Penn Medicine
University of Pennsylvania School of Medicine

A PHASE IV, OPEN LABEL STUDY OF THE EFFECTS OF APREMILAST ON VASCULAR INFLAMMATION AND CARDIOMETABOLIC FUNCTION IN PSORIASIS

Principal Investigator:

Joel M. Gelfand MD, MSCE
University of Pennsylvania Department of Dermatology
Perelman Center for Advanced Medicine
3400 Civic Center Boulevard
7th Floor, South Tower #730
Philadelphia, PA 19104
Phone: 215-614-0635
Fax: 215-615-3127
Joel.Gelfand@pennmedicine.upenn.edu

Co-Investigator:

Joy Wan MD, MSCE
University of Pennsylvania Department of Dermatology
Perelman Center for Advanced Medicine
3400 Civic Center Boulevard
7th Floor, South Tower #773
Philadelphia, PA 19104
Phone: 215-615-2937
Fax: 215-615-3127
joywan@pennmedicine.upenn.edu

Regulatory Sponsor:

Joel M. Gelfand MD, MSCE
University of Pennsylvania Department of Dermatology
Perelman Center for Advanced Medicine
3400 Civic Center Boulevard
7th Floor, South Tower #730
Philadelphia, PA 19104
Phone: 215-614-0635
Fax: 215-615-3127
Joel.Gelfand@pennmedicine.upenn.edu

Funding Source:

Amgen Corporation
110 Allen Rd
Basking Ridge, NJ 07920
Phone: 908-860-4000

Investigational Product: Apremilast (Otezla)

Protocol Number: 826652

Amgen Number: 20207136

ClinicalTrials.gov Number: NCT03082729

Initial version**:** 7-21-2016

Amended: v7.04-03-2017

Amended: v8.05-15-2017

Amended: v9 07-14-2017

Amended: v10: 10-09-17

Amended: v11: 07-18-19

Amended: v12: 08-18-2020

Amended v13:10.01.2021

Current: v14:12.13.21

Table of Contents

List of Abbreviations

AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
BSA	Body surface area
BUN	Blood urea nitrogen
cAMP	Cyclic adenosine monophosphate
CBC	Complete blood count
Cmax	Maximum serum concentration
CMP	Complete metabolic profile
CRF	Case report form
CRP	C-reactive protein
CYP	Cytochrome
CV	Cardiovascular
DCERN	Dermatology Clinical Effectiveness Research Network
DICOM	Digital Imaging and Communication in Medicine
DLQI	Dermatology Life Quality Index
ECG	12-lead electrocardiogram
EC	Ethics Committee
FDA	Food and Drug Administration
FDG	[18F]-fluorodeoxyglucose
HDL	High-density lipoprotein
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
IDS	Investigational Drug Services at the University of Pennsylvania
IRB	Institutional Review Board
IL	Interleukin
MRHD	Maximum Recommended Human Dose
NIH	National Institutes of Health
NSAIDs	Non-steroidal anti-inflammatory drugs
PASI	Psoriasis Area and Severity Index
PASI-##	Reduction of Psoriasis Area and Severity Index by ## (percent)
PDE4	Phosphodiesterase -4
Penn IRB	Institutional Review Board of the University of Pennsylvania
PET/CT	Positron emission tomography / computed tomography
PGA	Physician Global Assessment
PHI	Protected health information
PI	Principle Investigator
SAE	Serious adverse event
SD	Standard deviation
SUV	Standard uptake value
TAB	Total atherosclerosis burden
TB	Tuberculosis
TBR	Tissue-to-background ratio
Th1	T helper cell type 1
Th17	T helper cell type 17
Tmax	Time to reach maximum concentration
TNF	Tumor necrosis factor
VAS	Visual analog scale
WBC	White blood cell

Study Summary:

Title	A Phase IV, Open label Study of the Effects of Apremilast on Vascular Inflammation and Cardiometabolic function in Psoriasis
Short Title	Vascular Inflammation in Psoriasis-Apremilast (VIP-A)
IRB Number	826652
Protocol Number	97509210
Phase	Phase IV
Methodology	Single arm, open label, self-controlled trial
Study Duration	Up to 30 day screening period, treatment period of 52 weeks per subject
Study Center(s)	Multicenter within the Dermatology Clinical Effectiveness Research Network (DCERN). The lead site and coordinating center is the University of Pennsylvania.
Objectives	The primary objectives of this study are to determine the effect of apremilast on aortic vascular inflammation, cardiometabolic biomarkers and body composition in patients with moderate-severe psoriasis. FDG-PET/CT will be used to assess vascular inflammation, with multi-volumetric product, tissue-to-background ratio and total atherosclerotic burden, and body composition via volumetric quantification.
Number of Subjects	70 patients
Main Inclusion and Exclusion Criteria	Males and females 18 years of age and older with moderate to severe plaque psoriasis defined by ≥10% Body Surface Area affected and Psoriasis Area and Severity Index ≥12. Subjects must be candidates for systemic therapy and have active psoriasis despite treatment with topical agents.
Study Product:	Apremilast tablets, oral Day 1: 10 mg in AM Day 2: 10 mg AM and PM Day 3: 10 mg AM and 20 mg PM Day 4: 20 mg AM and PM Day 5: 20 mg AM and 30 mg PM Day 6: 30 mg PO BID Day 7-week 52: 30 mg PO BID
Duration of administration	52 weeks
Reference therapy	Not applicable
Endpoints	The primary endpoints to be measured in this study include: change from baseline in total vascular inflammation of the aorta, as assessed on FDG-PET/CT, and change in cardiometabolic biomarkers at week 16. The secondary endpoints to be measured are change in vascular inflammation between week 52 and earlier time points, change from baseline in cardiometabolic biomarkers at other time points (week 4, 8, 12, 52), volumetric changes in visceral and subcutaneous adipose tissue, changes in physician reported outcomes (PASI, PGA), changes in patient reported outcomes (DLQI, pruritus VAS) and safety endpoints.
Statistical Methodology	Descriptive statistics, Wilcoxon signed rank tests, multivariable linear regression, and exploratory analyses will be conducted
Safety Evaluations	• Monitoring for adverse events and serious adverse events • Vital signs, physical examination • Laboratory assessments (e.g., hematology, chemistry)

1. BACKGROUND AND STUDY RATIONALE

1.1 Background and Relevant Literature

Psoriasis is a common T-helper cell type 1 (Th1) and type 17 (Th17) mediated inflammatory disease, affecting 2-3% of the population.[1-3] Over 7.5 million Americans have been diagnosed with psoriasis and about 1 million have moderate to severe disease requiring systemic treatments.[4] Despite the broad array of therapeutic options, about 70% of patients with severe psoriasis affecting ≥10% body surface area (BSA) are not receiving treatment to control their disease.[5] It is now increasingly recognized that psoriasis, like rheumatoid arthritis and systemic lupus erythematosus, is a systemic inflammatory disorder and not only a disorder limited to the skin.[6] In support of this, increasing evidence identifies psoriasis, particularly severe disease, as an independent risk factor for diabetes mellitus, dyslipidemia, myocardial infarction, stroke, and cardiovascular (CV) mortality.[7-20]

The pathophysiology of psoriasis is characterized by inflammation with increased antigen presentation and lymphocyte activity and up-regulation of Th1/Th17 cytokines. Serum levels of inflammatory markers, including C-reactive protein (CRP) and tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-18, IL-12, IL-17 and IL-22 are chronically increased in patients with psoriasis and correlate with psoriasis severity.[21-27] Elevated levels of cytokines including IL-6 and TNF-α, cell adhesion molecules, and downstream acute-phase reactants such as CRP and fibrinogen have been associated with increased cardiovascular risk.[14,17,28-35] The role of Th17 cells in atherogenesis remains less clear, however, with evidence suggesting both pro- and anti-atherogenic effects.[36,37] It is evident, however, that, in general, systemic inflammation in psoriasis shares similar pathophysiology with atherosclerotic cardiovascular disease.[6,38-40]

A preliminary study on experimentally induced *in vivo* inflammation revealed that robust activation of TNF-α and IL-6 is followed by a systemic insulin-resistant state, metabolic dyslipidemia and decreased high-density lipoprotein (HDL) function.[41] Dysfunction of three inter-related pathways have been shown in patients with psoriasis: 1) Pro-atherogenic lipoprotein profiles (reduced HDL, elevated triglycerides, and increased small dense low-density lipoprotein particles),[42,43] 2) impaired macrophage cholesterol efflux and reverse cholesterol transport,[44,45] and 3) inflammation-induced adipose and metabolic dysfunction (increase in leptin and insulin, and decrease in adiponectin).[41,46] These data suggested potential biologic links to vascular inflammation and accelerated CV disease development.

