**Abbreviated Title:** Topical ruxolitinib in cGVHD

**CC Protocol #:** 18-AR-0035

**Version Date:** 01/25/2021

**NCT Number:** NCT03395340

**Title:** Phase II study of topical ruxolitinib for cutaneous chronic graft versus host disease (cGVHD)

**NIH Principal Investigator:** [redacted]

**Investigational Agents:**

| | |
|---|---|
| Drug Name: | Ruxolitinib |
| IND Number: | 136890 |
| Sponsor: | NIAMS |
| Manufacturer: | Incyte |

## PRÉCIS

**Background:**

- Chronic graft-versus-host disease (cGVHD) develops in approximately half of individuals who undergo allogeneic hematopoietic cell transplant (HCT) and is the leading cause of non-relapse mortality.
- There are no skin-targeted therapies for cutaneous cGVHD that are directed to the pathogenesis of cGVHD.
- Many inflammatory cytokines involved in the pathogenesis of cGVHD signal through the Janus kinase (JAK)-Signal Transducer and Activator of Transcription (STAT) pathway.
- Systemic JAK inhibitors have been studied in GVHD murine models and in humans with improvement at the cellular and clinical level.
- Topical JAK inhibitors have not been studied in cutaneous cGVHD, but have demonstrated the ability to decrease inflammatory markers as well as improve clinical findings of psoriasis.

**Objectives:**

- To determine the safety and tolerability of topical ruxolitinib 1.5% cream in patients with cutaneous cGVHD with epidermal involvement (non-sclerotic form)
- To determine the efficacy of topical ruxolitinib 1.5% cream in patients with cutaneous cGVHD with epidermal involvement (non-sclerotic form)

**Eligibility:**

Inclusion:

- Age ≥ 12 years old
- Histologically confirmed epidermal cGVHD (including lichen planus-like, papulosquamous, erythematous) involving at least 2 separate, non-ulcerated sites that can be delineated by body region (e.g. right forearm and left forearm)
- Stable systemic cGVHD treatment including immunosuppressant therapy for 4 weeks prior to enrollment
- Karnofsky or Lansky score ≥ 60%

Exclusion:

- Concurrent use of JAK inhibitors (topical or systemic), fluconazole, or strong CYP3A4 inhibitors
- Known hypersensitivity to JAK inhibitors or their components
- Active infection including CMV, EBV, HIV, HBV, and/or HCV
- Recurrent or progressive malignancy requiring anticancer treatment
- Patients receiving other investigational agents
- Pregnancy

**Design:**

- This is a Phase II, placebo-controlled, double-blinded study to determine the safety, tolerability and efficacy of topical ruxolitinib in patients with epidermal cGVHD.
- Participants with at least 2 non-ulcerated sites of epidermal cGVHD will apply topical ruxolitinib 1.5% cream to 1 prespecified site and vehicle cream to the second prespecified site twice a day for 6 weeks.
- Safety will be assessed according to CTCAE v5.0 criteria. Assessments will occur during visits and/or phone follow-up every 2 weeks during treatment.
- Efficacy will be assessed at 6 weeks. The initial surface areas of the 2 target lesions will be measured at baseline, week 2, and week 6 on evaluable patients, with the option for an in-person assessment at week 4. The percent decline in the surface area of the 2 lesions will be determined, and the difference in decline between the 2 lesions will be calculated, expressed consistently as ruxolitinib decline minus placebo decline.
- A skin biopsy and peripheral blood samples will be collected prior to treatment and at week 6 to evaluate the cutaneous immune compartment cellular infiltrate, cytokine profiling, STAT phosphorylation, gene expression profiling, and in situ cGVHD biomarkers.
- Pharmacokinetic studies will be performed at week 2.
- Up to 15 patients will be enrolled to achieve 10 evaluable patients, defined as participants who remain active at the time of the primary endpoint. 10 evaluable patients will provide 80% power to detect whether these paired differences in the changes from baseline are equal to one SD of the difference of the changes (effect size=1.0) using a two-tailed 0.05 significance level paired t-test. In practice, a Wilcoxon signed rank test may be used instead of a t-test if the differences are not consistent with a normal distribution ($p<0.05$ by a Shapiro-Wilks test).

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# 1 INTRODUCTION

## 1.1 STUDY OBJECTIVES

### 1.1.1 Primary Objective:

- To determine the safety and tolerability of topical ruxolitinib 1.5% cream in patients with cutaneous cGVHD with epidermal involvement (non-sclerotic form)
- To determine the efficacy of topical ruxolitinib 1.5% cream in patients with cutaneous cGVHD with epidermal involvement (non-sclerotic form) by calculating the percent decline in surface area involvement: ruxolitinib treated site decline minus the placebo treated site decline

### 1.1.2 Secondary Objectives:

- To determine the efficacy of topical ruxolitinib 1.5% cream on measures of disease activity in patients with epidermal cGVHD
- To describe pharmacokinetics and pharmacodynamics of topical ruxolitinib 1.5% cream in patients with epidermal cGVHD

### 1.1.3 Exploratory Objective(s)

- To characterize and analyze the effect of topical ruxolitinib 1.5% cream on inflammatory pathways in the skin and peripheral blood of patients with epidermal cGVHD using immunohistochemistry, and cytokine and gene expression studies

## 1.2 BACKGROUND AND RATIONALE

### 1.2.1 Chronic graft-versus-host disease

The Center for International Blood and Marrow Transplant Research estimates that as of 2013, over 8,000 allogeneic HCT are performed annually in the United States.(1) It is estimated that approximately one-half of allogeneic HCT recipients will develop cGVHD and the incidence is increasing.(2) After relapse of primary malignancy, cGVHD is the next leading cause of mortality in allogeneic HCT recipients.(3) cGVHD is a multisystem disorder characterized by immune dysregulation and impaired organ function including the lungs, gastrointestinal tract, liver, musculoskeletal system, and skin. The skin is the most commonly affected organ.

Cutaneous cGVHD has several manifestations which can involve the epidermis, dermis, and the subcutis.(4) Epidermal manifestations include erythema, papulosquamous lesions, and lichen planus-like lesions. Dermal and subcutaneous cGVHD result in skin thickening and tightness.(5) First-line therapy for cGVHD is systemic corticosteroids.(6) The side effects of corticosteroids are significant, including osteoporosis, avascular necrosis of the joints, hyperglycemia, hypothalamus-pituitary axis suppression, and increased risk of infection. Topical therapies that are available for cutaneous cGVHD include topical corticosteroids and topical calcineurin inhibitors.(7) Topical steroids also have significant side effects which can limit their use. The side effects include cutaneous atrophy, striae, infection, as well as risk of systemic side effects from absorption when

used over a large body surface area. There has been a paucity of targeted topical therapies for epidermal cGVHD.

### 1.2.2 JAK-STAT pathway in cGVHD

The JAK-STAT pathway is a signaling pathway for many cytokines, including several that are implicated in the pathogenesis of cGVHD such as IFNγ, common γ-chain cytokines, and IL-6. Of the four JAKs, JAK 1 and JAK2 are important in the signaling of relevant cytokines including IFNγ, TNFα, IL-1, IL-2, IL-6, IL-12, and IL-23. Studies have provided preclinical data to support the importance of the JAK-STAT pathway in the management of acute and chronic GVHD.(8-12) Choi *et al.* demonstrated that INCB018424 (ruxolitinib) reduced expression of CXCR3, a chemokine receptor important in T-cell trafficking to cGVHD target organs, and resulted in lower clinical GVHD score compared to placebo treated mice (Figure 1).(10)

**Figure 1:** Administration of INCB018424 for one month decreased the clinical GVHD score compared with DMSO treated mice.

Spoerl *et al.* studied a murine model of acute GVHD in which they demonstrated that phosphorylation and activation of STAT3, a transcription factor activated by JAK tyrosine kinase phosphorylation, was inhibited by ruxolitinib.(12) They also demonstrated that Treg cells were increased in the spleens of mice (Figure 2) and $CD4^+IFN\gamma^+$ cells were decreased (Figure 3) in the ileum of mice treated with ruxolitinib, findings that are consistent with improvement in cGVHD.

**Figure 2:** Absolute number of Treg cells in the spleen of mice on day 8, 14, and 29 of treatment with vehicle or ruxolitinib

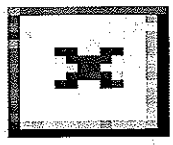

**Figure 3:** CD4+ IFNγ+ T cells from the ileum of vehicle-treated versus ruxolitinib-treated mice

1.2.3 Ruxolitinib

Ruxolitinib is a JAK inhibitor which is FDA approved in an oral formulation for treatment of myelofibrosis and polycythemia vera. A topical formulation has been studied in humans with psoriasis, alopecia areata, atopic dermatitis (AD), vitiligo and other inflammatory diseases. Ruxolitinib is a potent, reversible inhibitor of JAK1 ($IC_{50}$ = 1.68 nM) and JAK2 ($IC_{50}$ = 0.35 nM), with modest to marked selectivity against TYK2 ($IC_{50}$ = 2.80 nM) and JAK3 ($IC_{50}$ = 4.75 nM).(*13*) In cellular assays, INCB018424 inhibits JAK signaling and function in peripheral blood mononuclear cells and isolated T cells. Signaling of multiple inflammatory cytokines, including IL-6, IL-12, and IL-23, is inhibited at concentrations ≤ 100 nM. INCB018424 inhibits IL-2-induced proliferation of T-cells and cytokine-induced production of inflammatory factors such as IL-17, IL-22, and MCP-1. INCB018424 also inhibits cytokine mediated signaling in keratinocytes. Studies have demonstrated inhibition of IFNγ-induced upregulation of chemokines and expression of intercellular adhesion molecule 1 (ICAM-1) and IFNγ-induced STAT1 phosphorylation in these cells.

