Clinical Study Protocol

A Single Center Study to Evaluate the Effectiveness and Safety of add on Enstilar® in Patients Using OTEZLA® for Moderate to Severe Plaque Psoriasis

Testing Facility

Psoriasis Treatment Center of Central New Jersey
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Table of Contents

PROTOCOL SYNOPSIS:

OTEZLA® IN COMBINATION WITH ADD-ON ENSTILAR®

Study Title	A Single Center Study to Evaluate the Effectiveness and Safety of add on Enstilar® in Patients using OTEZLA® for Moderate to Severe Plaque Psoriasis
Sponsors	Jerry Bagel, MD
Study Objectives	**Primary Objective:** To determine if adding Enstilar® topical therapy can help OTEZLA® partial responders to achieve PASI 75 by week 12. **Secondary Objective:** To evaluate the efficacy of combining OTEZLA® and Enstilar® To evaluate the safety of combining OTEZLA® and Enstilar® To evaluate the subject quality of life when combining OTEZLA® and Enstilar®
Study Design	50 adult patients with moderate to severe plaque psoriasis will be given OTEZLA® for 8 weeks. At week 8, patients who achieved between PASI 25-74 response will receive 4 weeks of Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% in addition to continuing OTEZLA® therapy. Patients who do not meet PASI 25 at week 8 will be discontinued from the study. At week 12 (after 4 consecutive weeks of Enstilar® add on therapy), Enstilar® will be discontinued and these patients will continue Otezla® as monotherapy through week 16. Patients who achieve PASI 75 at week 8 will remain enrolled on Otezla® monotherapy through week 16.
Study Centers	Single Center
Study Population	Adult male and female subjects with moderate to severe chronic plaque psoriasis
Main Inclusion Criteria	Subjects must meet the following criteria to be enrolled in this study: 1.Male or female adult ≥ 18 years of age; 2. Diagnosis of chronic plaque-type psoriasis 3. Moderate to severe plaque type psoriasis as defined at baseline by:

	• PGA score of 3 or greater • BSA affected by plaque-type psoriasis of 10% or greater • PASI ≥ 12 4. Able and willing to give written informed consent prior to performance of any study-related procedures 5. 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).
Main Exclusion Criteria	Subjects who meet any of the following criteria will be excluded from participation in this study: 1. Other than psoriasis, any clinically significant (as determined by the investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major disease that is uncontrolled. 2. Forms of psoriasis other than chronic plaque-type (e.g., Pustular erythrodermic and/or guttate psoriasis) or drug induced psoriasis 3. Subjects who previously used any biologic agent for psoriasis. 4. Use of oral systemic medications for the treatment of psoriasis within 4 weeks (includes, but not limited to, oral corticosteroids, methotrexate, acitretin and cyclosporine). 5. Patient used topical therapies to treat psoriasis on the hands and/or feet within 2 weeks of the Baseline Visit (includes, but not limited to, topical corticosteroids, vitamin D analogs, or retinoids). 6. Patient received UVB phototherapy within 2 weeks of Baseline.
Study Drug Dosage and Administration	All patients will receive OTEZLA® 30mg twice daily at week 0 (baseline) through week 8. At week 8, patients who achieved between PASI 25-74 response will receive 4 weeks of add-on Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% once daily in addition to continuing OTEZLA® 30mg twice daily. At week 12 (after 4 consecutive weeks of Enstilar® add on therapy), Enstilar® will be discontinued and patients will continue OTEZLA® 30mg twice daily as monotherapy through week 16.

