STUDY PROTOCOL

Protocol Title	**Use of Apremilast in Patients Who Are Dissatisfied with Stable Maintenance Topical Therapy**
Protocol Number	**APR-2015**
Protocol Date	**June 20, 2016**
Investigator/Sponsor	**Leon Kircik, MD** **DermResearch, PLLC** **1169 Eastern Parkway, Suite 2310** **Louisville, KY 40217**

PROTOCOL SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the supplements, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and ICH-GCP guidelines.

Investigator

Printed Name	Signature	Date

† A female of childbearing potential is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months). [§] The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).

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STUDY RATIONALE & OBJECTIVE

Psoriasis vulgaris is a chronic inflammatory immunologic disorder which manifests primarily in the skin. It is characterized by sharply demarcated areas of affected skin which appear thickened, red, and scaly. The scalp, elbows, knees, lower back, hands, and feet are commonly affected sites. About 80% of affected patients complain of pruritus (Gottlieb, 1998). The psoriatic appearance of the skin is initiated by an antigen presenting cell (APC) – T-cell interaction leading to the release of multiple inflammatory cytokines (Nestle, 2009). Psoriasis is a chronic disease that requires long-term treatment, ideally with effective agents that offer convenient dosing and a low incidence of adverse events. The American Academy of Dermatology recommends use of topical treatments for patients with localized disease and recognizes that the systemic options for patients with more severe psoriasis are limited by potential risks of organ toxicities and immunosuppression (Menter, 2008). The use of topical steroids in moderate plaque-type psoriasis patients has been traditionally the mainstream treatment. However, most patients continue receiving the same treatment despite lack of efficacy and patient satisfaction. Therefore, a systemic treatment with a favorable safety profile and no monitoring requirement is an unmet need in those patients.

The use of apremilast in these patients will attempt to fulfill this need. Apremilast (CC-10004) is a specific phosphodiesterase type 4 (PDE4) inhibitor for use in the treatment of inflammatory conditions. PDE4 is one of the major phosphodiesterases expressed in leukocytes. PDE4 inhibition by apremilast elevates cyclic adenosine monophosphate (cAMP) levels in immune cells, which in turn down-regulates the inflammatory response by reducing the expression of pro-inflammatory mediators such as TNF-α, IL-23, IL-17, and other inflammatory cytokines, and increasing the production of anti-inflammatory mediators. In completed Phase 3 studies in subjects with moderate to severe plaque psoriasis and active psoriatic arthritis, treatment with apremilast was associated with statistically significant and clinically meaningful improvements in multiple efficacy measures. On the basis of these studies, apremilast (OTEZLA®) is approved within the United States for both moderate to severe plaque psoriasis and active psoriatic arthritis.

We propose to study plaque psoriasis patients who have previously used either high potency topical steroids for 2 weeks or mid potency topical steroids for 4 weeks and did not respond and failed the treatment. The purpose of this study is to reflect real life experience of patients with moderate plaque type psoriasis who don't respond to topical steroids and therefore we will not be using any control.

STUDY DESIGN

This is an open label, 16-week study of apremilast in combination with topical steroids with a 4 week safety follow up off treatment. 20 qualified subjects will be enrolled. Visits will consist of baseline, 8 weeks, and 16 weeks. Assessments will include sPGA, PASI, BSA, DLQI, pruritis, and patient satisfaction questionnaire. There will be a screening visit, baseline, week 4, week 8 visits. There will be an end of treatment visit at week 16 and there will be a follow up at week 20. Please see attached schedule of events for further details.

Primary and Secondary Objectives:

Primary Efficacy
Mean change and percent change in product of BSA (%) x sPGA (sPGA based on NPF psoriasis 6-point scale) at wk 16 compared to baseline

Secondary Efficacy
Mean percent change in product of BSA (%) x sPGA at wk 8 compared to baseline
Mean change in DLQI at wk 8 compared to baseline
Mean change in pruritis at wks 8 and 16 compared to baseline
Mean change in DLQI at wk 16 compared to baseline

Mean change and percent change in BSA (%) at wk 8 and wk 16 compared to baseline
Proportion of patients who achieve PASI 50 at wk 8 and wk 16
Proportion of patients who achieve PASI 75 at wk 8 and wk 16
Percent of patients achieving 0 (clear) or 1 (almost clear) on patient global assessment scale at wk 8 and wk16
Reduction of topical use
Satisfaction (TSQM, v2) at wk4, 8 and 16

Exploratory Objective:
The study will seek to obtain in vitro evidence that a PDE7A inhibitor (or combination) can inhibit cytokine secretion in blood from patients being actively treated with apremilast and determine how this inhibitory effect changes over length of treatment and across analytes.

