Apremilast for Erythema Multiforme (AEM)

ClinicalTrials.gov ID NCT05875714

Date of Approval: 04-Jan-2024

CLINICAL RESEARCH PROTOCOL

INVESTIGATIONAL PRODUCT(S):	Apremilast (Otezla), oral medication
Dosing (up titration and maintenance):	Day 1: 10 mg in the morning. Day 2: 10 mg in the morning and 10 mg in the evening. Day 3: 10 mg in the morning and 20 mg in the evening. Day 4: 20 mg in the morning and 20 mg in the evening. Day 5: 20 mg in the morning and 30 mg in the evening Day 6: 30 mg twice daily Maintenance dosing: 30 mg twice daily
STUDY/IRB NUMBER	842831
PROTOCOL TITLE:	Apremilast for the treatment of refractory erythema multiforme
PROTOCOL TITLE	Apremilast for erythema multiforme (AEM)
IND NUMBER:	N/A
REGULATORY SPONSOR:	The University of Pennsylvania.
FUNDING SPONSOR(S):	No funding requested. Amgen will provide IP.
PRINCIPAL INVESTIGATOR	Robert Gil Micheletti, MD
ORIGINAL PROTOCOL DATE:	19 November 2019
VERSION NUMBER:	7.0
VERSION DATE:	14 SEP 2023

PRINCIPAL INVESTIGATOR SIGNATURE

STUDY SPONSOR:	University of Pennsylvania
STUDY TITLE:	Apremilast for the treatment of refractory erythema multiforme
STUDY ID	842831
PROTOCOL VERSION	V7

I, the Principle Investigator (PI), have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines. I agree that the above-referenced Protocol Version is the most recent version of the Protocol approved by the IRB and the Study Team's activity will reflect the contents of this document.

PI Name	Robert Gil Micheletti, MD	Signature	
Affiliation:	University of Pennsylvania	Date	

Abbreviations

AE	Adverse Event
cAMP	Cyclic Adenosine Monophosphate
CFR	Code of Federal Regulations
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee; see also "IRB"
EM	Erythema Multiforme
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board; see also "EC"
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat

LSMEANS	Least-Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MP	Monitoring Plan
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PDE-4	Phosphodiesterase-4
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
DSMC	Data Safety Monitoring Committee
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
TNF-α	Tumor necrosis factor-alpha
UADE	Unanticipated Adverse Device Effect
UP	Unanticipated Problem
US	United States

1 STUDY SUMMARY

1.1 Synopsis

Title:	Apremilast for the treatment of refractory erythema multiforme
Short Title:	Apremilast for EM (AEM)
Study Description:	Prospective study completed at a single, academic institution (University of Pennsylvania) within the Department of Dermatology.
Objectives:	Assess the efficacy of apremilast in decreasing the number and severity of flares of erythema multiforme in a patient population with recurrent, refractory disease.
Primary Endpoint:	Primary endpoint: 1. Change in frequency and duration of EM flares at 24-week evaluation.
Secondary Endpoints:	Secondary endpoints: 1. Change in pain severity (on 0 to 10 scale) of EM flares at 24-week evaluation. 2. Change in frequency and duration of flares at 36-week follow-up. 3. Change in pain severity (on 0-10 numerical rating scale (NRS)) of EM flares at 36-week follow-up. 4. Use of prednisone as rescue therapy to treat flares.
Study Population:	We aim to enroll and treat 8 adult patients, aged 18-89 years old, diagnosed with erythema multiforme and in good general health. Patients will be enrolled from dermatology outpatient clinic at the University of Pennsylvania.
Phase:	2
Description of Sites/Facilities	Intellectual Environment of the Department of Dermatology:

The Department of Dermatology was founded in 1874 and is the oldest Dermatology Department in the USA. With approximately 60 full-time faculty members, Penn Dermatology has one of the largest dermatology faculty in the country pursuing basic science, epidemiologic, and clinical research on skin disease. Together, the faculty, staff and trainees create a robust, highly interactive and collaborative environment in which outstanding research, training and clinical programs co-exist and interact.

Our faculty members collaborate with each other, and with numerous other faculty across the Perelman School of Medicine, the School of Engineering, the School of Veterinary Medicine, the Dental School and the School of Arts and Sciences at Penn, as well as with investigators across the USA and internationally. Our faculty members are leaders in the cutaneous research community nationally, and internationally.

We have faculty interested in all aspects of clinical dermatology as well as a broad array of basic research. Our well-funded senior faculty conduct basic and translational research on epithelial development, stem cells and regeneration, autoimmune blistering diseases, epidermal differentiation, signaling and cancer, clinical trials and dermatoepidemiology studies, cutanous T-cell lymphoma, and cutaneous autoimmune diseases. The Department is composed of a mix of established, highly experienced senior and mid-level faculty, and junior faculty with exciting programs in new areas of investigation.

Our residency training and fellowship programs are also among the best in the nation, offering unparalleled excellence in training and first-rate mentorship. A Quality Improvement track administered through Graduate Medical Education is available to interested residents, and there are designated quality improvement faculty within the department.

Basic Science Laboratory Resources:

The basic research laboratories are housed within the 10th floor of the Biomedical Research Building (BRB10). BRB10 was renovated and occupied by Dermatology in 2013, allowing faculty from three separate buildings to work together on the same floor of a single building. A spacious and newly renovated conference room on BRB10 is used for laboratory meetings, faculty meetings, and collaborative discussions within the Department and with other researchers from Penn and outside

institutions. BRB is centrally situated on the PSOM campus, facilitating interactions with other Departments, Centers and Institutes. Almost 14,350 square feet of usable research space are dedicated to an integrated cutaneous biology initiative. The Perelman School of Medicine has committed the remaining space on BRB10 for Dermatology as the Department's research efforts continue to expand. Many of the facilities in BRB10 are shared across cores and programs in a collaborative and integrative fashion, with flexibility in facility utilization employed as needed to adapt to the dynamic nature of research.