Oral ruxolitinib has been studied in GVHD. Spoerl *et al.*(12) first reported ruxolitinib in patients with GVHD in *Blood* in 2014. Six patients with GVHD, 2 with cGVHD, were treated with ruxolitinib. Both cGVHD patients had only skin involvement and both experienced a response within 1 week (Figure 4) and systemic corticosteroids were reduced in both patients.

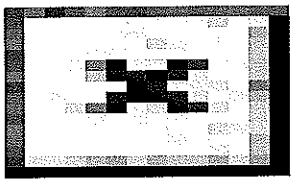

**Figure 4:** Patient with cutaneous, epidermal cGVHD shown before and 1.5 weeks after ruxolitinib. There is resolution of erythema and scale.

Khoury *et al.*(14) presented a poster abstract describing oral ruxolitinib treatment of 16 patients with cGVHD of different organs. All 16 patients had cutaneous involvement. They described complete response in the patients who had nonsclerotic, erythematous cutaneous cGVHD. Median response time was 14 days. 10/16 patients were able to discontinue corticosteroids and 2 patients decreased the dose to physiologic levels.

In the largest published report to date, Zeiser *et al.*(15) described 41 adult patients with cGVHD treated with systemic ruxolitinib. Overall response rate was 85% (35/41), including 32 partial responses and 3 complete responses (Figure 5). The median time to response was 3 weeks (range 1-25 weeks) after initiating ruxolitinib. Responses were seen in all organ systems involved. 7% experienced Grade 3 or 4 cytopenia, 14% had CMV reactivation, and 1 patient had a relapse of the primary malignancy. This retrospective study included patients with any organ involvement of moderate to severe severity.

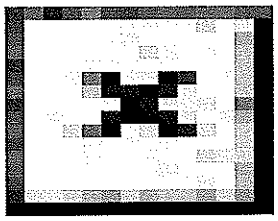

**Figure 5:** Patient with cutaneous cGVHD with epidermal involvement shown before and 3 weeks after ruxolitinib demonstrating significant improvement in scale and erythema.

Topical ruxolitinib has not been reported in GVHD, but it has been studied in psoriasis, alopecia areata atopic dermatitis (AD), vitiligo and other inflammatory diseases. (13, 16-19) At time of review, 11 clinical studies have been completed in the ruxolitinib cream clinical development program (5 studies in healthy participants, 3 studies in participants with psoriasis, 1 study in participants with alopecia aerata (AA), and 2 studies in participants with AD) and 6 studies are ongoing (3 studies in participants with AD, and 3 studies in participants with vitiligo). Safety was demonstrated, with no serious cutaneous toxicities noted. There was minimal systemic absorption, suggesting a decreased risk of AEs identified with systemic use of ruxolitinib, such as cytopenias. In the cGVHD population, this is particularly important as patients with cGVHD may have cytopenias at baseline and cannot tolerate further decline in hematopoietic cell lines. Efficacy of topical ruxolitinib was evaluated in the 3 studies. Figure 6 demonstrates a decrease in erythema, thickness, and scale of psoriatic plaques during a 28-day period of treatment with 1.5% ruxolitinib cream.(18)

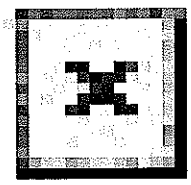

**Figure 6:** Individual components (erythema, thickness, scaling) of the total Lesion Scores in study of INCB018424 phosphate 1.5% cream twice a day.

# 2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

## 2.1 ELIGIBILITY CRITERIA

### 2.1.1 Inclusion Criteria

- Patients must have histologically confirmed epidermal cGVHD including lichen planus-like, papulosquamous, and erythematous cGVHD with clinical involvement at 2 separate body regions (e.g. right forearm and left forearm).
- Patients must have measurable disease, defined as at least 2 areas of cutaneous, nonulcerated, epidermal cGVHD involvement. Each site must involve at least 0.5% body surface area (1 palm equivalent) and cannot be a site of current or previous nonmelanoma skin cancer (NMSC).
- Stable immunosuppressant or immunomodulatory systemic cGVHD treatment, including phototherapy and extracorporeal photopheresis, for 4 weeks prior to enrollment.
- Age $\geq$ 12 years. There is no available safety or adverse events data available for children younger than 12 years of age.
- Karnofsky or Lansky $\geq$ 60, see APPENDIX A.
- Patients must have normal organ and marrow function as defined below:

| | |
|---|---|
| – absolute neutrophil count | $\geq$1,000/mcL |
| – platelets | $\geq$50,000/mcL |
| – hemoglobin | > 9 g/dL |
| – total bilirubin | <1.5X institutional upper limit of normal except if known history of Gilbert's disease |
| – AST(SGOT)/ALT(SGPT) | $\leq$5X institutional upper limit of normal |
| – creatinine clearance | $\geq$50 mL/min/1.73 $m^2$ for patients with creatinine levels above institutional normal. |

- Willingness to comply with twice daily application of 2 different creams to 2 separate, prespecified sites.
- The effects of ruxolitinib on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
- Ability of subject or Legally Authorized Representative (LAR) to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

- Patients concurrently receiving a JAK inhibitor (topical or systemic).
- Patients receiving any other investigational agents.
- Patients concurrently taking oral fluconazole.
- Patients concurrently taking strong CYP3A4 inhibitors (APPENDIX B)
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to ruxolitinib or other agents used in study.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection including EBV, CMV, HIV, HBV, and HCV, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Pregnant women are excluded from this study because ruxolitinib is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ruxolitinib, breastfeeding should be discontinued if the mother is treated with ruxolitinib. These potential risks may also apply to other agents used in this study.
- Recurrent or progressive malignancy requiring anticancer treatment.
- Other cancer (except that for which HCT was performed) within 2 years of study entry, except nonmelanoma skin cancer or carcinoma in situ of the breast, uterus, or cervix.
- History of cutaneous malignancy at target lesion site.
- Any participant who, in the investigator's opinion, would be unable to comply with study requirements or for whom participation may pose a greater medical risk.

2.1.3 Recruitment Strategies

Participants, including under-represented minorities, will be recruited for this study through the well-established NIH cGVHD multidisciplinary study group and its referral network. Patients who undergo HCT at NIH will be eligible as well. Recruitment will also occur through professional societies and patient advocacy forums.

### 2.1.4 Compensation

Cost associated with screening will not be reimbursed. Once consent is obtained, this study will assist with air or train travel through a government approved contractor. Mileage will be compensated per NIH guidelines. For long distance travelers, meals will be compensated per NIH guidelines. Lodging maybe provided through the Children's Inn or Safra Lodge, if space permits. If not available, we will provide compensation toward local lodging per NIH guidelines.

## 2.2 SCREENING EVALUATION

Screening procedures may be performed on a screening protocol, including 04-C-0281, "Natural History of Chronic GVHD," or 96-AR-0102, "Evaluation and Treatment of Subjects with Dermatologic Diseases".

All screening studies must be completed within 4 weeks prior to enrollment except where stated otherwise:

- History and physical examination including Karnofsky or Lansky performance status
- Skin biopsy to confirm diagnosis of epidermal cGVHD within 3 months of enrollment
- Laboratory studies:
    - CBC and differential
    - Blood urea nitrogen and serum creatinine
    - Hepatic function panel
    - Serum b-hCG in women of childbearing potential. Not required for women who are status-post hysterectomy or postmenopausal (no menses for > 1 year)
- Infectious studies:
    - Anti-HIV 1/2 antibody
    - HBsAg and anti-HCV antibody
    - CMV PCR
    - EBV PCR

For baseline evaluations, please see Section 2.4.

## 2.3 REGISTRATION PROCEDURES

The eligibility checklist is to be completed at study entry by the PI or MAI. The protocol research nurse will file the checklist in the participants research study binder.

