An Investigator Initiated Study of Monocyte Biomarkers in Moderate to Severe Plaque Psoriasis Subjects Treated with Apremilast

INVESTIGATIONAL PRODUCT (IP): Apremilast

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PROTOCOL SUMMARY

Study Title

Otezla Reversal of Psoriasis Aberrant Monocyte CVD Event-Risk Biomarkers

Indication

Psoriasis is a chronic disease that requires long-term treatment, ideally with effective agents that offer convenient dosing and a low incidence of adverse events. Currently available systemic therapies are limited by risks of hepatic, renal and neurological toxicities, teratogenicity, as well as an increased risk of infections and malignancies. Most biologic therapies designed to treat psoriasis are administered parenterally. Given the limitations of current systemic psoriasis treatments, there is an unmet medical need for an effective oral agent that is well tolerated and less immunosuppressive than the current oral agents and parenteral biologics.

Apremilast (Otezla) is a specific phosphodiesterase type 4 (PDE4) inhibitor used in the treatment of inflammatory conditions. PDE4 is one of the major phosphodiesterases expressed in leukocytes. Inhibitors of PDE4 cause accumulation of intracellular cyclic adenosine monophosphate (cAMP), resulting in inhibition of pro- inflammatory cytokine transcription and other cellular responses, such as neutrophil degranulation and chemotaxis.

Apremilast has demonstrated broad anti-inflammatory and immunomodulatory activity, as well as efficacy in psoriasis and psoriatic arthritis. Based on preclinical and clinical data to date, apremilast has a more favorable safety profile than the currently available systemic psoriasis treatments, while delivering efficacy with convenient oral dosing.

Objectives

Primary Objective

- Evaluate aberrant inflammatory profiles of activated blood monocytes known as the aberrant-monocyte endotype (i.e. AM-endotype)
- Assess the median reduction of abnormal monocyte biomarker values in AM-endotype patients treated with oral apremilast (Otezla) under recommended dosing:
  - 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 - Day 112: 30 mg twice daily

Secondary Objectives

- Evaluate the median change in serum myeloperoxidase, resistin, IL-17, and Tissue Factor in the AM-endotype.
- Evaluate the median change in flow cytometric quantitation of additional monocyte and neutrophil markers, including CD18/CD11b and NETotic neutrophils.
- Evaluate change in monocyte transcriptome biomarkers by WGS.

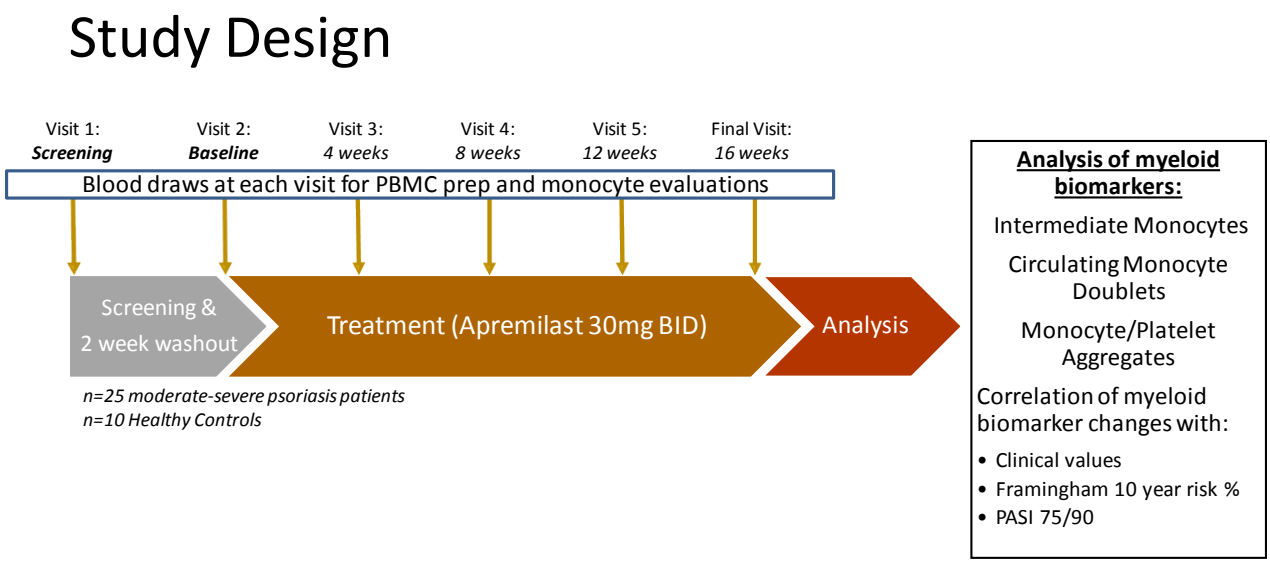
Other Objective(s)

- Evaluate Health Related Quality of Life (HRQoL) (Dermatology Life Quality Index (DLQI) and (Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO)) and changes in symptom severity of patients receiving apremilast 30 mg BID.
- Explore potential change in Framingham Risk profile of treated patients.

Study Design

This is an open label pilot study of the impact of treatment with standard dosing of APM for 16 weeks on AM-endotype psoriasis patients, identified by elevated (>150% of normal):

1. Intermediate ($CD14^{++}CD16^{+}$) monocytes (i.e. monocytes in circulation), OR
2. Circulating monocyte doublets (i.e adherent monocyte-monocyte pairs), OR
3. Circulating monocyte-platelet aggregates (i.e. monocytes adherent to platelets; MPA).



Approximately 25 psoriasis patients with the AM-endotype will be followed during treatment over 16 weeks with 5 monthly individual blood draws will be enrolled. 10 untreated healthy controls will also be enrolled and will provide two blood draws (baseline and 16 weeks). These are needed to maintain quality control of the normal levels of the biomarkers being tested. All treated psoriasis subjects will receive apremilast through Week 16

Study Population

Adult subjects 18-65 years of age with moderate-to-severe plaque psoriasis.

Healthy controls
Healthy participants will be recruited from a pool of generally healthy research volunteers. Healthy volunteers will be selected to match age, sex, and race of psoriasis subjects as closely as possible.

Length of Study

The study is designed as a 16 week study and consists of 6 distinct visits as described above. Screening will consist of a 1a and optional 1b visit. Visit 1b is optional. It exists so that the subject can pick up the Empatica E4 wrist device that cannot be given until their monocyte profile is known. Visits 3 and 5 will also be split into part a and b. Visit 5b will is optional. If the subject choses to participate, visit b is when the subject returns the wrist device.

Study Treatments

Apremilast will be dispensed in dose titration cards at Visit 2. At Visit 3, apremilast tablets will be supplied in high density polyethylene (HDPE) bottles containing approximately 60 tablets each.

Overview of Efficacy Assessments

Primary Clinical Assessment

The primary clinical assessment will be Psoriasis Area and Severity Index (PASI) scores.

Additional Clinical Assessments

- Static Physician's Global Assessment (sPGA)
- Body Surface Area (BSA)
- Subject's Assessment of Pruritus VAS
- Subject's Assessment of Skin Discomfort/Pain VAS
- Subject Global Assessment of Psoriasis Disease Activity VAS
- Subject's Assessment of Joint Pain VAS
- Subject Global Assessment of Psoriatic Arthritis Disease Activity VAS
- Health Related Quality of Life (HRQoL) questionnaires:
  - Dermatology Life Quality Index (DLQI)
  - Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO)

Overview of Safety Assessments

Safety Assessments

- Adverse events (AE)
- Physical examinations
- Vital signs
- Clinical laboratory tests
- Evaluation of psoriasis flare or rebound.

1. INTRODUCTION

1.1. Apremilast

Apremilast (Otezla) is an oral agent that modulates multiple inflammatory pathways through targeted phosphodiesterase type 4 (PDE4) enzyme inhibition. It is used for the treatment of inflammatory autoimmune disorders, such as psoriatic arthritis and psoriasis that involve elevated cytokine levels.

PDE4 is one of the major phosphodiesterases expressed in leukocytes. Inhibitors of PDE4 cause accumulation of intracellular cyclic adenosine monophosphate (cAMP), resulting in inhibition of pro-inflammatory cytokine transcription and other cellular responses such as neutrophil degranulation and chemotaxis.