Clinical Studies Unit:

The Department of Dermatology has maintained a dedicated Clinical Studies Unit (CSU) for over 3 decades. Joel Gelfand, MD, MSCE was appointed Medical Director of the CSU in 2003. The CSU is directed by Cynthia Clark, PhD, CRNP, the Director of Research Operations for Dermatology, and is robustly staffed by highly experienced members including a project manager, two clinical research nurses, five certified clinical research coordinators, and a research assistant as of July 2023. The CSU maintains the expertise to conduct investigator initiated and sponsored studies including studies conducted under INDs held by PENN investigators, and has served as coordinating center for investigator initiated, multi-center clinical studies. The CSU is located in the South Pavilion of the Perelman Center of Advanced Medicine and its space is well equipped for securely storing regulatory documents and study supplies, and includes four dedicated exam rooms for conducting clinical research visits, a dedicated clinical photography suite, a dedicated private room for conducting external or internal monitoring visits, as well as appropriate facilities for processing/storing blood specimens and storing/maintaining study investigational drugs. The Perelman Center of Advanced Medicine facilitates informal interactions between scientists and physicians in a collaborative environment that is in close proximity to the outpatient and clinical trial clinics.

Clinical/Translational:

The Dermatology Clinical Program has over 120,000 patient visits per year, and performs over 11,000 procedures each year. Physicians and providers score in the 98th percentile in "Likelihood to Recommend" and

consistently receive top scores for patient satisfaction. Additionally, the Department maintains a nationally recognized Dermatopathology Division with a state-of-the-art laboratory, which processes and reads approximately 90,000 patient specimens per year. The Ruth and Raymond Perelman Center for Advanced Medicine (PCAM) is a state-of-the-art, 500,000 square foot outpatient facility adjacent to the Hospital of the University of Pennsylvania. This is the main clinical practice site for Dermatology, which occupies 12,000 sf on the first floor of the center. Many patient oriented research activities are carried out at this site, including independently funded clinical trials in dermatology. The medical dermatology facility includes 19 exam rooms, 4 procedural treatment rooms, clinical laboratories, a nursing station, drug storage facilities and offices. The Mohs and Dermatologic surgery unit includes 8 surgical treatment rooms, a laboratory, nursing station, and drug storage facilities. PCAM is adjacent to the Translational Research Center (TRC), allowing for performance of more complex studies.

Among the department's many areas of excellence is its dedicated inpatient dermatology consult service, which handles approximately 800 new consults per year and is staffed by two attending physicians board certified in both internal medicine and dermatology. Facilitated by this active inpatient consult service, our faculty have a special expertise in diagnosis and management of adverse cutaneous drug reactions. Together with senior-level dermatoepidemiologists who have helped run drug registries and sat on drug safety boards and NIH working groups related to drug safety, there is ample expertise in this area to mentor junior faculty and trainees effectively.

Finally, our faculty benefit from collegial and collaborative relationships with colleagues in other departments and divisions, including Allergy / Immunology and Infectious Diseases, as well as at other institutions with which we have collaborative relationships. While this project will be fully administered within the department of dermatology, access to these additional resources place us in an excellent position to succeed in this endeavor.

Enrolling Participants: University of Pennsylvania Department of Dermatology (single site). No additional sites or sites outside of the United States will be included.

Description of Study Intervention: Apremilast will be prescribed for oral dosing with five-day titration up to 30 mg orally twice daily.

First patient enrolled: 13-Jan-2023

Primary completion goal: 31-Jul-2024

Study completion goal: 31-Jul-2025

Participant Duration: up to 37 weeks with screening, treatment, and follow-up

1.2 Key Roles and Study Governance

Investigator Initiator and Principal Investigator	*Sub- Investigator*
Robert G. Micheletti, MD *Assistant Professor Dept Dermatology*	*Claire Hannah, MD* *Resident Physician (PGY-5) Dept of Dermatology*
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1.3 Schema

	Goal first patient first visit: 13Sep2021	Baseline visit	4-week-visit in-person visit or phone call if patient unable to come to clinic	12-week visit	24-week visit	Enrollment completion
	Screening and enrollment begin	Patients reported severity assessment	Ensure understanding of treatment diary and review treatment diary for number and	Review of treatment diary for number and duration of flares. Assess for any medication	Review of treatment diary for number and duration of flares. Assess for any medication	36-week visit to capture endpoints and assess frequency/duration and pain associated with flares.

		duration of flares. Assess for any medication adverse events.	adverse events.	adverse events.	
Chart review to determine flares in preceding 6 months	Patient reported number and duration of flares	Patient reported severity assessment from flares	Patient reported severity assessment from flares	Patient reported severity assessment from flares	Begin manuscript preparation
	Initiation of apremilast	Corroboration with chart review if patient seen in clinic during flares.	Corroboration with chart review if patient seen in clinic during flares	Corroboration with chart review if patient seen in clinic during flares	
	Patient begins treatment diary		Corroboration with chart review of any prednisone or topicals required for flares	Corroboration with chart review of any prednisone or topicals required for flares	

2 INTRODUCTION AND RATIONALE

2.1 Study Rationale

Erythema multiforme (EM) is an acute, immune-mediated mucocutaneous condition that often eventuates in significant morbidity, pain, anorexia, hospitalization, and long-term sequelae (Viarnaud, et al. J Eur Acad Dermatol Venerol. 2018). In adults, the disease recurs in 40% of patients, significantly impacting quality of life (Wetter DA, Davis MD. J Am Acad Dermatol. 2010). Treatment of recurrent EM is often prolonged and challenging, with most patients

requiring multiple courses of systemic steroids (Wetter DA, Davis MD. J Am Acad Dermatol. 2010). Steroid-sparing immunosuppressives are typically attempted for patients with recurrent EM not responsive to antivirals. However, no single therapeutic agent has been consistently effective for long term management (Wetter DA, Davis MD. J Am Acad Dermatol. 2010).

2.2 Background

Erythema multiforme (EM) is an acute, immune-mediated mucocutaneous condition most frequently triggered by infection with herpes simplex virus (HSV) or *Mycoplasma pneumoni* (Zoghaib S, et al. J Am Acad Dermatol. 2019). Idiopathic EM is also commonly reported (Zoghaib S, et al. J Am Acad Dermatol. 2019). EM can manifest with severe mucocutaneous involvement resulting in significant morbidity, pain, anorexia, hospitalization, and long-term sequelae (Viarnaud, et al. J Eur Acad Dermatol Venerol. 2018). In adults, disease recurs in 40% of patients, significantly impacting quality of life (Wetter DA, Davis MD. J Am Acad Dermatol. 2010). While HSV has been implicated in recurrent EM, many patients never exhibit evidence of HSV infection, and many have repeated flares despite continuous antiviral therapy (Wetter DA, Davis MD. J Am Acad Dermatol. 2010). Treatment of recurrent EM is often prolonged and challenging, with most patients requiring multiple courses of systemic steroids (Wetter DA, Davis MD. J Am Acad Dermatol. 2010). Steroid-sparing immunosuppressives are typically attempted for patients with recurrent EM not responsive to antivirals. However, no single therapeutic agent has been consistently effective for long term management (Wetter DA, Davis MD. J Am Acad Dermatol. 2010).

