototherapy) and changes in dose of existing immunosuppressive agents such as corticosteroids, sirolimus, calcineurin inhibitors or other agents are acceptable at any time prior to enrollment. The use of immunosuppressants for short term period, for example 7 days, for indications other than GVHD will be acceptable.
15. Treatment with any other investigational agent, device, or procedure, within 21 days (or 5 half-lives, whichever is greater)
16. Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.

3.3 Inclusion of Women and Minorities

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

Section 4.0 Registration Procedure

4.1 Recruitment

Subjects who are referred to the UNMC/Nebraska Medicine or other IRB approved participating sites with sclerotic chronic GVHD may be eligible for this trial.

Screening eligibility is based on standard clinical care performed by the transplant physician. The subject's treating physician will determine eligibility based on the criteria listed in Section 3.0 prior to offering consent. All study personnel from UNMC and non-UNMC IRB approved sites will contact the UNMC IIT Office if a subject appears to meet the eligibility criteria (pending further screening tests) to confirm that target accrual has not been met.

Some insurance carriers may decline to cover the costs of usual medical care if the subject is participating in a clinical trial. The potential subject will be provided assistance by the research nurse coordinator or designated staff in determining if the insurance carrier will decline coverage. Insurance carriers may or may not pay for study related expenses. The potential subject can then decide if he/she wishes to participate.

If the subject is screened as potentially eligible, he/she will then be offered the option to participate. An informed consent will be signed by the subject after thorough review of the study is completed with the physician and his/her designee.

4.2 Eligibility Verification/Registration

Before subjects are registered into the study, the Eligibility Checklist form (Appendix F) must be completed to confirm whether the subject meets the eligibility criteria. The Eligibility Checklist form will be maintained in the study file as source documentation only if it has been reviewed, signed and dated prior to registration by the treating physician.

- Date of enrollment is defined as the date of informed consent.

All subjects will be registered through the sponsor site (UNMC). Study personnel from UNMC and non-UNMC IRB approved sites will contact the UNMC Project Coordinator if a potential subject appears to meet eligibility criteria. The site study coordinator will email the following information:

- Registration request with demographics form (located in the Study Site Manual),
- Copy of the signed/dated consent form with at least one viewable unique subject identifier,
- Completed Eligibility Checklist signed/dated by the PI or sub-I.

Once the UNMC Research Project Coordinator confirms that the subject meets criteria, and target accrual has not been met, approval for the subject will be given and study subject number assigned. The UNMC Research Project Coordinator will send a confirmation of registration

email to the site. The Project coordinator can assign a subject study number prior to final registration confirmation of a subject.

In the event of an after-hours potential enrollment (i.e., clinic coast time differences), or an immediate need for convenience for the subject, please contact the sponsor PI or Research Project Coordinator.

An electronic copy of the signed and dated consent form for each subject registered from all sites to the protocol is uploaded to the Clinical Trial Management System (CTMS) within 7 days that includes the required demographic information as noted in the UNMC SRC policies and procedures.

Section 5.0 Treatment Plan

The study is an open label, phase II multicenter trial designed to evaluate ruxolitinib as a salvage treatment for subjects with sclerotic GVHD (sclerosis or fasciitis).

5.1 Treatment Schedule and Administration: Ruxolitinib

Drug	Dose/Frequency	Duration	Administration
Ruxolitinib	10 mg BID	6 months, may extend up to 12 months	Oral

Subjects will receive oral ruxolitinib at a dose of 10 mg twice daily. Doses may not exceed 10 mg twice daily. Subjects will record their intake on a medication diary provided to them. Ruxolitinib will be continued for 6 months, unless there is intolerable toxicity, chronic GVHD progression requiring additional systemic treatment or relapse of the underlying malignancy. Subjects with mixed responses or chronic GVHD progression prior to 6 months of therapy that does not require initiation of additional agent are allowed to continue ruxolitinib for the complete 6 month duration. Therapy duration of 6 months will ensure adequate exposure to ruxolitinib, and is important because of the limited options for therapy in the study population and limitations of the current response assessment.

Extended treatment

Subjects who continue to have stable disease, mixed responses or partial/complete responses at the end of 6 months may continue the drug for a total of 12 months. Subjects with chronic GVHD progression (not including stable disease or mixed responses) at the end of 6 months will stop ruxolitinib, regardless of whether or not a new systemic therapy has been added.

Ruxolitinib taper prior to discontinuation

At the end of 6 months, or 12 months for subjects treated on extension study, ruxolitinib will be tapered over a month before discontinuation, for example, a dose reduction by 5 mg every 1-2 weeks. Ruxolitinib may be stopped without a taper in cases of unacceptable toxicities. If an

abrupt cessation of ruxolitinib is required, investigators are strongly encouraged to consider starting or dose-escalating systemic glucocorticoid (prednisone dose ≥0.5 mg/kg/day or equivalent dose) for at least a week to avoid rebound symptoms. While coming off ruxolitinib, subjects should be carefully monitored for worsening of GVHD symptoms or any other withdrawal symptoms.

5.1.1 Other immunosuppressive and topical therapies for GVHD

Investigators are strongly encouraged but not mandated to continue other immunosuppressive therapies such as tacrolimus until at least a partial response is achieved; dose adjustment to achieve a desired drug level is allowed. However, subjects on prednisone may continue to taper prednisone at the discretion of the treating physician. Increase in prednisone dose (or prednisone equivalent dose) to a dose lower than or up to the prednisone dose at enrollment is acceptable to control disease symptoms, however, an increase in the dose of prednisone higher than the dose at enrollment will be considered a new systemic treatment and thus, therapy failure (1).

Subjects who start a new systemic immunosuppressive agent to control chronic GVHD (1) are considered therapy failures for which ruxolitinib will be discontinued. A short course of an immunosuppressive agent (<2 weeks) for a clearly documented non-chronic GVHD indication (e.g., stress dose steroids in someone on chronic steroids, a short pulse of steroids for an allergic reaction) will not be considered treatment failure unless it extends longer than 2 weeks. Topical therapies (including FAM or intra-oral narrow-band UVB phototherapy) can be initiated or stopped at the discretion of the treating physician while ruxolitinib is continued and are not considered treatment failures. For the purpose of this study, "FAM" (fluticasone, azithromycin and montelukast) therapy for lung GVHD will be considered a topical therapy.

5.2 Ruxolitinib dose modifications for toxicities

Ruxolitinib doses may be reduced in the event of toxicities. **The lowest permissive dose of ruxolitinib is 5 mg daily.**

Subjects with sclerotic GVHD have limited therapy options and may be willing to accept certain degree of toxicities. As such, this trial will allow treating physicians to use discretion regarding dose modifications of ruxolitinib but only under certain situations as specified in this section.

For subjects with grade 2 or lower hematologic or non-hematologic toxicities, ruxolitinib may be continued at the current dose or dose reduced by 50% at the discretion of the treating physician. Dose reduction by 50% (i.e. reduction to 5 mg BID in subjects receiving 10 mg BID) or temporary drug cessation is allowed in subjects with certain grade ≥3 hematologic or non-hematologic toxicities (see table below). Subjects who require drug cessation will resume ruxolitinib at a dose no higher than 5 mg BID for at least 2 weeks before resuming their previous dose. Subjects with grade 3-4 toxicities are required to undergo close monitoring with repeat testing of any abnormal laboratory or clinical parameter(s) within 2-7 days depending on specific circumstances.

Ruxolitinib dose modifications for toxicities

Toxicity (CTCAE Version 4.03) possibly, probably or definitely related to ruxolitinib	Dose modification	Subsequent starting dose
Hematologic toxicities		
Grade 4 hematologic toxicities: (platelet count <25,000/μL, neutrophil count <500/μL, grade 4 febrile neutropenia with life-threatening consequences or requiring urgent interventions, life threatening anemia)	Temporary drug cessation until resolution to grade ≤2 or baseline[a] (mandatory)	5 mg BID for at least 2 weeks before considering dose escalation[b]
Grade 3 hematologic toxicities: (platelet count <50,000-25,000/μL, neutrophil count <1000-500/μL with or without fever [single episode of >38.3ºC or ≥38ºC for more than 1 hour] without serious consequences)	Dose reduction by 50%, or temporary drug cessation until resolution to grade ≤2 or baseline[a] (at the discretion of investigator)	5 mg BID for at least 2 weeks before considering dose escalation[b]
Grade 2 or lower neutropenia or thrombocytopenia; and grade 3 or lower anemia (hemoglobin <8 g/dl)	Maintain dose or dose reduction by 50% (at the discretion of investigator)	If dose reduced, dose escalation at the discretion of the treating physician
Non-hematologic toxicities		
Grade 4 renal, hepatic or other non-hematologic toxicities (e.g. creatinine >6.0 x ULN, total bilirubin >10.0 x ULN, AST/ALT >20.0 x ULN, grade 4 hypertension[c])	Temporary drug cessation until resolution to grade ≤2 or baseline[a] (mandatory)	5 mg BID for at least 2 weeks before considering dose escalation[b]
Grade 3 renal and hepatic toxicities (creatinine >3.0 - 6.0 x ULN, total bilirubin >3.0 - 10.0 x ULN, AST/ALT >5.0 - 20.0 x ULN)	Temporary drug cessation until resolution to grade ≤2 or baseline[a] (mandatory)	5 mg BID for at least 2 weeks before considering dose escalation[b]
Grade 4 increase in serum amylase or lipase (>5.0 x ULN)	Temporary drug cessation until resolution to grade ≤2 or baseline[a] (mandatory)	5 mg BID for at least 2 weeks before considering dose escalation[b]
Grade 3 or lower increase in serum amylase or lipase (≤5.0 x ULN)	Maintain dose or dose reduction by 50% (at the discretion of investigator)	If dose reduced, dose escalation at the discretion of the treating physician
Other grade 3 non-hematologic toxicities (e.g. grade 3 hypertension[d])	Dose reduction by 50%, or temporary drug cessation until resolution to grade ≤2 or baseline[a] (at the discretion of investigator)	5 mg BID for at least 2 weeks before considering dose escalation[b]
Any grade 2 or lower non-hematologic toxicities	Maintain dose or dose reduction by 50% (at the discretion of investigator)	If dose reduced, dose escalation at the discretion of the treating physician
Criteria for permanent cessation of the study drug		
Subjects who cannot tolerate the lowest permissive ruxolitinib dose of 5 mg daily AND require cessation of drug for ≥4 weeks will be permanently removed from the study. Subjects who do not recover from grade 4 hematologic or non-hematologic toxicities possibly, probably or definitely related to ruxolitinib within 2 weeks of drug cessation will be permanently removed from the study. Recovery will be defined as resolution to grade ≤2 or baseline.		

