Characterizing the Molecular Cutaneous Phenotype of Seborrheic Dermatitis and Treatment Response to Ruxolitinib 1.5% Cream
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BACKGROUND:

Seborrheic dermatitis (SD) is a very common skin condition affecting tens of millions of Americans, with over $300 million spent annually on over-the-counter treatment products (1, 2). Clinically, it is characterized by erythematous, yellowish scaly plaques in the scalp, eyebrows, ears, forehead, nasolabial folds, chest, axillae, and inguinal areas (3). The pathophysiology of SD is not well understood, with three general factors believed to play a role: Malassezia colonization, increased production of lipids by sebaceous glands, and immune abnormalities (4). SD is also more common in men, implicating androgens as a contributing factor. Current clear treatment guidelines are lacking, with some evidence to support topical antifungals (5) and broad-acting topical anti-inflammatory treatments such as steroids and calcineurin inhibitors (6), and non-pharmacological approaches also used (7). That these treatments have been shown to be better than placebo support the contributions of both Malassezia and immune dysregulation in the pathophysiology of the disease. However, as long-term use of steroids is contraindicated, alternative topical approaches are needed and remain under investigation (8, 9). The immune dysregulation underlying SD has not been well characterized, but upregulation of several cytokines and cytokine pathways have been suggested, including Th1, Th2, Th17, (i.e., IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, TNF-α, and IFN-γ) (10-12). Furthermore, treatment of SD with anti-inflammatory agents such as crisaborole has shown some promise in early studies (9).

TREATMENT RATIONALE:

Current treatments for SD center around topical antifungals, based on the role that Malassezia is believed to play in disease pathogenesis, and anti-inflammatory agents such as topical steroids, which are broad-acting and cannot be applied chronically due to the risk of multiple side effects (11). The pathogenesis of SD is poorly understood, but dysregulated immune markers from different pathways have been suggested, including Th1, Th2, Th17, (i.e., IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, TNF-α, and IFN-γ).

Ruxolitinib is an inhibitor JAK1 and JAK2 signaling, which suppresses the majority of the proposed SD-related cytokines simultaneously. In experimental models of dermatitis, ruxolitinib cream successfully reduced itch and down-regulated multiple inflammatory pathways (13). Although modulation of molecular biomarkers with application of ruxolitinib cream is lacking in humans, clinical efficacy has been shown in the Th2-driven disease atopic dermatitis in phase 2 (14) and phase 3 (15) studies, demonstrating the ability to normalize the pathogenic immune dysregulation in atopic dermatitis as well as in a phase 2 study of vitiligo (16), in which Th1 signaling is believed to play a major role. Furthermore topical approaches with immunomodulatory medications in SD [e.g., crisaborole (9)] have been used in small studies, supporting this approach.

Therefore, we hypothesize that topical ruxolitinib cream will be able to reverse the immune dysregulation seen in SD, leading to clinical improvement.

HYPOTHESIS:

Primary Hypothesis

- Twice daily application of ruxolitinib 1.5% cream for 4 weeks will be clinically efficacious in treating moderate-to-severe seborrheic dermatitis.

OBJECTIVES:

Primary Objectives

- To characterize the clinical responses to treatment with topical ruxolitinib 1.5% cream applied twice daily for 4 weeks in moderate-to-severe SD patients.

Secondary Objectives

- To characterize the molecular cutaneous phenotype of SD.
- To compare molecular biomarker expression in SD patients with healthy controls.
- To characterize the molecular responses to treatment with topical ruxolitinib 1.5% cream applied twice daily for 4 weeks in moderate-to-severe SD patients.
- To correlate the molecular and clinical responses to treatment with topical ruxolitinib 1.5% cream applied twice daily in order to identify biomarkers of treatment response in SD patients
- To validate a clinical SD disease severity score using assessments by two independent investigators
- To evaluate the safety and tolerability of topical ruxolitinib 1.5% cream applied twice daily for 4 weeks in moderate-to-severe SD patients

ENDPOINTS:

Primary Endpoint

- The proportion of patients who achieve an IGA 0/1 at 4 weeks of treatment with ruxolitinib 1.5% cream applied twice daily

Secondary Endpoints

- Change from baseline in IGA score at 4 weeks of treatment with ruxolitinib 1.5% cream applied twice daily
- Change from baseline in overall clinical SD score at 4 weeks of treatment with ruxolitinib 1.5% cream applied twice daily

- Change from baseline in each component of the clinical SD score at 4 weeks of treatment with ruxolitinib 1.5% cream applied twice daily (scale, erythema, pruritus)
- Change in overall clinical SD at 6 weeks (i.e., 2 weeks after treatment cessation) from baseline and from 4 weeks
- The frequency, duration, and severity of AEs
- Changes in vital signs
- Changes in laboratory data for hematology, serum chemistry, and urinalysis

Mechanistic (Exploratory) Endpoints

- Determine the molecular cutaneous phenotype of SD at baseline compared with healthy controls, using transcriptomic and proteomic approaches from skin samples acquired by tape-strips
- Identify molecular markers that correlate with disease activity in SD at baseline
- Characterize the change in molecular responses with treatment of topical ruxolitinib 1.5% cream after 4 weeks of treatment
- Identify molecular markers that correlate with treatment response at 4 weeks

STUDY DESIGN OVERVIEW:

This study is an open-label prospective interventional trial. The study will take place at Icahn School of Medicine at Mount Sinai.