An innovative method to investigate the systemic inflammatory burden of psoriasis is with [18F]-fluorodeoxyglucose (FDG) positron emission tomography / computed tomography (PET/CT). FDG-PET/CT is a validated imaging technique that enables highly sensitive and precise measurements of inflammation *in vivo*.[47] FDG uptake in arterial walls reflects metabolic activity of inflammatory cells, particularly macrophages, within atherosclerotic lesions.[48] In a pilot study, it was observed that psoriasis is associated not only with clinically observed inflammation in the skin, but also foci of subclinical inflammation within the liver, joints, tendons, and aorta that were not explained by traditional cardiovascular risk factors or co-morbidities.[49] Moreover, increasing severity of skin disease in psoriasis is associated with increasing severity of aortic vascular inflammation[50]. Since vascular inflammation on FDG-PET/CT strongly predicts future major vascular events and is responsive to even short term interventions for traditional CV risk factors, [51-55] it may also serve as a useful marker for evaluating vascular inflammation and, thus, cardiovascular risk in response to psoriasis treatments.

Cyclic adenosine monophosphate (cAMP) is a key modulator of immune cell responses and is predominantly regulated by phosphodiesterase 4 (PDE4). Apremilast is an oral selective PDE4 inhibitor that is FDA approved for the treatment of psoriasis (see section 1.2). PDE4 inhibition down-regulates the inflammatory response by reducing the expression of tumor necrosis factor (TNF)-α, interleukin (IL)-23, and other pro-inflammatory cytokines, while increasing anti-inflammatory cytokines, such as IL-10[56,57]. cAMP also plays an important role in regulation of macrophage inflammatory responses, and PDE4 inhibition has been shown to dramatically decrease the inflammatory response of macrophages[58].

Macrophages play an important role in the pathogenesis of atherosclerosis, contributing at all stages[59]. Macrophages ingest lipoproteins, transforming them into cholesterol-laden foam cells. These foam cells

persist in plaques and promote disease progression[60]. They represent a major component of vessel wall inflammation. Macrophages also recruit additional inflammatory cytokines and play a role in atherosclerotic plaque destabilization[61]. We, therefore, propose this open-label clinical trial to investigate the effects of apremilast, an oral PDE4 inhibitor, on aortic vascular inflammation, as measured by FDG-PET/CT imaging and cardiometabolic biomarkers in patients with moderate to severe psoriasis. In addition, metabolic syndrome and obesity are highly prevalent in psoriasis and it is therefore of special interest that in the phase III clinical trials for apremilast, 20.2% of patients had weight loss, not associated with gastrointestinal side effects[62]. Because of this, the above CT imaging will also be used to measure changes in abdominal fat composition in patients taking apremilast.

1.2 Name and Description of the Investigational Product: Apremilast

Apremilast is a phosphodiesterase 4 (PDE4) inhibitor. Apremilast is known chemically as N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide. Its empirical formula is C22H24N2O7S and the molecular weight is 460.5 g/mol. Each tablet contains apremilast as the active ingredient and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium. Apremilast is an oral small-molecule inhibitor of PDE4 specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels. The specific mechanism(s) by which apremilast exerts its therapeutic action in psoriatic arthritis patients and psoriasis patients is not well defined.

1.3 Non-clinical Data

Long-term studies were conducted in mice and rats with apremilast to evaluate its carcinogenic potential. No evidence of apremilast-induced tumors was observed in mice at oral doses up to 8.8-times the Maximum Recommended Human Dose (MRHD) on an AUC basis (1000 mg/kg/day) or in rats at oral doses up to approximately 0.08- and 1.1-times the MRHD, (20 mg/kg/day in males and 3 mg/kg/day in females, respectively).

Apremilast tested negative in the Ames assay, in vitro chromosome aberration assay of human peripheral blood lymphocytes, and the in vivo mouse micronucleus assay.

In a fertility study of male mice, apremilast at oral doses up to approximately 3-times the MRHD based on AUC (up to 50 mg/kg/day) produced no effects on male fertility. In a fertility study of female mice, apremilast was administered at oral doses of 10, 20, 40, or 80 mg/kg/day. At doses ≥1.8-times the MRHD (≥20 mg/kg/day), estrous cycles were prolonged, due to lengthening of diestrus which resulted in a longer interval until mating. Mice that became pregnant at doses of 20 mg/kg/day and greater also had increased incidences of early post-implantation losses. There was no effect of apremilast approximately 1.3-times the MRHD (10 mg/kg/day).

1.4 Clinical Data to Date

1.4.1 Human Pharmacokinetics

Absorption: Apremilast, when taken orally, is absorbed with an absolute bioavailability of ~73%, with peak plasma concentrations (Cmax) occurring at a median time (tmax) of ~2.5 hours. Co-administration with food does not alter the extent of absorption of apremilast.

Distribution: Human plasma protein binding of apremilast is approximately 68%. Mean apparent volume of distribution is 87 L.

Metabolism: Following oral administration in humans, apremilast is a major circulating component (45%) followed by inactive metabolite M12 (39%), a glucuronide conjugate of O-demethylated apremilast. It is extensively metabolized in humans with up to 23 metabolites identified in plasma, urine and feces. Apremilast is metabolized by both cytochrome (CYP) oxidative metabolism with subsequent glucuronidation and non-CYP mediated hydrolysis. In vitro, CYP metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6.

Elimination: The plasma clearance of apremilast is about 10 L/hr in healthy subjects, with a terminal elimination half-life of approximately 6-9 hours. Following oral administration of radio-labeled apremilast, about 58% and 39% of the radioactivity is recovered in urine and feces, respectively, with about 3% and 7% of the radioactive dose recovered as apremilast in urine and feces, respectively.

1.4.2 Clinical Studies in Adults

Two multicenter, randomized, double-blind, placebo-controlled trials (Studies PSOR-1 and PSOR-2) enrolled a total of 1257 subjects 18 years of age and older with moderate to severe plaque psoriasis [body surface area (BSA) involvement of ≥10%, Physician Global Assessment (PGA) of ≥3 (moderate or severe disease), Psoriasis Area and Severity Index (PASI) score ≥12, candidates for phototherapy or systemic therapy]. Subjects were allowed to use low-potency topical corticosteroids on the face, axilla and groin. Subjects with scalp psoriasis were allowed to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions.

Study PSOR-1 enrolled 844 subjects and Study PSOR-2 enrolled 413 subjects. In both studies, subjects were randomized 2:1 to apremilast 30 mg BID or placebo for 16 weeks. Both studies assessed the proportion of subjects who achieved PASI-75 at Week 16 and the proportion of subjects who achieved a PGA score of clear (0) or almost clear (1) at Week 16. Across both studies, subjects ranged in age from 18 to 83 years, with an overall median age of 46 years. The mean baseline BSA involvement was 25.19% (median 21.0%), the mean baseline PASI score was 19.07 (median 16.80), and the proportion of subjects with PGA score of 3 (moderate) and 4 (severe) at baseline were 70.0% and 29.8%, respectively. Approximately 30% of all subjects had received prior phototherapy and 54% had received prior conventional systemic and/or biologic therapy for the treatment of psoriasis with 37% receiving prior conventional systemic therapy and 30% receiving prior biologic therapy. Approximately one-third of subjects had not received prior phototherapy, conventional systemic nor biologic therapy. A total of 18% of subjects had a history of psoriatic arthritis.

The proportion of subjects who achieved PASI-75 responses, and PGA score of clear (0) or almost clear (1), are presented in Table 1. The median time to loss of PASI-75 response among the subjects re-randomized to placebo at Week 32 during the Randomized Treatment Withdrawal Phase was 5.1 weeks

Table 1: Clinical Response at Week 16 in Studies PSOR-1 and PSOR-2

	Study PSOR-1		**Study PSOR-2**	
	Placebo	**apremilast 30mg BID**	**Placebo**	**apremilast 30mg BID**
	N = 282	**N = 562**	**N = 137**	**N = 274**
PASI-75, n (%)	15 (5.3)	186 (33.1)	8 (5.8)	79 (28.8)
PGA of Clear of Almost Clear, n (%)	11 (3.9)	122 (21.7)	6 (4.4)	56 (20.4)

1.4.3 Clinical Studies in Children

The safety and effectiveness of apremilast in pediatric patients less than 18 years of age have not been established.

1.5 Dose Rationale

Apremilast is given with an initial dosage titration for the first five days (see Table 2) and then 30mg twice daily therefore after. This is the FDA-approved dose regimen for treatment of moderate to severe plaque psoriasis.

Table 2: Apremilast Dosage Titration Schedule

Day 1	**Day 2**		**Day 3**		**Day4**		**Day 5**		**Day 6 & thereafter**	
AM	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**	**AM**	**PM**
10mg	10mg	10mg	10mg	20mg	20mg	20mg	20mg	30mg	30mg	30mg

1.6 Potential Risk

The following side effects may be associated with the use of apremilast:

- Very common: diarrhea, nausea (stomach upset),
- Common: upper abdominal (stomach) pain, vomiting indigestion, frequent bowel movements, heartburn, fatigue, bronchitis (infection of the tubes to the lungs), redness/swelling/pain in the sinuses, inflammation or infections of the nose and throat, upper respiratory tract infection, decreased appetite, back pain, headache (including tension and migraine), difficulty sleeping, depression, cough,
- Uncommon: allergic reaction, weight loss, rash

Pregnancy Risks: Apremilast is pregnancy category C. Category C means that animal studies have revealed adverse fetal effects but that no controlled studies in women have been done, or that no studies in women or animals are available.

