NCT05293717

CLINICAL STUDY PROTOCOL

1. PROTOCOL SUMMARY

Title: Topical Ruxolitinib (Jak1/Jak2 inhibitor) in Chronic Hand Dermatitis attenuates inflammation and enhances skin barrier repair.
Principal Investigator: Anna De Benedetto, MD;
anna_debenedetto@urmc.rochester.edu

Single site: Department of Dermatology - University of Rochester Medical Center, Rochester, NY

Study phase: Open label, proof of concept study

Population: Females and Male, age 18 - 75 years, who have moderate to severe Chronic Hand Dermatitis (CHD)

Number of participants: Up to 25 will be enrolled with 15 completing full study term

Intervention: Ruxolitinib cream 1.5% is an investigational drug that will be applied twice daily (BID) for 12 weeks (IND exempt) by the study participant. Ruxolitinib (Other Name: INCB018424) cream is a topical formulation applied as a thin film to affected areas.

Objectives and Endpoints:
<u>Primary objective & outcome:</u>
1. To assess the efficacy of Ruxolitinib cream 1.5% on skin lesions in patients with Chronic Hand Dermatitis:

- proportion of patients achieving an Investigators Global Assessment (IGA) score of 0 or 1 with at least a 2-step improvement (IGA treatment success) at week 12
Hand Eczema Severity Index (HECSI)[i]-75% from baseline to week 12

<u>Secondary objective & outcome:</u>

- To assess the efficacy of Ruxolitinib cream 1.5% on other clinical domains: Time to IGA treatment success
- Change in HECSI score from baseline to week 4, 8 and 12.
- Proportion of subjects with a ≥ 2 and ≥ 4-point improvement in Itch Numerical Rating Scale (NRS) score from baseline to week 12.
- HECSI-75% at week 8
- HECSI-90% at week 12

2. To assess safety and tolerability of Ruxolitinib cream 1.5% in patients with chronic hand dermatitis:
   - incidence, frequency and severity of adverse events and laboratory data for hematology, serum chemistry and urinalysis
   - use of rescue medications

Exploratory objective & outcome:

1. To assess the effect of Ruxolitinib cream 1.5% on patient reported outcomes
   - Change from baseline to week 4, 8 and 12 in DLQI
   - Change from baseline to week 4, 8 and 12 in work productivity and activity impairment index

2. To assess the efficacy of Ruxolitinib cream 1.5% on skin barrier integrity in patients with Chronic Hand Dermatitis:
   - change in transepidermal water loss (TEWL) and barrier integrity score (TEWL recovery after tape stripping) and pH from baseline to week 4 and end of treatment on perilesion (normal appearing) skin
3. To identify translational skin biomarkers
   - change in the expression of selected biomarkers in skin samples obtained from tape stripping (d-squame) at baseline and end of treatment (week 12)
   - change in microbiome at baseline and end of treatment (week 12)

Treatment groups and Duration:
Will enroll up to 25 subjects with CHD; investigational drug will be applied twice a day for 12 weeks by the subjects. Subjects will be asked to come back for a safety follow up visit every 4 weeks until end of treatment.

2. STUDY RATIONAL

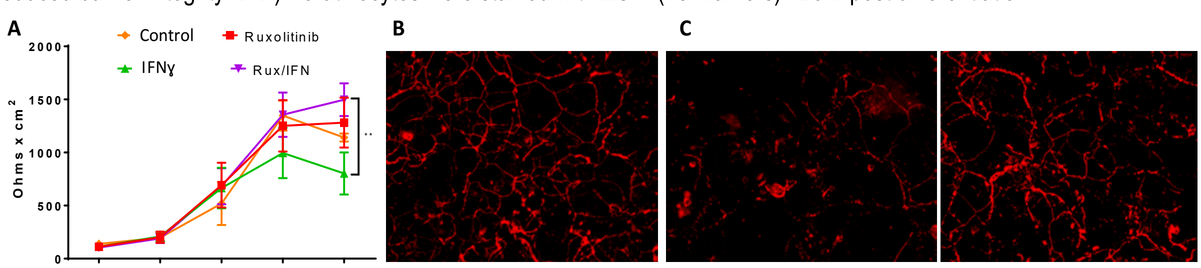
Background: Chronic hand dermatitis (also known as hand eczema; CHD) is one of the most disabling skin conditions that negatively affect quality of life and work capacity of affected patients. Hands and often wrists present with erythema, edema, scaling and fissuring accompanied by intense pruritus and pain. Thyssen JP et al, reported the point prevalence of hand dermatitis (1994-2007) was around 4%, the 1-year prevalence nearly 10%, whereas the lifetime prevalence reached 15%. A high incidence rate is associated with female gender, contact allergy, atopic dermatitis, and wet work environment.[ii] Hand dermatitis is a heterogeneous disease entity, with irritant and allergic contact dermatitis and atopic dermatitis (AD) as the main causative factors. The common denominator of CHD subtypes is a skin barrier dysfunction, which not only facilitates cutaneous penetration of allergens and irritants but also induces local immune activation. Currently, the management of CHD involves patient education about avoidance of irritants and allergens, skin protection measures, and topical (high and mid potency steroids, calcineurin inhibitors) or systemic anti-inflammatory therapy (e.g. corticosteroids, alitretinoin, cyclosporine, methotrexate, azathioprine). Overall the rate of treatment success is poor with great dissatisfaction from patients and providers. While previous approaches to CHD have been focused on broad spectrum suppression of immune responses, we are interested in a targeted approach to restore proper skin barrier integrity and resistance to absorption of environmental allergens/hapten/irritant while also blocking the cytokine mediated inflammation.