[a]Ruxolitinib may be stopped without a taper in cases of unacceptable toxicities. If an abrupt cessation of ruxolitinib is required, investigators are strongly encouraged to consider starting or dose-escalating systemic glucocorticoid for at least a week (see Section 5.1 "Ruxolitinib taper prior to discontinuation").
[b]If the drug is tolerated at a lower dose for at least two weeks, doses of ruxolitinib may be further increased to a maximum of 10 mg BID.
[c]Definition of grade 4 hypertension: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated.
[d]Definition of grade 3 hypertension: Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated.

5.2.1 Dose reduction for Concomitant Medications

50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole). **Avoid the concomitant use of ruxolitinib with fluconazole doses greater than 200 mg daily.**

When administering ruxolitinib with strong CYP3A4 inhibitors, the total daily dose should be reduced by approximately 50%. Strong CYP3A4 inhibitors include boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir,eltegravir/ritonavir, grapefruit juice, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, LCL161, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, and troleandomycin.

No dose adjustment is necessary when co-administering ruxolitinib with strong CYP3A4 inducers.

No dose adjustment is necessary when co-administering ruxolitinib with CYP3A4 substrates.

Ruxolitinib did not decrease the exposure of a fixed dose oral contraceptive metabolized via the CYP3A4 pathway, thus demonstrating lack of CYP3A4 induction potential.

5.3 Supportive Care

Supportive care will follow the institutional practice of prophylactic antimicrobials, antiemetics, blood product transfusions and other supportive care.

5.4 Duration of Study and Follow-up

We estimate that there will be 47 subjects dosed over a 2.5-year period. After accrual is met, we plan to follow the subjects for up to 2 years; the follow-up duration is discussed in detail in the table below.

GVHD response evaluation every 3 months	Therapy duration	End of therapy safety evaluation (30-40 days after the last dose of the study drug)	Last follow-up for GVHD evaluation	Data collection
Stable disease or mixed responses at the end of 6 months	6 to 12 months followed by taper over 1 month[1]	8 months; If therapy continued till 12 months and tapered over the next month,14 months[2]	At the end of 6 months; If therapy continued until 12 months, up to 24 months from the study enrollment[3]	Data on survival, relapse of malignancy, subsequent GVHD treatment will be collected till subjects are removed from the study, death or up to a total of 2 years. For subjects who have completed last follow-up for GVHD evaluation, further data may be collected via review of medical records or telephone interview.
Partial/complete responses at the end of 6 months	6 to 12 months followed by taper over 1 month[1]	8 months[4]; If therapy continued till 12 months and tapered over the next month,14 months[2]	Up to 24 months from the study enrollment[3]	
GVHD progression, toxicity or relapse[5]	<6 months (may stop without a taper)	About 30 days after the last dose	At the end of 6 months	

[1]If no intolerable toxicity, chronic GVHD progression requiring initiation of an additional systemic agent, or relapse of underlying malignancy within the 6 months of the study participation, ruxolitinib may be continued till 12 months

[2] If no toxicity concerns were raised at 12-month follow-up, this evaluation may be performed over the phone with a plan to see the subject in a follow-up at 15 months.

[3] The subject will be followed every 3 months until progression of chronic GVHD requiring initiation of an additional systemic agent, relapse of underlying malignancy or for a total of 2 years

[4]For subjects with partial or complete responses at 6 months, if no toxicity concerns were raised at 6-month follow-up, this evaluation may be performed over the phone with a plan to see the subject in a follow-up at 9 months.

[5]If the subject develops intolerable toxicity, chronic GVHD progression requiring initiation of an additional systemic agent, or relapse of underlying malignancy before the 6 months of the study participation. If the subject has GVHD progression that is not considered significant enough to necessitate additional systemic GVHD therapy, and the subject is tolerating ruxolitinib, ruxolitinib may be continued till the end of 6 months at the discretion of the treating physician. In such cases, GVHD status will be reassessed at the end of 6 months of therapy. At 6 months, if

the subject continues to have GVHD progression without any responses in any organ, ruxolitinib will be discontinued.

5.5 Assessment Schedule

Subjects should be evaluated for GVHD activity at the time of consenting, at the end of 3 months (+/-14 days) after starting ruxolitinib, and at the end of 6 months of therapy (+/-14 days) (see section 5.4 for duration of follow-up).

Subjects, who maintain complete or partial response at the end of 6 months, will be followed every 3 months until start of another systemic treatment for chronic GVHD**,** relapse of underlying malignancy or for a total of 2 years to determine the duration of response.

Subjects should also be evaluated if they develop grade 3 or higher toxicities. In an event that the subject cannot travel to the transplant center, the subject may be evaluated by a local physician until the subject is able to travel. Subjects may have to be seen more frequently, as clinically indicated.

5.5.1 Baseline assessment (-28 days)

Assessments at the time of enrollment will include:

- History and physical exam including Karnofsky performance status
- Clinical laboratory parameters (hematology, serum chemistry, lipid levels, pancreatic enzymes, Hepatitis B and C), and pregnancy testing in women with reproductive potential.
- Electrocardiogram (EKG)
- Comprehensive GVHD assessment including digital pictures of range of motion (if abnormal) and any visible skin lesions, mapping of sclerotic areas (Appendix I)
- Patient reported outcomes
- Research blood collection for correlative studies

5.5.2 Safety Monitoring (Study Days 14 and 28, End of Month 2, 4, and 5)

Subjects will undergo hematology and serum chemistry testing in 2 and 4 weeks +/- 4 days, then monthly +/- 14 days while receiving ruxolitinib. Lipid levels will be checked at the end of 2 months +/- 14 days. Pancreatic enzymes should be checked if triglyceride level ≥500 mg/dl. These laboratories may be tested locally if more convenient for the subject. When tests are done locally, and not at the study center, the subject will receive a phone call from the study personnel if there are abnormal results. All observed grade 3 or above treatment-emergent adverse events (new or worsening from baseline) and all serious adverse events will be collected. CTCAE version 4.03 (Appendix H) will be utilized to grade the severity of adverse events. Please also see sections 5.5.6 and 7.0.

5.5.3 End of Month 3 Visit (+/-14 days)

Assessments at the end of month 3 visit will include:

- History and physical exam
- Clinical laboratory parameters (hematology and serum chemistry)
- Comprehensive GVHD assessment including digital pictures of range of motion (if abnormal) and any visible skin lesions, mapping of sclerotic areas (Appendix I)
- Patient reported outcomes
- Research blood collection for correlative studies
- Adverse event monitoring

Data on relapse of the underlying malignancy, survival, chronic GVHD flares, prednisone dose and use of other immunosuppressive agents will be captured at scheduled time points, and verified at each visit.

5.5.4 End of Month 6 Visit (+/-14 days)

Assessments at the end of month 6 visit will include:

- History and physical exam
- Clinical laboratory parameters (hematology and serum chemistry)
- Comprehensive GVHD assessment including digital pictures of range of motion (if abnormal) and any visible skin lesions, mapping of sclerotic areas (Appendix I)
- Patient reported outcomes
- Research blood collection for correlative studies
- Adverse event monitoring

Data on relapse of the underlying malignancy, survival, chronic GVHD flares, prednisone dose and use of other immunosuppressive agents will be captured at scheduled time points, and verified at each visit.

5.5.5 End of Month 9, 12, 15, 18, 21 and 24 Visit (+/-30 days) (Extended Treatment)

Subjects who maintain complete or partial response at the end of 6 months, OR receive extended therapy (see section 5.4 for details) will be followed every 3 months (+/-30 days) until start of another systemic treatment for chronic GVHD**,** relapse of underlying malignancy or for a total of 2 years to determine the duration of response.

Assessments at these visits will include:

- History and physical exam
- Clinical laboratory parameters (hematology and serum chemistry)
- Comprehensive GVHD assessment including digital pictures of range of motion (if abnormal) and any visible skin lesions, mapping of sclerotic areas (Appendix I)
- Patient reported outcomes
- Adverse event monitoring if receiving ruxolitinib within the past 30 days

Data on relapse of the underlying malignancy, survival, chronic GVHD flares, prednisone dose and use of other immunosuppressive agents will be captured at scheduled time points, and verified at each visit.

5.5.6 End-of-therapy or Safety Follow-up Visit (30-40 days after the last dose of ruxolitinib)

Subjects will undergo this visit 30-40 days after the last dose of ruxolitinib (see section 5.4 for details).

