MiNIMA

(MIcrovascular dysfu**N**ction **I**n **M**oderate-severe psori**A**sis)

EFFECTS OF TILDRAKIZUMAB ON CORONARY MICROVASCULAR FUNCTION IN MODERATE-SEVERE PSORIASIS

Open-label, single-center, single-arm study to evaluate the effects of decreasing inflammation via Tildrakizumab on the coronary microvasculature in moderate-to-severe psoriasis patients

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1. BACKGROUND AND SIGNIFICANCE

The endothelium provides a permeability barrier for the vasculature, maintains a non-thrombogenic surface, regulates vascular tone and tissue flow, and inhibits vascular smooth muscle cell growth. In the presence of inflammatory cytokines, endothelial cells are activated which facilitates leukocyte adhesion and migration into the vessel wall, production of prothrombotic substances, and vasoconstriction, thereby creating a proatherogenic and procoagulant environment. Consequently, inflammation is a key mediator of a constellation of abnormalities that initiate and accelerate the progression of atherosclerosis[1–3].

Cardiovascular (CV) disease is the leading cause of death among patients with severe psoriasis[4–9]. Patients with severe psoriasis have approximately seven-fold increased risk of myocardial infarction and 57% increased risk of CV mortality compared to controls matched for age, sex and CV risk factors[10]. Although there is an increase in the prevalence of cardiovascular risk factors, including obesity, diabetes mellitus (DM), hypertension (HTN), dyslipidemia, and smoking in patient with psoriasis, studies have demonstrated an increased CV mortality that is independent of traditional CV risk factors[6,11–15]. Patients with psoriasis also have evidence of endothelial-cell dysfunction, as assessed by flow-mediated dilation[16]. Treatment with biologic therapies have shown inconsistent results of the influence of these therapies on reducing cardiovascular inflammation. For example, initiation of biologic therapy in patients with moderate-to-severe psoriasis was associated with reduced coronary inflammation as assessed by perivascular fat attenuation index on cardiac CT at one-year follow-up. This study compared patients with psoriasis who received biologic therapy (including anti-TNFα, anti-interleukin (IL) 12/23 or anti-IL-17) for one year compared to 52 patients who received topical or light therapy[17]. In the CARIMA trial, patients with moderate-to-severe psoriasis treated with secukinumab had evidence of improved endothelial function as measured flow-mediated dilation at week 52 compared to baseline[18]. However, the large NIH-funded randomized controlled trial, Vascular Inflammation in Psoriasis trial (VIP), assessed the impact of anti-TNF therapy on vascular inflammation by comparing adalimumab to UVB phototherapy and placebo and measuring the impact of aortic inflammation via 18F-FDG-PET/CT. At the study end-point of 12 weeks, there was no impact of TNF inhibition on vascular inflammation measured by aortic FDG uptake[19].

We believe that these mixed findings are the result of the different measured surrogate endpoints. There has not been a trial to date in psoriasis that has shown an improvement in long-term cardiovascular outcomes with a reduction in systemic inflammation. Positron emission tomography (PET) imaging allows precise and reproducible quantification of myocardial blood flow, thereby providing a direct assessment of coronary vascular health. Coronary flow reserve (CFR, calculated as the ratio of peak hyperemic myocardial blood flow over that at rest) is emerging as a powerful quantitative prognostic imaging marker of clinical cardiovascular risk. We are uniquely positioned to utilize our innovative cardiovascular imaging laboratory to perform cardiovascular stress testing via PET/CT imaging which will directly measure CFR, representing the integrated hemodynamic effects of epicardial coronary stenosis, diffuse atherosclerosis and vessel remodeling, and microvascular dysfunction on myocardial tissue perfusion.

CFR provides a robust and reproducible clinical measure of the *integrated* hemodynamic effects of epicardial coronary artery disease (CAD), diffuse atherosclerosis, vessel remodeling, and microvascular dysfunction resulting from endothelial cell dysfunction on myocardial tissue perfusion across the entire coronary circulation[20–23]. These processes have direct relevance to the underlying vascular pathobiology in patients with psoriasis. Consequently, quantitative CFR provides a unique opportunity to examine the potential impact of novel therapies on the biology of the disease and its association with cardiovascular outcomes. By testing the fundamental concept of whether treatment with anti-inflammatory agent

Tildrakizumab in psoriasis can lead to improved coronary blood flow and myocardial tissue perfusion, this study will provide important mechanistic insights into the impact of targeted biologic therapy and whether this will improve key determinants of cardiovascular clinical risk.

