

A Study to Evaluate the Safety and Efficacy of Brodalumab in Subjects With Moderate to Severe Plaque Psoriasis Who Have Failed IL-17A Therapies.

PI: Dr. Mark Lebwohl

NCT03403036

Document Date: Oct 12, 2017

**A Study to Evaluate the Safety and Efficacy of Brodalumab in  
Subjects With Moderate to Severe Plaque Psoriasis Who Have Failed  
IL-17A Therapies.**

**Protocol Version Date:** July 18, 2017

**Amendment #1:** October 2, 2017

**Amendment #2:** October 12, 2017

**Lead Investigator:** Mark Lebwohl, MD

**Lead Site:**  
Icahn School of Medicine at Mount Sinai  
Department of Dermatology  
5 East 98th Street - [REDACTED], Box 1048  
New York, NY 10029  
Tel: 212-241-3288

**Additional Sites:**  
Soo Jung Kim, MD, PhD  
Baylor College of Medicine  
1977 Butler Boulevard, [REDACTED]  
Houston, TX 77030  
Tel: 713-798-6131

Jerry Bagel, MD  
Windsor Dermatology  
D.B.A.Psoriasis Treatment Center of Central New Jersey  
59 One Mile Road  
East Windsor, NJ 08520  
Tel: 609-443-4500 ext 1402

## **INTRODUCTION/BACKGROUND**

Psoriasis is a common, chronic inflammatory skin disease that is characterized by the formation of sharply demarcated, scaly, erythematous plaques. It is a prevalent disease, affecting about 2.2% of the population in the United States.[1] Psoriasis has a high impact on patients' quality of life, with many reporting discomfort, itching, and significant social and emotional burden secondary to the disease. [2, 3] Without treatment, remission from psoriasis is unlikely. [4] Traditional treatment options include topical steroids and vitamin D analogues, and systemic immunosuppressive agents such as cyclosporine and methotrexate. However, these treatments are often not as efficacious as would be desirable, and are associated with significant side effects and risks. In the past several years, the development of biologic agents, in particular monoclonal antibodies, has revolutionized the treatment of psoriasis.

Brodalumab is a human interleukin-17 receptor A (IL-17RA) antagonist recently approved for the treatment of moderate-to-severe plaque psoriasis. Clinical trials of brodalumab included 3 multicenter, randomized, double-blind, controlled trials which enrolled a total of 4373 adult subjects with moderate-to-severe plaque psoriasis.[5] At week 12, PASI-75 and PASI-100 responses were seen in about 85% and 40% of patients, respectively. Nearly 80% of patients achieved static Physician's Global Assessment (sPGA) scores of clear (0) or almost clear (1) at week 12. Maintenance of treatment effect was also established, with high response rates seen through week 52. Of note, approximately 30% of patients reported previous treatment with a biologic, and 12% reported treatment failure with a previous biologic. [5] At present, other biologic drugs that target the IL-17 signaling pathway include secukinumab and ixekizumab, although these agents inhibit the IL-17A ligand, rather than its receptor. It is unknown how patients who have failed treatment specifically with other IL-17 targeting agents respond to brodalumab treatment.

This study will evaluate the safety and efficacy of brodalumab in the treatment of moderate-to-severe psoriasis in patients who have previously failed treatment with interleukin (IL)-17A therapies. Failure of IL-17A therapy will be defined as previous treatment with either secukinumab or ixekizumab for at least 3 months without achieving PASI-75 response or a 50% loss of original improvement. Forty patients will be enrolled in this 16-week open-label study. Patients will be enrolled at three to four different sites in the US. After enrollment, study visits will occur at monthly intervals, with patients receiving 210 mg of brodalumab subcutaneous injection at weeks 0, 1, and 2, followed by 210 mg every 2 weeks. At each visit, patients will be evaluated for change in sPGA (Physician's Global Assessment), PASI score, and any signs or symptoms of adverse events. Laboratory screening will include tests for tuberculosis and neutropenia. The primary efficacy endpoint will be the proportion of patients achieving a score of "0-clear" or "1-almost clear" in the sPGA score after 16 weeks of treatment. After completion of the 16-week trial, patients may desire to continue treatment with brodalumab. Efforts will be made to provide drug to these study patients, including those who do not have insurance.