Erythema multiforme is thought to be an immune mediated process secondary to autoreactive T-cells. Autoreactive T-cells release pro-inflammatory cytokines and chemokines resulting in epidermal damage (Samim F, et al. Dent Clin North Am. 2013). The process is thought to involve both B- and T-cell response pathways (Kokuba, et al. Br J Dermatol. 1998)(Kokuba, et al. J Invest Dermatol. 1999)(Kokuba, et al. Dermatology 1999). Phosphodiesterase 4 (PDE-4) is an enzyme that results in hydrolysis of cyclic adenosine monophosphate (cAMP), an intracellular second messenger involved in modulating inflammation. Apremilast is a PDE-4 inhibitor that increases cAMP and results in decreased expression of pro-inflammatory mediators including: inducible nitric oxide synthase, TNF-alpha, and interleukins-12 and 23, and simultaneous increased expression of anti-inflammatory interleukin-10 (Schafer P. Biochem Pharmacol. 2012)(Schafer PH, Day RM. J Am Acad Dermatol. 2013). In a series of three patients, apremilast has been used successfully in the treatment of refractory, recurrent EM (Chen, et al. Dermatol Online 2017). Apremilast has also been used to effectively treat recurrent oral ulcerations in Behcet's disease, a condition thought to be mediated by inflammatory cytokines also implicated in EM (Hatemi G, et al. N Engl J Med. 2015). EM may therefore represent a compelling novel target for this medication. Identification of a safe, steroid-sparing agent for affected patients could drastically improve quality of life and decrease long term sequelae in this challenging condition.

2.2.1 Pharmacokinetics, Pharmacodynamics and Toxicology

2.2.2 Assessment for Potential Study Products Drug-Drug, Drug-Device, Device-Device Interactions

See Investigator's Brochure

2.2.3 Clinical Adverse Event Profile

See Investigator's Brochure

2.2.4 Dosing Rationale

This is the current dose used in treatment of psoriasis, psoriatic arthritis, and Behcet's disease for oral aphthous ulcerations.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Apremilast may cause all, some, or none of the side effects listed below. These side effects can be mild but could also be serious, life-threatening, or even result in death.

You may also experience other side effects or an allergic reaction that has not been seen before.

As of 20 March 2023 about 10038 patients have received apremilast in research studies. Since it was first approved for sale in March 2014, about 846059 people have been prescribed apremilast. Side effects that other people have had that are thought to have been caused by *apremilast* are:

- **Very Common side effects** (which may affect more than 1 person in 10): Diarrhea, Nausea (feeling like you need to throw up), Headache, Upper respiratory tract infections (infections of the nose, throat, and airways)

- **Common side effects** (which may affect between 1 and 10 people in every 100): Upper abdominal (stomach) pain, Indigestion, Frequent bowel movement, Heartburn, Vomiting (throwing up), Fatigue (tiredness), Bronchitis (infection of the tubes to the lungs), Nasopharyngitis (common cold), Decreased appetite (feeling less hungry), Back pain, Tension headache, Migraine, Difficulty to falling or staying sleeping, Depression, Cough

- **Uncommon side effects** (which may affect between 1 and 10 people in every 1000): Allergic reaction, Rash, Weight loss
-

Severe diarrhea, nausea (feeling like you need to throw up), and vomiting (throwing up) have been reported with the use of apremilast. Most events occurred within the first few weeks of starting apremilast. Some patients were hospitalized. If you are 65 years of age or

older, and/or become dehydrated or experience low blood pressure, you may be at a higher risk of complications. If you experience severe diarrhea, nausea (feeling like you need to throw up), or vomiting (throwing up), please tell your study doctor immediately.

In clinical studies, weight loss has been seen. If you have unintentional or unexplained weight loss (for example, if you have weight loss without actively trying to lose weight), please tell your study doctor immediately.

Reports of various types of cancers, heart problems, stroke, and serious infections have been found from apremilast studies. However, these events in patients being treated with apremilast happened as often as those being treated with placebo (a substance that does not have any medicine in it but looks like the drug being tested. Researchers use a placebo to decide if the study drug works better than no treatment at all).

Depression (feeling sad/loss of interest) has been reported with the use of apremilast. If you have a history of depression and/or suicidal thoughts or behavior, please tell your study doctor. If you have any symptoms of depression or if your depression becomes worse, or if you have suicidal thoughts or other mood changes, contact your study doctor immediately.

Inflammation of the vessels was seen when apremilast was given to mice and rarely reported in humans. If you notice swelling, pain, or tenderness, please contact the study doctor.

Tell your study doctor if you are taking any other medications or were recently taking medications, including over-the-counter medications, since some medications could interfere with the effects of apremilast.

Please talk with your study doctor if you would like to know more about these problems. It is possible that the condition for which you are being treated may worsen during the study. You will be closely monitored. If your condition becomes worse, your doctor will stop your participation in this study. The doctor will treat you as he/she feels is best.

2.3.2 Known Potential Benefits

In clinical studies, weight loss has been observed. Direct benefit has been seen for other inflammatory skin conditions and ulcerations of the mucosa.

Long-range potential benefits of this medication include potential use for patients with refractory erythema multiforme.

2.3.3 Assessment of Potential Risks and Benefits

Apremilast has a good safety profile across many clinical trials. The current standard of care for recurrent, oral erythema multiforme is treatment with oral corticosteroids or strong immunosuppressive medications. Apremilast may serve as an alternative therapeutic option. The risk of exposure is necessary for us to understand if apremilast could be a viable option for this indication.