The study will include 25 adult patients with moderate-to-severe-SD as well as 20 age- and gender-matched healthy control subjects for comparison. The SD patients will have baseline clinical score of at least 6 using the SD Severity Score in Appendix 1, or an Investigator Global Assessment (IGA) score of at least 3. Enrolled SD subjects will apply topical ruxolitinib 1.5% cream twice daily for 4 weeks. They will return for visits at weeks 2, 4, and 6 following study treatment initiation for repeat clinical assessments, medication reviews, tape-strip, blood and urine sample collections, and monitoring for adverse events.

After providing consent, all subjects will be assessed for study eligibility, which includes a review of the subjects past and current medical conditions, familial medical history and detailed review of past and current medications. SD subjects will also undergo a review of past topical treatments/therapies for SD, and clinical assessments (clinical SD score and IGA).

Subjects who meet inclusion criteria for eligibility may continue with the Baseline Visit (Week 0) or can be scheduled to return for the Baseline Visit within 28 days of the Screening Visit.

SD Subjects:

At Baseline/Week 0, subjects will undergo clinical assessments (clinical SD Severity Score and IGA), review of concomitant medications, standardized clinical photography, and a Dermatology Life Quality index (DLQI) questionnaire (Appendix 2). Subsequent clinical assessments including standardized clinical photography, and questionnaire completion will be performed at follow up visits at Week 2, Week 4, and Week 6. Skin tape-strip samples will be collected for mechanistic studies (described below) at baseline (lesional and non-lesional facial skin), Week 2 (lesional facial skin), Week 4 (lesional facial skin), and Week 6 (lesional facial skin). Additional blood samples will be collected and stored at baseline and at Week 4 (or early termination, whichever is first) for potential future mechanistic analyses.

Control Subjects:
At Baseline/Week 0, subjects will undergo a review of concomitant medications, skin tape-strip samples will be collected for mechanistic studies (described below) of non-lesional facial skin, blood and urine sample collection for standard laboratory testing, and a blood sample for possible future mechanistic analyses.

MECHANISTIC ANALYSES:

We will characterize the molecular immune profiles of patients with SD at week 0 and week 4, with comparison to baseline profiles in healthy control subjects.

We plan to obtain lesional and non-lesional tape strip samples from facial skin of SD patients at week 0 and lesional facial skin samples at Week 4 (Primary Endpoint). Additionally, lesional facial skin samples will be collected at Week 2 and Week 6 and stored for potential future analysis. Blood samples at baseline and at Week 4 will be collected and stored for potential future analysis.

Gene expression studies on tape strip samples will be performed using Illumina NovaSeq 6000 for RNA-seq, and proteomic studies on tape strip samples will be performed using the Olink Explore panel, which includes >1,500 protein analytes.

PATIENT POPULATION:

Prior to enrollment, all subjects must meet the following inclusion and exclusion criteria:

Inclusion Criteria For SD Subjects:

1) Male or female subjects ≥ 18 years of age at the time of signing the informed consent document.

2) Subject is able to understand and voluntarily sign an informed consent document prior to participation in any study assessments or procedures.

3) Subject is able to adhere to the study visit schedule and other protocol requirements.

4) Baseline SD score of IGA ≥ 3 with facial involvement

5) Subject agrees to discontinue all treatments for SD from screening through study completion aside from the study drug

6) Subject has failed an adequate course of treatment with at least one available therapy (topical antifungals or low-potency topical corticosteroids)

7) Subject is judged to be in otherwise good overall health as judged by the investigator, based on medical history, physical examination, and laboratory testing. (NOTE: The definition of good health means a subject does not have uncontrolled significant co-morbid conditions).

8) Females of childbearing potential (FCBP) must have a negative pregnancy test at Screening and Baseline. While on the study drug and for at least 90 days after the last application of the study drug, male and female participants must be willing to take appropriate contraceptive measures to avoid pregnancy or fathering a child. FCBP who engage in activity in which conception is possible must use one of the approved contraceptive options described below:

   Option 1: Any one of the following highly effective contraceptive methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy.

   OR

   Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]); PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.

   The female subject's chosen form of contraception must be effective by the time the female subject is enrolled into the study.

Exclusion Criteria For SD Subjects:

The presence of any of the following will exclude a subject from enrollment:

1) SD clinical severity of IGA <3 and SD Severity Score <6.

2) Subjects with other skin diseases that would interfere with the study assessment in the opinion of the investigator.

3) Active bacterial, fungal, or viral skin infection within 2 weeks from study initiation.

4) Subject has clinically significant (as determined by the investigator) renal, hepatic, hematologic, intestinal, endocrine, pulmonary, cardiovascular, neurological, psychiatric, immunologic, or other major uncontrolled diseases (e.g., malignancy, TB, HIV, HBV, HCV, thromboembolic events) that will affect the health of the subject during the study, or interfere with the interpretation of study results.