JUSTIFICATION FOR THE USE OF CFR AS A SURROGATE MARKER OF CLINICAL RISK

Noninvasive quantification of CFR improves diagnosis and risk assessment in patients with CAD. Noninvasive quantification of coronary blood flow and flow reserve has been the research focus of our group for over 20 years. Our group has developed and validated methodology for flow quantification and disseminated this technology for broad access and use. We and others have demonstrated that CFR is a quantitative unique phenotyping tool to assess vascular health and pre-clinical atherosclerosis which, in higher risk patients, can reveal flow-limiting coronary artery stenosis, thereby improving the accuracy of myocardial perfusion imaging in the diagnostic evaluation of known or suspected CAD[20–23].

More recent data support the notion that coronary vascular dysfunction, as quantified by reduced CFR, is highly prevalent among patients with known or suspected CAD[21–24], increases the severity of inducible myocardial ischemia (beyond the effects of upstream coronary obstruction)[25] and sub-clinical myocardial injury, and identifies patients at high risk for serious cardiac adverse events, including cardiac death[26–28]. Thus, CFR is a robust measure of the *integrated* hemodynamic effects of epicardial CAD, diffuse atherosclerosis, vessel remodeling, and microvascular dysfunction on myocardial perfusion. In the presence of increased oxygen demand, a decreased CFR reflects an imbalanced supply-demand relationship that may lead to myocardial ischemia, subclinical LV systolic and diastolic dysfunction, clinical symptoms and, ultimately, death. There is also emerging evidence that a reduced global CFR may help identify patients who benefit most from revascularization[29].

Systemic inflammation is associated with coronary vascular dysfunction. There is increasing evidence that coronary vascular dysfunction is associated with systemic inflammation and may precede or coexist with high-risk coronary atherosclerosis. Compared to healthy subjects, patients with rheumatoid arthritis or systemic lupus erythematosus, without significant CAD on invasive angiography, have impaired CFR to a degree directly related to disease duration[30]. In patients with cardiac syndrome X (CSX) with exertional angina and ST-segment depression on exercise stress testing but normal luminal coronary angiography, only those with elevated high sensitivity C-reactive protein (hsCRP, >3 mg/L) have reduced CFR[31]. Among patients presenting with acute coronary syndrome and nonobstructive CAD by angiography, reduced CFR (assessed by invasive Doppler flow velocity monitoring) is associated with higher frequency of thin-cap fibroatheroma, greater plaque burden, and significantly higher levels of hsCRP, despite similar amounts of epicardial disease by luminal area and fractional flow reserve measurements[32]. These results reinforce previous observations[33–35] that inflammation is associated with impaired coronary vasoreactivity and, in the appropriate patient population, may be a better marker for poor outcomes related to diffuse and/or microvascular CAD than are conventional ischemic assessments.

Data from our laboratory demonstrates a reduction in CFR in patient with psoriasis compared to matched controls. We identified men and women with psoriasis or psoriatic arthritis who underwent clinically indicated rest/stress myocardial perfusion PET imaging between 1/2006 and 12/2018. We selected a comparison group from the same population that was matched for age, sex and cardiovascular risk factors. Patients with systemic inflammatory disease (such as RA, SLE), LVEF<40%, or obstructive coronary disease, defined as an abnormal myocardial perfusion study (summed stress score>3) were excluded. We studied 62 patients with a diagnosis of psoriasis and 119 matched controls. CFR was abnormal (defined as <2) in 61.3% (38/62) of the psoriasis population compared to 38.7% (46/119) of a matched control population. Overall, the mean CFR was 16.5% lower in PsO patients compared to the control group (1.92 +/- 0.65 versus 2.3+/-0.8 ml/min/g, p=0.002).These findings demonstrate that patients

with psoriasis without obstructive coronary artery disease who were clinically referred for cardiac PET testing have a high prevalence of coronary microvasculature dysfunction and a significant reduction in CFR compared to matched controls (Weber et al., *submitted American College of Cardiology (ACC) abstrac*t 10/2019). Furthermore, these findings highlight the importance of further mechanistic studies on whether reducing systemic inflammation in patients can lead to improved myocardial blood flow, tissue perfusion, and endothelial function.