2 Study Objectives

2.1 Primary Objectives

To assess the effects of apremilast, in patients with moderate to severe psoriasis on:

- Vascular inflammation as measured by FDG-PET/CT

Cardiometabolic biomarkers: lipid particle size, HDL function (cholesterol efflux), TNF-Alpha, IL-6, C reactive protein, leptin, adiponectin, insulin levels and glucose to yield HOMA-IR, apolipoprotein B, ferritin, interleukin-2 receptor A, , fetuin-A, GlycA,ICAM-1, Serum amyloid A, VCAM-1, IFN-g,IL-1b, ,IL-17A,IL-8, MCP-1, IL-9, IL-10, beta hydroxybutyrate, acetoacetic acid, Acetone, Ketone bodies, TRLTG, TRLC, TRLP, VL_TRLP, L_TRLP, M_TRLP, S_TRLP, VS_TRLP, Valine, Leucine, Isoleucine, BCAA, Alanine, ApoA1,Citrate and Diabetes Risk Index.

2.2 Secondary Objectives

To assess the effects of apremilast, in patients with moderate to severe psoriasis on:

- Body composition, as measured by FDG-PET/CT
- Psoriasis activity and severity
- Pruritus, as measured by a VAS
- Patient reported quality of life (DLQI)
- Safety

3 Investigational Plan

3.1 General Design

This study is a phase IV, open-label 52-week clinical trial to investigate the efficacy of apremilast in reducing vascular inflammation and cardiometabolic risk biomarkers in patients with moderate to severe psoriasis. The subject inclusion and exclusion criteria are shown in Sections 4.1 and 4.2. This will be a multicenter trial with a goal enrollment of 70 patients. Subjects will receive apremilast for a total of 52 weeks at the FDA approved dose for moderate-severe psoriasis.

All study procedures, including screening, will occur only after obtaining signed informed consent. During the screening period, baseline, weeks 4, 8, 12, 16, 28, 40 and 52 subjects will be evaluated by

investigators or designated research personnel. Psoriasis severity will be assessed using the Psoriasis Area and Severity Index (PASI) and the Physician Global Assessment (PGA), both widely accepted measurement tools for psoriasis[63]. The Dermatology Life Quality Index (DLQI) will also be measured to collect information regarding patient-oriented outcomes[64, 65].

FDG-PET/CT will be conducted at baseline, week 16 and week 52. Subjects will undergo a FDG-PET/CT scan using the standard protocol as described below. Subjects will be required to fast for 8 hours prior to the scan. At the imaging center, finger-stick serum glucose levels will be checked to ensure a glucose level <150 mg/dL prior to FDG administration. If the glucose level exceeds 150 mg/dL, consultation with the principal investigator prior to the imaging will be required to determine if the subject is eligible to continue in the study. Neck to iliac crests PET/CT image acquisition will begin about 120 minutes (± 10 minutes) after IV administration of 15 mCi of [18F]-FDG or other appropriate weight-based dose per imaging site's standard dosing protocol. Axial, sagittal, and coronal PET reconstructions will be interpreted with and without attenuation correction, using non-contrast CT images for anatomical correlation. Within approximately 24 hours after the completion of the FDG-PET/CT scan, the local nuclear medicine personnel will issue a clinical report determining if the subject has any clinically significant findings which could preclude the subject's continued participation in the study.

The arterial uptake of FDG will be measured by the maximum standardized uptake value (SUV) divided by the venous SUV mean, a previously reported method for quantifying vascular inflammation[65]. This will yield a maximum target to background ratio (TBR_{max}) which is considered the standard reporting variable in FDG-PET/CT vascular studies[66]. The PET/CT images obtained from each site's local imaging center will be de-identified and sent to the University of Pennsylvania Imaging Lab where trained nuclear medicine personnel will undertake a qualitative review of the PET/CT images. During this review, two-dimensional (2D) circular regions of interests (ROIs) will be manually placed on the PET images around the external aortic contour, around the hepatic margin, and around articular spaces on all transverse slices passing through these structures using low-dose CT images for anatomic guidance. The images will then be sent to the central core National Institutes of Health (NIH) Imaging Lab for measuring the SUVs. The NIH central PET/CT readers will be blinded to time point of scan via Digital Imaging and Communication in Medicine (DICOM) file editing applied by the University of Pennsylvania.

In addition to the mean SUV of the whole aorta, mean SUVs will be calculated for five segments of the aorta: ascending aorta, aortic arch, descending thoracic aorta, suprarenal abdominal aorta, and infrarenal abdominal aorta. These segments are defined to consider separately various regions of aortic disease that are associated with different clinical phenotypes (e.g., aortic arch disease with stroke, abdominal aortic disease with abdominal aortic aneurysm) [48,49,66,67,68].

Adipose tissue volumes will be assessed at L2–L3 using automated software, as has been previously reported[69]. The algorithm will consist of body masking, noise reduction, adipose tissue labeling, visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) separation, and quantitation. The adipose tissue volume inside the internal contour contributes to the VAT and the adipose tissue volume between the external contour and internal contour contributes to SAT.

Laboratory tests will be conducted at screening, baseline and weeks 4, 8, 12, 16 and 52. This includes labs for screening safety and cardiometabolic biomarkers. Blood will be collected as described in Appendix E. In summary, a total volume of 30 mL (34.5 mL for Penn participants at Week 0 and Week 16 only) will be drawn per patient. Tubes will be labeled with an ID that does not contain identifiable personal information. The date and time of sample collection will be also indicated on a lab transfer sheet. Tubes will be sent directly to a lab at the NIH where the samples will be processed and stored.

The blood will be used for making aliquots of plasma and serum for storage at -80° C after centrifugation of samples for 20 minutes at 2,400 RPM. Any remaining plasma and/or serum will be destroyed at the completion of the study, except as required for quality assurance. All samples are run in duplicate and normalized to a control pooled sample run simultaneously.

The expected duration of this open-label trial for each participant is 52 weeks, in addition, to an initial screening visit and screening period of up to 30 days.

3.1.1 Screening Phase

Before subjects may be screened for enrollment into this study, full IRB approval of the protocol and consent will be obtained. Subjects will be provided with the approved informed consent form and complete the informed consent process according to FDA regulations and Good Clinical Practice guidelines prior to any study related procedures. Upon signing consent, subjects will be screened to determine their eligibility for the study (see sections 4.1 and 4.2).

Subjects who meet the inclusion and exclusion criteria will undergo a screening assessment within 30 days of study enrollment. This includes a complete medical history and physical exam; vital signs and weight; routine blood work (CBC, CMP), HIV, hepatitis B surface antigen, hepatitis C antibodies, and urine pregnancy test. Details of the screening procedures can be found in Section 6.2. If a subject reports current use of a psoriasis therapy at time of screening assessment, the study physician will determine, based on psoriasis severity and overall medical history, whether the subject can undergo a washout period. The subject will then be informed of what to expect during a washout period and will be asked to decide whether they would like to continue with the study. If the subject decides to continue, he/she will be monitored for AEs during the washout period and routine blood work will be repeated for subjects who complete a washout period of greater than 30 days. Subjects who complete all screening visit procedures and meet the inclusion and exclusion criteria will undergo baseline FDG-PET/CT and cardiometabolic assessments. If screening assessment exceeds 30 days, the study PI should be consulted for guidance on determining whether all screening procedures should be repeated or findings are considered clinically stable and subject can continue with baseline visit procedures.

Administration of the initial dose of study treatment (apremilast) must occur 7 days or less from date of FDG-PET/CT scan. If initial dose cannot occur within 7 days of FDG-PET/CT scan, the study PI should be consulted for guidance on course of treatment.

3.1.2 Study Intervention Phase

All patients will receive apremilast at the FDA-approved dose for plaque psoriasis for a total of 52 weeks. At weeks 4, 8, 12, 16, 28, 40 and 52, subjects will be evaluated by investigators or designated research personnel. Psoriasis severity will be assessed using the Psoriasis Area and Severity Index (PASI) and the Physician Global Assessment (PGA). Laboratory tests will also be conducted at baseline and weeks 4, 8, 12, 16, and 52 for screening safety labs and/or cardiometabolic biomarker assessment. FDG-PET/CT will be conducted at baseline, week 16 and week 52.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary endpoints to be measured in this study include:

- Change in total vascular inflammation of the whole aorta as assessed on FDG-PET/CT between baseline and week 16
- Change in cardiometabolic biomarkers (lipid particle size, HDL function (cholesterol efflux), TNF-Alpha, IL-6, high sensitivity C reactive protein, leptin, adiponectin, insulin levels and glucose to yield HOMA-IR, apolipoprotein B, ferritin, interleukin-2 receptor A, interleukin-18, and fetuin-A) between baseline and week 16

3.2.2 Secondary Study Endpoints

The secondary endpoints to be measured in this study include:

- Change in total vascular inflammation of the five aortic segments as assessed on FDG-PET/CT between baseline and week 16, and between baseline and week 52
- Change in cardiometabolic biomarkers at week 4, 8, 12, 16 and 52 compared to baseline and earlier time points

- Change in total vascular inflammation of the aorta as assessed on FDG-PET/CT between week 52 and earlier time points (baseline and week 16)
- Changes in body composition as measured on FDG-PET/CT between week 52 and earlier time points (baseline and week 16)
- Changes in physician reported outcomes (PASI, PGA)
- Changes in the patient reported outcomes (DLQI, pruritus VAS)
- Safety endpoints

3.2.3 Primary Safety Endpoints

The safety endpoints will be assessed by subject interview (and physical exam, if indicated) as well as blood laboratory examination. Subjects will be monitored for any adverse event that occur during the study including serious adverse events (e.g., serious infection and malignancy). Non-serious adverse events, as defined in Section 8.1, will also be noted. A complete review of systems will also be assessed and physical exam performed at baseline and week 16. The following routine laboratory tests will be monitored as safety parameters and will be drawn during screening and at weeks16 and 52.