5) Subject has previously received treatment with oral or topical JAK inhibitors

6) Current other topical treatments (e.g., topical corticosteroids, topical calcineurin inhibitors) within 1 week of baseline

7) Use of systemic immunosuppressive medications, including, but not limited to, cyclosporine, systemic or intralesional corticosteroids, mycophenolate mofetil, azathioprine, methotrexate, tacrolimus within 4 weeks of study initiation

8) Concurrent use of strong CYP3A4 inhibitors within 7 days or 5 half-lives (whichever is longer). A list of CYP3A4 inhibiting medications can be found in Appendix 3.

9) History of adverse systemic or allergic reactions to any component of the study drug.

10) Current participation in any other study with an investigational medication

11) Subject who is pregnant or breast feeding

Inclusion Criteria For Control Subjects:

1) Male or female subjects ≥ 18 years of age at the time of signing the informed consent document.

2) Subject is able to understand and voluntarily sign an informed consent document prior to participation in any study assessments or procedures.

3) Subject does not currently have and does not have a history of SD.

4) Female of childbearing potential (FCBP) must have a negative pregnancy test at Screening and Baseline

Exclusion Criteria For Control Subjects:

1) Active bacterial, fungal, or viral skin infection within 2 weeks from Screening/Baseline visit.

2) Subject has uncontrolled clinically significant (as determined by the investigator) renal, hepatic, hematologic, intestinal, endocrine, pulmonary, cardiovascular, neurological, psychiatric, immunologic, or other disease.

3) Subject has previously received treatment with oral or topical JAK inhibitors

4) Current other topical treatments (e.g., topical corticosteroids, topical calcineurin inhibitors) within 1 week of baseline

5) Use of systemic immunosuppressive medications, including, but not limited to, cyclosporine, systemic or intralesional corticosteroids, mycophenolate mofetil, azathioprine, methotrexate, tacrolimus within 4 weeks of study initiation

6) Current participation in any other study with an investigational medication

7) Subject who is pregnant or breast feeding

POTENTIAL RISKS OF RUXOLITINIB 1.5% CREAM:

Based on phase 2 and phase 3 studies in atopic dermatitis, as well as phase 2 studies in vitiligo, topical application of ruxolitinib 1.5% cream shows a good safety profile. The most commonly experienced adverse events in the atopic dermatitis studies were application site burning and pruritus, which occurred more commonly in the vehicle control group (15). These results were mirrored in the phase 2 vitiligo study, with the additional observation of 18% of vitiligo patients experienced development of acne as a treatment-related adverse event (16). Although oral ruxolitinib has been associated with the risk of hematologic abnormalities in patients treated for polycythemia vera or myelofibrosis, pharmacokinetic analysis performed in the phase 3 studies in atopic dermatitis patients with up to 20% body surface area involvement demonstrated plasma ruxolitinib concentrations substantially lower than those required for systemic activity (17).

PRIOR TREATMENT:

All relevant treatment received by the subject within 30 days before screening will be recorded.

PROHIBITED TREATMENT:

All treatments prohibited during the screening period are also prohibited throughout the course of the study. All subjects treated previously with a topical or oral JAK inhibitor will be excluded from the study as above.

PROCEDURES:

Monitoring of Aes will begin at the time of signing the informed consent form and will be continued throughout the course of the study. All study procedures will be completed at designated times during the study period (see **Table 1**).

Trained assessors will perform clinical assessments. It is strongly recommended that the same assessor/s perform clinical assessments for a subject at all study visits.

For SD Subjects

Visit 1 – Screening (within 28 days of Baseline)*****

- Obtain signed IRB-approved informed consent and HIPPA agreement
- Review Inclusion and Exclusion Criteria
- Record gender, race, ethnicity, and medical history
- Review personal and family history of SD and other inflammatory skin diseases
- Record all concomitant medications as well as all those received within 30 days prior to screening
- Record all prior therapies for SD
- Urine pregnancy test for all female subjects of child-bearing potential
- SD Clinical assessments (IGA, SD Severity Score)
- Record adverse events

***** If subject meets all entry criteria at Screening, he/she can complete Baseline Visit on the same day (identical procedures do not need to be repeated). If more than 28 days has lapsed between screening and Baseline/Visit 2, then all procedures should be repeated except for re-obtaining informed consent. If subject has used a topical medication, then Baseline/Visit 2 will occur only after a 1 week washout period.