Anti-inflammatory therapies can modulate CFR. There is preliminary evidence that anti-inflammatory therapies lead to improved CFR. Indeed, treatment with statins in patients with dyslipidemia has been shown to improve CFR in a way that is modified among carriers of a specific polymorphism that reduces IL-1β expression[36]. Short-term inhibition of IL-1 activity with the IL-1 receptor antagonist anakinra in rheumatoid arthritis patients without perfusion abnormalities has been shown to improve echocardiographic measures of LV myocardial deformation (by speckle tracking) and CFR (by Doppler flow velocity in the left anterior descending artery (LAD))[37]. Finally, treatment with methotrexate led to reduced clinical scores of disease severity and improved CFR (as measured by echo Doppler flow velocity in the LAD) in patients with early rheumatoid arthritis, with no effect on common carotid intima-medial thickness[38].

Coronary vascular dysfunction is a powerful predictor of clinical risk. Emerging data have consistently shown that CFR measurements by PET can distinguish patients at high risk for serious adverse events, including cardiac death[26–28]. We recently reported that reduced global CFR is independently associated with higher rates of cardiac and all-cause mortality in a large cohort of patients with and without DM[39]. Relatively preserved CFR identifies patients with known or suspected CAD who have significantly lower risk of cardiac death, regardless of traditional semi-quantitative measures of stress-induced ischemia. Conversely, reduced CFR identifies patients at significantly higher risk of cardiac death, even among those without objective evidence of ischemia, probably due to diffuse atherosclerosis and/or microvascular dysfunction. PET measures of CFR improved risk stratification beyond comprehensive clinical assessment, LVEF and semi-quantitative measures of myocardial ischemia and scar, and led to clinically meaningful risk-reclassification of ~50% of intermediate risk patients[40]. Diabetics with impaired vs. preserved CFR experienced substantially higher cardiac mortality (7.6%/year vs. 1.3%/year, relative to 4.2%/year vs. 0.4%/year in nondiabetics, respectively, both $p<0.0001$)[39]. Importantly, diabetic patients without known CAD and with impaired CFR experienced a rate of cardiac death comparable to, and possibly higher than, that for nondiabetic patients with known CAD. Measures of CFR integrate the hemodynamic effects of focal epicardial coronary stenosis, fluid dynamic effects of diffuse atherosclerosis, and the effects of coronary microvascular dysfunction, all of which are prevalent among diabetics[41–43], and affected by systemic inflammation. These observations have implications for the classification of DM as a coronary disease risk equivalent[44]. *Specifically, only among diabetics with impaired vascular function is prognosis comparable to nondiabetic patients with known CAD.* Thus, differing levels of vascular health among previously studied cohorts may account for inconsistencies in relative mortality rates of diabetics without CAD and nondiabetics with CAD[45–47].

Coronary vascular dysfunction is independently associated with reduced measures of LV diastolic and systolic dysfunction. The imbalance in myocardial oxygen supply and demand caused by obstructive CAD and/or vascular and myocardial remodeling in response to chronic insults (e.g. hyperglycemia, hypertension, dyslipidemia) is thought to play a key role in the pathogenesis of LV dysfunction and heart failure. We evaluated the association between impaired coronary vasoreactivity with diastolic and systolic dysfunction in a consecutive cohort of 131 patients without overt obstructive CAD and with normal LV ejection fraction (LVEF)[48]. Patients underwent myocardial perfusion PET imaging to quantify myocardial blood flow and 2-D echocardiography to assess LV function. Diastolic function was assessed using mitral inflow Doppler (E, A wave velocities), tissue Doppler (TDI) early diastolic mitral annular velocity (E') and

