PDE4 Inhibition in the Treatment of Seborrheic Dermatitis and Papulopustular Rosacea With PF-07038124
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PDE4 Inhibition in the Treatment of Seborrheic Dermatitis and Papulopustular Rosacea With PF-07038124

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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).

Rosacea is a chronic inflammatory skin disease with an incidence of 5.46% globally (13), though it is more common in Caucasians and affects 10% or more of this population (14). It predominantly presents as episodic flares of facial erythema and as telangiectasias (15). However, rosacea may occur as any of 5 phenotypes: flushing, papulopustular, erythematotelangiectatic, ocular, and phymatous (16). Patients of all phenotypes may also concurrently experience pain, stinging, burning or itching of affected areas (17). Given the centrofacial presentation and associated physical discomfort, rosacea can have an immense impact on patients' self-esteem, mood, and quality of life (18). Treatment guidelines regarding first line therapy for each phenotype have been proposed. These support the use of laser therapy for persistent erythema, telangiectasias, and phymatous changes, topical a-adrenergic agonists for erythema, as well as topical/oral antimicrobials or topical azelaic acid for papules and pustules. However, evidence is mixed on the efficacy of many of these treatments and patients may require a combination of agents due to symptom type or severity (19-21). As such, the management of rosacea remains an area of intense study and many alternative light-based, topical, and oral approaches are currently under investigation.

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

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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).

Rosacea is known to involve aberrant regulation of the cutaneous vascular, neurovascular, and innate and adaptive immune systems (22, 23). While the exact pathomechanism of rosacea remains unclear, rosacea affected skin shows increased inflammatory markers including cytokines, antimicrobial peptides, chemokines, and matrix metalloproteinases (24). Specifically, an upregulation of the serine protease kallikrein 5 and subsequent activation of the antimicrobial peptide cathelicidin LL37 to its proinflammatory form resulting in erythema, inflammation, and vascular changes is considered a disease hallmark (22, 25). Th1 and Th17 cytokine pathways including IFN-γ, IL-18 and IL-17 and have been implicated as well (26). These pathways can be triggered by microbial stimuli, heat, stress, excessive emotion, spicy foods, alcohol use, and ultraviolet rays (15).

PF-07038124 is a PDE4 inhibitor, which is expected to suppress the majority of the proposed SD and papulopustular rosacea (PPR)-related cytokines simultaneously. Topical PDE4 inhibitory approaches in SD [e.g., crisaborole (9)] have been used in small studies, supporting this approach. More recently, a phase 2 study was published demonstrating efficacy in treating SD with a different PDE4 inhibiting cream, roflumilast (27). Subsequently, phase 3 data from 457 patients with moderate-to-severe seborrheic dermatitis confirmed efficacy of roflumilast vs. vehicle (28).

Therefore, we hypothesize that the topical PF-07038124 PDE4 inhibitor ointment will be able to reverse the immune dysregulation seen in SD and PPR, leading to clinical improvement.

HYPOTHESIS:

Primary Hypotheses

- Once daily application of PF-07038124 0.02% ointment for 8 weeks will be clinically efficacious in treating moderate-to-severe SD.
- Once daily application of PF-07038124 0.02% ointment for 8 weeks will be clinically efficacious in treating moderate-to-severe PPR.

OBJECTIVES:

Primary Objectives

- To characterize the clinical responses to treatment with topical PF-07038124 0.02% ointment applied once daily for 8 weeks in moderate-to-severe SD patients.

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- To characterize the clinical responses to treatment with topical PF-07038124 0.02% ointment applied once daily for 8 weeks in moderate-to-severe PPR patients.

Secondary Objectives

- To characterize the molecular cutaneous phenotype of SD and PPR.
- To characterize the molecular responses to treatment with topical PF-07038124 0.02% ointment applied once daily for 8 weeks in moderate-to-severe SD and moderate-to-severe PPR patients.
- To correlate the molecular and clinical responses to treatment with topical PF-07038124 0.02% ointment applied once daily for 8 weeks in order to identify biomarkers of treatment response in SD and PPR patients
- To evaluate the safety and tolerability of topical PF-07038124 0.02% ointment applied once daily for 8 weeks in moderate-to-severe SD and moderate-to-severe PPR patients

ENDPOINTS:

Primary Endpoint

SD
- IGA success: clear (0) or almost clear (1) and a reduction from baseline of ≥2 points score of 0 or 1 at 8 weeks

PPR
- Percent change from baseline in inflammation (papule/pustule) lesion count at 8 weeks

Secondary Endpoints

SD
- Change from baseline in overall SD score (composed of erythema, scaling, and pruritus components) at 8 weeks
- Change from baseline in each component of SD score (erythema, scaling, and pruritus) at 8 weeks

