Apremilast in Combination with Clobetasol Spray for the Treatment of Plaque Psoriasis

INVESTIGATIONAL PRODUCT (IP): Apremilast and Clobetasol 0.05% spray
PROTOCOL NUMBER:
DATE FINAL:
EudraCT NUMBER:
IND NUMBER:
SPONSOR NAME / ADDRESS: Ronald Prussick, MD / 6163 Executive Blvd Rockville, MD 20854

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

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PROTOCOL SUMMARY

Study Title - Apremilast in Combination with Clobetasol spray for the treatment of plaque psoriasis of the body with or without scalp involvement

Indication – Apremilast is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

Objectives

Primary Objective – Assessing the efficacy of combining Clobetasol spray with apremilast for the treatment of plaque psoriasis of the body with or without scalp

Secondary Objectives – Assessing the safety and quality of life in patients treated with Clobetasol spray and apremilast for the treatment of plaque psoriasis of the body with or without scalp

Study Design

Study Population- Adults 18 years and older with plaque psoriasis with at least 10% BSA involving the body with or without scalp lesions

Length of Study – 16 weeks

Study Treatments – Clobetasol is a superpotent topical corticosteroid. Many patients who use this may develop a rebound if stopped suddenly[1]. Therefore, in this study the drug will be slowly tapered over 6 weeks. Patients with plaque psoriasis on the body with or without scalp involvement (not solely face/folds/hands/feet) begin apremilast at the approved psoriasis dosage. Patients will also begin clobetasol spray 0.05% to affected plaques bid for 2 weeks, then qday for 2 weeks the qod for 2 weeks then stop clobetasol but continue apremilast for a total of 16 weeks.

Overview of Efficacy Assessments – Patients will have BSA x PGA and PASI 75 scores measured at baseline then at 2, 4, 6, 8, 12 and 16 weeks. We will also record pruritus VAS and TSQM version II at all visits. If scalp involvement, we will also report scalp PGA

Primary Clinical Assessment- Proportion of patients achieving PASI 75 at Week 16 from baseline

Additional Clinical Assessments – Adverse Events (AE), Scalp PGA, Pruritus VAS, TSQM version II. Clinical Benefit, mean percent change from baseline in BSA x PGA at Week 16

Overview of Safety Assessments – Follow up visits initially then at 2,4,6,8 and 12 and 16 weeks.

1. INTRODUCTION

Approximately 30% of patients with psoriasis vulgaris achieve PASI 75 reduction at 16 weeks with oral apremilast. In a study using clobetasol spray as monotherapy twice daily for 4 weeks, 35.7% achieved clearance and 37.3% were almost clear. Potent topical steroids have the potential for adrenal suppression and skin atrophy with long-term use. For these reasons, they are ideal for inducing remission but not long-term use[2]. The combination of clobetasol spray to induce rapid response with apremilast as a long-term treatment to maintain response may be a good treatment regimen.

1.1. Rationale for Dose Chosen

Apremilast dose as per FDA approval. Clobetasol spray given a slow taper over 6 weeks to reduce chance of skin flare.

1.2. Relevant Reference and Background:

In a survey conducted by the National Psoriasis Foundation from 2003-2011, 52.3% of patients reported dissatisfaction with their psoriasis treatments due to concerns about safety, tolerability or lack of efficacy[2].

The efficacy and safety of Apremilast was reported in 2 multicenter randomized, placebo-controlled phase 3 studies (ESTEEM 1 and ESTEEM 2). Apremilast demonstrated a significant increase in the proportion of patients achieving a PASI-75 response at week 16 in ESTEEM 1 (33.1% vs 5.3% in placebo) and in ESTEEM 2 (28.8% vs 5.8%)[3].

Clobetasol 0.05% spray was found to be safe and effective in moderate to severe plaque psoriasis when used bid for 4 weeks in a single center, randomized, double blind study[4].

2. STUDY OBJECTIVES

2.1. Primary Objective

Proportion of patients achieving PASI (Psoriasis area and Severity Index) 75 at Week 16 from baseline.

2.2. Secondary Objectives

Adverse Events (AE), proportion of patients with scalp psoriasis with improvement of ScPGA scores to 0 and 1 at Week 16, change from baseline in Pruritus VAS (Visual Analogue Scale) at Week 16, TSQM (Treatment Satisfaction Questionnaire for Medication) Version II. Clinical Benefit, mean percent change from baseline in BSA (Body Surface Area) x PGA (Physician Global Assessment) at Week 16.