It is our hypothesis that daily application of a topical JAK1/JAK2 inhibitor (Ruxolitinib) will induce clinical improvement of CHD by restoring skin barrier function and reducing skin driven inflammation.

Preliminary study: The epidermal skin barrier is composed of the stratum corneum (SC), which is made up of terminally differentiated keratinocytes surrounded by a complex lipid structure and the tight junctions (TJs), which are present just below the SC. TJs are made up of a number of adhesive and scaffolding proteins that control the passage of physiologic liquids, water, ions, and solutes through the paracellular pathway. Expression of key barrier proteins (e.g. claudin-1, loricrin, filaggrin and cytokeratin 10) was found to be reduced in biopsies from CHD patients. Notably, in patients treated with oral alitretinoin the improved expression of these markers correlated with clinical efficacy, suggesting that alitretinoin exhibits a disease-modifying activity by skin barrier repair mechanism[iii].

Janus kinase (JAK) inhibitors block cytokine-mediated signaling via the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, which plays an important role in immunoregulation and cell growth. Furthermore, recent studies have shown a critical role played by JAK1 signaling in sensory neurons driven chronic itch[iv]. JAK-STATs are heavily expressed in the epidermis and involved in critical epidermal barrier pathways. Studies on epithelial model have shown that JAKs play a role in TJ protein expression[v]. Consistently, preliminary data generated in our laboratory showed that <u>Ruxolitinib was able to rescue IFNɣ-induced TJ disruption (Fig 1).</u>

Fig 1. In Primary human keratinocytes IFNɣ reduced TransEpithelial Electric resistance (TEER) and this was associated to disruption of TJ - Ruxolitinib (Rux) rescued IFNɣ induced TJ damage. A) TransEpithelial Electric resistance measures TJ integrity: reduced TEER
reduced barrier integrity. B-D) Keratinocytes were stained with ZO-1 (TJ markers) 120hr post differentiation.



Design & Methodology. This is an investigator-initiated, proof of concept, open study to assess efficacy of a <u>topical Ruxolitinib</u> in subjects with CHD. The study will be conducted at the University of Rochester Medical center, Dermatology Department – Rochester, NY.

Qualified and enrolled subjects (see Inclusion/exclusion criteria) will be required to come to URMC Dermatology Clinic for at least five visits: visit 1 (V1, day 0), start of active treatment; visit 2 - 4 weeks treatment; visit 3 – 8 weeks and visit 4 – 12 weeks and end of the active study; visit 5 post treatment follow uo, 4 weeks (V5, 112+/- 3 days post V1). To ensure feasibility of enrollment, and in subjects requiring a washout period, we will include a screening visit (up to 28 days +/- 3 prior to V1). As part of the screening, subjects with possible contact allergy dermatitis (CAD) will undergo PATCH testing (70 common allergens, North America series; *see exclusion criteria*) or they must have documentation of test performed 3 years prior screening. In patient with CHD avoidance of the allergens should be the first measure to ensure successful treatment. Subjects with known antigen sensitization based on Patch test (with 3 years) that are unable to reduce contact with the specific antigen(s) will be excluded.

We will also exclude patients with active lesions of Atopic Dermatitis and Psoriasis (*see exclusion criteria*), as they might need additional systemic or topical treatment that could indirectly affect hand dermatitis severity during the study.