Visit 2 – Baseline (Week 0)

- Confirm all inclusion and exclusion criteria have been met
- Record concomitant medications and adverse events
- DLQI questionnaire
- Standardized clinical photography (including photographs of subject's entire face and close up photographs of the following facial regions: 1. Left cheek, 2. Right cheek, 3. Forehead and glabella)
- SD clinical assessments (IGA, SD Severity Score)
- Urine pregnancy test for all female subjects of child-bearing potential

- Collect blood samples for CBC with differential, Comprehensive metabolic panel (CMP), and C-reactive protein (CRP)
- Collect blood sample for possible future mechanistic analyses
- Urinalysis
- Perform tape strips of lesional and non-lesional skin. Lesional skin tape strips will be taken from area of worst clinical involvement
- Dispense/administer study drug

Visit 3 – Week 2

- Record concomitant medications and adverse events
- DLQI questionnaire
- SD clinical assessments (IGA, SD Severity Score)
- Urine pregnancy test for all female subjects of child-bearing potential
- Perform tape strips of lesional skin. Lesional skin tape strips will be taken from the same location as the lesional tape strips taken at Baseline.
- Dispense study drug and assess compliance. Subjects will report each study drug application, with 4 missed doses from Baseline considered non-compliance.

Visit 4 – Week 4

- Record concomitant medications and adverse events
- DLQI questionnaire
- Standardized clinical photography (including photographs of subject's entire face and close up photographs of the following facial regions: 1. Left cheek, 2. Right cheek, 3. Forehead and glabella)
- SD clinical assessments (IGA, SD Severity Score)
- Urine pregnancy test for all female subjects of child-bearing potential
- Collect blood samples for CBC with differential, Comprehensive metabolic panel (CMP), and C-reactive protein (CRP)
- Collect blood sample for possible future mechanistic analyses
- Urinalysis
- Perform tape strips of lesional skin. Lesional skin tape strips will be taken from the same location as the lesional tape strips taken at Baseline and Week 2.
- Assess study drug dosing compliance and retrieve all remaining study drug from subject. Subjects will report each study drug application, with 4 missed doses from Week 2 considered non-compliance.

Visit 5 – Week 6

- Record concomitant medications and adverse events
- DLQI questionnaire

- Standardized clinical photography including photographs of subject's entire face and close up photographs of the following facial regions: 1. Left cheek, 2. Right cheek, 3. Forehead and glabella)
- SD clinical assessments (IGA, SD Severity Score)
- Urine pregnancy test for all female subjects of child-bearing potential
- Perform tape strips of lesional skin. Lesional skin tape strips will be taken from the same location as the lesional tape strips taken at Baseline, Week 2, and Week 4.

Early Termination Visit (if applicable)

- Record concomitant medications and adverse events
- DLQI questionnaire
- Standardized clinical photography (including photographs of subject's entire face and close up photographs of the following facial regions: 1. Left cheek, 2. Right cheek, 3. Forehead and glabella)
- Urine pregnancy test for all female subjects of child-bearing potential
- Collect blood samples for CBC with differential, Comprehensive metabolic panel (CMP), and C-reactive protein (CRP)
- Collect blood sample for possible future mechanistic analyses
- Urinalysis
- SD clinical assessments (IGA, SD Severity Score)
- Perform tape strips of lesional skin. Lesional skin tape strips will be taken from the same location as the lesional tape strips taken at Baseline and Week 2 (if applicable)
- Assess study drug dosing compliance and retrieve all remaining study drug from subject

For Control Subjects

Visit 1 – Screening (within 28 days of Baseline)*****

- Obtain signed IRB-approved informed consent and HIPPA agreement
- Review Inclusion and Exclusion Criteria
- Record gender, race, ethnicity, and medical history
- Review personal and family medical conditions/diseases
- Record all concomitant medications as well as all those received within 30 days prior to screening
- Urine pregnancy test for all female subjects of child-bearing potential
- Record adverse events

***** If subject meets all entry criteria at Screening, he/she can complete Baseline Visit on the same day (identical procedures do not need to be repeated). If more than 28 days has lapsed between screening and Baseline/Visit 2, then all procedures should be repeated except for re-obtaining informed consent.

Visit 2 – Baseline (Week 0)

- Confirm all inclusion and exclusion criteria have been met
- Record concomitant medications and adverse events
- Urine pregnancy test for all female subjects of child-bearing potential
- Collect blood samples for CBC with differential, Comprehensive metabolic panel (CMP), and C-reactive protein (CRP)
- Collect blood sample for possible future mechanistic analyses
- Urinalysis
- Perform tape strips of non-lesional skin

SAFETY MONITORING:

The study will be conducted in accordance with our department's Standard Operating Procedures, which are based on US FDA Title 21 Code of Federal Regulations and ICH Good Clinical Practice guidelines. An investigator will review all laboratory results and assess for adverse events. The principal investigator will be informed of all adverse events. In the event that a subject's safety is compromised, the investigator will discontinue the subject immediately.

STUDY WITHDRAWAL:

In the event a study subject wants to withdraw early from the study for any reason, the subject will be asked to return for a final visit to have some or all of the following procedures and assessments as listed for Visit 5/Week 6: vital signs; blood test; pregnancy test (if applicable); clinical photography; SD clinical assessments; DLQI questionnaire, assessment of concomitant medication and adverse events; blood collection for future mechanistic analysis; lesional tape strip collection.

