Exploratory Study of Ruxolitinib Cream for the Treatment of Discoid Lupus Erythematosus

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TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS

AE	Adverse event
AIR	Allergy, Immunology and Rheumatology
BSA	Body surface area
CBC	Complete blood count
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CMP	Comprehensive metabolic panel
CTU	Clinical trials unit
DLE	Discoid lupus erythematosus
EI	Erythema index
FDA	U.S. Food and Drug Administration
IFM	Immunofluorescence microscopy
IFN	Interferon
IGA	Investigator's Global Assessment
IHC	Immunohistochemistry
IND	Investigational new drug
IRB	Institutional review board
JAK	Janus kinase
MACE	Major adverse cardiovascular event
MI	Melanin index
NRS	Numeric rating scale
PHI	Protected health information
PI	Principal investigator
RSRB	Research subjects review board
SAE	Serious adverse event
STAT	Signal transducer and activator of transcription
URMC	University of Rochester Medical Center

1. PURPOSE OF STUDY

The primary objective of this study is to assess the potential efficacy of topical ruxolitinib for the treatment of discoid lupus erythematosus (DLE). We propose a 12-week open-label clinical trial. An exploratory objective of this study is to analyze cellular and molecular features of discoid lesions before and after treatment with topical ruxolitinib to assess 1) predictors of treatment response, and 2) treatment response to ruxolitinib.

2. BACKGROUND AND RATIONALE

Standard of care for patients with DLE depends on disease severity, but can include topical steroids, topical calcineurin inhibitors, systemic antimalarials, and systemic immunosuppressive medications. The only FDA-approved medication for DLE is hydroxychloroquine. Consequently, topical steroids and calcineurin inhibitors, as well as a number of systemic immunosuppressive medications, are also used to treat DLE. Systemic immunosuppression is used infrequently. Topical calcineurin inhibitors are generally less effective than topical steroids, but arguably may have a more favorable safety profile. Topical steroids have the potential to induce skin atrophy, an especially devastating side effect on the face, head and neck, the most commonly affected areas in DLE. Though not often used on the face to treat other skin conditions, due to the severe nature of the disease, class I superpotent topical steroids are used in DLE for short periods of time (< 2 weeks), while weaker topical steroids are generally not very effective. Antimalarials and other systemic immunosuppressive medications are effective in some DLE patients, but have significant potential side effects including retinopathy, cytopenias, liver toxicity, and increased infection risk.

Type I interferons are key inflammatory cytokines in DLE pathogenesis.[1] These inflammatory mediators signal through the JAK-STAT pathway. Janus kinase (JAK) inhibitors, which block interferon (IFN) signaling, are a new class of therapeutics with potential efficacy in lupus. Systemic JAK inhibitors have been effective in murine models of lupus.[2-4] Of particular interest is one murine study in which oral ruxolitinib, a potent JAK1/2 inhibitor, attenuates cutaneous lupus development, without much effect on systemic disease.[2] This study suggests that ruxolitinib may be more selective in treating lupus skin disease.

Oral ruxolitinib is FDA-approved for the treatment of polycythemia vera, myelofibrosis and acute graft-versus-host disease. Topical ruxolitinib has been shown to be effective in a number of inflammatory human skin diseases including alopecia areata/universalis, vitiligo, and atopic dermatitis.[5-7] Systemic side effects have not been reported with topical use. The most common side effects from topical JAK inhibitors are mild and include local irritation, erythema, acne, or papular eruptions. In summary, we hypothesize that topical ruxolitinib may be both more effective and safer than topical steroids for the treatment of DLE.

3. ADMINISTRATIVE ORGANIZATION

This is a single-center study in the Department of Dermatology at the University of Rochester Medical Center (URMC). Dr. Christopher Richardson, who is a medical dermatologist with clinical and research expertise in lupus, will be the principal investigator (PI). The study will be performed in the URMC Dermatology Clinical Trials Unit (CTU), which will provide both administrative and coordinator support for the trial. Medication management will be handled by the Investigational Drug Service of the URMC Department of Pharmacy. Safety laboratory monitoring will be done through URMC labs. Laboratory analyses of deidentified skin samples will be performed in the Richardson laboratory and URMC core facilities.