Assessments at safety follow-up visit will include:

- History and physical examinations
- Clinical laboratory parameters (hematology and serum chemistry)
- Comprehensive GVHD assessment (if a subject withdraws from study treatment prior to 3 or 6 month assessment time points)
- Adverse event monitoring

Subjects with grade 3-4 toxicities are required to undergo close monitoring with repeat testing of any abnormal laboratory or clinical parameter(s) within 2-7 days depending on specific circumstances.

5.6 Criteria for Discontinuation of the Study Drug and Removal from Study

Subjects will discontinue the study drug for any of the following reasons:

- Progression of GVHD resulting in initiation of a new systemic immunosuppressive agent (also see Section 5.1.1)
- Development of an adverse reaction that necessitates discontinuation of the study drug, including any unresolved serious adverse event. Please see section 5.2 for further details.
- Development of a serious systemic allergic response or severe degree of intolerance to the study medication.
- Development of intercurrent medical problems that would make continued protocol therapy detrimental to the subject's safety.
- The subject chooses to discontinue treatment.

Subjects who stop study medication for GVHD progression or relapse of underlying malignancy will stop research visits except for the safety follow-up visit. Data may continue to be collected via chart review.

Subjects will be removed from the study **(study withdrawal)** for any of the following reasons:

- If at any time the requirements of this protocol are detrimental to the subject's wellbeing, the subject will be removed from the study. In this event, the reason(s) for withdrawal will be documented.
- The subject requests removal from the study.

The reason(s) for study withdrawal will be documented and no further information may be collected on the subject. The reason(s) for stopping study medication will be documented in the

case report form. If available, the following information will be recorded in the case report form: GVHD status, date of relapse of underlying malignancy, date of death, cause of death, and autopsy report. Subjects who stop the study drug but do not withdraw from the study may remain in the study.

5.7 Correlative Studies

The correlative objectives for this trial are to:

1. Determine the correlation between response at 6 months and change in the expression level of various cytokines (ST2, SPON1, , CXCR3, CXCL10, IFN gamma, soluble IL-2R, IL-2, IL-4, IL-5, IL-6, IL-12, TNF-α, TRAIL/TNSFSF10/7; profibrotic cytokines such as IL-1β and TGF-β).
2. Determine the correlation between response at 6 months and change in the percentage of peripheral blood T/NK-cell population (CD3-CD56+) [Treg (FoxP3+), effector T cell (CD8+T cell, CD4+ T_H1, T_H2 and T_H17 cells), CD3+, CD4-CD25+, Gr-1, Ter-119, and Antigen presenting cells (APC) APC-CD80+]

These studies aim to determine the correlation and to quantitate the changes of the above from plasma and peripheral blood samples obtained at baseline (pre-treatment), and at 3 and 6 month time points. Collection and handling instructions are provided in Study Site Manual. For each time point, 2x10 mL whole blood will be collected in EDTA treated tubes for quantitation of the various cytokines by various commercially available ELISA assays. Additionally, 8 mL blood will be collected in sodium heparin treated tubes and processed for peripheral blood mononuclear cells (PBMCs) prior to shipping to UNMC Central lab in order to perform flow cytometry to determine T/NK/APC population. If any samples remain after analysis for this study, these samples will be maintained at UNMC central lab for future unspecified use.

Please see study lab manual for additional information regarding processing before shipping to UNMC central lab for isolation and analysis of samples.

5.8 Patient Reported Outcomes (PROs)

5.8.1 Lee Chronic GVHD Symptom Scale

Lee Chronic GVHD Symptom Scale (26) measures the degree of "bother" that subjects have experienced due to symptoms in 7 domains. These domains potentially affected by chronic GVHD include skin, eyes and mouth, breathing, eating and digestion, muscles and joints, energy, emotional distress. This can be found in Appendix D and the Study Site Manual.

5.8.2 Modified Scleroderma Health Assessment Questionnaire

The Scleroderma Health Assessment Questionnaire is based on the Health Assessment Questionnaire, an instrument initially developed for rheumatoid arthritis patients. Both instruments contain 20 items measuring activities of daily living on a 4 point scale (0-3) from "without any difficulty" to "unable to do." The Scleroderma modification added 5 visual analog scales specific for scleroderma disease activity (pain, Raynaud's phenomenon, finger ulcers, intestinal problems, breathing problems, overall severity) (27, 28). Three of these problems (Raynaud's, finger ulcers and intestinal problems) are unlikely in sclerotic GVHD, and will not

be retained for the purpose of this study. This can be found in Appendix E and the Study Site Manual.

Section 6.0 Measurement of Effect

6.1 Assessment of therapeutic response in chronic GVHD

The established method for response determination in the majority of chronic GVHD therapy trials is clinician-determined response based on organ scoring. The Response Criteria Working Group Report from the 2014 NIH Consensus Conference on chronic GVHD has recommended three general categories of overall response: complete response (CR), partial response (PR), and lack of response (unchanged, mixed response, progression) (1). Further details are provided in the Appendix B and G.

The primary endpoint of this study is to determine the proportion of subjects with complete and partial responses in skin and/or joint, which are defined by 2014 NIH Criteria (1) as follow:

Complete response (CR) in skin and/or joint requires NIH skin and joint score 0, and P-ROM score of 25.

Partial response in skin and/or joint requires decrease in NIH skin score OR joint score by 1 or more points, or increase in P-ROM score by 1 point for any site.

Section 7.0 Study Parameters (also see section 5.5)

		Treatment				Follow-Up	
Procedures	Baseline (-28 days)	Study Day 1	Study Day 14 and 28 (±4 days)[7]	End of Month 2, 4, 5 (±14 days)[7]	End of Month 3, 6 (±14 days)	Visits every 3 months (end of month 9, 12, 15, 18, 21, 24) (±30 days)	End of Treatment Safety Follow-Up (30-40 days after last dose)
Informed consent	X						
Eligibility Verification	X						
History and Physical Exam	X				X	X	X
Karnofsky Performance Status	X						
Comprehensive GVHD assessment including digital pictures and body mapping[4]	X				X	X	X[2]
Hematology (CBC)	X		X	X	X	X	X
Serum creatinine, total bilirubin, AST, ALT, Albumin, Alkaline Phosphatase, Calcium, Sodium, Potassium, Blood Urea Nitrogen (BUN), Glucose	X		X	X	X	X	X
Total Cholesterol, LDL, HDL, Triglycerides	X			X (check at the end of 2 months+/-14 days, then as clinically indicated)			
Amylase, lipase	X			Check if triglyceride level ≥500 mg/dl			
Urine Pregnancy	X						
Hepatitis B Surface Antigen[1]	X						
Hepatitis C antibody[1]	X						
CMV DNA	Monthly for the first 3 months and as clinically indicated						
HIV testing[1]	X						
Electrocardiogram	X						
Other Laboratory tests	As clinically indicated						
Radiology Tests	As clinically indicated						
Patient Reported Outcomes Lee Chronic GVHD Symptom Scale Scleroderma Health Assessment Questionnaire	X				X	X	
Correlative study samples[3]	X				X		
Ruxolitinib		X	X	X	X	X[8]	
Adverse event monitoring		Monitor until 30 days after treatment					
Concomitant medications including systemic glucocorticoid[5]	X				X	X[6]	X[6]

1. Testing for Hepatitis B, C and HIV completed prior to transplant will be acceptable. No additional testing is required for study eligibility.
2. If a subject withdraws from study treatment prior to the end of 3 or 6 month assessment time points, the comprehensive GVHD assessment should be completed at the End of Treatment/Safety follow up visit,.
3. The correlative sample can be collected at any time during the scheduled visit.
4. Body mapping and digital pictures will be uploaded in the eCRF. The instructions are listed the CRF Completion Guidelines
5. For all subjects enrolled in this study including those enrolled in the past, data on only concomitant medications of interest (i.e. glucocorticoid, and other immunosuppressive agents including narrow band UVB phototherapy and extracorporeal photopheresis) should be collected at baseline, at each 3-monthly visit until the subject stops ruxolitinib and end of treatment/safety follow-up.
6. After the subjects stop ruxolitinib, if a new immunosuppressive agent is started for treatment of GVHD, only data on the new immunosuppressive medicine should be collected.
7. The subject should be called to check on dose compliance and lab results.
8. If the subject has stable disease, mixed responses or partial/complete response, the subject can continue to take ruxolitinib for a total of 12 months before tapering off the study drug. Please review section 5.1 for further details.

Section 8.0 Drug Formulation and Procurement

8.1 Ruxolitinib

Details available in the investigator brochure.

8.1.1 Mechanism of Action

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.

8.1.2 Clinical Formulation

Available for oral administration as 5 mg tablet. Ruxolitinib tablets are round and white to off-white in color.

8.1.3 Drug procurement

Open label ruxolitinib will be supplied by Incyte Corporation. Ruxolitinib tablets (5 mg) will be administered as oral doses without regard to food in an outpatient setting.

8.1.4 Packaging and Labeling

Ruxolitinib 5 mg tablets are packaged as 60-count in high-density polyethylene (HDPE) bottles. The bottles will include labeling “New Drug - Limited by Federal (USA) Law to Investigational Use”.

8.1.5 Storage/Stability

The bottles of tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F). Stability studies will be conducted on all clinical batches to support the clinical trial.

8.1.6 Administration

Subjects will receive oral ruxolitinib at a dose of 10 mg twice daily Doses may not exceed 10 mg twice daily. Any missed dose can be taken up to 8 hours after the scheduled time.