E/E' ratio, a marker of LV diastolic filling pressure. Subclinical systolic dysfunction was evaluated using TDI peak systolic mitral annual velocity (S'). The independent relationship between peak stress myocardial blood flow and echo parameters was measured by linear regression, adjusting for the effects of age, sex, body mass index, hypertension, DM, resting blood pressure, resting LVEF and LV mass. Median age of patients was 64 years (IQR 55-76), with female predominance and high rates of comorbidities including hypertension (75%), dyslipidemia (54%), DM (28%) and obesity (44%). We found significant correlations between peak stress myocardial blood flow and both early diastolic relaxation (E') and systolic velocity (S'), respectively[48]. Similar correlations have been reported in experimental models of diabetes[49]. These data suggest a relationship between impaired myocardial perfusion due to diffuse atherosclerosis and/or microvascular dysfunction and LV diastolic and systolic dysfunction.

Quantitative CFR is a modifiable imaging biomarker of disease. There is consistent evidence supporting quantitative CFR as a powerful marker of vascular health and, as such, a useful marker to improve diagnosis and risk stratification and to monitor response to treatment, particularly in the context of clinical trials. The accuracy of quantitative noninvasive PET measures of myocardial blood flow and flow reserve by PET has been extensively validated in experimental animals[50] and humans[50–53]. The reproducibility of this technique is also well-established[52,53]. PET is considered *the gold standard* for quantifying coronary blood flow and flow reserve. There is extensive data supporting its use in diagnosis of CAD[26,54,55]. *The data discussed above demonstrate that the presence of abnormal CFR as measured by PET provides incremental risk stratification that leads to significant and meaningful risk-reclassification of intermediate risk patients*[24,26–28]*, especially those with DM*[39]. Furthermore, quantitative CFR as a measure of coronary vascular dysfunction is a *modifiable* imaging biomarker, which has been tested in the context of clinical trials[36,56–63].

2. INNOVATION

We propose an open-label investigator-initiated trial to directly test whether reducing systemic inflammation in patients with moderate-to-severe psoriasis improves myocardial perfusion reserve, as measured by CFR, a novel quantitative imaging marker of clinical risk. CFR quantified using vasodilator PET can predict cardiac death and MI even in the absence of overt obstructive disease (i.e. independently of perfusion score)[24,26–28], and these associations are especially evident among high, but heterogeneous risk cohorts. The proposed research is *clinically innovative* for two reasons: (1) it will provide an answer to the important clinical question of whether reducing systemic inflammation in patients with psoriasis improves coronary and mechanical function in the heart; and (2) it has the potential to validate CFR as the first physiologic imaging biomarker targeting coronary function and integrate it into the continuum of clinical care for personalized medicine that could be used for guiding initiation and monitoring of therapeutic efficacy in a variety of pro-inflammatory disease states that have been linked with adverse cardiovascular outcomes (e.g., psoriasis, HIV, rheumatoid arthritis, lupus, etc.), and in clinical trials as well as in drug discovery programs. Furthermore, the proposed research is *pathophysiologically innovative* in that it will elucidate mechanistic links between inflammation, coronary atherosclerosis, microvascular function, and myocardial mechanics.

3. SPECIFIC AIMS

3.1 Hypothesis and Objectives

The *central hypothesis* of this study is that reducing systemic inflammation using Tildrakizumab will quantitatively improve myocardial blood flow and CFR as measured by PET over six months in patients with moderate-to-severe psoriasis. In doing so, improvement in coronary vasoreactivity, endothelial function, and tissue perfusion may have beneficial effects on myocardial mechanics, left ventricular deformation and function and, ultimately, symptoms and prognosis. Accordingly, the following specific aims are proposed:

Aim 1. To test the hypothesis that systemic inflammation is a critical determinant of CFR and myocardial tissue perfusion, as assessed by quantitative PET imaging, in patients with moderate-to-severe psoriasis. Specifically, we propose that treatment with Tildrakizumab at a target dose of 100mg SC for 6 months will result in:
Hypothesis #1: Improved global CFR in response to adenosine, reflecting coronary vasodilator function, as compared to baseline.