Subject Characteristics
Subjects with moderate plaque-type psoriasis who are uncontrolled or dissatisfied on topical therapy (either 2 weeks use of high potency topical steroids or 4 weeks use of mid potency topical steroids) within the 6 months. "Uncontrolled" on topical therapy is defined as lack of efficacy per treating physician discretion and/or lack of patient-reported satisfaction on topical treatment.
Total number of subject is 20.

SELECTION AND WITHDRAWAL OF SUBJECTS

Inclusion Criteria

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

1. Must be in general good health (except for disease under study) as judged by the Investigator, based on medical history, physical examination, clinical laboratories, and urinalysis. (NOTE: The definition of good health means a subject does not have uncontrolled significant co-morbid conditions).

2. Females of childbearing potential (FCBP)† 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, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive§ options described below:
   Option 1: Any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy;
   OR
   Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]; PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.

   Male subjects (including those who have had a vasectomy) who engage in activity in which conception is possible must use barrier contraception (male latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on investigational product and for at least 28 days after the last dose of investigational product.

3. 18 years of age or older
4. Understand and voluntarily sign ICF
5. Able to adhere to study visit schedule
6. Moderate plaque-type psoriasis (PGA=3)
7. BSA = 5-10% OR DLQI = 7 or more
8. History of uncontrolled plaque psoriasis after either stable dose of 2 weeks of high potency topical steroid or 4 weeks of mid potency topical steroid use within the last 6 months. "Uncontrolled" is defined as lack of efficacy per treating physician discretion and/or lack patient reported satisfaction on stable dose of topical treatment.

† A female of childbearing potential is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (that is, has had menses at any time during the preceding 24 consecutive months). § The female subject's chosen form of contraception must be effective by the time the female subject is randomized into the study (for example, hormonal contraception should be initiated at least 28 days before randomization).

Exclusion Criteria

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

1. Other than psoriasis, 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 he/she were to participate in the study.
3. Prior history of 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. Pregnant or breast feeding. FCBP who are not willing to use acceptable birth control methods
5. Active substance abuse or a history of substance abuse within 6 months prior to Screening.
6. Malignancy or history of malignancy, except for:
   a. treated [i.e., cured] basal cell or squamous cell in situ skin carcinomas;
   b. treated [i.e., cured] cervical intraepithelial neoplasia (CIN) or carcinoma in situ of cervix with no evidence of recurrence within the previous 5 years.
7. Washout for restricted treatment:
   a. Topical immunomodulators, topical vitamin D derivatives, tar, salicylic acid, anthralin or any other topical treatment for psoriasis except topical corticosteroids that they are already using within 2 weeks of baseline.
   b. Use of any biologics within 5 Half-lives of baseline and Ustekinumab use within 6 months
   c. Use of other systemic psoriasis treatments (ie, oral retinoids, methotrexate, cyclosporine, or other immunomodulators) within 4 weeks of baseline.
   d. Use of UVB or PUVA within 2 weeks of baseline.
   e. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half lives, if known (see washout Appendix F) (whichever is longer).
8. Known or suspected allergy to investigational product
9. Other types of psoriasis
10. Prior history of depression
11. Prior use of apremilast

Withdrawal of Subjects

It is the right and duty of the Investigator to discontinue the study participation of a subject when the subject's health or well-being is threatened by continuation in the study. Such subjects should be withdrawn from the study and not continued under a modified regimen. The following are circumstances that would result in the subject's discontinuation from the study:

- the subject experiences a serious adverse event rendering them unable to continue study participation;
- the subject is unable to physically or mentally tolerate the use of the test medication;
- an exclusion criterion becomes apparent at any time during the study; or
- the subject voluntarily withdraws.

In the event of premature discontinuation from the study, the Investigator should determine the primary reason for discontinuation.