## 2.4 BASELINE EVALUATION

The following baseline studies will be performed within one week of starting the study drug:

- History and physical examination, including Karnofsky or Lansky performance status
- Documentation of cGVHD diagnosis per 2014 NIH criteria, NIH organ and global score (APPENDIX C & APPENDIX D), date of cGVHD diagnosis, prior and current treatments including topical agents, prednisone or other steroid dose, and other patient, donor, and transplant characteristics

- Clinical examination of all cutaneous cGVHD with the following for the target epidermal cGVHD sites: measurement with a ruler or calipers, transparency tracing, automated photographic measurement, clinical photography, and completion of the Physician Global Assessment (PGA) (APPENDIX E)
- Laboratory studies:
  - CBC and differential
  - Blood urea nitrogen and serum creatinine
  - Hepatic function panel
  - Serum b-hCG in women of childbearing potential. Not required for women who are status-post hysterectomy or postmenopausal (no menses for > 1 year)
- Infectious studies:
  - CMV PCR
  - EBV PCR
- Patient-reported outcome (PRO) surveys completed for each of the 2 target lesion sites: Overall disease severity visual analog scale (VAS), pruritus VAS, pain VAS (APPENDIX F)
- Research blood samples
- Total body photography performed at the investigator's discretion

# 3 STUDY IMPLEMENTATION

## 3.1 STUDY DESIGN

This is a phase II, placebo controlled study to evaluate the safety, tolerability, and efficacy of 1.5% topical ruxolitinib cream, INCB018424, in patients with epidermal cGVHD. Case series and anecdotal reports of systemic JAK inhibitors in cGVHD have suggested a benefit for cGVHD involvement of the skin and other organs, warranting further study. For patients with cGVHD that manifests with primarily epidermal skin disease, effective topical therapy is desirable. Current topical therapies (corticosteroids and calcineurin inhibitors), can have significant side effects and are not specific to the disease pathology.

In this study, patients with a minimum of 2 distinct areas of involvement with intact (no ulceration) epidermal cGVHD that has been confirmed histologically, will be eligible for participation. Each participant will receive active study agent and placebo. Chronic GVHD is a heterogeneous disease with a waxing and waning course. Given the heterogeneity and the natural history of this disease as well as use of concurrent systemic medications, each participant will serve as his/her own control to allow for better comparison of placebo and active study drug. Randomization table generated by Seth Steinberg, statistician, will be provided to the pharmacy, such that the labeling of placebo and active study drug as container A and B will be randomized at the pharmacy. All participants will be provided with active study drug to apply to the designated affected area (maximum application BSA of 10%) twice a day and a second container containing a vehicle cream to be applied twice a day on a second affected area. Subjects who experience dose limiting toxicities (DLT) will have the dose adjusted as described in Section 3.1.1.

Participants will be evaluated in-person at baseline, at week 2 (+/- 3 business days), and at week 6 (+/- 3 business days). Clinical examination including surface area measurements, transparency tracing, photography for automated measurement, PGA score, clinical photographs, blood draw, and completion of PRO surveys will occur at the baseline visit. During the week 2 visit there will be an assessment for response and AEs. This visit will include surface area measurements, transparency tracing, photography for automated measurement, PGA score, clinical photographs, blood draw, and completion of PRO surveys. Pharmacokinetic studies will be conducted at this visit as well. Patients will either be seen in-person or receive a phone call from the study team (at the physician's discretion) at week 4 to assess AEs and for those seen in-person, assessment of response. Clinical examination including surface area measurements, transparency tracing, photography for automated measurement, PGA score, clinical photographs, blood draw, and completion of PRO surveys will occur for those who have an in-person visit at week 4. All participants will be evaluated in-person at week 6 (+/- 3 business days) for primary outcome assessment. Clinical examination including surface area measurements, transparency tracing, photography for automated measurement, PGA score, clinical photographs, and blood draw will occur during this visit. Patient will complete the PRO surveys at this visit. Patients will receive a follow up call at week 12 (+/- 4 weeks).

With the patient's or LAR's consent, at the discretion of the investigator, a skin biopsy for research will be taken from each treated site at week 6. The effect of ruxolitinib on the histologic findings of cGVHD in the epidermis, as well as the impact on the cutaneous cellular infiltrate, cytokine profile, STAT phosphorylation, gene expression profile (including lymphocyte receptor sequencing) and cGVHD biomarkers will be compared with the placebo treated site as well as the biopsy obtained during screening if available. Corresponding experiments may be done on peripheral blood mononuclear cells and serum samples to compare with the skin biopsy data when appropriate.

### 3.1.1 Dose Limiting Toxicity

DLT will be defined as any grade $\geq 3$ adverse event which is thought to be probably or definitely related to the investigational drug. Grade 3 toxicities that resolve within 72 hours to $\leq$ grade 1 with supportive care (e.g. pruritus, nausea, vomiting, fatigue, diarrhea) will not be counted as DLTs. Study drug and placebo will be held until resolution of any grade $\geq 3$ adverse event. If 2 subjects experience a grade 3 AE probably or definitely attributable to the study drug, the study will be stopped for safety review. In patients that have experienced disease progression, further dosing will cease in a patient at the occurrence of the first DLT. All patients will be evaluable for toxicity from the time of their first treatment with topical ruxolitinib until the end of study participation, regardless of inclusion in primary response evaluation.

## 3.2 Drug Administration

Topical ruxolitinib cream and vehicle cream will be supplied by Incyte in containers labeled with a perforated label as active study drug or placebo. The pharmacy will remove the perforated label and apply a label containing site of administration as well as label A or B according to the randomization table. Participants will be carefully instructed regarding the site of application of each cream. Neither the study drug nor the vehicle cream should be applied to areas of skin with ulceration. Participants will be provided with photographs of the body site to apply each cream as a guide at home for application. Application will be twice a day (12 hours apart) for 6 weeks.

Application should occur at approximately the same time each day and at least 2 hours before showering/bathing. Participants should wear gloves when applying cream. A new pair of gloves should be used when applying cream to the second site. This will minimize the possibility of cross contamination. Medication and vehicle cream will be applied as a thin layer. Patients will be asked to complete a medication diary (APPENDIX G).

If a dose is missed, it should be applied as soon as possible on the same day unless it is within 1 hour of the next dose. If it is within 1 hour of the next dose, the missed dose should not be applied. Missed doses will not be reported to the IRB as a protocol deviation unless the patient misses > 5 doses per month.

During application of the study drug and the vehicle, care should be taken to avoid the eyes and mouth. If study drug or vehicle are ingested, study staff should be contacted immediately. If the cream is applied to the participant's body by a pregnant individual, that individual should use gloves and a wooden applicator to apply the creams on to the participant.

### 3.3 DOSE MODIFICATIONS

**Table 1: Dose Modifications**

All dose modifications will be discussed with the PI or MAI.

| Adverse event | CTCAE grade/attribution | Protocol Action |
|---|---|---|
| Any adverse event (excluding ulceration, infection, treatment-related malignancy) | Grade 2 >7 days that is probably or definitely related to study drug. | Hold study drug; *If AE resolves to ≤ grade 1 or baseline within 7 days: resume dose. ** If AE does not resolve to ≤ grade 1 or baseline within 7 days: patient comes off drug. |
| Any adverse event (excluding ulceration, infection, treatment-related malignancy) | Same grade 2 >7 days recurs that is probably or definitely related to study drug. | Hold study drug; *If AE resolves to ≤ grade 1 or baseline within 7 days: decrease dose to once daily. **If AE does not resolve to ≤ grade 1 or baseline within 7 days: patient comes off drug. |
| Any adverse event (excluding ulceration, infection, treatment-related malignancy) | Same grade 2 >7 days recurs after dose reduction that is probably or definitely related to study drug. | Patient comes off drug. |
| Any adverse event (excluding ulceration, | Grade 3 that is probably or definitely related to study drug. | Hold study drug; *If AE resolves to ≤ grade 1 or baseline within 7 days: |

| | | |
|---|---|---|
| infection, treatment-related malignancy) | | decrease dose to once daily. **If AE does not resolve to ≤ grade 1 or baseline within 7 days: patient comes off drug. |
| Any adverse event (excluding ulceration, infection, treatment-related malignancy) | Same grade 3 recurs after dose reduction that is probably or definitely related to study drug. | Patient comes off drug. |
| Any adverse event (excluding ulceration, infection, treatment-related malignancy) | Grade 4 that is probably or definitely related to study drug. | Patient comes off drug. |
| Skin ulceration at treatment site | Any grade | Patient comes off drug. |
| Infection | Grade 2 that is probably or definitely related to study drug. | Hold study drug until completion of systemic antibiotic course and resolution of infection, then restart at same dose level. |
| Infection | Grade 2 recurs that is probably or definitely related to study drug. | Hold study drug until completion of systemic antibiotic course and resolution of infection, then decrease dose to once daily. |
| Infection | Grade 2 recurs after dose reduction that is probably or definitely related to study drug. | Patient comes off drug. |
| Infection | Grade 3 that is probably or definitely related to study drug. | Patient comes off drug. |
| Infection | Grade 4 | Patient comes off drug. |
| Treatment-related malignancy | Grade 3 | Patient comes off drug. |
| Treatment-related malignancy | Grade 4 | Patient comes off drug. |

Exceptions to the above treatment modifications:
1. Alopecia any grade

2. Dry skin any grade
3. Grade 2 skin or soft tissue infection at untreated site
4. Grade 2 paronychia

Doses withheld while recovering from an adverse event should not be made up.

### 3.4 QUESTIONNAIRES

The following scales will be administered twice at each indicated time point to independently assess the 2 treatment sites.