Subjects will apply <u>topical Ruxolitinib 1.5% cream twice a day</u> for 12 weeks on eczematous areas of hands and adjoining clinically normal (perilesional) area. We included non-lesional/perilesional skin to evaluate the safety (e.g. irritant or toxic effects) of the compound on irritated/atopic skin, as those subjects have a lower irritancy threshold[vi]. Also, skin barrier impairment (e.g. increase water loss/TEWL) can be already detected in normal appearing skin in atopic subjects and it is thought to allow penetration of hapten/allergen/irritant with consequent activation of an inflammatory response. It is our hypothesis that treatment with <u>topical Ruxolitinib, a JAK1/JAK2 inhibitor</u>, will normalize skin barrier integrity in perilesion skin. During the study, subjects will be allowed to stay on bland moisturizer and anti-histamine on a stabilized dose and expected to maintain this dose throughout the study. **In addition to clinical and safety outcomes,** the study design will include **exploratory** mechanistic outcomes, in a stepwise tactic. During the trial we will collect: 1) non-invasive skin barrier assessment (i.e. TEWL, SC integrity score); 2) stratum corneum extract to investigate potential biomarkers and skin microbiome (stored for future investigation); 3) Patient oriented outcomes. If the data gathered from the clinical trial demonstrates the clinical improvement we expect, the mechanistic studies will be extremely relevant to start clarifying specific target downstream to Ruxolitinib efficacy in CHD as well as biomarkers that could eventually be investigated in consequent larger clinical trials.

ADMINISTRATIVE ORGANIZATION

UR Dermatology at College Town is the only participating site in this research study.

3. STUDY POPULATION

Number of patients: Up to 25 total subjects. We might need to enroll additional subjects in case of subject early discontinuation to reach the total number of 15 evaluable subjects (complete data set).

Study population: Females and Male, age 18-75 years, who have Chronic Hand Dermatitis

Racial and Ethnic Origin: We will not have any restrictions based on racial or ethnic origin. We based our target research population racial and ethnic distribution on the data of the 2000 United States Census for the Monroe County Area.

Vulnerable subjects: We will not be targeting vulnerable subjects

Inclusion Criteria:

- Age 18-75 years.
- Diagnosis of chronic hand eczema defined as hand eczema, which has persisted for more than 3 months or returned twice or more within the last 12 months.
- Disease severity graded as moderate to severe according to IGA (i.e., IGA ≥2).
- Recent history (within 1 year before the screening visit) of inadequate response to topical corticosteroid and/or calcineurin inhibitors treatment or topical corticosteroid treatment being medically inadvisable.

Exclusion Criteria:

- Active atopic dermatitis in regions other than the hands requiring medical treatment.
- Active psoriasis in regions other than the hands requiring medical treatment.
- Clinically significant infection (e.g., impetiginized hand eczema or tinea manuum) on the hands.
- Patients with excessive contact of hands with water (longer than 2 hours a day; or > 20 hands washing at day) that is believed to be a predominant cause of the hand dermatitis.
- Subjects with known antigen sensitization based on Patch test (with 3 years) that are unable to reduce contact with the specific antigen(s).
- Subjects chronically and consistently exposed to known irritant or other substance known to impact skin barrier will be excluded based on PI judgement.
- Systemic treatment with immunosuppressive drugs, immunomodulating drugs, retinoids, or corticosteroids within 4 weeks prior to baseline.
- Systemic treatment with antibiotics within 4 weeks prior to baseline
- Phototherapy on the hands within 4 weeks prior to baseline.
- Use of topical immunomodulators (e.g., phosphodiesterase-4 (PDE-4) inhibitors, pimecrolimus, tacrolimus) or topical corticosteroids on the hands within 2 weeks prior to baseline.
- Use of topical antibiotics on the hands within 2 weeks prior to baseline.
- Change in systemic antihistamine therapy within 2 weeks prior to baseline i.e., subjects must not start antihistamine treatment or change the current dosage regimen within 2 weeks prior to baseline.

- Other topicals applied therapy on the hands (except for the use of subject's own emollients) within 1 week prior to baseline.
- Receipt of any marketed or investigational biologic agents within 6 months or 5 half-lives prior to baseline will be in the judgement of the investigator whether or not study drug may affect or interact with study drug's mechanism of action.
- Any disorder which is not stable and in the investigator's opinion could affect the safety of the subject, influence the findings of the trial, or impede the subject's ability to complete the trial.
- Participants with clinically significant cytopenia at screening.
- Participants with severely impaired liver or kidney function and unstable.
- Participants who have previously received JAK inhibitor therapy, systemic or topical.
- History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV), or the subject taking antiretroviral medications.
- Females who are breastfeeding, pregnant, or anticipate becoming pregnant during the study time frame.
- History of skin cancer on hands within 5 years.
- History of recalcitrant warts on hands within 1 year.

4. STUDY TREATMENT & DESIGN

Study design: This is an open label, proof of concept single site study and will be conducted at the Department of Dermatology, URMC
- Screening visit (-28 days before start of treatment)
- visit 1 - (V1, day 0), start of active treatment;
- visit 2 – 28 +/- 3 days (4 weeks) treatment;
- visit 3 – 56 +/- 3 days (8 weeks) treatment;
- visit 4 – 84 +/- 3 days (12 weeks) end of treatment
- visit 5 – 112 +/- 3 days (16 weeks) safety follow up 4 weeks post treatment
- during each visit a skin swab will be collected and stored in the lab for future microbiology study
-Skin Symptom questionnaire will be done during each visit.