TREATMENT OF SUBJECTS AND FOLLOW-UP

Study Procedures

Table 1. Assessment Schedule

Assessment	Screening -30days to -1 days	Baseline DAY 0	Wk 4	Wk 8	Wk 16 EOT	Wk 20 FU
Written informed consent	X					
Medical history	X					
Demographics	X					
Physical exam	X	X			X	X
Prior Disease therapies	X					
Vital signs with Weight	X	X	X	X	X	X
Height	X					
Urine pregnancy	X	X	X	X	X	X
CBC, Chemistry (screening, baseline, week 16, week 20) Assays for cytokines (baseline, week 8, week 16)	X	X		X	X	X
Review inclusion/exclusion	X	X				
Complete skin exam %BSA	X	X	X	X	X	
Static Physician global assessment (sPGA 0-5)	X	X	X	X	X	
PASI	X	X	X	X	X	
Patient Global Assessement (ptGA 0-4)		X	X	X	X	
Patient Satisfaction Survey TSQM v2	X	X	X	X	X	X
Subject assessment of pruritus (0-10 NRS)	X	X	X	X	X	
DLQI	X	X	X	X	X	
Study drug – D – dispense C – collect W – weigh topical corticosteroid	W	D W	C D W	C D W	C W	
Adverse events	X	X	X	X	X	X
Concomitant meds including TCS	X	X	X	X	X	X
Prior and concomitant procedures	X	X	X	X	X	X

Screening Visit

- Informed Consent/HIPAA
- Urine Pregnancy Test (if applicable)
- Subject Demographics/Medical History
- Concomitant Medication/Treatment
- Prior and concomitant procedures
- Inclusion/Exclusion Criteria
- Assessments
  - BSA (Affected Body Surface Area)

  - sPGA
  - PASI
- Physical Exam
- Prior disease therapies
- Vital signs with height and weight
- Adverse events
- CBC and chemistry
- Patient satisfaction survey
- Subject assessment of pruritus
- DLQI
- Weigh TCS (topical corticosteroid)

Baseline

- Urine Pregnancy Test (if applicable)
- Concomitant Medication/Treatment
- Prior and concomitant procedures
- Inclusion/Exclusion Criteria
- Assessments
  - BSA (Affected Body Surface Area)
  - sPGA
  - PASI
- Physical Exam
- Vital signs with weight
- Adverse events
- CBC and chemistry and assays for cytokines with 10-20ml whole blood in heparinized tubes
- Patient satisfaction survey
- Subject assessment of pruritus
- DLQI
- Dispense study drug
- Patient Global Assessment (Appendix H)
- Weigh TCS

Week 4

- Urine Pregnancy Test (if applicable)
- Concomitant Medication/Treatment
- Prior and concomitant procedures
- Assessments
  - BSA (Affected Body Surface Area)
  - sPGA
  - PASI
- Vital signs with weight
- Adverse events
- Patient satisfaction survey
- Subject assessment of pruritus
- DLQI
- Dispense study drug
- Collect study drug

- Patient Global Assessment
- Record TCS usage and weigh TCS

Week 8

- Urine Pregnancy Test (if applicable)
- Concomitant Medication/Treatment
- Prior and concomitant procedures
- Inclusion/Exclusion Criteria
- Assessments
  - BSA (Affected Body Surface Area)
  - sPGA
  - PASI
- Physical Exam
- Vital signs with weight
- Adverse events
- assays for cytokines with 10-20ml whole blood in heparinized tubes
- Patient satisfaction survey
- Subject assessment of pruritus
- DLQI
- Dispense study drug
- Collect study drug
- Patient Global Assessment
- Record TCS usage and weigh TCS

Week 16 / End of treatment

- Urine Pregnancy Test (if applicable)
- Physical Exam
- Concomitant Medication/Treatment
- Prior and concomitant procedures
- Inclusion/Exclusion Criteria
- Assessments
  - BSA (Affected Body Surface Area)
  - sPGA
  - PASI
- Physical Exam
- Vital signs with weight
- Adverse events
- CBC and chemistry and assays for cytokines with 10-20ml whole blood in heparinized tubes
- Patient satisfaction survey
- Subject assessment of pruritus
- DLQI
- Collect study drug
- Patient Global Assessment
- Record TCS usage and weigh TCS

