MSK PROTOCOL COVER SHEET

A Pilot, Prospective, Randomized, Double-Blinded, Vehicle- and Comparator-Controlled Trial on Safety and Efficacy of a Topical Inhibitor of Janus Kinase 1/2 (Ruxolitinib INCB018424 Phosphate 1.5% Cream) for Non-Sclerotic and Superficially Sclerotic Chronic Cutaneous Graft-Versus-Host Disease (GVHD)

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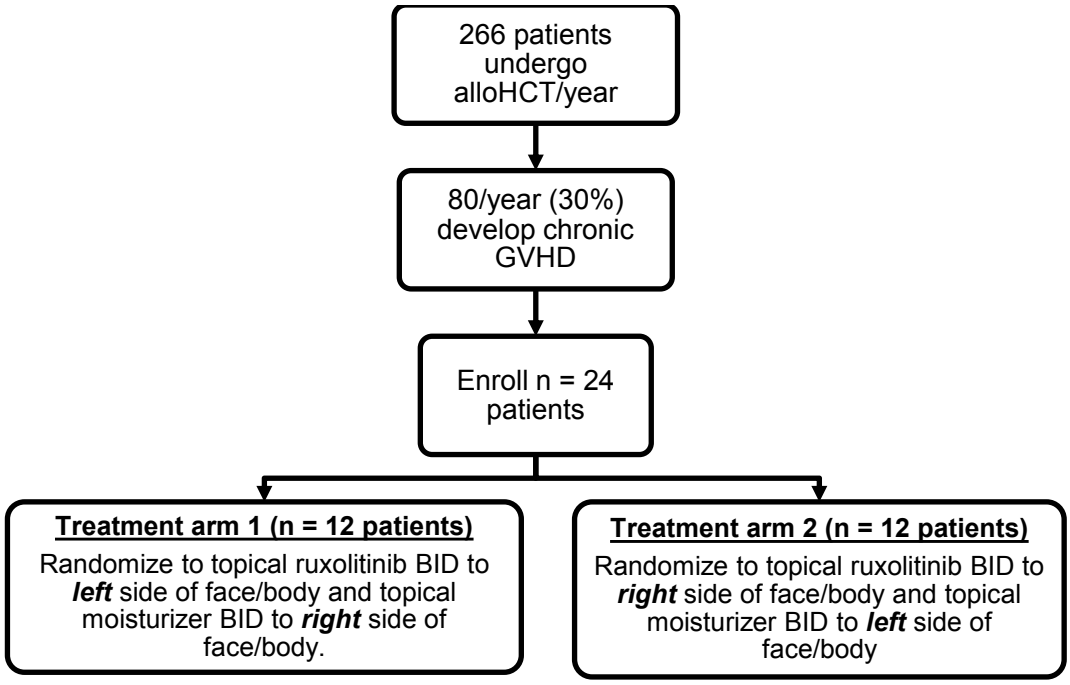
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title: A Pilot, Prospective, Randomized, Double-Blinded, Vehicle- and Comparator-Controlled Trial on Safety and Efficacy of a Topical Inhibitor of Janus Kinase 1/2 (Ruxolitinib INCB018424 Phosphate 1.5% Cream) for Non-Sclerotic and Superficially Sclerotic Chronic Cutaneous Graft-Versus-Host Disease (GVHD).

Total Study Follow-up per patient: 56 days

Schema



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- To obtain preliminary efficacy estimates of ruxolitinib 1.5% cream for the treatment of non-sclerotic and superficially sclerotic chronic cutaneous GVHD at day 28 as determined by the body surface area (BSA) of the GVHD rash on the side of the face/body treated with topical ruxolitinib cream versus contralateral side treated with vehicle at day 28 visit when applied beginning on day 1.

Secondary Objectives:

- To obtain preliminary efficacy estimates of ruxolitinib 1.5% cream for the treatment of non-sclerotic and superficially sclerotic chronic cutaneous GVHD at day 28 as determined by the Physician's Global Assessment of Clinical Condition (PGA) of the

GVHD rash on the side of the face/body treated with topical ruxolitinib cream versus contralateral side treated with vehicle at day 28 visit when applied beginning on day 1.

- To obtain preliminary efficacy estimates of ruxolitinib 1.5% cream for the treatment of non-sclerotic and superficially sclerotic chronic cutaneous GVHD at day 28 as determined by the objective Composite Assessment of Index Lesion Severity (CAILS) of the GVHD rash on the side of the face/body treated with topical ruxolitinib cream versus contralateral side treated with vehicle at day 28 visit when applied beginning on day 1.
- To obtain preliminary efficacy estimates of ruxolitinib 1.5% cream for the treatment of non-sclerotic and superficially sclerotic chronic cutaneous GVHD at day 14 as determined by the body surface area (BSA), Physician's Global Assessment of Clinical Condition (PGA), and the objective Composite Assessment of Index Lesion Severity (CAILS).
- Compare the difference in patient-reported outcomes between the side of the face and body treated with topical ruxolitinib cream versus the contralateral side treated with twice daily vehicle at day 14 visit and day 28 visit using the adapted National Cancer Institute Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) questionnaire
- Compare the difference in chronic cutaneous non-sclerotic and superficially sclerotic GVHD BSA between the sides of the face/body treated with topical ruxolitinib and vehicle by measuring the agreement of blinded independent physician's review of standardized photography of the right and left sides of the face and body respectively performed at day 28 visit
- Assess the safety and tolerability of topical ruxolitinib by physical examination and adverse event reporting
- To evaluate accrual, retainment and compliance with therapy
- To describe molecular expression profiles of lesional GVHD skin at baseline and after treatment with topical ruxolitinib or vehicle moisturizer via minimally invasive skin tape strip RNA sequencing

3.0 BACKGROUND AND RATIONALE

Non-sclerotic and superficially sclerotic chronic cutaneous graft-versus-host disease (cGVHD)

In 2016, Memorial Sloan Kettering Cancer Center Bone Marrow Transplantation Service performed 233 adult and 33 pediatric allogeneic hematopoietic stem cell transplantation (HCTs). Approximately 30-40% of the unmodified allograft recipients are expected to develop chronic GVHD (cGVHD). The skin is the most common site of cGVHD involvement (~75% of patients have cutaneous cGVHD)[1].

Classic chronic GVHD is diagnosed (and distinguished from aGVHD) by the presence of at least one diagnostic clinical manifestation (any of: poikiloderma, lichen planus-like features, keratosis pilaris-like features, maculopapular rash/erythema, deep sclerotic-like features, morphea-like features, lichen sclerosus-like features) OR at least one distinct manifestation (any of: depigmentation, sweat impairment, ichthyosis, keratosis pilaris, hypopigmentation, hyperpigmentation, etc) confirmed by pertinent biopsy or other relevant test (Table 2). Sclerotic

subtypes of chronic cutaneous GVHD includes deep sclerotic and superficially sclerotic subtypes (lichen sclerosus-like, morphea-like subtypes). Deep sclerotic cGVHD will be excluded from this study.

Chronic GVHD is the leading cause of nonrelapse mortality in patients surviving more than 2 years after allogeneic HCT with negative impact on quality of life and long-term outcomes[2]. While transplant practices have advanced over the last decades, the incidence and severity of cGVHD have continued to rise[2, 3]. Of organs affected by cGVHD, severe skin involvement has increased in recent years (from 51% of patients with cutaneous cGVHD at maximum severity in 1999, 65% 2003, and 71% in 2007[3]. Median onset of cGVHD is 4 to 6 months after allogeneic HCT, with 5-10% of cases diagnosed beyond 1 year[1]. The clinical manifestations of cGVHD are variable, and half of patients have 3 or more involved organs[1]. Median duration of cGVHD treatment is 2-3 years; however 15% of patients required treatment after 7 years[1].

Diagnostic *(Sufficient to establish the diagnosis of chronic GVHD)*	**Distinctive** *(Seen in chronic GVHD, but insufficient alone to establish a diagnosis of chronic GVHD)*	**Other Features** *(Can be acknowledged as part of the chronic GVHD symptomatology if the diagnosis is confirmed)*	**Common** *(Seen with both acute and chronic GVHD)*
• Poikiloderma • Lichen planus-like features • Morphea-like features • Lichen sclerosus-like features • Sclerotic features	• Depigmentation	• Sweat impairment • Ichthyosis • Keratosis pilaris • Hypopigmentation • Hyperpigmentation	• Erythema • Maculopapular rash • Pruritus

Current treatment recommendations

To date, there have been no randomized, controlled trials evaluating topical therapies for cutaneous cGVHD, nor are there any FDA-approved topical treatments.

Despite this lack of evidence, topical corticosteroids are the mainstay of mild chronic GVHD therapy[4-6]. As supported by case reports, topical calcineurin inhibitors (i.e., pimecrolimus cream, tacrolimus ointment) are used with variable efficacy in areas at greatest risk for topical corticosteroid side effects such as the intertriginous areas and face, as well as for patient who have developed steroid dependence[4, 5, 7, 8]. However, in one case series of 18 patients with cutaneous cGVHD treated with topical tacrolimus 0.1% ointment twice daily, all patients eventually went on to receive more aggressive treatment including increases in steroid dosage, psoralen-ultraviolet-A (PUVA) therapy, or extracorporeal photophoresis[7]. Emollients are also recommended as topical management for chronic cutaneous GVHD by the Ancillary Therapy and Supportive Care Working

Group[4]. For cutaneous cGVHD with extensive body surface area, skin-directed therapies include ultraviolet A and narrowband ultraviolet B phototherapy[4], which are associated with increased risk for skin cancer (including squamous cell carcinoma, basal cell carcinoma, and melanoma).