1. Pruritus Visual Analog Scale (VAS) is a self-administered psychometric response instrument which measures subjective characteristics or attitudes that cannot be directly measured. It ranges from 0-10. This scale has been used for measurement in a variety of dermatologic settings. This questionnaire will be administered at baseline, week 2, week 4 (for participants who come for an in-person study visit), and week 6. (1 minute)
2. Skin Pain VAS is a self-administered psychometric response instrument which measures subjective characteristics or attitudes that cannot be directly measured. It ranges from 0-10. This scale has been used for measurement in a variety of dermatologic settings. This questionnaire will be administered at baseline, week 2, week 4 (for participants who come for an in-person study visit), and week 6. (1 minute)
3. Overall Disease Severity VAS is a self-administered psychometric response instrument which measures subjective characteristics or attitudes that cannot be directly measured. It ranges from 0-10. This scale has been used for measurement in a variety of health settings. This questionnaire will be administered at baseline, week 2, week 4 (for participants who come for an in-person study visit), and week 6. (1 minute)

### 3.5 FOLLOW-UP

All persons will be followed for SAEs for 14 days after last application of topical ruxolitinib. All participants, including those who discontinue therapy for any reason, will receive a follow-up phone call 6 weeks (+/- 4 weeks) after discontinuation of topical ruxolitinib (week 12). The phone call will focus on a) survival status and cause of death if applicable, b) ongoing topical and/or systemic treatment for cGVHD and date of discontinuation, c) primary malignancy progression, d) any second primary malignancy, e) return to work part-time or full-time. Primary and contributing causes of death are to be recorded in the CRF and the patient's medical record.

### 3.6 STUDY CALENDAR

**Table 2: Study Calendar**

| *Procedure* | *Screen* | *Baseline* | *Week 2* | *Week 4* | *Week 6* | *Follow-up Week 12* |
|---|---|---|---|---|---|---|
| Visit window | *(D -28 to -1)* | | ± 3 bus. days | | ± 3 bus. days | ± 4 weeks |
| Informed consent | *X* | | | | | |

| *Procedure* | *Screen* | *Baseline* | *Week 2* | *Week 4* | *Week 6* | *Follow-up Week 12* |
|---|---|---|---|---|---|---|
| Visit window | *(D -28 to -1)* | | ± 3 bus. days | | ± 3 bus. days | ± 4 weeks |
| Ruxolitinib and placebo cream BID | | X | X | X | | |
| History and PE | X | X | X | * | X | |
| Vital signs | X | X | X | * | X | |
| Karnofsky or Lansky performance Score | X | X | X | | X | |
| PGA score | | X | X | * | X | |
| cGVHD diagnosis assessment (2014 NIH Criteria) | | X | | | X | |
| Labs: | | | | | | |
| CBC + differential | X | X | X | * | X | |
| BUN + Creatinine | X | X | X | * | X | |
| Hepatic Panel | X | X | X | * | X | |
| Serum b-hCG[1] | X | X | X | * | X | |
| HIV 1/2 antibody | X | | | | | |
| HBsAg | X | | | | | |
| Anti-HCV antibody | X | | | | | |
| CMV and EBV PCR | X | X | X | * | | |
| Surface area measures | | X | X | * | X | |
| Clinical photography | | X | X | * | X | |
| Skin biopsies | X | | | | * | |
| Total body photography | | * | * | * | * | |
| Correlative Research Studies | | X | | | X | |
| Pharmacokinetics | | | X | | | |
| Response Evaluation: Overall disease severity VAS, Pruritus VAS, Pain VAS | | X | X | * | X | |
| Adverse Events | | | X | X | X | X |
| Concomitant Medications | X | X | X | X | X | X |
| Study drug dispensation/ return/accountability | | X | X | * | X | |

*Optional

[1]Only in women of childbearing potential age. Exceptions include women status-post hysterectomy or in menopause > 1 year since last menstrual period.

### 3.7 SURGICAL GUIDELINES

A skin biopsy will be obtained during screening (may be performed at an outside facility) to confirm epidermal cGVHD. At week 6, skin biopsies will be obtained from the 2 treated sites at the investigator's discretion. Skin biopsy procedure will be explained to the patient and informed consent will be obtained.

The risk of infection, scarring, nerve damage, pigment change, numbness, bleeding, pain, and allergy to anesthesia will be reviewed. The biopsy site will be locally anesthetized. Size of punch biopsies will be up to 6mm. One punch biopsy will be performed from each of the 2 treatment sites. Sutures will be placed for hemostasis. Petrolatum and bandage will be applied to the wound site and wound care will be reviewed. Written wound care instructions will be given. We will instruct the patient regarding suture removal.

### 3.8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.8.1 Criteria for removal from protocol therapy

- Completion of 6-week protocol therapy
- Progressive disease in skin or other organ system requiring an increase or change in systemic therapy
- Participant requests to be withdrawn from active therapy
- Unacceptable toxicity as defined in Section 11.1.2
- Investigator discretion
- Pregnancy

3.8.2 Off-Study Criteria

- Completion of study follow-up period
- Participant requests to be withdrawn from study
- Death

## 4 CONCOMITANT MEDICATIONS/MEASURES

All prescription and nonprescription medications, including topical agents, used during the study period will be recorded on the appropriate pages of the CRF. Patients will be advised to contact the study team prior to initiating any new medication.

### 4.1 CONCOMITANT CORTICOSTEROID THERAPY

Participants may remain on systemic corticosteroids during the course of the 6-week study at a stable or tapering dose. If a pulse of corticosteroids is required for cutaneous or other organ cGVHD, the patient will be withdrawn from the study. Topical corticosteroids may not be used for the duration of this study.

### 4.2 OTHER TREATMENTS FOR cGVHD

- Other systemic treatments such as calcineurin inhibitors (tacrolimus or cyclosporine), sirolimus, mycophenolate mofetil, or other immunosuppressants must be maintained at a stable or tapering dose. Dose adjustments based on drug interactions or maintaining therapeutic drug level will be permitted.
- Patients cannot initiate new immunosuppressant or immunomodulatory therapeutic interventions, including extracorporeal photopheresis or phototherapy, during the 6 weeks of the study.
- Patients cannot apply topical medications, prescription or nonprescription, besides the study drugs for the duration of this study. All topical therapies, except emollients, should be discontinued at least 1 week prior to start of therapy.

## 5 BIOSPECIMEN COLLECTION

### 5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

#### 5.1.1 Skin biopsy

A skin biopsy will be obtained during screening and 2 skin biopsies will be obtained at week 6, at the discretion of the investigator, one from each of the 2 treatment sites. Skin biopsies will be bisected and a section will be sent to the Laboratory of Pathology in formalin for histologic assessment with hematoxylin and eosin stain. Unstained slides will be made for immunohistochemical studies to evaluate the T-cell infiltrates, IFN-induced transcription markers, pSTAT, and myofibroblast and pericyte markers. The additional tissue will either be placed in OCT and processed, stored, and analyzed at the ETIB pre-clinical core and/or in John O'Shea's lab or will be immediately processed for single cell RNA sequencing (gene expression and lymphocyte receptor sequencing) in the Dermatology Branch.

#### 5.1.2 Immunologic assays from blood

Peripheral blood will be obtained for immunologic assays. Heparinized plasma will be assayed for BAFF, CXCL9, CXCL10, IL-6, TNFa, and other IFN-induced chemokines. Whole blood will be collected for flow cytometry of lymphocyte populations. Changes in CD3, CD4, CD8, B cells, and NK cells will be assessed at baseline compared to week 6 in the Clinical Center's CLIA certified immunophenotyping lab. Additional assessments of regulatory, naïve, memory and effector T cells will be performed in the ETIB Preclinical Core lab. Single cell RNA sequencing, including lymphocyte receptor sequencing, may be done from peripheral blood in the Dermatology Branch.

#### 5.1.3 Measurement of ruxolitinib serum levels

Blood samples for the determination of plasma levels of ruxolitinib will be obtained from each patient via 6mL sodium heparin tube (BD, Franklin Lakes, NJ) collected during the first follow up visit, 2 weeks after commencement of twice daily topical treatment of a 1.5% cream formulation. A pre-dose trough sample will be collected just prior to application of the treatment on the day of their follow-up visit. After application in clinic, blood samples will be collected at 1hr, 2hr, and 4hr to understand the rate and extent of systemic exposure. Bioanalytical measurements will be

conducted on an ultra HPLC-MSMS system using an assay developed and validated by the Blood Processing Core.

This data will be used to monitor ruxolitinib plasma concentrations in order to primarily understand the rate and extent of systemic exposure of ruxolitinib from a 1.5% strength topical cream applied to skin affected with epidermal cGVHD. Secondarily, these plasma measurements can also be used to correlate to pharmacodynamic endpoints, clinical response, and toxicity.

The samples will be placed immediately on wet ice and refrigerated. The date and exact time of each blood draw should be recorded on the sample tube and the PK sheet.

Please e-mail [redacted] at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, [redacted].

For immediate help, [redacted]).

For questions regarding sample processing, contact [redacted]. Upon arrival in the Blood Processing Core (BPC), samples will be centrifuged and the plasma transferred into cryovials for storage at -80°C until the time of analysis. In addition, samples will be barcoded as described in Section 5.2.2.

