

Apremilast for Erythema Multiforme (AEM)

ClinicalTrials.gov ID NCT05875714

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**UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
INFORMED CONSENT AND HIPAA AUTHORIZATION FORM**

Protocol Title: Apremilast for the treatment of refractory erythema multiforme

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Research Study Summary for Potential Subjects

You are being invited to participate in a research study. Your participation is voluntary, and you should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at (215) 898-2614 for assistance.

The research study is being conducted to help physicians understand if apremilast, an oral medication, is effective in treating recurrent oral, genital, or cutaneous erythema multiforme (EM).

If you agree to join the study, you will be asked to complete the following research procedures at the screening visit: Physical exam which includes height, weight, vital signs, and a urine pregnancy test (if indicated). A medical history will also be obtained. In addition to the screening visit, you will complete four research study visits at weeks 0, 4, 12, 24, and 36. You will be asked to complete quality of life questionnaires at each visit and maintain a study diary each day at home during the course of this study. Your participation will last for 36 weeks.

Your recurrent erythema multiforme may or may not improve on apremilast. The most common risks of participation are diarrhea, nausea (feeling like you need to throw up), and vomiting (throwing up), all of which may be severe. Depression (feeling sad/loss of interest) has also been reported with the use of apremilast.

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the

full information with you. You are free to decline or stop participation at any time during or after the initial consenting process.

Amgen is a supporter of this study and will provide the study medication which is supplied at no cost to the study participant.

Why am I being asked to volunteer?

You are being invited to participate in a research study because you likely have recurrent erythema multiforme (EM) that has not resolved with traditional treatments.

Your doctor may be an investigator in this research study. You do not have to participate in any research study offered by your doctor. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. You may also decide to discuss the study with your family, friends, or family doctor. Being in a research study is different from being a patient. As an investigator, your doctor is interested both in your clinical welfare and in the conduct of this study.

If you decide to participate, you will be asked to sign this form.

What is the purpose of this research study?

The aim of this study is to assess the efficacy of apremilast in decreasing the number and severity of flares of erythema multiforme in patients with recurrent disease. Apremilast is a medication approved for use in psoriasis, psoriatic arthritis, and Behcet's disease but it has not been studied in erythema multiforme and thus is under investigation (experimental) for the treatment of your disease.

How long will I be in the study?

Once deemed eligible at screening visit, your participation will last for approximately 36 weeks and include 5 study visits in addition to the screening visit.

What am I being asked to do?

You are being asked to take an oral medication called apremilast to potentially treat your recurrent erythema multiforme.

Medication will be taken by mouth as follows:

- 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 thereafter

As a participant, you are expected to come to four clinical visits (weeks 0, 4, 12, 24, 36) and keep a daily treatment diary documenting medication administration and the progress of your EM.

Schedule of Events

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 \pm 7 days ²	Week 12 Study Visit 4 Week 12 \pm 7 days	Week 24 Study Visit 5 Week 24 \pm 7 days	Week 36 Study Visit 6 Week 36 \pm 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 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	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.

What are the possible risks or discomforts?

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 have other side effects or an allergic reaction that has not been seen before.

As of 20 March 2022, about 10038 patients have received apremilast in research studies. Since it was first approved for sale in March 2014, about 846,059 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) and headache (head might hurt), 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 and Migraine, Difficulty sleeping, Depression (feeling sad/loss of interest), 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 have low blood pressure, you may be at a higher risk of complications. If you have severe diarrhea, nausea, or vomiting, please tell your study doctor immediately.

In clinical studies, weight loss has been observed. 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 medication, 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.

What are the risks of using apremilast in combination with other drugs?

Tell the study doctor or the study staff about any drugs you are taking, have recently taken, or are planning to take, including herbal remedies, supplements, and drugs you take without a prescription. While Amgen does not know the side effects of using apremilast in combination with all drugs, Amgen does know drug that affect metabolism of other drugs, such as rifampin, may affect how apremilast works. Please discuss any concerns you may have with the study doctor.

Reproductive Risks

Because of the effects of this drug, there could be serious harm to unborn children or children who are breast-feeding. These effects could also harm the mother. It is also possible that harmful side effects that are not yet known could happen to both the mother and unborn or breast-feeding child. .

Apremilast has been found to cause abnormal fetal development in animals. Pregnant women, breastfeeding women and women planning to become pregnant should not participate in this study. If you or your partner become pregnant during this study, potential risks could include the loss of the pregnancy (a miscarriage) or birth defects. Please notify the study doctor if you become pregnant, or breastfeed, or father a child while you are taking *apremilast* because further information may be asked of you (the study doctor will discuss the details with you).

It is not known if apremilast is harmful to an unborn or breastfed baby. Apremilast should not be administered to pregnant or nursing women. Available data with apremilast use in pregnant women have not established a drug associated risk of major birth defects, loss of pregnancy or adverse maternal or fetal outcomes, but these data are extremely limited.

More loss of pregnancy were seen in mice and monkeys when apremilast was given at high doses. Also, baby mice from mothers that were treated with apremilast weighed less than normal baby mice.

If you are a person of childbearing potential who engages in sexual activity which could result in conception, please note:

If you are pregnant, planning to become pregnant, or you are nursing a baby, you cannot be in this study. If you are able to become pregnant, the study doctor will discuss with you the options for, as well as the correct and consistent use of, effective birth control methods in order to successfully prevent pregnancy during this study. Your chosen form of birth control must be effective by the time you receive your first dose of study drug. For example, birth control pills should be started at least 28 days before your first dose of study drug. If you are able to become pregnant, you must refrain from any sexual activity that may result in pregnancy or if you engage in activity that could result in pregnancy, you must use one of the approved options for birth control while taking the study drug and for at least 28 days after your last dose of study drug. Approved options for birth control are:

Any one of the following highly effective methods:

Hormonal contraception (for example, birth control pills, intravaginal ring, transdermal patch, injection, implant); intrauterine device (IUD); tubal ligation (tying your tubes); or a partner with a vasectomy. Certain drugs may reduce the effectiveness of hormonal contraceptives during and up to one month after discontinuation of these concomitant therapies. Please talk to your doctor for further information about contraceptives.