DISCONTINUATION OF TREATMENT AND WITHDRAWAL OF SUBJECTS:

The reasons why a subject may discontinue or be withdrawn from the study by the investigator include, but are not limited to the following: subject request, protocol violation, loss to follow up, subject non-compliance, defined as 4 missed applications during the 2 week period between study Visits, study termination by investigators, and a confirmed grade 3 or higher adverse event, which is suspected to be related to study drug administration. Subjects that elect to withdraw from the trial due to lack of efficacy and/or exacerbation of disease will undergo the following: vital signs; blood test; pregnancy test (if applicable); clinical photography; SD clinical assessments; DLQI questionnaire, assessment of concomitant medication and adverse events; blood collection for future mechanistic analysis; lesional tape strip collection.

Stopping Rules

Patients will be permanently discontinued from study treatment in the event of:

- Anaphylactic reaction or other severe systemic reaction to study drug application
- Pregnancy at anytime during the study period
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
- Any infection that is opportunistic, whose nature or course may suggest an immuno-compromised status
- Treatment with any prohibited concomitant medication or procedure
- Other reasons that may lead to the permanent discontinuation of study drug include certain Aes deemed related to the study drug.
- If the following lab results are abnormal, participants will be retested in a window of 7-10 days and reassessed. If the test results remain abnormal, participants will be discontinued from the study:
  Hematology
  Absolute Neutrophil Count:<1000/mm^3; <1.0 x109/L
  Hemoglobin: <8.0 g/dL; <4.96 mmol/L; <80 g/L
  Hemoglobin drop ≥2 g/dL from baseline on two consecutive blood draws with associated symptoms; or hemoglobin drop ≥3 g/dL from baseline on two consecutive blood draws without associated symptoms.
  Platelet count: <75,000/mm^3; <75.0x109/L
  Lymphocytes: <500/mm^3; <0.5x109/L
  Chemistry
  AST >3.0x ULN
  ALT >3.0x ULN
  Total bilirubin >1.5x ULN
  CPK >10x ULN
  Total bilirubin ≥1.5 x ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ ULN
- Other intercurrent illnesses or major surgery
- An infection that requires systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents or requires oral treatment with such agents for longer than 2 weeks
- Treatment with systemic corticosteroids or non-steroidal immunosuppressive/ immunomodulating medications (e.g., cyclosporine, methotrexate, azathioprine, mycophenalate-mofetil, Janus kinase inhibitors, biologic agents, etc.).

Safety Evaluation

Safety and tolerability will be evaluated from the Aes, physical examinations, and vital sign measurements. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator.

Aggregated Aes will be evaluated by the PI/research teams. The local IRB, FDA, and Incyte will be notified of adverse events.

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 14 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 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.

SUBJECT IDENTIFICATION

Subjects are numbered sequentially. Each subject will be assigned a unique screening number for the duration of the study. Subject screening numbers will not be reassigned or reused for any reason. The investigator must maintain a master log linking the subject number to the subject's name. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality.

STUDY DRUG SUPPLY:

Eligible patients will receive a supply of ruxolitinib 1.5% cream which they will apply to affected skin on the face only twice daily. Patients will be instructed not to use more than 60g of cream per week.

All study medication will be stored in a secure cool area between 15-30˚C. Study drug will be provided to subjects at each study visit, with initial application performed at that time and subsequent applications performed by the patients at home.

Subjects will be queried during each study visit on any missed applications.

STATISTICAL CONSIDERATIONS:

Sample Size Calculation

A sample size of n=20 SD patients guarantees 90% power at 2.1% significance to detect a minimum proportion of 75% of patients with IGA 0/1 at week 4. This calculation assumes the application of the one-sided binomial test with a null hypothesis proportion of 40%. This proportion is based on the vehicle response benchmark reported by Zirwas et al.(2021) when comparing IGA 0/1 at week 8 in 154 patients treated with roflumilast foam 0.3% vs. 72 patients in the vehicle-controlled group(18). Accounting for a 20% dropout rate, we, therefore, propose a sample size of n=25 patients.

Mechanistic Endpoint

To the best of our knowledge, this is the first study to evaluate differences in the transcriptome between SD and healthy subjects. A previous study (19) evaluated a fold-change (FCH) of 5 in IL-10 cell counts with coefficient of variation of 50% when comparing 10 SD subjects to 4 healthy volunteers. Assuming similar variability, a sample size of n = 20 SD subjects and n= 20 controls would provide 90% power at 5% significance to detect FCH>2.65 when comparing IL-10 expression between SD and controls, based on a two-sided unpaired t-test applied to log2-transformed RNA-seq data and fold-changes back transformed.

Demographics and Other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics of patients will be summarized. Other baseline characteristics include height, weight, vital signs, duration of SD disease, concurrent diagnoses from medical history and indications for concomitant medication, concomitant medication, and previous SD treatments.

Analysis of Primary Endpoint

The one-sided binomial test will be used to verify the hypothesis that the proportion of patients achieving IGA 0/1 at 4 weeks of treatment with ruxolitinib 1.5% cream applied twice daily is greater than 0.4.

Analysis of Secondary Endpoints

The two-sided Wilcoxon signed-rank test will assess the significance of changes from baseline in:

- IGA score at 4 weeks of treatment
- Components of clinical SD scoring (scale, erythema, and pruritus) at 4 weeks of treatment.