Week 20 / Follow up

- Urine Pregnancy Test (if applicable)
- Physical Exam
- Concomitant Medication/Treatment
- Prior and concomitant procedures
- Inclusion/Exclusion Criteria
- Physical Exam
- Vital signs with weight
- Adverse events
- CBC and chemistry

Patient satisfaction survey

Study Procedures

Details of Study Treatment

Apremilast dosed as per label for 16 weeks and a 4 week follow up period after treatment. Total study period is 20 weeks. TCS will be used up to week 4 as per label and then patients will be using on as needed basis until week 16. The usage of TCS will be recorded and tubes will be weighed.

Optional whole blood samples will be obtained with consent from patients participating in this study. See Appendix G for blood sample collection and processing.

Treatment Assignment

The study medication will be administered only to subjects included in this study following the procedures set out in the Study Protocol. All subjects who have signed an ICF will receive a 2-digit subject number, starting at 01. This subject number will be used to identify the subject throughout the study at that particular study site. Therefore, TANs (Treatment Assignment Number) are not the same a subject numbers.

Subjects withdrawn from the study will retain their subject number and their TAN, if already allocated. New subjects will be allotted a new subject number and, if qualified for entry, a new TAN.

Packaging, and Labelling

Study medication will be provided to the study site in bulk. Study treatments will be provided to subjects. The Study Nurse will write, with indelible ink, the Subject TAN and initials on all items dispensed to the subject.

Supplies and Accountability

The Investigator or study coordinator will inventory and acknowledge receipt of all shipments of study medication. All study medication must be kept in a locked area with access restricted to designated study personnel. The study medication must be stored in accordance with the instructions provided with the shipment. The investigator or study coordinator will also keep accurate records of the quantities of study medication dispensed and returned by each subject.

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 females of childbearing potential (FCBP) must use one of the approved contraceptive options as described in section 2.3 while on investigational product and for at least 28 days after administration of the last dose of the investigational product.

When a female 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.

Treatment Compliance

Subject compliance to study treatment regimen will be assessed at each visit; study personnel will ask each subject whether they missed any doses of study medication since the previous visit.

Concomitant Medication/Treatment

Subjects must comply with the restrictions based on prohibited medications and treatments as detailed in the exclusion criteria. Other necessary therapies that will not interfere with the response to treatment may be provided at the discretion of the Investigator. The use of any concurrent medication, including topical steroids and any other prescription or over-the-counter drug, is to be recorded in the CRF along with the reason the medication was taken.

ASSESSMENTS OF EFFICACY

Affected Body Surface Area Assessment (BSA)

The area of body affected by psoriasis will be estimated as a percentage of the subject"s total body surface area. As means to standardize measurements, the area of the subject's palm will be considered as 1% of total BSA. Static Physician Global Assessment (sPGA) (based on NPF psoriasis 6 point scale) – see Appendix A

The Investigator will grade the current severity of psoriasis as per sPGA

Psoriasis Severity and Area Index (PASI) & Body Surface Area (BSA)– see Appendix B
Mean percent change in product of BSA X SPGA – to be calculated

Subject Assessments (To be completed prior to Investigator Assessments)

1. Subject assessment of pruritus on visual analog scale (VAS) see Appendix C
2. DLQI – see Appendix D
3. Patient satisfaction survey – see Appendix E

ASSESSMENTS OF SAFETY

Adverse Event

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a 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 From 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. (30 days after the last dose of study medication or any time after that if the PI feels it was related to the study drug.)
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.

Serious adverse event

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.
Classification of severity
For both AEs and SAEs, the investigator(s) must assess the severity of the event. The AEs will be evaluated for severity according to the following scale:
Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Classification of Relationship/Causality of adverse events (SAE/AE) to study drug
The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

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

Immediate reporting of serious adverse events

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 Celgene Safety by facsimile. A written report (prepared by the Investigator(s) using an SAE Report Form or a 3500A Medwatch form is to be faxed to Safety (see below for contact information).
Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

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 Celgene as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form or Medwatch form and sent to Celgene.
The Investigator(s) is responsible for informing the Institutional Review Board/Ethics Committee (IRB/IEC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator(s) must keep copies of all SAE information, including correspondence with Celgene and the IRB/IEC, on file. All SAEs that have not resolved upon discontinuation of the 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).