	Patients who achieve PASI 75 at week 8 will remain enrolled on OTEZLA® 30mg BID monotherapy through week 16.
Study Endpoints	Primary Endpoints: PASI 75 at week 12 for patients in the OTEZLA® + Enstilar® combination arm. Secondary Endpoints: PASI 25-74 at week 8. PASI, PGA, BSA, PGAxBSA and DLQI improvement at week 8 PASI, PGA, BSA, PGAxBSA and DLQI improvement at week 12 PASI PGA, BSA, PGAxBSA and DLQI improvement at week 16 Serious Adverse Events (SAE's)
Study Duration	***16 weeks*** The subject may continue to participate in this study until one of the following occurs: • Subject has not achieved PASI 25 at week 8 • The subject experiences a significant or serious adverse event related to study drug; • Subjects who initially achieved PASI 75 at week 8 and lose response by week 12 may withdraw at their own request. • Subjects who received Enstilar® add-on therapy for 4 weeks and have not achieved PASI 75 at week 12 may withdraw at their own request. • The subject is not willing to continue participation in the study; • Subject completes 16 weeks of study drug and evaluations • The Sponsor decides to terminate the study for any reason.

2 ETHICS AND REGULATORY OBLIGATIONS

2.1 Institutional Review Board (IRB)

Written IRB approval of this protocol must be obtained before the study is initiated. Compliance with Title 21 of the US Code of Federal Regulations (CFR), Part 56, is required in order to protect the rights and welfare of human subjects involved in this study.

2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and its amendments. In addition, the study will be performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents.

2.3 Subject Information and Consent

The Informed Consent Form will be reviewed and approved by the IRB. The purpose, duration and possible risks and benefits will be explained to each potential subject. Consent in writing must be obtained from the subject before enrollment into the study. Consents will be signed and dated as required by Title 21 of CFR, Part 50. The consent will also comply with the requirements of the Health Insurance Portability and Accountability Act (HIPAA). The original, signed Informed Consent Form will be retained by the Investigator. A signed copy of the Informed Consent Form will be given to the subject. Each subject will be assigned a subject number that will be used in lieu of the subject's name on further research documentation.

3 INTRODUCTION

3.1 Overview of Psoriasis

Psoriasis is a chronic immunological disease characterized by infiltration of the skin with activated T cells and by abnormal keratinocyte proliferation and differentiation, resulting in marked inflammation and thickening of the epidermis. Psoriasis affects 1-3% of the world population, making it one of the most prevalent inflammatory immunological diseases.[1] There are several clinical subtypes of psoriasis: plaque, guttate, erythrodermic, inverse, and pustular. Plaque psoriasis is the most common type of

psoriasis affecting 75-80% of psoriasis sufferers.[2] It presents as raised silvery scale, which can cover large areas, with underlying erythema, itching, and discomfort.

3.2 Rationale for Treating Plaque Psoriasis with OTEZLA® + Enstilar®

OTEZLA® and Enstilar® are both effective in treating psoriasis. The pivotal OTEZLA® Phase III trials (ESTEEM) determined that apremilast was effective in treating moderate to severe plaque psoriasis. The primary endpoint at week 16 demonstrated significantly more apremilast-treated patients (33.1%) achieved the primary end point (PASI-75 at week 16) than did placebo patients (5.3%).[3] Combination regimens that utilize a systemic agent with light therapy and/or a topical agent are becoming the standard of care in the United States[4] and Europe[5], confirming the observation of Lebwohl et al[6] in 2004, that the use of two or more therapies to treat patients with moderate to severe psoriasis seems to be the rule rather than the exception. Topical steroids play an in important role in the long term management of psoriasis and data from the COBRA trial suggests that super potent topical corticosteroids are appropriate and well tolerated for use when added to existing therapeutic regimens i.e. phototherapy, systemic and biologic therapy.[7] A post hoc analysis of the Phase 3 ESTEEM 1 trial of apremilast was conducted to assess the efficacy and safety of apremilast with and without topical therapies and/or UVB phototherapy. The analysis focused on the sub-group of patients who did not achieve PASI 75 at week 32. At week 52, more patients receiving topical therapy and/or phototherapy achieved PASI 75 than did patients with apremilast alone.[8] This study is being conducted to determine if adding topical Enstilar® to Otezla® therapy can help patients who received a partial response at week 8 reach PASI 75 by week 12.

