An investigator initiated open label study evaluating the efficacy and tolerability of oral apremilast for the treatment of nail psoriasis

Study Protocol & Statistical Analysis Plan

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Sponsor: Investigator Initiated

Introduction:

Psoriasis vulgaris is a common inflammatory condition of the skin that results in scaly red itchy plaques. In addition to affecting the skin, psoriasis can also cause disease in the finger and toe nails. Nail psoriasis is a chronic disease and can present with the following clinical findings: splinter hemorrhage, leukonychia, red spots in the lunula, nail pitting, nail plate crumbling, hyperkeratosis, and/or nail plate separation from the nail bed. The most characteristic nail findings associated with nail psoriasis are nail pitting, onycholysis with a rim of erythema, and oil spots. Special interest will be paid to identifying these particular nail findings in patients, however all potential nail psoriasis symptoms will be assessed in patients in this study. Due to the highly visible nature of disease in the fingernails, nail psoriasis often results in a substantial deleterious effect on a patient's quality of life. Patients also can have significant pain and disability due to nail psoriasis.

Psoriasis patients who have nail involvement are known to have more severe psoriasis disease and diminished quality of life when compared to psoriasis patients without nail disease. Patients with nail psoriasis often also have psoriatic arthritis, and untreated psoriatic arthritis is known to lead to joint destruction with potentially severe morbidity. Nail psoriasis has a reported incidence of 80 to 90% (Jiaravuthiasan, *et al*). Because nail psoriasis causes a substantial disease burden for patients, it is critical that safe and effective treatments are found for this specific type of psoriasis. Unfortunately, nail psoriasis is often difficult to treat.

Apremilast is an orally available small molecule inhibitor of phosphodiesterase 4 (PDE4) that is FDA approved for the treatment of psoriasis and psoriatic arthritis. PDE4 is one of the main phosphdiesterases expressed in immune cells, and its inhibition by apremilast is thought to increase cyclic adenosine monophosphate and thereby decrease the

inflammatory response. Specifically, apremilast is believed to down regulate pro-inflammatory cytokines including TNF-α, IL-23, IL-17, and others.

Apremilast has shown promising results for treating psoriatic arthritis and nail disease; however more data is needed regarding its effect on nail psoriasis (Kavanaugh, *et al*). We hypothesize that apremilast will prove to be highly effective in treating nail psoriasis. We propose to conduct an open label clinical trial to investigate the efficacy and tolerability of apremilast in treating nail psoriasis, where we will follow the package insert guidelines for treating patients with apremilast.

STUDY OBJECTIVES

Primary Objective
To determine the efficacy and safety of oral apremilast in the treatment of nail psoriasis. The primary efficacy outcomes will be the change in the modified Nail Psoriasis Severity Index (mNAPSI), which has been validated as a reliable tool for measuring nail disease (Cassell, et al).
Primary Outcome Measure:
• Mean percent change of mNAPSI at week 36 compared to baseline for all nails. mNAPSI score ranges from 0 (no nail disease) to 130 (complete nail involvement in all ten nails.)

Secondary Objectives
• Mean percent change in mNAPSI of target nail at weeks 12, 24, 36, 48, and 52 compared to baseline. The target nail will be defined as the nail that has the highest mNAPSI singe nail score at baseline. This nail will remain the target nail for the remainder of the study.
• Proportion of patients achieving mNAPSI of 0 in all fingernails at weeks 36 and 52.
• Change in patient reported nail pain, as based on the Nail Pain VAS score, at week 52 compared to baseline score.
• Pain Change in psoriatic arthritis symptoms at week 52 compared to baseline, in patients who self-identify as having psoriatic arthritis at baseline. Symptoms will be assessed using a visual analogue scale (VAS) for reporting psoriatic arthritis pain.
• Safety Adverse effects will be assessed at each visit

• Proportion of patients achieving a mNAPSI 75 response, as defined by 75% or greater reduction over baseline in mNAPSI score at weeks 12, 24, 36, 48, and 52 for the target fingernail.
• Mean change in the total number of nails involved assessed at weeks 36 and 52 compared to baseline.

STUDY DESIGN

Study Outline

This is an open-label pilot study aimed at evaluating the efficacy and safety of treating nail psoriasis using oral apremilast. Inclusion and exclusion criteria, as well as dosing and safety monitoring will mirror recommendations from the apremilast package insert (www.celgene.com/therapies).

Number of Subjects

Twenty eligible patients will be enrolled. Patients will be treated for 52 weeks. During treatment patients will be evaluated in clinic every 4 weeks for the first three months and then every 12 weeks till week 48, followed by a final visit at week 52. All patients will be treated with active apremilast; there will be no placebo arm in this study.