Chronic cutaneous non-sclerotic and superficially sclerotic GVHD may be topical- or systemic steroid- dependent/ refractory, prompting additional immunosuppressive systemic therapies or extracorporeal photophoresis/phototherapy. No topical therapies have been approved, and off label use of topical corticosteroids and topical tacrolimus are mainstays of therapy, despite limited efficacy and established side effects. Topical corticosteroid use increases risk for development of localized infections, striae, skin atrophy/thinning, bruising, acne, discoloration, dependence and with widespread use: hyperglycemia, adrenal suppression, and moon-facies [9]. Erythema, burning, edema may be experienced on discontinuation of long-term topical steroid use[10]. Half of patients experience a burning sensation upon application of topical calcineurin inhibitors. Given the variable efficacy and adverse event profile of currently available topical and systemic therapies for chronic cutaneous GVHD, there is an unmet need to have new options for anti-inflammatory treatment in this patient population.

Systemic Janus kinase inhibitors and Graft-versus-host disease

Janus kinase (JAK) are intracellular nonreceptor tyrosine kinases which play critical functions in T-cell activation, inflammation, and tissue damage and predicted to be involved in the pathogenesis of GVHD [11, 12]. JAK inhibitors, including ruxolitinib (JAK 1/2 inhibitor) and tofacitinib (JAK 1/3 inhibitor), inhibit the signal transduction and activation of transcription (STAT) pathway that is essential for downstream growth factors and inflammatory cytokines[5].
JAK inhibitors' anti-inflammatory properties have been investigated in several immunopathogenic disorders. Systemic ruxolitinib is a potent oral selective JAK1/JAK2 inhibitor with equipotent activity toward JAK1 and JAK2[12] and has been approved by the FDA for the treatment of intermediate or high-risk myelofibrosis, including primary myelofibrosis, post polycythemia vera myelofibrosis and post essential thrombocythemia myelofibrosis, and patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea[12]. Systemic ruxolitinib has demonstrated efficacy for management of acute and chronic GVHD in animal models as well as in patients with GVHD in several small studies and retrospective clinical reports[11, 12]. However, the systemic use of ruxolitinib is associated with several adverse events including anemia, thrombocytopenia, neutropenia, liver dysfunction, diarrhea and infection risk that could limit a broader use, particularly in allo-HCT recipients with GVHD who commonly have cytopenias, GI and hepatic dysfunction.

Topical ruxolitinib (JAK 1/2 inhibitor)

While not commercially available, the topical JAK inhibitors ruxolitinib (JAK 1/2 inhibitor) and tofacitinib (JAK 1/3 inhibitor) have been investigated for management of alopecia areata[13], vitiligo, psoriasis and atopic dermatitis with efficacy[14-16].
In patients with active psoriasis, topical ruxolitinib (INCB018424) 1.5% cream twice daily for 28 days was pharmacologically active, modulated proinflammatory cytokines, and was well tolerated; treatment resulted in improvements in psoriasis lesion scores[17]. No significant inhibition of pSTAT3 in peripheral blood cells was observed following topical application, consistent with the

generally low steady-state plasma concentrations of INCB018424 measured[17]. A 20-week, open-label, proof-of-concept trial of twice daily topical ruxolitinib 1.5% cream in 12 patients provided significant repigmentation in facial vitiligo[18]. A topical JAK/spleen tyrosine kinase (SYK) dual inhibitor has demonstrated efficacy for ocular GVHD with a higher mean decrease in total corneal fluorescein staining in the group treated with an ophthalmic JAK/SYK solution as compared to the vehicle-treated group at 12 weeks [19].

Topical ruxolitinib and chronic cutaneous non-sclerotic and superficially sclerotic GVHD
Given efficacy of ruxolitinib with oral use in GVHD and with topical use in other dermatoses, we hypothesize topical ruxolitinib may be used for the treatment of chronic cutaneous (non-sclerotic) and superficially sclerotic (lichen sclerosus-like; morphea-like) GVHD and will be more effective in decreasing the body surface area of chronic cutaneous GVHD when compared to topical vehicle.

Of note, topical ruxolitinib treatment in a murine model of skin GVHD was associated with less severe skin GVHD scores, reduced T-cell infiltration of the skin and maintenance of LGR5+ hair follicle stem cell levels that are normally reduced with the onset of GVHD[12, 20, 21]. Skin GVHD targets Lgr5+ hair follicle stem cells in association with impaired hair regeneration and wound healing[20]. Topical ruxolitinib, unlike corticosteroids, protects Lgr5+ skin stem cells and maintains skin homeostasis in skin GVHD[20].

This study utilizes a novel method of delivery and active agent for the topical treatment of cutaneous GVHD, potentially expanding the therapeutic options for patients with GVHD. Topical ruxolitinib would augment the armamentarium of agents available to treat these patients, without resorting to systemic immunosuppressive therapies, nor causing side effects of skin atrophy, bruising, and tachyphylaxis due to topical steroids.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Design: This is a prospective, randomized double-blinded, vehicle- and comparator-controlled pilot study followed by an open label extension for all patients who wish to continue on study

Purpose: This study was designed to test the safety and efficacy of topical ruxolitinib in treating non-sclerotic and superficially sclerotic chronic cutaneous graft-versus-host disease.

Patient population: Male or female patients 12 years or older with clinically or histologically confirmed non-sclerotic chronic and superficially sclerotic cutaneous graft-versus-host disease after allogeneic hematopoietic stem cell transplantation.

Study duration: The study will span 28 ± 3 days. An end of study visit will occur on the last day of topical therapy day 28 ± 3 days, followed by a safety visit 4 weeks later (day 56 or 84). All eligible patients determined by the attending dermatologist at day 28 will be given the opportunity to continue topical ruxolitinib for an additional 28 days. Safety follow-up will continue for an additional 28 days (day 84). In general, each participant will be followed for

up to 28 ± 5 days (day 56 or 84) following the last dose of study therapy, and the study is expected to meet accrual goals over a period of 6-24 months. Data analysis will take an additional 12 months, making the total duration of the study 3 years. The first interim data analysis will occur after the study has accrued 10 evaluable participants. Only the biostatician and Dermtech personnel will be unblinded during the analysis. The second interim data analysis will occur with the remaining 14 evaluable participants. Only the biostatician and Dermtech personnel will be unblinded during the analysis.

4.2 Intervention

Lesional areas will be chosen by the attending dermatologist. Lesional areas of the same corresponding size on the left and right hand sides of the participant will be evaluated, demarcated, imaged. In this study, participants will provide both treatment and vehicle control lesions. Eligible patients will be randomized to one of two treatment groups: Group 1 will be randomized to topical ruxolitinib BID to ***left*** side of face/body and topical moisturizer BID to ***right*** side of face/body; Group 2 will be randomized to topical ruxolitinib BID to ***right*** side of face/body and topical moisturizer BID to ***left*** side of face/body. Randomizing the treatment side is to maintain blinding of the physician. For example: if patients are all assigned to apply topical ruxolintib to their right side and are showing clinical improvement on each patient's right side consistently, the physician will be aware that the right side is the treated side, possibly adding bias to the study. Variability in application side will also help to account for inter-patient variability in application with right- versus- left hand. Participants and their study doctor will be blinded from knowing which side of the face/body will be treated with the study cream, and which side of the face/body will be treated with the vehicle. For study purposes, Study Day 1 is defined as the first day of topical application. Patients will self-administer topical ruxolitinib and vehicle topically to affected rash area on directed side of face/body and record topical application on study diaries that will be provided by the study doctor or a member of the research team. On Study Day 28, end of treatment day, all patients will be eligible for the open label portion of the study. The attending will determine the patient's response, and if the patient wishes to continue, then they will be given the opportunity to use the topical ruxolitinib for an additional 28 days. If the patient wishes to continue then pharmacy will dispense open label ruxolitinib for the patient to apply to both sides of the body, not to exceed 20% total BSA. The PI, the Clinical Research Coordinator, and the patient will remain blinded to the initial treatment arm, but will become unblinded during the open label portion."

Topical ruxolitinib 1.5% cream: After gently washing skin and patting dry, the patient will apply thin layer in morning and at least 60 minutes before bedtime to one side of face/body. The patient will wash hands after application. (If caregiver is applying creams, he/she should wear nitrile gloves prior to application and discard after each cream use.)

Patients will be instructed to wash hands between applications of each cream.

Topical vehicle/moisturizer cream: After gently washing skin and patting dry, the patient will apply thin layer in morning and at least 60 minutes before bedtime to contralateral side of

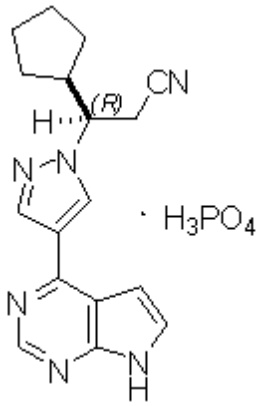
face/body. The patient will wash hands after application. (If caregiver is applying creams, he/she should wear nitrile gloves prior to application and discard after each cream use.)

At initial study visit, BSA of the rash will be calculated, and all patients will be directed to apply a dose of cream based on BSA involved (same BSA will be used for treatment and placebo sides). For each side at this initial study visit, the skin area targeted for treatment will be outlined with surgical marker, photographed, and a photograph of each outlined target treatment area will be provided to the patient as an application reference. After BSA calculation at initial visits, patients will all be required to apply each cream to lesional skin as directed based on body surface area (1 adult fingertip unit (FTU) = 0.5g = ~ 2% BSA). Patients can apply a maximum of 10 adult fingertip units (5 grams; total maximum daily dose, 10 grams) of topical ruxolitinib 1.5% cream onto the randomized side of face/body and an equivalent amount of the vehicle to the contralateral side of face/body in morning and prior to bedtime, on Days 1-28 (56 applications).

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Study drug, packing, and labeling

The study drug to be used in the course of this study is INCB018424 (ruxolitinib) phosphate cream.



INCB018424 Phosphate Structural Formula:

Physical Properties: INCB018424 phosphate drug substance is a white to off-white to light pink powder.

