A Phase 2, Open Label Single Arm Study for Evaluating Safety & Efficacy of Apremilast in the Treatment of Cutaneous Disease in Patients with Recalcitrant Dermatomyositis.

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I. PRINCIPAL INVESTIGATOR AND RESEARCH SITE

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3. # of Participants Sites: 1**,** Tulane University
4: Participant Countries: United States

II. PRODUCT INFORMATION

1. Study Title: A phase 2, open label single arm study for evaluating safety & efficacy of apremilast in the treatment of cutaneous disease in patients with recalcitrant dermatomyositis.

2. Clinical Phase: Phase II clinical trial

3. Primary Celgene Product: Apremilast

4. Secondary Celgene Product: None

5. Tertiary Celgene Product: None

6. Non- Celgene Products: None

III. CONCEPT DESIGN AND RATIONAL

1. Therapeutic Area: Immunology

2. Specialty: Connective tissue disease

3. Disease State: Dermatomyositis

4. if Other Specify: None

5. Study Rationale: Dermatomyositis is an inflammatory disease that predominantly involves the skin with or without proximal muscle weakness. First line treatment for dermatomyositis is systemic steroids however due to long-term side effects, patients are usually treated with a steroid sparing agent. There is no known consensus on treatment guidelines for dermatomyositis and many anti-inflammatory medications have been successfully used. Tulane University is a referral center for recalcitrant dermatomyositis cases. We present the case of a 57 y.o female patient with multidrug recalcitrant dermatomyositis showing complete remission of her skin disease with apremilast and improvement of her muscle disease. This patient was diagnosed with dermatomyositis. Over a 6-year period, she was treated with adequate trials of multiple immunosuppressive agents, including hydroxychloroquine, mycophenolate mofetil, azathioprine, methotrexate, soriatane, Intravenous immunoglobulin (IVIG), tacrolimus, chlorambucil, infliximab and rituximab. For the last four years, we were unable to lower corticosteroids below 40 mg per day. Her disease continued to flare despite these therapies. Chronic steroid use resulted in insulin dependent diabetes mellitus as well as other steroids associated side effects. While on stable doses of mycophenolate mofetil, prednisone and

rituximab, the patient developed arthritis and was started on apremilast 30 mg twice a day. Two months into her treatment she noticed significant improvement of her skin disease and then nearly complete clearance of the skin. Her muscle weakness lagged behind and she noticed improvement after 9 months of being on apremilast with normalization of her aldolase and CK. The patient was able to wean off all immunosuppressive agents and prednisone. She was in remission for over 2 years and off all medications. She experienced a mild flare of skin disease recently and she resumed apremilast only and cleared immediately and continues on apremilast as a monotherapy. Patient experienced mild nausea and diarrhea with apremilast that improved four weeks into the treatment. She was able to discontinue insulin, lose weight and she has continued to be clear of both skin and muscle symptoms for over 1.5 years.

This case will be presented as a poster presentation at the 2018 Annual Meeting of the American Academy of Dermatology "Poster #: 6672 - Apremilast: a Potential Treatment for Dermatomyositis."

Following our successful outcome, we initiated apremilast in 3 other patients with recalcitrant dermatomyositis. Two of them had recalcitrant cutaneous disease and responded to add on therapy of apremilast in 2 months with significant improvement of their skin disease. The third patient had refractory dermatomyositis to several steroid-sparing agents and with severe muscle disease was started on apremilast for arthritis. She experienced significant improvement of her muscle weakness together with decrease in her muscle enzyme creatine kinase.

These very exciting findings triggered the idea of studying apremilast as an adjunct treatment for recalcitrant cutaneous disease in dermatomyositis patients. This is a novel idea; apremilast was never studied for dermatomyositis. Apremilast may have more advantages in dermatomyositis compared to other immunosuppressive treatments. Dermatomyositis patients may have lung involvement, and apremilast is an agent that doesn't have lung side effects in contrast to methotrexate for example which is one of the main steroid sparing agents used for dermatomyositis.