4. STUDY DESIGN

This is a 12-week, single-center, open-label study of ruxolitinib 1.5% cream for the treatment of discoid lupus. The primary endpoint is a ≥ 2-point reduction in Investigator's Global Assessment (IGA) score at Week 12 compared to baseline. Secondary endpoints at Week 12 include the mean percentage change from baseline in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), CLASI-A (activity) and CLASI-D (damage) scores; the change in erythema and pigmentation as determined by quantitative photographic analysis; and the change in numeric rating scale (NRS) for pain and pruritus. Exploratory endpoints of skin biopsies will evaluate cellular and molecular features of discoid lesions pre- and post-treatment for 1) predictors of treatment response, and 2) treatment response to ruxolitinib. Quantitative and qualitative measures of the cutaneous inflammatory response, including evaluation of the immune cell infiltrate and IFN signature, will be assessed.

4.1. SUBJECT POPULATION

4.1.1 Number of Subjects

Fifteen subjects will be consented to enroll in this study. This small sample size is justified by the rarity of this condition and the exploratory nature of the study.

4.1.2 Gender and Age

DLE has a female predominance, but both men and women may participate. Subjects will be 18 years old or older.

4.1.3 Racial and Ethnic Origin

DLE affects all racial and ethnic groups, but is more frequent and more severe among African Americans than among Caucasians. Racial and ethnic origin of subjects will be monitored to reflect the diversity of our community. However, no subjects will be excluded based on race or ethnic origin.

4.1.4 Vulnerable Subjects

Vulnerable subjects will not be targeted, including children, pregnant women, prisoners, and decisionally impaired adults. Employees and students of the University may participate but will not be targeted or coerced.

4.2. STUDY INTERVENTIONS

The active drug used in this trial will be ruxolitinib 1.5% cream. Ruxolitinib cream will be applied topically twice daily to areas of active disease. Ruxolitinib cream will be supplied by Incyte. Incyte's IND number for ruxolitinib is #77,101. Inventory control and storage, drug accountability, packaging and labeling, and dispensing will be managed by the URMC Investigational Drug Services. Standard topical therapies will be replaced with the study drug, and only systemic antimalarials will be continued as standard of care during this study. Details of potential risks associated with this drug is discussed in detail in **Section 9, Risks to Subjects**. Subjects are free to withdraw from the study at any time.

5. INCLUSION AND EXCLUSION CRITERIA

5.1 Inclusion Criteria

Individuals who meet all of the following criteria are eligible for enrollment as study participants:

- Ability to understand and comply with the protocol and provide informed consent.
- Speaks English.
- Age ≥ 18 years.
- Clinical diagnosis of discoid lupus as assessed by the PI.
- At least one active (inflamed) discoid lesion with an IGA score of ≥ 3 and with a diameter ≥ 1cm at screening and baseline. Two lesions with equal scores will be necessary if consenting to pre-and post-treatment biopsies.
- Maximum body surface area of 20%.

5.2 Exclusion Criteria

Individuals who meet any of these criteria are not eligible for enrollment as study participants:

- Unwillingness or inability to complete informed consent process or comply with the study protocol.
- Pregnant or breast-feeding women, or women planning to become pregnant or breastfeed during the study.
- History of coagulopathy, pulmonary embolism or deep venous thrombosis.
- History of cutaneous squamous cell carcinoma localized to the treatment area.
- Serum creatinine > 1.5 mg/dL, or alanine aminotransferase or aspartate aminotransferase > 1.5 × upper limit of normal.
- Other dermatologic disease besides discoid lupus whose presence or treatments could complicate assessments.
- Other diseases besides dermatologic disorders whose treatment could complicate assessments. Subjects with systemic lupus erythematosus are permitted as long as they

do not have unstable disease and meet all other criteria, including the exclusion criteria for systemic immunosuppressive or immunomodulating drugs (below).