Chemical Properties: 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. INCB018424 phosphate has a molecular formula of C17H21N6O4P and a molecular weight of 404.36.

INCB018424 phosphate cream is a topical formulation of an investigational product under development for the treatment of patients with psoriasis, alopecia areata (AA), atopic dermatitis (AD), vitiligo, and other potential autoimmune diseases of the skin. INCB018424

phosphate (ruxolitinib) is an inhibitor of the JAK family of protein tyrosine kinases. Mitogenic and inflammatory cytokines are strongly implicated in the pathogenesis of psoriasis, AA, AD, and other potential autoimmune diseases of the skin. Inhibition of specific cytokine function using antibodies directed against the common p40 subunit of IL-12 and IL-23 has demonstrated proof-of-concept validating cytokine signaling as a therapeutic target for the treatment of psoriasis. Oral treatment with JAK inhibitors has been shown to benefit patients with AA. Because JAKs serve to translate extracellular signals from a number of relevant cytokines and growth factors upregulated in inflammatory diseases such as psoriasis, AA, AD, and other potential autoimmune diseases of the skin, JAK inhibitors represent potential therapeutic agents for these disease states.
An oral formulation of INCB018424 phosphate has been clinically evaluated for the treatment of patients with myeloproliferative diseases, hematologic malignancies, and solid tumors and is currently approved for the treatment of myelofibrosis (MF) and polycythemia vera (PV) in multiple countries. In addition to the safety pharmacology and toxicology studies that were completed to support development of INCB018424 phosphate cream, the toxicologic and toxicokinetic profiles of INCB018424 phosphate have also been characterized following oral administration.

INCB018424 represents a novel, potent, and selective inhibitor of the JAKs. INCB018424 potently (IC50 < 5 nM) inhibits JAKs, yet it does not significantly inhibit (< 30% inhibition) a broad panel of 26 kinases when tested at 200 nM (approximately 100× the average IC50 value for JAK enzyme inhibition). Moreover, in cell-based assays relevant to the pathogenesis of psoriasis, such as IL-2–stimulated phosphorylation of STATs and IL-2–induced proliferation of T cells, INCB018424 demonstrates excellent potency (IC50 values of 10-40 nM). This effect was not due to general cytotoxicity because INCB018424 (up to 10 μM) had no effect on the survival of resting T cells (without IL-2 stimulation). INCB018424 also potently inhibited the phosphorylation of STAT proteins and the production of proinflammatory factors induced by cytokines such as IL-23 and IFN-γ. Topical application of INCB018424 demonstrated excellent efficacy in an *in vivo* model of immune-based skin inflammation, the delayed-type hypersensitivity (DTH) model in mice, including reduced ear swelling, reduced immune cell infiltrates, and normalization of tissue histology. Further, INCB018424 was also efficacious in the inflammatory phase of the dorsal DTH model when applied in a clinically relevant cream formulation. In summary, pharmacological data obtained with *in vitro* and *in vivo* model systems supports the potential utility of topically applied INCB018424 in the treatment of psoriasis.

Formulation: INCB018424 phosphate cream has been formulated in 4 strengths (0.15%, 0.5%, 1.0%, and 1.5% w/w free base equivalent) that are actively being investigated. All excipients in both the INCB018424 and vehicle cream formulations are compendial grade or are approved for use in topical products. The matching vehicle cream is an identical formulation to the active product except for the absence of drug substance.

Labeling: To help ensure blinding, tubes of ruxolitinib and moisturizer will be labeled by pharmacy. The pharmacist will tear off a perforated label section with randomization group, before dispensing to the patient. Medication labels will comply with US legal. They will supply no information about the patient. The same storage conditions will be described on each medication label. If the patient decides to continue the treatment after day 28, the pharmacy will label the drug based on the labels provided by Incyte.

5.2 Drug supply and storage

The drug will be shipped by Incyte Corporation directly to the MSKCC pharmacy. It will be received by a designated person at the MSKCC pharmacy, handled and stored properly and safely, and kept in a secured location to which only the investigator/pharmacist and/or designated assistants will have access. Upon receipt, INCB018424 phosphate cream and vehicle should be stored according to the instructions specified on the drug labels [Store at 15°C to 30°C (59°F to 86°F). These instructions will also be made clear to the patient for storage and self-administration of ruxolitinib at home (Patient information sheet, Appendix VI). Upon registration of a new study participant, MSKCC pharmacy will clearly label the two study creams (ruxolitinib and vehicle) according to which side of the body each cream should be applied based on the patient's randomized treatment arm.

At their baseline visit, patients will receive two 45gm tube(s) of topical ruxolitinib phosphate cream, 1.5% and two 45gm tube(s) of the vehicle as indicated by their involved BSA. An additional tube of each cream will be made available to the patient, after using up the initial tube (as per study instructions) and returning the empty tube to the study staff.

At their Day 28 visit, patients who wish to continue on study will receive a tube of the treatment. The pharmacy will dispense open label ruxolitinib for the patient to apply to both sides of the body, not to exceed 20% total BSA, for an additional 28 days.

Study drug may be dispensed in real time or shipped to patients for the initial dispensation. Patients will not be charged for the shipment of the drug.

5.3 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit using information provided by the patient and/or caregiver in the Medication Application Diary (Appendix VII). This record will capture information of medication used, dosages administered, and intervals between visits and the completion of the study. Patient is required to bring both vehicle and control tubes to study visits for drug diary review and drug accountability return. Patients in the open label extension and optional extension period will be required to bring in the ruxolitinib tube to study visits. For both the open label extension and optional extension portions of the study, the patient does not have to fill out a drug diary. Re-consent is required for the optional extension period to ensure that the participant agrees to continue treatment with ruxolitinib study drug.

5.4 Ruxolitinib cream administration

All participants will initiate treatment within 7 days of informed consent/ registration (exceptions can be made per PI discretion). The ruxolitinib cream will be administered each day in the morning and before bedtime for the entire course of treatment. Only on Day 1, application of the first dose of study medication will be done preferably by the research physician with use of nitrile gloves—subsequently, the medication will be self-administered twice each day by the patient (or caregiver), as per the instructions provided. Nitrile gloves will be worn by caregiver for any caregiver-administered applications.

5.5 Supportive care guidelines and concomitant medications

Participants must be instructed not to apply any (new) topical additional medications, including over-the-counter products during the trial without prior consultation with the

investigator. All topical products applied to the skin within 14 days of screening should be recorded. This includes all moisturizers, sunscreen, sunblock etc. If concomitant therapy must be added or changed, including over-the-counter medications, or alternative therapies, the reason and name of the drug/therapy should be recorded by the investigator.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

Any patients age 12 years and older with clinical or histologically confirmed non-sclerotic or superficially sclerotic chronic cutaneous graft-versus host disease after allogeneic hematopoietic stem cell transplantation will be considered for protocol participation.

6.1 Subject Inclusion Criteria

- Patients (≥ 12 years)
- History of allogeneic hematopoietic stem cell transplantation
- BSA of at least 2% of clinically or histologically confirmed non-sclerotic or superficially sclerotic cutaneous chronic graft-versus-host disease (diagnosed and BSA calculated in accordance with the National Institutes of Health Chronic Graft-versus-Host Disease Consensus for Clinical Trials: I. The 2014 Diagnosis and Staging Working Group Report)
- Patients age ≥ 18 years must provide written informed consent; or patients age ≥12 years and <18 years must provide assent and have at least one guardian provide written informed consent to participate in the study.
- Able to self-administer topical interventions or provide for another person to apply the topical interventions (while wearing nitrile gloves)
- If on systemic therapy for GVHD, systemic therapy must be stable for past 4 weeks; however, any planned systemic corticosteroid taper during the study will be permitted. Changes in systemic therapy during the study period will be allowed for the management of non-skin GVHD.
- Any concurrent topical therapies including topical corticosteroids, topical calcienurin inhibitors, moisturizers, phototherapy (narrowband UVB or UVA1); or excimer laser therapy must be discontinued on Study Day 0.

6.2 Subject Exclusion Criteria

- Known history of allergy to any ingredient of the study medication
- Patients with deep sclerotic cutaneous graft-versus-host disease including deep sclerotic subtypes of chronic cutaneous GVHD
- Use of concurrent topical therapy including topical corticosteroids, topical calcienurin inhibitors, moisturizers, phototherapy (narrowband UVB or UVA1); or excimer laser therapy after Study Day 0 up to and including Study Day 28.
- Changes in systemic therapy during study period for the purpose of treating skin GVHD.
- Special populations:
    - vulnerable populations e.g. decisionally impaired (cognitive, psychiatric), terminally ill, prisoners
    - patients who, in the opinion of the investigator have a condition that precludes their ability to provide an informed consent
- Concurrent participation in another topical trial of a drug(s) or medical device, or the subject is in an exclusion period after a previous trial of drug(s) or medical device

- Pregnancy or lactation
- Patients with inadequate liver function (ALT above 4 × upper limit of normal [ULN] for the patient's age or direct bilirubin 4 × ULN for the patient's age and the laboratory abnormalities are considered to be due to underlying liver dysfunction) unless attributed to GVHD (if direct bilirubin is not in the medical record, it is acceptable to use total bilirubin x4 ULN).
- Active uncontrolled infection requiring systemic therapy. Subjects with a controlled infection receiving definitive therapy for 48 hours prior to enrollment are eligible.

7.0 RECRUITMENT PLAN

A member of the patient's treatment team, a protocol investigator, or research staff, at Memorial Sloan Kettering Cancer Center (MSKCC) will identify potential research subjects. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects may also be referred to the investigator/research staff of the study by the treating physician or any MSKCC physician. Patients may also be referred from physicians at Hackensack Medical Center for participation in this study. Generally, the patient's primary hematologist and primary dermatologist will identify potential research subjects.