8.1.7 Instruction to Subjects for Handling Ruxolitinib

The subject should be instructed in the handling of study drug as follows:

- •To store the study drug at room temperature.
- •To only remove from the study drug bottle/kit the number of tablets needed at the time of administration.
- •Not to remove doses in advance of the next scheduled administration.
- •To make every effort to take doses on schedule. However, doses can be taken up to 8 hours after scheduled time.
- •To report any missed doses.
- •To take study drug without regard to food with a glass of water.
- •Not to take another dose if vomiting occurs after taking study drug.
- •To keep study drug in a safe place and out of reach of children.
- •To bring all used and unused study drug kits to the site at each visit.

8.1.8 Clinical Pharmacology

Fifteen Phase I, nine Phase II and three Phase III clinical studies (two in MF, one in PV) provided clinical pharmacology data on ruxolitinib in healthy volunteers and in patients with MF, ET, PV, subjects with renal or hepatic impairment, prostate cancer, pancreatic cancer, multiple myeloma (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 concentration (Cmax) is achieved 1-2 hour 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% ex vivo. 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]-ruxolitinib 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 hour 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 total of 8 active metabolites contribute to 18% of the overall PD activity of ruxolitinib.
- Ruxolitinib PK in healthy volunteers was largely comparable between Japanese, Chinese and Western subjects and did not lead to a conclusion of meaningful ethnic differences.
- Baseline elevations in inflammatory markers such as tumor necrosis factor alpha (TNFα), interleukin (IL)-6, and C-reactive protein (CRP) noted in patients with MF was 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 patients became refractory to the effects of ruxolitinib treatment.

8.1.9 Potential Drug Interactions

50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole). **Avoid the concomitant use of ruxolitinib with fluconazole doses greater than 200 mg daily.**

- 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.
- No dose adjustment is necessary when co-administering ruxolitinib with CYP3A4 substrates.
- Ruxolitinib did not decrease the exposure of a fixed dose oral contraceptive metabolized via the CYP3A4 pathway, thus demonstrating lack of CYP3A4 induction potential.

8.1.10 Drug toxicities

The following drug toxicities were noted in trials mostly involving patients with myelofibrosis and polycythemia vera.

Blood and lymphatic system disorders:
Anemia (40.8-82.4%), thrombocytopenia (16.8-69.8%), neutropenia (16.6%). Also includes febrile neutropenia. Cytopenias are dose dependent and reversible with dose reduction/ interruption.

Infections and infestations:
Urinary tract infections (6-12.6%) Including urosepsis, Cystitis, Kidney infection, Urinary tract infection bacterial, Nitrite urine present, and pyuria. Pneumonia (8.3%) Herpes zoster (4.0-4.3%) Tuberculosis (0.3%)

Gastrointestinal disorders:
Flatulence (3.3%) and Constipation (8.7%).

Hepatic dysfunction:
Raised alanine aminotransferase (22.3-27.2%) and aspartate aminotransferase (19.9-26.1%)

Metabolism and nutrition disorders:
Weight gain (7.6-12.3%), Hypercholesterolemia (16.9-20.7%), Hypertriglyceridemia (9.8%)

Nervous system disorders:
Dizziness (12.0-15.3%%), Headache (14.0%)

Skin and subcutaneous tissue disorders:
Bruising (21.6%) including hematoma, petechiae and purpura

Vascular disorders:
Hypertension (6.5%)

General disorders and administration site conditions:
In clinical studies in myelofibrosis, fatigue, bone pain, pyrexia, pruritus, night sweats, splenomegaly and weight loss noted in 60.4% after discontinuation of ruxolitinib.

In a retrospective study of ruxolitinib in patients with chronic GVHD, cytopenia and CMV reactivation was observed in 17% and 15% of patients. Cytopenias preceded the use of ruxolitinib in most of the patients (15%).

Progressive Multifocal leukoencephalopathy (PML) has been reported with ruxolitinib treatment. Physicians should be alert for neuropsychiatric symptoms suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded.

Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma have been reported in patients treated with ruxolitinib. Most of these patients had histories of extended treatment with hydroxyurea and prior histories of NMSC or pre -malignant skin lesions. A causal relationship to ruxolitinib has not been established. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

8.1.11 Drug Accountability

Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign some of the drug accountability duties to an appropriate pharmacist or designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study medication until the end of the study. The Investigator or designee must maintain records that document:

- investigational product delivery to the study site
- the inventory at the site
- use by each subject including pill/unit counts from each supply dispensed
- product returned to the investigator or designee.

These records should include dates, quantities, batch/serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study subjects.

The investigational product must be used only in accordance with the protocol. The investigator will also maintain records adequately documenting that the subjects were provided the study medication specified.

Completed accountability records will be archived by the site. If any unused ruxolitinib bottles remain at the end of the study, they will be accounted for by the site prior to study closure. If a site is able to destroy ruxolitinib at their premises, or through a certified vendor, they may do so upon authorization by the sponsor, provided their destruction policy is made available to the sponsor.

Section 9.0 Toxicity and Adverse Event Reporting Guidelines

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC Fred & Pamela Buffett Cancer Center Data Monitoring plan. The protocol will adhere to the institutional and FDA guidelines for the toxicity reporting.

All subjects will be closely followed for toxicity from the time of informed consent until 30 days after last administration of study medication. The reporting is only for “study medication,” until 30 days after last administration of study medication.

Adverse events (AEs) will be assessed by reports from subjects to their physician/Investigator and by physical examinations. Per NCI guidelines, serious adverse events (SAEs) and AEs will be graded and toxicity will be assessed using the revised NCI CTCAE version 4.03 (Appendix H). Adverse event will be followed until resolution, baseline or ≤ grade 1 levels.

Serious adverse events should be followed until resolution, baseline or ≤ grade 1 levels, death, or until no further improvement is reasonably expected. Deaths occurring within 30 days of study treatment regardless of relationship will be reported to the Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC).

9.1 Definitions

Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

An elective surgery or procedure that is scheduled to occur during a study will not be considered an adverse event if the surgery or procedure is being performed for a pre-existing condition and the surgery or procedure has been planned before study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (*e.g.,* the surgery is performed earlier than planned), then the deterioration of the condition for which the elective surgery or procedure is being done will be considered an adverse event.

Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events if they result in discontinuation from the study, necessitate therapeutic medical intervention, require dose modifications and/or if the investigator considers them to be adverse events.

Unexpected Adverse Event

An unexpected adverse event is any adverse drug event that is not listed in the current labeling/Investigator's Brochure. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Serious Adverse Event

A serious adverse event is one that at any dose (including overdose) and regardless of causality:

- Results in death
- Is a serious threat to life, health, safety or welfare-fare of subject [1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Requires intervention to prevent permanent impairment or damage
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is another serious important medical event[3]
- Is any medical event in an investigational drug study that requires treatment to prevent one of the outcomes listed above
- Seriously jeopardizes the rights, safety, or welfare of subjects

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.
[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.
[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that

may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such 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. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

9.2 Adverse Event Reporting and Definitions Per University of Nebraska Medical Center, IRB and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) and Incyte Corporation

This protocol will adhere to all institutional guidelines for adverse event reporting. Adverse events will be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (Appendix H).

9.2.1 IRB Reporting

All internal serious adverse events (AE) must be reported to the local IRB promptly per institutional policy and in no case later than two (2) business days following PI notification that the event occurred *if* the principal investigator determines that conditions A, and B, are met:

a. The AE is unexpected, *AND*
b. The AE is related to, or possibly related to, the drug, biologic, device, or other research intervention

All *unexpected*, internal, fatal AEs must be reported promptly to the local IRB per institutional policy, but no later than *24 hours* following PI notification that the event occurred. If documentation is still pending, the IRB office must be notified by a telephone call or e-mail.

All *expected*, internal, fatal AEs (i.e., due to progressive disease or which reflect a risk currently found in the consent form) must be reported to the local IRB per institutional policy no later than ten (10) business days following PI notification that the event occurred.

9.2.2 Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) Reporting

In its initial review, the DSMC will make a recommendation for the frequency of DSMC monitoring based on an assessment of risk associated with study-associated therapy, per the DSMC policy. Reporting of the following will be done in accordance with DSMC guidelines:

- All Serious adverse events (SAEs) and toxicity reporting will be reported to the DSMC.
- All adverse events grade 3 or higher (expected or unexpected, regardless of attribution) will be reported to the DSMC.

Attribution of AE: The likelihood of relationship of the AE to the study drugs will be determined by the investigator based on the following definitions:

Not related: The subject was not exposed to the study treatment or another cause is obvious.

Probably not related: The AE is most likely explained by another cause, and the time of occurrence of the AE is not reasonably related to the study treatment.

Possibly related: Study treatment administration and AE occurrence reasonably related in time, and the AE is explained equally well by causes other than study treatment, or treatment administration and AE occurrence are not reasonably related in time, but the AE is not obviously a result of other causes.

Probably related: Study treatment administration and AE occurrence are reasonably related in time, and the AE is more likely explained by study treatment than by other mechanisms.

Definitely related: The occurrence and timing of the AE are clearly attributable to the study treatment.

AEs will be collected from the time the subject signs the consent form and ending 30 days following the final dose of study drug. All AEs will be followed until resolution, a cause is identified, or until no further improvement is expected. AEs judged by the investigator as not related or probably not related to the treatment will NOT be followed beyond the 30 days after the final dose of study drug.

All SAEs and AE reporting will be completed using DSMC approved forms. Detailed policy and procedures for this section may be reviewed at:
http://www.unmc.edu/cancercenter/clinical/prms.html

9.2.3 Incyte Reporting

To ensure subject safety, every Serious Adverse Event (SAE), occurring after the subject has consented and until at least 30 days after the subject has stopped taking the Incyte study product (ruxolitinib) must be reported to Incyte ***within twenty four (24) hours*** of learning of the event.