1.2. Psoriasis

***Disease significance*:** The prevalence of skin disease exceeds those of obesity, hypertension or cancer. One in three Americans suffers with a skin disease, and ~2-3% of these individuals have psoriasis. Costs of treating these patients are believed to exceed $1B, including over $350M in prescriptions alone [1-5]. Chronic inflammation in psoriasis is often not limited to the skin, as evidenced by a high frequency of other significant co-morbidities including psoriatic arthritis, inflammatory bowel disease, lymphoma, obesity and metabolic syndrome [6-8], and recent evidence indicates that psoriasis patients have increased risk of developing and dying of cardiovascular diseases (**CVD**) [9]. Psoriasis patients also experience increased emotional burden via increased depression, mood disorders and suicidal ideation [10], an impact which may be purely from reactions to disfigurement, but which may also be a result of sensors in the brain of distant (skin) inflammation. Intervention at several points during the inflammatory disease cycle of psoriasis has revolutionized the understanding of psoriasis, and can produce clinical resolution in many, but not all patients. Improving understanding of psoriasis benefits not only the quality of life for patients with psoriasis, but also other inflammatory diseases of skin and other organs, as drugs initially developed for psoriasis have been extended to other indications. In particular, work that can be leveraged to other conditions remains to be done in unraveling the complex systemic interactions involving neurologic, immunologic, genetic, cellular and cutaneous biology responsible for the inflammatory responses in other organ systems when initiated by the skin of active psoriasis, or cutaneous GVHD, or dermatitis [11]. Toward that end, improved understanding of psoriatic inflammation progressively moved treatment upstream from broad immunologic suppression (i.e., cyclosporine or steroids) to somewhat more targeted but still fairly broad approaches (LFA-3-FcIgG, anti LFA-1, TNF inhibitors), to upstream Monocyte/Dendritic cell cytokine-initiated pathways (i.e., IL-12 p40, IL-23, PDE4) that drive a highly specific T cell lineage (Th17) mediating skin psoriasis.

CELLULAR COMPONENTS

Monocytes: Monocytes (Mon's) and their derived subpopulations are highly plastic and sensitive sentinels of inflammation. They play a critical role in psoriasis, are extremely strong candidates for mediating aspects of co-morbidities associated with psoriasis, and appear to be useful as biomarkers of Framingham Risk associated with psoriasis. However, there is extremely limited understanding of how Mon's respond to the chronic inflammatory stimuli they encounter either as developing precursors in the bone marrow (BM) or upon egress into circulation and interaction with the activated endothelium of a psoriatic lesion. Distinct circulating Mon populations arise from a common granulocytic-macrophage myeloid precursor in the BM, and have been genotyped; classical

monocytes (Mon-1, $CD14^{++}$ $CD16^{neg}$), intermediate monocytes (Mon-2, $CD14^{++}$ $CD16^{+}$) and non-classical monocytes (Mon-3, CD14- $CD16^{++}$) [12-18]. It is believed that Mons do not proliferate in circulation and reconstitution of the Mon pool is accomplished through maturation of a common BM-derived common myeloid progenitor. Mon-1s comprise the majority of circulating Mons that interact with endothelial cells (EC) and plasma proteins for approximately 1-3 days [19, 20], and then traverse the endothelium and enter tissue. Initial Mon-1 binding to EC are postulated to result in two potential outcomes; 1) **cells that adhere and extravasate** directly into surrounding tissue are likely to differentiate into macrophages and/or dendritic cell subsets, and 2) Mon-1 **cells that do not extravasate**, but transiently interact with endothelia and release, triggering transition to Mon-2 intermediate cells.

Among the Mon subsets [12-18] Mon-2s have been reported to produce elevated levels of TNFα upon challenge, and exhibit reduced levels of IL-10 production--they have therefore been identified as pro-inflammatory. Mon-2 are also the main producers of reactive oxygen species (ROS) [16] and secrete pro-atherogenic micro-particles (MP's) (also elevated in psoriasis) [21, 22]. Indeed, myeloperoxidase (MPO) is elevated in psoriasis serum and appears derived from tissue Mon's/macrophages [23]. Activated Mon-2 cells also exhibit high levels of the angiogenic factors ENG and Tie2 (TEK), and appear upregulated for trans-endothelial migration to tissue via CCR2, CX3CR1, CXCR4,and ICAM-1 receptors [16]. They demonstrate enhanced antigen processing, and can be precursors to tissue macrophages, dendritic cells and other professional antigen presenting cells that initiate and direct T cell mediated response to antigenic challenge. Mon-2's also express the highest level of the toll-like receptor 4 (TLR-4) [24, 25] for which a number of endogenous ligands are overexpressed in psoriasis (i.e., EDA fibronectin, S100 A8/9/12) [26, 27] .

Circulating Mon-2 cells are biomarkers of inflammation in numerous diseases [28-35], and are validated predictive biomarkers of cardiovascular disease (CVD) events [36], including myocardial infarction and death [24, 37, 38] Indeed, psoriasis patients have elevated levels of circulating $CD16^{+}$ cells, which contain the Mon-2 population [29, 39], and we and others have shown that Mon-2s are elevated in a subset of psoriasis patients [29, 39, 40]. We also discovered, in addition to elevations of Mon2's that Mons in psoriasis are more highly aggregated and can carry adherent platelets. These self-aggregated Mons exhibit a differential transcriptional profile from other singlet Mon populations [40].

Skin inflammation, most explored in psoriasis, but also apparent in GVHD, dermatitis, and skin injury, appears to be detected by distant cells of the myeloid lineage, with clinical functional consequences. Monocytic cells are designed to be sensors of inflammatory perturbations, and have the capability to differentiate down multiple pathways, as appropriate to the signals. Their timing is intermediate between neutrophils and lymphocytes (3-14 days in circulation), and as such are very attractive candidates for giving us a practical "smoking gun" regarding recent signals that have been received, as well as giving us a handle on what type of effector functionality has been triggered.

1.3. Key Findings from Non-clinical Studies

1.3.1. In Vitro Activity

In lipopolysaccharide (LPS)-challenged peripheral blood mononuclear cells (PBMCs), apremilast inhibited, in order of increasing potency, IP-10, IFN-γ, MIG, TNF-α, IL-12p70, MIP-1α, MCP-1, and GM-CSF production. Reduction of TNF-α, IFN- γ, IL-12, and IL-23

expression occurred at the mRNA level. It also inhibited IFN-γ and IL-2 production by PBMC stimulated with staphylococcal enterotoxin B. In purified human NK cells, apremilast inhibited production of TNF-α and GM-CSF. Production of IL-8 and leukotriene B4 by PMN and TNF-α production by human epidermal keratinocytes were also blocked by apremilast in vitro. Apremilast was tested in a model of psoriasis utilizing normal human skin xenotransplanted onto beige-severe combined immunodeficient (SCID) mice and triggered with human psoriatic NK cells. Orally administered apremilast (5 mg/kg/day) significantly reduced epidermal thickness and proliferation and decreased the general histopathologic appearance of psoriasiform features. Staining for TNF-α, HLA-DR, and ICAM-1 in lesional skin was also qualitatively reduced by apremilast treatment [41].

1.3.2. In Vivo Anti-arthritic and Anti-inflammatory Activity in Animals

In a mouse xenograft model of human psoriasis, apremilast reduced the appearance of psoriasiform lesions, reduced epidermal thickness and keratinocyte proliferation, and inhibited HLA-DR and ICAM-1 expression in the engrafted human skin [41]. Apremilast reduced TNF-α production in mice in response to LPS and reduced paw edema in a type II collagen-induced model of arthritis in mice.

1.4. Rationale for Dose Chosen

Apremilast

Apremilast will be given as approved by the FDA for the treatment of moderate-to-severe plaque psoriasis. An initial dosage titration from Day 1 to Day 5 will be performed as shown below:

Dosing titration schedule for week 1									
Day 1		Day 2		Day 3		Day 4		Day 5+	
am	pm	am	pm	am	pm	am	pm	am	pm
10mg	x	10mg	20mg	20mg	20mg	20mg	30mg	30mg	30mg

Following the titration, the recommended maintenance dosage of 30 mg twice daily taken orally will be continued throughout the study.