Screening visit (-28 days)

1) Consenting and confirmation of inclusion & exclusion criteria
2) Medical history
3) Physical exam with focus on skin exam
4) Collection of concomitant medications
5) Fasting blood draw for safety labs (CBC with diff, Chemistry, Lipid panel)
6) Urinalysis
7) Possible washout period

8) Possible schedule PATCH test if investigator believes clinically necessary to r/o contact dermatitis
9) Urine Pregnancy test for woman of childbearing potential
10) Scheduling visit 1

Visit 1 (Day 0):

1) Confirmation of inclusion & exclusion criteria
2) General history
3) Physical exam
4) Review of concomitant medications
5) Urine pregnancy test for woman of childbearing potential at each visit. Counseling on acceptable birth control measures to use throughout treatment period including 30 days after stopping study drug (16 weeks or 112 days)
6) Clinical scores for chronic hand dermatitis
7) Itch and other QoL assessments; review daily diary
8) Digital pictures of the target area/hands
9) Non-invasive skin barrier Measurements: TransEpidermal Water Loss (TEWL) and optional pH may also be performed
10) Repeated tape stripping (Cuderm™ tape) of peri-lesional (0, 5, 10, 15, 20 tape) locations from treated area will be collected as part of the TEWL assessment and to assess for SC cohesion/integrity (rate of change in TEWL with repeated stripping). Serial measurements of TEWL will be performed after tape stripping as previously described[vii]. This will also allow collecting proteins (eluded from the tape) for validation of biomarkers
11) Dispense Investigational drug for 4 weeks
12) Provide instructions to complete at home diary.
13) Provide date of Visit 2
14) Weight of the tube to check for subject's compliance
15) Skin swabs (optional)
16) Skin symptom questionnaire (optional)

Visit 2 (Day 28 +/-3) and Visit 3 (Day 56 +/-3) and Visit 4 (Day 84 +/-3):

1) Review subject diary and address any questions, concerns, or missed doses
2) Review of concomitant medications
3) Adverse events assessment
4) Questionnaire to clinically characterize CHD
5) Urine Pregnancy test for woman of childbearing potential.
6) Clinical score for CHD
7) Itch and other QoL assessments, review daily diary

8) Digital pictures of the targeted area
9) Non-invasive skin barrier Measurements: transepidermal water loss. Optional: pH
10) Repeated tape stripping (Cuderm™ tape)
11) Dispense investigational drug for following 4 weeks (except Visit 4, end of treatment)
12) Review Diary instructions
13) Weight of the tube to check for subject's compliance
14) Provide date for next visit
15) Skin swabs (optional)
16) Skin symptom questionnaire (optional)

Visit 5 (Day 112 +/-3):

1) Review subject diary and address any questions, concerns, or missed doses
2) Review concomitant medications
3) Adverse Events Assessment
4) Questionnaire to clinically characterize CHD
5) Urine Pregnancy test for woman of childbearing potential.
6) Clinical score for CHD
7) Itch and other QoL assessments; review daily diary
8) Digital pictures of the targeted area
9) Non-invasive skin barrier Measurements: transepidermal water loss. Optional: pH and skin swab
10) Repeated tape stripping (Cuderm™ tape)
11) Weigh returned tubes

Unscheduled Visit(s)

Any follow-up assessment that is performed to monitor a subject will be collected as an unscheduled visit. The study team is responsible for review of any side effects, concomitant medications, and a brief physical examination. The remaining elements of the unscheduled visit are up to the discretion of the investigator and may include any of the events listed in Visits 1 through Visit 5.

<u>Study procedures & methods</u>

- **Disease status assessment: 1)** Investigator Global Assessment (IGA), which will provide information of the overall disease (5-point scale: clear, almost clear, mild, moderate, severe) and it is the score requested by FDA for clinical study. Data will be reported as and **2)** Hand Eczema Severity Index (HECSI)[viii], a well-accepted and validated scoring system for disease activity. It incorporates both the extent and the intensity of the disease. Each hand is divided into five areas: fingertips, fingers (except the tips), palms, back of hands and wrists. Each area will be score for extension and intensity of the six following clinical signs: erythema, induration/papulation, vesicles, fissuring, scaling and edema; which are graded on the following scale: 0, no skin changes; 1, mild disease; 2, moderate and 3, severe (see appendix). Data will be reported as percent change in HECSI score from baseline to week 4, 8 and 12.

The presence or absence of skin irritation (e.g. macular/papular eruption), redness, atrophy and telangiectasia will be noted at each study visit.

