A Pilot Study Evaluating the Efficacy of Apremilast in the Treatment of Subjects with Severe Recurrent Aphthous Stomatitis (RAS)

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Study Product: Otezla (apremilast) 30mg

Protocol Number: (IRBe)

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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
RAS	Recurrent Aphthous Stomatitis
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	A Pilot Study Evaluating the Efficacy of Apremilast in the Treatment of Subjects with Severe Recurrent Aphthous Stomatitis (RAS)
Running Title	A Pilot Study on the use of apremilast for Recurrent Aphthous Stomatitis (RAS)
Protocol Number	N/A
Phase	Pilot
Methodology	
Overall Study Duration	24 weeks
Subject Participation Duration	24 weeks
Single or Multi-Site	Single Site
Objectives	Determination of treatment efficacy and safety of Apremilast in patients with RAS
Number of Subjects	15
Diagnosis and Main Inclusion Criteria	Males and females, between 18 and 70 years old, with Recurrent Aphthous Stomatitis (RAS)
Study Product, Dose, Route, Regimen	Apremilast 30mg orally twice daily for 16 weeks
Treatment duration	Sixteen weeks on active study. Posttreatment follow-up period of 8 weeks.
Statistical Methodology	Wilcoxon signed rank test for comparison of outcomes between treatments and McNemar's exact test for categorical outcome variables

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable federal regulations and Mayo Clinic research policies and procedures.

1.1 Background

Recurrent aphthous stomatitis (RAS), or canker sores, represents a very common mucosal disorder, occurring in men and women of all ages, races and geographic regions and affecting up to 60% of North Americans.[1] The word 'aphthous' originates from the Greek word aphtha referring to an ulcer of the mucosal surface and 'stomatitis' refers to inflammation of the oral mucosa. Patients suffer from simple aphthosis, meaning they develop only occasional canker sores a few times per year which are a nuisance, but are not otherwise a difficult problem.

However, a subset of individuals with RAS suffer from a severe variant with persistent, refractory ulcers which may be present more often than not. This subset of canker sore sufferers tend to have more painful, persistent canker sores which may be larger, with multiple lesions occurring synchronously. These ulcers can take several weeks to heal, and as one episode resolves, another bout of ulcers develops. Patients often have ulcers present more than 50% of the time, and go from one episode of aphthosis into another so that they are seldom ulcer free.

Severe RAS (ulcers present more often than not/multiple, large ulcers/present synchronously/ slow to heal) – is sometimes referred to as "complex aphthosis" a term suggested by Jorizzo and Rogers[2], experts in the field of oral dermatology. Such patients are otherwise healthy, with no systemic disease and few to no comorbid conditions. It is thought that this phenomenon may represent an "up regulation" of the immune system.[3] Attacks of RAS may be precipitated by local trauma, stress, food intake, drugs, hormonal changes and vitamin and trace element deficiencies.[1] Local and systemic conditions, and genetic, immunological and microbial factors all may play a role in the pathogenesis of RAS.[1]

1.2 Investigational Agent

Otezla (apremilast) 30mg.

1.3 Clinical Data to Date

To date, no principal cause for RAS has been established. The lesions of RAS are painful and disabling to many patients and there are a large number of patients who seek treatment for this debilitating condition. Unfortunately, the disorder is not well understood and often managed by generalists or oral surgeons.
Since the etiology is unknown and there are no specific diagnostic tests, the diagnosis is based on history and clinical criteria. The long-term prognosis for patients with severe RAS is excellent because with time and increasing age, the condition may remit. However, patients may face 10 to 15 years of recurrent aphthosis and hence, treatment during this phase is warranted, to improve the severity of oral ulcers.[1]

By way of clarification, – severe RAS (or complex aphthosis) – is quite discrete from Behçet's disease, which also is characteristically associated with oral ulceration. In contradistinction, Behçet's disease is a rare, chronic, multisystemic disorder characterized by mucocutaneous, ocular, vascular and central nervous system

manifestations, and is thought to be a systemic vasculitis.[4] The clinical spectrum is wide and may include oral and genital ulcers among the many clinical features. The etiopathogenesis of Behçet's disease remains unknown, although genetic predisposition, environmental factors and immunological abnormalities have been implicated.[5] The prognosis of Behçet's disease is very different and may be guarded depending on the extent of the systemic vasculitis and treatment may be lifelong. Despite the distinction between severe RAS and Behçet's disease, it is postulated that treatments that attenuate the mucosal manifestations of Behçet's may also be effective in management of severe RAS.