1.5. Relevant Reference and Background

Psoriasis is a chronic disease that requires long-term treatment, ideally with effective agents that offer convenient dosing and a low incidence of adverse events. Currently available systemic therapies are limited by risks of hepatic, renal and neurological toxicities, teratogenicity, as well as an increased risk of infections and malignancies. Given the limitations of current systemic psoriasis treatments, there is an unmet medical need for an effective oral agent that is well tolerated and less immunosuppressive than the current oral agents and parenteral biologics. In completed studies in psoriasis and psoriatic arthritis, apremilast has demonstrated broad anti-inflammatory and immunomodulatory activity. Efficacy in psoriasis and psoriatic arthritis has also been demonstrated. Based on preclinical and clinical data to date, apremilast has a favorable safety profile compared to the currently available systemic psoriasis treatments, while delivering efficacy with convenient oral dosing.

Methotrexate (MTX), retinoids, cyclosporine (CsA), and psoralen plus long-wave ultraviolet radiation (PUVA) form the group of most commonly used conventional systemic therapies for moderate to severe plaque-type psoriasis. These treatments have varied levels of effectiveness and are often associated with adverse reactions and dose limiting toxicities, such as myelosuppression (MTX), hepatotoxicity (MTX), nephrotoxicity (CsA), teratogenicity (MTX, retinoids), and increased risk of malignancy and serious infections (CsA, PUVA).

Advances in the understanding of the biochemical mechanisms associated with psoriasis have led to the development of more specific therapies for this disease [42]. During the past 10 to 15 years, a number of biologic agents that act on specific steps in the immunologic cascade that controls psoriasis have been identified. Examples include infliximab, adalimumab and etanercept (inhibitors of TNF), and ustekinumab (inhibitor of IL-12 and IL-23). Etanercept, adalimumab and infliximab work by inactivation of TNF ([43]; [44]). Ustekinumab is a monoclonal antibody that acts by binding to the p40 subunit of human IL-12 and IL-23 [45], and blocking their interaction with Th1 and Th17 cells, respectively. While the biological agents have demonstrated efficacy in moderate-to-severe psoriasis, they may be associated with several safety concerns including injection site reactions, opportunistic infections, reactivation of tuberculosis, congestive heart failure, and new onset or exacerbation of demyelinating disease ([46]; [47]).

2. Study Objectives

Primary Objective

- Evaluate aberrant inflammatory profiles of activated blood monocytes known as the aberrant-monocyte endotype (i.e. AM-endotype)
- Assess the median reduction of abnormal monocyte biomarker values in AM-endotype patients treated with oral apremilast (Otezla) under standard dosing for 16 weeks in subjects with moderate to severe plaque psoriasis.

Comparisons will be from baseline to 16 weeks within each patient using baseline as the starting point and following 16 weeks as the comparators. This comparison is also true for the secondary objectives.

Secondary Objectives

- Evaluate the median change in serum myeloperoxidase, resistin, IL-17, and Tissue Factor in the AM-endotype.
- Evaluate the median change in flow cytometric quantitation of additional monocyte and neutrophil markers, including CD18/CD11b and NETotic neutrophils.
- Evaluate change in monocyte transcriptome biomarkers by WGS.

Other Objective(s)

- Evaluate Health Related Quality of Life (HRQoL) (Dermatology Life Quality Index (DLQI) and (Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO)) and changes in symptom severity of patients treated with apremilast 30 mg BID.
- Explore potential change in Framingham Risk profile of treated patients

3. OVERALL STUDY DESIGN

This is an open label pilot study of the impact of treatment with standard dosing of apremilast for 16 weeks on AM-endotype psoriasis patients, identified by elevated (>150% of normal):

1.) Intermediate ($CD14^{++}CD16^{+}$) monocytes, OR
2.) Circulating monocyte doublets, OR
3.) Circulating monocyte-platelet aggregates (MPA).

Study Population

Adult subjects 18-65 years of age with moderate-to-severe chronic plaque psoriasis.

Length of Study

The study is designed as a 16 week study starting from the time the patient is enrolled at baseline. The preceding screening period is 35 days.

3.1 Data and Safety Monitoring Plan

The investigators will closely monitor the subjects in this study and safety monitoring will be performed and adverse event data will be collected by the primary investigator and sub-investigator at University Hospitals Cleveland Medical Center (UHCMC) at each study visit. If any serious adverse or unexpected events were to occur, subjects will be asked to call Dr. Neil Korman or the primary dermatologist providing care to the subject. The subject will be asked to come in as soon as possible for evaluation by a physician co-investigator. After appropriate measures are carried out, the adverse event and how it was handled will be documented and reported to the IRB according to UHCMC IRB policy. The PI and the IRB will then decide if changes to the protocol or consent form are needed.

3.2. Study Design Rationale

Most of the currently available oral systemic therapies for psoriasis are associated with significant cumulative toxicities which have often required physicians to use different treatment regimens (e.g., rotational, intermittent, sequential) in order to balance drug toxicities with their therapeutic effect. Given the chronic nature of psoriasis, there is a need for medication that can be dosed chronically with less risk. It is, therefore, important for new medications to demonstrate both efficacy and safety with continuous use.

This study will evaluate aberrant inflammatory profiles of activated blood monocytes (aberrant-monocyte endotype patients (AM-endotype) and assess the median reduction of abnormal monocyte biomarker values in AM-endotype patients treated with oral apremilast (Otezla) under standard dosing protocol for 16 weeks in subjects with moderate to severe plaque psoriasis.

3.3. Study Duration

Subjects who complete the entire study will spend a total of approximately 16 weeks in the study:

- Up to 35 days in the Screening Phase
- Weeks 0 to 16 (i.e., 16 weeks) in the Apremilast treatment phase.

4. TABLE OF EVENTS

	Screening Part 1	Screening Part 2	Baseline 2A	Baseline 2B	Apremilast Treatment					
Visit	**1a**	**1b**	**2A**	**2B**	**3**	**3b**	**4**	**5**	**5b**	**6**
Week	Up to 35 days		0	1	4	5	8	12	13	16
Informed Consent	**X**		**-**	**-**						
Inclusion/Exclusion Criteria	**X**									
Medical and Disease History	**X**		**X**							
Prior/Concurrent Medications/ Therapies	**X**	**X**	**X**		**X**		**X**	**X**		**X**
Peripheral blood draw	**X**		**X**		**X**		**X**	**X**		**X**
Safety Assessments										
Pregnancy Test and Contraception Education for Females of Child-bearing Potential (FCBP)	**X**		**X**							
Vital Signs	**X**		**X**		**X**		**X**	**X**		**X**
Height	**X**		**-**							
Weight / Waist Circumference/BMI	**X**		**X**		**X**		**X**	**X**		**X**
Complete Physical Examination	**X**		**-**							
Limited Physical Examination	**-**		**X**		**X**		**X**	**X**		**X**
Complete blood count with differential, , comprehensive metabolic panel, phosphorous, high sensitivity C-reactive protein			**X**		**X**		**X**	**X**		**X**
Total cholesterol, triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol, fasting glucose level, insulin, hemoglobin A1C, glucose tolerance test (GTT; optional), Plasma catecholamines fractioned (epinephrine,			**X**							**X**

norepinephrine, dopamine)										
Monocyte Assessment (Doublet %, Classical, Intermediate, Non-Classical circulating %, Total PBMCs , Viability, Monocyte Number/ml blood and , Monocyte gene expression)	**X**		**X**		**X**		**X**	**X**		**X**
Dispense monitoring device for electrodermal activity (Empatica E4 wristband) ± laptop (Optional)		**X**			**X**			**X**		
Return Empatica E4 wristband ± laptop (Optional)			**X**			**X**			**X**	
Psoriasis Flare or Rebound Assessment	**-**		**X**		**X**		**X**	**X**		**X**
Adverse Events	**X**	**X**	**X**		**X**		**X**	**X**		**X**
Clinical Efficacy Assessments										
PASI, BSA, sPGA	**X**		**X**		**X**		**X**	**X**		**X**
Pruritus VAS	-		**X**		**X**		**X**	**X**		**X**
Skin Discomfort/ Pain VAS	-		**X**		**X**		**X**	**X**		**X**
Subject Assessment of Joint pain VAS; Subject Global PsA VAS; HAQ-DI[n]	-		**X**		**X**		**X**	**X**		**X**
Subject Global Assessment of Psoriasis Disease Activity VAS	-		**X**		**X**		**X**	**X**		**X**
Health-related Quality of Life Assessments										
DLQI,	-		**X**		**X**		**X**	**X**		**X**
WPAI,	-		**X**		**X**		**X**	**X**		**X**
Stress Response Assessment										
Numerical N-Back			**X**	**X**						**X**
Investigational Product Dosing										
Dispense IP titration cards	-		**X**							
Dispense IP bottles	-		-		**X**		**X**	**X**		
Return IP tablets, Count for Compliance	-		–		**X**		**X**	**X**		**X**
Dispense Medication Log			**x**		**X**		**X**	**X**		
Return Medication Log					**X**		**X**	**X**		**X**

*Except for screening, all visits have a +/- 3 day window in which they can be completed.
**Diabetic patients will not undergo the glucose tolerance test for patient safety.