- The **pruritus** intensity will be assessed using Itch Numerical Rating Scale (NRS; see appendix). Data will be reported as proportion of participants with a ≥ 2 and 4-point improvement in Itch Numerical Rating Scale (NRS) score from baseline to week 4, 8 and 12. The NRS comprised of one item and represents the numbers 0 (“no itch”) to 10 (“worst imaginable itch”). Subjects are asked to rate the intensity of their itch using this scale. The **Dermatology Life Quality Index (DLQI)** measured 6 disease-specific domains (symptoms and feelings, leisure, daily activities, work and school, personal relationships, and treatment) during the last week; individual items were summed to generate an overall score. Data will be reported as change from baseline to week 12 in DLQI. The **Work Productivity and Activity Impairment-Chronic Hand Dermatitis (WPAI-CHD**) questionnaire elicited the number of work hours missed, hours worked, and impairment while working/performing usual daily activities as a result of chronic hand dermatitis during the past 7 days. The sum of work time missed and work impairment while working yielded the overall work impairment measure. All scores were expressed as percentages, with higher scores indicating greater impairment[ix]. Data will be reported as change from baseline to week 12 in work productivity and activity impairment index. Will also collect Skin Symptom Questionnaire routinely used by the URMC dermatology department
- **Digital pictures:** A digital picture will be taken with a dedicated digital camera using the Haiku App. The pictures will be labeled with the subject’s study ID and date. Pictures will not include identifying information (e.g. facial features, tattoo, etc). Pictures will be taken at a distance for easy identification of the anatomical area and closer to better capture clinical changes. Digital photographs will be used to record the location and monitor the size of target lesions.
- **Venous blood sample:** blood will be obtained for safety lab
- **Skin barrier measurements:** Transepidermal water loss/**TEWL,** +/- pH will be obtained on treatment area at a perilesional site. This measurement asses the dryness and health of the skin. For each of the specific measurements, a probe will be gently applied on the skin surface for up to 1 minute. We will perform all measurements in a climate-controlled examination room with consistent temperature (~23℃) and humidity (~50%). The patient must be very comfortable in the room in which they are being tested to ensure that perspiration due to stress

or acclimatization does not alter the TEWL. TEWL will be assessed using a non-invasive skin probe that measures skin hydration - or other similar device available in the CTU. The URMC department of Dermatology owns the devices and has experience with measurements. **Stratum Corneum (SC) integrity:** the most superficial layers of the skin will be collected by tape stripping using D-squame (D-squame®, CuDerm, Dallas TX, USA). This is a well-established method used in clinical research to gently perturb the skin barrier. The first tape will be discarded to eliminate dirt and remnants of skin products. Each tape will be gently pressed against the skin with standardized pressure for 5-10 seconds (sec) using a standardized pressurizer (D500–D-squame® pressure instrument, CuDerm)). All subjects will have 20consecutive tapes collected from lesional skin as part of this study. TEWL will be measured after each set of 5 tape strippings. These measurements should provide data to determine if the treatment has an effect on skin barrier integrity. Dsquame tapes will be collected and stored in -80 C freezer (see below). Expression of relevant biomarkers can be investigated using RNA or protein eluted from the tapes. Dr. De Benedetto's lab is familiar with the methods and analysis

- **Skin swab:** will be collected at each visit. Briefly a sterile swab will be rolled on the dorsal hand (non-dominant hand) at each visit and stored at -80C for future analysis
- **Study Drug Diary:** subjects will be provided with a prepopulated dated calendar to record their twice daily (AM and PM) application of study medication as well as the time the medication is applied. Also, on this diary the subject can indicate if a missed dose occurred and there is a blank space they can write in the reason it was missed. At the END of each day the subject will need to indicate on the same study diary their level of hand dermatitis itch throughout the day – 0=no itch and 10=worst imaginable itch. Subjects will indicate their level 0-10 by circling the number that best applies to them for that particular date. Detailed instructions are provided on the Incyte Study Diary as well as contact information of coordinator.

Prohibited Medications and procedures: use of topical or systemic immunosuppression/immunomodulators medications and Phototherapy is not permitted during the study. Hand surgery or other procedures (including but not limited to Cryotherapy, ED&C, skin biopsy) are disallowed during the study. If medically necessary, the investigator will withdraw the patients from the study.

5. RISK, BENEFITS and PROTECTION AGAINST RISKS

Risks Associated with Digital Picture

There are no known risks for the digital picture. The image will not include identifying features and will be labeled with study subject ID and date. ~~Pictures will be taken with a dedicated camera, stored on a secure server.~~ Pictures will be taken through the Haiku App and stored in the patients EMR in Epic.

Risks Associated with Barrier Assessments

There are no known risks for the barrier assessments.