The two-sided paired t-test will assess the significance of changes from baseline in:

- Overall clinical SD scoring at 4 and 6 weeks of treatment.
- Vital signs measured in interval or ratio scale
- Analytes measured in interval or ratio scale from laboratory tests (hematology, serum, chemistry, and urinalysis) at 4 weeks of treatment

The p-values will be adjusted by the Bonferroni method. The frequency, duration, and severity of AEs will be summarized with tables and summary statistics.

Analysis of Mechanistic (Exploratory) Endpoints

The baseline immune and molecular cutaneous profile of SD at baseline compared with healthy controls and the change in the immune and molecular cutaneous profile of SD with treatment will be assessed by MMRM approach. Gene/Protein expression data will be modeled using a mixed effect model with the interaction between tissue type (non-lesional/ lesional / healthy) and timepoint as fixed effects and a random effect for each subject.

RNA-sequencing data will be profiled by Illumina NovaSeq 6000. RNA-sequencing data will be pre-processed using standard quality control metrics, such as FastQC and MultiQC, sequence alignment by STAR RNA-sequencing aligner and sequencing reads assignment to genomic features by featureCounts, followed by *voom*-transform. Mixed effect models will be used on R's limma framework and p-values for the moderated t-tests and paired-t-test will be adjusted by Benjamini-Hochberg procedure. Extensive bioinformatics tools will be employed to gain insights into the results. This will include (but will not be limited to) pathway and gene-set enrichment analyses by R package GSVA (Gene Set Variation Analysis) and by eXploring Genomic Relations (XGR) that uses prior biological knowledge and relationships from public databases.

We will perform proteomic biomarker studies in serum using the OLINK high-throughput proteomic platform, with the Explore panel that evaluates >1,500 protein analytes. Protein expression data will be modeled using a MMRM approach, with the interaction of study group (treatment /control) and timepoint as fixed effects and a random effect for each subject.

We will use the Spearman coefficient to correlate: 1) molecular markers with disease activity in SD at baseline; 2) changes from baseline in molecular markers with changes from baseline in IGA and overall clinical SD scoring at 4 weeks of treatment.

Data Transfer and Management

Data including the patient info, demographics, clinical scores and treatment allocation code will be sent to our Biostatistical Team in password-protected files.

Data from the Guttman Lab (where all mechanistic studies will be done), including sequencing data and proteomics will be deposited in the Mount Sinai Box, which has the necessary safeguards for protection of human subjects research.

All data management steps taken to reformat and merge the clinical and laboratory data will be carried out using R codes, so all the steps of the processes can be reproduced.

Management of the Analysis
Analyses will be run in our desktops, with a backed-up copy in the Mount Sinai Box account. Once the analysis is finalized, all data will be deposited into the central file storage system (CFS), which is accessible to all research members. Both Mount Sinai Box and the CFS have backup capabilities and are encrypted and password protected.

Analysis of Safety and Tolerability
Safety will be evaluated by tabulations of adverse events (AEs) and will be presented with descriptive statistics at each visit. AEs will be coded using the CTCAE, Common Terminology Criteria for Adverse Events, V 5.0. The number and percentage of subjects/lesions experiencing an AE/SAE will be stratified by system organ class, or a preferred term, and/or severity of the adverse event, and recorded and tabulated overall by each sub-strata. Each subject will be counted only once within a system organ class or a preferred term using the adverse events with the highest severity within each category. All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim given by the investigator, preferred term, system organ class, date of onset, date of resolution, severity, and relationship to treatment. A tabulation of AEs will be provided by subject.

DLQI (Dermatology Life Quality Index)

The DLQI is a validated questionnaire consisting of 10 questions that has been used in many randomized controlled trials in dermatology (20, 21).

Scoring
The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0

Question unanswered	scored 0

The DLQI is calculated by summing the score of each question. The maximum score is 30 and minimum score is 0. Higher score represents a quality of life that is more impaired.

Definition of DLQI Scores
0-1 = no effect at all on patient's life
2-5 = small effect on patient's life
6-10 = moderate effect on patient's life
11-20 = very large effect on patient's life
21-30 = extremely large effect on patient's life

A change in DLQI score of at least 4 points is considered clinically important (22). Such change suggests that there has actually been a meaningful change in that patient's quality of life since the previous measurement of his/her DLQI scores.

Table 1. Schedule of Events

Visit Week	(Up to -28 Days before Baseline)	**0**	**2**	**4**	**6**	**X**	**Control Subjects**
Visit #	**1**	**2**	**3**	**4**	**5**	**Early Term-ination**	**1**
Visit Type	**Screening**	**Baseline**	**Tx**	**Tx**	**F-up**		**Screening / Baseline**
Informed Consent	X						X
Inclusion / Exclusion Criteria	X	X[3]					X
Demographics and Medical Hx[1]	X						X
Urine Pregnancy Test	X	X[3]	X	X	X	X	X
CBC w/differential; CMP; Urinalysis		X		X		X	X
Blood Sample Stored for Future Analysis		X		X		X	X
CRP		X		X			X
SD Clinical Assessments (IGA, SD Severity Score)	X	X[3]	X	X	X	X	
Dermatology Life Quality Index (DLQI)		X	X	X	X	X	
Standardized Photographs		X		X	X	X	
Dispense Drug		X	X				
Assess Application Compliance			X	X		X	
Lesional Tape Strip		X	X	X	X	X	
Non-lesional Tape Strip		X					X
Concomitant Medications	X[2]	X[3]	X	X	X	X	X
Adverse Events	X	X[3]	X	X	X	X	X

[1] Includes current and past medical conditions in addition to personal and family history of inflammatory skin diseases

[2] Includes prior therapies/treatments for SD and any medications received within 30 days of screening.