Aim 2. To test the hypothesis that Tildrakizumab at a target dose of 100mg SC over 6 months will result in improved left ventricular (LV) myocardial mechanics, as assessed by transthoracic echocardiography, and that this functional improvement will be correlated with the change in CFR after 6 months of treatment. In this population of patients with moderate-severe psoriasis and at heightened cardiovascular risk, we propose to test the following hypotheses:
Hypothesis #2: Tildrakizumab for 6 months will result in improved LV systolic function, as assessed by measures of LV peak global longitudinal strain, and diastolic function, as assessed by measures of tissue Doppler mitral annular early diastolic relaxation velocity (E').
Hypothesis #3 Changes in LV systolic and diastolic function after 6 months of Tildrakizumab therapy will be correlated with changes in CFR.

3.2 Primary Endpoint:

Change (from baseline) in global CFR, as measured by PET imaging at 24 weeks after initiation of Tildrakizumab therapy.

3.3 Secondary Endpoints:

3.3.1. Correlation between the change (from baseline) in global CFR and psoriasis skin severity scores (Body surface area [BSA], Physician's Global Assessment [PGA], Psoriasis Area and Severity Index [PASI]) at 24 weeks after initiation of Tildrakizumab;

3.3.2. Change (from baseline) in peak-stress global myocardial blood flow (in mL/min/g) at 24 weeks after initiation of Tildrakizumab;

3.3.3. Change (from baseline) in peak-stress global coronary vascular resistance (in mm Hg/mL/min/g) at 24 weeks after initiation of Tildrakizumab

3.3.4 Change (from baseline) in LV peak global longitudinal strain (GLS) and E' at 24 weeks after initiation of Tildrakizumab

3.3.5 Correlation of the change (from baseline) in LV peak GLS and E' with the global CFR at 24 weeks after initiation of Tildrakizumab

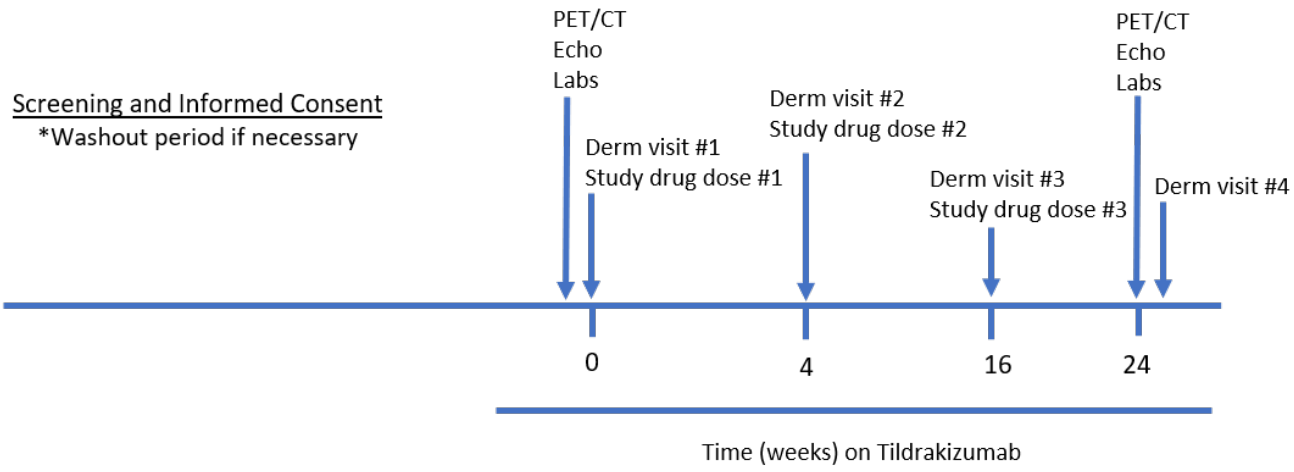
3.3.6. Change in serum biomarkers of inflammation (hs-CRP), myocyte injury and strain (hs Troponin, NT-proBNP) at baseline and 24 weeks after initiation of Tildrakizumab.

3.3.7 If the primary endpoint is positive, secondary exploratory analyses will use stored aliquots of plasma and serum to IL-6, TNFRII, ICAM, Glyc-A, p-selectin, e-selectin, sCD40L, adiponectin, and MCP-1.