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

At Screening and at Baseline, and at any time during the study when a female subject of childbearing potential's contraceptive measures or ability to become pregnant changes, the Investigator will educate the subject regarding contraception 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, as defined in the electronic Case Report Form (eCRF) Completion Guidelines and the Study Manual, should be recorded, including smoking and alcohol history, as well as previous relevant surgeries. Disease history includes history of psoriasis and psoriatic arthritis.

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, such as previous treatment for tuberculosis (TB) or relevant diseases, will be recorded.

All medications and therapies for psoriasis, including topicals (used within the last 5 years), systemics, and all medications and therapies for psoriatic arthritis, will be recorded. The stop dates for all medications and therapies prohibited in the study will be recorded. Responses to prior psoriasis therapies will also be recorded.

Safety Assessments

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

- **Vital Signs, Height, and Weight**

  Vital signs, including temperature, pulse, and seated blood pressure, will be taken during the visits indicated in Table of events. Height will be measured and recorded at Screening; weight and waist circumference will also be measured and recorded at Screening and then as indicated in

Table of events. Body mass index (BMI) will be calculated.

- **Complete/Limited Physical Examination**

  A complete physical examination includes evaluations of skin, nasal cavities, eyes, ears, lymph nodes, and respiratory, cardiovascular, gastrointestinal, neurological, and musculoskeletal systems. The complete physical examination is done at Screening and other designated visits. A limited physical examination includes evaluations of skin, lymph nodes, and respiratory, cardiovascular, and musculoskeletal systems. The limited physical examination is done at Baseline and other designated visits as indicated in Table of events.

- **Clinical Laboratory Evaluations**

Clinical laboratory evaluations will be performed as indicated in Table of Events. Clinical laboratory evaluations will include a complete blood count with differential (WBC, nucleated RBC, RBC, HGB, HCT, MCV, MCHC, PLT, RDW-CV, WBC differential, WBC absolute cell counts), a comprehensive metabolic panel (glucose, sodium, potassium, chloride, bicarbonate, anion gap, urea nitrogen, creatinine, GFR, calcium, albumin, alkaline phosphatase, total protein, AST, ALT, bilirubin total), phosphorus, and high sensitivity C-reactive protein. Total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), fasting glucose level, insulin, hemoglobin A1C, glucose tolerance testing (GTT; optional), and plasma catecholamines fractioned (epinephrine, norepinephrine, and dopamine) measurements are only required at baseline and week 16 as indicated in the table of events. Those subjects determined to have elevated lipids may elect to participate in a separate assessment characterizing their HDL. Monocyte labs will also be collected at each visit (Doublet %, Circulating Monocyte % (Classical, Intermediate, Non-Classical), Total PBMCs, Viability, Monocyte Number/ml blood). Patients with diabetes mellitus type I and type II will not undergo the GTT in order to maintain patient safety.

- **Monitoring Epidermal Activity (Optional)**

  The Empatica E4 wearable wrist device will be monitoring for epidermal activity to measure sympathetic nervous system arousal and to derive features related to stress, engagement, and excitement, as well as activity. The device is able to record continuous heart rate, activity, temperature, and photoethysmography. Patients will be asked to wear the wrist device (Empatica E4) for 7 days prior to enrollment, 7 days after a month of apremilast usage, and again for 7 days after 3 months of apremilast use.

  In order to use this device, the subject must have access to reliable internet and be able to download the compatible data manager interface onto an appropriate electronic device. If the patient does not have such a device, a laptop will be provided to the subject to be used solely for the study and to be returned with the device.

- **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 [48]. 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.

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 [49].

- **Pregnancies/lactation 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, lactation, suspected pregnancy, or positive pregnancy test must be reported to AmgenAmgen Safety immediately facsimile using the Pregnancy Report form provided by Amgen.

  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 Amgen 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 Amgen Safety by facsimile within 24 hours of the Investigator's knowledge of the event).

  In the case of a live "normal" birth, Amgen 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 Amgen 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.

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

- **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.

Psoriasis Area Severity Index (PASI)

PASI will be determined for all subjects throughout the study. The PASI calculation is described in Appendix A.

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 [50]. 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)**

  BSA is a measurement of involved skin. The overall BSA affected by psoriasis is estimated based on the palm area of the subject's hand (entire palmar surface or "handprint"), which equates to approximately 1% of total body surface area.

- **Physician Global Assessments (PGAs)**

  - **Static Physician's Global Assessment (sPGA)**

  The sPGA is the assessment by the Investigator of the overall disease severity at the time of evaluation. The sPGA is a 5-point scale ranging from 0 (clear) to 4 (severe), incorporating an assessment of the severity of the three primary signs of the disease: erythema, scaling and plaque elevation. When making the assessment of overall severity, the Investigator should factor in areas that have already been cleared (i.e. have scores of 0) and not just evaluate remaining lesions for severity, i.e., the severity of each sign is averaged across all areas of involvement, including cleared lesions. Areas of cleared lesions may be directly assessed if outlines of the original lesions can be directly visualized (e.g., residual hyperpigmentation) or, if not, by factoring in the minimum BSA for inclusion in the study (i.e., at least 10%). In other words, if there are small lesions of mild severity covering 1% BSA, but there are cleared lesions covering 9+% BSA, over 90% of the severity is clear; this should be integrated into the final assessment. In the event of different severities across signs of psoriasis, the sign that is the predominant feature of psoriasis should be used to help determine the sPGA score. See Appendix B for grading criteria.

- **Health Assessment Questionnaire Disability Index (HAQ-DI)**

  The HAQ-DI [51]is a 20-question, self-administered instrument that measures the subject's functional ability on a 4-level difficulty scale (0-3, with 0 representing normal or no difficulty; and 3 representing inability to perform). Eight categories of functioning are included: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities [52]. This scale is sensitive to change and is a good predictor of future disability [53]. See Appendix C.

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. See Appendix D.

- **Skin Discomfort/Pain 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 skin discomfort/pain, and the right-hand boundary represents skin discomfort/pain as severe as can be imagined. The distance from the mark to the left-hand boundary will be recorded. See Appendix D.

- **Subject Global Assessment of Psoriasis Disease Activity (VAS)**

  The subject will be asked to place a vertical stroke on a 100 mm VAS on which the left-hand boundary represents very well, and the right-hand boundary represents very poor. The distance from the mark to the left-hand boundary will be recorded. See Appendix D.

- **Subject's Assessment of Joint Pain (VAS)**

  If the subject has a history of Psoriatic Arthritis and it is active at Baseline, the subject will be asked to place a vertical stroke on a 100 mm VAS on which the left- hand boundary represents very well, and the right-hand boundary represents very poor. The distance from the mark to the left-hand boundary will be recorded. See Appendix D.

- **Subject's Global Assessment of Psoriatic Arthritis Disease Activity (VAS)**

  If the subject has a history of Psoriatic Arthritis and it is active at Baseline, then the subject will be asked to place a vertical stroke on a 100 mm VAS on which the left-hand boundary represents no pain, and the right-hand boundary represents pain as severe as can be imagined. The distance from the mark to the left-hand boundary will be recorded. See Appendix D.

Health-Related Quality of Life Assessments

Questionnaires should be administered to the subject in the order that they are described below and as indicated in Table of Events Table 1:

- **Dermatology Life Quality Index (DLQI)**

  DLQI [54] will be assessed by the subject upon arrival at the site before any other procedures or assessments are performed. The DLQI was developed as a simple, compact, and practical questionnaire for use in a dermatology clinical setting to assess limitations related to the impact of skin disease [54]. The instrument contains 10 items dealing with the subject's skin. With the exception of Item Number 7, the subject responds on a four-point scale, ranging from "Very Much" to "Not at All." Item Number 7 is a multi-part item, the first part of which ascertains whether the subject's skin prevented them from working or studying (Yes or No), and if "No," then the

subject is asked how much of a problem the skin has been at work or study over the past week, with response alternatives being "A lot," "A little," or "Not at all."