Risks Associated with Tape Stripping

The risks associated with tape stripping, theoretically, include the rare possibility of an allergic reaction to the tape and infection. Since the tape is removed immediately after application, the risk of reaction is extremely low. In previous and ongoing studies involving tape stripping, it has been noted that a very mild erythema may develop immediately after a series of tape strippings on one localized area of skin, presumably due to the mild mechanical disturbance. The erythema is expected to resolve within 12 hours without sequelae. The risk of skin infection is extremely low since only superficial skin layers are removed. Subjects will be provided with wound care information and a department phone number to contact should they have any concerns.

Risks of Phlebotomy

The risks of having blood drawn include some pain when the needle goes in, and a small risk of bruising and/or infection at that site. Some people will get lightheaded, nauseous, or faint. Approximately 3 teaspoons of blood will be drawn and is not likely to cause lightheadedness, however subjects will be observed after blood draw to be sure they are comfortable with ambulation. Subjects will be encouraged to drink plenty of water prior to the blood draw. Phlebotomy will be performed at the antecubital fossa to minimize pain and bruising. Subjects will be seated during the blood draw to minimize dizziness and any risk of falling. Pressure will be applied to the site after the draw and a band-aid will be applied to minimize the risk of bleeding and infection. Fasting laboratories will be processed at URMC local lab. We require fasting laboratories as the lipid panel can be influenced by food intake and it is routine care to do fasting laboratories of at least 6 hours. Due to known side effects of systemic class of medication we want to screen patients for leucopenia, high lipids, liver or kidney diseases; normal or non-clinical significant labs at baseline are useful to rule out these problems and can be helpful in case we have side effects during the study.

The clinical trial team will receive and review the laboratory results between 24-48 hours.

Risks of Ruxolitinib 1.5% cream

Skin-related side effects of ruxolitinib cream are rare, but have included local irritation, pain, itch, redness, acne, and rash. While other side effects are not expected and have not been seen in other studies of ruxolitinib cream, there is a potential risk of side effects that have been observed with much higher doses of ruxolitinib when given by mouth. These risks include infection, low blood counts, liver inflammation, elevated cholesterol, dizziness, headache, fatigue, insomnia, diarrhea, and abdominal pain. As with any treatment, there is a small risk of an allergic reaction, though this has not been documented for ruxolitinib cream.

There is a risk of no change or worsening of disease, as would be true with any change in treatment.

FDA approved medication label information, risks include:

- Patients treated with oral JAK inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death
- Reported infections include:
  - Active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease
  - Invasive fungal infections (eg, candidiasis, pneumocystosis)
  - Bacterial, viral, and other infections due to opportunistic pathogens
- Avoid use in patients with an active, serious infection, including localized infections
- If a serious infection develops, interrupt therapy until infection is controlled
- Do not resume until the infection is controlled.
- Carefully consider the risks and benefits of treatment before initiating therapy in patients with chronic or recurrent infection
- Closely monitor for developing signs and symptoms of infection during and after treatment

Reproductive Risks

Women of childbearing potential will be counseled to use acceptable birth control methods. Women will not be allowed to participate in this study if they are pregnant, become pregnant, or are nursing an infant.

General Risks

When participating in any research study there is a possibility for invasion of privacy or breach of confidentiality. As with any research study, there may be additional risks that are unknown or unexpected. The subjects are advised to contact their study team with any questions and/or concerns. At that time the study team will determine whether or not any untoward medical occurrence is associated with the study and/or study drug and will be recorded on the Medical History and/or Adverse Event page of the source document.

Adverse Event Reporting

An adverse event (AE) is any observation whether or not considered to be product related, that is unfavorable and unintended and that occurs after any use of an investigational medicinal product.

Any observation of abnormality will be documented on the Adverse event form. The Investigator will document the date of occurrence, severity, resolution, and will assess the relationship of the adverse event to the study drug by assigning a causality assessment. Results from laboratory evaluations which are outside of the laboratory reference range will constitute an adverse event only if the Investigator determines that the result is clinically significant.

Severity will be assessed by the following system:

- Mild: easily tolerated, causing minimal discomfort
- Moderate: sufficiently discomforting to interfere with every day activities
- Severe: prevents normal every day activities

Serious Adverse Events (SAE)
FDA definition: A serious adverse event results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, results in a congenital anomaly / birth defect. Events fitting these descriptions will be considered adverse events if they occur after treatment with the study drug.
As soon as reasonably possible, subjects will contact the Investigator to report any unfavorable events. The Investigator will assess the case, determine the need for treatment, and consult with Incyte, Inc, particularly in the occurrence of:

- A serious adverse event.
- An unusual frequency of non-serious adverse events.
- Death, even if this does not appear to be related to therapy with the study drug.

The Investigator will notify the URMC Institutional Review Board within approximately 3 working days if a serious adverse event occurs.

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.

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 that 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.