- Topical treatments for discoid lupus within 2 weeks of Visit 2.
- Systemic immunosuppressive or immunomodulating drugs (e.g. oral or injectable corticosteroids, methotrexate, cyclosporine, mycophenolate mofetil, azathioprine) other than antimalarials (hydroxychloroquine, chloroquine, quinacrine) within 4 weeks or 5 half-lives of Visit 2 (whichever is longer).
- Potent systemic cytochrome P450 3A4 inhibitors or fluconazole within 2 weeks or 5 half-lives, whichever is longer, before Visit 2 (topical agents with limited systemic availability are permitted).
- Prior use of JAK inhibitors, systemic or topical, within the last 12 months.
- Ultraviolet (UV) therapy or tanning within 2 weeks prior to Visit 2 or during the duration of the treatment period.
- Any systemic or local infection that, in the opinion of the investigator, may compromise the safety of the subject or complicate assessments.
- Subjects allergic to lidocaine or with a history of keloids will not be allowed to provide an optional skin biopsy, but will be eligible for the remainder of the study.

6. RECRUITMENT METHODS

Eligible subjects will be identified and recruited in the following ways:

- Subjects with DLE may be recruited from the contact database of Med/AIR Subject Database and Tissue Repository (RSRB#276) or the Evaluation of the Pathogenesis of Cutaneous Lupus Erythematosus study (RSRB#3215) if subjects have previously indicated their interest in being contacted for future studies. The PI of this study (Dr. Richardson) is also the PI of RSRB#3215 and a sub-investigator on RSRB#276.
- This study will identify potential subjects for recruitment using the UR CTSI Research Participant Registry, STUDY00001978. Subjects enrolled in the URMC Research Participant Registry may be contacted to enroll in this study.
- Subjects may be recruited during routine clinic visits by providers and staff involved in their care. These providers may also include the PI and Sub-investigators. To assist in identifying subjects who have not yet been recruited into this study, the study coordinators may review eRecord charts of individuals prior to their clinic visits to prompt the provider to discuss research with them. Subjects will be approached by staff providing care to obtain the subject's agreement to be contacted by the study team.
- As standard of care, subjects who have been evaluated in the Department of Dermatology or Allergy, Immunology and Rheumatology (AIR) Division, and who have been coded with a lupus specific ICD-9 or ICD-10 code, may have providers reach out and offer for them to be seen in a Dermatology or AIR clinic. They may also be

offered enrollment in this study. Subjects who do not want to be seen in clinic will still have the option to enroll into this study.

Potential subjects may be contacted via telephone call to discuss the study, field questions and assess interest; an IRB approved Telephone Script will be followed. If the potential subject is interested in participating in the study they will be offered to have the consent form mailed or emailed to them to READ ONLY with an IRB approved Information Sheet with instructions that the consent is for review only. Prior to the consent being mailed or emailed to the potential subject a study team member will cross out the signature page to eliminate confusion. The potential subject will sign a NEW clean consent upon their clinic and/or study visit along with the study team member.

7. CONSENT PROCESS

7.1 **Process of Consent**

The consent process will provide information about the study to a prospective participant and will allow adequate time for review and discussion prior to his/her decision. The PI or a qualified study member listed in the CLICK IRB protocol will review the consent form with the participant and answer questions. Consent designees will be listed on the site delegation of responsibilities log, complete consenting certification, and have knowledge of the protocol and study procedures. The PI or designee will meet directly with subjects in a private room and the consent form will be read in its entirety. Any questions will be answered to the subject's satisfaction. The subject's capacity to comprehend the information in the consent form will be assessed by asking questions about the content and encouraging the subject to describe briefly the study procedures. Subjects will be assured that enrollment is voluntary and that they are free to not participate or to withdraw at any time, without risking loss of present or future care that they would otherwise receive. It will be explained to the subject that those who consent to participate in this study will have their contact information and medical history stored in the database. Subjects will be informed that if they withdraw consent, no new information will be collected, and they can choose to have any stored samples discarded. However, data generated from previously used samples may be retained. Subjects will be allowed as much time as necessary to provide consent. Subjects will provide consent by signing the informed consent form for this study. Subjects will receive a signed copy of the consent form. The consent process will be ongoing. The consent form will be revised, and the subjects re-consented, when important new safety information is available, the protocol is amended, and/or new information becomes available that may affect participation in the study.