The pathogenesis of dermatomyositis is multifactorial with environmental, genetic and immune factors contribution.[1] T helper-1 (Th1) and T helper-2 (Th2) immune pathways play a fundamental role in dermatomyositis.[2] There is increase in proinflammatory cytokines including tumor necrosis factor alpha (TNF-α), interleukin (IL) 1, IL 6, and interferon (INF) α,γ shifting the immune balance to a Th1 response.[1] Th1 immune response was also involved in the pathogenesis of interstitial pneumonia in the setting of dermatomyositis.[3] IL4 released by lymphocytes infiltrating skin and muscles in dermatomyositis patients contributes to increase in Th2 response in conjunction with Th1 response. [2] Apremilast is a PD4-E inhibitor currently used for psoriasis and psoriatic arthritis.[4] However, its usage on patients with dermatomyositis has not been investigated.

By inhibiting PDE-4 apremilast increases the level of cyclic adenosine monophosphate (c-AMP), leading to decreased expression of proinflammatory cytokines including TNF-α and INF-γ thus inhibiting Th1 response.[5] Apremilast can also block Th2 response by interfering with the level of IL6 secreted by type2 macrophages.[4] While the mechanism of action of apremilast in dermatomyositis is unknown, we suggest that apremilast can be a potential treatment option for dermatomyositis through interfering with Th1 and Th2 response.

Apremilast is a well-tolerated oral medicine with transient gastrointestinal side effects.[4] Apremilast offers an additional treatment option for those patients with recalcitrant dermatomyositis, unresponsive to more conventional therapy.

6. Treatment and Dosing: We will enroll patients seen at our facilities with a known diagnosis of dermatomyositis who are still experiencing cutaneous disease after a trial of steroid-sparing agent and/or systemic steroids.

We will add apremilast to their treatment regimen according to the approved dosage for psoriasis and psoriatic arthritis: 10 mg orally one time on day 1, 10 mg orally twice daily on day 2, 10 mg orally in

AM and 20 mg orally in PM on day 3, 20 mg orally twice daily on day 4, 20 mg orally in AM and 30 mg orally in PM on day 5, then 30 mg orally twice daily thereafter.

7. Brief Study Synopsis: With limited treatment options available for dermatomyositis, we hypothesize that apremilast, a phosphodiesterase-4 (PDE-4) inhibitor, is a safe and efficacious add-on treatment in patients with recalcitrant cutaneous dermatomyositis.
The study will investigate the efficacy, safety and toxicity of apremilast given at 30 mg twice daily to patients with recalcitrant cutaneous dermatomyositis. Clinical response will be assessed at 1 and 3 months. Patients will also be evaluated for durability of their response for up to 6 months.
Treatment will be monitored with frequent clinical visits (0, 1, 3 and 6 months) and blood tests (CBC, CMP, CK, aldolase). Treatment will be discontinued at disease progression or unacceptable adverse events. Disease progression is defined as a 4 points increase in CDASI score, worsening of muscle disease by MMT-8 score and 5 points increase in DLQI.
5 mm skin biopsies from lesional skin will be performed before treatment with apremilast and after 3 months of treatment for gene expression profiling and confirmatory immunohistochemical stains.

8. Inclusion Criteria:

- Must understand the risks and the benefits/purpose of the study and provide signed and dated informed consent.
- Must be 18 years at time of signing the informed consent form.
- Willing to participate in all required evaluations and procedures in the study including the ability to swallow pills without difficulty.
- Patients must have a diagnosis of DM based upon the characteristic cutaneous findings proposed by Sontheimer[6] and/or a skin biopsy consistent with DM.
- Patients must be candidate for systemic therapy for their DM skin disease defined by inadequate response to aggressive sun protection along with the use of potent topical corticosteroids and/or immunomodulators.
- Patients with a diagnosis of dermatomyositis on steroid-sparing agent and/or systemic steroids (maximum dose of prednisone 1mg/Kg) and still having cutaneous disease activity of at least 5 on the CDASI scale.
- If on immunosuppressive treatments and/or steroids, patients must be on stable doses for at least 4 weeks (28 days).
- Patients must undergo age appropriate cancer screening.
- Females of childbearing potential (FCBP) must have a negative pregnancy test at screening (day 0 of the study and every month throughout the study). While on investigational product and for at least 28 days after taking the last dose of investigational product.

- **9. Exclusion Criteria:**

- Increasing or changing dose of topical therapy within 14 days of study day 0 (including but not limited to topical corticosteroids, tacrolimus, pimecrolimus).
- Increasing or changing systemic steroids dosing within 28 days of study day 0.
- Increasing or changing dosing for concurrent therapy agents within 28 days or 5 half-lives of the biologic agent, whichever is longer, before study day 0: methotrexate, azathioprine, mycophenolate mofetil, hydroxychloroquine, dapsone, leflunomide, cyclosporine, biologic agents (anti-TNFs), IVIG, rituximab.