If a subject experiences a SAE after signing informed consent, but prior to receiving ruxolitinib, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure. Previously planned (prior to signing the informed consent document) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

All SAEs are to be captured on Incyte's Adverse Event Report Form.

The study sites will submit the SAEs to Incyte via IncyteSafety@Telerx.com. If critical or outstanding information is missing from the Adverse Event Report Form or additional clarification is needed, the Incyte representative will submit a Data Clarification Form (DCF) to the Sponsor-Investigator. The Sponsor will be required to complete all queries listed on the DCF and return the completed DCF to Incyte.

The Sponsor-Investigator must report to Incyte all Serious Adverse Events regardless of the causality assessment.

Follow- up Reporting

When new information regarding an SAE becomes available, this information must be reported to Incyte on a new or updated Adverse Event Report Form ***twenty four (24) hours*** of becoming aware of the information.

Reconciliation

On a periodic basis (quarterly at minimum), the Sponsor-Investigator will provide a listing of all Safety Information recorded for the study to Incyte for reconciliation purposes. The Sponsor-Investigator will forward the listing via email to IncytePhVOpsIST@incyte.com

Interventional Investigator Initiated Trials

The Sponsor-Investigator reports all Suspect Unexpected Serious Adverse Reactions (SUSARs) to the relevant Health Authority where the Investigational New Drug (IND) was approved for the Sponsor-Investigator and distributes Investigator Notifications (IN) as required by local regulations.

Incyte will submit to the relevant Health Authorities outside of Sponsor-Investigator's approved countries and distributes Investigator Notifications to other Investigators as applicable.

- The Sponsor-Investigator will author the Development Safety Update Report (DSUR) and share the completed DSUR with Incyte for comment prior to submission to the health authority.

Pregnancies

Pregnancy, in and of itself, is not regarded as an adverse event, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive medication or method. The procedures to be followed based on a confirmed pregnancy by a positive serum test result are listed below:

- Investigator and subject must notify each other immediately
- Investigator must notify the Investigator –Sponsor and Incyte immediately
- Discontinue study medication immediately
- Perform the required End-of-treatment visit study evaluations
- Investigator must complete and submit the Pregnancy Initial and Follow-up report forms to the Sponsor

To ensure subject safety, each pregnancy in a subject during maternal or paternal exposures to study drug must be reported within 24 hours of learning of its occurrence.

Any SAE experienced during pregnancy must be reported on the SAE Report Form and needs to be reported to the Investigator-Sponsor and Incyte.

9.3 Monitoring

Various methods will be implemented by the sponsor (UNMC) to exchange information with participating sites:

- Site Initiation/Orientation

- Regular Teleconferences including group wide progress within the agenda
- Investigator meetings as feasible (remote or on an as needed basis, possibly in conjunction with larger meetings)
- Email distributions/reports as needed

9.3.1 Data Monitoring

For this study, data monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirement(s). Monitoring is a Quality Control, continuous process during the entire trial.

All participating sites will perform routine data monitoring for this study by each site's institution according to the institution's internal guidelines and policies. A copy of the site's monitoring report will be submitted to UNMC.

9.4 Auditing

Auditing is a systematic and independent examination of trial-related activities and documents to determine:

- whether the evaluated trial-related activities were conducted
- the data were recorded, analyzed, and accurately reported, according to the protocol, to the sponsor's SOPs, GCP, and applicable regulatory requirement(s).

Auditing is a Quality Assurance, one point process during the trial.

The UNMC Fred & Pamela Buffett Cancer Center Scientific Review Committee (SRC) will review this protocol on at least an annual basis.

This study will undergo audit on at least a semi-annual basis by the UNMC Fred & Pamela Buffett Cancer Center Audit Committee.

Detailed policy and procedures for this section may be reviewed at:
https://www.unmc.edu/cancercenter/clinical/prms.html.

Section 10.0 Statistical Considerations

10.1 Study Design and Sample Size Description

The study is an open label, phase II, multicenter trial designed to evaluate ruxolitinib as a salvage treatment for subjects with sclerotic GVHD (sclerosis or fasciitis).

If a subject receives one dose of ruxolitinib then the subject will be included in the safety analysis set.

The full analysis set will include all subjects that are evaluable at 6 months as well as subjects who are considered a treatment failure (including deaths) prior to 6 months. Subjects who drop out of the study prior to 6 months for reasons unrelated to treatment will be excluded from the full analysis set.

The primary endpoint is complete and partial responses in skin and/or joint, as determined by 2014 NIH Criteria (1) at 6 months from initiation of ruxolitinib without addition of any other systemic chronic GVHD treatment, relapse of the underlying disease, or death. The historical benchmark for overall response for steroid refractory sclerotic chronic GVHD is 25% in a randomized phase II trial by Arai et al., comparing imatinib and rituximab (15). In the trial by Arai et al., a significant clinical response was defined as "2 or more point improvement on the Vienna Skin Score without worsening elsewhere or at least a 1-point improvement in the 4-level P-ROM scale or a 2-point improvement in the 7-level scale without worsening elsewhere." The Vienna Skin Score is different from the 2014 NIH criteria (1) for responses in skin and/or joint. According to the 2014 NIH guidelines (1), "because the NIH 0 to 3 Skin Score is now recommended for response assessment, even substantial improvement in sclerotic features will not be considered responses unless the NIH Skin Score improves." For this reason, for the purpose of the stopping rules, responses will include complete and partial responses in skin and/or joint, at least a 2-point improvement on 0-10 semiquantitative scale for capturing clinician-perceived severity of sclerosis, or clinically significant improvement (improvement by ≥6 point) on the skin subscale of the Lee symptom scale, consistent with the recommendations of the 2014 NIH Criteria (1). Additionally, improvement in percentage of BSA involved with deep sclerosis/fasciitis will also be taken into consideration as a marker of responses.

A two-stage design is planned to test the null hypothesis that the overall response rate $p \leq 0.250$ versus the alternative that $p \geq 0.450$. The first stage will occur once 18 subjects have completed 6 months of treatment. If only 4 or fewer out of the 18 subjects respond at the end of 6 months of treatment, the trial will be stopped for futility. At stage two, an additional 24 subjects will be enrolled for a combined total of 42 from both stages. If only 15 or fewer respond out of 42 subjects at the end of stage two, then no further investigation is warranted. If 16 or more respond then further investigation is warranted. This design achieves 84% power with a significance level of 0.044. Retrospective studies (31, 32, 40) have demonstrated that ruxolitinib is well tolerated and effective in patients with steroid-refractory chronic graft-versus-host disease (GVHD) in general and sclerotic GVHD. Therefore, the accrual will not be put on hold for interim analysis.

To meet our statistical endpoints, a sample size of 42 is required; however, to account for dropout rate of approximately 10%, the study will dose 47 subjects.

10.2 Analysis plan

Descriptive statistics will be computed for subject characteristics. Mean, standard deviation (SD), median and range will be reported for continuous variables and frequencies and percentages will be used to describe categorical variables.

10.2.1 Efficacy Endpoints

Primary and secondary objectives

The primary objective of the study is to determine the complete and partial responses in skin and/or joint after 6 months of therapy. The response rate will be reported as a proportion and 95% exact confidence interval. This analysis will be conducted on the full analysis set.

The secondary objective is to determine the overall complete and partial responses after 6 months of therapy. The response rate will be reported as a proportion and 95% exact confidence interval.

Exploratory Objectives

Treatment failure (treatment failure defined as: administration of additional systemic therapy for chronic GVHD, malignancy relapse or mortality) by 6 months from study enrollment.

Time to treatment failure will be defined as study enrollment to failure event. Kaplan-Meier methods will be used to estimate the distribution for time to treatment failure. The failure rate at 6 months will be estimated from the Kaplan-Meier curve, and the rate and 95% confidence interval will be reported.

Time to non-relapse mortality will be computed as study enrollment to non-relapse death. Cumulative incidence methods will be used to estimate the distribution with relapses and relapse related deaths as competing events. The rate at 6 months will be estimated from the curve along with 95% confidence intervals.

For subjects treated on the extension study, the response rate at 12 months will be reported as a proportion and 95% exact confidence interval.

For subjects on steroids at baseline, we will explore the change in dose of steroids at 6 months. We will calculate the average percent change in dose for each subject along with a 95% CI. We will also determine the number and proportion of subjects that had a dose reduction greater than 50% as well as an exact 95% confidence interval.

10.2.3 Safety endpoint

Safety endpoints will be assessed on the safety analysis set. All adverse events recorded during the study will be summarized by each subject. The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by severity and type of adverse event. Listings of deaths, severe adverse events, and adverse events leading to early termination of study treatment or premature withdrawal from study will also be provided.

10.2.4 Analysis of patient reported outcomes and Correlative data

Descriptive statistics will be computed for patient reported outcomes Lee Chronic GVHD Symptom Scale, and Scleroderma Health Assessment Questionnaire at study enrollment and 6 months. Changes in patient reported outcomes from study enrollment to 3 and 6 months will be assessed with paired t-tests or Wilcoxon sign rank test depending on whether test assumptions are met.

For **correlative studies**, changes in measured parameters from baseline to defined time points after therapy initiation will be measured. We will graphically display biomarker levels over time for each subject individually as well as averages at each time point for responders and non-responders separately. Univariate and multiple logistic regression will be used to determine if the change in biomarker level from baseline to 3 and 6 months is predictive of responder status at 6 months, looking at the biomarkers individually as well as in combination.