Risks were minimized in this trial by maintaining dosing utilized in other trials with good safety data. Risk is also minimized as patients are able to opt out of the study at any time.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Assess the efficacy of apremilast in decreasing frequency and duration of EM flares at 24-week evaluation.	Patients will be asked to report the number of EM flares and average flare duration (in days) in the six months prior to enrollment. Pennchart records including physician documentation, prednisone prescriptions, and hospital admissions will be reviewed to reconcile patient-reported answer. Following enrollment, apremilast will be initiated with five-day titration to 30 mg orally twice daily. Additionally, patients will be asked to keep a treatment diary documenting flare presence (yes or no) each day and duration of flares will be computed by the study team on diary review. Patients will be assessed and diaries will be reviewed at every study visit.	
Secondary		
Assess the efficacy of apremilast in decreasing in pain severity (on a 0-10 scale) of EM flares at 24-week evaluation. Change in frequency and duration of flares at 36-week follow-up. Change in pain severity (on 0-10 visual analogue scale) of EM flares at 36-week follow-up.	Patients will be asked to report the usual or average pain rating (on a 0-10 scale) during EM flares in the six months prior to enrollment. As part of their treatment diary, they will also record total dose of apremilast taken daily and worst-pain related to their disease, if any, experienced in last 24 hours. Patients will be assessed and diaries will be reviewed at every study visit. Above endpoints of EM flare frequency/duration will also be evaluated at 36-week follow-up. Above endpoints related to pain associated with EM flares will also be evaluated at 36-week follow-up.	These outcomes have been previously validated in a Phase II Clinical Trial for Apremilast in Behcet's Disease.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Use of prednisone as rescue therapy to treat flares.	Prednisone use will be documented at each planned and unscheduled visit to calculate change in use of prednisone as a proxy of disease severity.	

4 STUDY PLAN

4.1 Study Design

Study Question: Does treatment with apremilast affect the frequency, duration, and severity of EM flares?

Null hypothesis: Patients treated with apremilast will not experience a decrease in frequency, duration, and severity of EM flares during the 24-week treatment period.

Alternative hypothesis: Patients treated with apremilast will experience a decrease in frequency, duration, and severity of EM flares during the 24-week treatment period.

Phase: 2

Prospective study completed at a single, academic institution (University of Pennsylvania) within the Department of Dermatology. The overall aim of the study is to assess the efficacy of apremilast in decreasing the frequency and severity of flares of erythema multiforme in a patient population with recurrent, refractory disease. Recurrent, refractory disease will be characterized by ≥2 flares in the six months prior to enrollment (or ≥4 flares in the year prior to enrollment).

Chart review with patient confirmation will be used to determine numbers of flares qualifying patients for enrollment. Following enrollment, patients will be asked for baseline severity assessment (average pain measured on a 0-10 scale, with higher numbers correlating with more pain) for the flares 6 months prior to enrollment. Patients will be asked to report the number and average duration (in number of days) of their flares. This information will be corroborated via PennChart review and physician documentation.

Apremilast will be initiated with five-day titration to 30 mg orally twice daily. Patients will be assessed at 4-week, 12-week, 24-week, and 36-week follow up intervals tracking flare recurrence and symptom severity. Additionally, patients will be asked to keep a treatment diary documenting medication adherence, flares as they occur, duration of flares when present, and pain severity scoring in a diary which will be reviewed at each study visit. If flares occur while in the study and the patient is able to be seen in clinic, the patient will be offered a clinic visit or televisit within 5 days of flare onset as a protocol-defined Unscheduled Visit. At that time, we will document the flare with photographs in PennChart Haiku and review patient diary for reported medication adherence, flare tracking, and pain (again measured on a 0-10 scale, with higher numbers correlating with more pain) prior to starting prednisone. A 36-Week clinical visit or phone call (if the patient is unable or

unwilling to return to clinic) will take place to continue monitoring and to assess if there is a change in frequency/duration and pain with flares.

Note: The primary endpoint is assessed at Week 24. The study treatment as provided by Amgen is assigned through Week 24. Subjects will be followed through Week 36 for safety and evaluation of secondary endpoints. While it is anticipated that some subjects will not continue taking the drug under investigation during the time between Week 24 and Week 36 Visits, some subjects may continue on apremilast if their insurances approve this off-label use and/or the subject is willing and able to pay for the medication out of pocket.

Rescue treatment: Flares will be treated with topical corticosteroids and, if needed, oral prednisone (standardized protocol of 30 mg daily x 3 days, 20 mg daily x 3 days, 10 mg daily x 3 days) as deemed warranted by a physician.

4.2 Scientific Rationale for Study Design

Erythema multiforme (EM) is an acute, immune-mediated mucocutaneous condition that often eventuates in significant morbidity, pain, anorexia, hospitalization, and long-term sequelae. (Viarnaud, et al. J Eur Acad Dermatol Venerol. 2018).[2] In adults, the disease recurs in 40% of patients, significantly impacting quality of life. Treatment of recurrent EM is often prolonged and challenging, with most patients requiring multiple courses of systemic steroids. Steroid-sparing immunosuppressives are typically attempted for patients with recurrent EM not responsive to antivirals. However, no single therapeutic agent has been consistently effective for long term management (Wetter DA, Davis MD. J Am Acad Dermatol. 2010).[3]

4.3 Justification for Dose

This is the currently FDA approved dose for other inflammatory conditions including psoriasis, psoriatic arthritis, and Behcet's disease

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Appendix Section 12.1.

5 STUDY POPULATION

5.1 Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Presence of oral, genital, or cutaneous erythema multiforme (EM) diagnosed or confirmed by a dermatologist based on clinical and/or histopathologic data.
2. EM must be recurrent, defined as having ≥2 flares in the six months prior to enrollment (or ≥4 flares in the year prior to enrollment).
3. EM must be refractory to standard therapy defined as 3-month treatment course with valacyclovir and/or a systemic immunomodulatory therapy such as colchcine, dapsone, azathioprine, mycophenolate mofetil, or methotrexate.
4. Must be in general good health (except for disease under study) as judged by the Investigator, based on medical history, physical examination, and clinical laboratories. (NOTE: The definition of good health means a subject does not have uncontrolled significant co-morbid conditions).
5. Willing and able to provide personally signed and dated informed consent form.
6. Stated willingness and ability to comply with all study procedures including adhering to oral apremilast regimen and availability for the duration of the study.
7. Adults aged 18-89 years old.
8. People of childbearing potential (PCBP) must have a negative pregnancy test at Screening and Baseline. While on investigational product and for at least 28 days after taking the last dose of investigational product, PCBP who engage in activity by which conception is possible must use one of the approved contraceptive options described below:

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

   OR

   Option 2: External or internal 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.