PPR
- IGA success: clear (0) or almost clear (1) and a reduction from baseline of ≥2 points score of 0 or 1 at 8 weeks
- Change from baseline in clinical erythema assessment at 8 weeks
- Change from baseline in patient severity assessment of erythema at 8 weeks
- Change from baseline and from 8 weeks in inflammatory (papule/pustule) lesion count at 12 weeks

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Both SD and PPR

- Change and percent change from baseline in IGA score at 4 and 8 weeks
- Change from baseline and from 8 weeks in IGA at 12 weeks (i.e., 4 weeks after treatment cessation)
- Change from baseline in PP-NRS at 8 weeks
- Frequency, duration, and severity of AEs

Mechanistic (Exploratory) Endpoints

- Determine the molecular cutaneous phenotype of SD and PPR at baseline, using transcriptomic and proteomic approaches from skin samples acquired by tape-strips in lesional and non-lesional skin
- Identify molecular markers that correlate with disease activity in SD and PPR at baseline
- Characterize the change in molecular responses with treatment for 8 weeks
- Identify molecular markers that correlate with treatment response at 8 weeks

STUDY DESIGN OVERVIEW:

This study is a double-blind, vehicle-controlled clinical trial. The study will take place at Icahn School of Medicine at Mount Sinai.

The study will include 33-39 adult subjects with moderate-to-severe-SD as well as 33-39 adult subjects with moderate-to-severe PPR. The SD subjects will have baseline Investigator Global Assessment (IGA) score of at least 3 with facial involvement. The PPR subjects will have baseline Investigator Global Assessment (IGA) score of at least 3 and at least 12 inflammatory lesions. Subjects will be randomized 2:1 to receive study drug or vehicle.

Enrolled subjects will apply topical PF-07038124 0.02% ointment once daily for 8 weeks. They will return for visits at weeks 4, 8, and 12 following study treatment initiation for repeat clinical assessments, medication reviews, tape-strip, blood and urine sample collections, and monitoring for adverse events.

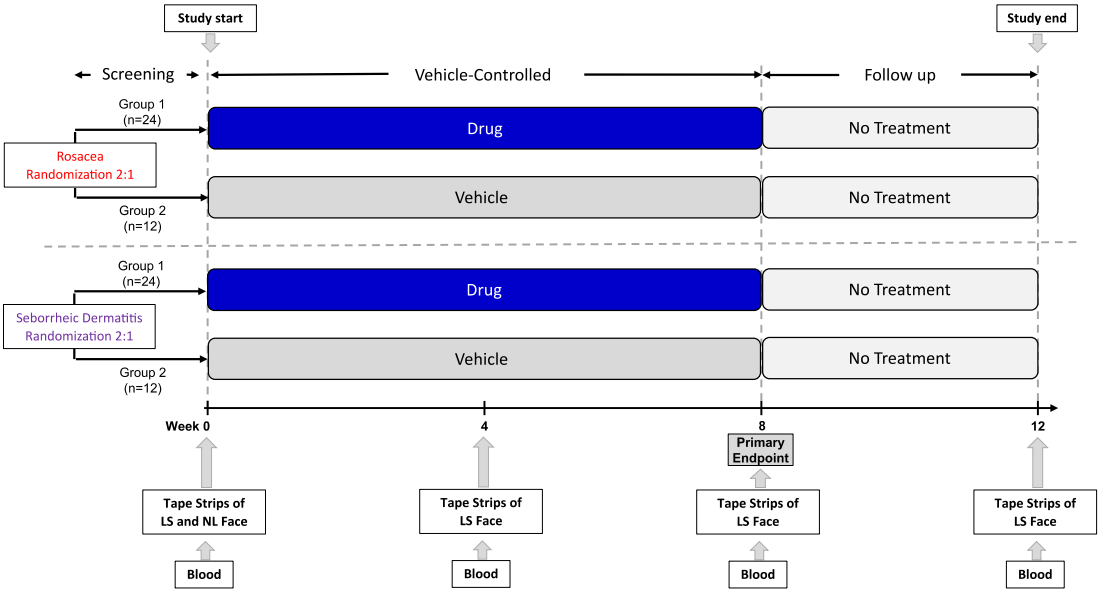
After providing consent, all subjects will be assessed for study eligibility, which includes a review of the subjects past and current medical conditions, familial medical history and detailed review of past and current medications. Subjects will also undergo a review of past topical treatments/therapies for SD or PPR, and clinical assessments (SD: clinical SD score, IGA, Peak Pruritus Numerical Rating Scale [PP-NRS]; PPR: inflammatory lesion count, IGA, PP-NRS).

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.