[3] Does not need to be repeated if Screening and Baseline occur on the same day.

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Appendix 1. Clinical Assessments

SD Severity Score

Clinical Feature	Score[a]
Scale	0-4
Erythema	0-4
Pruritus	0-4
Total Score	0-12

[a]0-4 for each clinical feature (0 = absence, 1 = mild, 2 = moderate, 3 = significant, 4 = severe)

Investigator Global Assessment

Clinical severity	Scored	Features
Clear	0	No signs of SD
Almost Clear	1	Just perceptible erythema and just perceptible scaling
Mild	2	Mild erythema and mild scaling
Moderate	3	Moderate erythema and moderate scaling
Severe	4	Severe erythema and severe scaling

Appendix 2.

Dermatology Life Quality Index

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

Appendix 3 CYP3A4 Inhibitors.

CYP3A4 Inhibitors

Amiodarone
Amprenavir
Aprepitant
Atazanavir
Boceprevir
Casopitant
Cimetidine
Ciprofloxacin
Clarithromycin
Cobicistat
Conivaptan
Crizotinib
Cyclosporine
Danoprevir
Darunavir
Delavirdine
Diltiazem
Dronedarone
Elvitegravir
Erythromycin
Faldaprevir
Fluconazole
Gestodene
Grapefruit Juice, marmalade
Idelalisib
Imatinib
Indinavir
Isavuconazole
Itraconazole
Ketoconazole
Lopinavir
Mibefradil
Mifepristone (RU486)
Nefazodone
Nelfinavir
Netupitant
Nilotinib
Norfloxacin
Norfluoxetine
Posaconazole
Ritonavir
Saquinavir
Schisandra sphenanthera
Telaprevir
Telithromycin
Tipranavir
Tofisopam
Troleandomycin
Verapamil
Viekira pak
Voriconazole

Appendix 4 – Study Drug Label

Mount Sinai School of Medicine

Department of Dermatology
212-241-3288

GCO#22-0672 Seborrheic Dermatitis and Treatment Response to Ruxolitinib 1.5% Cream

Subject #_____ Subject Initials:_____ Date:_____

Ruxolitinib 1.5% Cream - Apply as directed by the study doctor
PI: Dr Benjamin Ungar (212) 241-3288.
Store at controlled room temperature, away from light and humidity.
Caution: New Drug--Limited by Federal (USA) law to investigational use.

Appendix 5. Amendment Details

Amendment #1 May 25, 2022

Page 1 – Title Page – Added Amendment #1: May 25, 2022; Revised Date of protocol in footer.

Page 2 Table of Contents – Revised Page numbers and added Subject Identification and Appendices 3, 4 and 5.

Page 7 Inclusion Criteria for SD Subjects – Removed SD Severity Score as a criterion and added inclusion criterion: “Subject has failed an adequate course of treatment with at least one available therapy (topical antifungals or low-potency topical corticosteroids).”

Page 8 Exclusion Criteria for SD Subjects – Added Exclusion criterion: “Concurrent use of strong CYP3A4 inhibitors within 7 days or 5 half-lives (whichever is longer). A list of CYP3A4 inhibiting medications can be found in Appendix 3.”

Page 14 Stopping Rules – Added the following stopping rules:

- If the following lab results are abnormal, participants will be retested in a window of 7-10 days and reassessed. If the test results remain abnormal, participants will be discontinued from the study:
  Hematology
  Absolute Neutrophil Count: <1000/mm^3; <1.0 x109/L
  Hemoglobin: <8.0 g/dL; <4.96 mmol/L; <80 g/L
  Hemoglobin drop ≥2 g/dL from baseline on two consecutive blood draws with associated symptoms; or hemoglobin drop ≥3 g/dL from baseline on two consecutive blood draws without associated symptoms.
  Platelet count: <75,000/mm^3; <75.0x109/L
  Lymphocytes: <500/mm^3; <0.5x109/L
  Chemistry
  AST >3.0x ULN
  ALT >3.0x ULN
  Total bilirubin >1.5x ULN
  CPK >10x ULN
  Total bilirubin ≥1.5 x ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is ≤ ULN
- Other intercurrent illnesses or major surgery
- An infection that requires systemic treatment with antibiotic, antifungal, antiviral, anti-parasitic, or anti-protozoal agents or requires oral treatment with such agents for longer than 2 weeks
- Treatment with systemic corticosteroids or non-steroidal immunosuppressive/ immunomodulating medications (e.g., cyclosporine, methotrexate, azathioprine, mycophenalate-mofetil, Janus kinase inhibitors, biologic agents, etc.).