The DLQI Total score has a possible range from 0 to 30, with 30 corresponding to the worst quality of life, and 0 corresponding to the best score. The developers suggest that the DLQI can be grouped into six subscales: symptoms and feelings; daily activities; leisure; work/school; personal relationships; and treatment. Scores for four of the subscales (symptoms and feelings, daily activities, leisure, and personal relationships) range from 0 to 6; scores for two of the subscales (work/school and treatment) range from 0 to 3. Higher scores correspond to poorer quality of life. See Appendix E.

- **The Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI: PSO)**

  The WPAI: PSO questionnaire is a validated, 6-item self-administered instrument used to assess the impact of disease on work productivity in psoriasis due to general health or a specified health problem ([55]; Appendix F).

Stress Response Assessment (Only required if subject participates in the optional Monitoring of Epidermal Activity)

- Numerical N-Back Test

  The Numerical N-back test will be performed while the subject is wearing the Empatica device to assess stress response. The test will be performed by asking the subject to count backwards from one thousand by sevens. The test will terminate at 5 minutes time or at the point in which the subject completes the task, whichever comes sooner. This test will be performed at baseline, visit 2B (+/-5 days), and visit 6.

6. STUDY POPULATION

6.1. Number of Subjects and Sites

Approximately 55 subjects will be enrolled at UHCMC, University Hospitals Dermatology Fairlawn, or Wright State University Boonshoft School of Medicine. UHCMC investigational pharmacy will coordinate investigational product (IP) shipment to WSUSOM investigational pharmacy. Goal is to have 25 psoriasis patients aged 18-65 years old and 10 healthy controls complete the trial (35 total). Total enrollment of 55 is to account for screen fails and early terminations.

6.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Males or females, ≥ 18 and ≤ 65 years of age at the time of signing the informed consent document.
2. Understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Patients must exhibit AM-endotype psoriasis patients, identified by elevated (>150% of normal) levels of *any one of the following criteria*:
   - Intermediate ($CD14^{++}CD16^{+}$) monocytes, OR
   - Circulating monocyte doublets, OR
   - Circulating monocyte-platelet aggregates (MPA).
5. Diagnosis of chronic plaque psoriasis for at least 12 months prior to Screening.
6. Have moderate to severe plaque psoriasis at Screening and Baseline as defined by
   a. BSA ≥5%
   b. sPGA ≥3 (moderate to severe)
7. Must be a candidate for phototherapy and systemic (including Otezla) therapy.
8. Must be in good health (except for psoriasis) as judged by the Investigator, based on medical history and physical examination.
9. Subject must have completed 5-7 days of successful Empatica device data collection. (Optional: Only if subject choses to participate)
10. Subject must have consistent internet access and the ability to successfully download the Empatica data manager user interface.
    (Optional: Only if subject choses to participate)

11. 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 non-latex 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.

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

Male subjects (including those who have had a vasectomy) who engage in activity in which conception is possible must use barrier contraception (male latex condom or non-latex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on investigational product and for at least 28 days after the last dose of investigational product.

6.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Other than psoriasis, history of any clinically significant (as determined by the Investigator) cardiac (clinically advanced cardiovascular disease including; Stent, past history of MI, thrombotic event or arterial calcification), endocrine, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major uncontrolled disease.
2. Any condition, including the presence of laboratory abnormalities, which would place the subject at unacceptable risk if he/she were to participate in the study.
3. Any condition, including other inflammatory diseases or dermatologic conditions that confound the ability to interpret data from the study.
4. 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.
5. Pregnant or breast feeding.
6. Have failed more than 3 systemic agents for treatment of psoriasis.
7. History of allergy to any component of apremilast.
8. Had a serious infection (including, but not limited to, hepatitis, pneumonia, sepsis, cellulitis, meningitis or pyelonephritis) or have been hospitalized for an infection. Subject must be cured of infection > 4 weeks before Screening.

9. Have a history of, or ongoing, chronic or recurrent infectious disease, including, but not limited to, chronic renal infection, chronic chest infection (e.g., bronchiectasis), sinusitis, recurrent urinary tract infection (e.g., recurrent pyelonephritis, chronic nonremitting cystitis), an open, draining, or infected skin wound or ulcer.
10. Had a Bacillus Calmette-Guérin (BCG) vaccination within 1 year prior to screening.
11. History of positive human immunodeficiency virus (HIV), or have congenital or acquired immunodeficiency (e.g., common variable immunodeficiency disease).
12. Active substance abuse or a history of substance abuse within 6 months prior to Screening.
13. Bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks of Screening. Any treatment and cure for such infections must have been completed at least 4 weeks prior to Screening.
14. Malignancy or history of malignancy, except for:
    a. treated [i.e., cured] basal cell or squamous cell in situ skin carcinomas;
    b. treated [i.e., cured] cervical intraepithelial neoplasia [CIN] or carcinoma in situ of the cervix with no evidence of recurrence within the previous 5 years.
15. Topical therapy within 2 weeks of study entry (including, but not limited to, topical corticosteroids, retinoids or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol). Exceptions: low-potency corticosteroids will be allowed as background therapy and restricted to treatment of the face, axillae, and groin in accordance with the manufacturers' suggested usage during the course of the study (this restricted usage should be documented). Subjects with scalp psoriasis will be permitted to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions. An unmedicated skin moisturizer (e.g. Eucerin®) will be also permitted for body lesions only. Subjects should not use these topical treatments within 24 hours prior to the clinic visit.
16. Systemic therapy for psoriasis within 4 weeks prior to study entry (including, but not limited to, cyclosporine, corticosteroids, methotrexate, retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, and fumaric acid esters).
17. Use of phototherapy within 4 weeks prior to study entry.
18. Use of any investigational drug within 4 weeks prior to study entry, or 5 pharmacokinetic/pharmacodynamic half-lives, if known (whichever is longer).
19. Prolonged sun exposure or use of tanning booths or other ultraviolet (UV) light sources.
20. Prior treatment with Apremilast
21. Inability to wash out from biologics (e.g., TNF inhibitors IL-17 inhibitors, IL-12/23 inhibitors, for 8 weeks).

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

7.1.1. Description of Apremilast

The chemical name of apremilast (CC-10004, Otezla) is acetamide, N-[2-[(1S)-1-(3-ethoxy-4- methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl].

Apremilast will be provided as 10, 20, or 30 mg tablets in blister cards for titration purposes (see Appendix N). Apremilast will be provided as 30 mg tablets in HDPE bottles (approximately 60tablets) with child-resistant caps for routine dosing.

7.1.2 Treatment Administration and Schedule

Apremilast

Investigational product tablets will be taken orally twice daily, approximately 12 hours apart, without restriction of food or drink. To attempt to mitigate potential mild to moderate headache and gastrointestinal (GI) adverse events (primarily nausea), dose titration will be implemented in this study at specific times.

Dosing

During Week 0 (Days 1-7), subjects will be dispensed blister cards with standardized dosing of apremilast tablets.

7.1.3. Packaging and Labeling

Tablets

The label(s) for apremilast will include drug name, dosage form and strength (where applicable), amount of apremilast per container, lot number, expiry date (where applicable), dosing instructions, storage conditions. All apremilast will be supplied by Amgen in HDPE bottles with child-resistant caps.

7.1.4. Product Accountability and Disposal

The 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 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 Amgen.

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

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

7.1.5. Investigational Product Compliance

Study personnel will review the instructions printed on the package with the study subjects prior to dispensing Otezla. The subjects will be instructed to return the Otezla containers, 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 as instructed at each study visit and will be required to complete a medication log at home that will be returned at study visits 3-6. Any problems with compliance will be reviewed with the subject.