   NOTE: This criterion is satisfied as "not applicable" (N/A) for those who practice abstinence as part of their usual and customary way of life, so long as this is maintained throughout study period plus 28 days post-treatment; are postmenopausal; or are of male sex/assigned male at birth (AMAB).

5.2 Exclusion Criteria

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

1. Other than disease under study, any clinically significant (as determined by the Investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major disease that is currently uncontrolled.
2. Any condition, including the presence of laboratory abnormalities, which would place the subject at unacceptable risk if they were to participate in the study.
3. Prior history of unmanaged depressive symptoms, suicide attempt at any time in the subject's life time prior to screening or randomization, or major psychiatric illness requiring hospitalization within the last 3 years.
4. A score of 4 or higher on Patient Health Questionnaire at screening.
5. Pregnant or breast feeding.
6. Active substance abuse or a history of substance abuse within 6 months prior to Screening.
7. Malignancy or history of malignancy, except for:
    a. treated [ie, cured] basal cell or squamous cell in situ skin carcinomas;
    b. treated [ie, cured] cervical intraepithelial neoplasia (CIN) or carcinoma in situ of cervix with no evidence of recurrence within the previous 5 years.
8. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer).
9. Prior treatment with apremilast.
10. Patient unable to comply with study or conform to treatment diary or regular follow up visits.
11. Patients with ocular EM.
12. Concomitant use of immunosuppressive medications for treatment of other diseases.
13. Patients with contraindications to Apremilast according to package insert.

5.3 Lifestyle Considerations

None

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Patients may be rescreened at the discretion of the PI. In event of a rescreened subject who meets enrollment criteria, they will be assigned a new subject number.

5.5 Strategies for Recruitment and Retention

Patients will be recruited from dermatology outpatient clinic at the University of Pennsylvania. Healthy adults 18-89 years old will be considered. Vulnerable populations will not be included.

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

See Investigator's Brochure

6.1.2 Dosing and Administration

Dosing will be consistent with the previously approved FDA dosing for other inflammatory conditions. Dose for healthy patients that meet screening criteria will be 5-day up-titration to full dosing, as below:

- Day 1: 10 mg in the morning.
- Day 2: 10 mg in the morning and 10 mg in the evening.
- Day 3: 10 mg in the morning and 20 mg in the evening.
- Day 4: 20 mg in the morning and 20 mg in the evening.
- Day 5: 20 mg in the morning and 30 mg in the evening.
- Day 6: 30 mg twice daily.
- Maintenance dosing: 30 mg twice daily.

Patients with renal disease (elevated creatinine above normal) will receive renal dosing with up-titration to 30 mg once daily

- Mild-to-moderate (CrCl ≥30): No dosage adjustment required
- Severe (CrCl <30 mL/min)
    - Reduce dose to 30 mg PO qDay
    - For initial dosage titration, titrate using only the AM schedule listed above and skip the PM doses

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability

Please refer to CSU Investigative Drug Handling Procedure SOP.

6.2.2 Formulation, Appearance, Packaging, and Labeling

See Investigator's Brochure for formulation, appearance, and packaging. Please refer to CSU Investigative Drug Handling Procedure SOP for guidance regarding labeling of IP.

6.2.3 Product Storage and Stability

See Investigator's Brochure and Package Insert.

6.2.4 Preparation

See Investigator's Brochure and Package Insert.

6.3 Measures to Minimize Bias: Randomization and Blinding

Blinding is considered unnecessary to reduce bias, as our endpoints are patient-reported, and the study treatment is open-label. Both study team and subjects are aware that all participants are receiving the investigational medication. Study subjects also will keep a daily treatment diary to track progress and prevent recall bias at follow-up appointments.

6.4 Study Intervention Compliance

Patients are asked to complete a mandatory treatment diary documenting medication adherence, flares, and pain severity with flares. This will be corroborated by the medical record if patients are seen during flares.

6.5 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications, and supplements.

Patients will be excluded if requiring concomitant use of immunosuppressive medications for other conditions. Patients will be encouraged to continue treatments for the disease under investigation current at the time of informed consent throughout their study participation unless directly contraindicated, a dose-limiting-toxicity is experienced, or for any reason at the discretion of the investigator.

6.5.1 Rescue Therapy

The study site will not supply prednisone rescue medication that will be obtained locally. The following rescue medications may be used: prednisone or topical steroids.

The use of rescue medications is allowable at any time during the study. The date of rescue medication administration, as well as the name and dosage regimen of the rescue medication, must be recorded. We have attempted to standardize all rescue medications prescribed by our department. Flares will be treated with topicals steroids and, if needed, oral prednisone (standardized protocol of 30 mg daily x 3 days, 20 mg daily x 3 days, 10 mg daily x 3 days), as deemed warranted by a physician.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Continued documentation of medication adherence through 24 weeks of treatment, in addition to patient-reported flares and pain throughout the 36-week follow-up interval will be reported by the patient and monitored by the study team. Date of discontinuation of apremilast for any reason will be documented.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy;
- Significant treatment non-adherence, defined as <70% of protocol-defined treatment doses taken in any given week during the 24-week treatment period, as evaluated by the study team's review of the subject diary;
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant;
- Disease progression which requires discontinuation of the apremilast;
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation; or
- Participant unable to receive apremilast for >1 week

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

7.3 Lost To Follow-Up

Participants will be considered lost to follow-up if they fail to return for each of the scheduled follow up visits and are unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record and/or study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENT AND PROCEDURES

8.1 Efficacy Assessments

Dermatological-limited physical examination to include oral mucosa, face, full body examination, hands and feet, nails, and genital mucosa (if applicable). Patients will be offered a chaperone for skin examination.

Review of treatment e-diary weekly for adherence and study staff retraining as needed for non-adherence. Review of paper diary for subjects who are unable to complete e-diary at 4-week, 12-week, 24week, and 36week follow-up visits.

Review of electronic medical record for collection of baseline demographics (age, sex, race, ethnicity, and medical record documentation review between visits, including clinical visits, documented flares, and prednisone prescribed between scheduled visits.

Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements should be followed, as applicable. If this is the case, this section should note which information is to be obtained through review of existing data.