- History of any clinically significant (as determined by the investigators) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic, or other major uncontrolled disease.
- Any condition, including the presence of laboratory abnormalities, which places the patient at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
- Pregnant or breastfeeding.
- Untreated Latent Mycobacterium tuberculosis infection or active tuberculosis infection as indicated by a positive Purified Protein Derivative (PPD) skin test or T-spot.
- Any condition, including the presence of laboratory abnormalities that places the patient at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
- Patients with acute dermatomyositis onset and rapid progression of muscle disease or significant systemic involvement including pulmonary diseases associated with DM.
- Prior major surgery or major life-threatening medical illness within 2 weeks.
- Inflammatory bowel disease, malabsorption or any other gastrointestinal motility disorders that limit the absorption of the study drug.
- Active hepatitis B or C infection with detectible viral nucleic acid in the blood or known Human Immunodeficiency Virus (HIV) positivity.
- Prior history of suicide attempt at any time in the patient's lifetime prior to screening or randomization, or major psychiatric illness requiring hospitalization within the last 3 years.
- Active substance abuse or a history of substance abuse within 6 months prior to screening.
- Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer).
- Prior treatment with apremilast.
- Any severe systemic illness requiring IV antibiotics within the two weeks prior to initiation of the study drug.
- Malignancy or history of malignancy within the past four years, except for:
    - treated [ie, cured] basal cell or squamous cell in situ skin carcinomas;
    - treated [ie, cured] cervical intraepithelial neoplasia (CIN) or carcinoma in situ of cervix with no evidence of recurrence within the previous 4 years.

10. Sampling and correlative analysis

Although, the proposed mechanism of action of apremilast is though PDE-4 inhibition resulting in c-AMP upregulation, the exact biological process that leads to dermatological response in dermatomyositis remains ill-defined. We propose to perform gene expression profiling (GEP) using RNA sequencing on skin biopsies collected before and after treatment with apremilast. In addition, we plan to confirm our GEP findings at the protein level using immunohistochemical (IHC) stains.

A. Tissue sampling and preparation

a. Tissue collection

5 mm punch biopsy from dermatomyositis skin lesions will be performed at baseline and another 5 mm punch biopsy will be performed at the 3-month time point. Each biopsy will be vertically split in two pieces and snap frozen on dry ice then it will be stored at -80C for further analysis with RNA sequencing and IHC stains.

b. RNA extraction

At the end of all timeline collections, each skin biopsy will be mechanically broken down followed by mRNA extraction using the RNeasy extraction Kit from QIAGENzz. mRNA will then be stored at -80°C for subsequent RNA sequencing as detailed below.

B. Correlative Analysis

Determining the mechanism of action of apremilast in dermatomyositis.

a. Gene expression profiling

RNA extracted form skin biopsies collected before and after *in vivo* treatment with apremilast (as detailed above) will be subjected to RNA sequencing. Illumina strand-specific TruSeq libraries will be prepared from the polyA selected RNA and subjected to 1x100 base sequencing on an Illumina HiSeq2500 machine. The number of samples proposed here (10 samples before treatment and 10 samples after treatment) is expected to yield sufficient statistical power for this approach; smaller numbers have been used in similar approaches to investigate drugs' mechanism of action (usually three samples).[7-9]

RNA-seq analysis will be performed in conjunction with the Tulane Cancer Crusaders Next Generation Sequence Analysis Core (Tulane Cancer Center - https://tulane.edu/som/cancer/research/core-facilities/cancer-crusaders/). Gene and isoform expression will be determined using RSEM [10] and differential expression will be analyzed using EB-seq.[11] Genes that are identified as differentially expressed between the two groups with a False Discovery Rate (FDR) of < 0.05 will be subjected to analysis by *Ingenuity* (IPA, Redwood City, CA). This analysis will group the identified genes into specific pathways, cell types, or disease process. A similar approach will be conducted using *Gene Set Enrichment Analysis (GSEA).* These experiments and GEP analysis will be performed in conjunction with our collaborator's (Dr. Nakhle Saba) lab, given his extensive experience in this field.[12, 13]

b. Protein analysis

Information identified by Ingenuity or GSEA (signaling pathways, regulatory molecules, etc…) will be verified using IHC staining on select samples.