A phase 2, double-blind, placebo-controlled study was published in 2015 which demonstrated apremilast to be effective in treating the oral ulcers manifested in Behçet's disease.[6] Given that oral ulcers are the cardinal manifestation of Behçet's disease, it has been suggested that apremilast may also be effective in patients with severe RAS.

To date, there has been one case[7] reported in which a patient with RAS was treated with apremilast. This was a male in his 60's with a history of recurrent oral ulcers for 3 years duration. After not responding to topical and systemic corticosteroids, antibiotics, and colchicine, apremilast monotherapy was initiated and gradually titrated to a maintenance dose of 30 mg twice daily. Within 6 weeks, there was complete clearance of all lesions and there was no disease recurrence over 12 months of follow-up.

Further investigation is needed to better define the role of apremilast in patients with severe RAS, as it may represent a safe and effective alternative to current management options.

1.4 Dose Rationale and Risk/Benefits

Based on the safety and efficacy of previous studies using apremilast for Behçet's disease and psoriasis, the dose of apremilast 30mg was chosen for the present study. Subjects will receive apremilast 30mg twice daily for 16 weeks. Since apremilast is known to be associated with gastrointestinal side effects and headaches, the dose will be increased gradually during the first week of treatment until the full 30mg dose is reached.
The expected benefits from apremilast use include reduction in the number and duration of oral ulcers, decreased oral ulcer pain, improved physical function and quality of life in patients with RAS. Risks associated with apremilast therapy include possible gastrointestinal side effects, headaches, upper respiratory tract infection, hypersensitivity reactions and depression.

2 Study Objectives

Primary Objective

- To evaluate the efficacy of apremilast for the treatment of RAS.

Secondary Objectives

- To evaluate the safety and tolerability of apremilast in subjects with RAS.

3 Study Design

3.1 General Design

The study will be a pilot study using apremilast 30mg orally twice daily, for treatment of RAS in males and females between 18 and 70 years old.

Subjects will be recruited from the clinical practice of the Department of Dermatology or Division of Rheumatology at Mayo Clinic Florida. Fifteen males and females with RAS will be enrolled.

The study will consist of 3 phases: a screening phase, a 16 week treatment phase and an 8 week posttreatment observational follow-up phase.

The screening phase will consist of: obtaining informed consent, demographic information, medical history, inclusion and exclusion criteria, prior and concomitant medication use, adverse events; collecting vital signs and weight; performing complete physical examination and limited physical examination; obtaining hematology, serum chemistry, urinalysis, pregnancy test and providing contraception education.

During the 16-week treatment phase, all subjects receive apremilast.

All subjects who complete the active treatment phase are to enter the 8-week posttreatment observational follow-up phase.

3.1.1 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 4.1.1 while on investigational product (IP) and for at least 28 days after administration of the last dose of the IP.
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.

3.2 Study population

Male and female subjects between 18 and 70 years old at the time of consent, who have diagnosis of RAS and who have had at least 2 oral ulcers in the 4 weeks prior to enrollment at baseline.

3.3 Primary Study Endpoints

Improvement in the following parameters of the RAS lesions: %change in the number of ulcers at the end of treatment, duration of ulcers and duration of the remission period between ulcer episodes.

3.4 Primary Safety Endpoints

- Type, frequency, severity and relationship of the adverse events to apremilast
- Number of subjects who prematurely discontinue treatment due to any adverse event
- Frequency of clinically significant changes in vital signs and/or laboratory findings

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

1. Male and female subjects between 18 and 70 years of age
2. Oral ulcers that occurred at least monthly in the 6 month period prior to enrollment
3. Had at least 2 oral ulcers in the 4 weeks prior to enrollment at baseline
4. At least 3 oral ulcers during an ulcer flare
5. Patients must be candidates for systemic therapy for the treatment of oral ulcers, those that are considered unsuitable for topical therapy alone based on severity of disease, or whose oral ulcers cannot be adequately controlled with topical therapy.
6. Female premenopausal subjects must use one of the approved contraceptive options while taking apremilast and for at least 28 days after administration of the last dose of apremilast
7. Patients are able and willing to provide written informed consent after the nature of the study is fully explained.
8. No evidence of systemic disease

4.1.1 Contraception Requirements

Females of childbearing potential[a] (FCBP) must have a negative pregnancy test at screening. 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.