4. STUDY OBJECTIVE

To explore the effectiveness and safety of combining OTEZLA® and Enstilar® and to determine if add-on Enstilar® therapy can help partial responders at week 8 achieve PASI 75 at week 12.

5. INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

50 subjects affected with plaque psoriasis with body surface area greater than or equal to 10%, and physician's global assessment greater than or equal to 3 and PASI greater than or equal to 12 will receive OTEZLA® 30 mg twice daily for 8 weeks.

Patients who do not achieve at least a PASI 25 at week 8 will be discontinued from treatment and study procedures.

At week 8, subjects who have achieved a PASI 25-74 will receive Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% once daily for 4 weeks in addition to continuing OTEZLA® BID. These patients will then discontinue Enstilar® at week 12 and remain on OTEZLA® monotherapy through week 16.

Patients who achieve PASI 75 at week 8 will remain enrolled in the study and continue OTEZLA® 30mg BID through week 16. These subjects will not receive Enstilar® add-on therapy.

5.2 Study Population Criteria

Males and females ≥ 18 years of age with moderate-to-severe chronic plaque psoriasis

5.2.1 Inclusion Criteria

Patients who meet all of the following criteria will be enrolled in the study:

1.Male or female adult ≥ 18 years of age

2. Diagnosis of chronic plaque-type psoriasis

3. Moderate to severe plaque type psoriasis as defined at baseline by:
• Physcian's Global Assessment (PGA) score of 3 or greater
• Body Surface Area (BSA) affected by plaque-type psoriasis of 10% or greater
• Psoriasis Area Severity Index of 12 or greater

4. Able and willing to give written informed consent prior to performance of any study-related procedures

5. 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).

6. Females of childbearing potential (FCBP)† must have a negative pregnancy test at Screening and Baseline. While on investigational product and for at least 28 days after taking the last dose of investigational product, FCBP who engage in activity in which conception is possible must use one of the approved contraceptive§ options described below:

Option 1: Any one of the following highly effective methods: hormonal contraception (oral, injection, implant, transdermal patch, vaginal ring); intrauterine device (IUD); tubal ligation; or partner's vasectomy;

OR

Option 2: Male or female condom (latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]; PLUS one

additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.

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

5.2.2 Exclusion Criteria

Patients will NOT be enrolled in this study if they meet any of the following criteria:

1. Other than psoriasis, any clinically significant (as determined by the Investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major disease that is currently uncontrolled.
2. 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.
3. Pregnant or breast feeding, or considering becoming pregnant during the study.
4. Active substance abuse or a history of substance abuse within 6 months prior to Screening.
5. Malignancy or history of malignancy, except for:
    a. treated [ie, cured] basal cell or squamous cell 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.
6. Use of any investigational drug within 4 weeks prior to randomization, or within 5 pharmacokinetic/pharmacodynamic half lives, if known (whichever is longer).
7. Prior treatment with apremilast.
8. Forms of psoriasis other than chronic plaque-type (e.g., Pustular erythrodermic and/or guttate psoriasis) or drug induced psoriasis
9. Subject has previously used any biologic agent for psoriasis.

10. Use of oral systemic medications for the treatment of psoriasis within 4 weeks (includes, but not limited to, oral corticosteroids, methotrexate, acitretin and cyclosporine).

11. Patient used topical therapies to treat psoriasis on the hands and/or feet within 2 weeks of the Baseline Visit (includes, but not limited to, topical corticosteroids, vitamin D analogs, or retinoids).

12. Patient received UVB phototherapy within 2 weeks of Baseline.

13. Patient has a known hypersensitivity to the excipients of OTEZLA® or Enstilar® as stated in the label.

14. Any conditionwhich would place the subject at unacceptable risk if he/she were to participate in the study.

5.3 Source of Subjects and Recruitment Methods

The Investigator will manage the recruitment of subjects upon approval of the study by the Institutional Review Board. Subjects may be recruited from internal patient lists and outside IRB approved advertisements.