8.2 Safety and Other Assessments

Dermatological-limited physical examination to include oral mucosa, face, full body examination, hands and feet, nails, and genital mucosa (if applicable). Patients will be offered a chaperone for skin examination.

Assessment of study intervention adherence.

Administration and review of treatment diary for patient-reported outcomes.

Assessment of adverse events, including of depression and anxiety (PHQ-4).

As medical records will be collected, Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements will be followed and disclosed to the subject as part of the combined Informed Consent and HIPAA Authorization Form.

8.3 Adverse Events and Serious Adverse Events

- The study involves an investigational drug (apremilast)

8.3.1 Definition of Adverse Events (AE)

An adverse event (AE) is any noxious, unintended, or untoward medical event occurring at any dose that may appear or worsen in a subject 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 subject'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 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.

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.

8.3.2 Definition of Serious Adverse Events (SAE)

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 subject 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 subject'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 subject 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.

8.3.3 Classification of an Adverse Event

8.3.3.1 Severity of Event

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

8.3.3.2 Relationship to Study Intervention

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.

8.3.3.3 Expectedness

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for apremilast.

8.3.4 Time Period and Frequency for Event Assessment and Follow-Up

Safety will be assessed by monitoring and recording potential adverse effects using the protocol defined grading system at each study visit. Participants will be monitored by medical histories and physical examinations.

At each contact with the subject, the investigator will seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events will be recorded in the source documentation. To the extent possible, adverse events will be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Severity grade: mild, moderate, or severe
2. Duration: start and end dates
3. Relationship to the study treatment or process – reasonable possibility that AE is related:
    a. Not suspected. Unrelated or unlikely related to the investigational treatment.
    b. Suspected. Possibly related, probably related, or definitely related to the investigational treatment.
4. Expectedness to study treatment or process – Unexpected – if the event severity and/or frequency is not described in the investigator brochure (if applicable) or protocol.
5. Action taken with respect to study or investigational treatment or process: none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable.

6. Whether medication or therapy taken: no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy.

7. Whether the event is serious or not serious.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.3.5 Adverse Event Reporting

Reporting Period

Adverse events will be reported from the time of informed consent until study completion.

Investigator Reporting: Notifying the Study Sponsor

Every SAE, regardless of suspected causality (e.g., relationship to study product(s) or study procedure(s) or disease progression) must be reported to the sponsor within **24 hours** of learning of its occurrence.

Recurrent episodes, complications, or progression of the initial SAE must be reported to the Sponsor as a follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE considered completely unrelated to a previously reported one should be reported separately as a new event.

Send the SAE report to the PI.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). The investigator must follow the event to resolution or until the event is deemed and documented irreversible, whichever is longer.

Investigator Reporting: Local Reporting Requirements

The investigator will report AEs and SAEs to the IRB/EC of record and other local regulatory groups per the local requirements.

8.3.6 Serious Adverse Event Reporting

Any AE that meets the any 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 subject's last dose of study drug, and those made known to the investigator(s) at any time 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 Amgen 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).

8.3.7 Amgen Drug Safety Contact Information:

All transfer of individual case safety reports (ICSRs) to Company will be made through the designated contact fax or email address listed below, which may be updated by written notice from Company from time to time as required and as becomes necessary.

If Study is in the United States or is a multi-country Study, Company will provide under separate cover the designate contact information:

Fax: 888-814-8653 (toll-free, US)
+44-20-7136-1046 (UK hub)
E-mail: svc-ags-in-us@amgen.com

For provision of periodic reports, aggregate reports and reconciliation line listings, Company will provide under separate cover the designate contact information.

The SAE report should provide a detailed description of the SAE. If a subject has died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Amgen 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 Amgen.

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 Amgen and the IRB/IEC, on file. All SAEs that have not resolved upon discontinuation of the subject'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).

Timeframes for Submission of Safety Data to Amgen

For Interventional studies with Amgen IMP[a]:

Safety Data	Timeframe for submission to Amgen	Send to
Suspected Unexpected Serious Adverse Reaction (SUSARs)	At time of regulatory submission	Amgen Safety

Pregnancy/Lactation exposure and any associated reports/outcomes (i.e. unexpected pregnancy, pregnancy of partner, spontaneous abortion, congenital anomaly etc.)	Within 1 business day of Sponsor awareness, for reports meeting serious criteria Not to exceed 15 calendar days of Sponsor awareness, for non-serious reports	Amgen Safety

[a] Specific requirements are to be outlined in the Research Agreement.

For all study types – aggregate reports[a] (as applicable):

Safety Data	Timeframe for submission to Amgen	Send to
Listing for Safety data reconciliation[b]	Once per year and at the end of the study	NASCR Manager
Annual Safety Report (eg, EU Clinical Trial Directive DSUR and US IND Annual Report)	Annually	NASCR Manager
Other aggregate analyses (any report containing Safety data generated during the course of the study)	At the time of Sponsor submission to any body governing research conduct (eg. RA, IRB etc.)	NASCR Manager
Final (End of Study Report, including): • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	At the time of Sponsor submission to any body governing research conduct (eg. RA, IRB etc.) but no later than 1 calendar year of study completion	NASCR Manager

[a] Specific requirements are to be outlined in the Research Agreement.

[b] Listing for reconciliation should include all ICSRs submitted to Amgen Safety per contract (i.e. for studies in Table 1 listing should include ADRs, SADRs, Other Safety Findings, USADEs, SADEs and non-serious ADEs ; for studies in Table 2 listing should contain SUSARs, pregnancy and lactation exposure (and any associated reports/outcomes), USADEs, SADEs and non-serious ADEs; studies in table 3 do not require reconciliation).

8.3.8 Reporting Events to Participants

Patients will be notified of AE in real time during clinical visits if deemed secondary to apremilast.

8.3.9 Events of Special Interest

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 subject 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.

8.3.10 Reporting of Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject occurring while the subject is on study drug, or within 30 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject 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 Amgen Safety immediately facsimile using the Pregnancy Report form provided by Amgen.

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 subject until completion of the pregnancy and must notify Amgen 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 Amgen Safety by facsimile within 24 hours of the Investigator's knowledge of the event).

In the case of a live "normal" birth, Amgen 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 Amgen 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 subject's continued participation in the study will be determined by the Investigator.