10.3 Accrual goal

It is expected that 20 subjects will be enrolled in the trial each year. To meet the accrual goals of 47, we require approximately 2.5 years of enrollment with 2 years of follow up.

10.4 Stopping rule

Serious adverse events and deaths will be reviewed by the study team and principal investigators on an ongoing basis.

The risk of treatment-related mortality is 10-20% in patients with steroid refractory chronic GVHD (15, 42). The study will have continuous mortality monitoring, and if ≥20% have treatment-related mortality that is possibly, probably or definitely related to the study drug, accrual will be halted (see stopping rules below). Subjects, who are already enrolled in the study, and are tolerating the study drug may continue the drug at the discretion of the treating physician.

Continuous monitoring (43) will be performed after each subject has received the first dose of ruxolitinib, beginning when the 2nd subject has received the first dose of ruxolitinib, with K=47 interim analyses, a null hypothesis mortality rate of 0.10, an alternative hypothesis of 0.20, and power of 0.80. The sample size is too small to control alpha and power simultaneously, so alpha is 0.19 to allow for 80% power (see below table for operating characteristics). The table below displays the boundaries b_k for each interim analysis k. If the observed number of treatment-related mortality is greater than b_k, accrual will be terminated. Stopping boundaries were calculated with the R package "clinfun" based on Ivanova (41), using this code: toxbdry(0.1 ,0.2, 3:47, cP0=0.1, cP1=0.8, priority="alt").

Continuous monitoring boundaries for K=47 when the true mortality rate is 0.10 and the alternative hypothesis is 0.20 and alpha=0.05, 80% power
Stop if treatment-related mortality is greater than or equal to the boundary (>=b_k)

K	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
b_k	-	2	2	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	4	4	5

K	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
b_k	5	5	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7

K	44	45	46	47
b_k	7	8	8	9

Operating characteristics of the stopping rule

P(death)	P(stopping)	Expected sample size
0.10	0.192	41.1
0.12	0.309	37.8
0.14	0.443	34.1
0.16	0.577	30.2
0.18	0.697	26.4
0.20	0.795	22.9

All grade 3 and above or serious adverse events recorded during the study will be summarized. Listings of deaths, serious adverse events, and adverse events leading to early termination of study treatment or premature withdrawal from study will also be provided to the DSMC.

Section 11.0 Records to be Kept

Information regarding the actual treatments, adverse events, and laboratory tests are to be recorded on appropriate forms. See attached Data forms. Serious adverse events, when noted, will be recorded on site via the standard serious adverse effects form.

11.1 Quality Assurance

Complete records must be maintained in a research chart on each subject treated on the protocol. Research chart can be maintained either as an electronic record, paper chart or a combination of both. These records should include primary documentation (e.g., laboratory report slips, physician notes, etc.) which confirm that:

- The subject met the eligibility criteria.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given and reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (dated notes on clinical assessment, laboratory reports as appropriate).

11.2 Advarra Electronic Data Capturing (EDC) System

Data will be stored electronically for this study on the Advarra secure server. Data forms will not differ from the paper versions with the exception of an electronic format containing the UNMC Fred & Pamela Buffett Cancer Center and Advarra logo.

Advarra EDC provides for remote data collection that meets FDA 21 CFR Part 11 requirements as well as HIPAA and other regulatory requirements designed to enhance data security and protect patient confidentiality. Authorized users log into Advarra through a secure connection and must provide a valid username, password, and database ID. This data may be made available to the public at large.

Section 12.0 Subject Consent

12.1 Human Subjects Research Protection Training

All personnel involved in this research project will have completed the OHRP-approved computer based training course on the Protection of Human Research Subjects. All clinical and correlative research included in this protocol will have approval by the institutional review board.

12.2 Study Population

Subjects are from all socio-economic groups and will be entered into the study without bias with respect to gender or race. Attempts will be made to recruit minorities. No vulnerable subjects will be included in the study.

12.3 Sources of Material

Only material collected for this trial is the blood specimen for the correlative studies. No other pathology material is necessary.

12.4 Recruitment and Informed Consent

Subjects with the diagnosis of sclerotic GVHD seen and evaluated at UNMC/Nebraska Medicine or other IRB-approved sites will be available for recruitment. These patients will be informed of the nature of this study, and will be asked to participate on a voluntary basis after informing them of the possible risks and benefits of the study. A number of public registries may be accessible to health care providers and prospective subjects as listed on the title page of this protocol.

12.5 Subject Competency

Subjects will be eligible to participate in the study only if they are competent to give informed consent. A subject that the investigators judges to be incompetent will not be enrolled.

12.6 Process of Informed Consent

If the patient chooses to be a participant in this study, informed consent will be obtained by the investigators. The study and procedures involved including the risks will be explained in detail to each subject. It will be clearly explained to the subject that this is a research study and that participation is entirely on a voluntary basis. Subjects will be given the option to discuss the study with a family member, friend, counselor or, another physician. The participating investigators will be available to discuss the study with them.

12.7 Subject/Representative Comprehension

When the process of informed consent is completed, the subject will be asked to state in his/her own words, the purpose of the study, the procedures that will be carried out, potential risk, potential benefits to the subject, the alternatives and the right to withdraw from the study. If there is any indication that a given subject's comprehension is anything less than accurate, the points of confusion will be discussed and clarified.

12.8 Information Purposely Withheld

The results of the tests done solely for research purposes will not be disclosed to the subject. No other information will be purposely withheld from the subject.

12.9 Potential Benefits of the Proposed Research to the Subjects

It is hoped that the use of ruxolitinib may result in improvement in GVHD.

12.10 Potential Benefits to Society

Information obtained from this study may help other GVHD patients by establishing the role of ruxolitinib.

12.11 Potential Risks

The use of ruxolitinib is associated with numerous potential risks as described in section 8.1.10 under drug toxicities.

12.12 Therapeutic Alternatives

If patients choose not to participate in this study, they may elect to receive other therapy as per their treating physician.

12.13 Risk/Benefit Relationship

Although there are inherent risks involved because of the use of ruxolitinib, the risk is considered to be acceptable in this setting.

12.14 Consent Form Documents

The results of the tests done solely for research purposes will not be disclosed to the subject. No other information will be purposely withheld from the subject. The consent document used in this study will include the adult consent document.

Section 13.0 References

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Section 14.0 Data Collection Forms

Please refer to the Study Site Manual for the forms.

Appendix A: Manifestations of chronic graft-versus-host disease

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of chronic GVHD)	Distinctive* (Seen in chronic GVHD, but Insufficient Alone to Establish a Diagnosis)	Other Features or Unclassified Entities†	Common‡ (Seen with Both Acute and chronic GVHD)
Skin	Poikiloderma Lichen planus–like features Sclerotic features Morphea-like features Lichen sclerosus–like features	Depigmentation Papulosquamous lesions	Sweat impairment Ichthyosis Keratosis pilaris Hypopigmentation Hyperpigmentation	Erythema Maculopapular rash Pruritus
Nails		Dystrophy Longitudinal ridging, splitting or brittle features Onycholysis Pterygium unguis Nail loss (usually symmetric, affects most nails)		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Loss of body hair Scaling	Thinning scalp hair, typically patchy, coarse or dull (not explained by endocrine or other causes) Premature gray hair	
Mouth	Lichen planus–like changes	Xerostomia Mucoceles Mucosal atrophy Ulcers Pseudomembranes		Gingivitis Mucositis Erythema Pain
Eyes		New onset dry, gritty, or painful eyes Cicatricial conjunctivitis KCS Confluent areas of punctate keratopathy	Photophobia Periorbital hyperpigmentation Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus–like features Lichen sclerosus–like features	Erosions Fissures		
Females	Vaginal scarring or clitoral/labial agglutination	Ulcers		
Males	Phimosis or urethral/meatus scarring or stenosis			
GI Tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children
Liver				Total bilirubin, alkaline phosphatase > 2 × upper limit of normal ALT > 2 × upper limit of normal
Lung	Bronchiolitis obliterans diagnosed with lung biopsy BOS§	Air trapping and bronchiectasis on chest CT	Cryptogenic organizing pneumonia Restrictive lung disease‖	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to fasciitis or sclerosis	Myositis or polymyositis¶	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and Immune			Thrombocytopenia Eosinophilia Lymphopenia Hypo- or hyper–gammaglobulinemia Autoantibodies (AIHA, ITP) Raynaud's phenomenon	
Other			Pericardial or pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Myasthenia gravis Cardiac conduction abnormality or cardiomyopathy	

ALT indicates alanine aminotransferase; AIHA, autoimmune hemolytic anemia; ITP, idiopathic thrombocytopenic purpura.

* In all cases, infection, drug effect, malignancy, or other causes must be excluded.

† Can be acknowledged as part of the chronic GVHD manifestations if diagnosis is confirmed.

‡ Common refers to shared features by both acute and chronic GVHD.

§BOS can be diagnostic for lung chronic GVHD only if distinctive sign or symptom present in another organ (see text).

|| Pulmonary entities under investigation or unclassified.

¶ Diagnosis of chronic GVHD requires biopsy.

Appendix B: Organ scoring of chronic graft-versus-host disease per 2014 NIH consensus

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† **SCORE % BSA** ☐ *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

Figure 1. Organ scoring of chronic GVHD. ECOG indicates Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; LPS, Lansky Performance Status; BSA, body surface area; ADL, activities of daily living; LFTs, liver function tests; AP, alkaline phosphatase; ALT, alanine aminotransferase; ULN, normal upper limit. *Weight loss within 3 months. †Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring. ‡To be completed by specialist or trained medical providers (see Supplemental Figure). **Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS** **Symptom score**:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: % FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				

Figure 1. (*continued*).