[a] A female of childbearing potential is a sexually mature female who has not undergone a hysterectomy or bilateral oophorectomy or has not been postmenopausal for at least 24 consecutive months.

4.2 Exclusion Criteria

1. Prior use of apremilast.
2. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer).
3. Having received concomitant immune modulating therapy 12 weeks prior to enrollment, systemic steroids 6 weeks prior to enrollment or topical steroids within 4 weeks prior to enrollment.
4. Pregnant women or breast-feeding mothers.
5. Systemic or opportunistic fungal infection.
6. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (tuberculosis and atypical mycobacterial disease, hepatitis B and C and herpes zoster, histoplasmosis, coccidiomycosis) or any major episode of infection requiring hospitalization or treatment with IV or oral antibiotics within 4 weeks of the screening phase.
7. History of positive test for, or any clinical suspicion of, human immunodeficiency virus (HIV), or congenital or acquired immunodeficiency.
8. History of depression.
9. 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.
10. 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.
11. 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.
12. 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.
13. Active substance abuse or a history of substance abuse within 6 months prior to screening.
14. Presence of any of the following vitamin deficiencies - B1, B2, B6, B12, vitamin C, zinc, folate, iron.
15. Celiac disease.
16. Inflammatory Bowel Disease.
17. Genital aphthous ulcers.
18. Behçet's disease.
19. History of positive patch test for allergic contact stomatitis.
20. Positive anti-endomysial or anti-gliadin antibodies.
21. A diagnosis of uveitis (current or previous).
22. Erythema nodosum-like lesions (current or previous).
23. An established diagnosis of a systemic disease (SLE, Reiter's, Sweet's and MAGIC syndrome).

4.3 Subject Recruitment, Enrollment and Screening

Subjects will be recruited from the clinical practice of the Department of Dermatology or Division of Rheumatology, Mayo Clinic Florida. Patients seeking treatment for RAS will be offered standard conservative medical therapy for RAS as part of routine dermatological treatment. As an alternative, patients will be informed of the study protocol, and offered the option to enroll if they meet the study eligibility criteria.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may withdraw from the study at any time for the following:

- Subject safety issues related to serious reactions such as bacterial or viral skin infection, fever, or tissue hypertrophy.
- Subject decision to withdraw from the study (withdrawal of consent)
- Subject's decision to pursue other therapeutic regimens, either surgical or non-surgical

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Even though a subject has withdrawn from the study, it will be important to collect follow-up or survival data on subjects throughout the protocol defined follow-up period. Such data are important to the integrity of the final study analysis. If a subject withdraws consent to participate in the study for subject safety reasons, attempts will be made to obtain permission to collect follow up information whenever possible. Patients will be analyzed by intention to treat principles.

5 Study Drug

5.1 Description

Apremilast is an oral small-molecule inhibitor of phosphodiesterase (PDE) 4 that works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE 4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNF-alfa, IL-23, IL-17 and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10. Apremilast has immunomodulatory activity and, therefore, has the potential to be effective in the treatment of RAS.

5.2 Treatment Regimen

Subjects will receive apremilast 30mg twice daily for 15 weeks. Since Apremilast is known to be associated with gastrointestinal side effects and headaches, the dose will be increased gradually in the first week according to the following schedule:

Day 1: 10mg in morning
Day 2: 10mg in morning and 10mg in evening
Day 3: 10mg in morning and 20mg in evening
Day 4: 20mg in morning and 20mg in evening
Day 5: 20mg in morning and 30mg in evening
Day 6 and thereafter: 30mg twice daily

5.3 Administration of Study Drug

Subjects will receive apremilast 30mg twice daily orally for 15 weeks after 1 week of titration. Patients will be advised to take the medication in the morning and evening, with water.

5.4 Prior and Concomitant Therapy

Subjects will be allowed the following concomitant therapies to control flares: Tylenol, lidocaine 2% topical mouth wash and lidocaine 2% plus diphenhydramine plus Maalox topical mouth wash.
No topical and systemic therapies for RAS may be used 3 months prior to study enrollment.