- Hematology: complete blood count (CBC) with differential
- Complete metabolic profile: sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, total protein, albumin

4 Study Population and Duration of Participation

4.1 Inclusion Criteria

1) Males and females 18 years of age and older.
2) Clinical diagnosis of psoriasis for at least 6 months as determined by subject interview of his/her medical history and confirmation of diagnosis through physical examination by Investigator.
3) Stable plaque psoriasis for at least 2 months before screening and at baseline (Week 0) as determined by subject interview of his/her medical history.
4) Moderate to severe psoriasis defined by ≥ 10 percent Body Surface Area (BSA) involvement at the baseline (Week 0) visit.
5) PASI score of ≥ 12 at the Baseline (Week 0) visit.
6) Subject is a candidate for systemic therapy and has active psoriasis despite prior treatment with topical agents.
7) Women are eligible to participate in the study if they meet one of the following criteria:
   a) Females of childbearing potential (FCBP) must have a negative pregnancy test at screening and baseline. Women of childbearing potential must undergo periodic pregnancy testing during the study and agree to use at least one of the following methods of contraception throughout the study duration and for at least 28 days after taking the last dose of investigational product:
      i) Oral contraceptives
      ii) Transdermal contraceptives
      iii) Injectable or implantable methods
      iv) Intrauterine devices
      v) Vaginal ring
      vi) Vasectomized partner
      vii) Barrier methods Male or female condom PLUS one additional barrier method: (a) diaphragm with spermicide; (b) cervical cap with spermicide; or (c) contraceptive sponge with spermicide.);
   b) Women who are postmenopausal (for at least one year), sterile, or hysterectomized;
   c) Women who have undergone tubal ligation will be required to undergo periodic pregnancy testing during the duration of the study
   d) Sexual abstinence, defined as total abstinence from sexual intercourse, is considered an adequate form of contraception. (Agreement to comply with sexual abstinence must be recorded in the source document).

e) Subjects using oral or parenteral forms of contraceptives must have been using these methods for at least 90 days prior to baseline visit.

8).Subject is judged to be in good general health as determined by the Principal Investigator based upon the results of medical history, laboratory profile and physical examination performed at screening.

4.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. Prior treatment with apremilast is permissible under the following conditions:
    a. Prior exposure did not result in a clinical outcome such as side effect or lack of efficacy that would contraindicate future treatment with apremilast
    b. For patients who have only taken the apremilast two week starter pack (defined as 13-tablet blister titration pack containing: (4) 10-mg, (4) 20-mg, and (5) 30-mg tablets with an additional (14) 30-mg tablets), apremilast must be discontinued at least 30 days prior to baseline (week 0)
    c. For patients with apremilast exposure greater than one two week starter pack, apremilast must be discontinued at least 90 days prior to baseline (week 0).
2. Diagnosis of erythrodermic psoriasis, generalized or localized pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis.
3. Diagnosis of other active skin diseases or skin infections (bacterial, fungal, or viral) that may interfere with evaluation of psoriasis.
4. Cannot avoid topical prescription medications for psoriasis for at least 14 days prior to the baseline visit (week 0) and during the study, with the exception of hydrocortisone 2.5% for the face and intertriginous areas.
5. Cannot avoid UVB phototherapy or Excimer laser for at least 14 days prior to the Baseline (Week 0) visit and during the study.
6. Cannot avoid psoralen-UVA phototherapy for at least 30 days prior to the Baseline (Week 0) visit and during the study.
7. Use of systemic therapies for the treatment of psoriasis, or systemic therapies known to improve psoriasis, during the study:
    a. Systemic therapies must be discontinued at least 30 days prior to the Baseline (Week 0) visit except for biologics and apremilast exposure greater than one two week starter pack.
    b. All biologics, except IL-12/IL-23 antagonists, must be discontinued for at least 90 days prior to Baseline (Week 0).
    c. Any IL-12/IL-23 antagonist (e.g., ustekinumab, briakinumab) must be discontinued for at least 180 days prior to Baseline (Week 0).
    d. Investigational agents must be discontinued at least 30 days or 5 half-lives (whichever is longer) prior to the Baseline (Week 0) visit.
8. Subject is ≥ 300lbs (136.1 kg) at Baseline (Week 0).
9. Subject is taking or requires oral or injectable corticosteroids during the study. Inhaled corticosteroids for stable medical conditions are allowed.
10. Subject is taking a medication that interferes with metabolism of apremilast, including but not limited to rifampin, phenobarbital, carbamazepine, phenytoin
11. Poorly controlled medical condition, such as unstable ischemic heart disease, cerebrovascular accident or myocardial infarction within the prior 6 months, psychiatric disease requiring frequent hospitalization, and any other condition, which, in the opinion of the Investigator, would put the subject at risk by participation in the study.
12. Prior history of suicide attempt at any time in the subject's life time prior to screening or randomization, or major psychiatric illness requiring hospitalization within the last 3 years.
13. Uncontrolled hypertension, with measured systolic blood pressure >180 mmHg or diastolic blood pressure >95 mmHg
14. Subject has infection or risk factors for severe infections, for example
    a. Positive serology or known history of HIV, hepatitis B or C, or other severe, recurrent, or persistent infections;

   b. Excessive immunosuppression or other factors associated with it, including human immunodeficiency virus infection;
   c. Active tuberculosis (TB) disease;
   d. Any other significant infection requiring hospitalization or intravenous (IV) antibiotics in the 30 days prior to baseline;
   e. Infection requiring treatment with oral or parenteral (other than IV) antibiotics within 14 days prior to baseline;
   f. Subject has received vaccination with a live viral agent within 30 days prior to screening or will require a live vaccination during study participation including up to 30 days after the last dose of study drug.
15. Subject has history of hematological or solid malignancy other than successfully treated basal cell carcinoma, non-metastatic cutaneous squamous cell carcinoma or cervical intraepithelial neoplasia or carcinoma in situ of cervix with no evidence of recurrence within the previous 5 years.
16. Female subject who is pregnant or breast-feeding or considering becoming pregnant during the study.
17. Screening clinical laboratory analyses showing any of the following abnormal results:
   a. White blood cell (WBC) count <3.0 x 10^9/L. (Subject can be included if WBC count is <3.0 x 10^9/L and absolute neutrophil count (ANC) is >1000 cells / mm^3.)
   b. WBC count > 15 x 10^9/L;
   c. Hemoglobin (Hgb) < 9.0 x 10^9/L;
   d. Platelet count < 100 x 10^9/L;
   e. Serum creatinine >1.5 mg/dL ;
   f. Serum aspartate transaminase or alanine transaminase >2.0 upper limits of normal
18. Recent history of substance abuse, within 365 days of Baseline (Week 0) visit that could preclude compliance with the protocol.
19. Alcohol use of more than 14 drinks per week within 14 days of the baseline visit
20. If subject is on cholesterol-lowering medication (e.g. statin), dose and form of medication must be stable for 90 days prior to week 0 and remain stable throughout the duration of the study.

4.3 Subject Recruitment

This study is a multicenter clinical trial with subjects recruited from clinical practices within the Dermatology Clinical Effectiveness Research Network (DCERN). At the primary site, the Principal Investigator has extensive experience in clinical research in psoriasis, and the University of Pennsylvania is a referral center for patients with psoriasis. All recruitment materials will be submitted to the Institutional Review Board (IRB) of the University of Pennsylvania and receive written approval prior to their use.

Before subjects may be screened for enrollment into this study, full IRB approval of the protocol and consent will be obtained. Subjects will be provided with the approved informed consent form and complete the informed consent process according to FDA regulations and Good Clinical Practice guidelines prior to any study related procedures. Upon signing consent, subjects will be screened to determine their eligibility for the study (see sections 4.1 and 4.2).

Subjects who meet the inclusion and exclusion criteria will undergo a screening assessment within 30 days of study enrollment. Details of the screening procedures can be found in Section 6.2. Subjects who complete all screening visit procedures, and meet the inclusion and exclusion criteria, will undergo baseline FDG-PET/CT and cardiometabolic biomarker assessments.