Causality assessments

Probable

All of the following apply:

- Reasonable association in time between the administration of the study drug and onset and duration of the reported event.
- Description of the clinical phenomenon should be consistent with, or at least plausible, given the known pharmacology and toxicology of the product.
- There should be no other equally plausible explanation(s) of the case. In particular, concurrent use of other products (and possible interactions) or concurrent disease should be taken into account in the assessment.

Possible

- The causality is one (of other) possible and plausible causes for the described event, but the data do not meet the criteria for inclusion in Category A.

Unknown

- An association with the study drug cannot be discounted, but other factors prevent a conclusion from being drawn.

Unlikely

- Sufficient information exists to establish beyond reasonable doubt that the product was not likely to be the cause of the event.

Classification of adverse events
At the conclusion of the study, Medicinal Dictionary for Drug Regulatory Authorities (MeDDRA) terms will be assigned to all adverse events and will be included in the final study report.

Stopping Criteria
If more than 5 patients report a greater than moderate local side effect (irritation, worsening of rash, vesicles/bulla etc) or if the clinical dermatological score in the treatment area as assessed by the clinician has worsened by more than 50% from baseline in more than 5 patients, then all patients will stop medication until further review and changes made to the protocol. If any unanticipated serious adverse effects are noted all subjects will be notified and changes will be made to future protocols and submitted for approval.

6. DATA ANALYSIS AND DATA MONITORING

Objectives and Endpoints:
Primary objective & outcome:
1. To assess the efficacy of Ruxolitinib cream 1.5% on skin lesions in patients with Chronic Hand Dermatitis:
   - proportion of patients achieving an Investigators Global Assessment (IGA) score of 0 or 1 with at least a 2-step improvement (IGA treatment success) at week 12
   - HECSI-75% from baseline to week 12

Secondary objective & outcome:
1. To assess the efficacy of Ruxolitinib cream 1.5% on other clinical domains (e.g. pruritus, pain, work productivity and activity impairment; daily quality of life index/DLQI, Hand Eczema Severity Index/HESI):
   - Time to IGA treatment success
   - Change in HECSI score from baseline to week 4, 8 and 12.
   - Proportion of subjects with a ≥ 2 and ≥ 4-point improvement in Itch Numerical Rating Scale (NRS) score from baseline to week 4, 8 and 12.
   - HECSI-75% at week 8
   - HECSI-90% at week 12
2. To assess safety and tolerability of Ruxolitinib cream 1.5% in patients with chronic hand dermatitis:
   - Incidence, frequency and severity of adverse events and laboratory data for hematology, serum chemistry and urinalysis
   - use of rescue medications

Exploratory objective & outcome:
1. To assess the effect of Ruxolitinib cream 1.5% on patient reported outcomes
   - Change from baseline to week 4, 8 and 12 in DLQI

- Change from baseline to week 4, 8 and 12 in work productivity and activity impairment index

2. To assess the efficacy of Ruxolitinib cream 1.5% on skin barrier integrity in patients with Chronic Hand Dermatitis:
   - change in transepidermal water loss (TEWL) and barrier integrity score (TEWL recovery after tape stripping) and pH from baseline to week 4 and end of treatment on perilesion (normal appearing) skin
3. To identify translational skin biomarkers
   - change in the expression of selected biomarkers in skin samples obtained from tape stripping (d-squame) at baseline and end of treatment (week 12)
4. To identify change in microbiome after treatment

Side effects and baseline characteristics will be tabulated qualitatively. The blinded pre-vs post evaluation will be analyzed for IGA scores by the Wilcoxon sign-rank test.

Data Storage and Confidentiality

All data from the clinical trial will be securely stored using the REDCap. Only the minimal necessary data is being collected. This includes: name, contact information, age, sex, MRN, history of allergies, dermatologic diagnosis, history of other medical conditions, current medications and clinical scores. Subjects may be asked to sign an Authorization for Release/Disclosure of Medical Health Information form if a chart is not established at the University of Rochester. Access to this protected health information will be restricted to the principal investigator, sub-investigator and study coordinators. Information obtained will be stored in REDcap. Samples will be assigned unique identifiers and stored separately from the key linking the sample to the identifiers. The electronic key will be stored in REDcap file, accessible only to study personnel. Any paper documents containing identifiers will be kept in a binder in a locked cabinet accessible only to study personnel.

Data Monitoring

The study will be monitored in compliance with the relevant parts of 21 CFR and according to the ICH GCP Guidelines.
Case Report Forms will be completed as information becomes available or within five days of a Study Visit.

The Principal Investigator or a Sub-investigator will sign and date the indicated places of the Case Report Form. This signature will indicate that thorough inspection of the data therein has been made and will thereby certify the contents of the form.