The participating investigators may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study, and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

The following procedure will be employed in enrolling all participants into the study. (Potentially) eligible patients identified by the mechanism described in the preceding paragraphs, will be offered participation in the study. This will be accomplished by the treating physician, clinician, or research staff, in person. The purpose of the study will be explained to the patient and informed consent will be obtained from willing participants. Potential participants will also be offered the opportunity to consider participation and review the consent documents (e.g. at home) with the option of providing consent in the future. Subsequently, a consenting professional will call potential adult study participants to invite them to participate. For potential pediatric patients, a parent will be contacted to see if their child would like to participate. If they agree, then the eligible participants will be scheduled for in-person consenting and eventual baseline assessments. This visit will preferably coincide with patients' standard-of-care visit. Potential participants who decline participation will not be contacted again for the purpose of recruitment into the study.

We will only retain participants' basic information (e.g. questionnaire responses, eligibility checklist, etc.) that is needed for study reporting purposes. These records will be maintained on a secured Dermatology shared drive. We will also maintain a list of all participants approached throughout the entire study to record reasons for refusal and avoid re-approaching healthy volunteers that have been identified as ineligible or refusing participation. This list will be destroyed at the completion of the study.

The investigators participating in this research include physicians and research staff from Memorial Sloan Kettering Cancer Center, as listed on the face page of this protocol, who have successfully completed training for protection of human research subjects in compliance with MSKCC clinical research policy. Written consent will be obtained by one of these individuals or his/her designee, who must also have successfully completed training for protection of human subjects in compliance with MSKCC clinical research policy.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or in the medical record to confirm that the patient is eligible, and to contact the patient regarding research enrollment. If the patient turns out to be ineligible for the research study, the study personnel will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.0 PRETREATMENT EVALUATION

Patients may be screened and consented starting from up to 7 days before study initiation.

The following initial baseline procedures can take place at any time during this period, or on the day of initiation (Day 1)

1. Medical history, including concomitant medications
2. Study assessments (serve as baseline measures for the study):
    - Patient-reported Outcomes (Appendix III):
        - Adapted PRO-CTCAE™ for each side of face/body affected by GVHD rash
    - Clinical assessments (Appendices I, II, IV, V)
        - Skin examination with calculation of body surface area (BSA), Physician's Global Assessment of Clinical Condition (PGA), and the objective Composite Assessment of Index Lesion Severity (CAILS) for each side
    - Standardized photography and 3D photography
        - During the first and third study visit, if the participant gives consent, the research photographer will take 3D photography, also called Total Body Photography of the patient.

- For each side, the skin area targeted for treatment will be outlined with surgical marker, photographed, and a photograph of each outlined target treatment area will be provided to the patient as an application reference.

- Laboratory investigations
  - Laboratory analyses and skin biopsy will be performed only as clinically indicated for routine care.
  - Minimally invasive skin tape strip RNA sequencing will be performed on each face/body side by the study dermatologist (Appendix VIII)

Visit # **Study day:** **Reason for visit**	**Pre-study Screening or Day 1**
Informed consent	X
Medical history	X
Pregnancy test (if applicable for females of child-bearing potential)	X
Clinical assessment (i.e., BSA, PGA, and CAILS on each side; adverse events/CTCAE assessment)	X
Skin examination	X
Lesional skin tape stripping on each side	
Patient-reported outcomes questionnaire for each side	X
Standardized photography	X
Drug application	X
Drug diary return	X
Drug accountability	X

9.0 TREATMENT/INTERVENTION PLAN

Patients will be prescribed twice daily use of topical ruxolitinib 1.5% cream (randomized half of face/body) and vehicle/moisturizer (for contralateral side of face/body) to a maximum of 20% BSA on each side for 28 ± 3 days. Topical ruxolitinib will be provided as topical cream.

In the morning and evening (at least 60 minutes before bedtime), patients will be instructed to apply a pre-designated number of fingertip units of each topical intervention (ruxolitinib and moisturizer) to each side of the face/body unit as outlined in provided photograph for each side. Patients will receive detailed instructions at the baseline visit and receive clear, written instructions on the standarized application technique (see Patient Instructions: Topical Medications). Patients will apply topical ruxolitinib cream and vehicle cream to the equivalent BSA on each side (e.g., if one side has

15% lesional skin and contralateral side has 10% lesional skin, the subject will treat only 10% on each side) and no more than to 20% BSA on each side.

Before topical applications, patients will be instructed to gently wash the face and body with a gentle cleanser (examples include Cetaphil, Purpose, Aveeno, Vanicream products) and pat skin dry with a clean towel. Patients will not be encouraged to apply topical emollients to the treated face and body during the study, but if desired, they may apply to untreated areas. Patients will be advised not to use products with chemicals or perfumes.

We do not anticipate the need for any adjustments to the treatment plan as consequence of adverse reactions to ruxolitinib (see section 11.0), but any patients with adverse cutaneous reactions to treatment with topical ruxolitinib 1.5% cream, or moisturizer will be advised to return to clinic to see a dermatologist right away. Adverse event reporting will be based on CTCAE v5.0, as applicable[22].

In the event of a patient emergency, the principal investigator and study pharmacist will be able to unblind the patient.

All patients will be advised to follow photo-protective measures during the study, and avoid unnecessary sun exposure. Daily sunscreen use will not be recommended, because the effect on topical ruxolitinib activity is unknown. Instead, when outside, patients should be careful to wear clothing that protects as much of their skin as possible, as well as hats with wide brims to protect the face. Patients will also be asked to use a diary to improve their compliance with the application of topical ruxolitinib 1.5% cream/vehicle to unilateral sides of the face and body, as well as to record any adverse effects of treatment, and will be asked to bring diaries to all patient visits. Patients will be allowed to continue applying topical ruxolitinib 1.5% cream to both sides of the face and body (≤20% BSA) for another 28 ± 3 days after the completion of the study (day 28 ± 3 days) if they have a partial or complete response during the treatment portion of the study.

Skin examinations will be part of the evaluation performed during baseline visit at day 1, day 14, day 28, and day 56 visits; as well as day 84 visit for those patients who repeat a subsequent topical ruxolitinib 28-day course. Patients will also complete adapted PRO-CTCAE™ questionnaires to measure dermatology-specific patient-reported symptoms and outcomes at each of the aforementioned visits for each side of the face/body. Study questionnaires should take the participant no more than 10 minutes to complete at each time point. Standarized photography will be performed on , day 1, day 14 ± 3 days, day 28 ± 3 days, day 56 ± 5 days, and day 84 ± 5 days for those patients who repeat a study drug course. Total body photography will be perfomed on day 1 and day 3, if participant consents. Patients will be seen in the BMT clinics, and their clinical response will be assessed in the Dermatology clinic of Memorial Sloan-Kettering Cancer Center located in Manhattan.

9.1 Treatment period extensions

After completion of the open-label portion of the study, interested subjects may continue to participate on the Treatment Extension with topical ruxolitinib cream as long as they meet criteria* to continue to receive therapy, tolerate the treatment regimen, do not discontinue topical ruxolitinib, do not withdraw consent, or until topical ruxolitinib becomes commercially available for the treatment of cutaneous graft-versus-host disease. Subjects who continue on

the treatment period extension, will have a safety follow-up visit 28 days after completion of therapy. Visit 5 will be replaced by Visit 6 for participants who enroll in the extension period. Re-consent is required to be obtained on Visit 4 for the optional extension period to ensure that the particioant agrees to continue treatment with ruxolitinib study drug.

*However, subjects who participate in the treatment period extension are permitted to use other topicals and/or phototherapy concurrently.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Table 1. Assessments: 4 to 5 study visits

Visit #	Pre-study	1	2	3	4	5	6
Study Day	Day -7 to Day 0	Day 1	Day 14 ± 3 days	Day 28 ± 3 days	Day 56 ± 5 days	Day 84 ± 5 days	28 Days ± 5 days after treatment completion
Reason for visit	Screening	Pre-treatment baseline evaluation	Interval follow-up evaluation	Blinded Treatment ends	Safety follow-up visit/Open label extension follow-up evaluation	Open-label extension safety follow-up visit	Safety follow-up visit after treatment extension period ends
Informed consent	**X**				**X****		
Medical history	**X**						
Pregnancy test (if applicable for females of child-bearing potential)	**X**			**X**			
Clinical assessment (i.e., BSA, PGA, and CAILS on each side; adverse events/CTCAE assessment)		**X**	**X**	**X**	**X**	**X**	**X**
Skin examination		**X**	**X**	**X**	**X**	**X**	**X**
Lesional skin tape stripping on each side				**X**			
Patient-reported outcomes		**X**	**X**	**X**	**X**	**X**	**X**

questionnaire for each side							
3D Photography**		X		X			
Standardized photography		X	X	X	X	X	X
Drug application		X	X	X	X***		
Drug diary return			X	X			
Drug accountability			X	X	X***		

* Day 1 assessments can also be done at day 0
** Optional for the study. Participant does not need to complete in order to participate on the study.
*** For those patients who enroll onto open label portion, but do not enroll into the extension period of the study: patients apply study drug up to Visit 4 but not after this visit. Patients who enroll into the extension period will continue to apply drug until they withdraw from the extension period.
****For patients who enroll into treatment extension period.

For study purposes, Study Day 1 is defined as the first day of topical application.

10.1 Clinical

All study assessments/ procedures will be obtained in the course of routine outpatient dermatologic care. Therefore, this study places minimal burden on the patient.

Patients will receive evaluation in the Dermatology outpatient clinic of Memorial Sloan Kettering Cancer Center located in Manhattan. The medical history and other relevant details (demographics, concomitant medications) will be obtained as listed in Table 1. Patients will start treatment to an equivalent body surface areas to each side with ruxolintib cream to the designated affected side and vehicle cream to the contralateral side. Following the start of application of topical ruxolintib cream, patients will be seen by a physician and research staff for interim medical history, concomitant medications, study assessments, and AEs, on days 1, 14, 28, 56, ± 84.