IV. OBJECTIVES AND ENDPOINTS

1.Primary Objective Description

To determine the overall response rate (ORR) of apremilast in cutaneous disease of patients with recalcitrant dermatomyositis at 3 months.
The ORR will be measured using the Cutaneous Dermatomyositis Activity and Severity Index (CDASI) at months 0, 1, and 3.
CDASI is a validated tool to measure skin disease activity in dermatomyositis.[14] ORR includes partial and complete responses. Complete response is defined by a CDASI score of zero. Partial response is defined by a decrease of CDASI score of at least 4 points. Calculation is performed as the CDASI score at 1, and 3 month(s) minus the score at baseline.
All investigators (PI and Sub-Is) will be trained on how to screen the patients per the CDASI score tool.
Photograph of skin rash will be taken at months 0,1 and 3 and compared to baseline.

2. Secondary Objective(s) Description

To determine the durability of responses for up to 6 months on apremilast for responders at 3 months. The durability of responses includes partial and complete response durability.
The durability of response will be measured using the CDASI at 6 months minus CDASI at 3 months. Complete response durability is defined as zero or minus difference between CDASI score at 6 months and CDASI score at 3 months. Partial response is defined as >4 points difference between CDASI score at 6 months and CDASI score at 3 months.

We will assess the response of all patients at 6 months to identify possible delayed response. Complete response is defined by a CDASI score of zero at 6 months. Partial response is defined by a decrease of CDASI score of at least 4 points at 6 months compared to baseline. Calculation is performed as the CDASI score at 6 month(s) minus the score at baseline.

Photograph of patient's rash will be taken at 6 months and compared to 3 months and baseline.

To determine the safety and toxicity of apremilast when administered at 30 mg twice daily in patients with dermatomyositis. The safety assessment will include the assessment of adverse events, serious adverse events, laboratory testing and physical examination.

An additional secondary endpoint will be to determine if patients who experience remission of their disease can be maintained on apremilast as monotherapy.

To determine the patient quality of life using the Dermatology Life Quality Index (DLQI)[15] at baseline, 1, 3 and 6 months.

Patient will be assessed 1 month after discontinuing apremilast (follow up visit) to assess change in response post discontinuation of apremilast. Patients will be examined and, CDASI, MMT-8 and DLQI will be performed. Photograph of patient's rash will be taken. CBC, CMP, CK, aldolase and urine pregnancy test will be performed.

3. Exploratory Objectives:
We will measure muscle enzymes (creatine kinase (CK) and aldolase) at 0, 1, 3, and 6 month(s) of apremilast in patients with muscle disease.
We will assess disease activity using the manual muscle testing-8 (MMT-8) in patients with muscle disease.[16]
Skin biopsies from lesional skin will be performed before treatment with apremilast and after 3 months of treatment for gene expression profiling and IHC stain. IHC will be performed on the protein product of the genes showing the largest fold change from the RNA-sequencing.
All investigators (PI and Sub-Is) will be trained on how to screen the patients per the MMT-8 score tool.

V. STUDY ENROLLMENT AND TIMELINES

1. # of Patients Expected to Enroll: 10

2. Date of planned FSI: 04/02/2018

3. Date of planned LSI: 11/01/2018

4. Date of planned LSO: 05/01/2019

5. Patient treatment duration (# months): 6 months

6. Is an interim Analysis Planned? Yes

7. Date on planned Interim Analysis: 03/01/2019

8. Date of planned final report: 06/03/2019

9. Are patients reported outcomes measured: Yes

VI. STATISTICAL PLAN:

Results of the study will be analyzed using descriptive statistics:

- Proportion of patients with complete ORR at 1,3 months
- Proportion of patients with partial ORR at 1,3 months
- Proportion of patients with complete durability response at 6 months for the 3 months responders
- Proportion of patients with partial durability response at 6 months for the 3 months responders
- Proportion of patients with complete response at 6 months
- Proportion of patients with partial response at 6 months
- Mean change from baseline in muscle enzymes (CK and aldolase in patients with muscle disease)
- MMT-8 change will be calculated as mean change from baseline at 1,3 and 6 months
- DLQI change will be calculated by identifying the proportion of patients with minimal clinically important difference of at least 5 points.