Pregnancies

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 Celgene Safety immediately by facsimile, using the Pregnancy Report form provided by Celgene.

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

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

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

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

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

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

Overdose

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

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

In the event of an overdose, the 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 tablets in any 24 hour period whether by accident or

intentionally.

STATISTICS

Descriptive statistics will be reported for primary and secondary endpoints.
Since this will reflect real life situation, we will not be using comparator or placebo control.

Analyses

Statistical analyses will be conducted on an intent-to-treat population that includes all subjects who were enrolled and received study medication. All statistical tests will be two-sided and interpreted at a 5% significance level. Descriptive statistics (i.e., mean, standard deviation, etc.) will be provided for all continuous variables and frequencies for all categorical variables collected in this study. Summary tables will be used to present patient population characteristics at Baseline; data from the study questionnaires will be included. Analyses of study treatment will be performed using an ANCOVA technique with the Baseline value as the covariate provided the necessary assumptions for parametric tests are satisfied. The Wilcoxon Rank-Sum test will be used if the necessary assumptions for parametric tests are not satisfied. Mean scores will also be analyzed. Safety analyses will be performed in terms of incidence and severity of local tolerance signs and symptoms and adverse and/or unexpected events.

RESPONSIBILITIES OF THE INVESTIGATOR

Good Clinical Practice

Investigators must adhere to the procedures outlined in this Study Protocol. The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abides by GCP as described in the ICH Guidelines Topic E6: "Guideline for Good Clinical Practice." Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. The study will also be carried out in keeping with local legal and regulatory requirements.

Ethics

The appropriate IRB must review the Study Protocol and Informed Consent Form prior to initiating the study. Any significant modifications to the IRB-approved protocol or informed consent must be made in consultation with the IRB.

Confidentiality of Subjects

Any information that identifies subjects with respect to this research study will be kept confidential. However, records identifying the subject may be inspected by representatives of the IRB, Celgene Corporation (the funding partner) and/or the FDA. Subjects' identity will remain strictly confidential during all record reviews, as well as in any publication that may result from this research. Subjects will be identified by study code only; their names will not be used.

Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Appropriate discussion of risks

and possible benefits of this therapy will be provided to the subjects. Consent forms describing in detail the study interventions/products, study procedures and risks will be given to the subject and written documentation of informed consent is required prior to starting intervention/administration study product.

Consent forms will be IRB approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. The subjects will sign the informed consent document prior to any procedures being done specifically for the study. The subjects should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects 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.

Data Handling and Record Keeping

Investigators must ensure that proper source documentation for all study activities are diligently maintained and securely kept. Investigators will transfer all relevant data from source documents to the Case Report Form as stipulated in this Study Protocol and his/her signature on the Case Report Form guarantees completeness and integrity of these data. Investigators will maintain reliable study device dispensing/dosing records and will store study supplies in a secure, locked location. In addition, Investigators will ensure that all study-related source documentation and Case Report Forms will be maintained for a period of two years after the conclusion of the study.

Direct Access to Source Data/Documents

Investigators must ensure that the Informed Consent Form clearly permit study-related monitoring, audits, IRB review, and regulatory inspections providing direct access to source data and documents.

References

Atkinson MJ, Kumar R, Cappelleri JC, Hass SL. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. Value Health 2005;8 Suppl 1:S9-S24.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19(3):210-6.

Walsh JA, McFadden M, Woodcock J, Clegg DO, Helliwell P, Dommasch E, et al. Product of the Physician Global Assessment and body surface area: a simple static measure of psoriasis severity in a longitudinal cohort. J Am Acad Dermatol 2013;69(6):931-7.

Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008;58(5):826-50.

Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009;361(5):496-509.

Gottlieb AB. Psoriasis – Enhanced epidermal differentiation and reduced cell-mediated inflammation are unexpected outcomes. Dis Manag Clin Outcomes 1998;1(6):195-202.

Appendix A: Static PHYSICIANS GLOBAL ASSESSMENT
PSORIASIS

___ 0. Clear: no signs of psoriasis (Hyper/hypopigmentation changes alone are acceptable). Plaque elevation = 0. Scaling = 0. Erythema = +/- (hyperpigmentation, pigmented macules, diffuse faint pink or red coloration).