7.2 **Consent Forms**

Attached in the RSRB application.

7.3 **Documentation of Consent**

Both the study subject and the person obtaining consent will sign and date the consent form in order to document consent.

8. STUDY PROCEDURES

This study will be a single-arm trial of ruxolitinib 1.5% cream applied twice daily for 12 weeks. Only active lesions will be treated, defined as those with erythema, scale, pain, or pruritus. Each subject will be provided with ruxolitinib cream.

8.1 **Subject Visits**

Each subject will have a total of 7 visits. The initial visit will be the Screening visit, which will occur 7 to 28 days before the start of the trial. Treatment visits will be at weeks 0, 2, 4, 8, and 12, at which times the subject will have assessments performed to document DLE severity and assess safety. A follow-up visit to assess safety will be performed at 16 weeks.

8.2 **Study Procedures**

Clinical assessments, safety procedures, and research procedures will be performed as outlined below per the schedule of activities. In the event that one of these is not able to be completed, disease activity increases or other concerns arise, the subject may be asked to return to the clinic for an "unscheduled visit" to reassess the subject and perform as needed any clinical assessments, safety procedures, or research procedures as outlined below.

8.2.1 **Clinical Assessments**

Clinical Assessments: A detailed physical exam, past medical history and vital signs will be performed at study visit 1. A problem-focused physical exam, interval history and vital signs (heart rate, blood pressure, temperature, weight) will be performed at visits 2-7. Adverse events will be assessed at study visits 2-7.

IGA: The Investigator's Global Assessment will be performed at study visits 2-6. The IGA is an instrument to rate the severity of the subject's global disease. This IGA is comprised of a 5-point scale of disease activity ranging from 0 to 4 as follows:

0: "clear," no erythema or scale
1: "almost clear," pink erythema without scale
2: "mild," pink erythema with scale
3: "moderate," red erythema with scale
4: "severe," purple/violaceous or hemorrhagic/crusted erythema OR hypertrophic/ verrucous scale

CLASI: The Cutaneous Lupus Area and Severity Index will be performed at study visits 2-6. This is a validated measurement instrument designed for use in clinical trials to assess disease activity and damage in subjects with cutaneous lupus. The CLASI is comprised of two parts, CLASI-A that measures disease activity (erythema and scale), and CLASI-D that measures disease damage (pigmentation and scarring).

NRS: Subjects will maintain a symptom diary every day for 12 weeks. Specifically, subjects will rate pain and itch separately using a numeric rating scale (NRS) and the questions below. Symptom diaries will be reviewed at study visits 2-6.

On a scale of no itch (0) to worst imaginable itch (10), how itchy was the worst discoid

lupus lesion in the last 24 hours?

On a scale of no pain (0) to worst imaginable pain (10), how painful was the worst discoid lupus lesion in the last 24 hours?

Photography: Photographs of all discoid lesions will be taken at study visits 2-6. The Haiku app or Canto app will be used to directly load photos into the secure Epic medical record system. Images will be extracted from Epic, and analyzed as described.[8] In brief, a melanin index (MI) and an erythema index (EI) will be generated for each lesion using Image J software analysis. The analysis uses perilesional skin to normalize the photograph. Images from serial visits will then be compared, as well as between treatment groups.

Compliance: Tubes of cream will be weighed at each visit. Additional jars/tubes will be supplied as needed at study visits, which will vary depending on the percent body surface area (BSA) involved.

8.2.2 **Safety Monitoring**

History & Exam: An interval history and problem focused physical exam will be performed at each visit. Subjects will also be asked about recent systemic infections. The focused exam will also include an assessment of the skin immediately surrounding the DLE lesion for irritation using a standard 8-pt scale. This scale was developed by Berger and Bowman[9] to assess the effect of topicals on normal skin; any visual assessment methodology for irritation on an already inflamed DLE lesion would not be informative.

Phlebotomy: Blood draws will be performed by a trained phlebotomist. A complete blood count (CBC), comprehensive metabolic panel (CMP), and lipid panel will be assessed at the screening visit. Additional labs will be drawn as follows: CBC and CMP at 4 and 12 weeks, lipid panel at 12 weeks. Standard of care laboratories may be drawn at the same time for subject convenience. The venipuncture site will be covered with gauze and a band-aid.