**Table 3: Research Blood**

| **Test/assay** | **Volume blood (approx.)** | **Type of tube** | **Collection point (+/- 48hrs)** | **Location of specimen analysis** |
|---|---|---|---|---|
| Immunemonitoring | 48 mls (baseline) 48 mls (week 6) | 6 Sodium heparin | Baseline, Week 6 | ETIB Preclinical Core lab |
| PK (pre & post at week 2) | 12 mls (4 draws) | Sodium heparin | Week 2 | Dr. Figg's lab |
| Flow cytometry for regulatory, naïve, memory and effector T cells | 3 ml | 1 EDTA | Baseline, Week 6 | ETIB Preclinical Core lab |
| Immunophenotyping panel (CD3, CD4, CD8, B cells, and NK cells) | 3ml | 1 EDTA | Baseline, Week 6 | Clinical Center CLIA certified lab |
| RNA sequencing | 10ml | Sodium heparin | Week 6 | Dermatology Branch |

### 5.1.4 Machine learning imaging process

Through a collaboration with Dr. Eric Tkaczyk at Vanderbilt University Medical Center, we will share de-identified clinical images of cGVHD skin lesions taken with both 2D and 3D cameras to build a repository necessary for training a machine to identify cutaneous cGVHD. The images will be used to determine a set of parameters and variations on optical assessments which collectively assess skin optical properties at an equivalent or superior level to subjective dermatologic exam.

## 5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

### 5.2.1 ETIB Procedures

Blood and tissue samples, collected for the purpose of research under IRB-approved protocols will be stored and may be archived by the ETIB Preclinical Service, with the exception of blood samples for ruxolitinib analysis, which will be stored separately by the Blood Processing Core (BPC) until analysis. Any RNA or cDNA generated during the research process may be archived by the ETIB Preclinical Service. All data associated with archived clinical research samples is entered into the ETIB Preclinical Service's Microsoft Excel databases on frozen cells and plasma. These databases are stored on the NCI group drive in the ETIB Preclinical Service folder. Access to this folder is limited to ETIB clinical staff, requiring individual login and password. All staff in the Preclinical Service laboratory have received annually updated NIH/CIT training and maintain standards of computer security.

The data recorded for each sample includes the patient ID, name, trial name/protocol number, date drawn, treatment cycle/post-transplant time point, cell source (e. g. peripheral blood or skin biopsy) as well as box and freezer location. Patient demographics that correlate treatment outcomes and therapies with the samples can be obtained only through the NCI/ETIB clinical records or C3D. All samples currently receive a unique bar code number, which is included in the Preclinical Service Stored Sample database. Only this bar code will be recorded on the sample vial, and the vials will not be traceable back to patients without authorized access to the Preclinical Service database.

Samples are stored in locked freezers at -85°C (sera, plasma, RNA and cDNA) or under liquid nitrogen (cells), according to stability requirements. These freezers are located onsite at the ETIB Preclinical Service laboratory (12C216). Access to samples from a protocol for research purposes will be by permission of the Principal Investigator of that protocol or through his/her submission and IRB approval of the NIH IRB Authorization Form stipulating whether IRB review is not necessary or IRB approval is granted for the pursuit of this new research activity. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with objectives of the original protocol for which the samples were collected, or (using only unlinked or coded samples) for an IRB-approved protocol as stipulated on the IRB Authorization Form, and that any unused samples must be returned to the Preclinical Service laboratory.

#### 5.2.1.1 Protocol Completion/Sample Destruction

Once primary research objectives for the protocol are achieved, researchers can request access to remaining samples, providing they have both approval of the Principal Investigator of the original

protocol under which the samples or data were collected and either an IRB-approved protocol and patient consent or the IRB Authorization Form stipulating that the activity is exempt from IRB review. Samples, and associated data, will be stored permanently unless the patient withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to the Preclinical Service laboratory.

If a patient withdraws consent, the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved. The Preclinical Service staff will report to the Principal Investigators any destroyed samples, if samples become unsalvageable because of environmental factors (e.g., broken freezer or lack of dry ice in a shipping container), lost in transit between facilities or misplaced by a researcher. The Principal Investigators will annually report this information to the IRB. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB and the NIAMS Clinical Director.

### 5.2.2 Blood Processing Core

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts. Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

#### 5.2.2.1 Sample Storage and Destruction

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per IRB approved protocol) and that any unused samples must be returned to the BPC.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

Sample barcodes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the LABrador. It is critical that the sample remains linked to patient information such as race, age,

dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed and reported as such to the IRB. The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. Broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB and the NIAMS Clinical Director.

# 6 DATA COLLECTION AND EVALUATION

## 6.1 DATA COLLECTION

All data will be entered into C3D using predesigned CRFs. The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. Complete records will be maintained on each patient including the medical record with any supplementary information obtained from outside laboratories or physician's records. These records are the primary source documents that form the basis for the research record and will be uploaded in CRIS. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for 30 days after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

**End of study procedures:** Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

**Loss or destruction of data:** Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

6.1.1 Adverse Events

Grade 1 adverse events will not be collected on this protocol.

## 6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

**What data will be shared?**

I will share human data generated in this research for future research as follows:

_X__ De-identified data in an NIH-funded or approved public repository.

_X__ De-identified data in BTRIS (automatic for activities in the Clinical Center)

_X__ De-identified or identified data with approved outside collaborators under appropriate agreements.

**How and where will the data be shared?**

Data will be shared through *(check all that apply):*

_X__ An NIH-funded or approved public repository, i.e., www.clinicaltrials.gov.

_X__ BTRIS (automatic for activities in the Clinical Center)

_X__ Approved outside collaborators under appropriate individual agreements.

_X__ Publication and/or public presentations.

**When will the data be shared?** *(check all that apply)*

_X__ Before publication.

_X__ At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

## 6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response at week 2 and week 6.

6.3.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with topical ruxolitinib.

Evaluable for objective response: Patients who complete 6 weeks of treatment will be evaluable for the primary endpoint of efficacy. Patients who have progression of the skin disease earlier will also be included in the analysis of efficacy.

### 6.3.2 Disease Parameters

Measurable disease: Measurable lesions are defined as areas that are clinically consistent with epidermal cGVHD that are at least 8cm (or approximately 1 palm size for children) in shortest diameter.

Target lesions. Two areas of measurable disease that are on separate body regions (e.g. right arm and left arm) at least 10 cm apart, amenable to topical application of medicine will be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), and be representative of the morphology of epidermal cGVHD present in the patient, be nonulcerated, show no evidence of cutaneous infection, show no evidence of current or prior NMSC, and in addition should be sites that lend themselves to reproducible repeated measurements.

### 6.3.3 Methods for Evaluation of Measurable Disease

All measurements will be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 1 week before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical examination: Clinical photographs, photographs for automated measurements, and transparency tracing will be used at each visit for accurate measurements of the target areas of affected skin. Surface area of each target lesion will be calculated. An overall Physicians Global Assessment score will be documented at each visit.

### 6.3.4 Response Criteria

#### 6.3.4.1 Evaluation of Target Lesions

No definition of response exists for epidermal cGVHD. The 2014 Response Criteria Working Group of the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease recommended a scoring system (0-3) for cutaneous GVHD that takes into account total BSA for cutaneous cGVHD findings, depth of sclerotic cGVHD, and presence of ulceration.(20) This scoring system cannot be used for our purposes, as such there is no validated or defined scale and response criteria for epidermal cGVHD.

This pilot study will evaluate the percent decline surface area after 6 weeks of treatment with topical ruxolitinib cream and vehicle cream to define a clinically relevant difference. This will potentially define a response criteria to be used for a subsequent, larger trial of topical ruxolitinib for epidermal cGVHD.

### 6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

## 7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

### 7.1 DEFINITIONS

Please refer the Policy 801 for definitions of reportable events.

### 7.2 EXPEDITED REPORTING TO NIH INTRAMURAL IRB

Please refer to the Policy 801 for expedited reporting requirements.

### 7.3 NIH INTRAMURAL IRB REQUIREMENTS FOR PI REPORTING AT CONTINUING REVIEW

Please refer to the reporting requirements in Policy 801

### 7.4 NIAMS CLINICAL DIRECTOR REPORTING

All serious adverse events (SAEs) that meet the definition per Policy 801, must be reported to NIAMS Clinical Director via colbertr@mail.nih.gov

### 7.5 IND SPONSOR REPORTING CRITERIA

An investigator must immediately report to the sponsor, using the mandatory MedWatch form 3500a or equivalent, any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

- All Grade 5 (fatal) events (except death due to progressive disease) must be reported via email within 24 hours. A complete report must be submitted within one business day.
- All other serious adverse events including deaths due to progressive disease must be reported within one business day

Study endpoints that are serious adverse events (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

Events will be submitted to PI and study coordinator.

Events will be submitted to [redacted], authorized representative for the IND Sponsor (NIAMS) at:

7.5.1 Reporting Pregnancy

7.5.1.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately and the pregnancy reported to the Sponsor. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agents (s) should be documented in box B5 of the MedWatch form "Describe Event or Problem".