3. OVERALL STUDY DESIGN

Open label, pilot trial with 20 patients with psoriasis vulgaris involving the body with or without scalp plaques

The study is designed as a 16-week study and consists of 8 visits as described in the table of events.

Screening
To reduce risk of gastrointestinal symptoms, titrate to recommended dose of 30 mg BID according to the following schedule:

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

Weeks 0-2
Patients will receive apremilast 30 mg BID and clobetasol spray 0.05% to affected plaques BID for 2 weeks. The first week of IP dosing will consist of apremilast dose-titration card.

Weeks 2-4
Patients will receive apremilast 30 mg BID and clobetasol spray 0.05% to affected plaques once daily for 2 weeks

Weeks 4-6
Patients will receive apremilast 30 mg BID and clobetasol spray 0.05% to affected plaques every other day for 2 weeks, then stop clobetasol spray 0.05%

Weeks 6-16
Patients will continue to receive apremilast 30 mg BID

3.1. Data and Safety Monitoring Plan

Study Design Rationale

Approximately 30% of patients with psoriasis vulgaris achieve PASI 75 reduction at 16 weeks with oral apremilast. In a study using clobetasol spray 0.05% as monotherapy twice daily for 4 weeks, 35.7% achieved clearance and 37.3% were almost clear[2]. Potent topical steroids have the potential for adrenal suppression and skin atrophy with long-term use. For these reasons they are ideal for inducing remisssion but not long-term use. The combination of clobetasol spray to induce rapid response with apremilast as a long-term treatment to maintain response may be a good treatment regimen.

3.2. Study Duration- 16 weeks

4. TABLE OF EVENTS

	Screening	Baseline	Apremilast Treatment					
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Week	Up to 7 days	0	2	4	6	8	12	16
Informed Consent	x							
Inclusion/Exclusion Criteria	x	x						
Medical and Disease History	x							
Height	x							x
Weight	x							x
Sex	x							
Race	x							
Prior/Concurrent Medications/Therapies	x	x	x	x	x[a]	x	x	x
Safety Assessments								
Pregnancy Test and Contraception Education for Females of Child- bearing Potential (FCBP)	x	x						x
Psoriasis Flare or Rebound Assessment	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x
Clinical Efficacy Assessments								
BSAxPGA	x	x	x	x	x	x	x	x
PASI	x	x	x	x	x	x	x	x
Pruritus VAS	x	x	x	x	x	x	x	x
Scalp PGA	x	x	x	x	x	x	x	x
TSQM version II	x	x	x	x	x	x	x	x
Investigational Product Dosing								
Dispense IP		x	**x**	**x**	**x**	**x**	**x**	**x**
Return IP tablets, Count for Compliance			x	x	x	x	x	x

[a] Discontinue clobetasol spray 0.05% at Week 6

5. PROCEDURES

The following procedures will be conducted as outlined in the Table of Events.

Informed Consent

An Informed Consent Document will be signed by the subject before any study-related assessments are performed.

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 4.2 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 Sponsor Investigator will educate the subject regarding options and correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

Inclusion/Exclusion Criteria

Subjects must meet all inclusion criteria and must not have any of the conditions specified in the exclusion criteria to qualify for participation in the study. The subject's source documents must support his/her qualifications for the study (e.g., if a female subject does not require pregnancy testing and birth control because of a hysterectomy, the date of the hysterectomy must be included in the medical history).

Medical and Disease History

Relevant medical history should be recorded, including smoking and alcohol history, as well as previous relevant surgeries. Disease history includes history of psoriasis, psoriatic arthritis and chronic infections.

Prior/Concurrent Medications and Therapies

All medications and therapies being taken/used by the subject at the time of consent or at any time during the study will be recorded. Other key medications and therapies will be recorded.

Safety Assessments

The following assessments will be conducted as outlined in the Table of Events**.**

Psoriasis Flare and Rebound Assessments

Psoriasis flare is an AE (and will be recorded as an AE) and represents an atypical or unusual worsening of disease during treatment. It is defined as a sudden intensification of psoriasis requiring medical intervention or a diagnosis of new generalized erythrodermic, inflammatory, or pustular psoriasis. A more typical, gradual worsening of plaque psoriasis would not be recorded as an AE.[5]

Rebound is an AE and is defined as a severe and sudden worsening of disease that occurs after treatment has been discontinued. This exacerbation is characterized by a PASI $\geq$ 125% of baseline or a new generalized pustular, erythrodermic or more inflammatory psoriasis after stopping therapy[6].