6 Study Procedures

a. The screening phase will consist of: obtaining informed consent, demographic information, medical history, inclusion and exclusion criteria, prior and concomitant medication use, adverse events; collecting vital signs and weight; performing complete physical examination, hematology, serum chemistry (vitamins B1, B6, B12, C, iron, folate, zinc, TTG, ANA), urinalysis, pregnancy testing, contraception education. Patients will also be assessed in regards to number of oral ulcers and pain visual analog scale for oral ulcers. A diary will be provided to the patient for keeping record of number and pain intensity of oral ulcers throughout the study.

b. At baseline (week 0) all patients will undergo a complete medical history and limited physical examination, suitability assessment (inclusion and exclusion criteria), and safety assessments (adverse events, vital signs, weight, contraception education). Patients will also be assessed in relation to number of oral ulcers, pain visual analog scale for oral ulcers, physician's global assessment of oral lesions and Chronic Oral Mucosal Disease Questionnaire – COMDQ) and the investigational product will be dispensed.

c. At week 2 all patients will undergo safety assessments (adverse events, vital signs, weight, and contraception education), efficacy assessments (number of oral ulcers, pain visual analog scale for oral ulcers, physician's global assessment of oral lesions) and investigational product accountability.

d. At week 4 all patients will undergo safety assessments (adverse events, vital signs, weight, and contraception education), efficacy assessments (number of oral ulcers, pain visual analog scale for oral ulcers, physician's global assessment of oral lesions) and investigational product accountability. The investigational product will be dispensed.

e. At week 8 all patients will undergo safety assessments (adverse events, vital signs, limited physical examination, weight, contraception education, and optional lab work per Investigator's discretion, including hematology and serum chemistry), efficacy assessments (number of oral ulcers, pain visual analog scale for oral ulcers, physician's global assessment of oral lesions and Chronic Oral Mucosal Disease Questionnaire – COMDQ) and investigational product accountability. The investigational product will be dispensed.

f. At week 12 all patients will undergo safety assessments (adverse events, vital signs, weight, and contraception education) and efficacy assessments (number of oral ulcers, pain visual analog scale for oral ulcers and physician's global assessment of oral lesions) and investigational product accountability. The investigational product will be dispensed.

g. At week 16 all patients will undergo safety assessments (adverse events, vital signs, weight, complete physical examination, contraception education and optional lab work per Investigator's discretion, including pregnancy testing, hematology and serum chemistry), efficacy assessments (number of oral ulcers, pain visual analog scale for oral ulcers, physician's global assessment of oral lesions and Chronic Oral Mucosal Disease Questionnaire – COMDQ) and investigational product accountability.

h. At week 24 patients will undergo safety assessments (vital signs, weight, and complete physical examination) and efficacy assessments (number of oral ulcers, pain visual analog scale for oral ulcers, physician's global assessment for oral lesions and Chronic Oral Mucosal Disease Questionnaire - COMDK).

6.1 Apremilast table of events

Schedule of Events

Procedure	Screening phase	Baseline (Week 0)	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24
Informed Consent	X							
Demography	X							
Medical History	X	X						
Inclusion/Exclusion Criteria	X	X						
Safety Assessments								
Adverse Events	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X
Complete Physical Examination	X						X	X
Limited Physical Examination	X	X			X			
Weight	X	X	X	X	X	X	X	X
Hematology	X				X*		X*	
Serum Chemistry	X				X*		X*	
Urinalysis	X							
Pregnancy test	X						X*	
Contraception Education	X	X	X	X	X	X	X	
Efficacy Assessments								
Number of Oral Ulcers	X	X	X	X	X	X	X	X
Pain VAS for oral ulcers	X	X	X	X	X	X	X	X
Physician's Global Assessment of Oral Lesions	X	X	X	X	X	X	X	X
Chronic Oral Mucosal Disease Questionnaire – COMDQ	X	X			X		X	X
Investigational Product								
Dispense IP		X		X	X	X		
IP Accountability	X		X	X	X	X	X	

* lab work, including pregnancy testing, is optional per Investigator's discretion.

Statistical Plan

6.2 Sample Size Determination

A total of 15 patients will be enrolled in this study. This sample size will be sufficient in order to gain valuable data that could be used in the design of a future, larger study. Given the pilot/feasibility nature of the study, no formal power calculations were performed.