## **HYPOTHESIS:**

### **Primary Hypothesis:**

1. It is hypothesized that treatment with brodalumab, an IL-17RA antagonist, will be effective in the treatment of moderate-to-severe psoriasis patients who have previously failed treatment with IL-17A therapies.

## **OBJECTIVES:**

**Primary objective:** To evaluate the efficacy of brodalumab in the treatment of moderate-to-severe psoriasis patients who have previously failed treatment with IL-17A therapies by measuring different scoring systems for psoriasis (PASI, BSA, sPGA; see appendix) at week 16.

**Secondary objective:** To determine the safety of brodalumab in the treatments of moderate-to-severe psoriasis patients who have previously failed treatment with IL-17A therapies.

## **ENDPOINTS:**

**Primary endpoint:** Proportion of patients achieving a score of “0-clear” or “1-almost clear” in the sPGA score after 16 weeks of treatment.

### **Secondary endpoints:**

1. Proportion of patients achieving PASI-100 response after 16 weeks of treatment.
2. The proportion of patients who achieve an improvement of 50% or greater in BSA involvement after 16 weeks of treatment.
3. Proportion of patients achieving PASI-75 response after 16 weeks of treatment.
4. Proportion of patients achieving PASI-90 response after 16 weeks of treatment.

## **RESEARCH DESIGN:**

This is an open-label study of a total of 40 subjects enrolled at 3 to 4 sites, with moderate-to-severe psoriasis who have previously failed treatment with an IL-17A agent. Subjects will receive brodalumab 210 mg via subcutaneous injection at weeks 0, 1, and 2, followed by 210 mg every 2 weeks; total study length is 16 weeks.

## **METHODS:**

Informed consent will be obtained at the study site at the time of the first consultation for participation in this study.

After providing informed consent, subjects will be assessed for study eligibility at the Screening visit (day -28 to day -1). At the Screening visit the following procedures will be performed:

1. Medical history and concomitant as well as prior medications/treatments will be reviewed
2. Skin examination will be performed (including assessment of PASI, sPGA, and BSA)
3. Approximately 14 cc (approximately 3 teaspoons) of blood will be drawn for a complete blood count (including differential) (not required if subject can provide results from a previous test performed within 4 months of screening visit).
4. Approximately 5 cc (approximately 1 teaspoon) of blood will be drawn for a QuantiFERON TB-Gold test (QFT) assay; or subjects will undergo tuberculin purified protein derivative (PPD) testing (not required if subject can provide results of a negative test performed within 8 months of screening visit).
5. Females of child bearing potential will have 5 cc (approximately 1 teaspoon) of urine collected for a pregnancy test. This test must be negative in order to qualify for the study.

Subjects will be deemed eligible as per inclusion/exclusion criteria. Qualified subjects meeting all the inclusion and exclusion criteria will be start treatment at Day 0/Baseline (within 28 days of signing the consent form). Female subjects of child-bearing potential will have 2 teaspoons of urine collected for a pregnancy test prior to treatment. This test must be negative in order to continue to qualify for the study. Assessments at this Day 0/Baseline visit include skin examination with assessment of PASI, sPGA, and BSA scores.

Subjects will receive brodalumab (210 mg) via subcutaneous injection using prefilled syringes at Weeks 0, 1, 2, and every 2 weeks thereafter through and including Week 16. Patients will be taught how to administer the drug subcutaneously by a study investigator or designated research staff member at the Baseline visit. They will be dispensed a one-month supply of medication at baseline and each subsequent visit for self-administration at home.