Visit Schedule

<u>Screening Period</u>

Patient eligibility will be determined within 28 days prior to enrollment in study. Subjects who meet the inclusion and exclusion criteria may proceed to the first dosing visit at baseline.

<u>Study Visit</u>

Subjects will report to the investigational site for disease and safety assessments every 4 weeks for the first three months (week 0, 4, 8, 12), then every 12 weeks until week 48 (week 24, 36, 48) followed by a final study visit at week 52. Patients will have photos taken of their target nail and of all of their finger nails at baseline, week 12 and week 52. Photos will be a required feature of participation in this study. Patients will have a

mNAPSI of their target nail on week 4, 8, 12, 24, and 48, and of all of their nails on screening, week 0, 36, and week 52.
Patients will have a physician global assessment of fingernail psoriasis and a sPGA (using the NPF Score version) done at every visit. On week 0, 24, and 52 patients will have a PASI and BSA done. There will be PRO questions at each visit. PASI/PGA assessments will be compared to the nail improvement noted in the NAPSI.

Dosing schedule

Twenty eligible patients will be enrolled. Patients will be treated for 52 weeks. During treatment patients will be evaluated in clinic every 4 weeks for the first three months and then every 12 weeks till week 48, followed by a final visit at week 52. All patients will be treated with active apremilast; there will be no placebo arm in this study.
Treatment will be delivered just as it would be for patients with psoriasis receiving apremilast outside of this clinical trial. By treating patients as they would be treated in clinic, we hope to capture an accurate portrayal of the efficacy and safety of apremilast on the treatment of psoriatic nail disease.
Dosing will follow package insert guidelines as follows:
Day 1: 10mg am dose
Day 2: 10mg BID
Day 3: 10mg am dose, 20mg pm dose
Day 4: 20mg BID
Day 5: 20mg am dose, 30mg pm dose
Day 6 and beyond: 30 mg BID

Discontinuation of the Study

The study may be discontinued at the discretion of the investigator at any time without replacement

STUDY ENTRY CRITERIA

Patients will be recruited from the university hospital clinic as well as resident's continuity clinics. Inclusion and exclusion criteria reflect recommendations in the package insert for

apremilast (www.celgene.com/therapies). To be eligible to participate in this study, candidates will meet the following eligibility criteria at the time of enrollment:

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. Patients 18 and older
3. Give written informed consent prior to any study procedures being conducted, and candidates will authorize the release and use of protected health information (PHI)
4. Be willing and consent to having photos taken of their fingernails
5. Diagnosis of chronic plaque psoriasis that has been present for at least 6 months prior to baseline
6. Plaque psoriasis involving at least 5% of the patient's body surface area
7. Nail psoriasis in at least one finger nail with a mNAPSI of 5 or greater
8. A Nail Pain VAS score (0-10 cm) of 4 or higher. The Nail Pain VAS will assess the severity of pain linked to the nail disease.
9. Must have discontinued all systemic therapies for the treatment of psoriasis or psoriatic arthritis at least 4 weeks or 5 half-lives, and biologics 2 months or 5 half-lives (whichever is longer) prior to baseline visit
10. Must have discontinued all topical therapies for the treatment of psoriasis at least 2 weeks prior to baseline visit
11. Subjects must have discontinued UV therapy at least 2 weeks prior to baseline and PUVA at least 4 weeks prior to baseline.
12. Subjects must be in good general health without significant uncontrolled comorbidities, other than psoriasis, as determined by the investigator based on

exam findings, medical history, and clinical laboratories. Patients with stable mild renal insufficiency are eligible for enrolling in this trial.

13. Females of childbearing potential must use an approved birth control method while receiving treatment and for 28 days following the last dose of apremilast, and there must be a documented negative pregnancy tests prior to initiating treatment. Approved birth control methods include hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring), intrauterine device, tubal ligation (tying your tubes), partners vasectomy, or male or female condoms that are not made of natural materials PLUS a diaphragm with spermicide, cervical cap with spermicide, or a contraceptive sponge with spermicide. Females not of child bearing potential are defined as being at least 1 year postmenopausal or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy).
14. Male subjects, including those who have had a vasectomy, must use condoms not made of natural materials for the duration of the trial and for at least 28 days after the last dose of apremilast if conception is possible.

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 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.
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 [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.

7. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half lives, if known (whichever is longer).
8. Prior treatment with apremilast.
9. Unable to comply with the protocol (as defined by the Investigator; i.e. drug or alcohol abuse or history of noncompliance)
10. Concomitant therapy with medications that are strong cytochrome P450 inducers, including rifampin, phenobarbital, carbamazepine, or phenytoin
11. Any other dermatologic conditions that prohibit or confound the ability of the investigator to interpret skin and/or nail exam findings.
12. Patients who will be unable to avoid the use of systemic steroids, excluding intranasal or inhaled steroids that will be permitted, for the duration of the trial
13. Any known hypersensitivity to apremilast

STUDY PROCEDURES & TREATMENT PLAN GUIDELINES

Informed Consent:

A written, signed informed consent form (ICF) and written authorization to release and use PHI, will be obtained prior to performing any tests or evaluations under this protocol. Patients will have the option to ask questions and will be given at least 24 hours to review the ICF before signing. Patients may request the 24 hour review to be waived due to work or travel constraints.