4.4 Duration of Study Participation

The duration of study participation will be 52 weeks.

4.5 Total Number of Subjects and Sites

Recruitment will end when 70 subjects are enrolled. It is expected that 70 subjects will be enrolled in order to produce about 35 evaluable subjects, assuming a dropout rate at week 52 of 50%.

4.6 Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study Drug

5.1 Description

Apremilast is a phosphodiesterase 4 (PDE4) inhibitor. Apremilast is known chemically as N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]acetamide. Its empirical formula is C22H24N2O7S and the molecular weight is 460.5. Tablets are supplied in 10-, 20-, and 30-mg strengths for oral administration. Each tablet contains apremilast as the active ingredient and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide red, iron oxide yellow (20 and 30 mg only) and iron oxide black (30 mg only).

5.2 Intervention Regimen

See section 1.3

5.3 Receipt

Apremilast is an FDA-approved drug manufactured by Amgen Corporation. It will be provided by Amgen Corporation, and delivered to the attention of Kenneth Rockwell, PharmD to the following address:

University of Pennsylvania Investigational Drug Service (Penn IDS)
Ground Floor Maloney Building
3600 Spruce Street
Philadelphia, PA 19104
(215) 349-8817

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented in the study files. The investigator must notify Amgen Corporation, of any damaged or unusable study treatments that were supplied to the investigator's site.

5.4 Storage

Apremilast should be stored between 15 - 30° Celsius.

5.5 Preparation and Packaging

For details regarding the preparation and packaging, see Appendix A

5.6 Administration and Accountability

Study product will be labeled, dispensed, and stored by IDS. After the baseline FDG-PET/CT scan has been reviewed, patients will receive a 28-day supply of the study medication (apremilast) and instructed to take oral tablets daily according to the initial titration schedule. At subsequent visits, they will receive pill bottles with a 30 day supply (60 pills) and will continue twice daily dosing. (see section 1.3). Packages of study product will be shipped from IDS to study sites outside of the University of Pennsylvania (Penn). The process for study drug dispensing and return at these sub-sites will conducted using a similar approach as Penn.

Penn IDS will perform ongoing product reconciliation for all study sites by tracking and verifying shipment dates, dispensing dates and amounts, administration dates and amounts, local product inventory, and return or destruction of unused product.

5.7 Subject Compliance Monitoring

During monthly study visits, patients will be asked to bring the empty blister packs or pill bottles, with any remaining medication. The number of pills remaining will be noted and the patient will be provided with an additional 30-day supply.

5.8 Return or Destruction of Investigational Product

Unused study drugs will be destroyed with signed documentation of drug administration sent to the IDS. At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, drug destroyed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed, and dated. Any discrepancies noted will be investigated, resolved, and documented prior to destruction of unused study drug.

6 Study Procedures

The study procedures for each visit are summarized in the Appendix C.

6.1 Screening (Day -30 to Day -1)

- Sign informed consent
- Review of inclusion and exclusion criteria
- Record demographic information (i.e., sex, date of birth, race/ethnicity, etc.)
- Record height and weight
- Record vital signs, including temperature, pulse, respiratory rate and blood pressure
- Medical and surgical history including date of onset of psoriasis and documentation of history of psoriatic arthritis, including specialty of diagnosing physician
- Social history, including alcohol, tobacco, and other recreational drug use
- Review of systems
- Physical exam
- % BSA assessment
- PASI and PGA score
- Laboratory evaluation for safety (within 30 days of baseline visit)
    - Hematology: CBC with differential
    - Complete Metabolic Profile: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, total protein, albumin
    - HIV, hepatitis b surface antigen, hepatitis C antibody
    - Urine pregnancy test for women of childbearing potential (includes women who have had a tubal ligation)
- Review and document medications or therapies and any discontinued medications or therapies in the last 90 days
- Review and document all prior and current psoriasis medications or therapies, including duration of therapy, and if applicable, when and why therapy was discontinued

6.2 Study Intervention Phase

6.2.1 Visit 1 / Baseline Visit (Day 0)

- Review of inclusion and exclusion criteria
- Review and update of medical history for any interim events between screening and baseline
- Review and update of any changes in medications/therapies between screening and baseline
- Monitor concomitant psoriasis therapy
- Monitor alcohol and tobacco use
- Review of systems
- Vital signs, weight
- Physical exam,
- % BSA assessment

- PASI and PGA score
- DLQI
- Pruritus VAS
- Urine pregnancy test for women of childbearing potential (includes women who have had a tubal ligation)
- FDG-PET/CT scan prior to treatment initiation
- Collection of blood samples for cardiometabolic biomarkers prior to treatment initiation
- Review of clinical findings on FDG-PET/CT
- Review and evaluation of any adverse events or serious adverse events
- Dispense a 28-day supply of apremilast within 7 days of FDG-PET/CT, if no medical contraindications are identified on PET/CT

6.2.2 Visit 2 / Week 4 Visit (Day 28 +/- 7 days)

- Review and evaluation of any adverse events or serious adverse events
- Monitor concomitant psoriasis therapy
- Review of systems
- Vital signs, weight
- Physical exam, if indicated by patient report of adverse events
- % BSA assessment
- PASI and PGA score
- Collection of blood for cardiometabolic biomarkers
- Collect remaining pills and dispense a 30-day supply of apremilast

6.2.3 Visit 3 / Week 8 Visit (Day 56 +/- 7 days)

- Review and evaluation of any adverse events or serious adverse events
- Monitor concomitant psoriasis therapy
- Review of systems
- Vital signs, weight
- Physical exam if indicated by patient report of adverse events
- % BSA assessment
- PASI and PGA score
- Collection of blood samples for cardiometabolic biomarkers
- Collect remaining pills and dispense a 30-day supply of apremilast

6.2.4 Visit 4 / Week 12 Visit (Day 84 +/- 7 days)

- Review and evaluation of any adverse events or serious adverse events
- Monitor concomitant psoriasis therapy
- Review of systems
- Vital signs, weight
- Physical exam if indicated by patient report of adverse events
- % BSA assessment
- PASI and PGA score
- Collection of blood samples for cardiometabolic biomarkers
- Collect remaining pills and dispense a 30-day supply of apremilast

6.2.5 Visit 5 / Week 16 Visit (Day 112 +/- 7 days)

- Review and evaluation of any adverse events or serious adverse events
- Monitor concomitant psoriasis therapy
- Review of systems
- Vital signs, weight
- Physical exam
- % BSA assessment

- PASI and PGA score
- DLQI
- Pruritus VAS
- Laboratory evaluation for safety
    - Hematology: CBC with differential
    - Complete Metabolic Profile: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, total protein, albumin
    - Urine pregnancy test for women of childbearing potential (includes women who have had a tubal ligation)
- Collection of blood samples for cardiometabolic biomarkers
- FDG-PET/CT scan
- Collect remaining pills and dispense a 30-day supply of apremilast

6.2.6 Visit 6 / Week 28 Visit (Day 196 +/- 7 days)

- Review and evaluation of any adverse events or serious adverse events
- Monitor concomitant psoriasis therapy
- Review of systems
- Vital signs, weight
- Physical exam if indicated by patient report of adverse events
- % BSA assessment
- PASI and PGA score
- Collect remaining pills and dispense a 30-day supply of apremilast

6.2.7 Visit 7 / Week 40 Visit (Day 280 +/- 7 days)

- Review and evaluation of any adverse events or serious adverse events
- Monitor concomitant psoriasis therapy
- Review of systems
- Vital signs, weight
- Physical exam if indicated by patient report of adverse events
- % BSA assessment
- PASI and PGA score
- Collect remaining pills and dispense a 30-day supply of apremilast

6.2.8 Visit 8 / Week 52/EOS Visit (Day 364 +/- 7 days)

- Review and evaluation of any adverse events or serious adverse events
- Monitor concomitant psoriasis therapy
- Review of systems
- Vital signs, weight
- Physical exam
- % BSA assessment
- PASI and PGA score
- DLQI
- Pruritus VAS
- Laboratory evaluation for safety
    - Hematology: CBC with differential
    - Complete Metabolic Profile: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, total protein, albumin
    - Urine pregnancy test for women of childbearing potential (includes women who have had a tubal ligation)
- Collection of blood for cardiometabolic biomarkers
- FDG-PET/CT scan

- Collect remaining pills

6.3 Unscheduled Visits

- Review and evaluation of any adverse events or serious adverse events
- Monitor concomitant therapy
- Review of systems, if indicated
- Vital signs, weight
- Physical exam, if indicated
- Laboratory evaluation, if indicated by patient symptoms and deemed appropriate by investigator

6.4 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules, or AEs. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. Subjects who withdraw early will have one final visit to collect the remaining study drug, follow up regarding adverse events and undergo clinical, laboratory and imaging assessment as described below in section 6.5.