___ 1. Almost Clear: Plaque elevation = +/- (possible but difficult to ascertain whether there is slight elevation above normal skin). Scaling = +/- (surface dryness with some white discoloration). Erythema = up to moderate (up to definite red coloration).

___ 2. Mild: Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped). Scaling = fine (fine scale partially or mostly covering lesions). Erythema = up to moderate (up to definite red coloration).

___ 3. Moderate: Plaque elevation = moderate (moderate elevation with rough or sloped edges). Scaling = coarse (coarse scale covering most or all of the lesions). Erythema = moderate (definite red coloration).

___ 4.Severe: Plaque elevation = marked (marked elevation typically with hard or sharp edges). Scaling = coarse (coarse, nontenacious scale predominates, covering most of all lesions). Erythema = severe (very bright red coloration).

___ 5. Very Severe: Plaque elevation = very marked (very marked elevation typically with hard, sharp edges). Scaling = very coarse (coarse, thick, tenacious scale over most of all lesions; rough surface). Erythema = very severe (extreme red coloration; dusky to deep red coloration).

Source: Walsh, 2013.

Appendix B:PSORIATIC BODY SURFACE AREA

BODY AREA	% of BODY AREA AFFECTED	% of TOTAL BODY SURFACE AREA	% of TOTAL BODY SURFACE AFFECTED
HEAD		10%	
TRUNK		30%	
UPPER LIMBS		20%	
LOWER LIMBS		40%	
TOTAL	----------	100%	

Appendix B: PSORIASIS AREA SEVERITY INDEX (PASI)

Row		Head	Trunk	Upper Limbs	Lower Limbs
1	Erythema*				
2	Thickness*				
3	Scaling*				
4	Total each column				
5	Degree of Involvement**				
6	Multiply Row 4 by Row 5				
7		x 0.10	x 0.30	x 0.20	x 0.40
8	Multiply Row 6 By Row 7				

*Rank severity of psoriatic lesions:
- **0** = none
- **1** = slight
- **2** = moderate
- **3** = severe
- **4** = very severe

**Rank area of psoriatic involvement:
- **0** = none
- **1** = <10%
- **2** = 10% to <30%
- **3** = 30% to <50%
- **4** = 50% to <70%
- **5** = 70% to <90%
- **6** = 90% to 100%

Appendix C: Subject Assessments of Pruritis (itching)

Subjects will be instructed to assess the level of the indicated symptom over the previous 24-hour period using the following scale:

Rate the severity of pruritis (itching)

None — Unbearable

0 1 2 3 4 5 6 7 8 9 10

CIRCLE A NUMBER

Appendix D: Dermatology Life Quality Index (DLQI)

Score:

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

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

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

Please check you have answered EVERY question. Thank you.

Source: Finlay, 1994.

Appendix E:

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it.* For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

□1 Extremely Dissatisfied □3 Dissatisfied □5 Satisfied □7 Extremely Satisfied
□2 Very Dissatisfied □4 Somewhat Satisfied □6 Very Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

□1 Extremely Dissatisfied □3 Dissatisfied □5 Satisfied □7 Extremely Satisfied
□2 Very Dissatisfied □4 Somewhat Satisfied □6 Very Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

□1 Yes □0 No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (e.g., strength, energy levels)?

□1 A Great Deal □2 Quite a Bit □3 Somewhat □4 Minimally □5 Not at All

5. How dissatisfied are you by side effects that interfere with your mental function (e.g., ability to think clearly, stay awake)?

□1 A Great Deal □2 Quite a Bit □3 Somewhat □4 Minimally □5 Not at All

6. How dissatisfied are you by side effects that interfere with your mood or emotions (e.g., anxiety/fear, sadness, irritation/anger)?