Urine pregnancy test: Urine pregnancy tests will be performed at screening and monthly during treatment for all females of childbearing potential. Menopause is defined as at least 12 consecutive months without menses; if in question, a follicle stimulating hormone of ≥25 U/mL must be documented. Hysterectomy, bilateral oophorectomy, or bilateral tubal ligation must be documented, as applicable; if documented, a urine pregnancy test is not required for women with these conditions.

8.2.3 **Research Procedures**

Optional skin biopsies at weeks 0 and 12 will be analyzed as follows:

- Histology: H&E, immunohistochemistry (IHC), and/or immunofluorescence microscopy (IFM)
- Flow cytometry/cell sorting: composition of inflammatory infiltrate
- RNAseq: IFN signature

Biopsy: For subjects that are willing to provide an optional skin biopsy, two discoid lesions with equal IGA scores (3 or 4) will be selected at Visit 2, one of which will be biopsied at that visit. At visit 6, the other lesion will be biopsied.

After obtaining informed consent, a skin biopsy will be obtained by a study practitioner trained in this procedure. A biopsy will consist of removing a piece of skin with a 4-mm skin biopsy punch. The biopsy will be performed after injecting a local anesthetic (lidocaine with epinephrine) to minimize pain and blood loss. At the biopsy site one or two sutures may be placed to improve healing, reduce blood loss and scar formation. A pressure bandage will be applied to the biopsy site to minimize the risk of bleeding and infection. The biopsy will be divided as appropriate for subsequent analysis.

All study subjects will be given the option to visit the study center for suture removal 7-14 days after the biopsy was taken. Our experience is that some of our study subjects, especially the ones who live far from the study center, prefer to have their sutures removed by a local physician, health care provider, family member or friend trained on removing sutures. Nevertheless, we will strongly recommend in each case that the study subject return to the study center for removal of suture so that we can evaluate whether the biopsy site is healing well.

We will provide each subject with a wound care instruction sheet which says:
"If non-absorbable stitches were placed, they should be removed either by returning to the University of Rochester Department of Dermatology or by a local physician, health care provider, family member or friend with experience removing sutures in 7 to 10 days from their placement. If possible, keep the biopsy site completely dry for the first 24 hours after the biopsy. After that, change the band-aid and apply petroleum jelly to the site on a daily basis. We have provided you with the supplies to do this. The site will appear a bit red and may be itchy after several days and that is a normal healing response. Please contact us if at the site of the skin biopsy the pain increases, the dressing continues to be saturated with blood or there is foul-smelling, pus-like drainage from the site (after the first 2 days). For any questions or concerns, or to arrange for stitch removal, call the Clinical Coordinators - at 585-273-2909 or 585-273-4195."

Histology: We will analyze the DLE skin tissue using IHC and/or IFM. Common features of DLE histology will be evaluated, including hyperkeratosis, epidermal atrophy, follicular plugging, interface change, and immunoglobulin deposition. A quantitative analysis of immune cell counts will be performed. Markers of IFN response will be analyzed.

Flow Cytometry: We will evaluate the immune and other cell types from disaggregated DLE skin tissue by multi-color flow cytometry per lab protocols.

Transcriptomics: The IFN signature will be evaluated by RNAseq.

8.2.4 **Schedule of Activities**

Study Procedure	Screening	Treatment					F/U	Unscheduled
Visit	1	2	3	4	5	6	7	
Week	-4 to -1	0	2	4	8	12	16	
Study day	-28 to -7	0	14	28	56	84	112	
Window in days			+/-3	+/-3	+/-3	+/-3	+/-3	
Screening/Baseline								
Informed Consent	X							
Review eligibility	X							
Medical history	X							
Detailed physical exam	X							
Demographics	X							
Confirm eligibility/Enroll		X						
Assessment								
Vital Signs	X	X	X	X	X	X	X	X
Interval history		X	X	X	X	X	X	X
Problem-focused Exam		X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
IGA		X	X	X	X	X		X
CLASI		X	X	X	X	X		X
Symptom Diary Review		X	X	X	X	X		X
Photography		X	X	X	X	X		X
Laboratory Testing								
CBC, CMP	X			X		X		X
Lipid panel	X					X		X
Urine Pregnancy	X	X		X	X	X		X
Treatment								
Weigh product		X	X	X	X	X		X
Dispense product (as needed)		X	X	X	X			X
Return product						X		X
Research Procedure								
Skin biopsy (*optional*)		X				X		X