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment under study may have interfered with the effectiveness of a contraceptive medication. However, as patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, the CCR is requesting that pregnancy should be reported in an expedited manner as **Grade 3** "***Pregnancy, puerperium and perinatal conditions - Other (pregnancy)***" under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

If any pregnancy occurs in the course of the study, then the investigator should inform the Sponsor within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative will work with the investigator to ensure that all relevant information is provided to the Sponsor within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

7.5.1.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 7 days after the last dose of topical ruxolitinib.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 7 days after the last dose should, if possible, be followed up and documented.

## 7.6 Safety Reporting Criteria to the Pharmaceutical Collaborators

All Serious Adverse Events ("SAE") required to be reported pursuant to the Protocol shall be provided to Incyte and its representatives by Institution or Principal Investigator within twenty-

four (24) hours of learning of the event as well as any additional reports (including follow-up) agreed upon by Institution or Principal Investigator and Incyte. SAE Reports will be sent to [redacted]. By sending to this e-mail address, the Incyte Pharmacovigilance group will receive copies of the reports. This process will be tested and established before the first patient is enrolled in the Study. Notwithstanding anything to the contrary herein, Institution will have the primary responsibility of reporting adverse events ("AE") to regulatory authorities.

Leidos will send all reports to the manufacturer.

## 7.7 DATA AND SAFETY MONITORING PLAN

### 7.7.1 Principal Investigator/Research Team

The clinical research team will meet on a biweekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or the medical advisory investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS and to the Sponsor.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

### 7.7.2 Sponsor Monitoring Plan

As a sponsor for clinical trials, FDA regulations require NIAMS to maintain a monitoring program. The NIAMS program allows for confirmation of: study data, specifically data that could affect the interpretation of primary study endpoints; adherence to the protocol, regulations, and SOPs; and human subject's protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

This trial will be monitored by personnel employed by Leidos, a NIAMS contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

# 8 STATISTICAL CONSIDERATIONS

## 8.1 STATISTICAL HYPOTHESES

### 8.1.1 Primary efficacy endpoints:

The primary objectives are to determine the safety and tolerability as well as the efficacy of topical ruxolitinib 1.5% cream in patients with epidermal cGVHD.

The primary safety and tolerability endpoint will be counts of the grades of adverse events noted. The primary efficacy endpoint will be the percent change in the surface area of the target lesions for ruxolitinib-treated vs. placebo-treated lesions.

### 8.1.2 Secondary Efficacy endpoints:

The secondary endpoints are: 1) change in pain, pruritus, and overall severity VAS scales and 2) the pharmacokinetics and pharmacodynamics of topical ruxolitinib 1.5% cream in patients with epidermal cGVHD.

## 8.2 SAMPLE SIZE DETERMINATION:

The primary objectives are to determine the safety and tolerability as well as the efficacy of topical ruxolitinib 1.5% cream in patients with epidermal cGVHD. Patients who are compliant with protocol requirements through the primary endpoint, week 6, are considered evaluable. To analyze the efficacy of the treatment, we will measure surface area percent change. The initial surface area of each of the two target lesions will be measured at baseline and again at week 2, week 4 (optional), and week 6 on evaluable patients after one lesion has received treatment with ruxolitinib 1.5% cream and the other lesion has received treatment with the vehicle control. Following 6 weeks of treatment, the percent decline in the surface area of the two lesions will be determined, and the difference between the two decline percentages between the two lesions will be formed, expressed consistently as ruxolitinib decline minus placebo decline. If there are 10 evaluable patients (complete all study requirements through week 6) who have differences in decline percentages determined, then there will be 80% power to detect whether these paired differences in the changes from baseline are equal to one SD of the difference of the changes (effect size=1.0) using a two-tailed 0.05 significance level paired t-test. In practice, a Wilcoxon signed rank test may be used instead of a t-test if the differences are not consistent with a normal distribution ($p<0.05$ by a Shapiro-Wilks test).

The anticipated accrual rate is 1 patient per month. Enrollment is open to individuals at least 12 years of age, regardless of gender or racial/ethnic background. Given the complexity of this disease, which is often multiorgan in nature with intermittent flares of disease, the drop-out rate is expected to be high. In order to allow for a modest percentage of patients who are not able to comply with the proper administration of the two agents, the accrual ceiling will be set at 15 patients. Therefore, it is anticipated that the study will last approximately 17 months to reach 10 evaluable patients.

## 8.3 POPULATIONS FOR ANALYSIS

Per protocol analysis dataset: patients who receive at least 80% of scheduled doses of the agent in order to measure the change from baseline to 6 weeks will be included in the statistical analyses performed.

## 8.4 STATISTICAL ANALYSES

### 8.4.1 General approach

The analysis will primarily focus on evaluating the difference in the surface area of the target lesions receiving active agent or placebo in each patient and testing whether the target lesions improve more with active agent compared to placebo.

### 8.4.2 Analysis of the primary efficacy endpoints

To analyze the efficacy of the treatment, the initial surface area of each of the two target lesions will be measured at baseline and again at week 2, week 4 (optional), and week 6 on evaluable patients after one lesion received treatment with ruxolitinib 1.5% cream and the other lesion received treatment with the vehicle control. Following 6 weeks of treatment, the percent decline in the surface area of the two lesions will be determined, and the difference between the two decline percentages between the two lesions will be formed, expressed consistently as ruxolitinib decline minus placebo decline. The magnitude of the paired differences will be calculated and tested for whether the difference is equal to zero by a two-tailed 0.05 significance level paired t-test. In practice, a Wilcoxon signed rank test may be used instead of a t-test if the differences are not consistent with a normal distribution ($p<0.05$ by a Shapiro-Wilks test).

### 8.4.3 Analysis of the secondary efficacy endpoints

The secondary objectives will be assessed using the following measures. Measures of disease activity in patients with epidermal cGVHD will be determined. These include the pain, pruritus, and overall disease severity VAS scales.

To describe pharmacokinetics and pharmacodynamics of topical ruxolitinib 1.5% cream in patients with epidermal cGVHD, standard pharmacokinetic parameters such as AUC, clearance, concentration and half-life will be reported using descriptive statistics, along with pharmacodynamic parameters such as pSTAT3.

### 8.4.4 Safety Analyses

Safety of the agent will be assessed by reporting the grade of adverse events noted in each patient, and reporting the fraction with grade 3 and grade 4 adverse events. Safety data will be presented in individual listings. Summaries will also be prepared. The safety data will consist of the reporting of all adverse events, vital signs, physical examination data, and appropriate laboratory safety data.

### 8.4.5 Baseline Descriptive Statistics

Limited demographic and clinical characteristics of all patients will be reported.

8.4.6 Planned interim analyses

None planned.

8.4.7 Subgroup analyses

None will be performed.

8.4.8 Tabulation of individual participant data

Changes in affected lesion sizes may be reported on a per-patient basis or may be summarized.

8.4.9 Exploratory analyses

The exploratory objective is to characterize and analyze the effect of topical ruxolitinib 1.5% cream on inflammatory pathways in the skin and peripheral blood of patients with epidermal cGVHD using immunohistochemistry, and cytokine and gene expression studies. These analyses will be done using appropriate descriptive statistical methods with all results being considered exploratory and hypothesis generating.

# 9 COLLABORATIVE AGREEMENTS

## 9.1 CRADA

9.1.1 A CRADA has been executed with Incyte, who will provide Ruxolitinib for use in this protocol. CRADA number C-011-2018.

## 9.2 MATERIAL TRANSFER AGREEMENTS (MTAS)

9.2.1 An MTA will be executed for the studies noted in Section 5.1.4.

# 10 HUMAN SUBJECTS PROTECTIONS

## 10.1 RATIONALE FOR SUBJECT SELECTION

No subjects will be excluded from participation based on gender, race, or ethnicity. The study will be open to all subjects who satisfy the inclusion criteria and provide an informed consent to the protocol. Recruitment strategies are listed in Section 2.1.3.

## 10.2 PARTICIPATION OF CHILDREN

Children aged 12 to 17 are included in this study as children undergo allogeneic stem cell transplantation, develop chronic graft-versus-host disease, and suffer from a lack of organ-targeted measures to control skin GVHD without the systemic side effects associated with oral therapies. Furthermore, the topical formulation of administration in this study is anticipated to be of much lower relative risk compared to the known toxicity associated with systemic therapies employed for GVHD.

Approximately 3,000 pediatric hematopoeitic cell transplants are performed in the US each year. These children are at significant risk of developing skin GVHD, the systemic treatments for which confer long-term risk of multiple severe adverse events, particularly infection and end organ

damage (e.g. nephrotoxicity from calcineurin inhibitor use). Therefore, skin directed interventions that potentially confer less long-term risk should be studied in this population in order to determine if they may be a safe and efficacious alternative for use in children.

Recruitment is drawn from an existing NCI GVHD Natural History Study that recruits both children and adults, ongoing NCI pediatric transplant protocols, and outreach to area transplant programs, including Children's National Medical Center.

## 10.3 Participation of Adult Subjects Unable to Consent

Adults unable to provide consent are excluded from enrolling in the protocol. However, it is possible that subjects enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study. In the event this occurs, the subjects will remain in the study because for decisionally impaired subjects, it is unlikely that this trial would pose an equivalent or greater risk of adverse events compared to the risks of standard systemic immunosuppression to treat GVHD (mentioned above), and therefore, we believe it is ethically appropriate to allow clinical trial access to this skin-directed therapy. If subjects will remain in the study, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR.