6.5 Early Termination Visits

- Review and evaluation of any adverse events or serious adverse events
- Monitor psoriasis concomitant therapy
- Review of systems
- Vital signs, weight
- Physical exam
- % BSA assessment
- PASI and PGA score
- DLQI
- Pruritus VAS
- Laboratory evaluation for safety, at the discretion of the investigator
    - Hematology: CBC with differential
    - Complete Metabolic Profile: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total and direct bilirubin, total protein, albumin
    - Urine pregnancy test for women of childbearing potential (includes women who have had a tubal ligation)
- FDG-PET/CT scan, if previous FDG-PET/CT scan (baseline and/or Week 16) was performed more than 28 days ago, or at the discretion of the investigator
- Collection of blood for cardiometabolic biomarkers, if last labs were drawn more than 28 days ago, or at the discretion of the investigator

7 Statistical Plan

7.1 Primary Endpoint

The primary endpoints to be measured in this study include:

- Change in total vascular inflammation of the whole aorta as assessed on FDG-PET/CT between baseline and week 16
- Change in cardiometabolic biomarkers between baseline and week 16

7.2 Secondary Endpoints

The secondary endpoints to be measured in the study include:

- Change in total vascular inflammation of the five aortic segments as assessed on FDG-PET/CT between baseline and week 16, and between baseline and week 52
- Change in cardiometabolic biomarkers at week 4, 8, 12, 16 and 52 compared to baseline and earlier time points
- Change in total vascular inflammation of the aorta as assessed on FDG-PET/CT between week 52 and earlier time points (baseline and week 16)
- Changes in body composition as measured on FDG-PET/CT between week 52 and earlier time points (baseline and week 16)
- Changes in physician reported outcomes (PASI, PGA)
- Changes in the patient reported outcomes (DLQI, pruritus VAS)
- Safety endpoints

7.3 Sample Size and Power Determination

The sample size is based on primary and secondary outcome of changes in tissue-to-background ratio (TBR) of the standardized uptake values (SUV) of the tracer measured by FDG-PET/CT. Using a two sided test with alpha=0.05 and prior standard deviation (SD) estimate of the change in TBR (SD=0.263), 35 patients will provide 90% power to detect a clinically significant change of 0.15 TBR between pre and post treatment measurements. The 35 patients will also provide 90% power to detect clinically relevant differences in biomarkers between pre- and post-treatment of approximately 0.57 SD, well below the general threshold for significance of one SD. To accommodate potential dropout of up to 50% at 52 weeks, we intend to accrue 70 patients. However, at 16 weeks we assume our dropout rate will only be 20%. Assuming 56 patients will have a FDG-PET/CT at 16 weeks, we will have 98.7% power to detect the 0.15 change in TBR as discussed above.

7.4 Statistical Methods

Stata 14.0 or a more current version (StataCorp, College Station, TX) will be used for all analyses. All data will be summarized using descriptive statistics (mean, SD, range for continuous variables; frequencies for categorical variables) and graphical techniques (histograms, scatterplots). Tables will be produced describing any missing data patterns due to either withdrawal or other reasons.

Primary Analysis

The primary analysis will consist of comparisons of total vascular inflammation of the aorta and cardiometabolic biomarkers between week 16 and baseline using the endpoints of change as defined in Section 3.2. Statistical significance of the change from baseline to 16 week will be assessed using a one sample t-test, and the use of a mixed linear model will also be considered. Because the primary outcome is a change score, the analysis will be restricted to subjects who have completed both the baseline and week 16 FDG-PET/CT scans, regardless of their level of adherence to apremilast.

Secondary Analysis

Secondary analyses will include comparisons in total vascular inflammation of the aorta and its five segments, change in cardiometabolic biomarkers and change in body composition between weeks 52, 16 and at baseline. We will also perform multiple imputation to address possible sensitivity to missing data. Additional analyses will also include longitudinal models of psoriasis activity over time, using repeated-measures approaches to accommodate the correlation within subjects over time. We will explore the use of random effects models as well. The linear trend between changes in TBR and psoriasis will be analyzed using multivariable linear regression with TBR as the dependent variable, and covariates in the model being age, sex, major cardiovascular disease risk factors.

7.4.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics, including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as sex.

7.4.2 Safety Analysis

Subjects will be monitored for any adverse event that occur during the study treatment period. Laboratory evaluation for safety will be completed at baseline, week 16 and week 52.

7.5 Subject Population(s) for Analysis

Primary analyses will be conducted according to the intention-to-treat principle, including all people who enrolled in the study and completed an FDG-PET/CT scan at week 16 regardless of their level of adherence to apremilast. Additional analyses will be conducted in patients who were at least 90% adherent with apremilast dosing.

8 Safety and Adverse Events

8.1 Definitions

8.1.1 Adverse Event

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition, this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the Case Report Form rather than the individual signs or symptoms of the diagnosis or syndrome. All AEs will be recorded by the Investigator(s) from the time of signing the informed consent through the end of the designated follow-up period.

Abnormal laboratory values defined as adverse events:
An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

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

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

8.1.2 Serious Adverse Event

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

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

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or

surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

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

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

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

8.2 Recording of Adverse Events

For each subject, AEs and SAEs occurring after informed consent is obtained should be recorded until the subject has completed his/her participation in the study. A serious adverse event must be reported if it occurs during a subject's participation in the study and/or within 30 days of receiving the last dose of the study drug.

Any serious adverse event that is ongoing when a subject completes his/her participation in the Study must be followed until any of the following occurs:

- The event resolves or stabilizes;
- The event returns to baseline condition or value (if a baseline value is available);
- The event can be attributed to agents(s) other than the Study Product, or to factors unrelated to Study conduct.

Any subsequent AE felt to be causally related to the use of the study product should be reported.

8.3 Relationship of AE to Study

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

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

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

8.4 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Immediate reporting of serious adverse events:

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

Investigators who are not Penn faculty or affiliated with a Penn research site are responsible for reporting consistent with timeframes and guidance here as well as consistent with their local IRB requirements.

The SAE must be reported immediately (i.e., within 24 hours of the Principal Investigators' knowledge of the event) to Amgen Safety by facsimile (see below for contact information). A written report, prepared by the sub-site Investigator or Penn Principal Investigator(s) using an SAE Report Form or a 3500A Medwatch form, is to be faxed to Amgen Safety (see below for contact information).

The SAE report should provide a detailed description of the SAE. If a subject has died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Amgen as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form or Medwatch form and sent to Amgen Safety.

The Investigator(s) is responsible for informing the Institutional Review Board/Ethics Committee (IRB/IEC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator(s) must keep copies of all SAE information, including correspondence with Amgen and the IRB/IEC, on file. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until either the event resolves completely, stabilizes/resolves with sequelae, or returns to baseline (if a baseline value is available).

Pregnancies:
When a female subject of childbearing potential's contraceptive measures or ability to become pregnant changes at the time of study entry or at any time during the study, the Investigator will educate the subject regarding options and correct and consistent use of effective contraceptive methods in order to successfully prevent pregnancy.

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject or the female partner of a male subject occurring while the subject is on study drug, or within 30 days of the subject's last dose of study drug, are considered immediately reportable events. Study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the investigator(s). The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Amgen Safety immediately facsimile (see below for contact information) 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(s) and the Amgen Medical Monitor.

Overdose:
Abuse, withdrawal, sensitivity, or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported as an AE. Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE.

If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form but should not be reported as an SAE itself.

In the event of an overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for apremilast overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

Overdose for this protocol, on a per dose basis, is defined as ingestion of any more than the amount prescribed of apremilast tablets in any 24 hour period whether by accident or intentionally.

8.4.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to Amgen Safety and the IRB. The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

8.4.2 Investigator reporting: notifying Amgen

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 enclosed ISS Safety Fax Transmittal Cover Sheet and faxed to 888-814-8653.

Investigator Reporting: Notifying the Penn IRB

The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a)the research procedure described in this protocol and the informed consent document and (b) the characteristics of the population being studied
- Related or possibly related to participation in the research
- Suggests that the research places subjects or other at a greater risk of harm (physical, psychological, economic or social harm) than was previously known or recognized

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB via the HS-ERA online system (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation) within 10 working days from the time the Investigator becomes aware of the event. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Reporting Deaths:

Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Penn IRB for specific situations:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Penn IRB may be made by contacting the IRB Director or Associate Director. The SAE report can follow via the HS-ERA online system.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the Penn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause Amgen to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.

8.5 Stopping Rules

Since these study treatments are FDA-approved treatments for psoriasis, standard of care for monitoring apremilast treatment will be used to ensure primary safety endpoints outlined in Section 3.2. Subjects will be monitored for adverse events and serious adverse events by the Investigators at each study visit. Subjects who experience adverse events may be removed from study participation at the discretion of the Investigator.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include regular assessments of the number and type of adverse and serious adverse events as well as implementation of a Data and Safety Monitoring Plan (Appendix F).

8.6.1 Data and Safety Monitoring Plan

See AppendixF.