Contraception Education

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

All people of childbearing potential (PCBP) must use one of the approved contraceptive options as described in the Inclusion Criteria while on investigational product and for at least 28 days after administration of the last dose of the investigational product.

When a subject 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.

Males should alert their childbearing partners of their participation in an investigational drug trial.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.]

8.4.2 Unanticipated Problem Reporting

Unanticipated problems (UPs) such as:

- Post-marketing withdrawal of a drug, device, or biologic used in a research protocol due to safety concerns.
- FDA ban of a drug, device, or biologic used in a research protocol due to safety concerns.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study
- Premature closure of a study (e.g., due safety, lack of efficacy, feasibility, financial reasons, etc.)

should be reported by the investigator to Amgen, reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC), and PI. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported as any other SAE.

- Any other UP will be reported to Amgen, IRB and to the DCC/study sponsor within 72 hours of the investigator becoming aware of the problem.

- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) in accordance with the IRB's receipt of the report of the problem from the investigator.

8.4.3 Reporting Unanticipated Problems To Participants

Not-applicable

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

1. **Primary Efficacy Endpoint(s)**: Change in frequency and duration of EM flares at 24-week evaluation.

2. Null: There is no difference in frequency or duration of EM flares in subjects before and after taking apremilast.

3. Alternative: Patients on apremilast have decreased frequency and duration of EM flares at 24-week evaluation.

1. **Secondary Efficacy Endpoint(s)**: Change in severity (on a 0-10 scale) of EM flares at 24-week evaluation. Change in frequency, severity, or duration of EM flares at 36-week evaluation off treatment.

2. Null: There is no difference in EM associated pain severity (on a 0-10 scale) before and after treatment with apremilasat. There is not difference in frequency, severity, or duration of EM flares at 36-week evaluation off treatment.

3. Alternative: Patients have decreased frequency and duration of EM flares at 24-week evaluation after treatment with apremilast. There is a difference in frequency, severity, or duration of EM flares at 36-week evaluation off treatment.

9.2 Sample Size Determination

Patients will be recruited and enrolled from the University of Pennsylvania outpatient dermatology department. The enrollment goal is for a total of 8 patients with diagnosed EM as defined in the Inclusion Criteria to be enrolled and treated through the entirety of the 24-week treatment phase in order to have adequate data to test our hypotheses and support proof of concept. Including patients who drop out or otherwise stop the study prior to its completion, total enrollment in the study shall not exceed 10 patients.

Patients will be enrolled sequentially and at random.

9.3 Populations for Analyses

Primary analysis will be based on the full, intention-to-treat data set of enrolled patients. Per-protocol analyses will also be performed, as appropriate, including only those patients who complied with the protocol sufficiently to ensure outcomes represent the effects of study intervention according to the underlying scientific model (e.g., participants who took at least 70% of study intervention within the maintenance period).

9.4 Statistical Analyses

9.4.1 General Approach

Descriptive statistics will be used to summarize baseline characteristics. Continuous variables will be summarized with medians and interquartile ranges. Categorical variables will be reported as proportions and percentages.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

Primary Efficacy Endpoint(s): Decrease in frequency and duration of EM flares at 24-week evaluation. Patients will report average number of flares occurring in the 6 months prior to study enrollment. At 24-week evaluation, both patient reported and chart documented flares will be calculated and compared against their flares in the prior 6 months. Flare duration (in average number of days) will also be asked retrospectively for the 6 months prior (at time of enrollment) with repeat flare duration calculated via patient report and via treatment diary at follow up visits. Requirements for prednisone duration will be documented as this is often associated with increased flare severity. These are discrete, quantitative variables (number of flares that will compare frequency counts). This will be measured as three, single end points at 12 week and 24 week follow up visits. Missing data or patients lost to follow up will be noted.

9.4.3 Analysis of the Secondary Endpoint(s)

Secondary Efficacy Endpoint(s): Decrease in severity (on a 0-10 scale) of EM flares at *12-week and* 24-week evaluation. This will be assessed via patient reported pain scale (on a 0-10 scale) for flares present in the 6 months prior to apremilast initiation. A 0-10 scale will be provided to each patient enrolled via the treatment diary and patients will be asked to report pain associated with flares. If pain is reported over the course of a flare, the highest value will be recorded and used for analysis against the pain scale six months prior. These are discrete, quantitative variables (number on numerical rating scale at different time points). This will be measured as two, single end points at 12 week and 24 week follow up visits. Missing data or patients lost to follow up will be noted. Change in frequency, severity, or duration of EM flares at 36-week evaluation off treatment will also be assessed using measures as described in this section.

9.4.4 Safety Analyses

Safety endpoints will be analyzed as summary statistics during treatment.

9.4.5 Baseline Descriptive Statistics

Baseline demographics will be collected and reported for each patient but given the small n, subgroup analysis will not be completed. Patients will not be compared.

9.4.6 Planned Interim Analyses

Not applicable

9.4.7 Sub-Group Analyses

Sub-group analyses will not be done given the small N and proof of concept study.

9.4.8 Tabulation of Individual Participant Data

Individual participant data will be listed by measure and time point.

9.4.9 Exploratory Analyses

None

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided To Participants

Consent forms describing in detail the initiation of apremilast for EM, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering apremilast. The following consent materials are submitted with this protocol.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. Participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated by the Sponsor or the PI at any site if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the

termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a

secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Pennsylvania Department of Dermatology. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by dermatology department research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived within in the Department of Dermatology at Penn.

10.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored within the department of dermatology at the University of Pennsylvania. After the study is completed, the archived data will be stored at University of Pennsylvania's University Records Center for a minimum of two years after study completion. Their location and contact information is as below:

UNIVERSITY RECORDS CENTER
4015 Walnut Street, Mezzanine
Philadelphia, PA 19104
(215) 898-9432
https://archives.upenn.edu/archives-info/other-archives

10.1.5 Clinical Monitoring

Site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the PI and clinical trial's research team within the Department of Dermatology at Penn.

- Onsite monitoring will occur throughout the study with targeted random review of data verification of endpoint, safety and other key data variables.

- Independent audits or compliance reviews may be conducted by the Clinical Studies Unit or other Regulatory/Compliance Groups within the University of Pennsylvania such as

the Office of Clinical Research (OCR) or IRB to ensure monitoring practices are performed consistently.