5.4 Subject Enrollment and Treatment Assignment

50 subjects of either gender with moderate-to severe plaque psoriasis will randomized to receive OTEZLA® 30mg BID for 8 weeks. Participation beyond week 8 will be determinate of subject response according to the study design.

5.5 STUDY TREATMENT

5.5.1 Apremilast Treatment (OTEZLA®)

5.5.1.1 Apremiliast (OTEZLA®) Description

OTEZLA® is manufactured by Celgene Corporation. The active ingredient in OTEZLA® tablets is apremilast. Apremilast is a small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). The chemical name of apremilast is acetamide, N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl].PDE4 inhibition results in increased intracellular cAMP levels. The specific mechanism(s) by which apremilast exerts its therapeutic action in psoriasis patients is not well defined.

5.5.1.2 OTEZLA® Warnings and Precautions

Diarrhea, Nausea, and Vomiting

There have been postmarketing reports of severe diarrhea, nausea, and vomiting associated with the use of OTEZLA. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued OTEZLA generally improved quickly. Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

Depression

Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur.

Psoriatic arthritis

During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.0% (10/998) of subjects treated with OTEZLA reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. During the clinical trials, 0.3% (4/1441) of subjects treated with OTEZLA discontinued treatment due to depression or depressed mood compared with none in placebo treated subjects (0/495). Depression was reported as serious in 0.2% (3/1441) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/495). Instances of suicidal ideation and behavior have been observed in 0.2% (3/1441) of subjects while receiving

OTEZLA, compared to none in placebo treated subjects (0/495). In the clinical trials, 2 subjects who received placebo committed suicide compared to none in OTEZLA-treated subjects.

Psoriasis

During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (12/920) of subjects treated with OTEZLA reported depression compared to 0.4% (2/506) treated with placebo. During the clinical trials, 0.1% (1/1308) of subjects treated with OTEZLA discontinued treatment due to depression compared with none in placebo-treated subjects (0/506). Depression was reported as serious in 0.1% (1/1308) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) of subjects while receiving OTEZLA, compared to 0.2% (1/506) in placebotreated subjects. In the clinical trials, one subject treated with OTEZLA attempted suicide while one who received placebo committed suicide.

Weight Decrease

During the controlled period of the studies in psoriatic arthritis (PsA), weight decrease between 5%-10% of body weight was reported in 10% (49/497) of subjects treated with OTEZLA 30 mg twice daily compared to 3.3% (16/495) treated with placebo [see Adverse Reactions (6.1)]. During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (96/784) of subjects treated with OTEZLA compared to 5% (19/382) treated with placebo. Weight decrease of ≥10% of body weight occurred in 2% (16/784) of subjects treated with OTEZLA 30 mg twice daily compared to 1% (3/382) subjects treated with placebo. Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered.

Drug Interactions

Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended. .

5.5.1.3 OTEZLA® Dosing Schedule

OTEZLA® tablets will be supplied by Celgene Corporation and administered and taken approximately 12 hours apart without regard to meals. In order to minimize risks of gastrointestinal symptoms associated with initial therapy, all subjects will receive OTEZLA® for the first 5 days according to the titration schedule in the package insert. See Appendix A

5.5.1.4 OTEZLA® Dispensing and Dosing Record

Subjects will return all unused OTEZLA® tablets to the study site. Site personnel will keep a record of OTEZLA® dispensed to and returned by each subject and note any missed doses.

5.5.1.5 OTEZLA® Dosage Adjustments

If an SAE or an adverse event that is thought to be related to OTEZLA® and is not alleviated by symptomatic intervention, OTEZLA® will be discontinued.

Subjects who permanently discontinue OTEZLA® therapy under this protocol should receive standard care of psoriasis treatment as prescribed by their physician.