Adverse Events

Details of AE reporting may be found in Section 10.

Clinical Efficacy Assessments

The following assessments will be conducted as outlined in the Table of Events, **Table 1**.

Psoriasis Area Severity Index (PASI)

PASI will be determined for all subjects throughout the study.

The PASI is a measure of psoriatic disease severity taking into account qualitative lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. The PASI is a validated instrument that has become standard in clinical trials for psoriasis.

Psoriasis Area Severity Index scores range from 0 to 72, with higher scores reflecting greater disease severity.[7] Erythema, thickness, and scaling are scored on a scale of 0 (none) to 4 (very severe) on 4 anatomic regions of the body: head, trunk, upper limbs, and lower limbs. Degree of involvement on each of the 4 anatomic regions is scored on a scale of 0 (no involvement) to 6 (90% to 100% involvement). The total qualitative score (sum of erythema, thickness, and scaling scores) is multiplied by the degree of involvement for each anatomic region and then multiplied by a constant. These values for each anatomic region are summed to yield the PASI score.

Body Surface Area (BSA) x Physician Global Assessment (PGA)

BSA is determined by calculating the number of palms of psoriasis on the scalp and body. One palm of psoriasis represents 1% BSA. PGA is a 5-point scale from 0 (clear) to 4 (severe).

Scalp Physician Global Assessment (ScPGA)

ScPGA will assess scalp involvement, if present at baseline. ScPGA is a 6-point scale from 0 (clear) to 5 (very severe).

Visual Analog Scale (VAS) Assessments

The following assessments will be conducted as outlined in the Table of Events.

Pruritus Visual Analog Scale (VAS) Assessment

The subject will be asked to place a vertical stroke on a 100 mm VAS on which the left-hand boundary represents no itch, and the right-hand boundary represents itch as severe as can be imagined. The distance from the mark to the left-hand boundary will be recorded.

TSQM Version II

The subject will fill out a treatment satisfaction survey consisting of 11 questions on each visit.

6. STUDY POPULATION

6.1. Number of Subjects and Sites

One site and 20 patients

6.2. 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 Sponsor Investigator, based on medical history, and physical examination. (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.
   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

3. Plaque psoriasis with at least 10% BSA involving the body with or without scalp lesions in adults aged 18 years and older.

† 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 enrolled into the study (for example, hormonal contraception should be initiated at least 28 days before baseline).

6.3. 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 Sponsor Investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major disease that is currently uncontrolled.
2. Any condition 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 baseline, 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 baseline, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer).
8. Prior treatment with apremilast.
9. Concomitant use of drugs that treat psoriasis including but not limited to methotrexate, acitretin, cyclosporine within 4 weeks of baseline.
10. Adalimumab, etanercept, efalizumab, infliximab, or certolizumab pegol within 12 weeks prior to baseline.
11. Alefacept, briakinumab, ixekizumab, brodalumab or ustekinumab within 24 weeks prior to baseline.
12. Use of phototherapy within 4 weeks prior to baseline (i.e., UVB, PUVA)
13. Plaque-type psoriasis with BSA<10%
14. Psoriasis predominantly involving the face or folds (groin or axilla)
15. Psoriasis only of the palms/soles, pustular or other forms of psoriasis
16. Concurrent skin or systemic infection
17. History of intolerance to topical steroids or apremilast.
18. Topical therapy within 2 weeks of baseline (including but not limited to topical corticosteroids, topical retinoids or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol). Exceptions: Clobetasol Spray 0.05%.

7. DESCRIPTION OF STUDY TREATMENTS

7.1.1. Treatment Administration and Schedule

Otezla is given as an initial 5-day titration schedule starting at 10 mg on day 1, 10 mg BID on day 2, 10 mg qam and 20 mg qhs day 3, 20 mg BID day 4, 20 mg qam and 30 mg qhs day 5. At and after day 6 the dose is 30mg BID.

Clobetasol 0.05% spray is applied to plaques on body and scalp, but not face and folds, BID for 2 weeks. Then qd for 2 weeks then qod for 2 weeks.