At Weeks 4, 8, 12 and 16 subjects will return for assessment of concomitant medications and adverse events, and skin assessments including PASI, sPGA, BSA scores, and photography of target lesion(s). In addition, females of child-bearing potential will have 2 teaspoons of urine collected for a pregnancy test at each visit.

## **PATIENT POPULATION:**

Prior to enrollment, all subjects must meet the following inclusion and exclusion criteria:

### **Inclusion criteria:**

1. Male or female subject at least 18 years of age
2. Subject is able to provide written informed consent and comply with the requirements of this study protocol.
3. Have both a sPGA score of  $\geq 3$  and BSA  $\geq 5\%$  prior to randomization.

4. Subjects who are women of childbearing potential must have a negative urine pregnancy test at screening and must be practicing an adequate, medically acceptable method of birth control for at least 30 days before Day 0 and at least 6 months after the last study drug administration. Acceptable methods of birth control include intrauterine device (IUD); oral, transdermal, implanted or injected hormonal contraceptives (must have been initiated at least 1 month before entering the study); tubal ligation; abstinence and barrier methods with spermicide. Otherwise, if not of childbearing potential, subjects must: have a sterile or vasectomized partner; have had a hysterectomy, a bilateral oophorectomy or be clinically diagnosed infertile; or be in a menopausal state for at least a year.
5. Tuberculin purified protein derivative (PPD) or QuantiFERON TB-Gold test (QFT) negative at the time of screening, or if patient has a history of positive PPD or QuantiFERON, he/she has initiated or completed the appropriate prophylaxis.
6. Subject is judged to be in good general health as determined by the principal investigator based upon the results of medical history and laboratory profile.
7. Subject has previously failed treatment with an IL-17A agent, secukinumab or ixekizumab, (where available, defined as previous treatment with either drug for at least 3 months without achieving PASI-75 response or a 50% loss of original improvement).
8. Last administration of secukinumab or ixekizumab  $\geq$  28 days prior to Baseline.

**Exclusion criteria:**

1. Have predominantly pustular, erythrodermic, and/or guttate forms of psoriasis.
2. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis infection as defined by a positive tuberculin purified protein derivative (PPD) or QuantiFERON TB-Gold test (QFT) at Screening. Subjects with a positive or indeterminate PPD or QFT test may participate in the study if a full tuberculosis work up (according to local practice/guidelines) is completed within 12 weeks prior to randomization and establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment must have been initiated at least for 4 weeks prior to randomization and the course of prophylaxis is planned to be completed.
3. Subjects with a history of HIV, or history of positive HCV or HBV
4. Use of any of the following therapies within 4 weeks prior to Baseline (Visit 2): systemic non-biologic psoriasis therapies (including, but not limited to): psoralens and ultraviolet A (PUVA) therapy, cyclosporine, methotrexate, azathioprine, corticosteroids, apremilast, tofacitinib, oral retinoids, mycophenolate mofetil, sirolimus; 1, 25 dihydroxyvitamin D analogs; or phototherapy (including UVB or self-treatment with tanning beds or therapeutic sunbathing) or topical psoriasis therapy with psoralens.
5. Use of topical corticosteroid preparations, topical calcineurin inhibitors, or other topical preparations with immunomodulatory properties within 2 weeks prior to Baseline (Visit 2).