6.3 Statistical Methods

Data Analysis – Given the design, all statistical analysis will be descriptive. Continuous outcome measures will be summarized using the sample mean, standard deviation, median, minimum, 25th and 75th percentiles, and maximum. Categorical variables will be summarized with number and percentage. 95% confidence intervals (CIs) will be estimated where appropriate.

Descriptive Statistics

We will summarize continuous variables using the sample mean, standard deviation, median, minimum, 25th and 75th percentiles, and maximum. We will summarize categorical variables with number and percentages. Ordinal variables will be summarized using the sample median, minimum, 25th and 75th percentiles, and maximum, as well as with number and percentage.

Handling of Missing Data

Given the prospective nature of the study, we expect to encounter little if any missing data. However in the event of missing data, no attempt to impute this missing data will be made in this pilot study; missing data will be treated as missing.

Multiplicity

No adjustment for multiple testing will be made owing to the exploratory, pilot nature of the study.

Primary Hypothesis:

We hypothesize that apremilast administration for RAS will decrease the number of ulcers at the end of treatment compared to baseline.

The primary endpoints of the study is the change in number of ulcers at the end of treatment compared to baseline.

The secondary endpoints of the study, occurrence of adverse reactions and morbidity, are both dichotomous categorical variables. As such, the proportion for which these outcomes occur will be estimated along with 95% confidence interval.

Interim Analysis

No interim analysis will be performed in this pilot study.

6.4 Subject Population(s) for Analysis

All-treated population: Any subject randomized into the study that received study drug.

7 Safety and Adverse Events

7.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e., unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, **AND**
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event

An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization inpatient, new, or prolonged;
- disability/incapacity
- persistent or significant birth defect/anomaly

- 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.

  or other events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period
For this study, the study treatment follow-up period is 6 months after enrollment. The adverse event monitoring period will end at the end of the follow-up period. If an event is reported after this time it would need to be determined whether or not it is study related.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if it was exhibited as a severe reaction i.e. swelling, that required hospitalization or additional clinical intervention.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

7.2 Recording of Adverse Events

All adverse events will be documented as required, under 21 CFR part 1271. Depending on the nature and seriousness of the adverse reaction, the IRB will be notified according to the Mayo Clinic IRB policy. If An SAE occurs it will also be reported to the FDA as per regulations

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF) or separate worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome.

7.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and/or log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

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
[redacted].
Summit, NJ 07901
Fax: [redacted]
E-mail: [redacted]

7.3.1 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.

7.3.2 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

7.4 Stopping Rules

Study enrollment and treatment procedures will be suspended in the event that a subject experiences treatment related Adverse Event while on study. The study would only be resumed after a thorough review of the incidents and any corrective and preventative actions have been put in place along with consultation between the study team and the IRB.

7.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 - "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8 Data Handling and Record Keeping

8.1 Data Handling

Data will be collected and entered by the study coordinator assigned to the project, and stored into a REDCap database.

Variables to be collected include: (please list variables to be collected, at different time points if applicable)

8.2 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

Hard copy data such as consent forms will be stored in locked file cabinets; electronic data will be stored in secure web-based database (REDCap) that will be designed with the help of the statistician.

8.3 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and

complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Data Management
Study data will be managed in a study specific REDCap system

Data Security and Confidentiality

The REDCap system has built in systems for control of access, data integrity and audit trails. Access and confidentiality are controlled in a manner similar to other institutional systems.

8.4 Records Retention

1. As outlined in the Mayo Clinic Research Policy Manual "Access to and Retention of Research Data Policy" [redacted].

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The study specific DSMP will be submitted to the IRB as a separate document in the IRB application.

This will assist investigators in complying with Food and Drug Administration regulations.

9.2 Auditing and Inspecting

This study may be monitored during the conduct of the study by internal quality assurance auditors. The investigator will permit monitoring, audits, and inspections by the IRB, Mayo internal auditing, and government regulatory agencies of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).
Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

10 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study

procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

11 Study Finances

11.1 Funding Source

Celgene Biopharmaceutical company funding.

11.2 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

11.3 Subject Stipends or Payments

No subject payments or reimbursement will be offered.

12 Publication Plan

The Principal Investigator will be responsible for manuscript preparation and submission to a suitable dermatologic journal for publication of results.

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