For this reason and because there is a prospect of direct benefit from research participation (Section 10.4), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 and NIH HRPP Policy 403 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

Evaluation of Benefits and Risks/Discomforts

### 10.3.1 Related to topical ruxolitinib

Subjects participating in this research protocol may benefit from an improvement in symptoms of cGVHD. Potential risks of topical ruxolitinib include the toxicities described in Section 11.1.2 and in the consent form. There is the potential for unexpected adverse events. All subjects will be monitored for development of side effects.

### 10.3.2 Related to blood collection

Side effects of blood draws include pain, bleeding, bruising, and hematoma formation at the site of the blood draw.

10.3.3 Related to skin biopsy

Appropriate measures will be taken to minimize the risks that can potentially be associated with skin biopsy. Procedure related risks including bleeding, infection, pain, and scarring will be explained during informed consent will all questions answered.

## 10.4 Risks/Benefits Analysis

Cutaneous manifestations of cGVHD represent one of the most common manifestations of this complex, multisystem disease. Cutaneous cGVHD has significant impact on quality of life and can increase the risk of infection when ulcerations develop. Based on current scientific knowledge, JAK inhibition modulates graft-versus-host disease. The benefit of this study includes the potential to treat epidermal cGVHD in subjects enrolled in the study as well as to potentially gain greater insight into the pathophysiology of epidermal cGVHD and the effect of ruxolitinib on the cells in the tissue and in circulation of patients with active epidermal cGVHD. The risks of the study of topical ruxolitinib are minimal compared to the potential benefits to them and compared to diagnostic procedures and therapeutic options that are currently used for this disease.

Adult and Pediatric subjects entered on the trial will be treated with therapeutic intent and response to the therapy will be closely monitored. Therefore, this protocol involves greater than minimal risk, but presents the potential for direct benefit to individual for Adult subjects and meets Category 2.45 CFR 46.405 regulations for Pediatric subjects.

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation if an adult subject becomes decisionally impaired while on-study guidelines outlined in Section 10.3 will be followed.

## 10.5 Consent and Assent Process and Documentation

A discussion regarding the purpose of the study, alternatives to participating in the research, the treatment plan, research objectives, and follow-up of the trial will be reviewed with each subject, in-person, by an associate or principal investigator. Participation is voluntary and potential subjects will be made aware of alternatives to participating in the research. All participants, or legal guardian, must sign the IRB-approved informed consent document. The original signed consent will be kept by medical records and a copy will be provided to the patient and another copy will be placed in the research record. Documentation of the informed consent process will be placed in the medical record. At any time during participation if new information about risks, adverse events, or toxicities becomes available, the information will be shared with all enrolled and prospective participants.

Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. Written assent will not be obtained from children as the study holds out the prospect of direct benefit that is important to the health and well-being of the child and is available only in the context of the research. Verbal assent will be obtained as appropriate for children ages 12-17 and the parent or guardian will sign the designated line on the informed

consent attesting to the fact that the child has given assent. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

### 10.5.1 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require consenting of the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. Given the length of time that has transpired for some of the subjects since their last visit for this study, we request waiver of informed consent for those individuals who have completed their participation in the research study or have been lost to follow up.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.
   a. Analysis of samples and data from this study involves no additional risks to subjects.
(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.
   a. Retention of these samples or data does not affect the welfare of subjects.
(3) The research could not practicably be carried out without the waiver or alteration.
   a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of samples analyzed is likely to impact the quality of the research.
(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
   a. We plan to request a waiver of reconsent for those subjects who have been lost to follow-up.

### 10.5.2 Telephone consent

In the event of a phone consent, the informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was received by the investigator.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator with the date the telephone consent was obtained and a copy of the informed consent document and note will be kept in the subject's research record.

### 10.5.3 Telephone assent

The informed consent and assent documents will be sent to the parents/guardian and child. An explanation of the study will be provided over the telephone after the parents/guardian and child have had the opportunity to read the documents. Age-appropriate language will be used to discuss the study with the child. The parents/guardian will sign and date the informed consent, including the line for verbal assent of a child if appropriate. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

The original signed informed consent and assent documents will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was received by the investigators.

A fully executed copy will be returned via mail to the subject.

The informed consent and assent process will be documented on a progress note by the consenting investigator with the date the telephone consent was obtained and a copy of the informed consent document and note will be kept in the subject's research record.

### 10.5.4 Informed consent of non-English speaking subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2), 21 CFR 50.27 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

## 11 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

### 11.1 TOPICAL RUXOLITINIB 1.5% CREAM, IND # 136890

### 11.1.1 Source

Topical ruxolitinib 1.5% cream and a placebo cream will be supplied by Incyte. Ruxolitinib is an approved oral agent, but the topical application of this drug is not approved by the FDA. The NIAMS will hold the IND for the study agent.

### 11.1.2 Toxicity

Topical ruxolitinib has been evaluated in over 2350 subjects in at least 17 clinical studies in healthy volunteers and participants with psoriasis, atopic dermatitis, alopecia aerata and vitiligo for a duration of 1-26 months.

There have been no treatment related deaths. To date, only one severe, and/or life-threatening treatment emergent adverse event (TEAE), dermatitis atopic, has been attributed to the study drug. All other SAEs were considered unlikely related or unrelated to study drug.

Other TEAEs that led to discontinuation of topical ruxolitinib include mild to moderate occurrences of application site irritation, a Grade 3 elevation in GGT, headache, fatigue, nausea, atopic dermatitis and hypertriglyceridemia.

In an ongoing study of atopic dermatitits, a total of 67 pediatric participants (aged 2 to 17 years) received ruxolitinib cream 0.5%, 1.5%, or 0.75% cream BID. No participant had a fatal TEAE, SAE, or TEAE leading to discontinuation of ruxolitinib cream.

Cutaneous AEs were seen with similar frequency for vehicle-treated lesions and active comparator treated lesions when compared with topical ruxolitinib treated lesions.
The most common AEs that were considered possibly related to the study drug include transient hypoaesthesia, transient leukopenia and reticulocytosis, pruritus, upper respiratory infections, nasopharyngitis, headache, acne, dermatitis atopic, and transient application site irritation. All were considered mild to moderate and resolved with or without the need for concomitant medications.

Oral ruxolitinib is FDA approved for treatment of myelofibrosis and polycythemia vera in adults. The most common AEs with oral administration include thrombocytopenia, anemia, neutropenia, infection, nonmelanoma skin cancer, elevation of AST and ALT. Systemic exposure with topical ruxolitinib is several fold below the doses that are associated with AEs following oral dosing.

*Phototoxicity*

Topical ruxolitinib tested positive in a photoclastogenicity assay, therefore there may be a risk of skin reaction with the combination of topical ruxolitinib and sunlight.(*13*) For this reason, subjects are cautioned to avoid excessive exposure to either natural or artificial sunlight.

*Potential for genotoxicity*

A potential for genotoxicity was not found when assessed by standard *in vitro* and *in vivo* assessments.(*13*)

### 11.1.3 Formulation and preparation

Ruxolitinib (INCB018424) cream will be formulated in a 1.5% strength. All excipients in both the INCB018424 and placebo cream formulations are compendial grade or are approved for use in topical products. The placebo cream is an identical formulation to the active product except for the absence of drug substance.

11.1.4 Stability and Storage

Topical ruxolitinib cream and placebo cream should both be stored between 15°C and 30°C (59°F and 86°F)

11.1.5 Administration procedures

Study agent and placebo agent are applied topically to the designated areas. Application sites should avoid ulcerated and/or mucosal surfaces. The maximal BSA to receive study drug is 10%.