- The Department of Dermatology has maintained a dedicated Clinical Studies Unit (CSU) for over 3 decades. Joel Gelfand, MD, MSCE was appointed Medical Director of the CSU in 2003. The CSU is directed by Cynthia Clark, PhD, CRNP, the Director of Research Operations for Dermatology, and is adequately staffed by highly experienced members including a project manager, two clinical research nurses, five certified clinical research coordinators, and a research assistant as of July 2023. The CSU maintains the expertise to conduct investigator initiated and sponsored studies including studies conducted under INDs held by PENN investigators, and has served as coordinating center for investigator initiated, multi-center clinical studies. The CSU is located in the South Pavilion of the Perelman Center of Advanced Medicine and its space is well equipped for securely storing regulatory documents and study supplies, and includes four dedicated exam rooms for conducting clinical research visits, a dedicated clinical photography suite, a dedicated private room for conducting external or internal monitoring visits, as well as appropriate facilities for processing/storing blood specimens and storing/maintaining study investigational drugs. The Perelman Center of Advanced Medicine facilitates informal interactions between scientists and physicians in a collaborative environment that is in close proximity to the outpatient and clinical trial clinics.

10.1.6 Quality Assurance and Quality Control

All monitoring and audits are to be performed according to ICH GCP E6(R2).

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), including the Penn Dermatology Clinical Studies Unit Monitoring Plan for Investigator-Initiated Studies, the monitors will verify that the clinical trial is conducted and data are generated, and specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.7 Data Handling and Record Keeping

10.1.7.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Source data will follow the Good Documentation Practice of ALCOA + C: attributable (identity of who documented readily discernable); legible (easy to read and interpret); contemporaneous (information documented and signed/dated as it happens); original (first record of the information or is a certified copy); accurate (consistent and representative of facts); and complete (to answer who, what, when, where, why, and how).

Hardcopies of the study visit data, including printed copies of electronic medical record (EMR) notes, worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Photocopies of source documents may be scanned and maintained in folders located on the T-Drive, a HIPAA- and 21 CFR Part 11-compliant UPHS server used by Penn Dermatology, and made accessible only to members of the study team verified and maintained by the PI. Data will be entered into a REDCap database and will not include any PHI. Data entered into REDCap will match source documentation exactly and will be monitored for accuracy randomly, to include prior to data analysis and manuscript submission (if applicable).

10.1.7.2 Study Records Retention

Study documents including source documentation and the contents of the regulatory binder(s) should be retained for a minimum of 2 years after study closure These documents should be retained for a longer period, however, if required by local regulations. Study records will be maintained at:

UNIVERSITY RECORDS CENTER
4015 Walnut Street, Mezzanine
Philadelphia, PA 19104
(215) 898-9432
https://archives.upenn.edu/archives-info/other-archives

10.1.8 Protocol Deviations

The PI and the study team should document all scenarios where the protocol is not followed and provide, in particular:

- Who deviated from the protocol
- What was the deviation
- When did the deviation occur
- How did the deviation happen
- What is the impact of the deviation
- A root cause analysis of why the deviation occurred

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact:

- having the potential to adversely affect subject safety; OR
- increases risks to participants; OR
- adversely affects the integrity of the data; OR
- violates the rights and welfare of participants, OR
- affects the subject's willingness to participate in research.
- there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

10.1.9 Publication and Data Sharing Policy

This study will comply with the data sharing agreement.

The Sponsor must approve all sharing of information/data prior to its occurrence.

10.1.10 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 Additional Considerations

Not applicable

10.3 Protocol Amendment History

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the PI and with approval from Amgen. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the investigator must await approval before implementing the changes.

If in the judgment of, the sponsor, the IRB/IEC, and/or the investigator, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the subject and/or has an impact on the subject's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for subjects enrolled in the study before continued participation.

11 REFERENCES

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12 APPENDIX

Procedures	Screening Visit Study Visit 1 Day -7 to 1[1]	Baseline/Enrollment Visit Study Visit 2 Day 1	Week 4 Study Visit 3 Week 4 ± 7 days[2]	Week 12 Study Visit 4 Week 12 ± 7 days	Week 24 Study Visit 5 Week 24 ± 7 days	Week 36 Study Visit 6 Week 36 ± 7 days	Unscheduled Visit (for flares or safety/AE concerns)[2]
Informed consent	X						
Demographics	X						
Medical history and update	X	X	X	X	X	X	X
Prior/Concomitant Meds	X	X	X	X	X	X	X
Administer study intervention and study diary		X					
Review study diary and re-educate subject[3]			X	X	X	X	X
Physician Global Assessment		X		X	X	X	X
Pemphigus Disease Area Index (PDAI)		X		X	X	X	X
ABQOL		X		X	X	X	X
Skindex-16		X		X	X	X	X

Patient Global Assessment		X		X	X	X	X
PHQ-4	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X
Height	X						
Weight	X	X	X	X	X	X	X
Urine Pregnancy test (if applicable)	X	X	X	X	X	X	X
Complete Blood Count	X	X	X	X	X	X	X
Chemistry Panel	X	X	X	X	X	X	X
AE Review			X	X	X	X	X

1 Screening Visit may happen on the same day as Baseline Visit if subject satisfies all Eligibility Criteria to include recent Complete Blood Count and Chemistry Panel within 30 days of the visit. A negative pregnancy test (as applicable) must be obtained same day as study visit and confirmed by PI prior to subject initiating treatment with apremilast.

2 Visit may be conducted remotely. Subject should present to a clinical laboratory of choice ±7 days of the study visit to undergo necessary safety labs. Subject should send an electronic copy of their study diary, if possible, to the study team for review. Study team must review treatment adherence and re-educate subject if they report missing any doses. If the study visit is conducted in person, physical exam and vitals should be collected as with routine care. If the study visit is completed remotely, subjects will be queried to provide any data they can (for example, if they have a scale at home and can report a current weight).

3 Study diary should be reviewed at every study visit and, at a minimum, personally signed and dated by the subject and PI or designee. Study team will collect previous diary at Weeks 12, 24, and 36, and administer new diaries to last 12 weeks until next routine visit. Photocopies should be provided to study subjects who wish to retain for their records.

4 The Investigator will conduct a dermatology-specific physical exam only, unless a physical examination of other body systems is indicated based upon subject-reported concerns, AEs, or Investigator discretion.