See Protocol Flowchart for detailed timing of tests and evaluations.

General Concomitant Therapy:

Subjects should advise the investigator if they start taking any new medications, including over the counter and complementary andalternative medications.

Concomitant Therapy

Concomitant medications for psoriasis will not be permitted, except for topical therapies for skin limited disease that is not adequately controlled by apremilast after week 8. Patients will discontinue all topical psoriasis treatments 2 weeks before baseline, and

discontinue systemic treatments for psoriasis or psoriatic arthritis 4 weeks or 5- half-lives (whichever is longer) prior to baseline. Patients must discontinue UV therapy 2 weeks prior to baseline and discontinue PUVA 4 weeks prior to baseline.

SAFETY PLAN

Clinical Safety Assessments

The following clinical safety assessments will be performed: (See study flowchart)

- Physical examinations
- Vital signs (temperature, heart rate, blood pressure, and weight)
- Monitoring for adverse events
- Monitoring for concomitant therapy
- Laboratory evaluations (complete metabolic panel, complete blood count with differential, Hepatitis C, Hepatitis B, QuantiFERON gold) will be done at baseline. Fasting will not be required prior to laboratory evaluations. Continued monitoring will be done at the discretion of the investigator, but continued laboratory monitoring will not be required during the trial. Patients with a positive QuantiFERON gold (QGT) will be referred to the health department for recommended treatment.

Laboratory Safety Assessments

The following laboratory tests will be performed at screening, baseline, and week 52:

- Urine pregnancy test, if applicable.
- Laboratory evaluations (complete metabolic panel, complete blood count with differential, Hepatitis C, Hepatitis B, QGT) will be done at baseline. Continued monitoring will be done at the discretion of the investigator, but continued laboratory monitoring will not be required during the trial.

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 “Inclusion Criteria” 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.

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.

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).

Apremilast	Screening		Treatment						
Test / Evaluation	Within 28 Days Prior to baseline	Visit 1 W k 0	Visit 2 Wk 4	Visit 3 Wk 8	Visit 4 Wk 12	Visit 5 Wk 24	Visit 6 Wk 36	Visit 7 Wk 48	Visit 8 Wk 52
Informed Consent	X								
Inclusion/exclusion criteria reviewed	X	X							
Medical History	X								
Concomitant medications	X	X	X	X	X	X	X	X	
Physical Exam	X								X
Vital Signs	X	X	X	X	X	X	X	X	X
Laboratory assessment*	X	X							
Urine pregnancy test	X	X							
Adverse Events	X	X	X	X	X	X	X	X	X
Photos of nails***		X			X				X
PASI		X				X			X
sPGA	X	X	X	X	X	X	X	X	X
BSA		X				X			X
mNAPSI	X	X	X**	X**	X**	X**	X	X**	X
Physician's Global Assessment of Fingernail Psoriasis	X	X	X	X	X	X	X	X	X
Nail pain VAS	X	X	X	X	X	X	X	X	X
Psoriatic arthritis pain VAS	X	X	X	X	X	X	X	X	X
IP dispensing		X	X	X	X	X	X	X	
IP accountability			X	X	X	X	X	X	X

* Complete metabolic panel, complete blood count with differential, Hep B, Hep C, QGT at screening. Unscheduled laboratory assessments will be done at the discretion of the investigator.

**mNAPSI only of the target nail on these visits.

***Photos of nails may be taken at other time points at the discretion of the investigator. If clearance achieved, photos will be taken**STATISTICAL REPORTING**

Descriptive statistics will be done.

SAFETY REPORTING

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 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 <u>if</u> 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 anytime that are suspected of being related to study drug.

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

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
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 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 (or matching placebo) tablets in any 24 hour period whether by accident or intentionally.

Citations

Cassell SE, Bieber JD, Rich P, et al. The modified Nail Psoriasis Severity Index: validation of an instrument to assess psoriatic nail involvement in patients with psoriatic arthritis. J Rheumatol. 2007;34(1):123-9.

Jiaravuthiasan MM, Sasseville D, Vender RB, et al. Psoriasis of the nail: anatomy, pathology, clinical presentation, and review of the literature on therapy. J Am Acad Dermatol. 2007;57(1):1-27.

Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, Hochfeld M, Teng LL, Schett G, Lespessailles E, Hall S. Longterm (52-week) Results of a Phase III

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