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Photographic Range of Motion (P-ROM)

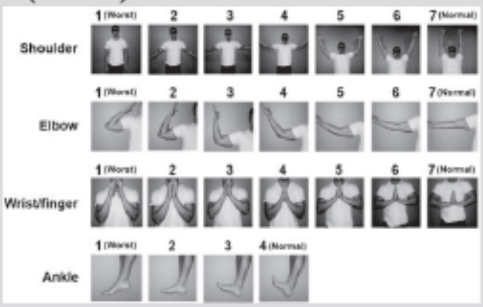


Figure 1. (*continued*).

Appendix C: NIH Global Severity of chronic GVHD

NIH Global Severity of chronic GVHD
Mild chronic GVHD 1 or 2 Organs involved with no more than score 1 *plus* Lung score 0 Moderate chronic GVHD 3 or More organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score 1 Severe chronic GVHD At least 1 organ with a score of 3 OR Lung score of 2 or 3 Key points: In skin: higher of the 2 scores to be used for calculating global severity. In lung: FEV1 is used instead of clinical score for calculating global severity. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Appendix D: Lee Symptom Scale

By circling one (1) number per line, please indicate how much you have been bothered by the following problems in the past 7 days:

	SKIN:	Not at all	Slightly	Moderately	Quite a bit	Extremely
1.	Abnormal skin color……..	0	1	2	3	4
2.	Rashes……	0	1	2	3	4
3.	Thickened skin……...……...	0	1	2	3	4
4.	Sores on skin…….	0	1	2	3	4
5.	Itchy skin……...…….	0	1	2	3	4
EYES AND MOUTH:		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
6.	Dry eyes…….	0	1	2	3	4
7.	Need to use eye drops frequently..	0	1	2	3	4
8.	Difficulty seeing clearly……	0	1	2	3	4
9.	Need to avoid certain foods due to mouth pain…….	0	1	2	3	4
10.	Ulcers in mouth…….	0	1	2	3	4
11.	Receiving nutrition from an intravenous line or feeding tube....	0	1	2	3	4
BREATHING:		**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
12.	Frequent cough…….	0	1	2	3	4
13.	Colored sputum…….	0	1	2	3	4
14.	Shortness of breath with exercise..	0	1	2	3	4
15.	Shortness of breath at rest……...	0	1	2	3	4
16.	Need to use oxygen……..	0	1	2	3	4

EATING AND DIGESTION:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
17. Difficulty swallowing solid foods….	0	1	2	3	4
18. Difficulty swallowing liquids…….	0	1	2	3	4
19. Vomiting…….	0	1	2	3	4
20. Weight loss……	0	1	2	3	4
MUSCLES AND JOINTS:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
21. Joint and muscle aches……...	0	1	2	3	4
22. Limited joint movement……	0	1	2	3	4
23. Muscle cramps……..	0	1	2	3	4
24. Weak muscles……...	0	1	2	3	4
ENERGY:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
25. Loss of energy…….	0	1	2	3	4
26. Need to sleep more/take naps…..	0	1	2	3	4
27. Fevers……	0	1	2	3	4
MENTAL AND EMOTIONAL:	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
28. Depression……	0	1	2	3	4
29. Anxiety……...	0	1	2	3	4
30. Difficulty sleeping…….	0	1	2	3	4

Appendix E: Modified Scleroderma Health Assessment Questionnaire (SHAQ)

In the past seven (7) days,	Without any difficulty	With some difficulty	With much difficulty	Unable to do
Are you able to: Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
Are you able to: Stand up from an armless straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
Are you able to: Cut your meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new carton of milk?	☐	☐	☐	☐
Are you able to: Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up 5 steps?	☐	☐	☐	☐
Are you able to: Wash and dry your entire body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
Are you able to: Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	☐	☐	☐	☐
Bend down and pick up clothing from the floor?	☐	☐	☐	☐
Are you able to: Open car doors?	☐	☐	☐	☐
Open jars which have previously opened?	☐	☐	☐	☐
Turn regular taps on and off?	☐	☐	☐	☐
Are you able to: Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any Aids or Devices that you usually use:

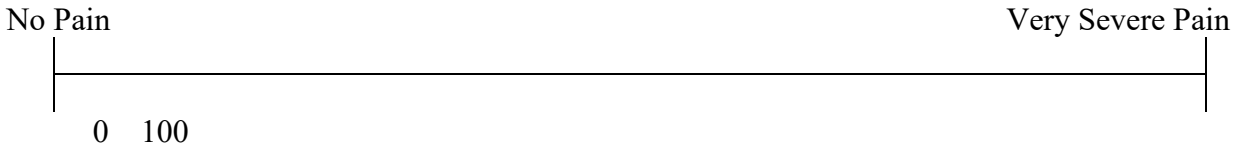
Cane ☐	Dressing Devices (button hook, long shoe horn, etc.) ☐
Walker ☐	Built up or Special Utensils ☐
Bathtub seat ☐	Long Handled Appliances for reach ☐
Bathtub Bar ☐	Long Handled Appliances for Bathroom ☐
Jar Opener ☐	Raised Toilet seat ☐
Crutches ☐	Special or Built-up Chair ☐
Wheelchair ☐	Other (Specify)

Please check any categories for which you usually need help from another person:

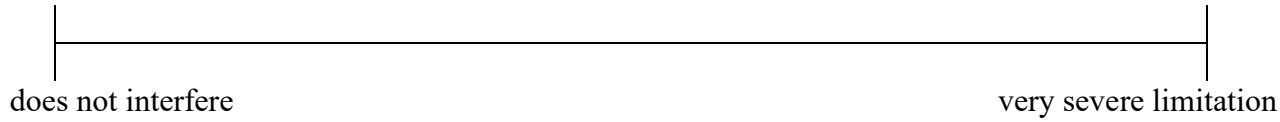
Hygiene ☐	Gripping and Opening Things ☐
Reach ☐	Errands and Chores ☐
Arising ☐	Dressing and Grooming ☐
Eating ☐	Walking ☐

Place a mark on the line to indicate the severity of the pain.

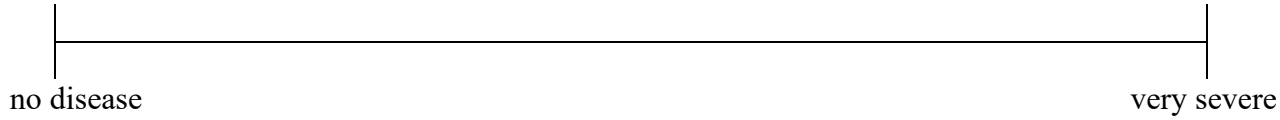
How much pain have you had because of your illness ***in the past week***?



1. In the past week, how much have your breathing problems interfered with your activities?



2. Overall, considering how much pain, discomfort, limitations in your daily life and other changes in your body and life, how severe would you rate your disease ***today***?



Appendix F: Eligibility Checklist

Date Completed:	Site #:	Subject ID#:	
IRB # 333-18 Title: A Single Arm, Open Label, Phase II Study of Ruxolitinib in Sclerotic Chronic Graft-Versus-Host Disease after Failure of Systemic Glucocorticoids		Waiver #: Incyte Ref #: Investigator:	

Inclusion criteria:	Yes	No	NA
1. Sclerotic chronic GVHD (classic chronic or overlap syndrome) that meets 2014 NIH Consensus Criteria. Eligible patients will have superficial or deep skin sclerosis, fasciitis or joint contractures.	☐	☐	☐
2. The subject must have received the following therapy for chronic GVHD (not necessarily for sclerotic manifestations): a. Systemic corticosteroids for >12 months and at least one additional line of systemic therapy OR b. Systemic corticosteroids and at least two additional lines of systemic therapy for chronic GVHD (not necessarily for sclerotic manifestations). For the purpose of this study, intra-oral narrow-band UVB phototherapy and "FAM" (fluticasone, azithromycin and montelukast) therapy for lung GVHD will be considered a topical therapy. Investigators are encouraged but not mandated to use ibrutinib for appropriate patients prior to enrollment in this trial.	☐	☐	☐
3. Adults, Age ≥18 years. (state of Nebraska, Age ≥19 years)	☐	☐	☐
4. Karnofsky performance status ≥60% at the time of enrollment	☐	☐	☐
5. All allogeneic donor sources and all conditioning regimens are allowed.	☐	☐	☐
6. Absolute neutrophil count (ANC) greater than 1000/μL, and platelet count ≥50,000/μL without the use of growth factors or platelet transfusion.	☐	☐	☐
7. Able to take orally-administered medication.	☐	☐	☐
8. Female subject of reproductive potential must have a negative serum or urine pregnancy test ≤7 days prior to starting the study drug. Women are considered NOT to have reproductive potential if they have had 12 months of amenorrhea with an appropriate clinical profile (i.e. ≥51 years, history of vasomotor symptoms, OR supportive hormone levels such as low estrogen and high follicle-stimulating hormone levels), OR surgical sterilization.	☐	☐	☐