□1 A Great Deal □2 Quite a Bit □3 Somewhat □4 Minimally □5 Not at All

7. How satisfied or dissatisfied are you with how easy the medication is to use?

□1 Extremely Dissatisfied □3 Dissatisfied □5 Satisfied □7 Extremely Satisfied
□2 Very Dissatisfied □4 Somewhat Satisfied □6 Very Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

□1 Extremely Dissatisfied □3 Dissatisfied □5 Satisfied □7 Extremely

Satisfied

□2 Very Dissatisfied □4 Somewhat Satisfied □6 Very Satisfied

9. How satisfied or dissatisfied are you by how often you are expected to use/take the medication?

□1 Extremely Dissatisfied □3 Dissatisfied □5 Satisfied □7 Extremely Satisfied
□2 Very Dissatisfied □4 Somewhat Satisfied □6 Very Satisfied

10. How satisfied are you that the good things about this medication outweigh the bad things?

□1 Extremely Dissatisfied □3 Dissatisfied □5 Satisfied □7 Extremely Satisfied
□2 Very Dissatisfied □4 Somewhat Satisfied □6 Very Satisfied

11. Taking all things into account, how satisfied or dissatisfied are you with this medication?

□1 Extremely Dissatisfied □3 Dissatisfied □5 Satisfied □7 Extremely Satisfied
□2 Very Dissatisfied □4 Somewhat Satisfied □6 Very Satisfied

Appendix F: Washout for Psoriasis Medications

a. Topical immunomodulators, topical vitamin D derivatives, tar, salicylic acid, anthralin or any other topical treatment for psoriasis except topical corticosteroids that they are already using within 2 weeks of baseline.
b. Use of any biologics within 5 Half-lives of baseline and Ustekinumab use within 6 months
c. Use of other systemic psoriasis treatments (ie, oral retinoids, methotrexate, cyclosporine, or other immunomodulators) within 4 weeks of baseline.
d. Use of UVB or PUVA within 2 weeks of baseline.
e. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half lives, if known (whichever is longer)

Appendix G: Exploratory Cytokine Assays
Whole blood samples will be obtained with consent from patients participating in the clinical trial. Drugs used will include PDE7A inhibitor(s) alone or in combination with apremilast. Assays will include measurement of inflammatory cytokines following stimulation with LPS or anti-CD3

Methods: please draw one or two 10 mL heparin tubes per patient per visit (B, 8, 12) and label each tube as follows:

Pt. number

Pt. initials

Date sample taken

Timepoint of sample (Baseline, Wk 8, Wk 12)

Please have a note in the box stating that the shipment is from Dr. Kircik's ITT.

Ship tubes At ambient temperature promptly via overnight (FED EX) courier to Celgene San Diego for testing in ex vivo assays. The site will contact to alert prior to shipping the samples to the below address.

Celgene San Diego
Attn: RJ Bates
10300 Campus Point Drive, Suite 100
San Diego, CA 92121
Ph: 858-795-4795
rbates@celgene.com

Work flow and brief description of whole blood assay: Whole blood samples from each patient, at each of the three clinical trial time points (baseline , week 8 and week 16) will be run immediately in the whole blood assay at Celgene labs

Compounds will be prepared, alone or as a combination, in triplicate as a 6-point dose, 1:3 dilution series starting at final concentration of 10uM. Whole–blood will be diluted 1:1 with warmed RPMI and pre-incubated with compounds for 1 hour in a tissue culture incubator. Compound-treated whole blood will then be transferred to a plate for stimulation with LPS or anti-CD3 and placed in tissue culture incubator for an additional 24 or 48 hours, repectively. The plates will then be spun down for 10 minutes, supernatant collected and frozen for later or transferred to directly to plates for analysis of specific cytokines including TNF-α, IFN-γ, IL-17 among others.

Outcomes: The study will seek to obtain in vitro evidence that a PDE7A inhibitor (or combination) can inhibit cytokine secretion in blood from patients being actively treated with

apremilast and determine how this inhibitory effect changes over length of treatment and across analytes. Because clinical assessments of disease will be collected throughout this study, it will be possible to compare these in vitro effects with clinical outcomes. Of note , inhibition of cytokine secretion does not always correlate with clinical efficacy.

Appendix H: Patient Global Assessment (PtGA)

Score	Category	Category Description
0	Clear	No psoriasis symptoms at all
1	Very mild	Very slight psoriasis symptoms, does not interfere with daily life
2	Mild	Slight psoriasis symptoms, interferes with daily life only occasionally
3	Moderate	Definite psoriasis symptoms, interferes with daily life frequently
4	Severe	Intense psoriasis symptoms, interferes or restricts daily life very frequently