8.2.5 **Data Analysis**

***Primary Endpoint*:** A ≥ 2-point reduction in IGA score at Week 12 compared to baseline.

***Secondary Endpoints*:** The mean percentage change at Week 12 from baseline in CLASI, CLASI-A and CLASI-D scores; erythema (EI) and melanin indices (MI); and NRS for pain and pruritus.

***Exploratory Endpoints*:** The change in inflammatory response, which includes the degree of inflammation, composition of inflammatory infiltrate, and interferon (IFN) signature.

9. RISKS TO SUBJECTS

9.1 **Risks of Participation**

As with any change in treatment, there is a risk of no change or worsening of disease. All subjects in this study will have active discoid lesions. This means that their current therapeutic regimen is inadequate to control their disease. Stopping any current topical therapies may lead to worsening of disease, but continuing the same treatment regimen will not lead to clearance of disease activity.

Ruxolitinib cream: Skin-related side effects of ruxolitinib 1.5% cream are rare, but local irritation, pain, itch, erythema, acne, or papular eruptions have been observed.[5, 6, 11] Systemic side effects are not expected. In the largest trial of ruxolitinib cream to date (307 patients with atopic dermatitis, 3-20% BSA), no clinically significant laboratory changes were observed.[11] As of June 28, 2020, a total of 2350 study participants have been exposed to topical ruxolitinib, with no serious adverse events or fatal or life-threatening serious adverse reactions identified as treatment-related (Incyte, Global Investigator's Brochure v9, Aug 2020). In this study, we anticipate few effects from systemic absorption since most patients with DLE have even less cutaneous involvement than in prior studies, typically only 1-2% BSA.

While systemic side effects have not been seen with topical ruxolitinib, and the amount applied to the skin will be limited given the small area of treatment, there is a theoretical risk of side effects that have been observed with much higher oral doses. The most common side effects of oral ruxolitinib include increased risk of infection, laboratory abnormalities (cytopenias, elevated transaminases, and elevated cholesterol & triglycerides), and mild neurologic and gastrointestinal symptoms (dizziness, headache, fatigue, insomnia, diarrhea, abdominal pain). Ruxolitinib is a pregnancy Category C drug.

As with any treatment, there is a small risk of an allergic reaction, though this has not been documented for ruxolitinib cream. There is no known risk of interaction between antimalarials and the study drug ruxolitinib.

Safety monitoring and mitigating risk associated with the use of ruxolitinib cream is addressed in Section 8.2.2.

Phlebotomy: The risks of having blood drawn include some pain with needle insertion and a small risk of bruising and/or infection at that site. Some people may get lightheaded, nauseous, or faint. The risks of phlebotomy will be reduced by its performance by trained phlebotomists.

Skin Biopsy: The skin punch biopsy procedure involves the momentary pain of the needle prick used to insert the local anesthetic. There is a low risk of having an allergic reaction to the anesthetic used (lidocaine with epinephrine), which could result in a rash, itching, swelling,

dizziness, or trouble breathing. There is also a low risk of skin discoloration, temporary bleeding/bruising, and infection. Subjects may have a scar at the site of each biopsy and there is a risk of delayed or difficult healing at the site of the biopsy. Standard precautions will be taken to minimize these risks. For example, the procedure will be performed by a trained professional who will discuss the risks of the procedure and actions to be taken in the event of a complication. Participants will be given a handout with wound care instructions and a number to call in the unlikely event that a complication arises. Additionally, subjects will be asked if they have any allergies to lidocaine. If the subject does not return for suture removal, a member of the study team will call the participant to check on the healing of the skin biopsy, and to see if there are additional questions or concerns.