9. Male and female patients of reproductive potential must be willing to avoid pregnancy or fathering children from enrollment to one month after the end of study treatment. This will require either a total abstinence, OR exclusively non-heterosexual activity (when this is in line with the preferred and usual lifestyle of the subject), OR two methods of contraception (male or female condom with or without a spermicidal agent, diaphragm or cervical cap with spermicide, or hormonal based contraception including intrauterine device).	☐	☐	☐
10. Life expectancy greater than 6 months	☐	☐	☐
11. Written informed consent to participate in the study.	☐	☐	☐
All of the above must be **yes** to be eligible.			
Exclusion criteria	Yes	No	NA
1. Fibrosis of internal organs such as gut, liver or lung as the sole manifestation of sclerosis.	☐	☐	☐
2. Fluconazole at a dose more than 200 mg daily. Subjects should stop fluconazole or lower dose to less than or equal to 200 mg daily before starting ruxolitinib.	☐	☐	☐
3. Current evidence of malignancy after allogeneic transplant.	☐	☐	☐
4. History of progressive multifocal leuko-encephalopathy (PML)	☐	☐	☐
5. Active uncontrolled bacterial, fungal, parasitic, or viral infection. Infections are considered controlled if appropriate therapy has been instituted and, at the time of screening, no signs of infection progression are present. Progression of infection is defined as hemodynamic instability attributable to sepsis, new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection	☐	☐	☐
6. Presence of known HIV infection, active hepatitis B or C infection.	☐	☐	☐
7. Active tuberculosis infection that developed after allogeneic HCT	☐	☐	☐
8. Total bilirubin 1.5 x the upper limit of the normal range	☐	☐	☐
9. Creatinine clearance <30 mL/min	☐	☐	☐
10. Presence of uncontrolled cardiopulmonary conditions such as ongoing cardiac arrhythmias, unstable angina or myocardial infarction, uncontrolled hypertension (e.g. blood pressure higher than 150/90), New York Heart Association class III/IV congestive heart failure, or requirement of supplemental oxygen at rest or having a resting O2 saturation <90% by pulse oximetry	☐	☐	☐
11. Any other condition that is judged by the physician to potentially interfere with compliance to the study protocol or pose a significant risk to the subject.	☐	☐	☐
12. Pregnancy, breastfeeding or planning to be pregnant.	☐	☐	☐

13. Exposure to JAK inhibitor therapy for any indication after allogeneic transplant	☐	☐	☐
14. Initiation of a new systemic immunosuppressant for management of chronic GVHD within 8 weeks prior to enrollment. However, patients who develop disease progression can enroll as early as 4 weeks after initiation of a new systemic immunosuppressant. Also, patients who are unable to tolerate current therapy can enroll any time after initiation of a new systemic immunosuppressant, as long as the "new" immunosuppressant is stopped in these cases prior to initiation of ruxolitinib. Initiation of any new topical therapy (including FAM or intra-oral narrow-band UVB phototherapy) and changes in dose of existing immunosuppressive agents such as corticosteroids, sirolimus, calcineurin inhibitors or other agents are acceptable at any time prior to enrollment. The use of immunosuppressants for short term period, for example 7 days, for indications other than GVHD will be acceptable.	☐	☐	☐
15. Treatment with any other investigational agent, device, or procedure, within 21 days (or 5 half-lives, whichever is greater)	☐	☐	☐
16. Known allergies, hypersensitivity, or intolerance to any of the study medications, excipients, or similar compounds.	☐	☐	☐
All of the above must be **no** to be eligible.			

Eligibility: ☐ Subject satisfies all criteria.

☐ Subject not formally eligible, but admitted to study because (state reason)

Subject Initials: _____MR #_____DOB _____

ELIGIBILITY Reviewed and Confirmed By:

Site Investigator Signature _____ Date_____

Appendix G: Response Determination for Chronic GVHD Clinical Trials based on Clinician Assessments

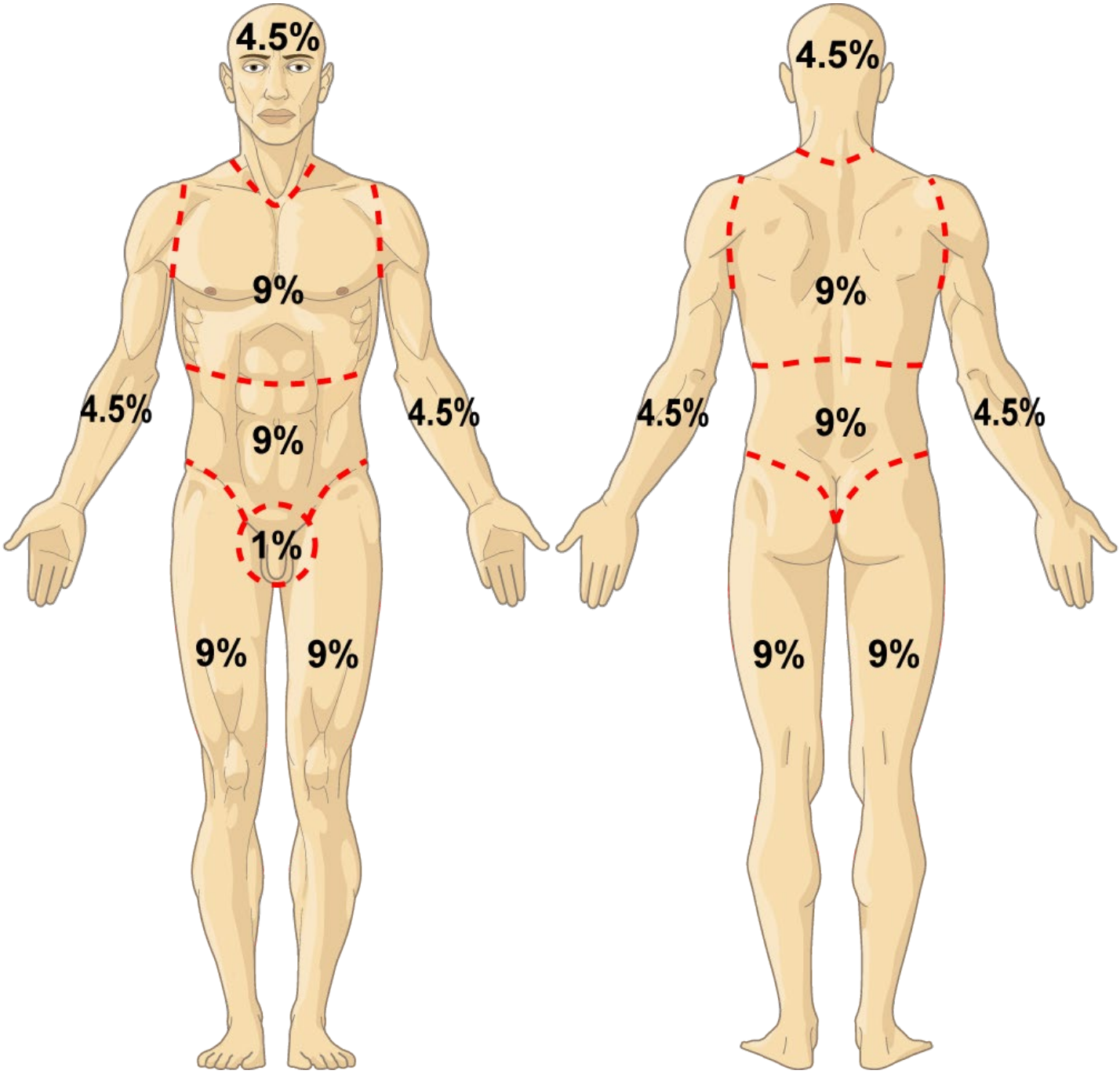
Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified OMRS 0 after previous involvement	Decrease in NIH Modified OMRS of 2 or more points	Increase in NIH Modified OMRS of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of 1 or more	Decrease by 50%	Increase by 2 × ULN
Lungs	- Normal %FEV1 after previous involvement - If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	- Increase by 10% predicted absolute value of %FEV1 - If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	- Decrease by 10% predicted absolute value of %FEV1 - If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least 1 measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0-10 scale	Clinician overall severity score increases by 2 or more points on a 0-10 scale

ULN indicates upper limit of normal.

Appendix H: NCI Common Toxicity Criteria Version 4.03 (CTCAE), Active Date: June 14, 2010

Toxicity will be scored using NCI CTC Version 4.03 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.03 can be downloaded from the CTEP homepage: (https://ctep.cancer.gov/). All appropriate treatment areas have access to a copy of the CTC Version 4.03.

Appendix I: Tool for Body Mapping



Source: https://www.qxmd.com/calculate/file_source_15/rule-of-nines

Appendix J: Dosing Diary

Ruxolitinib Dosing Diary

IRB#: 333-18 Subject ID: Subject Initials:

Study Drug Storage:
Store the drug at room temperature in a safe place that is out of reach of children.

Subject Instructions:
1. Complete one form for each month of treatment
2. Take Ruxolitinib tablets by mouth at the same time each day with a glass of water. It can be taken with or without food.
3. Wash hands thoroughly before and after handling Ruxolitinib. Only remove the number of tablets needed at the time of dosing AND do not remove extra tablets in advance of the next scheduled dose.
4. Record the date and the number of tablets you took each time.
5. DO NOT retake another dose if vomiting occurs after you have taken study drug.
6. If you have any side effects or other comments, please record them in the Comments section.
7. Bring this form and all used and unused medication to your doctor's visit.
8. DO NOT consume Grapefruit Juice while on this study drug.
9. Please talk to the study staff PRIOR to taking any new medications, including any supplements.

Total Daily Dose: mg Take # of tablet(s) in **AM** Take # of tablet(s) in **PM**

Date	# Tablets Taken		Comments
	AM Dose	**PM** Dose	

Date	# Tablets Taken		Comments
	AM Dose	**PM** Dose	

Date	# Tablets Taken		Comments
	AM Dose	**PM** Dose	

Date	# Tablets Taken		Comments
	AM Dose	**PM** Dose	