6. Use of any investigational drug or any systemic drug for psoriasis within four weeks prior to Baseline (Visit 2).
7. Serious concomitant illness that could require the use of systemic corticosteroids or otherwise interfere with the patient's participation in the trial.
8. Clinically important deviation as judged by the investigator (such WBC< 3) from normal limits in physical examination, vital sign measurements, clinical laboratory tests results, not associated with a chronic, well-controlled medical condition.
9. Any active live-vaccines 3 months prior to baseline and throughout the study.
10. Have a current or history of lymphoproliferative disease within 5 years prior to Baseline (Visit 2); or have current or history of any malignant disease within 5 years prior to Baseline (Visit 2).
11. History of suicide attempt, or are clinically judged by investigator to be at risk of suicide.
12. History of Crohn's disease.
13. Had a serious infection, been hospitalized, or received IV antibiotics for an infection, within 12 weeks prior to Baseline (Visit 2).
14. Known immunodeficiency, or history of infection typical of an immunocompromised host.
15. At screening, have a neutrophil count <1500 cells/uL.
16. At screening, have a lymphocyte count <800 cells/uL.
17. At screening, have a platelet count <100,000 cells/uL.
18. At screening, have a total white blood count (WBC) < 3000 cells/uL.
19. At screening, have a hemoglobin <8.5 g/dL.
20. Have donated >450 mL of blood within 4 weeks prior to screening (Visit 1), or intend to donate blood during the course of the study.
21. Women who are lactating or breastfeeding.
22. Any other condition that precludes the patient from following and completing the protocol, in the opinion of the investigator.

#### **STATISTICAL METHODS:**

Individual efficacy variables, the sum of those variables, and safety parameters will be analyzed separately. Subjects who discontinue prematurely because of inadequate response or because of adverse events will have their last results carried forward for purposes of analysis.

#### **ADVERSE EVENTS:**

As of July 19, 2016, the brodalumab safety package across multiple indications included 6243 brodalumab-treated patients. The majority of patients were followed for 1 to 2 years, with 102 having follow up for over 5 years. The safety profile of brodalumab in psoriasis patients include 4464 patients, using integrated safety data from the phase 2 and phase 3 trials, and their open-label extensions. Overall, the safety profile of brodalumab was found to be consistent with other biologic agents targeting the IL-17 pathway.

The most common adverse events ( $\geq 2\%$  of patients) in patients exposed to brodalumab 210 mg q2w were nasopharyngitis, upper respiratory tract infection, arthralgia, and headache. Adverse drug reactions include headache, arthralgia, fatigue, oropharyngeal pain, diarrhea, nausea, myalgia, influenza, injection site reactions, neutropenia, and tinea infections, conjunctivitis, and candida infections.

Through the end of the psoriasis studies, a total of 23 deaths were reported among the patients who received brodalumab. This includes a total of 4 completed suicides, including one reported as an intentional overdose. There was no increase in overall risk of death above what would be expected in the patient population.

There were no differences in the rates of serious adverse events at week 12 of treatment between brodalumab, ustekinumab, or placebo. Overall, the rates of adverse events leading to discontinuation of treatment were low and comparable to placebo at week 12 and ustekinumab at week 52, with no increase through the long term period. Serious adverse events with incidence rates  $\geq 0.1\%$  in the brodalumab patients at week 12 were cellulitis, appendicitis, gastroenteritis, and acute pancreatitis. Major Adverse Cardiovascular Events (MACE) were reported at 0.2% at 12 weeks in brodalumab exposed patients, and 0.61 per 100 patient years in the all-brodalumab group at week 52 as compared to 0.40 in the ustekinumab group. The sponsor concluded that there was no evidence for a causal association between MACE and brodalumab.

Other identified and potential risks of brodalumab treatment include: worsening of Chron's disease; higher rate of infections with the majority reported as nonserious, mild, and self-limited; neutropenia at a rate of 0.7% in the 12-week trial, with most cases reported as transient and reversible; hypersensitivity at a rate of 1.7% for brodalumab 210 mg q2w; and malignancy, with exposure-adjusted event rates at 52 weeks of 0.3 in the all-brodalumab group as compared to 0.4 in the ustekinumab group, with no increase over long term follow up. [5, 6]

Brodalumab was FDA-approved in February, 2017 with a Risk Evaluation and Mitigation Strategy to ensure that prescribers and patients are aware of the risk of suicidal ideation. Investigators will be REMS certified and Study Subjects will sign the Patient-Prescriber Agreement Form prior to initiating study drug.