5.5.2 ENSTILAR® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%

5.5.2.1 Enstilar® Description

Enstilar® Foam is a combination of calcipotriene, a vitamin D analog, and betamethasone dipropionate, a corticosteroid, indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older. Each gram of Enstilar® Foam contains 52.2 mcg calcipotriene hydrate (equivalent to 50 mcg of calcipotriene) and 0.643 mg of betamethasone dipropionate (equivalent to 0.5 mg of betamethasone).

5.5.2.2 Enstilar® Dosing Schedule

Enstilar® will be supplied by LEO Pharma A/S. and applied once daily for 4 weeks.

5.5.2.3 Enstilar® Dispensing and Dosing Record

Enstilar® will be dispensed to the study subjects by the authorized site personnel following instructions in Enstilar® Label. Subjects will return all unused Enstilar® to the

study site. Site personnel will keep a record of Enstilar® dispensed to and returned by each subject and missed doses will be recorded on a subject diary. See Appendix B

5.5.2.4 Enstilar® Dosage Adjustments

If an SAE or an adverse event that is thought to be related to Enstilar® and is not alleviated by symptomatic intervention, Enstilar® will be discontinued.

5.5.3 Permitted Concomitant Therapy

The use of steroid-free topical emollients is allowed during the study. Appropriate interventions (e.g., prescribed medications) may be performed as the investigator deems necessary to treat concomitant illnesses and/or safeguard the subjects' wellbeing. No investigational product or device may be used during the study.

5.6 Study Procedures and Assessments

This protocol will consist of a Screening Period (0-30 days), followed by an open-label treatment period of OTEZLA® for 8 weeks (Period A). At week 8 (Part B), subjects PASI scores will be evaluated and patients who achieve PASI 25-74 will be given add-on Enstilar® treatment for 4 weeks (through week 12) followed by OTEZLA® monotherapy through week 16.

Subjects who do not achieve PASI 25 at week 8 will be discontinued from the study and follow standard of care from their provider.

Subjects who achieve PASI 75 at week 8 will remain on OTEZLA® monotherapy and will not initiate treatment with Enstilar®.

5.6.1 Informed Consent

This Study will be conducted in compliance with CFR Title 21, Part 50 (Informed Consent of Human Subjects). Informed consent will be obtained from each subject in writing before participation in the Study. A signed copy of the Informed Consent Form will be provided to each subject. A provision to obtain a signed authorization to provide protected health information to the study sponsor, internal quality assurance agencies, health insurance agencies, and other parties as specified in the Federal Health Insurance Portability and Accountability Act (HIPAA) privacy regulation will be included in the Informed Consent Document. HIPAA authorization is voluntary. However, since the use and release of health information is critical to the conduct of the study, subjects who do not provide authorization to use and disclose their health information will not be enrolled into the study. Subjects who withdraw their authorization to use and release health

information during study participation will be formally discontinued from the study. The investigator may use and release at any time all the information collected prior to a subject's withdrawal of the authorization to all authorized parties to satisfy scientific, regulatory, and financial concerns.

5.6.2 Inclusion and Exclusion Criteria

Subjects' eligibility to participate in the study will be determined according to the Inclusion and Exclusion Criteria during the screening period (0 – 30 days prior to the first dose of the study drug). Subjects who ultimately do not satisfy the eligibility criteria except changing treatments and undergoing a washout period, will not be enrolled into the study. Subjects who need to meet eligibility requirements will be asked to make the necessary changes. Subjects who agree and comply will be re-evaluated prior to Baseline.

5.6.3 Demographics and Medical History

The following information will be obtained for each subject during screening: date of birth, sex, race/ ethnic origin, medical and surgical history, including history of alcohol and drug abuse, year of diagnosis of plaque psoriasis, and current and previous anti-psoriasis treatments. All current therapies for other medical conditions will be documented. Medical history will be reviewed and updated at the Baseline Visit to ensure that the patient remains eligible to participate in the study.