7.1.2. Packaging and Labeling

Tablets

The label(s) for Otezla will include drug name, dosage form and strength (where applicable), amount of Otezla per container, lot number, expiry date (where applicable), dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

All apremilast will be supplied by Celgene.

Clobetasol 0.05% spray is supplied in a 120ml bottle with spray pump.

7.1.3. Product Accountability and Disposal

The Sponsor Investigator, or designee, is responsible for taking an inventory of each shipment of Otezla received, and comparing it with the accompanying Otezla shipping order/packing list. The Sponsor Investigator, or designee, will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene.

The Sponsor Investigator, or designee, is responsible for taking an inventory of each shipment of clobetasol 0.05% spray received. Disposal and /or destruction will be performed by the Sponsor or designee.

Investigational product will be stored per the storage conditions identified on drug label. At the study site, all Otezla and clobetasol 0.05% spray bottles will be stored in a locked, safe area to prevent unauthorized access.

Celgene will instruct the Sponsor Investigator on the return, disposal and/or destruction of Otezla if applicable.

7.1.4. Investigational Product Compliance

Study personnel will review the instructions printed on the package with the study subjects prior to dispensing Otezla and clobetasol spray. The subjects will be instructed to return the Otezla containers and clobetasol spray bottles, including any unused medication, to the study site at each visit for tablet counts and reconciliation. Subjects will be asked whether they have taken their Otezla and clobetasol spray as instructed at each study visit. Any problems with compliance will be reviewed with the subject.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

8.1. Permitted Concomitant Medications and Procedures

Subjects may take any medication that is not restricted by the protocol and would not be expected to interfere with the conduct of the study or affect assessments. Chronic medication should be dosed on a stable regimen.

All medications (prescription and non-prescription), treatments and therapies taken by the subject from screening throughout their entire participation in the study, including those initiated prior to the start of the study, must be recorded on the subject's source document and on the appropriate page of the CRF. The dose, unit, frequency, route, indication, the date the medication was started and the date the medication was stopped (if not ongoing) must be recorded. The recording of any permitted topical medications taken for psoriasis should also include the area of the body to which they are applied.

The following topical therapies will be permitted:

- Unmedicated skin moisturizer (e.g., Eucerin or Cetaphil) permitted for body lesions only

8.2. Prohibited Concomitant Medications and Procedures

The following psoriasis medications cannot be administered for the duration of the study:

- Topical corticosteroids, except for study drug, Clobetasol Spray 0.05%
- Phototherapy
- Oral systemic drugs for psoriasis including: methotrexate, cyclosporine, acitretin
- Biologics treatments for psoriasis: adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab

8.3. Required Concomitant Medications and Procedures

Clobetasol spray 0.05% spray is applied to plaques on body and scalp, but not face and folds, BID for 2 weeks. Then qd for 2 weeks then qod for 2 weeks

9. STATISTICAL ANALYSES

9.1. Overview

We will report the number of patients who achieve a clinical response to the primary and secondary objectives as outlined.

9.2. Sample Size

The proposed sample size is based on clinical setting, practice size, number of patients able to be included within the 1-year time period. Approximately 20 patients will be enrolled into the study.

9.3. Background and Demographic Characteristics

Patients' age, weight, height and other continuous demographic and baseline characteristics will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum), while gender, race and other categorical variables will be summarized. Medical history data will be summarized using frequency tabulations.

9.4. Subject Disposition

Patient disposition (analysis population allocation, entered, completed, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent by phase.

9.5. Efficacy Evaluation

Efficacy analysis will be based on all patients enrolled as specified in the protocol. Responders are those who achieve at least a PASI-75 at Week 16; non-responders are defined as those who do not achieve a PASI-75 at Week 16 and/or those who have missing data at any time point during the study.