10.2 Study Assessments

The subjects will be assessed by the study dermatologist on day 0,1, 14, at the end of study day 28 days, at the safety visit 4 weeks later (day 56), as well as 28 days after last dose of study drug for subjects who continue in the open-label extension (day 84). The assessments will include (Table 1):

Clinical assessment:

- **Skin examination with calculation of:**
  - ***Lesional Body Surface Area***: As per the 2014 NIH consensus criteria for chronic GVHD: Body surface area calculation of each face/body side that will be targeted with topical therapy will be performed by the study dermatologist on study visit on day 1, 14 ± 3 days, 28 ± 3 days, 56 ± 5 days[, and day 84 ± 5 days for subjects who continue in the open-label extension]. Patient will be photographed, and subsequently treatment-targeted BSA will be additionally calculated from these study visit photos by

one bone marrow transplantation hematologist blinded to treatment side. Standardized photography will be performed at each evaluation visit. (Table 1, Appendix I-II). Marked treatment areas will not change if improvement or worsening is seen.

- ***Physician's Global Assessment of Clinical Condition (PGA):*** area calculation of each face/body side will be performed by the study dermatologist on study visit on day 1, 14 ± 3 days, 28 ± 3 days, 56 ± 5 days [, and day 84 ± 5 days for subjects who continue in the open-label extension] (Appendix IV)
- ***Composite Assessment of Index Lesion Severity (CAILS) for each side***: area calculation of each face/body side will be performed by the study dermatologist on study visit on day 1, 14 ± 3 days, 28 ± 3 days, 56 ± 5 days[, and day 84 ± 5 days for subjects who continue in the open-label extension] (Appendix V)
- ***Adverse events*** *will be assessed* and graded as per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, and as applicable.

- ***Patient-reported outcomes assessment****:* Patients will complete an adapted skin-specific PRO-CTCAE™ on study visit on day 1, 14 ± 3 days, 28 ± 3 days, 56 ± 5 days[, and day 84 ± 5 days for subjects who continue in the open-label extension] for each side of the face/body (two questionnaires in total per visit). (Table 1, Appendix III). This questionnaire should take patients less than 10 minutes to complete.
- ***Safety follow-up:*** After completion of the 28 day ± 3 days study interval, patients will return for a final safety and follow-up visit at day 56 ± 5 days. Additionally, any patients who repeat a study drug course will return for an additional safety visit at day 84 ± 5 days. At this visit, patients will have a safety evaluation for possible adverse events (Table 1).
- ***Diagnostic interventions:*** Laboratory analyses and skin biopsy will be performed as clinically indicated. Minimally invasive skin tape strip RNA sequencing will be performed on each face/body side by the study dermatologist on study visit on day 28 ± 3 days. These skin strips will be shipped to DermTech, Inc. (11099 N. Torrey Pines Rd, Suite 100, La Jolla, CA 92037) Appendix VIII)
- Compliance with the topical agent will be assessed by reviewing the patient's application diary (Appendix VII).

11.0 TOXICITIES/SIDE EFFECTS

Topical ruxolitinib (INCB018424) 1.5% cream application results in a markedly (~90%) lower relative bioavailability than that following oral administration[23].

INCB018424 tested positive in a photoclastogenicity assay, hence there may be a risk of skin reaction to the combined exposure of INCB018424 and sunlight[23]. Subjects should be cautioned to avoid excessive exposure to either natural or artificial sunlight (including tanning booths, sun lamps, etc), and when outdoors, should be advised to wear loose-fitting clothing that protects the treated area from the sun[23].

The primary clinical risks noted with orally administered INCB018424 (ruxolitinib) treatment are the potential sequelae of decreased hematopoietic proliferation secondary to the inhibition of growth factor pathways by JAK2 antagonism[23]. Systemic exposure with topical INCB018424 is several fold below that which is associated with hematologic changes that may be seen following oral

dosing[23]. Dose-dependent, reversible thrombocytopenia has been observed in subjects with MF who were treated orally with ruxolitinib, as well as anemia and risks of possible transfusion, and less frequently neutropenia. An increased rate of infection is an additional potential risk of immunomodulation. GI side effects including diarrhea, nausea and liver dysfunction have been reported with oral Ruxolitinib. A few subjects have had an apparent worsening of their premorbid disease symptoms following rapid cessation of oral ruxolitinib therapy for MF[23]. A gradual tapering and use of steroids in fragile patients may be considered when stopping oral ruxolitinib therapy[23]. Leukemic transformation has been observed, but was considered to be consistent with the natural history of the underlying disease and unrelated to drug. In healthy volunteers and RA patients with greater bone marrow reserve, the effects on hematopoietic proliferation appear to be less pronounced[23].

INCB018424 phosphate cream has been evaluated topically in over 350 subjects in 6 clinical studies with administration of 1 to 24 months in duration[23].

Topical INCB018424 [23]

Study INCB 18424-201: In the topical proof-of-concept study in 29 subjects with psoriasis, 47 TEAEs were reported by 18 subjects. No deaths or other SAEs occurred. No subjects experienced life-threatening AEs or were discontinued from study drug or the study due to an AE. Pruritus and dry skin were the AEs reported by the greatest number of subjects (3 and 4 subjects, respectively). Cutaneous AEs were seen with similar frequency for vehicle-treated lesions and active comparator treated lesions when compared with INCB018424-treated lesions. All TEAEs resolved except 1 of QTcF prolonged, which began 14 days after the last application of study medication and was assessed as ongoing at the follow-up visit.

Application of INCB018424 0.5% to 1.5% cream QD or BID resulted in mean plasma concentrations of INCB018424 ranging from 0.34 ± 0.4 nM (Cohort A) through 2.10 ± 1.78 nM (Cohort C) at steady state. The mean INCB018424 steady-state concentration increased approximately proportional to application dose per day. The size of the lesion areas treated ranged from 9 to 63 cm^2. Application of INCB018424 0.5% to 1.5% cream QD or BID resulted in a mean skin flux of INCB018424 ranging from 54 ± 41 $ng/cm^2/h$ (Cohort A) through 422 ± 200 $ng/cm^2/h$ (Cohort C). The mean skin flux of INCB018424 increased with increasing application strength. The mean systemic bioavailability was 2.8 ± 3.2%, 3.0 ± 1.9%, 3.0 ± 1.9%, 2.7 ± 1.1%, and 2.7 ± 2.3% for Cohorts A through E, respectively. The systemic bioavailability of INCB018424 applied as a topical cream appears independent of the strength of the cream formulation.

Study INCB 18424-202: In the topical subtotal inunction study in 25 subjects with psoriasis, there were no subjects who discontinued from the study due to an AE and there were no deaths reported during the study. Overall, 4 TEAEs were considered at least possibly related to the study drug. These included transient leukopenia (unconfirmed on repeat testing), reticulocytosis, transient hypoesthesia, and transient application site irritation [23].

The average plasma concentrations of INCB018424 for Cohort A , Cohort B, Cohort C, Cohort D, and Cohort E were 7.00 ± 2.11 nM, 29.38 ± 13.10 nM, 24.42 ± 10.07 nM, 34.96 ± 20.43 nM, and 60.99 ± 73.85 nM, respectively, at the steady state. The mean INCB018424 C_{ss} increased

approximately proportional to application dose per day. The mean skin flux of INCB018424 was estimated to be 180 ± 126 ng/cm2/h, 131 ± 92 ng/cm2/h, 60 ± 43 ng/cm2/h, 151 ± 126 ng/cm2/h, and 152 ± 74 ng/cm2/h, respectively, for Cohorts A, B, C, D, and E. The mean topical bioavailability was estimated to be 3.8 ± 2.5%, 4.1 ± 3.4%, 3.4 ± 1.9%, 3.9 ± 1.3%, and 5.2 ± 1.9%, respectively, for Cohorts A, B, C, D, and E. Based on this result, it is concluded that the systemic bioavailability of INCB018424 applied as a topical cream is independent of the strength of the cream formulation and BSA.

Study INCB18424-203: In the double-blind, vehicle-controlled study in 199 subjects with psoriasis, 30 subjects (15.1%) across treatment groups experienced treatment-related TEAEs. Overall, these events were mild or moderate in intensity and generally resolved with or without the need for concomitant medication; 6 events that were possibly related to treatment resulted in subject discontinuation from the study. Across groups, 15 subjects (7.5%) discontinued from the study due to AEs and 17 subjects (8.5%) discontinued study drug application due to AEs. Four subjects (2 subjects each in the INCB018424 1.0% and 1.5% treatment groups) had their study drug temporarily withdrawn, and 1 subject in the INCB018424 1.5% treatment group had their study drug dosage reduced due to application site papules (unrelated to treatment). The most frequent AEs were nasopharyngitis, upper respiratory tract infection, application site irritation, and application site pruritus. There were no deaths reported during the study. Nine subjects reported 12 serious, severe, and/or life-threatening TEAEs, of which only 1 was considered related, a Grade 3 event of GGT increased in a 51-year-old woman. Three subjects discontinued study participation because of serious, severe, and/or life-threatening TEAEs. Since all but one of the serious, severe, and/or life-threatening AEs were not related to treatment, the cumulative events are considered to not contribute to the overall risk assessment[23].

Application of INCB018424 0.5%, 1.0%, and 1.5% cream QD resulted in a $C_{ss,min}$ of INCB018424 of 9.19 ± 11.77 nM, 16.99 ± 19.05 nM, and 19.97 ± 25.13 nM, respectively, for 0.5% QD to 1.5% QD. Thus, the mean INCB018424 $C_{ss,min}$ increased approximately proportional to application dose. As the severity of lesion thickness, erythema, and scale increased, the INCB018424 $C_{ss,min}$ appeared to be decreased for the same treatment. The subjects with less severe lesion thickness, erythema, and scale seemed to have higher trough INCB018424 exposures.