5.6.4 Urine Pregnancy Test

Pregnancy testing (urine β-human chorionic gonadotrophin [β-HCG]) will be conducted in all female subjects, except those without childbearing potential at Screening (-30 to -1) and Baseline Visits (Week 0) prior to the first dose of OTEZLA®, and then again at week 16. An interim urine pregnancy test may be performed if there is reason to believe the subject may have become pregnant during the study. Subjects with a positive pregnancy test will not be eligible to participate or to continue to receive study treatment.

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

5.6.5 Physical Examination

A physical examination, including vital signs measurements, will be performed according to the schedule of events. Resting pulse and blood pressure (systolic and diastolic) measurements should be obtained in the sitting position with the subject resting for at least 5 minutes before measurements being taken. The physical examination should include a thorough evaluation of the subject's skin. Blood pressure and pulse should be measured before blood draws are performed. Any clinically significant abnormalities discovered during physical examinations after the Screening / Baseline visit should be documented and evaluated as potential adverse events.

5.6.6 Physician's Global Assessment (PGA)

PGA will be determined for all subjects throughout the study. PGA is a 6 point scale that records the overall disease severity at each clinical evaluation based on the average degree of erythema, induration, and scaling of areas affected by psoriasis. PGA uses a scale of 0 = Clear, 1 = Minimal, 2 = Mild, 3 = Moderate, 4 = Severe, and 5 = Very Severe. *See Appendix C*

5.6.7 Psoriasis Area Severity Index (PASI)

PASI will be determined for all subjects throughout the study. Four anatomical sites (head, trunk, upper and lower limbs) are assessed for erythema, thickness, and scaling on a scale of 0-4 and degree of skin surface area on a scale of 6. The PASI is a validated instrument that has become standard in clinical trials for psoriasis. The sum of the scores are then totaled for the PASI score. Psoriasis Area Severity Index scores range from 0 to 72, with higher scores reflecting greater disease severity.[9] *See Appendix D*

5.6.8 Body Surface Area (BSA)

BSA will be determined for all subjects throughout the study. The subjects palm will be selected for the measuring unit of body surface area. The physician will equate the number of palms affected by psoriasis to derive the BSA total.

5.6.9 Patient Reported Outcomes

Subjects will complete the PRO's based on the schedule of assessments. Questionnaires should be prior to medical procedures and clinical evaluations.

Dermatology Life Quality Index (DLQI)[10] to assess symptoms and impacts of dermatologic diseases on quality of life. *See Appendix E*

5.6.10 Early Discontinuation Procedures

Subjects will be prematurely discontinued from the study under the following conditions:

1. Subject does not reach PASI 25 or greater at week 8
2. Subject requests to withdraw from the study.
3. Subject is noncompliant with protocol schedule, restrictions, and/or requirements as deemed per investigator.
4. Subject experiences an adverse event that makes it difficult or intolerable for the subject to continue treatment, or increases risk to the subject, or interferes with the investigator's ability to clinically evaluate the progress of the subject's treatment.
5. Subject begins an unapproved concomitant therapy for psoriasis or another medical condition that may increase risk to the subject if continuing study treatment.
6. Subject cannot be reached / lost to follow-up.
7. The study investigator suspends or terminates the study.
8. Other unanticipated reason.

Any subject who prematurely discontinues the study should complete the week 16 (End of Study) assessments. Any subject who withdraws consent to participate in the study will be removed from further treatment and/or study observation immediately upon the date of request.

6 ADVERSE EVENTS

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 if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study.
- Requires treatment, modification/interruption of study drug dose, or any other therapeutic intervention.
- Is judged by the Investigator(s) to be of significant clinical importance.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Serious adverse event

A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (i.e., in the opinion of the Investigator(s) the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

If an AE is considered serious, both the AE pages of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator(s) will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

Classification of severity

For both AEs and SAEs, the investigator(s) must assess the severity of the event. The AEs will be evaluated for severity according to the following scale:

Grade 1 = Mild

Grade 2 = Moderate

Grade 3 = Severe

Classification of Relationship/Causality of adverse events (SAE/AE) to study drug

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

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

Immediate reporting of serious adverse events

Any AE that meets the any criterion for a SAE requires the completion of an SAE Report Form in addition to being recorded on the AE pages of the CRF. The Investigator(s) is required to ensure that the data on these forms is accurate and consistent. This applies to all SAEs, regardless of relationship to study drug, that occur during the study, those made known to the Investigator(s) within 30 days after a subject's last dose of study drug, and those made known to the investigator(s) at 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
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 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.