## **SAFETY MONITORING**

The study will be conducted in accordance with our department's Standard Operating Procedures, which are based on US FDA Title 21 Code of Federal Regulations and ICH Good Clinical Practice guidelines.

An investigator will review all laboratory results and assess for adverse events. The principal investigator will be informed of all adverse events. In the event that a subject's safety is compromised, the investigator will discontinue the subject immediately.

A DSMB will be formed and will be comprised of two board certified dermatologists experienced in prescribing biologic treatments. All SAEs will be reported to the DSMB board within 24 hours of our being informed of the event. In addition, the DSMB will receive a compiled list of all related adverse events, from all sites, every three months, so that they can determine if the risks have changed and whether or not the study should continue as planned.

**Definition of an AE:** Any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the investigational medicinal product.

Investigational Medicinal Product (IMP) includes the drug under evaluation and the comparator drug(s) if specified as part of the research objective, given at any time during the study. Medical conditions/diseases present before starting the drug of interest are only considered adverse events if they worsen after starting the drug of interest.

The occurrence of adverse events will be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events will be recorded in the study database including the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the drug(s) of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

A SAE is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is otherwise a significant medical event.

This includes any SAEs likely to arise from the trial indication or progression of underlying/concomitant illness (es) (e.g. progression of cancer in oncology trials), unless specified in the protocol as study specific exemptions.

Any SAE, irrespective of causality, occurring after the subject has provided informed consent and until four weeks after the subject has stopped study participation must be reported unless otherwise stated in the protocol. SAEs occurring after four weeks from ending study participation should only be reported if considered by the Investigator

attributable to the exposure to the investigational drug(s) during the trial period. This includes the period in which the study protocol interferes with the standard medical treatment given to a subject, even if study treatment has not yet started (e.g. withdrawal of previous treatment during washout period, change in treatment to a fixed dose of concomitant medication).

**Timelines:** All serious adverse events (SAEs) from interventional clinical trials must be reported by the sites to the Lead PI within 24 hours of occurrence of the SAE and to the site's own IRB as required. The Lead PI will then report to the manufacturer and any other authorities.

**Follow-up reports:** All related SAEs will be followed until resolution or until it is judged to be permanent, and an assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome.

**Pregnancies:** Any occurrences of a pregnancy in a patient (or a patient's partner) during study participation will be collected. All pregnancies will be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Should a temporary or permanent suspension occur, we would report the occurrence to all appropriate authorities.

## **EARLY TERMINATION**

Any individual whose health or well-being may be threatened by continuation in this study will be discontinued by the investigator.

If a female subject becomes pregnant at any time during the study, she will be discontinued immediately. She will be asked to provide the investigator with medical updates throughout her pregnancy and on the final outcome of the pregnancy.

Any subject who chooses to discontinue the study, or is discontinued from the study by the investigator will be asked to return for a final visit to have some or all of the following procedures: assessment of adverse events and concomitant medications, questionnaires, pregnancy test, blood draw for complete blood count, and skin evaluation including PASI, sPGA, and BSA.

## **INVESTIGATIONAL DRUG SUPPLY**

In this open-label study, Brodalumab will be provided by Valeant Pharmaceuticals as 210 mg brodalumab pre-filled syringes. Each site will be provided with a supply of brodalumab 210 mg for up to 15 subjects.

All study medication will be shipped to and stored by a REMS certified pharmacy in a secure cool area between 2-8°C (under refrigeration). Study drug will be dispensed to subjects at each visit, and any unused study drug will be kept at the study site. Subjects will be given a cooler to transport medication home, and instructed to keep the medication refrigerated. The number of missed doses will be documented for each subject. Each investigative site will account for all study drug dispensed and stored during the study.

### **LABORATORY SPECIMEN**

All blood and urine samples will be processed through the investigative's site local lab.

### **INSTITUTIONAL REVIEW BOARD**

Prior to beginning this study, approval for all study related documents (protocol, consent form, advertising) will be obtained from the investigative site's IRB.