Study INCB 18424-204: This was a 2-part, open-label and double-blind, vehicle-controlled study in 90 subjects with AA. In Part A through Week 24, 9 subjects (75.0%) had a TEAE. One subject had Grade 3 SAEs of noncardiac chest pain, infected neoplasm, and sepsis, all judged not related to study drug by the investigator, that led to interruption of study drug; these events resolved, and the subject resumed study drug. All of the TEAEs in Part A occurred in 1 subject each. The majority of TEAEs were mild or moderate. In the open-label extension for Part A, 7 subjects (77.8%) had a TEAE. One subject had an SAE of lentigo maligna judged not related to study drug by the investigator; the lesion was excised and no action was taken with study drug. The most frequently reported TEAE during the open-label extension of Part A was back pain (2 subjects [22.2%]); all other TEAEs occurred in 1 subject each. The majority of TEAEs were mild or moderate. In Part B through Week 24, 23 subjects (59.0%) in the INCB018424 cream group and 27 subjects (71.1%) in

the vehicle group had a TEAE. The most frequently reported TEAE in subjects receiving INCB018424 cream was nasopharyngitis (6 subjects, 15.4% compared with 5 subjects [13.2%] in the vehicle group). The only other TEAEs reported in more than 1 subject receiving INCB018424 cream included pruritus (5 subjects, 12.8% in the INCB018424 group and 3 subjects [7.9%] in the vehicle group), headache (3 subjects, 7.7% in the INCB018424 group and 0 subjects in the vehicle group), and skin exfoliation (2 subjects, 5.1% in the INCB018424 group and 3 subjects, 7.9% in the vehicle group). One subject had an SAE of generalized anxiety disorder that was judged not related by the investigator and led to interruption of study drug. In Part B through the data cutoff, of the 63 subjects treated with open-label INCB018424 cream, 10 subjects (32.3%) randomized to INCB018424 and 22 subjects (68.8%) randomized to vehicle had a TEAE. The most frequent TEAE reported was nasopharyngitis, which was reported in 5 subjects (16.1%) randomized to INCB018424 cream and 2 subjects (6.3%) randomized to vehicle. One subject in Part B had an SAE of diverticulitis during open-label treatment that was judged by the investigator as not related to study drug; the subject remained on study drug during this event [23].
Twelve subjects were enrolled in Part A (INCB018424 1.5% cream BID). Similar mean plasma concentrations were observed between trough and C_{ss} in Part A.

Table 17: Summary of INCB018424 Steady-State Plasma Concentration or Trough Plasma Concentrations by Visit for Part A of Study INCB 18424-204

Treatment	Week 4	Week 12	Week 24
	C_{ss}[a] (nM)		
1.5% BID	25.4 ± 15.9 21.6	37.4 ± 29.9 30.1	31.7 ± 28.4 19.6
	Trough (nM)		
1.5% BID	26.2 ± 16.7 22.0	37.5 ± 24.2 31.5	26.3 ± 26.2 NA

Note: Values are presented as mean ± SD with geometric mean.
[a] C_{ss} is calculated as the mean of concentrations over predose, 1, 2, and 4 hours.

Higher trough plasma concentrations were observed in Part A compared with Part B. Similar mean trough concentrations were observed between Weeks 12 and 24 for both strata in Part B. Trough concentrations for subjects with 50% to 100% of scalp involvement with AA at baseline was almost double of that for subjects 25% to < 50% of scalp involvement with AA at baseline in Part B.

Table 18: Summary of INCB018424 Trough Plasma Concentration by Visit for Part B of Study INCB 18424-204

Strata[a]	Trough (nM)	
	Week 12	Week 24
Scalp involvement of 25% to < 50% at baseline	8.53 ± 6.41 NA	9.72 ± 11.3 NA
Scalp involvement of 50% to 100% at baseline	20.6 ± 25.9 NA	20.3 ± 35.7 NA

[a] All subjects in Part B received INCB018424 1.5% cream BID.

Study INCB 18424-206: This was a double-blind, active- and vehicle-controlled study in adults with AD. One hundred forty-seven subjects were randomized, and 132 subjects were treated with blinded study drug as of the cutoff date (28 JUN 2017). Blinded, unaudited data showed that 23 of the 132 treated subjects (17.4%) had a TEAE. The most frequently reported TEAE was nasopharyngitis, which occurred in 3 subjects (2.3%). One SAE of myocardial infarction was reported but was assessed by the investigator as not related to study drug; the subject had elevated cholesterol at baseline and was a long-time smoker, which likely contributed to the event. Of the 35 subjects who entered the open-label extension, 6 subjects (17.1%) had a TEAE. All TEAEs reported in the open-label extension occurred in 1 subject each. No SAEs occurred during the open-label extension[23]. No PK data were available as of the data cutoff date.

Topical ruxolitinib cream's limited adverse cutaneous events has been supported by clinical trials to date where cutaneous AEs have been infrequent and of similar frequency and severity as with vehicle control treatment. Adverse events reported with topical ruxolitinib were mostly related to application site, mostly mild to moderate (and judged to be unrelated to study medication), resolved, and did not require treatment discontinuation. Cutaneous AEs (dryness, pruritus, eczema, skin peeling) were seen with similar frequency in vehicle and topical ruxolitinib cream groups. Laboratory and ECG evaluations have not suggested any safety issues, specifically no instances of neutropenia, thrombocytopenia, or leukopenia. Based on vehicle controlled studies with topical ruxolitinib 1.5% cream, we do not expect significant systemic toxicities or local side effects from treatment with topical ruxolitinib 1.5% cream[23].

All toxicities will be graded as per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, and as applicable. All AEs (or clinically severe cutaneous adverse events, when CTCAE v5.0 grading not applicable) grade ≥2 with any attribution will be reported from initial application of topical intervention through the 56 day (and in those patients with a day 84) follow-up visit, and will be followed until the event resolves. If the AE does not stabilize/ resolve within a reasonable time (approximately 30 days), it should be followed until its clinical relevance and etiology can be reasonably explained[23].

Less common expected application-side adverse events include[23]:

- Dry skin
- Erythema
- Skin peeling
- Application site reactions irritation
- Skin burning
- Application site pruritus

General adverse events (unlikely or possibly to be related to topical ruxolitinib 1.5% cream), in both topical ruxolitinib 1.5% cream and vehicle arms of clinical trials include (in order of frequency)[23]:

- Upper respiratory tract infection
- Nasopharyngitis
- Sinusitis
- Influenza

- Back pain
- Electrocardiogram QT interval abnormal
- Diarrhea
- Gastroenteritis
- Headache
- Seasonal allergy
- Transient leukopenia
- Reticulocytosis
- Transient hypoesthesia

Based on a review of the extent of exposure, the incidence of AEs (including nonserious events, serious, severe, and/or life-threatening events, treatment-related events, and events that led to subject discontinuation), the clinical laboratory outcomes, the vital sign measurements, and the ECG findings, no safety signals or trends were observed.

All serious adverse events will be reported from initial application of study interventions through the day 56 ± 5 days safety visit, and the day 84 ± 5 days safety visit for those who repeat a topical ruxolitinib course, and will be followed until resolution.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary outcome of this study is the difference in body surface area (BSA) (Appendix I-II) of non-sclerotic and superficially sclerotic cutaneous cGVHD between ruxolitinib treated side and vehicle treated sides of the face/body at study completion (day 28 ± 3 days). Clinical assessment at all study visits, including baseline BSA will be performed by a dermatologist (Dr. Alina Markova,Dr. Mario E. Lacouture, Dr Veronica Rotemberg, or Dr. Sarah Noor). , and subsequently BSA will be calculated via photos by a single bone marrow transplantation hematologist.

Criteria for evaluation of clinical efficacy

No validated instruments for clinical assessment of chronic cutaneous GVHD exist[24]; we propose to use efficacy criteria that have been previously developed for evaluation of cutaneous T-cell lymphoma[25]. The body surface area (BSA) is the primary endpoint of efficacy. Secondary endpoints of efficacy include: Physician's Global Assessment of Clinical Condition (PGA), or the Composite Assessment of Index Lesion Severity (CAILS) grading scales are the secondary end points of efficacy[25]. The PGA will be the investigators' subjective assessment of the overall improvement or worsening in disease compared with the baseline assessment[25].

The CAILS assessment will generate a separate composite score for the treated and non-treated sides of the study participant. The assessment data to generate the composite score will be generated from case report form from the study visit. The treatment and vehicle sides of the body will be assessed for erythema, scaling, pruritus and size. For erythema, scaling and pruritus, the following grading system will be used.

CAILS Grading Tool for Erythema, Scaling, Pruritus [25]

Scale	Grade
0	No evidence of sign or symptom
1	Intermediate interval
2	Mild: less than average presentation of sign or symptom
3	Intermediate interval
4	Moderate: average disease presentation of sign or symptom
5	Intermediate interval
6	Severe: >25% worse than average severity of sign or symptom
7	Intermediate interval
8	Very severe: the near worst severity of sign or symptom

*Intermediate intervals 1, 3, 5, and 7 serve as midpoints between the defined grades of 0, 2, 4, 6 and 8.