7.1.6. Rescue Therapy

The initiation of non-study drug therapy to treat worsening of psoriasis, or flare of previously inactive skin disease, is strongly discouraged throughout the treatment period. However, should rescue therapy be required for the safety and well-being of the subject, such use will be permitted. The subject may remain on study drug, unless the rescue therapy is any therapy that may jeopardize the subject's safety if study drug is continued, in the investigator's and/or Sponsor's opinion.Because the study is not a randomized trial, any subjects that are required to be placed on rescue therapy, but continue in the study will have any data after rescue treated as missing values. Missing values will be imputed from the average of all subjects completed for those data points. Alternatively if rescue therapy is required for > 50% of the patients, then these individuals would be analyzed as a separate cohort of patients and will not be analyzed in the grouped data.

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 eCRF. 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:

- Low-potency or weak corticosteroids (e.g., Class 6 or 7 in US, such as hydrocortisone, desonide, alclometasone dipropionate) will be allowed as background therapy and restricted to treatment of the face, axillae, and groin in accordance with the manufacturers' suggested usage during the course of the study (this restricted usage should be documented).
- Subjects with scalp psoriasis will be permitted to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions.
- An unmedicated skin moisturizer (e.g. Eucerin) will be also 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 therapy
  - Topical therapy, unless otherwise specified (including, but not limited to, topical corticosteroids, retinoids or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol; or as specified as in Section 8.1).
- Systemic Therapy
  - Systemic therapy including but not limited to cyclosporine, corticosteroids, methotrexate, retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, fumaric acid esters.

- Phototherapy
  - UVB or PUVA unless otherwise specified as in Section 8.1
- Biologic agents, including:
  - Adalimumab, etanercept, infliximab, or certolizumab pegol
  - Ustekinumab
  - IL-17-inhibitors, brodalumab, ixekizumab and secukinumab
- Use of any investigational drug or device
- Prolonged sun exposure or use of tanning booths or other ultraviolet light sources

8.3. Required Concomitant Medications and Procedures

Not applicable.

9. STATISTICAL ANALYSES

9.1. Overview

The objective of the statistical analysis will be to evaluate change in aberrant inflammatory profiles of activated blood monocytes (aberrant-monocyte endotype patients (AM-endotype). Subjects with moderate to severe plaque psoriasis will be treated with oral apremilast (Otezla) with standard dosing for 16 weeks. For each subject, we will identify a target biomarker of abnormally elevated monocytes, among intermediate, doublets, and platelet doubles. Each subject will thus have one identified monocyte biomarker for which relative percent change will be its basis for analysis in the primary outcome. If more than one category is abnormally elevated, then among abnormally elevated monocyte biomarkers we will first select doublets if elevated. If not, then we will select intermediate monocytes. For each of the selected abnormally elevated monocyte biomarkers, our focus will be on relative percent reduction. We will specifically assess change from baseline to 16 weeks by computing relative percent reduction for each subject being treated. Note for example that a change of 1.5% to 1.2% is (1 – (1.2/1.5))*100% = 20% reduction. The median and other summary statistics of these percent change values will be computed. Wilcoxon's signed rank test will be used to evaluate the null hypothesis of the median percent change being 0. In other words, we will test whether or not there has been a reduction in abnormally elevated monocytes.

Secondarily, in an exploratory manner, we will longitudinally model these percent change values across time points (baseline, 4, 8, 12, and 16 weeks), to assess trajectory of percent change values. We will test for time effects, and consider post-hoc pairwise analyses of time points. Time will be considered as both a continuous covariate with slope parameter, as well as a categorical variable, which does not require linearity assumptions.

In analyses treating time as a continuous variable, actual measurements of time (as compared to fixed time points by week) will be used in the analyses.

Other outcomes such as PASI will be analyzed similarly. Note that we will also correlate change in our abnormally elevated monocyte markers at various time points with change in PASI, to explore possible mechanistic associations. For a two-sided Wilcoxon test with Type I error of 0.05, power is 0.80 if the effect size is 0.60 or greater (assuming an underlying normal distribution). For 20% median reduction, as long as standard deviation of percent change is not larger than 33%, we will have effect size of at least 0.60. These are plausible assumptions given our prior work on treatment related monocyte reductions [40].

Because the study is not a randomized trial, any subjects that are required to be placed on rescue therapy, but continue in the study will have any data after rescue treated as missing values and these missing values will be imputed from the average of all subjects completed. Alternatively if rescue therapy is required for > 50% of the patients, then these individuals would be analyzed as a separate cohort of patients and will not be analyzed in the grouped data.

9.2. Background and Demographic Characteristics

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

9.3. Subject Disposition

Subject disposition (analysis population allocation, entered, completed, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent by phase. A summary of subjects randomized by site will be provided. Protocol violations/deviations will be summarized using frequency tabulations.

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 eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

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.

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.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of Otezla.AEs and serious adverse events (SAEs) will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to Amgen Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

Psoriasis flare and psoriasis rebound, will be captured as adverse events. General worsening of psoriasis should be considered a lack of therapeutic effect and will not be captured as an adverse event.

10.2. Evaluation of Adverse Events

A qualified 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 (i.e. in the opinion of the 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 for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the eCRF and the SAE Report Form must be completed.

For each SAE, the 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 Investigator must assess the severity / intensity of the event.

Mild

- Asymptomatic or mild symptoms; clinical or diagnostic observations only
- Intervention not indicated
- Activities of daily living (ADLs) minimally or not affected
- No or minimal intervention/therapy may be required

Moderate

- Symptom(s) cause moderate discomfort
- Local or noninvasive intervention indicated
- More than minimal interference with ADLs, but able to carry out daily social and functional activities
- Drug therapy may be required

Severe (could be non-serious or serious)

- Symptoms causing severe discomfort/pain
- Symptoms requiring medical/surgical attention/intervention
- Interference with ADLs, including inability to perform daily social and functional activities (e.g., absenteeism and/or bed rest)
- Drug therapy is required

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The 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.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Amgen, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

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

10.2.5. Action Taken

The Investigator will report the action taken with Otezla 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.

10.2.6. 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).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of Otezla dose; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

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/screen of the eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

10.4. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the eCRF. All SAEs must be reported to Amgen Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent to at least 30 days after the last dose of Otezla), and those made known to the Investigator at any time thereafter that are suspected of being related to Otezla. SAEs occurring prior to treatment will be captured.

The SAE report should provide a detailed description of the SAE and include summaries of

hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Amgen Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Amgen Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Amgen and the IRB/EC.

10.4.1. Safety Queries

Queries pertaining to SAEs will be communicated from Amgen Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (e.g., missing causality assessment) may be handled by phone.

10.5. Expedited Reporting of Adverse Events

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

Amgen shall notify the 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 (i.e., 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 Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

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

Amgen Drug Safety Contact Information:

Amgen should receive copies of all safety reports submitted to the FDA, or any other regulatory agency, IRB or IEC, within 24 hours of such submission. Such notifications should be submitted as E2B, MedWatch or CIOMS I reports using the ISS Safety Fax Transmittal Cover Sheet and faxed to 888-814-8653. Cover sheet can be found here:

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Amgen Drug Safety Contact Information:

Amgen Global Safety
Toll-free #:1-888-814-8653
For countries where the U.S. toll-free # cannot be used: +44-20-7136-1046
Email (Only for sponsors with a secure email connection with Amgen):
svc-ags-in-us@amgen.com

For Interventional studies with Amgen IMP[a]:

Safety Data	Timeframe for submission to Amgen	Send to
Suspected Unexpected Serious Adverse Reaction (SUSARs)	At time of regulatory submission	Amgen Safety
Pregnancy/Lactation exposure and any associated reports/outcomes (i.e. unexpected pregnancy, pregnancy of partner, spontaneous abortion, congenital anomaly etc.)	Within 1 business day of Sponsor awareness, for reports meeting serious criteria Not to exceed 15 calendar days of Sponsor awareness, for non-serious reports	Amgen Safety

[a] Specific requirements are to be outlined in the Research Agreement.

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

Pregnancies/lactation 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, lactation, suspected pregnancy, or positive pregnancy test must be reported to Amgen Safety immediately facsimile using the Pregnancy Report form provided by Amgen.

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 Amgen 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 Amgen Safety by facsimile within 24 hours of the Investigator's knowledge of the event).

In the case of a live "normal" birth, Amgen 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 Amgen 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.

Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should

notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.6 Analysis of AEs

A listing of AEs in the entire study with their demographic characteristics, adverse event data like start date, end date, severity, seriousness, treatment start date, and treatment end date will be recorded. Along with this listing, listing of serious adverse events, listing of subjects discontinued from study due to adverse events will also be created as a part of an adverse event analysis submission.