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 eligibility 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.

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.

7 INVESTIGATIONAL PRODUCT HANDLING

7.1 Investigational Product Receipt

At study initiation and as needed thereafter, OTEZLA® and Enstilar® will be shipped to a responsible person (e.g., a pharmacist) at the investigator's institution, who will check the amount and condition of the drug, and maintain a record of this information.

7.2 Investigational Product Storage

Investigational product will be stored per the storage conditions identified on drug label. At the study site, all IP will be stored in a locked, safe area to prevent unauthorized access.

Records of the actual storage conditions during the period of the study will be maintained.

8 RECORD RETENTION

The investigator must retain these documents according to local laws or requirements. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC; Composition of the IRB/EC;
- Record of all communications between the Investigator and Celgene.
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- All other source documents (subject records, hospital records, laboratory records, etc);
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented. All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

8.1 Study Monitoring

The investigator will self-monitor all study records for accuracy, completeness, and compliance with the protocol and GCPs and federal regulations. All study records will be made available to Celgene Corporation representatives upon request. Study site facilities and study records will be made available to regulatory authorities' inspectors if an inspection takes place. The investigator will notify Celgene Corporation if this occurs.

8.2 Statistics

It is desired to enroll 50 patients based on the data from the Esteem trial which showed 55% of subjects achieved between a PASI 25- PASI 74 response at week 8, hence it is expected that 30-40 patients will fit the continuation criteria at week 8 and be followed through week 16.

The study will analyze data based on the non-responder imputation (NRI) method. This will be performed for each arm of the study (PASI 75 responders at week 8 and PASI 25-74 responders at week 8. Subjects who do not complete week 16 assessments will be classsifed as non-responders.

Since this is a pilot study with no formal hypothesis testing, statistical power/sample size is not formally presented in this protocol.

Analysis will be performed by the Investigator on proportion of subjects achieving Psoriasis Area Severity Index (PASI) 75 response at week 12

The investigator will also analyze PASI 25-74 at week 8, PASI, PGA, BSA, PGAxBSA and DLQI improvement at week 8, BSA, PGA and BSA x PGA and DLQI improvement at week 12. PASI, BSA, PGA, BSA x PGA and DLQI at week 16. This analysis will be done separately for both cohorts (PASI 75 responders at week 8 and PASI 25-74 responders at week 8) using summary statistics. The Investigator will also analyze SAE's by cohort.

8.2.1 Additional Statistical Considerations

Additional statistical procedures may be detailed in and performed according to a separate statistical plan at the discretion of sponsor-investigator.

8.3 Schedule of Events

Procedure	Screening	BASELINE	Week4	Week 8	Week 12	Week 16
Informed Consent	X					
Demographics/Medical History	X	X				
Inclusion/Exclusion	X	X				
Physical Exam	X	X		X	X	X
Concomitant Medications	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X
Urine Preg Test	X	X				X
PASI	X	X		X	X	X
BSA	X	X		X	X	X
PGA	X	X		X	X	X
DLQI		X		X	X	X
Vital Signs	X	X		X	X	X
IP dispensing/accountability		X	X	X	X	X

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7. APPENDICES

Appendix A

OTEZLA® dosing schedule

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6 & thereafter
AM	AM/PM	AM/PM	AM/PM	AM/PM	AM/PM
10MG	10MG/10MG	10MG/20MG	20MG/20MG	20MG/30MG	30MG/30MG

Appendix B
Subject Diaries

Storage

●Keep study medication at room temperature.
●Keep out of reach of children

Enstilar Dosing

●Apply once daily
●Do not apply on face, underarms or groin
●Avoid heat, flames or smoking when applying.
●Do not bandage, cover, or wrap the treated area
●Apply to affected areas and gently rub in.
●Avoid bathing, showering or swimming right after applying the study medication.