An estimate for the % involvement of the right and left areas will be assessed on scale of 0 to 11 as follows:

CAILS Grading Tool for BSA Involvement

Grade	BSA within marked treatment area on each side
0	0
1	>0 and ≤2
2	>2 and ≤4
3	>4 and ≤6
4	>6 and ≤8
5	>8 and ≤10
6	>10 and ≤12
7	>12 and ≤14
8	>14 and ≤16
9	>16 and ≤18
10	>18 and <20
11	20

Composite Assessment of Index Lesion Disease Severity (CAILS): Signs and Symptoms and BSA Grade for Each of the 2 Selected Sides[25] (Extracted by unblinded Research Study Assistant from Physician-completed Appendix V)

Clinical Sign and Size	Non-Treated Area	Treated Area
Erythema	a (range 0-8)	e (range 0-8)
Scaling	b (range 0-8)	f (range 0-8)
Pruritus	c (range 0-8)	g (range 0-8)
Size (BSA)	d (range 0-11)	h (range 0-11)
Total	a+b+c+d (range 0-35)	e+f+g+h (range 0-35)

Separate summary scores for the treated and non-treated sides of the face/body will be created by summing ∑(a-d) and ∑(e-h), respectively. We will calculate a ratio of the day 28 assessment total score to baseline assessment total score for the treated and non-treated sides of the participant. We

will evaluate the difference in the ratios between the treated and non-treated sides of the face/body for each study participant.

Physician's Global Assessment of Clinical Condition (PGA)[25]

Grade	Description	Response
0	Completely clear: no evidence of disease (100% improvement)	Clinical Complete Response
1	Almost clear: very significant clearance (>90% to <100%); only traces of disease remains	Partial Response
2	Marked improvement: significant improvement (≥75% to <90%); some evidence of disease remains	
3	Moderate improvement: intermediate between slight and marked improvement (≥50% to <75%)	
4	Slight improvement: some improvement (≥25% to <50%); however, significant evidence of disease remains	Stable Disease
5	No change: disease has no changed from baseline condition (±<25%)	
6	Worse: disease is worse than at baseline evaluation by ≥25% or more	Progressive Disease

All patients who complete the day 28 +/- 3 days study visit will be eligible for the primary outcome of the study. The primary outcome of this study is the difference in body surface area (BSA) of non-sclerotic and superficially sclerotic cutaneous cGVHD between ruxolitinib treated side and vehicle treated sides of the face/body at study completion (day 28 visit). Assessment for BSA involvement, PGA, and CAILS will be made by a single dermatologist during the patient encounter. The dermatologist will record an estimate of involved BSA, PGA, and CAILS for both sides of the body in a blinded fashion. The CAILS score will be subsequently calculated by research study assistant (RSA), as described above, and the dermatologist and hematologist will be blinded to that score. In addition, clinical images will be taken of the treatment and placebo sides of the body at each patient visit to additionally document BSA involvement. The clinical evaluation, by the dermatologist, will be used for the efficacy assessment.

The secondary outcomes of this study are: (1) The difference in the Physician's Global Assessment of Clinical Condition (PGA) of non-sclerotic and superficially sclerotic cutaneous cGVHD between ruxolitinib treated side and vehicle treated sides of the face/body at study completion (day 28 visit); (2) The difference between the ratios of the day 28 CAILS total score to baseline CAILS total score of non-sclerotic and superficially sclerotic cutaneous cGVHD between ruxolitinib treated side and vehicle treated sides of the face/body at study completion; (3) Difference in the body surface area (BSA), Physician's Global Assessment of Clinical Condition (PGA), and the objective Composite Assessment of Index Lesion Severity (CAILS) of non-sclerotic and superficially sclerotic cutaneous cGVHD between ruxolitinib treated side and vehicle treated sides of the face/body at study completion (day 14 visit); (4) The difference in patient-reported outcomes between the side of the face and body treated with topical ruxolitinib cream versus the contralateral side treated with twice daily vehicle at day 14 visit and day 28 visit using the adapted National Cancer Institute Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) questionnaire; (5) The difference in chronic cutaneous non-sclerotic and superficially

sclerotic GVHD BSA between the sides of the face/body treated with topical ruxolitinib and vehicle by measuring the agreement of blinded independent physician's review of standardized photography of the right and left sides of the face and body respectively performed at day 28 visit; (6) The safety and tolerability of topical ruxolitinib by physical examination and adverse event reporting; (7) Accrual, retainment and compliance with therapy

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study (and will not be replaced) if:

- They develop an adverse event necessitating discontinuation of topical interventions.
- They require greater than 14 days off therapy due to a treatment-related adverse event.

Patients will be removed from the study and replaced if:

- They enroll in an alternate systemic clinical trial which prohibits concurrent topical clinical trial participation.
- They choose to withdraw consent for continued participation.
- Death occurs.

All patients who receive ruxolitinib and report using the treatment will be evaluable for toxicity.

14.0 BIOSTATISTICS

Target sample size is 24 patients, wherein 12 patients will be randomized to topical ruxolitinib to right side and 12 patients to the left side, with placebo cream on contralateral side. For each side of the face/body, non-sclerotic and superficially sclerotic chronic cutaneous GVHD BSA, PGA, and CAILS will be assessed in real-time by the study dermatologist observer blinded to the treatment status. The methodology for the real-time BSA calculation is available in Appendix I,II. The efficacy endpoint for the primary objective will be the difference in body surface area (BSA) as recorded by the dermatologist of non-sclerotic and superficially sclerotic cutaneous cGVHD between the topical ruxolitinib and vehicle treated sides of the face/body at study day 28. In this pilot study, we are utilizing three different measures to assess efficacy to qualitatively evaluate which works best for the clinician within the context of the patient visit. The bone marrow transplantation oncologist will subsequently calculate the BSA via total body photographs taken during the visit. Maximum BSA for topical ruxolitinib application will be 20% of overall BSA. All BSA, PGA, and CAILS assessments performed at study days 14± 3 days and study day 28 ± 3 days will be performed by the study dermatologist in real-time and serve as the data for the efficacy analysis. All BSA will also be calculated virtually by one bone marrow transplantation hematologist in review of total body photographs performed during visit, blinded to treatment, but will not contribute to efficacy assessments. Participants will only be included in the primary endpoint analysis if they complete the 28 ± 3 days assessment. Descriptive statistics and graphical methods will be employed to evaluate participant characteristics and the distribution BSA, PGA, and CAILS differences at each evaluation time point. Paired t-tests will be performed to assess differences in BSA. In addition, since the overall area treated may vary slightly between participants, we will use linear regression with the difference between treatment and control areas at day 28 as the dependent variable, and the total

treatment area BSA as the independent variable. Regresion coefficients along with 95% confidence intervals will be reported for this treatment area adjusted difference.
The primary aim is to assess the efficacy of ruxolitinib 1.5% cream for the treatment of non-sclerotic and superficially sclerotic chronic cutaneous GVHD at day 28 visit. This is a pilot study. With the average body surface area for male and female adult cancer patients has been estimated to be 1.9m^2 and 1.7m^2, respectively[26].Using an average BSA of 1.8m^2 (18,000 cm^2) for our mixed sample; if we and treat, on average, 5.0% BSA per participant, we expect to have equivalent areas of 0.09m^2 or 900cm^2 of treatment and control areas per participant.

Table. Effect size calculations for the minimum detectable difference in area between treatment and control sides of the participant based on varying levels of correlation between treatment and control areas within participant.

Effect Size	Difference in area between treatment and control areas (cm^2)	Control area (cm^2)	Treatment area (cm^2)	SD of the difference	SD Control area	Correlation between treatment and control areas
-0.5972	-400.6	900	499.4	670.8	500	0.1
-0.5972	-377.7	900	522.3	632.5	500	0.2
-0.5972	-353.3	900	546.7	591.6	500	0.3
-0.5972	-327.1	900	572.9	547.7	500	0.4
-0.5972	-298.6	900	601.4	500	500	0.5
-0.5972	-267.1	900	632.9	447.2	500	0.6
-0.5972	-231.3	900	668.7	387.3	500	0.7
-0.5972	-188.8	900	711.2	316.2	500	0.8

So, based on these estimates, if we select lesional areas on a patient equivalent to 5% BSA (which is roughly 900cm^2 for both treatment and control sides), and we have an estimated common standard deviation of 500, with 80% power, a two-sided test, an alpha level of 5%, and a correlation between treatment and control areas of 0.4, we can expect to detect a 327.1cm^2 difference between treatment and control areas at the day 28 evaluation. The effect size calculation is based on a paired t-test. Since we do not have any pilot data for these calculations, the estimate for the standard deviation that utilized for these estimates comes from experience with conditions with a similar presentation. The Table above lists the expected differences between treatment and control areas based on a range of correlations.

Secondary endpoints include:

1. Physician's Global Assessment of Clinical Condition (PGA) at day 28

   The difference in the PGA score of non-sclerotic and superficially sclerotic cutaneous cGVHD between the topical ruxolitinib and vehicle treated sides of the face/body will be calculated. The Wilcoxon signed rank test will be used to assess differences in these paired assessments for the day 28 assessment.

2. Composite Assessment of Index Lesion Severity (CAILS)

The difference between the ratios of the day 28 CAILS score to baseline CAILS score of non-sclerotic and superficially sclerotic cutaneous cGVHD between ruxolitinib treated side and vehicle treated sides of the face/body at study completion.We will use descriptive statistics to describe the distribution of the difference in CAILS ratios between treated and vehicle sides of the body. The difference in ratios will be assessed using a paired t-test.

3. Efficacy at day 14

Little is known about the efficacy of this treatment in this patient population. As a secondary aim, we will assess efficacy at the 14 day visit as we described for the primary aim of the study using paired t-tests and linear regression to control for potential differences in overall treatment areas between study participants.

4. Patient-reported Outcomes

Patient reported outcomes measured by the NCI Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE™) for each side of face/body affected by GVHD rash; a Likert-scale patient-reported assessment of change in the treated areas has been appended to adapt the PRO-CTCAE™ for this study. PRO-CTCAE™ instrument will be scored as ascribed by methods published for this instrument. Overall summary measures and subdomain measures will be summarized using descriptive statistics. To evaluate differences in the paired responses, for the overall PRO-CTCAE score and for each of the subdomain scores, the Wilcoxon signed rank test will be used.