OR

Double barrier method: External or internal condom PLUS one of the following additional barrier methods: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.

If at any time during the study your birth control method changes, or you have a problem with your current birth control method, or your ability to become pregnant changes (for example, you have an IUD removed, accidentally miss taking any of your birth control pills, or enter menopause), you must inform the study doctor and have a discussion with the study doctor or study nurse about an alternative birth control method.

If you suspect that you have become pregnant during the study or within 28 days of the last dose of study drug, you must tell the study doctor right away. Your study doctor must then require that you stop taking the study drug and will want to check on you during the pregnancy and ask you questions about the pregnancy. If you become pregnant during the study, we will ask permission to collect information on the outcome of your pregnancy including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, abnormalities, or complications, and the health status of your child. A subject pregnancy consent form will be obtained to allow us to collect this information.

Male Participants

Male participants are not required to use birth control during treatment with apremilast. However, you should let your female partner know you are in this study.

If your partner is pregnant when you begin this study or becomes pregnant during treatment and for an additional 28 days after stopping apremilast, you must tell the study doctor or the study staff as soon as possible.

The study doctor will tell Amgen of the pregnancy and ask to obtain information on the pregnancy outcome for both the mother and baby.

Although male participants are not required to use contraception during treatment with apremilast, Amgen would like to collect pregnancy information when a female partner of a male participant in the study gets pregnant. Information will only be collected after Amgen obtains voluntary consent from you and your partner. Collection of such data will contribute to the body of knowledge that could ultimately help patients and their healthcare providers (HCPs) make more informed decisions about taking apremilast during pregnancy.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will tell you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You may not get any benefit from being in this research study.

It is possible others with EM may benefit from this study if apremilast is an effective treatment for EM.

What other choices do I have if I do not participate?

Other treatments for oral, recurrent EM include continued suppressive dose Valtrex, topical and oral corticosteroids, and other immunosuppressive medications. Supportive

care with no additional disease-directed therapy has also been used. You may also discuss alternatives with your personal physician.

Will I be paid for being in this study?

There is no compensation for your participation in this study.

Will I have to pay for anything?

You will not need to pay any additional fees beyond that which you typically pay for the care you receive at Penn Dermatology. The study medication, apremilast, will be covered by Amgen.

You are still responsible for any deductibles or applicable co-pays for routine office visits, scans and blood work. Please talk to your doctor and study team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance.

Will I receive the results of research testing?

No research testing will be done and so there will be no results to return.

What happens if I am injured from being in the study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed on page one of this consent form.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This will take about 15 months from the start of the study, although your participation will only last about 36 weeks. You may leave the study at any time. If you have medication side effects that are not tolerated you may wish to leave the study. This study may also be stopped at any time by your physician, Amgen, or the Food and Drug Administration (FDA) without your consent because:

- The Primary Investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- Amgen, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study.

If you decide to participate, you are free to leave the study at any time by contacting the research team or doctor by phone or mail. Withdrawal will not interfere with your future care.

How will my personal information be protected during the study?

We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Institutional Review Board (IRB) at the University of Pennsylvania will have access to your records. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records.

Your 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.

Consent will be obtained prior to any data collection. To ensure that all information is kept confidential, all study personnel will maintain patient confidentiality. All necessary measures will be implemented to safeguard the PHI (Protected Health Information) from unauthorized use or disclosure. All identifying information will be destroyed after conclusion and publication of the study results.

Will information about this study be available to the public?

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you.

At most, the website will include a summary of the results. You can search this website at any time.

What may happen to my information collected on this study?

Your records will be collected but we will be able to identify you so we can track you over time by chart review matched up with your treatment diary. Information will be used by researchers in the study and used for publications.

There is a risk of breach of confidentiality (unintentional release of your information). We will do our best to make sure that this doesn't happen. However, we cannot guarantee total privacy. We will protect your confidentiality during storage and sharing by only allowing approved research team members access to your data.

If you have questions about the storage of your information, or have changed your mind, you can contact Joshua Bryer, BA at 215-662-6597 or 267-251-6819. If you change your mind, we will stop all research and remove you from our research tracking list. We will destroy any previously recorded patient data.

What information about me may be collected, used or shared with others?

- Name
- Medical record number
- Dates, such as date of birth, medical events, and follow-up
- Information in your medical record

- Results from physical examinations, tests, or procedures

Why is my information being used?

Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right
- to evaluate and manage research functions.

Who may use and share information about me?

The following individuals may use or share your information for this research study:

- The investigator for the study and the study team
- Other authorized personnel at Penn, including offices that support research operations
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of the School of Medicine, might receive my information?

- All members of the research team
- Amgen as study supporter

Oversight organizations

- The U. S. Office of Human Research Protections (OHRP)

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

By signing this document, you are permitting the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

Future Use of Data

Your information will not be stored or shared for future research purposes.

Electronic Medical Records and Research Results**What is an Electronic Medical Record and/or a Clinical Trial Management System?**

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any information produced from your participation in this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Information related to your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR or in the CTMS, your information may be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. Health Insurance Company, disability provider, etc.).

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the IRB at the number on page one of this form.

When you sign this form, you are agreeing to take part in this research study. This means that you have read this combined consent and HIPAA authorization form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

Name of Subject (Please Print)

Signature of Subject

Date

Name of Person Obtaining Consent
(Please Print)

Signature

Date