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At Baseline/Week 0, subjects will undergo clinical assessments (SD: clinical SD Severity Score, IGA, PP-NRS; PPR: inflammatory lesion count, IGA, PP-NRS), 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 4, Week 8, and Week 12. Skin tape-strip samples will be collected for mechanistic studies (described below) at baseline (lesional and non-lesional facial skin), Week 4 (lesional facial skin), Week 8 (lesional facial skin), and Week 12 (lesional facial skin). Additional blood samples will be collected and stored at baseline and at Week 8 (or early termination, whichever is first) for potential future mechanistic analyses.



MECHANISTIC ANALYSES:

We will characterize the molecular immune profiles of patients with SD and PPR at week 0 and week 8.

We plan to obtain lesional and non-lesional tape strip samples from facial skin of SD and PPR patients at week 0 and lesional facial skin samples at Week 8 (Primary Endpoint). Additionally, lesional facial skin samples will be collected at Week 4 and Week 12 and stored for potential future analysis. Blood samples at baseline, Week 4, and at Week 8 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 platform for ~500 analytes.

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PATIENT POPULATION:

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

Inclusion Criteria:

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) Diagnosis of SD and baseline IGA ≥ 3 with facial involvement
OR
Diagnosis of PPR, baseline IGA ≥ 3, and baseline inflammatory lesion count ≥ 12

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

6) 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).

7) 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.

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

Exclusion Criteria:

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

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

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

3) 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, thromboembolic events) that will affect the health of the subject during the study, or interfere with the interpretation of study results.

4) Subject has previously received treatment with oral or topical PDE4 inhibitors.

5) Current other topical treatments (e.g., topical corticosteroids, topical calcineurin inhibitors, topical JAK inhibitors, topical metronidazole, topical minocycline, topical ivermectin, topical azelaic acid, topical brimonidine, topical oxymetazalone, topical antihistamines, topical antibacterials) within 2 weeks of baseline.

6) Use of systemic non-biologic immunosuppressive medications, including, but not limited to, cyclosporine, systemic or intralesional corticosteroids, mycophenolate mofetil, azathioprine, methotrexate, tacrolimus, oral JAK inhibitors within 4 weeks of study initiation.

7) Use of systemic biologic immunosuppressive medications, including, but not limited to inhibitors of IL-17, IL-12/23, or IL-23, TNF inhibitors, dupilumab, and abatacept within 12 weeks of baseline.

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

9) Current participation in any other study with a biologic investigational medication within 6 months of baseline, or non-biologic investigational medication within 12 weeks of baseline.

10) Subject who is pregnant or breast feeding.

11) SD or PPR Baseline IGA < 3; PPR inflammatory lesion count <12; SD with no facial involvement.

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12) Active hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or positive HIV serology at the time of screening for subjects determined by the investigators to be at high-risk for this disease.

POTENTIAL RISKS OF PF-07038124 0.02% OINTMENT:

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention PF-07038124		
Skin Sensitization - non-clinical findings	The potential for skin sensitization was identified as a risk in nonclinical species at dermal concentrations 50x above the planned dose concentration of 0.01%, with a no observed effect level of 0.06% ointment.	Participants will be assessed for safety at regular intervals throughout the study, including assessment of the administration site. Participants with any history of angioedema or anaphylaxis to topical products or known sensitivity to any of the components of the investigational products will be excluded from the study. Study treatment may be temporarily discontinued if severe or very severe application site reaction occur.
PDE4-related nervous system and gastrointestinal effect (a class effect of AEs observed with PDE4 inhibitors) – non-clinical findings	Clinical signs indicative of nervous system effects (eg, ataxia, decreased activity, hunched posture, twitching, and/or tremors) and gastrointestinal effects (emesis, salivation, and/or soft/liquid feces) were observed in rats, dogs, and/or minipigs, at non-tolerated doses.	IP application will be up to 10% BSA reducing the risk of systemic exposure. Systemic exposure will be assessed in the study. Participants will be assessed for safety at regular intervals throughout the study.
Worsening of disease (SD or PPR)	1. Participants in vehicle (or in lower dose arm) may experience a worsening of disease. 2. Participants may experience a worsening of disease during washout and/or follow-up periods.	SD and PPR are not life-threatening diseases. Participants may discontinue treatment or withdraw from the study at any time for any reason. Participants meeting withdrawal/discontinuation criteria may be able to use alternative

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		treatments after withdrawal from the study. Participants will be assessed for safety at regular intervals throughout the study.

PRIOR TREATMENT:

All relevant treatment received by the subject within 30 days before screening will be recorded. All prior treatment history with PDE4 inhibitors 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 PDE4 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.

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, PPR, and other inflammatory skin diseases
- Record all concomitant medications as well as all those received within 30 days prior to screening
- Record all prior previous and current therapies for SD or PPR
- Limited physical examination and vital signs (BP, P)
- Collect blood samples for CBC with differential, Comprehensive metabolic panel (CMP), and HIV, HBV, and HCV screening.
- Urine pregnancy test for all female subjects of child-bearing potential (and verify contraceptive use)
- Clinical assessments (SD: IGA, SD Severity Score, PP-NRS; PPR: IGA, inflammatory lesion count, PP-NRS, CEA, PSA)

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***** 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 30 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 an exclusionary medication, then Baseline/Visit 2 will occur after the appropriate washout period.