5. Agreement between GVHD BSA Measurements
GVHD BSA measurements will be evaluated during the patient visit by a dermatologist, and by an additional bone marrow transplant physician using digital clinical images captured during the patient visit. The GVHD BSA assessments for both evaluations will be visually assessed using scatterplots of the two independent assessments and compared using Lin's concordance correlation coefficient.

6. Safety and Tolerability
All patients will be evaluable for adverse events (toxicities) from the time of their first treatment with ruxolitinib until the end of the study visits or until they are lost to follow-up. All reported adverse events (AEs grade ≥2 with any attribution) during the study period through day 56 follow-up [,and day 84 ± 5 days for subjects who continue in the open-label extension] visit will be coded using Medical dictionary for regulatory activities (MedDRA) Version 20.0. For all adverse events, all treatment-emergent adverse events, all serious adverse events, and all adverse leading to discontinuation frequency distributions by system organ class and preferred term will be calculated and presented for each patient and each treatment side, when applicable. The safety of all patients enrolled in this study will be monitored throughout the study, and at safety visit 28 ± 5 days following the last study dose. Safety monitoring will include history and physical examination with adverse event reporting. A follow-up safety evaluation will be done until end of study visit after discontinuing topical ruxolitinib cream treatment or withdrawal from the study for any reason. In addition, patients should notify the study staff of any problems that occur between visits by telephone and, if

necessary, be evaluated by the Investigator or study staff at an unscheduled interim hospital visit.

Treatment adjustments:Patients who report or exhibit treatment-related AEs should have their treatment exposure reduced or discontinued. If no frequency of study drug application is tolerated for any of the patient's lesional skin, then the patient must be withdrawn from the study. Treatment interruptions for non-medical reasons are at times unavoidable and are permissible under this protocol but must be documented. However, every attempt should be made to avoid any non-medical treatment delays

- Grade 1 – 2: No change to study drug dose. Continue clinical monitoring.
- Grade 3 (with attribution possibly, probably, or definitely related): Hold study drug until AE improves to grade ≤2.
- Grade 4 (with attribution possibly, probably, or definitely related): Discontinue study drug.

Adverse Event Definitions
The following definitions of terms guided by the International Conference on Harmonization and the US Code of Federal Regulations apply to this section:
An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment.
Serious adverse event (SAE) is any adverse event that is fatal or life-threatening, is permanently disabling, requires or prolongs inpatient hospitalization, or is a congenital anomaly, or any important medical event.

- Life-threatening, for the purpose of reporting adverse events, refers to an event in which the patient was, in the view of the initial reporter, at immediate risk of death at the time of the event as it occurred (i.e., it does not refer to an event which might have resulted in death if it were more severe).
- Hospitalization describes a period of at least 24 hours. Over-night stay for observation, stay at emergency room or treatment on an out-patient basis do not constitute a hospitalization. However, medical judgment must always be exercised and when in doubt the case should be considered serious (i.e. if case fulfills the criterion fora medically important event).
    - Hospitalizations for administrative or social purposes do not constitute a serious adverse event.
    - Hospital admissions and/or surgical operations planned before trial inclusion are not considered AEs, if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial. Associated with the use of the drug means that there is a reasonable possibility that the event may have been caused by the drug.

Toxicity information will be presented on an individual basis and will be summarized using descriptive statistics.

7. Accrual, retainment and compliance with therapy

Since this study involves a novel patient population for our department, we will evaluate metrics on the number of patient accrued relative to the number approached. We will also assess retainment at each study time point. Compliance with application of the study

medications will be assessed via patient logs.

Descriptive statistics will be provided for patient characteristics, efficacy, patient-reported outcomes, safety and tolerability, and minimally invasive skin tape strip molecular profiles as appropriate. Patients will be evaluable for the efficacy assessment if they complete the 28 day (+/-3 day) assessment. If patients miss other planned assessments, they will still be evaluable for the primary objective.

We expect to accrue 1 – 4 patients per month, and expect to complete enrollment in 6-26 months.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

This is a double blind randomized comparison of topical ruxolitinib to topical vehicle: Topical ruxolitinib 1.5% cream on left or right side of face/body vs. vehicle on contralateral side of face/body. Patients will be randomized to determine which side of the face/body (i.e., right or left) will be treated with topical ruxolitinib 1.5% cream, and the contralateral side will be treated with the control vehicle. Randomizing the treatment side is to maintain blinding of the physician. For example: if patients are all assigned to apply topical ruxolintib to their right side and are showing clinical improvement on each patient's right side consistently, the physician will be aware that the right side is the treated side, possibly adding bias to the study. Variability in application side will also help to account for inter-patient variability in application with right- versus- left hand. After eligibility is established and immediately after consent is obtained, patients will be registered in the Clinical Trail Management System (CTMS). After registration, patients will be randomized in the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block. Since this is a double-blinded study, the patients' treatment assignments can be viewed in the CRDB only by the hospital pharmacists who are dispensing the study drugs.

At the end of the 28 ± 3 days study visit, patients will remain blinded to treatment arms.After trial completion (day 28 ± 3 days), all patients will be offered repeated treatment cycle with topical ruxolitinib or standard of care therapy .

The PI will contact DMR to obtain patients' treatment assignments at trial conclusion for data analysis.

16.0 DATA MANAGEMENT ISSUES

Data forms will be developed for recording all information pertinent to the observations and tests described in this protocol. All study data will be collected by an assigned data manager who will enter this information into MSK Medidata in a timely and accurate manner. All data and forms gathered for this study will be collected and stored in a secure location in facilities of the Dermatology Service. Regular meetings attended by the data manager and the Principal Investigators will be held to review study progress and to manage any difficulties encountered.

The data manager will collect toxicity and self-reported compliance data via patient's diaries and patient interviews. Adverse events, including all toxic effects related to treatment will be recorded individually according to toxicity date.

All clinical photographs will be maintained in digital format in a computerized archive (DermagraphixTM). This system labels each clinical photograph with study subject MRN, lesion number, and photograph date.

All patient data and questionnaires will be accessed on the Health Information System (HIS) and Mirror Dermagraphix database, which are password protected with user level access. All the data will be entered and maintained in MSK Medidata.During data analysis, de-identified data will be sent to investigators at Hackensack Medical Center for collaboration and manuscript preparation. All de-identified shared with Hackensack Medical Center invstigators will be sent via MSK secure email.

The first interim data analysis will occur after the study has accrued 10 evaluable participants. Only the biostatician and Dermtech personnel will be unblinded during the analysis.

The second interim data analysis will occur with the remaining 14 evaluable participants. Only the biostatician and Dermtech personnel will be unblinded during the analysis.

Estimated time of accrual: 26 months
Accrual Rate: 1-4 patients per month
Time to complete study: 36 months

16.1 Quality Assurance

Study personnel will generate monthly registration reports to monitor patient accrual and completeness of registration data. Routine data quality reports will be generated to access missing data and inconsistencies. Accrual rates, extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Data quality and protocol compliance audits will be conducted by the study team on a regular basis throughout the study period

16.2 Data and Safety Monitoring

Data and safety monitoring audits will be conducted by the study team on a regular basis throughout the study period. The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible side effects. Patients reserve the right to withdraw participation from this study at any time.

Risks: It's unlikely that significant risks will be associated with the limited use of topical ruxolitinib 1.5% cream planned in this study.

Benefits: The early use of topical ruxolitinib 1.5% cream is hypothesized to reduce BSA of non-sclerotic and superficially sclerotic chronic cutaneous. This would serve as a novel topical therapy for management of non-sclerotic and superficially sclerotic chronic cutaneous GVHD and would improve patients' symptoms during treatment.

Possible toxicities/ adverse events. Local application-site side effects anticipated with ruxolitinib include dry skin, erythema, pruritus, skin peeling, and irritation. These adverse effects are not expected to necessitate treatment interruption. Systemic toxicities are rare, including upper respiratory tract infection and nasopharyngitis. Toxicities of topical ruxolitinib 1.5% cream are elaborated in section 11.0 of this protocol. The investigators will use a standardized form to assess irritation, pruritus, erythema and during the visits, as well as rare reactions that could be reported by the patient.

Consent process: Participation in this protocol is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSKCC IRB guidelines.

Costs: Patients will not be charged for protocol related costs

Alternatives: There are no FDA-approved topical therapies for the treatment of non-sclerotic or superficially sclerotic chronic cutaneous GVHD; however, efficacy has been reported with topical corticosteroids.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate personnel may review patient records as required.

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols: The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1

SAE Reporting to Incyte

Incyte needs to be notified within **24 hrs** of learning of an event. Incyte also needs to be provided a completed SAE form via email. SAE reporting for each subject begins the day the informed consent is signed by the patient and within 30 days after subject has completed or discontinued from the study or has taken last dose of the study drug. Any SAEs occurring more than 30 days after the last dose of protocol treatment should be reported only if the investigator suspects a causal relationship to the protocol treatment.

Initial Serious Adverse events (SAEs) and/or subsequent follow-up reports will be reported via email to: SafetyReporting@Incyte.com, fax (+) 1-866-981-2057. SAE reports will be for a single subject.

SAE forms will be emailed with a cover sheet to the IST email address: SafetyReporting@Incyte.com, fax (+) 1-866-981-2057.

Reporting of Pregnancy to Incyte

An “Initial Pregnancy Report” or equivalent will be completed in full and emailed to SafetyReporting@Incyte.com, fax (+) 1-866-981-2057 within **24 hrs** of discovery of a pregnancy of a subject who has taken ruxolitinib. The “Follow-up Pregnancy Report Form” or equivalent must be completed and emailed to SafetyReporting@Incyte.com, fax (+) 1-866-981-2057 within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy.

Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Pregnancy form and reported by the investigator. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process will be followed and the timelines associated with an SAE will be followed.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

- Appendix I: Adult Body Surface Area Calculator
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- Appendix IIIA: PRO-CTCAE™ (LEFT)
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