Adverse event (AE) will be reported as summary tables display the number of subjects experiencing an AE in each treatment group and will include a standard percentage calculation where the number of subjects experiencing an AE are divided by the number of subjects at risk who received a particular treatment. Contingency tables will be used to analyze AEs, employing either Chi-square or Fisher's exact test.

Rates of AE occurrence associated with exposure will be expressed as a percentage of the number of subjects exposed and experiencing a certain event divided by the total number of subjects exposed, regardless of duration of follow-up.

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 eCRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

13. REGULATORY CONSIDERATIONS

13.1. 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 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 Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

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

The 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 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 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.

13.3. Subject Information and Informed Consent

The 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 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 Investigator's study files and a copy given to the study subject.

Remote consenting

Remote consenting will be carried out according to the IRB Guidelines for Remote Electronic Consent. The preferred process will utilize audiovisual software (e.g. Zoom) and the Redcap e-Consent Framework according to the following guidelines:

1. The potential participant must be in possession of the full IRB-approved informed consent document. This could have been transmitted by email/fax/scan/letter/text.
2. The study team will arrange a mutually convenient time for a full informed consent process with the potential participant. Once the time is arranged ahead, the study team member who will be consenting sends a text message "invitation" to the potential participant.
3. Once both parties are able to see each other over the virtual visit, the next step involves completing identity verification (details must be documented in the study team records). The study team member can explain the need to verify identity just as if the interaction was in person. The potential participant is asked his/her full name and DOB, and is asked to display his/her driver's license or if not available, any state or government-issued picture identification card.
4. If the bandwidth or connection does not permit a virtual visit with audiovisual capabilities, the potential participant can take a picture of their face (also known as a "selfie") and a picture of their photo ID and email* both of these photographs to the study team's University Hospitals e-mail address to verify identity. We strongly recommend that any information from the potential participant NOT be sent to the personal device or personal email of the study team member, and that a study team UH email only be used if this process is needed.
5. Once identity verification is completed, the full informed consent process must occur in real-time during the virtual (or audio) visit.
6. If the potential participant decides to enroll, an electronic signature may be obtained during the virtual visit. The study team member must be able to witness the signature. Study teams can utilize the process available in REDCap to build this electronic capture.
7. If the potential participant is unable to utilize the electronic format for signature, the prospective participant can sign a paper copy during the virtual visit, take a picture of the signature page, and email that photograph to the study team's University Hospitals e-mail address at the end of the virtual visit.
8. **A signature must be received before study procedures begin.**
9. If a minor is also assenting during this process, the same steps should be followed, but the legal guardian/parent's attestation can substitute for a picture ID. If the adult is the minor's court-approved legal guardian, a photo of the legal documentation must be provided, a picture must be taken, and all information must be emailed to the study team's University Hospitals e-mail address.

Important Note: If you are using a third-party application (e.g., Doxy.me) for a telehealth visit, UH recommends saying or otherwise communicating (i.e., in writing via text or e-mail): "Your care is being offered through a third-party internet application. By continuing your visit you acknowledge that University Hospitals does not control this application or its security and privacy policies." The Office of Research Compliance has provided guidance on WebEx Cloud and Doxy.me per the COVID-19 exception telehealth modalities. The platform Doxy.me is recommended as it is pre-approved by UH IT. Other UH approved platforms include MDLIVE and Zoom for Healthcare.

When using a virtual visit platform (or if using a hospital phone instead due to inadequate bandwidth or connection with the potential participant), ready access to:

- University Hospitals e-mail account for sharing documents and receipt of any emailed pictures (ID, "selfie", signature); and
- Study team and/or medical records for documentation is required.

13.4. Confidentiality

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 Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by Amgen. 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 Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Otezla can only be supplied to an Investigator by Amgen after documentation on all ethical and legal requirements for starting the study has been received by Amgen. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

13.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;

- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Closure of the Study

Amgen reserves the right to withdraw support from 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…).

13.9. • Annual Reporting: sponsor's annual reporting obligations to the Regulatory Authorities

For all study types – aggregate reports[a](as applicable):

Safety Data	Timeframe for submission to Amgen	Send to
Listing for Safety data reconciliation[b]	Once per year and at the end of the study	NASCR Manager
Annual Safety Report (eg, EU Clinical Trial Directive DSUR and US IND Annual Report)	Annually	NASCR Manager
Other aggregate analyses (any report containing Safety data generated during the course of the study)	At the time of Sponsor submission to any body governing research conduct (eg. RA, IRB etc.)	NASCR Manager
Final (End of Study Report, including): • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	At the time of Sponsor submission to any body governing research conduct (eg. RA, IRB etc.) but no later than 1 calendar year of study completion	NASCR Manager

[a] Specific requirements are to be outlined in the Research Agreement.

[b] Listing for reconciliation should include all ICSRs submitted to Amgen Safety per contract (i.e. for studies in Table 1 listing should include ADRs, SADRs, Other Safety Findings and serious and non-serious adverse device effects ; for studies in Table 2 listing should contain SUSARs, pregnancy and lactation exposure (and any associated reports/outcomes) and serious and non-serious adverse device effects; studies in table 3 do not require reconciliation).

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The 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 eCRFs or CD-ROM.

14.2. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the formal discontinuation of the study. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. 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 Amgen;
- 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 eCRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- 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).

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.

14.3. Sharing Data with Participants

If a participant requests information regarding the outcome of our study using their individual samples, we will provide a summary of their immune response based on monocyte cell counts monitored over the course of the trial. We will provide information based on baseline and final visit stating the immune cells either: 1) increased, 2) remained steady, or 3) decreased. The summary will state that research is ongoing and this data will not be used to influence clinical care. See email/letter template for sharing this information. This will be emailed to participants or sent via standard mail if the patient does not have an email.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by the Investigator/sponsor (Dr. Korman) with applicable government regulations with respect to current GCP and standard operating procedures.

15.1. Study Monitoring and Source Data Verification

The study site ensures that appropriate monitoring procedures are performed before, during and after the study

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17. APPENDICES

Appendix A: Psoriasis Area Severity Index (PASI)

PSORIASIS AREA AND SEVERITY INDEX (PASI)

Please write in the appropriate number for rows 1 - 3 using the scale below:
0 = None 1 = Slight 2 = Moderate 3 = Severe 4 = Very Severe

	Head	Trunk	Upper Limbs	Lower Limbs
1. Erythema				
2. Thickness				
3. Scaling				
4. Total Each Column				
AREA OF PSORIATIC INVOLVEMENT				
5. Degree of Involvement	0 = No involvement 1 = < 10% 2 = 10 < 30% 3 = 30 < 50% 4 = 50 < 70% 5 = 70 < 90% 6 = 90 - 100%			
6. Insert Degree of Involvement from Row 5				
7. Multiply Row 4 by Row 6				
8.	x .10	x .30	x .20	x .40
9. Multiply Row 7 by Row 8				

10. Total PASI SCORE (Add together each column in Row 9)	

NOTE: Shaded areas are not to be completed.

Source: Frederiksson, 1978.

Appendix B: Physician's Global Assessments (PGA)

Static Physician's Global Assessment (sPGA)

Score	Category	Description
0	Clear	**Plaque elevation** = 0 (no elevation over normal skin) **Scaling** = 0 (no evidence of scaling) **Erythema** = 0 (except for residual hyperpigmentation/ hypopigmentation)
1	Almost Clear	**Plaque elevation** = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) **Scaling** = ± (surface dryness with some desquamation) **Erythema** = ± (faint, diffuse pink or slight red coloration)
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** = mild (light red coloration)
3	Moderate	**Plaque elevation** = marked (marked definite elevation with rough or sloped edges) **Scaling** = coarser (coarser scale covering most or all of the lesions) **Erythema** = moderate (definite red coloration)
4	Severe	**Plaque elevation** = marked (marked elevation typically with hard or sharp edges) **Scaling** = coarser (coarse, non-tenacious scale predominates covering most or all of the lesions) **Erythema** = severe (very bright red coloration)

Appendix C: Disability Index of the Health Assessment Questionnaire

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
DRESSING & GROOMING				
Are you able to:				
Dress yourself, including shoelaces and buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
Stand up from a straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
Cut your own meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Devices used for Dressing (button hook, zipper pull, etc.)
☐ Built up or special utensils
☐ Crutches
☐ Cane
☐ Wheelchair
☐ Special or built up chair
☐ Walker