9.2 **Alternatives to Participation**

Non-participation. Study participation is voluntary. Subjects are free to not participate or to withdraw at any time, without risking loss of present or future care that they would otherwise receive. If they choose not to participate, standard of care treatment will be available.

10. POTENTIAL BENEFITS TO SUBJECTS

There may or may not be any direct benefits for the participants who elect to enroll in this study. The potential direct benefits to the subjects include more frequent provider evaluation and management of their disease as well as potential efficacy of a new therapy (ruxolitinib).

11. COSTS FOR PARTICIPATION

There will be no additional costs to the subject due to this study in addition to those incurred as part of routine standard of care. Insurance will not be billed for any study-specific visits or procedures associated with the study. The normal costs related to the subject's care during the course of the study will be up to the subject's insurer:

- Physician visits outside of study visits
- Emergency room or urgent care visits
- Hospitalizations

12. PAYMENT FOR PARTICIPATION

Subjects enrolled in this protocol will receive $35 for each visit and $100 for each individual skin biopsy. Subjects will only be compensated for the activities they complete. For subjects who will complete all of the visits (#7) and optional biopsies (#2), the total compensation will be $445. Subjects will be reimbursed $35 if they are asked to come in for an unscheduled visit (and compensated an additional $100 if a skin biopsy is performed).

For this study we use a subject payment system called Advarra Participant Payments. The system allows three ways to provide payment. Subjects can choose: a reloadable debit card; direct deposit; or mailed paper checks. The study team will help the subject create a "subject

profile" in the system. In order to provide payment, the subject will need to enter their name and date of birth into their subject profile which is required to set up a subject account and for customer service purposes. Depending on which payment method they choose, they may also need to enter their email address and banking information. If they already have an Advarra account (because they are in another study that uses this system), their existing profile will be used to provide payment. See the 'Information Sheet for Advarra Participant Payments" for additional information.

Payment received for participation in research is considered taxable income. If the subject receives payment for their participation in studies at the University of Rochester and its affiliates of $600.00 or more in any one calendar year, the University is required to report this information to the Internal Revenue Service (IRS) in a 1099 (Miscellaneous Income) form. They will be sent a copy of this form and a copy will be sent to the IRS. Depending on the amount they are paid, they may be asked to submit a W-9 form, which includes their Social Security Number.

13. SUBJECT WITHDRAWALS

Subjects will be notified by the study coordinator and advised in the written informed consent provided that they have the right to withdraw from the study at any time without prejudice.

If participants of the study at any point meet the exclusion criteria established in this protocol, including pregnancy, study drug will be discontinued. In addition, study drug will be discontinued for any subject who experiences any of the following (per Common Terminology Criteria for Adverse Events v5.0):

- Grade 2 event in Cardiac Disorders
- Grade 3 event in any other System Organ Class

Current research does not suggest a treatment-associated increased risk for these events. Standard treatment will proceed as necessary to ensure optimal health for the subject. In this situation, long term data will no longer be collected, and only the data collected during the duration of participation of the clinical trial will be included in the data analysis and conclusions of the study.

14. PRIVACY AND CONFIDENTIALITY OF SUBJECTS AND RESEARCH DATA

Steps to ensure privacy and confidentiality of subjects and research data will include:

- The PI will be responsible for all aspects of this study, including privacy and confidentiality of subjects and research data.
- All study personnel will be appropriately trained in Good Clinical Practice.
- Study investigators or coordinators will meet with subjects in a private room, where they will conduct all aspects of this study that involves direct subject interaction.

- Subjects will not be re-contacted without prior consent. During the process of consent, subjects will be given the option to be re-contacted regarding opportunities to participate in future studies.
- All electronic and physical documentation that includes protected health information (PHI) will be stored in files and/or folders with access limited to authorized study personnel only.
- Physical files will be kept in a locked secure area of the URMC Dermatology CTU.
- Computers on which electronic PHI data is accessed will be password protected and will not be left unattended while in use.
- Passwords and system IDs will not be shared.
- Physical security of computers/files will be maintained.
- Subjects and samples will be assigned a unique code to facilitate deidentification of the data. Codes will not be generated from existing identifiers, such as initials or enrollment date.
- Only authorized study personnel will have access to data containing PHI.
- Other research personnel conducting experiments on tissue samples and analyzing data will have access to deidentified samples and data only.
- Data will be stored for at least 6 years after the completion of the study, or for at least two years following marketing approval (or, if not approved, 2 years following shipment and delivery of the investigational product is discontinued), whichever is longer.