Visit 2 – Baseline (Week 0)

- Confirm all inclusion and exclusion criteria have been met
- Record concomitant medications and adverse events
- DLQI questionnaire
- Limited physical examination and vital signs (BP, P)
- 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)
- Clinical assessments (SD: IGA, SD Severity Score, PP-NRS; PPR: IGA, inflammatory lesion count, PP-NRS, CEA, PSA)
- Urine pregnancy test for all female subjects of child-bearing potential (and verify contraceptive use)
- C-reactive protein (CRP)
- Collect blood sample for possible future mechanistic analyses
- 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 4

- Record concomitant medications and adverse events
- DLQI questionnaire
- Limited physical examination and vital signs (BP, P)
- Clinical assessments (SD: IGA, SD Severity Score, PP-NRS; PPR: IGA, inflammatory lesion count, PP-NRS, CEA, PSA)
- Urine pregnancy test for all female subjects of child-bearing potential (and verify contraceptive use)
- 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 8 missed doses from Baseline considered non-compliance.

Visit 4 – Week 8

- Record concomitant medications and adverse events
- DLQI questionnaire
- Limited physical examination and vital signs (BP, P)

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- 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)
- Clinical assessments (SD: IGA, SD Severity Score, PP-NRS; PPR: IGA, inflammatory lesion count, PP-NRS, CEA, PSA)
- Urine pregnancy test for all female subjects of child-bearing potential (and verify contraceptive use)
- 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 4.
- Assess study drug dosing compliance and retrieve all remaining study drug from subject. Subjects will report each study drug application, with 8 missed doses since Week 4 considered non-compliance.

Visit 5 – Week 12

- Record concomitant medications and adverse events
- DLQI questionnaire
- Limited physical examination and vital signs (BP, P)
- 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)
- Clinical assessments (SD: IGA, SD Severity Score, PP-NRS; PPR: IGA, inflammatory lesion count, PP-NRS, CEA, PSA)
- Urine pregnancy test for all female subjects of child-bearing potential (and verify contraceptive use)
- 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 4, and Week 8.

Early Termination Visit (if applicable)

- Record concomitant medications and adverse events
- DLQI questionnaire
- Limited physical examination and vital signs (BP, P)
- 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

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- Clinical assessments (SD: IGA, SD Severity Score, PP-NRS; PPR: IGA, inflammatory lesion count, PP-NRS, CEA, PSA)
- 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 4 (if applicable)
- Assess study drug dosing compliance and retrieve all remaining study drug from subject

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; 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 8 missed applications during the 4 week period between study Visits, study termination by investigators, and either a confirmed CTCAE grade 2 or higher adverse event on the treatment area or a confirmed grade 3 or higher adverse event not on the treatment area, 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; 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 <u>permanently</u> discontinued from study treatment in the event of:

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- 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:
  Chemistry
  (AST >3.0x ULN or ALT >3.0x ULN) and Total bilirubin >2x 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 Sponsor will be notified of adverse events.

The Principal Investigator (PI) must report all Serious Adverse Events (SAEs) to the Sponsor 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 PF-07038124, 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.

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TRIAL STOPPING CRITERIA:

Due to the favorable risk profile of this trial drug to date in atopic dermatitis, plaque psoriasis and healthy volunteer studies, and the small sample size (n=30 per disease indication) of this early sign of efficacy study, the need to stop this trial is deemed unlikely. If, however, more than 6 patients in a specific treatment group experience a treatment related AE with greater or equal to grade 2 on the face, or non-facial treatment related AE of grade 3, the study will be stopped for safety review.

The study may be stopped for other reasons such as: regulatory authority decision, change in opinion of the IRB, or change in benefit-risk assessment.

Additionally, during the study, safety will be continually assessed at a participant and study level to assess for clinically significant treatment emergent events.

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 PF-07038124 0.02% ointment or vehicle control which they will apply to affected skin on the face as well as other affected areas (up to 10% body surface area in total) only once daily. A thin layer of study intervention ointment will be applied at a target application rate of approximately 3 mg/cm^2 by using a fingertip unit method.

All study medication will be stored in a secure cool area between 2-8˚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 Determination for Seborrheic Dermatitis
A sufficient number of participants will be screened to achieve approximately 30 participants randomly assigned to study intervention. The sample size calculation is based on the primary efficacy estimate: IGA success at Week 8. Assuming 40% IGA

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success rate for the vehicle arm, a sample size of 20:10 (active: vehicle) will have 68% power to detect a treatment difference of 35% under a 1-sided Type 1 error 0.1 by the unconditional exact test. Assuming 20% drop out rate, approximately 36 total participants may be enrolled. Additional participants with a total up of up to 39 participants may be enrolled when possible and interim analysis result is promising.