9 Study Administration, Data Handling and Record Keeping

9.1 Confidentiality

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

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

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

The study will take the following precautionary measures to protect subjects' privacy and the confidentiality of research and/or medical records. Research records are kept in offices that are locked, only accessible by study staff. Computerized records are entered only with subject ID, are kept in databases on institutionally secure servers and managed network drives maintained and backed-up on a regular basis, protected using firewall technologies, and restricted to individuals authorized to work on the study with regular monitoring for unauthorized access and other potential security and operational events. External laboratories that will analyze biologic samples from this study will not receive information that could identify the subject. These laboratories will only receive a number to identify the samples. It is a requirement that subjects involvement in the study be noted in his/her medical records. Medical records also include electronic medical records or EMR. If a subject's primary care physician is different from the study doctor for this study, he/she may also be notified. Medical records may also be reviewed and copies made by members of either the institutional review board/independent ethics committee responsible for this trial site, or a regulatory agency. These individuals will see subjects name, other personal information such as date of birth and gender, and medical information, but shall not disclose this information to anyone else. At the conclusion of the data collection phase of the study, de-identified data sets will be prepared for analyses purposes. Only the study data manager will retain the ability to re-identify data, if needed for AE reporting or medical monitoring.

9.2 Data Collection and Management

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (CRF) using fully validated software that conforms to US 21 CFR Part 11 requirements. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify via electronic approval that the data entered into the CRFs are complete and accurate. After database lock, the Investigator will receive copies of the subject data for archiving at the investigational site.

The Investigator must maintain source documents for each subject in the study. Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Electronic study case report form (CRF) is the primary data collection instrument for the study. If data is recorded directly on the CRF (i.e. no prior written or electronic record of data), the CRF is to be considered the source data (per ICH GCP Section 6.4.9). All data requested on the CRF must be

recorded. All missing data must be explained. If any entry error has been made, all correction changes must be initialed and dated. For clarification of illegible or uncertain entries, the clarification must be initialed and dated.

The Investigator must also keep the original informed consent form signed by the subject (A signed copy is given to the subject).

9.3 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the final study results are presented in a public forum. These documents should be retained for a longer period if required by an agreement with Amgen. In such an instance, it is the responsibility of Amgen to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Auditing and Inspecting

The Investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, Amgen, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to Amgen before commencement of this study. The investigator should keep a list of EC/IRB members and their affiliate on file.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. (See Appendix B for a copy of the Subject Informed Consent Form.) This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

11.1 Risks

Apremilast is a FDA-approved, first-line treatment for psoriasis with very low risk of serious side effects with short-term exposure and minimized by careful adherence to FDA prescribing guidance and strict exclusion of subjects with significant contraindications to the medication. Subjects will undergo regular medical monitoring for any adverse reactions.

Potential risks from the study assessment procedures are low. Exposure to radiation from this study is not significant and is within the acceptable range for research studies involving the administration of radiopharmaceuticals and use of CT as outlined by the regulatory agencies. This radiation dose is not necessary for medical care and will occur only as a result of subject participation in the study. At doses

much higher than the subject will receive in this study, radiation is known to increase the risk of developing cancer after many years. At the doses of radiation subjects will receive in this study, it is very likely that no effects will be seen. There is a risk of allergic or other adverse type reaction to FDG but this is extremely rare. Phlebotomy required for cardiometabolic assessments is potentially associated with pain, bruising, bleeding, vasovagal syncope, thrombosis, and, rarely, infection at the venipuncture site.

11.2 Benefits

Direct Benefits: Potential benefits for study participation include comprehensive laboratory safety tests and FDG-PET/CT assessment at no cost, the results of which will be reviewed with each subject and that can be brought to each subject's medical provider(s) for optimization and management of their CV risk. Subjects will receive apremilast, an FDA-approved psoriasis treatment with substantial efficacy and established safety profile, at no cost for 52 weeks.

Indirect Benefits: Data derived from this study will provide critical information on the impact of apremilast on vascular inflammation cardiometabolic function and body composition.

11.3 Risk Benefit Assessment

Overall, we expect that the risks of the research study are outweighed by the potential benefits to the participants and others.

11.4 Informed Consent Process / HIPAA Authorization

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

12 Study Finances

12.1 Funding Source

The study is financed through a grant from Amgen Corporation.

12.2 Conflict of Interest

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

12.3 Subject Stipends or Payments

Subjects will be asked to commute to study sites at 4 week intervals for monitoring visits and to receive the study drug. Visits that involve laboratory evaluation without FDG-PET/CT scan are estimated to take up to two hours. Visits that involve FED-PET/CT scan are estimated to take up to 6 hours.

For each study visit, including the screening visit, subjects will be reimbursed $30 to offset travel and other indirect costs for study participation. For visits including an FDG-PET/CT scan subjects will receive $150 per visit. Additional assistance for travel-related expenses may be available. In the event additional assistance is made available, the costs would have to be paid for by the participant up front and would be reimbursed by the study as set forth by the study team. When the subject has reached the end of study

participation, after the last study visit, the subject will receive a check in the mail with the total amount to be reimbursed for all study visits, minus any amount they have already received for their travel and/or related costs associated with travel to study visits. If the subject does not complete all study visits the amount received will be pro-rated to reflect the number and type of visits completed. Subjects will need to complete a W-9 form which is required by the IRS when study participation will result in a subject receiving more than $600 in a calendar year. This form will be provided for subjects.

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by Amgen and University of Pennsylvania for the purposes of performing the study, will be published or passed on to any third party without the consent of the study principal investigator and Amgen. Any investigator involved with this study is obligated to provide Amgen with complete test results and all data derived from the study.

14 References

1. Gelfand JM, Wang X, Qing L, et al. Epidemiology and Treatment Patterns of Psoriasis in the General Practice Research Database (GPRD). *Pharmacoepidemiology and drug safety.* 2005;14:S23.
2. Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. *Journal of the American Academy of Dermatology.* Feb 2009;60(2):218-224.
3. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. *J Investig Dermatol Symp Proc.* Mar 2004;9(2):136-139. National Psoriasis Foundation. Statistics. http://www.psoriasis.org/netcommunity/learn_statistics. . Accessed November 4, 2009.
4. Horn EJ, Fox KM, Patel V, Chiou CF, Dann F, Lebwohl M. Are patients with psoriasis undertreated? Results of National Psoriasis Foundation survey. *Journal of the American Academy of Dermatology.* Dec 2007;57(6):957-962.
5. Alexandroff AB, Pauriah M, Camp RD, Lang CC, Struthers AD, Armstrong DJ. More than skin deep: atherosclerosis as a systemic manifestation of psoriasis. *Br J Dermatol.* Jul 2009;161(1):1-7.
6. Qureshi AA, Choi HK, Setty AR, Curhan GC. Psoriasis and the risk of diabetes and hypertension: a prospective study of US female nurses. *Archives of dermatology.* Apr 2009;145(4):379-382.
7. Brauchli YB, Jick SS, Meier CR. Psoriasis and the risk of incident diabetes mellitus: a population-based study. *Br J Dermatol.* Dec 2008;159(6):1331-1337.
8. Cohen AD, Dreiher J, Shapiro Y, et al. Psoriasis and diabetes: a population-based cross-sectional study. *Journal of the European Academy of Dermatology and Venereology : JEADV.* May 2008;22(5):585-589.
9. Solomon DH, Love TJ, Canning C, Schneeweiss S. Risk of diabetes among patients with rheumatoid arthritis, psoriatic arthritis and psoriasis. *Ann Rheum Dis.* Dec 2010;69(12):2114-2117.
10. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and the risk of psoriasis in women: Nurses' Health Study II. *Archives of internal medicine.* Aug 13-27 2007;167(15):1670-1675.
11. Mallbris L, Granath F, Hamsten A, Stahle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. *Journal of the American Academy of Dermatology.* Apr 2006;54(4):614-621.
12. Ahlehoff O, Gislason GH, Charlot M, et al. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. *J Intern Med.* Oct 29 2010.
13. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA : the journal of the American Medical Association.* Oct 11 2006;296(14):1735-1741.
14. Lin HW, Wang KH, Lin HC. Increased risk of acute myocardial infarction in patients with psoriasis: a 5-year population-based study in Taiwan. *J Am Acad Dermatol.* Mar 2011;64(3):495-501.
15. Brauchli YB, Jick SS, Miret M, Meier CR. Psoriasis and risk of incident myocardial infarction, stroke or transient ischaemic attack: an inception cohort study with a nested case-control analysis. *The British journal of dermatology.* May 2009;160(5):1048-1056.
16. Gelfand JM, Dommasch ED, Shin DB, et al. The risk of stroke in patients with psoriasis. *The Journal of investigative dermatology.* Oct 2009;129(10):2411-2418.
17. Kimball AB, Guerin A, Latremouille-Viau D, et al. Coronary heart disease and stroke risk in patients with psoriasis: retrospective analysis. *Am J Med.* Apr 2010;123(4):350-357.
18. Ahlehoff O, Gislason GH, Lindhardsen J, et al. Prognosis following first-time myocardial infarction in patients with psoriasis: a Danish nationwide cohort study. *J Intern Med.* Mar 1 2011.

19. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. *Eur Heart J.* Apr 2010;31(8):1000-1006.
20. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. *Mediators Inflamm.* Oct 24 2005;2005(5):273-279.
21. Krueger JG. The immunologic basis for the treatment of psoriasis with new biologic agents. *Journal of the American Academy of Dermatology.* Jan 2002;46(1):1-23; quiz 23-26.
22. Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. *Annals of the rheumatic diseases.* Mar 2005;64 Suppl 2:ii30-36.
23. Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. *Nature.* Feb 22 2007;445(7130):866-873.
24. Lowes MA, Kikuchi T, Fuentes-Duculan J, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *The Journal of investigative dermatology.* May 2008;128(5):1207-1211.
25. Takahashi H, Tsuji H, Hashimoto Y, Ishida-Yamamoto A, Iizuka H. Serum cytokines and growth factor levels in Japanese patients with psoriasis. *Clinical and experimental dermatology.* Aug 2010;35(6):645-649.
26. Lo YH, Torii K, Saito C, Furuhashi T, Maeda A, Morita A. Serum IL-22 correlates with psoriatic severity and serum IL-6 correlates with susceptibility to phototherapy. *Journal of dermatological science.* Jun 2010;58(3):225-227.
27. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation.* Apr 3 2001;103(13):1813-1818.
28. Ridker PM, Buring JE, Rifai N. Soluble P-selectin and the risk of future cardiovascular events. *Circulation.* Jan 30 2001;103(4):491-495.
29. Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. *Lancet.* Jan 10 1998;351(9096):88-92.
30. Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. *Circulation.* 2000;101(18):2149-2153.
31. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med.* Nov 14 2002;347(20):1557-1565.
32. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation.* Apr 18 2000;101(15):1767-1772.
33. Ridker PM, Stampfer MJ, Hennekens CH. Plasma concentration of lipoprotein(a) and the risk of future stroke. *Jama.* Apr 26 1995;273(16):1269-1273.
34. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. *Eur Heart J.* Dec 27 2009.
35. Lahoute C, Herbin O, Mallat Z, Tedgui A. Adaptive immunity in atherosclerosis: mechanisms and future therapeutic targets. *Nature reviews. Cardiology.* Jun 2011;8(6):348-358.
36. Chen S, Crother TR, Arditi M. Emerging role of IL-17 in atherosclerosis. *Journal of innate immunity.* 2010;2(4):325-333.
37. Ghazizadeh R, Shimizu H, Tosa M, Ghazizadeh M. Pathogenic mechanisms shared between psoriasis and cardiovascular disease. *Int J Med Sci.* 2010;7(5):284-289.
38. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *The New England journal of medicine.* Apr 21 2005;352(16):1685-1695.
39. Hansson GK. Immune mechanisms in atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2001;21(12):1876-1890.
40. Mehta NN, McGillicuddy FC, Anderson PD, et al. Experimental Endotoxemia Induces Adipose Inflammation and Insulin Resistance in Humans. *Diabetes.* Sep 30 2009.
41. Heffron SP, Parastatidis I, Cuchel M, et al. Inflammation induces fibrinogen nitration in experimental human endotoxemia. *Free Radic Biol Med.* Oct 15 2009;47(8):1140-1146.
42. Anderson PD, Mehta NN, Wolfe ML, et al. Innate immunity modulates adipokines in humans. *J Clin Endocrinol Metab.* Jun 2007;92(6):2272-2279.
43. Alexander ET, Vedhachalam C, Sankaranarayanan S, et al. Influence of apolipoprotein A-I domain structure on macrophage reverse cholesterol transport in mice. *Arterioscler Thromb Vasc Biol.* Feb 2011;31(2):320-327.
44. Khera AV, Cuchel M, de la Llera-Moya M, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med.* Jan 13 2011;364(2):127-135.

45. Boehncke S, Salgo R, Garbaraviciene J, et al. Effective continuous systemic therapy of severe plaque-type psoriasis is accompanied by amelioration of biomarkers of cardiovascular risk: results of a prospective longitudinal observational study. *J Eur Acad Dermatol Venereol.* Jan 17 2011.
46. Basu S, Zaidi H, Houseni M, et al. Novel quantitative techniques for assessing regional and global function and structure based on modern imaging modalities: implications for normal variation, aging and diseased states. *Semin Nucl Med.* May 2007;37(3):223-239.
47. Bural GG, Torigian DA, Chamroonrat W, et al. Quantitative assessment of the atherosclerotic burden of the aorta by combined FDG-PET and CT image analysis: a new concept. *Nucl Med Biol.* Nov 2006;33(8):1037-1043.
48. Mehta NN, Yu Y, Saboury B, et al. Systemic and Vascular Inflammation in Patients With Moderate to Severe Psoriasis as Measured by [18F]-Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (FDG-PET/CT): A Pilot Study. *Arch Dermatol.* May 16 2011.
49. Aziz K, Berger K, Claycombe K, Huang R, Patel R, Abela GS. Noninvasive detection and localization of vulnerable plaque and arterial thrombosis with computed tomography angiography/positron emission tomography. *Circulation.* Apr 22 2008;117(16):2061-2070.
50. Naik HB, Natarajan B, Stansky E, et al. Severity of Psoriasis Associates with Aortic Vascular Inflammation Detected by FDG PET/CT and Neutrophil Activation in a Prospective Observational Study. Arterioscler Thromb Vasc Biol. 2015;ATVBAHA.115.306460. Published online before print October 8 2015, doi:10.1161/ATVBAHA.115.306460.
51. Paulmier B, Duet M, Khayat R, et al. Arterial wall uptake of fluorodeoxyglucose on PET imaging in stable cancer disease patients indicates higher risk for cardiovascular events. *J Nucl Cardiol.* Mar-Apr 2008;15(2):209-217.
52. Rominger A, Saam T, Wolpers S, et al. 18F-FDG PET/CT identifies patients at risk for future vascular events in an otherwise asymptomatic cohort with neoplastic disease. *J Nucl Med.* Oct 2009;50(10):1611-1620.
53. Tahara N, Kai H, Ishibashi M, et al. Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. *J Am Coll Cardiol.* Nov 7 2006;48(9):1825-1831.
54. Lee SJ, On YK, Lee EJ, Choi JY, Kim BT, Lee KH. Reversal of vascular 18F-FDG uptake with plasma high-density lipoprotein elevation by atherogenic risk reduction. *J Nucl Med.* Aug 2008;49(8):1277-1282.
55. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet.* May 17 2008;371(9625):1665-1674.
56. Schafer P. Apremilast Mechanism of Action and application to psoriasis and psoriatic arthritis. *Biochem Pharmacol*. 2012; 83: 1583-1590.
57. Houslay MD, Schafer P, Zhang KYJ. Phosphodiesterase-4 as a therapeutic target. *Drug Discov Today*. 2005. 10(22); 1503-1519. .
58. Serezani CH, Ballinger MN, Aronoff DM, et. al. Cyclic AMP: Master regulator of immune cell function. *Am J Respir Cell Mol Bio*l. 2008; 39(2):127-132.
59. Hansson GK, Hermansson A. The immune system in atherosclerosis. *Nat Immunol.* 2011; 12(3):204-212.
60. Moore KJ, Sheedy FJ, Fisher EA. Macrophages in atherosclerosis: a dynamic balance. *Nat Rev Immunol.* 2013; 13(10):709-721.
61. Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. *Cell.* 2011; 145(3):341-355.
62. Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, Crowley J, Hu C, Stevens RM, Shah K, Day RM, Girolomoni G, Gottlieb AB. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *The British Journal of Dermatology.* Dec 2015;173(6):1387-99.
63. Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. *The British journal of dermatology.* Sep 2008;159(3):513-526.
64. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clinical and experimental dermatology.* May 1994;19(3):210-216.
65. Mazzotti E, Picardi A, Sampogna F, Sera F, Pasquini P, Abeni D. Sensitivity of the Dermatology Life Quality Index to clinical change in patients with psoriasis. *The British journal of dermatology.* Aug 2003;149(2):318-322.
66. Mehta NN, Torigian DA, Gelfand JG, et al. Quantification of atherosclerotic plaque activity and vascular inflammation using [18-F] fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). *J Vis Exp.* 2012; 22(63):e3777.
67. Bural GG, Torigian DA, Chamroonrat W, et al. FDG-PET is an effective imaging modality to detect and quantify age-related atherosclerosis in large arteries. *Eur J Nucl Med Mol Imaging.* Mar 2008;35(3):562-569
68. Chen W, Bural GG, Torigian DA, Rader DJ, Alavi A. Emerging role of FDG-PET/CT in assessing atherosclerosis in large arteries. *Eur J Nucl Med Mol Imaging.* Jan 2009;36(1):144-151.
69. Summers RM, Liu J, Sussman D, Swyer AJ, Rehani B, Pickhardt PJ, Choi JR, Yao J. Association Between Visceral Adiposity and Colorectal Polyps on CT Colonography. *AJR Am J Roentgenol.* Jul 2012;199(1):48-57.

15 Attachments

15.1 Appendix A - Apremilast Prescribing Information

15.2 Appendix B - Informed Consent

15.3 Appendix C - Study Flow Chart

15.4 Appendix D - Dermatology Life Quality Index (DLQI)

15.5 Appendix E - Sample Preparation and Handling

15.6 Appendix F - Data Safety and Management Plan