Missing data will be handled using the last observation carried forward approach (LOCF).

GEP will be analyzed using inferential statistics with a False Discovery Rate (FDR) of < 0.05.

VII. INFORMED CONSENT:

The protocol and the informed consent will be reviewed by the Institutional Review Board (IRB) prior to the start of the study. The proposed form must contain a full explanation of the possible risks, benefits and alternate treatment options. It should be written in a way that is easily understandable and comprehensible by the patient. If the patients does not understand English or is not fluent in the language than appropriate translation must be made available. It should also indicate that by signature, the patient or the legal guardian (where appropriate), permits access to medical records by the sponsor and by representatives of FDA. The primary investigator (PI) will be responsible for obtaining written informed consent from the patient prior to the study. A copy of the signed informed consent will be given to the patient and a copy will be submitted to the sponsor.

1. Risks of Apremilast

The PI will monitor patients for side effects of Apremilast throughout the study period.
The most commonly reported side effects of apremilast include: headache, upper respiratory tract infections, nausea, vomiting and diarrhea. Most of these side effects are usually mild to moderate and resolve with continued treatment.

Depression has been reported with the use of apremilast. The PI will screen patients for any sign or symptom of depression using PHQ2 questionnaire.

2. Pregnancy Risks

The risks to an unborn child (fetus) or nursing child from apremilast are not known at this time. Results of the animal and in vitro studies can be found in the IB.

Women of child bearing potential will be screened with urine pregnancy test at day zero of the study and every month through out the study.

If a women of child bearing age engage in activity that could result in pregnancy, they must use one of the approved options for birth control while taking the study drug and for at least 28 days after the last dose of study drug.

When a female patient of childbearing potential's contraceptive measures or ability to become pregnant changes at the time of study entry or at any time during the study, the Investigator will educate the subject regarding options and correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

Approved options for birth control are:

- Option 1: Any one of the following: hormonal contraception (for example, birth control pills, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation (tying your tubes); or a partner with a vasectomy

OR

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

In the event of any pregnancy, the PI will discontinue the study medication, and will follow on the patient through out her pregnancy.

VIII. ADVERSE EVENT

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a patient during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the Case Report Form (CRF) rather than the individual signs or symptoms of the diagnosis or syndrome.

All AEs will be recorded by the Investigator(s) from the time of signing the informed consent through the end of the designated follow-up period.

1. Abnormal laboratory values defined as adverse events

An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study.

- Requires treatment, modification/interruption of study drug dose, or any other therapeutic intervention.
- Is judged by the Investigator(s) to be of significant clinical importance.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

2. Serious adverse events

A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (i.e., in the opinion of the Investigator(s) the patient is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (a substantial disruption of the patient ’s ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

If an AE is considered serious, both the AE pages of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator(s) will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

3. Classification of severity

For both AEs and SAEs, the investigator(s) must assess the severity of the event. The AEs will be evaluated for severity according to the following scale:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

4. Classification of Relationship/Causality of adverse events (SAE/AE) to study drug

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	The temporal relationship of the adverse event to study drug administration makes **a causal relationship unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
Suspected:	The temporal relationship of the adverse event to study drug administration makes **a causal relationship possible,** and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

5. Immediate reporting of serious adverse events

Any AE that meets the criterion for a SAE requires the completion of an SAE Report Form in addition to being recorded on the AE pages of the CRF. The Investigator(s) is required to ensure that the data on these forms is accurate and consistent. This applies to all SAEs, regardless of relationship to study drug, that occur during the study, those made known to the Investigator(s) within 30 days after a patient's last dose of study drug, and those made known to the investigator(s) at anytime that are suspected of being related to study drug.

The SAE must be reported immediately (i.e., within 24 hours of the Investigators' knowledge of the event) to Celgene Safety by facsimile. A written report (prepared by the Investigator(s) using an SAE Report Form or a 3500A Medwatch form is to be faxed to Safety (see below for contact information).

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
86 Morris Ave.
Summit, NJ 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

The SAE report should provide a detailed description of the SAE. If a patient has died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form or Medwatch form and sent to Celgene.