15. DATA / SAMPLE STORAGE FOR FUTURE USE

Clinical labs drawn as standard of care and as part of this study will be recorded in the subject's medical record and will be available to the subject. Since the non-clinical testing is being done strictly for research purposes, the results of these tests will not be recorded in the subject's medical record and subjects will not be informed of the results of these research assays.

Data and samples collected as part of this protocol will be used to perform the studies related to the primary, secondary and exploratory endpoints of this study. Any tissue that remains after these analyses have been performed will be deidentified and may be stored and used for future studies. These stored samples may also be shared with companies that are providing support for this study; this includes Incyte and their affiliates.

16. DATA AND SAFETY MONITORING PLAN

16.1 **Data and Safety Monitoring**

During the conduct of the study, the PI and his designee(s) will continually monitor the study to ensure that the study is conducted in compliance with the IRB-approved study protocol and that subject safety is maintained. Safety data will be reviewed by the PI or designee as soon as it is received. The review will include: the number of subjects consented/enrolled/completed, possible adverse events, and any other responses observed.

The FDA defines an adverse event (AE) as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" and a serious adverse event (SAE) as an AE that "results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect" (Electronic Code of Federal Regulations, 13 Jan 2020).

The PI and study coordinator are the primary individuals charged with identification and reporting of all AE and SAE occurrences as well as protocol deviations. All SAEs that are considered serious, unexpected and related to the study participation will be reported to the IRB within 10 calendar days and all non-serious adverse events will be reported annually with the continuing review. The investigator will also notify the IRB of any serious deviations from the protocol, and any new information indicating added risk to subjects.

16.2 **SAE Reporting to Incyte**

The Principal Investigator (PI) must report all Serious Adverse Events (SAEs) to Incyte within 24 hours of learning of an event, regardless of the PI's causality assessment. This notification should be provided on a completed Serious Adverse Event (SAE) form. 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, or as described in the protocol.

SAEs, occurring using Incyte study drug, are reported in accordance with the effective protocol. SAEs occurring with any other commercial drug are reported to the manufacturer of that drug in accordance with regulations and protocol.

Initial SAEs and/or subsequent follow-up reports should be reported via email to SafetyReporting@Incyte.com or fax (+) 1-866-981-2057. SAE reports should be for a single subject. SAE forms should be sent with a cover sheet and any additional attachments.

All adverse event information is reported to Incyte on the Principal Investigator's/Institution's Adverse Event Report Form, or a CIOMS-I or MedWatch Form FDA 3500A, or on an Adverse Event Report Form which may be provided by Incyte upon request. The Principal Investigator does not provide medical records (e.g., discharge summary) to Incyte, unless specifically requested.

16.3 **Reporting of Pregnancy to Incyte**

An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 within 24 hours of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner for a subject who has taken the Incyte product. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet

the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with a SAE should be followed.

17. DATA ANALYSIS PLAN

This exploratory study has a sample size of 15 subjects. Given the small sample size, a robust statistical analysis will be limited. The primary endpoint will be a ≥ 2-point reduction in IGA score. The mean percentage change from baseline will be assessed for the secondary endpoints (CLASI, CLASI-A, CLASI-D, NRS, EI, MI). Statistical analysis of exploratory endpoints comparing skin tissue before and after ruxolitinib treatment will be performed in accordance with the technique being used (histology, flow cytometry, RNAseq). Analyses of DLE histology (H&E, IHC, IFM) will include common histologic features (follicular plugging, interface change, etc.), cell counts of the immune infiltrate, and markers of IFN response. Flow cytometric analysis will evaluate the immune infiltrate, including T and B cell subsets. The focus of the RNAseq analysis will be on interferon expression, though other analyses may be performed. Differences will be considered significant at $p < 0.05$.

18. REFERENCES

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