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming ☐ Arising ☐ Eating ☐ Walking

Appendix C: Disability Index of the Health Assessment Questionnaire

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
HYGIENE				
Are you able to:				
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open previously opened jars?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat ☐ Bathtub bar ☐ Long-handled appliances for reach

☐ Bathtub seat ☐ Long-handled appliances in bathroom ☐ Jar opener (for jars previously opened)

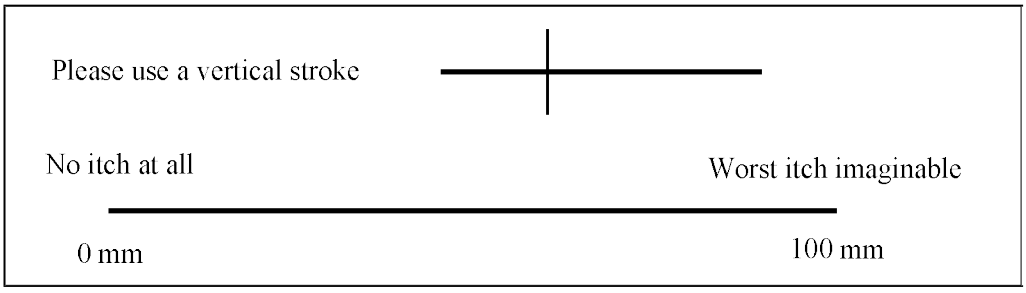
Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene ☐ Reach ☐ Gripping and opening things ☐ Errands and chores

Appendix D: Visual Analog Scales (VAS)

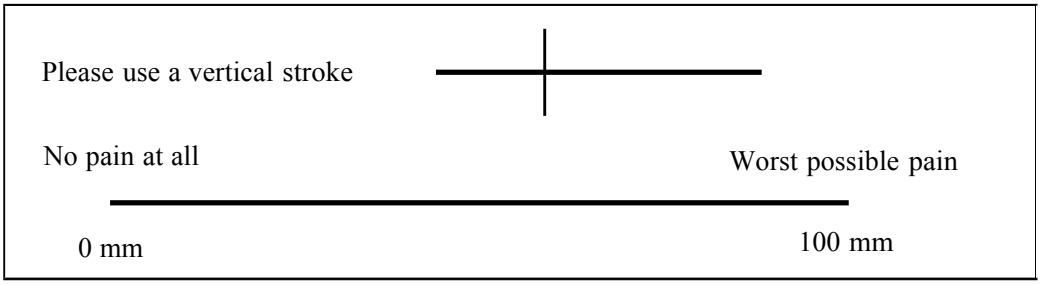
Subject's Assessment of Pruritus (Itch)

On average, how much itch have you had because of your condition in the past week?



Subject's Assessment of Skin Discomfort/Pain

On average, how much skin discomfort/pain have you had because of your condition in the past week?

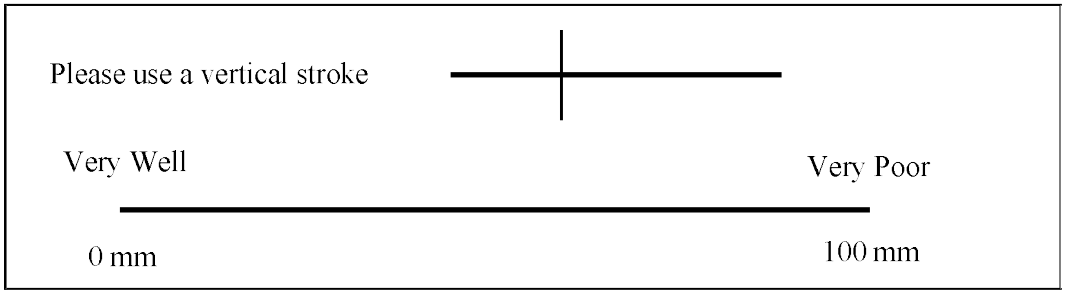


Please note: VAS above is not drawn to scale and is for illustrative purposes only.

Appendix D: Visual Analog Scales (VAS) (Continued)

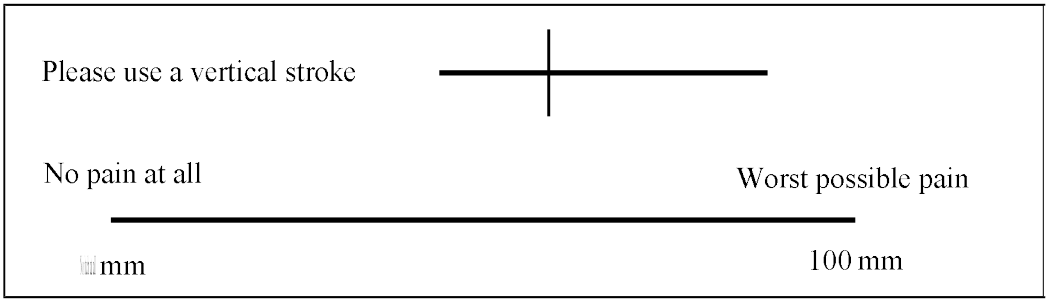
Subject's Global Assessment of Psoriasis Disease Activity

Considering all the ways your psoriasis affects you, on average, how have you been doing in the past week?



Subject's Assessment of Joint Pain

On average, how much pain have you had in your joints because of your psoriatic arthritis condition in the past week?

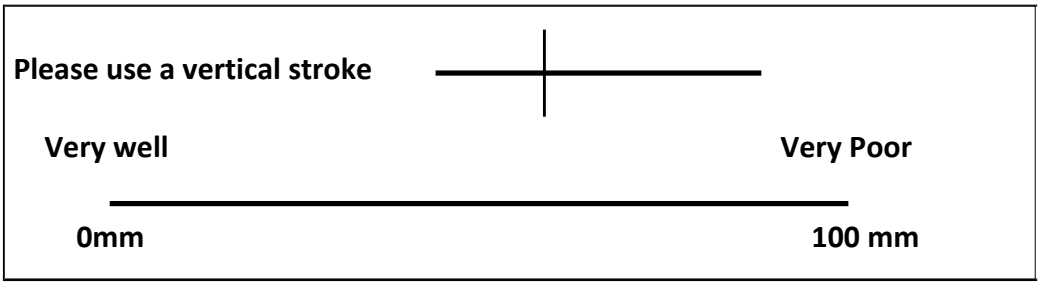


Please note: VAS above is not drawn to scale and is for illustrative purposes only.

Appendix D: Visual Analog Scales (VAS) (Continued)

Subject's Global Assessment of Psoriatic Arthritis Disease Activity

Considering all the ways your arthritis affects you, on the average, how have you been doing in the past week?



Please note: VAS above is not drawn to scale and is for illustrative purposes only.

Appendix E: The Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

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 **work** or **studying**?	A lot A little 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.

Appendix F: Work Productivity and Activity Impairment Questionnaire: Psoriasis (WPAI:PSO)

The following questions ask about the effect of your psoriasis on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1) Are you currently employed (working for pay)? ____NO ___YES
   If NO, check "NO" and skip to question 6

The next questions are about the **past seven days**, not including today.

2) During the past seven days, how many hours did you miss from work because of problems associated with your psoriasis? *Include hours you missed on sick days, times you went in late, left early, etc. because of psoriasis. Do not include time you missed to participate in this study.*
   _____HOURS

3) During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
   _____HOURS

4) During the past seven days, how many hours did you actually work?
   _____HOURS *(If "0", skip to question 6)*

5) During the past seven days, how much did psoriasis affect your productivity while you were working? *Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If psoriasis affected your work only a little, choose a low number. Choose a high number if psoriasis affected your work a great deal.*

Psoriasis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Psoriasis completely prevented me from working

CIRCLE A NUMBER

6) During the past seven days, how much did psoriasis affect your ability to do your regular daily activities, other than work at a job? *By regular activities, we mean the usual activities you do, such as work around the house, shopping, child care, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If psoriasis affected your activities only a little, choose a low number. Choose a high number if psoriasis affected your activities a great deal.*

Psoriasis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Psoriasis completely prevented me from doing my daily activities

CIRCLE A NUMBER

Appendix G: Blister Card Configuration

CC-10004-PSOR-010 30m