Sample Size Determination for Papulopustular Rosacea

A sufficient number of participants will be screened to achieve approximately 30 participants randomly assigned to study intervention. The sample size calculation is based on the primary efficacy estimate: % change in ILC at Week 8. Assuming a normal distribution for the % change in ILC with a standard deviation of 36%, a sample size of 20:10 (active: vehicle) will have 70% power to detect a treatment difference of 25% under a 1-sided Type 1 error 0.1 by the two-sample Z-test. Assuming 10% drop out rate, approximately 33 total participants may be enrolled. Additional participants with a total up to 39 participants may be enrolled when possible and interim analysis result is promising.

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 disease, concurrent diagnoses from medical history and indications for concomitant medication, concomitant medication, and previous treatments.

Analysis of Primary Endpoints

For IGA success at week 8 for SD, Blyth-Still-Casella method will be used for estimates and confidence interval for each treatment arm. The risk differences and the corresponding 2 sided unconditional exact 80% confidence intervals will be computed using Chan and Zhang (1999)[1] method. All missing IGA success, except missing due to COVID 19 pandemic, will be set to a failure. As a sensitivity analysis, GLMM (generalized linear mixed model) may be used to model IGA success including treatment, visit, and treatment by visit interaction as fixed effects, a random intercept for subjects, and baseline IGA as a covariate when there are enough subjects in each category (moderate and severe).

A landmark analysis of percent change in inflammatory lesion count for PPR at week 8 will be performed by ANCOVA with baseline as a covariate. Missing data, except missing due to COVID-19 pandemic, will be imputed using a control-based imputation method. PROC MI will first be called to impute missing vehicle observations under the assumption data are missing at random (MAR) and impute missing active treatment observations assuming they are similar to corresponding vehicle arm. The imputation will utilize ANCOVA model including baseline as a covariate fitted using only vehicle arm data. The analysis will combine the results from the multiple imputations using Rubin's rule as implemented in SAS PROC MIANALYZE. MMRM model will be used on change in inflammatory lesion count for PPR at all time points as sensitivity analyses. The fixed effects of treatment, visit, and treatment by visit interaction will be included. Baseline value will be included as a covariate. Unstructured covariance will be used when possible.

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Analysis of Secondary Endpoints
Change from baseline at week 8 in overall SD score, PPR clinical erythema assessment score, and PPR patient severity assessment of erythema score will be analyzed by ANCOVA model in the same way as change in inflammatory lesion count. IGA success rate at week 8 for PPR will be analyzed the same way as IGA success for SD. Other endpoints will be summarized descriptively by treatment and time.

Analysis of Mechanistic (Exploratory) Endpoints
The baseline immune and molecular cutaneous profiles of SD and PPR (lesional vs non-lesional skin) and the change in the immune and molecular cutaneous profile of SD and PPR 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.

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, for ~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.

Interim analysis
An interim analysis may be performed to assess efficacy and safety when approximately 80% of the planned participants, i.e., approximately 24 participants in SD have completed or had the chance to complete Week 8 visit. Similarly, an interim analysis may be performed to assess efficacy and safety when approximately 80% of the planned participants, i.e., approximately 24 participants in PPR have completed or had the chance to compete Week 8 visit. Interim analysis results may be used for decisions regarding sample size increase. Additional interim analysis may be performed.

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 OneDrive, which has the necessary safeguards for protection of human subjects research.

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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 OneDrive 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 OneDrive 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 descriptive statistics at each visit for other safety assessments. 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 for each disease population. 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.

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Table 1. Schedule of Events

Visit Week	(Up to -28 Days before Baseline)	0	4	8	12	X
Visit #	**1**	**2**	**3**	**4**	**5**	**Early Termination**
Visit Type	**Screening**	**Baseline**	**Tx**	**Tx**	**F-up**	
Informed Consent	X					
Inclusion / Exclusion Criteria	X	X				
Demographics and Medical Hx[1]	X					
Limited physical examination and vital signs (BP, P)	X	X	X	X	X	X
Urine Pregnancy Test	X	X	X	X	X	X
HIV[3], HBV[3], HCV[3]	X					
CBC w/differential; CMP; Urinalysis	X			X		X
Blood Sample Stored for Future Analysis		X		X		X
CRP		X		X		
Clinical Assessments (SD: IGA, SD Severity Score, PP-NRS PPR: IGA, inflammatory lesion count, PP-NRS, CEA, PSA)	X	X	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				
Concomitant Medications	X[2]	X	X	X	X	X
Adverse Events	X	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] HIV testing, either in blood or POCT, HBS-ag and HCV-ab