The procedures outlined in the protocol and case report forms will be carefully reviewed by the Sponsor, Investigator and staff prior to Study Initiation to ensure appropriate interpretation and implementation. No deviations from the protocol shall be made except in emergency situations where alternative treatment is necessary for the protection, proper care and well-being of subjects.

Amendments will be submitted to the IRB for their review and approval prior to implementation. When an amendment to a protocol substantially alters the study design or increases potential risk to the study subject, the Informed Consent form will be revised and if applicable, subject's consent to continue participation will again be obtained.

7. SUBJECTS IDENTIFICATION, RECRUITMENT AND CONSENT

Method of subject identification and recruitment

Dr. Anna De Benedetto and study team will identify potential subjects in URMC dermatology clinics, screening upcoming clinic schedules in eRecord for potential eligible subjects with a diagnosis of hand dermatitis as well as referrals from dermatologists within URMC dermatology clinics. The study team may contact the potential eligible subjects via telephone call prior to their clinic visit to discuss the study, field questions and assess interest. If a patient is found to have a history of diagnosed hand dermatitis in which they have been treated at URMC dermatology, as well as a history of having been seen by Dr. Anna De Benedetto during a prior clinic visit, the potential subject may be contacted via URMC MyChart. 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 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 participant will sign a NEW clean consent upon their clinic and/or study visit along with the study team member.

In the case of clinical subjects, Dr. De Benedetto or other URMC faculties will provide the subject with a contact phone number for the study coordinator who is approved to enroll and consent subjects. While Dr. De Benedetto will be available for questions, consent might be obtained by other study personnel for subjects she sees in her clinical practice. It will be made clear to the potential subjects that their participation is voluntary and their care at the Department of Dermatology will not be affected by their decision to participate in this study.

Process of consent

Dr. De Benedetto or other team members (e.g. coordinator, nurse, co-investigator) will meet directly with the subjects in a private suite. The consent form will be discussed with the potential subject. Time allotted to consenting will be dependent on the subjects' needs, questions, and comprehension of the information in the consent form. Each subject will be encouraged to read the consent form on his/her own and ask any specific questions as well as have the option to take the consent home to review with family and/or friends.
Subjects will be given a copy of the signed consent.

Subject capacity
We will not be recruiting subject incapable of giving informed consent**.**

Subject/representative comprehension
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.

Documentation of consent
The consent will be documented by signing and dating the consent form by both the study subject and the person obtaining consent. A copy of the consent form will be provided to the subject.

Costs to the subject
Procedures performed during the study will be at no cost to the subject.

Payment for participation
Subjects that agree to participate in the study will receive compensation for their time: $35.00 for the screening visit. Each complete study visit will be $50.00. For a total of up to $285.00 including if all visits are completed.

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 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 is chosen, the subject may also need to enter their email address and banking information. If the subject already has an Advarra account (because they are in another study that uses this system), their existing profile will be used to provide payment.

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

Potential benefits to the subjects
There are no benefits for the individual participant. The investigational medication may temporally improve or worsen the lesion in the target area of application. The nature of this pilot study does not promise benefit for the individual. We hope that this research will

lead to a better understanding of atopic dermatitis pathogenesis and pave the way for development of topical medications that aim to repair skin barrier and skin driven inflammation.

References

[i] *Br J Dermatol. 2005 Feb;152(2):302-7*
[ii] Thyssen JP, Johansen JD, Linneberg A, MennéT. The epidemiology of hand eczema in the general population--prevalence and main findings. Contact Dermatitis. 2010;62(2):75.
[iii] Kumari V, Timm K, Kühl AA, Heine G, Worm M. Impact of systemic alitretinoin treatment on s kin barrier gene and protein expression in patients with chronic hand eczema**.** Br J Dermatol. 2016 Dec;175(6):1243-1250. doi: 10.1111/bjd.14921
[iv] Bordon Y Neuroimmunological disorders: JAK in the itch. Nat Rev Drug Discov. 2017 Oct 30;16(11):753. doi: 10.1038/nrd.2017.204.
[v] Naydenov NG, Baranwal S, Khan S, Feygin A, Gupta P, Ivanov AI. Novel mechanism of cytokine-induced disruption of epithelial barriers: Janus kinase and protein kinase D-dependent downregulation of junction protein expression. Tissue Barriers. 2013;1(4):e25231.doi: 10.4161/tisb.25231. Epub 2013 Jun 3.
[vi] Nassif A, Chan SC, Storrs FJ, Hanifin JM. Abnormal skin irritancy in atopic dermatitis and in atopy without dermatitis. Arch Dermatol. 1994 Nov;130(11):1402-7
[vii] *Br J Dermatol, 2011. 165(2): p. 329-34*
[viii] *Br J Dermatol. 2005 Feb;152(2):302-7*
[ix] *J Am Acad Dermatol. 2003 Jan;48(1):128-30.*