The proportion of patients who achieve at least a PASI-75 at Week 16 (responders) reference to the baseline, proportion of patients with scalp psoriasis with improvement of ScPGA scores to 0 and 1 at Week 16, change from baseline in Pruritus VAS at Week 16, mean percent change from baseline in BSA x PGA at Week 16 will be summarized using descriptive summary statistics for continuous variables, while frequency and percentages will be provided for discrete variables

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence 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

worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

All AEs will be recorded by the Sponsor Investigator(s) from the time of signing the informed consent through the end of the designated follow-up period.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

10.2. Evaluation of Adverse Events

A qualified Sponsor Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Sponsor Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- 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 page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Sponsor Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

10.2.2. Severity / Intensity

For both AEs and SAEs, the Sponsor 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

10.2.3. Causality

The Sponsor Investigator must determine the relationship between the administration of IP 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 IP 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 IP administration makes **a causal relationship possible**, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

10.2.4. Duration

For both AEs and SAEs, the Sponsor Investigator will provide a record of the start and stop dates of the event.

10.3. Action Taken

The Sponsor Investigator will report the action taken with Otezla and Clobetasol spray as a result of an AE or SAE, as applicable (e.g., discontinuation of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.4. Outcome

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause), or death (due to the SAE).

10.5. 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.

10.6. 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 Sponsor 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 Sponsor Investigator(s) within 30 days after a subject's last dose of study drug, and those made known to the Sponsor investigator(s) at any time that are suspected of being related to study drug.

The SAE will be reported to the manufacturer of Clobetasol spray.

The SAE must be reported immediately (i.e., within 24 hours of the Sponsor Investigators' knowledge of the event) to Celgene Safety by facsimile. A written report (prepared by the Sponsor 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
86 Morris Ave.
Summit, NJ 07901
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 Sponsor 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 Sponsor 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).

10.7. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to apremilast based on the Sponsor Investigator's Brochure.

Celgene or its authorized representative shall notify the Sponsor Investigator of the following information:

- Any AE associated with the use of Otezla in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Sponsor Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Sponsor Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC, (see Section 14.2 for record retention information).

Please refer to the Serious Adverse Event Report Form / Completion Guidelines or to the Pregnancy Report Form / Completion Guidelines

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 Sponsor 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 Sponsor 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 Sponsor Investigator(s) should follow the procedures for reporting SAEs (i.e., report the event to Celgene Safety by facsimile within 24 hours of the Sponsor 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 Sponsor 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 Sponsor 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 Sponsor 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 Sponsor Investigator.

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the Sponsor Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11. DISCONTINUATIONS

The following events are considered sufficient reasons for discontinuing a subject from the investigational product and/or from the study:

- Adverse event(s)
- Lack of efficacy
- Non-compliance with study drug
- Withdrew consent
- Study terminated by PI/Sponsor
- Lost to follow-up
- Death
- Protocol violation
- Other

The reason for discontinuation should be recorded in the CRF and in the source documents.

12. REGULATORY CONSIDERATIONS

12.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor Investigator abides by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Sponsor Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

12.2. Sponsor-Investigator Responsibilities

Sponsor Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations.

The Sponsor Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The Sponsor Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Sponsor Investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

12.3. Subject Information and Informed Consent

The Sponsor Investigator must obtain informed consent of a legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Sponsor Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the Sponsor Investigator's study files and a copy given to the study subject.

12.4. Confidentiality

Sponsor-investigator affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent).

Should direct access to medical records require a waiver or authorization separate from the subject's signed informed consent document, it is the responsibility of the Sponsor Investigator to obtain such permission in writing from the appropriate individual.

12.5. Protocol Amendments

Any amendment to this protocol must be approved by Celgene prior to IRB submission. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Sponsor Investigator name, protocol number, study title and amendment number(s) that is applicable.

12.6. Closure of the Study

Celgene reserves the right to terminate support of this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/EC, regulatory authorities, etc…).

13. DATA HANDLING AND RECORDKEEPING

13.1. Data/Documents

The Sponsor Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and

retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

14. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by the Sponsor-investigator for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

14.1. Study Monitoring and Source Data Verification

The Sponsor-investigator ensures that appropriate monitoring procedures are performed before, during and after the study.

15. REFERENCES

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[4] Beutner K, et al. An intra-individual randomized safety and efficacy comparison of clobetasol propionate 0.05% spray and its vehicle in the treatment of plaque psoriasis. J Drugs in Dermatol 2006; 5(4):357-60.

[5] Carey, W., et al., *Relapse, rebound, and psoriasis adverse events: an advisory group report.* J Am Acad Dermatol, 2006. **54**(4 Suppl 1): p. S171-81.

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[7] Fredriksson, T. and U. Pettersson, *Severe psoriasis -- oral therapy with a new retinoid.* Dermatologica, 1978. **157**: p. 238-244.