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REFERENCES:

1. Borda LJ, Wikramanayake TC. Seborrheic Dermatitis and Dandruff: A Comprehensive Review. J Clin Investig Dermatol. 2015;3(2).
2. Manuel F, Ranganathan S. A new postulate on two stages of dandruff: a clinical perspective. International journal of trichology. 2011;3(1):3-6.
3. Naldi L, Rebora A. Clinical practice. Seborrheic dermatitis. The New England journal of medicine. 2009;360(4):387-96.
4. Adalsteinsson JA, Kaushik S, Muzumdar S, Guttman-Yassky E, Ungar J. An update on the microbiology, immunology and genetics of seborrheic dermatitis. Experimental dermatology. 2020;29(5):481-9.
5. Okokon EO, Verbeek JH, Ruotsalainen JH, Ojo OA, Bakhoya VN. Topical antifungals for seborrhoeic dermatitis. The Cochrane database of systematic reviews. 2015(5):CD008138.
6. Kastarinen H, Okokon EO, Verbeek JH. Topical anti-inflammatory agents for seborrheic dermatitis of the face or scalp: summary of a Cochrane Review. JAMA dermatology. 2015;151(2):221-2.
7. Piquero-Casals J, Hexsel D, Mir-Bonafe JF, Rozas-Munoz E. Topical Non-Pharmacological Treatment for Facial Seborrheic Dermatitis. Dermatol Ther (Heidelb). 2019;9(3):469-77.
8. Piquero-Casals J, La Rotta-Higuera E, Francisco Mir-Bonafe J, Rozas-Munoz E, Granger C. Non-Steroidal Topical Therapy for Facial Seborrheic Dermatitis. Journal of drugs in dermatology : JDD. 2020;19(6):658-60.
9. Pena SM, Oak ASW, Smith AM, Mayo TT, Elewski BE. Topical crisaborole is an efficacious steroid-sparing agent for treating mild-to-moderate seborrhoeic dermatitis. Journal of the European Academy of Dermatology and Venereology : JEADV. 2020;34(12):e809-e12.
10. Schwartz JR, Messenger AG, Tosti A, Todd G, Hordinsky M, Hay RJ, et al. A comprehensive pathophysiology of dandruff and seborrheic dermatitis - towards a more precise definition of scalp health. Acta dermato-venereologica. 2013;93(2):131-7.
11. Wikramanayake TC, Hirt P, Almastadi M, Mitchell H, Tomic-Canic M, Romero L, et al. Increased IL-17-expressing gammadelta T cells in seborrhoeic dermatitis-like lesions of the Mpzl3 knockout mice. Experimental dermatology. 2018;27(12):1408-11.
12. Wikramanayake TC, Borda LJ, Miteva M, Paus R. Seborrheic dermatitis-Looking beyond Malassezia. Experimental dermatology. 2019;28(9):991-1001.
13. Wollina U. Is rosacea a systemic disease? Clinics in dermatology. 2019;37(6):629-35.
14. Gallo RL, Granstein RD, Kang S, Mannis M, Steinhoff M, Tan J, et al. Standard classification and pathophysiology of rosacea: The 2017 update by the National Rosacea Society Expert Committee. Journal of the American Academy of Dermatology. 2018;78(1):148-55.
15. Coda AB, Hata T, Miller J, Audish D, Kotol P, Two A, et al. Cathelicidin, kallikrein 5, and serine protease activity is inhibited during treatment of rosacea with azelaic acid 15% gel. Journal of the American Academy of Dermatology. 2013;69(4):570-7.
16. Zhang H, Zhang M, Wang Y, Zheng Q, Tang K, Liu R, et al. Murine models of rosacea: a review. Journal of cosmetic dermatology. 2021.