The Investigator(s) is responsible for informing the Institutional Review Board/Ethics Committee (IRB/IEC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator(s) must keep copies of all SAE information, including correspondence with Celgene and the IRB/IEC, on file. All SAEs that have not resolved upon discontinuation of the patient's participation in the study must be followed until either the event resolves completely, stabilizes/resolves with sequelae, or returns to baseline (if a baseline value is available).

6. Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female or the female partner of a male patient occurring while the patient is on study drug, or within 30 days of the patient's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the patient instructed to return

any unused portion of the study drug to the investigator(s). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Safety immediately facsimile using the Pregnancy Report form provided by Celgene.

The female should be referred to an obstetrician-gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator(s) will follow the female patient until completion of the pregnancy, and must notify Celgene Safety of the outcome of the pregnancy as a follow-up on the follow up Pregnancy Reporting form.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator(s) should follow the procedures for reporting SAEs (i.e., report the event to Celgene Safety by facsimile within 24 hours of the Investigator's knowledge of the event).

In the case of a live "normal" birth, Celgene Safety should be advised by facsimile within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator(s) suspects is related to the in utero exposure to the study drug should also be reported to Celgene Safety by facsimile within 24 hours of the Investigators' knowledge of the event.

If the female is found not to be pregnant, any determination regarding the patient's continued participation in the study will be determined by the Investigator.

7. Overdose

Abuse, withdrawal, sensitivity, or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported as an AE. Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE.

If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form but should not be reported as an SAE itself.

In the event of an overdose, the patient should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for apremilast overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

Overdose for this protocol, on a per dose basis, is defined as ingestion of any more than the amount prescribed of apremilast (or matching placebo) tablets in any 24 hour period whether by accident or intentionally.

IX. PATIENT'S WITHDRAWAL

The patient may withdraw from the study or withdrawn due to the many reasons:

- Loss to follow-up

- Adverse Event
- Non-Compliance
- Minimal/no therapeutic effect.
- Withdrawal of the patient by the investigator.
- Other reasons

Efforts should be made to follow-up patients with adverse events to know the final outcome of the event.

The patient and/or investigator, both have the right to terminate the patient's participation in the study. The reason for termination/withdrawal will be documented.

X. DATA MANAGEMENT

All data must be entered into the clinical data management system before initiating treatment. Electronic case report form (CRF) will be used for the collection of all study data entry at the clinical trial site. The PI will enter the data. All requested information must be entered in the CRF in a timely manner and the CRF for each visit must be completed during the visit. The completed CRF must be reviewed, signed and dated by the PI as well as any missing data should be recorded. Files containing electronic data will be password protected and encrypted and will be closed when computers are left unattended. Contact lists, recruitment records, or other documents that contain Protected Personally Identifiable Information (PPII) will be stored securely in locked cabinets or rooms and access to key codes will be limited.

XI. PUBLICATION PLAN

1.Target Journal: JAAD

2. If Other Specify: JAMA

3. Date of Planned manuscript: September 2019

XII. SUPPORT REQUESTED FROM CELEGENE RESOURCES

1. Requesting Study Drug? Yes

2. Requesting Study funding? Yes

3. Support Requested from other companies? No

4. Non-Celegene Support Sources: None

XII. BUDGET

1.Currency Type: US Dollars.

3. **Total requested Amount from Celgene:** $ 40,000

Schedule of Events

Procedure	Screening phase	Baseline (Day 0)	Month 1	Month 3	Month 6	Follow up visits
Informed Consent	X					
Demography	X					
Medical History	X	X				
Inclusion/Exclusion Criteria	X	X				
Photograph		X	X	X	X	
Hematology	X		X	X	X	X
Serum Chemistry	X		X	X	X	X
Muscle enzymes (CK, aldolase)	X		X	X	X	X
T-spot	X					
Skin biopsy		X		X		
Safety Assessments						
Adverse Events		X	X	X	X	X
Vital Signs	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X
Weight	X	X	X	X	X	X
Urine Pregnancy test (every month)	X	X	X	X	X	X
Contraception Education	X	X	X	X	X	X
Efficacy Assessments						
CDASI	X	X	X	X	X	X
MMT-8		X	X	X	X	X
DLQI		X	X	X	X	X
PHQ-2	X	X	X	X	X	X
Dispense ID **(every month)**		X	X	X	X	

Timeframe between screening phase and day 0 of the study should not exceed 1 month.

I. REFERENCES

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