## **REFERENCES**

1. Lebwohl MG, Bachelez H, Barker J, Girolomoni G, Kavanaugh A, Langley RG, Paul CF, Puig L, Reich K, van de Kerkhof PC: **Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey**. *Journal of the American Academy of Dermatology* 2014, **70**(5):871-881.e871-830.
2. Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T: **The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey**. *Archives of dermatology* 2001, **137**(3):280-284.
3. Pariser D, Schenkel B, Carter C, Farahi K, Brown TM, Ellis CN: **A multicenter, non-interventional study to evaluate patient-reported experiences of living with psoriasis**. *The Journal of dermatological treatment* 2016, **27**(1):19-26.
4. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, Lebwohl M, Koo JYM, Elmets CA, Korman NJ et al: **Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics**. *Journal of the American Academy of Dermatology* 2008, **58**(5):826-850.
5. Valeant Pharmaceuticals International ,Inc: **SILIQ (Package Insert)**. 2017.
6. Valeant Pharmaceuticals International, Inc: **BRODALUMAB Injection. Sponsor Briefing Document, Food and Drug Administration Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC)**. July 19, 2016.

## Appendix A

### Schedule of Events

	Screening	Baseline/Randomization	Treatment Phase			
	V1	V2	V3	V4	V5	V6/ET
Visit number	V1	V2	V3	V4	V5	V6/ET
Weeks since randomization	-4	0	w4	w8	w12	w16
Informed Consent	x					
Patient-Prescriber Agreement Form		x				
Medical History	x					
Demographics	x					
Inclusion/Exclusion	x	x				
Concomitant Medications	x	x	x	x	x	x
Adverse Events		x	x	x	x	x
Administer IP		x	x	x	x	
Dispense IP		x	x	x	x	
Clinical Efficacy						
sPGA	x	x	x	x	x	x
PASI	x	x	x	x	x	x
BSA	x	x	x	x	x	x
Photographs of target lesion(s) <sup>1</sup>		x	x	x	x	x
Laboratory Tests						
Quantiferon Gold/PPD (if not done in past 8 months)	x					
Urine Pregnancy (Females of child bearing potential)	x	x	x	x	x	x
Complete Blood Count w/ differential (if not performed in past 4 months)	x					

1 – **Photographs of at least one target lesion should be taken at baseline and then again at every visit thereafter.**  
**The same target lesion is to be photographed at each visit according to the site's SOPs.**

## Appendix B

### Psoriasis Area and Severity Index (PASI):

<b>PASI</b>	Head	Trunk	Upper Limbs	Lower Limbs	Symptom Score
Erythema (E)					0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very Severe
Infiltration (I)					
Desquamation (D)					
<b>Sum = E + I + D</b>					
<b>Area Score</b>					0 = none 1 = <10% 2 = 10-29% 3 = 30-49% 4 = 50-69% 5 = 70-89% 6 = 90-100%
<b>Sum x Area</b>					
x	x 0.1	x 0.3	x 0.2	x 0.4	
<b>Total</b>	<b>+</b>	<b>+</b>	<b>+</b>	<b>=</b>	

## Appendix C

### Static Physician Global Assessment (sPGA)

<u>sPGA</u>	0	1	2	3	4
<b>Induration (I) Averaged over all lesions</b>	no evidence of plaque elevation	minimal plaque elevation (0.25 mm)	mild plaque elevation (0.5 mm)	moderate plaque elevation (0.75 mm)	severe plaque elevation (> 1 mm)
<b>Erythema (E) Averaged over all lesions</b>	no erythema, hyperpigmentation may be present	faint erythema	light red coloration	moderate red coloration	bright red coloration
<b>Scaling (S) Averaged over all lesions</b>	no evidence of scaling	minimal; occasional fine scale over <5% of lesion	mild; fine scale dominates	moderate; coarse scale predominates	severe; thick scale predominates

Add I + E + S = \_\_\_\_\_ / 3 = \_\_\_\_\_ (Total Average)