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17. Steinhoff M, Schauber J, Leyden JJ. New insights into rosacea pathophysiology: a review of recent findings. Journal of the American Academy of Dermatology. 2013;69(6 Suppl 1):S15-26.
18. Zhang H, Tang K, Wang Y, Fang R, Sun Q. Rosacea Treatment: Review and Update. Dermatol Ther (Heidelb). 2021;11(1):13-24.
19. Schaller M, Almeida LM, Bewley A, Cribier B, Dlova NC, Kautz G, et al. Rosacea treatment update: recommendations from the global ROSacea COnsensus (ROSCO) panel. The British journal of dermatology. 2017;176(2):465-71.
20. Schaller M, Almeida LMC, Bewley A, Cribier B, Del Rosso J, Dlova NC, et al. Recommendations for rosacea diagnosis, classification and management: update from the global ROSacea COnsensus 2019 panel. The British journal of dermatology. 2020;182(5):1269-76.
21. van Zuuren EJ, Fedorowicz Z, Tan J, van der Linden MMD, Arents BWM, Carter B, et al. Interventions for rosacea based on the phenotype approach: an updated systematic review including GRADE assessments. The British journal of dermatology. 2019;181(1):65-79.
22. Deng Z, Chen M, Liu Y, Xu S, Ouyang Y, Shi W, et al. A positive feedback loop between mTORC1 and cathelicidin promotes skin inflammation in rosacea. EMBO Mol Med. 2021;13(5):e13560.
23. Two AM, Wu W, Gallo RL, Hata TR. Rosacea: part I. Introduction, categorization, histology, pathogenesis, and risk factors. J Am Acad Dermatol. 2015;72(5):749-58; quiz 59-60.
24. Egeberg A, Hansen PR, Gislason GH, Thyssen JP. Patients with rosacea have increased risk of dementia. Ann Neurol. 2016;79(6):921-8.
25. van Zuuren EJ, Arents BWM, van der Linden MMD, Vermeulen S, Fedorowicz Z, Tan J. Rosacea: New Concepts in Classification and Treatment. American journal of clinical dermatology. 2021;22(4):457-65.
26. Woo YR, Lim JH, Cho DH, Park HJ. Rosacea: Molecular Mechanisms and Management of a Chronic Cutaneous Inflammatory Condition. International journal of molecular sciences. 2016;17(9).
27. M Z, ZD D, J D, L K, A M, L SG, et al. Efficacy and safety of roflumilast foam 0.3% in patients with seborrheic dermatitis in a randomized, double-blind, vehicle-controlled phase 2 study. JAAD. 2021;85(3).
28. https://www.arcutis.com/arcutis-announces-positive-topline-results-from-stratum-pivotal-phase-3-trial-of-roflumilast-foam-0-3-in-seborrheic-dermatitis/ [
29. Le Cleach L, Chassany O, Levy A, Wolkenstein P, Chosidow O. Poor reporting of quality of life outcomes in dermatology randomized controlled clinical trials. Dermatology. 2008;216(1):46-55.
30. Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. J Invest Dermatol. 2007;127(12):2726-39.
31. Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology. 2015;230(1):27-33.
32. https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021946.pdf

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33. DelRosso JQ, Draelos ZD, Effron C, Kircik LH. Oral Sarecycline for Treatment of Papulopustular Rosacea: results of a Pilot Study of Effectiveness and Safety. J Drug Dermatol. 2021;20(4). doi:10.36849/JDD.5923

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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 (SD)[32]

Clinical severity	Scored	Features
Clear	0	Complete clear, no signs of SD
Almost Clear	1	Only slight pink color or trace amounts of scaling
Mild	2	Pink to red color, or slight
Moderate	3	Distinct redness or clearly visible scaling
Severe	4	Severe score in erythema or scaling

Investigator Global Assessment (PPR)[33]

Clinical severity	Scored	Features
Clear	0	No inflammatory lesions present, no erythema
Almost Clear	1	Very few, small papules/pustules, very mild erythema present
Mild	2	Few small or large papules/pustules, moderate erythema
Moderate	3	Several small or large papules/pustules, moderate erythema
Severe	4	Numerous small and/or large papules/pustules, severe erythema

Peak Pruritus Numerical Rating Scale

“On a scale of 0 to 10, with 0 being ’no itch‘ and 10 being ’worst itch imaginable‘, how would you rate your itch at the worst moment during the previous 24 hours?”

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Clinical Erythema Assessment (CEA)

Clinical severity	Scored	Features
Clear	0	Clear skin with no signs of erythema
Almost Clear	1	Almost clear; slight redness
Mild	2	Mild erythema; definite redness
Moderate	3	Moderate erythema; marked redness
Severe	4	Severe erythema; fiery redness

Clinical Patient Severity Assessment (PSA)

Clinical severity	Scored	Features
Clear	0	Clear of unwanted redness
Almost Clear	1	Nearly clear of unwanted redness
Mild	2	Somewhat more redness than I prefer
Moderate	3	More redness than I prefer
Severe	4	Completely unacceptable redness

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Appendix 2. 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 (29, 30).

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	☐ ☐ ☐	

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		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 ☐

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

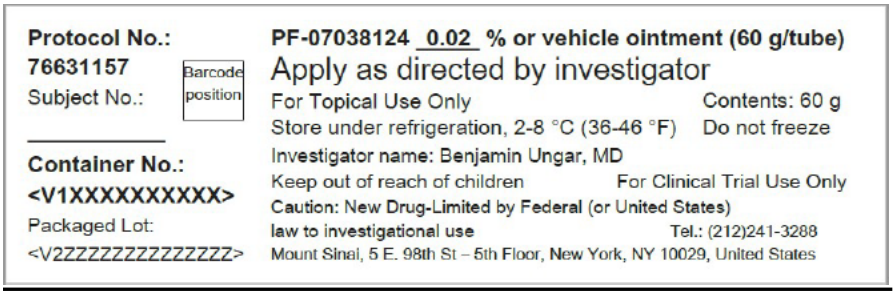
The DLQI is calculated by summing the score of each question. The maximum score is 30 and minimum score is 0. Higher score represents a quality of life that is more impaired.