11.1.6 Incompatibilities

The chemical name of INCB018424 phosphate is (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)- 1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate (Figure 7). INCB018424 phosphate has a molecular formula of $C_{17}H_{21}N_6O_4P$ and a molecular weight of 404.36.(13)

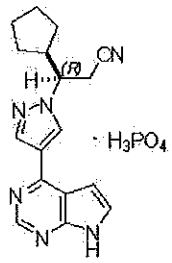


**Figure 7:** INCB018424 Phosphate structural formula

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# 13 APPENDICES

## 13.1 APPENDIX A – PERFORMANCE STATUS CRITERIA

| % | Karnofsky† | Score | Lansky Scale# |
|---|---|---|---|
| 100 | Normal; no complaints/ no evidence of disease . | 100 | Fully Active |
| 90 | Able to carry on normal activity; minor signs or symptoms of disease | 90 | Minor restrictions in physically strenuous play |
| 80 | Normal activity with effort; some signs or symptoms of disease | 80 | Restricted in strenuous play, tires more easily, otherwise active |
| 70 | Cares for self; unable to carry on normal activity or do active work | 70 | Both greater restrictions of and less time spent in active play |
| 60 | Requires occasional assistance but is able to care for most of his needs | 60 | Ambulatory up to 50% of time, limited active play with assistance / supervision |
| 50 | Requires considerable assistance and frequent medical care | 50 | Considerable assistance required for any active play; fully able to engage in quiet play |
| 40 | Disabled, requires special care and assistance | 40 | Able to initiate quiet activities |
| 30 | Severely disabled; hospitalization is indicated though death not imminent | 30 | Needs considerable assistance for quiet activity |
| 20 | Very sick; hospitalization is necessary | 20 | Limited to very passive activity initiated by others e.g. TV |
| 10 | Moribund; fatal process progressing rapidly | 10 | Completely disabled, not even passive play |
| | | 0 | Unresponsive, coma |

† **Karnofsky = D.A., et al., Cancer 1: 634-656, 1948**

# **Lansky Scale = Lansky, et. al., Cancer Oct 1; 60(7): 1651-1656, 1987**

## 13.2 Appendix B - Strong Cyp3a4 Inhibitors

| | |
|---|---|
| Clarithromycin | Nelinavir |
| Itraconazole | Ritonavir |
| Ketoconazole | Saquinavir |
| Atazanavir | Tipranavir |
| Darunavir | Nefazodone |
| Indinavir | |

## 13.3 APPENDIX C – ORGAN SPECIFIC AND GLOBAL SCORING OF CHRONIC GVHD

| | 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):*_____

| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **EYES**<br><br>*Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:*<br>☐ **Yes**<br>☐ **No**<br>☐ **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**<br>***Check all that apply:***<br>☐ Esophageal web/ proximal stricture or ring<br>☐ Dysphagia<br>☐ Anorexia<br>☐ Nausea<br>☐ Vomiting<br>☐ Diarrhea<br>☐ Weight loss ≥5%*<br>☐ 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****<br>**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:**<br>% FEV1 ☐ | ☐ FEV1≥80% | ☐ FEV1 60-79% | ☐ FEV1 40-59% | ☐ FEV1 ≤39% |
| *Pulmonary function tests*<br>☐ Not performed<br>☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____ | | | | |

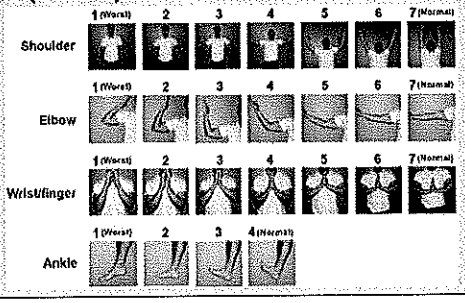
| | SCORE 0 | SCORE 1 | SCORE 2 | SCORE 3 |
|---|---|---|---|---|
| **JOINTS AND FASCIA**<br>P-ROM score<br>*(see below)*<br>Shoulder (1-7):___<br>Elbow (1-7): ____<br>Wrist/finger (1-7):___<br>Ankle (1-4):___ | ☐ No symptoms | ☐ Mild tightness of arms or legs, normal or mild decreased range of motion (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**<br>(*See Supplemental figure*‡)<br>☐ Not examined<br>*Currently sexually active*<br>☐ Yes<br>☐ 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)**



## 13.4 APPENDIX D – GLOBAL SCORING OF CGVHD

| STAGE | DEFINITION |
|---|---|
| Mild | 1 or 2 organs involved with no more than score 1<br>*plus*<br>Lung score 0 |
| Moderate | At least 1 organ (not Lung) with a score of 2<br>OR<br>Lung score 1<br>OR<br>3 or more organs involved with no more than score 1 |
| Severe | At least 1 organ with a score of 3<br>OR<br>Lung score of 2 or 3 |

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

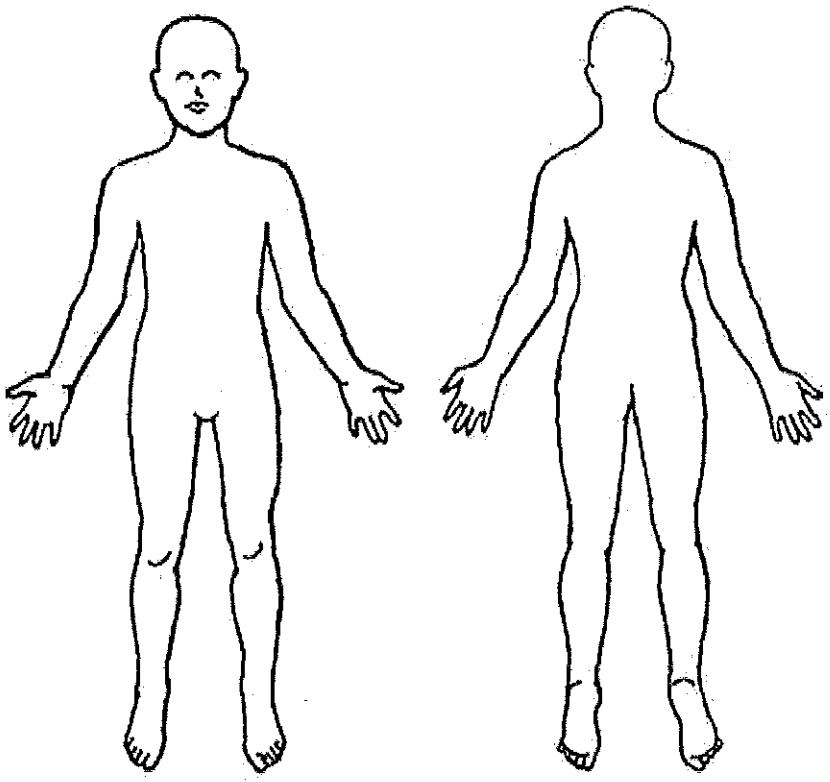
If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.

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 cause (no downgrading of organ severity).

## 13.5 APPENDIX E – PHYSICIAN'S GLOBAL ASSESSMENT

### Physician's Global Assessment of epidermal cGVHD

| SCORE | DEFINITION | DESCRIPTION |
|---|---|---|
| 0 | Clear | Residual hyperpigmentation may be present |
| 1 | Almost clear | Light erythema, papules and/or scale involving 0-20% of target area |
| 2 | Mild | Erythema, fine scale and/or papules involving >20% of target area |
| 3 | Moderate | Confluent erythema and scale and/or papules covering >50% of target area |
| 4 | Severe | Confluent erythema and scale and/or papules covering >80% of target area |



## 13.6 APPENDIX F – PATIENT REPORTED OUTCOME SURVEYS: PATIENT VISUAL ANALOG SCALES

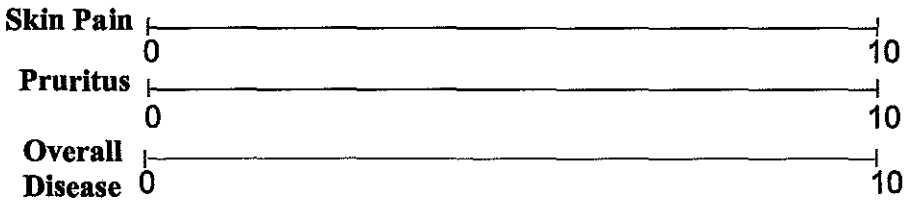
**Patient Visual Analog Scales**

**Definitions:** Pain due to skin disease from zero (no pain) to 10 (worst imaginable pain)

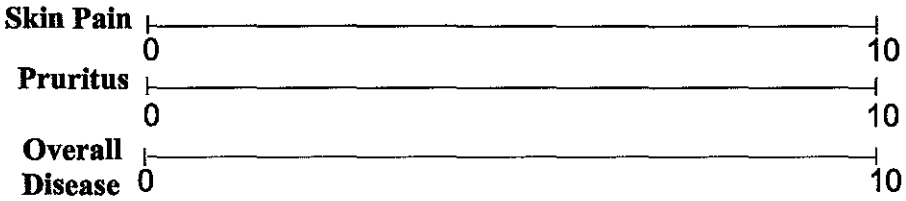
Pruritus is level of discomfort from itching from zero (no itching) to 10 (worst imaginable itching)

Overall disease is patient's assessment of degree of disease activity on the skin

**SITE 1:** _____




**SITE 2:** _____




**COMPLETED BY INVESTIGATOR:**

| | SKIN PAIN (0-10) | PRURITUS (0-10) | OVERALL DISEASE SEVERITY (0-10) |
|---|---|---|---|
| Site 1 | | | |
| Site 2 | | | |

## 13.7 APPENDIX G – MEDICATION DIARY

MEDICATION DIARY FOR TOPICAL RUXOLITINIB
18-AR-0035

SUBJECT ID:_____ SITE #_____LOCATION:_____

| Study Day | Date | Medication administered/Time | Reason if not administered (i.e. forgot/held) | Observations (i.e. irritation, itching, pain, improvement) |
|---|---|---|---|---|
| 1 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 2 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 3 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 4 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 5 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 6 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 7 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 8 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 9 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 10 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 11 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 12 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 13 | | Y/N _____AM | | |
| | | Y/N _____PM | | |
| 14 | | Y/N _____AM | | |
| | | Y/N _____PM | | |

Diary completed by:_____ Relationship to patient:_____

Signature:_____ Date:_____

**Study Team Review**

Name:_____Reviewer Signature_____

Date Reviewed: _____