Page 22 Appendix 1. Clinical Assessments – added a description of features associated with the individual scores of the Investigator Global Assessment.

Page 25 – Added Appendix 3 CYP3A4 Inhibitors

Page 26 – Added Appendix 4 Study Drug Label

Page 27 – Added Appendix 5 Amendment Details

Amendment #2 - October 24, 2022

Page 1 – Title Page – Added Amendment #2: October 24, 2022; Revised Date of protocol in footer.

Page 4 – Primary Endpoint

Revised from: "Percent of patients who achieve an IGA of 0 or 1 at 4 weeks of treatment with ruxolitinib 1.5% cream applied twice daily"

To: "The proportion of patients who achieve an IGA 0/1 at 4 weeks of treatment with ruxolitinib 1.5% cream applied twice daily"

Page 16 - Sample Size Calculation

Revised from: "30 moderate-to-severe patients treated with crisaborole for four weeks showed 67.8% average improvement in IGA with a standard deviation of approximately 50% (9). Assuming similar biological variation (sd = 50%), a sample size of n=20 SD patients provides 95% power at 5% significance to detect a minimum average improvement in IGA of 42.5% with the application of a two-sided paired t-test. Accounting for a 20% dropout rate, we, therefore, propose a sample size of n=25 patients."

To: "A sample size of n=20 SD patients guarantees 90% power at 2.1% significance to detect a minimum proportion of 75% of patients with IGA 0/1 at week 4. This calculation assumes the application of the one-sided binomial test with a null hypothesis proportion of 40%. This proportion is based on the vehicle response benchmark reported by Zirwas et al.(2021) when comparing IGA 0/1 at week 8 in 154 patients treated with roflumilast foam 0.3% vs. 72 patients in the vehicle-controlled group(18). Accounting for a 20% dropout rate, we, therefore, propose a sample size of n=25 patients. "

Page 16 - Analysis of Primary Endpoint

Revised from "A Mixed-effects ordinal logistic regression model will be used to test differences in IGA between time points with time (Weeks 0, 2, 4, and 6) as a fixed effect, a random intercept for subjects, and inclusion of baseline characteristics as covariates. "

To: "The one-sided binomial test will be used to verify the hypothesis that the proportion of patients achieving IGA 0/1 at 4 weeks of treatment with ruxolitinib 1.5% cream applied twice daily is greater than 0.4.

Page 16 – Analysis of Secondary Endpoints

Revised from: “The mixed-effects model for continuous outcomes will also be used to detect any overall changes in clinical SD scoring over time compared with baseline with time (Weeks 0, 2, 4, and 6) as a fixed effect, a random intercept for subjects, and potential covariates. Changes in each component of the SD Severity Score, will also be evaluated using the same approach.”

To: “The two-sided Wilcoxon signed-rank test will assess the significance of changes from baseline in:

- IGA score at 4 weeks of treatment
- Components of clinical SD scoring (scale, erythema, and pruritus) at 4 weeks of treatment.

The two-sided paired t-test will assess the significance of changes from baseline in:

- Overall clinical SD scoring at 4 and 6 weeks of treatment.
- Vital signs measured in interval or ratio scale
- Analytes measured in interval or ratio scale from laboratory tests (hematology, serum, chemistry, and urinalysis) at 4 weeks of treatment

The p-values will be adjusted by the Bonferroni method. The frequency, duration, and severity of AEs will be summarized with tables and summary statistics.”

Page 17 - Analysis of Mechanistic (Exploratory) Endpoints

Revised from: “The baseline immune and molecular cutaneous profile of SD at baseline compared with healthy controls and the change in the immune and molecular cutaneous profile of SD with treatment will be assess by MMRM approach. Gene/Protein expression data will be modeled using a mixed effect model with tissue type and time as a fixed effect and a random effect for each subject.”

To: “The baseline immune and molecular cutaneous profile of SD at baseline compared with healthy controls and the change in the immune and molecular cutaneous profile of SD with treatment will be assessed by MMRM approach. Gene/Protein expression data will be modeled using a mixed effect model with the interaction between tissue type (non-lesional/ lesional / healthy) and timepoint as fixed effects and a random effect for each subject.”

Revised from: “We will perform proteomic biomarker studies in serum using the OLINK high-throughput proteomic platform, with the Explore panel that evaluates >1,500 protein analytes. Protein expression data will be modeled using a MMRM approach, with time interaction as a fixed effect and a random effect for each subject.”

To: “We will perform proteomic biomarker studies in serum using the OLINK high-throughput proteomic platform, with the Explore panel that evaluates >1,500 protein analytes. Protein expression data will be modeled using a MMRM approach, with the interaction of study group (treatment /control) and timepoint as fixed effects and a random effect for each subject.

We will use the Spearman coefficient to correlate: 1) molecular markers with disease activity in SD at baseline; 2) changes from baseline in molecular markers with changes from baseline in IGA and overall clinical SD scoring at 4 weeks of treatment."