Dosing Diary

●Record all doses on the diary as soon as possible.
●Return diary and medication to all of your appointments.
●Record any comments or information in “remarks” section for missed dose, adverse event, or change in medication.
●Please make recordings clear and legible.

	Date (MMM/DD)	Dose (Circle One)	Time (HH:MM)	Remark
Ex	Jan/01	AM / PM	0800	
1		AM / PM		
2		AM / PM		
3		AM / PM		
4		AM / PM		
5		AM / PM		
6		AM / PM		
7		AM / PM		
8		AM / PM		
9		AM / PM		
10		AM / PM		
11		AM / PM		
12		AM / PM		
13		AM / PM		
14		AM / PM		

	Date (MMM/DD)	Dose (Circle One)	Time (HH:MM)	Remark
15		AM / PM		
16		AM / PM		
17		AM / PM		
18		AM / PM		
19		AM / PM		
20		AM / PM		
21		AM / PM		
22		AM / PM		
23		AM / PM		
24		AM / PM		
25		AM / PM		
26		AM / PM		
27		AM / PM		
28		AM / PM		

Appendix C

Physician's Global Assessment

Physician's Global Assessment (PGA)

Score	Grade	Definition
0	**Clear**	Plaque elevation = 0 (no elevation) Scaling = 0 (no scale) Erythema = 0 (residual post-inflammatory hyperpigmentation or hypopigmentation may be present)
1	**Minimal**	Plaque elevation = ± (possible, but difficult to ascertain whether there is a slight elevation) Scaling = ± (surface dryness with some white coloration) Erythema = up to moderate (up to definite red color)
2	**Mild**	Plaque elevation = slight (slight, but definite elevation, typically edges are indistinct or sloped) Scaling = fine (fine scale partially or mostly covering lesions Erythema = up to moderate (up to definite red coloration)
3	**Moderate**	Plaque elevation = moderate (moderate elevation with rough or sloped edges) Scaling = coarser (course scale covering most of all of the lesions) Erythema = moderate (definite red coloration)
4	**Severe**	Plaque elevation = marked (marked elevation typically with hard or sharp edges) Scaling = course (course, non-tenacious scale predominates) Erythema = severe (very bright red coloration)
5	**Very Severe**	Plaque elevation = very marked (very marked elevation typically with hard sharp edges) Scaling = very coarse (course, thick tenacious scale of over most of all of the lesions; rough surface) Erythema = very severe (extreme red coloration; dusky to deep red coloration)

Appendix D

Psoriasis Area Index Severity

PASI Scoring

Four anatomic sites – head, upper extremities, trunk, and lower extremities – are assessed for erythema, induration (plaque thickness), and desquamation (scaling) as seen on the day of the examination. The severity of each sign is assessed using a 5-point scale:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Marked
- 4 = Very marked

The table below outlines the characteristics of each category.

	Erythema[a]	Desquamation	Induration
0 = none	No redness	No scaling	No elevation over normal skin
1 = slight	Faint redness	Fine scale partially covering lesions	Slight but definite elevation, typically edges indistinct or sloped
2 = moderate	Red coloration	Fine to coarse scale covering most of all of the lesions	Moderate elevation with rough or sloped edges
3 = marked	Very or bright red coloration	Coarse, non-tenacious scale predominates covering most or all of the lesions	Marked elevation typically with hard or sharp edges
4 = very marked	Extreme red coloration; dusky to deep red coloration	Coarse, thick, tenacious scale over most or all lesions; rough surface	Very marked elevation typically with hard sharp edges

a. Do not include residual hyperpigmentation or hypopigmentation as erythema.

Appendix E

Dermatology Life Quality Index

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

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

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

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

Please check you have answered EVERY question. Thank you.