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 (31). 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.

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Appendix 3. Study Drug Label



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Appendix 4. Summary of Protocol Amendments

Amendment #1 – April 4, 2023 – Revisions made in response to FDA's recommendations in the Study May Proceed letter dated 03/01/2023

All pages – Footer updated to April 4, 2023

Page 1 – Amendment # 1 April 4, 2023 added

Page 2 – Table of Contents

- Pagination corrected
- Trial Stopping Criteria section added
- Appendix 3 Study Drug label added
- Appendix 4 Summary of Protocol Amendments added

Page 6 – Study Design overview

- The required # of inflammatory lesions in the PPR group at baseline was increased from a minimum of 10 to a minimum of 12.

Page 8 – Inclusion Criteria # 4

- The required # of inflammatory lesions in the PPR group at baseline was increased from a minimum of 10 to a minimum of 12.

Page 9 – Exclusion Criteria

- # 3 HIV, HBV and HCV were removed and moved to exclusion criterion #12
- # 5 topical antihistamines, topical antibacterials were added to restricted topical agents
- # 6 "non-biologic" was added to exclusionary systemic immunosuppressants
- #7 Criteria was added: "Use of systemic biologic immunosuppressive medications, including, but not limited to inhibitors of IL-17, IL-12/23, or IL-23, TNF inhibitors, dupilumab, and abatacept within 12 weeks of baseline"
- #7-11 Numbering was increased to accommodate the addition of Criteria # 7 above
- #8 "Current participation in any other study with an investigational medication" was updated to "Current participation in any other study with a biologic investigational medication within 6 months of baseline, or non-biologic investigational medication within 12 weeks of baseline."

Page 10 – Exclusion Criteria # 12

- Added: "Active hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or positive HIV serology at the time of screening for subjects determined by the investigators to be at high-risk for this disease."

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Page 11-14 – Procedures

- At screening, HIV HBV and HCV screening will be performed
- At all visits, limited physical examination and vitals (BP and pulse) were added to each visit.

Page 14 Discontinuation of Treatment and Withdrawal of Subjects

- Section was updated: 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 8 missed applications during the 4 week period between study Visits, study termination by investigators, *"and either a confirmed CTCAE grade 2 or higher adverse event on the treatment area or"* a confirmed grade 3 or higher adverse event "*not on the treatment area*," which is suspected to be related to study drug administration.

Page 16 - TRIAL STOPPING CRITERIA section added:

"Due to the favorable risk profile of this trial drug to date in atopic dermatitis, plaque psoriasis and healthy volunteer studies, and the small sample size (n=30 per disease indication) of this early sign of efficacy study, the need to stop this trial is deemed unlikely. If, however, more than 6 patients in a specific treatment group experience a treatment related AE with greater or equal to grade 2 on the face, or non-facial treatment related AE of grade 3, the study will be stopped for safety review.

The study may be stopped for other reasons such as: regulatory authority decision, change in opinion of the IRB, or change in benefit-risk assessment.

Additionally, during the study, safety will be continually assessed at a participant and study level to assess for clinically significant treatment emergent events."

Page 20 - Table 1 Schedule of Events

- Limited physical examination and vital signs (BP, P) added to each visit.
- HIV, HBV and HCV added at Screening visit.
- Superscript 3 was revised to: 3. HIV testing, either in blood or POCT, HBS-ag and HCV-ab

Page 22-23 – References

- Two additional references (#32 and 33) were added related to the change in description of features in the IGA for both SD and PPR.

Page 23 – Appendix 1, Clinical Assessments

- Investigator Global Assessment (SD) and (PPR)
  Definitions for features were updated for each severity grading.

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Page 27 – Appendix 3. Study Drug Label added

Page 28 - Appendix 4. Summary of Protocol Amendments

Amendment #2 – April 12, 2023

All pages – Footer updated to April 12, 2023

Page 1 – Amendment # 2 April 12, 2023 added

Page 16 – Study Drug Supply
Revised storage conditions for study drug from 15-30^{0}C to 2-8˚C as the drug should be refrigerated.

Amendment #3 – May 30, 2023

All pages – Footer updated to May 30, 2023

Page 1 – Amendment # 3 May 30, 2023 added

Page 1 – Redefined Emma Guttman, MD PhD as Co-Investigator

Page 18 Data Transfer and Management – Storage of data platform changed from Mount Sinai Box to Mount Sinai OneDrive.

Page 19 Management of the Analysis - Storage of data platform changed from Mount Sinai Box to Mount Sinai OneDrive.

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