3. SUBJECT SELECTION

3.1. Study Design

Open label, single-center, single arm pilot study. Patients with moderate-to-severe psoriasis and evidence of cardiovascular risk factors will be recruited from Skin and Related Musculoskeletal Diseases Clinic and the Rheumatology Clinic from the Brigham and Women's Hospital. After giving written informed consent to participate in the study and fulfilling criteria for inclusion, patients will be scheduled for baseline cardiac PET/CT, echocardiogram and dermatology visit. On the day of the cardiovascular testing, patients will undergo rest and vasodilator-stress PET/CT scan for measurement of CFR at baseline), and again after completion of 24 weeks of therapy as well as echocardiogram. Labs will be drawn at the baseline visit and at the 24-week final cardiovascular visit. The baseline and follow-up cardiovascular visits will be scheduled within +/- 7 days of the Dermatology clinic visits for feasibility to allow patient and departmental coordination. Patients will be encouraged to remain on stable medical therapy throughout the enrollment period.



3.2. Study group:

In order to target a higher-risk population, we will enroll patients with evidence of moderate-to-severe psoriasis, which is the most closely linked to increased cardiovascular risk[13,64,65]. We plan to target patients at heightened cardiovascular risk and coronary microvasculature dysfunction. In order to maintain feasibility, inclusion criteria will include *at least one* of the following: presence of DM, metabolic syndrome, or elevated hsCRP>mg/dl. We chose to use the cut-off of hsCRP≥ 2mg/dl which has been used as a cut point in large-scale clinical trials, including the CANTOS trial. CANTOS was the first trial in cardiology to show that in patients with a history of MI and elevated hsCRP ≥ 2mg/dl, treatment with

canakinumab resulted in a reduction in recurrent cardiovascular events compared to placebo[66,67]. Similarly, metabolic syndrome and DM are both well-known cardiovascular risk factors and studies from our research group have demonstrated reductions in CFR. Reduced CFR, which reflects coronary microvascular dysfunction, was further shown to be associated with major adverse cardiovascular events (MACE) across the spectrum of metabolic disease[68].

3.2.1. Inclusion criteria:

- Moderate-to-severe psoriasis
- Ages 18-90
- Body surface area (BSA) involvement ≥3% **or** 5-point Physician Global Assessment (PGA) Score ≥ 3 **or** Psoriasis Area and Severity Index (PASI) Score ≥12
- Patients who have failed biologic therapy, topical steroids, phototherapy, or other systemic therapies will be required to have a wash-out period, which will be calculated accordingly to the specific drug (Appendix 1).
- Evidence of at least one cardiovascular risk factor which includes hsCRP ≥2 mg/L, DM, obesity (BMI>25), hyperlipidemia, hypertension, family history of early coronary artery disease, or evidence of metabolic syndrome
    - Metabolic syndrome defined as at least three of the following: glucose≥100mg/dl or taking hypoglycemic agent, HDL<40mg/dl (men) or 50 mg/dl (women), triglycerides ≥ 150mg/dl, waist circumference >40 in mean or >35 in women, or blood pressure ≥130/85 or taking anti-hypertensive.
- If the patient is on a statin therapy, they must be on a stable dose for at least 6 months prior to enrollment.

3.2.2. Exclusion criteria:

- Documented history of other systemic inflammatory diseases, including SLE and RA, which in the opinion of the investigator would be inappropriate for enrollment.
- Prior history of untreated chronic infection (tuberculosis (Appendix 2), severe fungal infection, or known HIV positive, chronic hepatitis B or C infection), history of active solid malignancy, myeloproliferative or lymphoproliferative disease within 5 years, excluding treated non-melanoma skin cancer
- Renal insufficiency (CrCl <40 ml/min)
- NYHA class IV heart failure
- Patients requiring chronic treatment with oral prednisone >10mg/day, methotrexate, or other immunosuppressive agents.
- Pregnancy and Breastfeeding

There are certain vaccines, such as live attenuated vaccines, that are an exclusion for the study. This includes MMR, rotavirus, smallpox, chickenpox and yellow fever. The COVID-19 vaccine can be received while on study (https://pubmed.ncbi.nlm.nih.gov/33549649/, https://pubmed.ncbi.nlm.nih.gov/33422626/). As part of the screening process, we will confirm that potential subjects are not scheduled to receive one of the above live attenuated vaccines while on study and if so, they will be excluded from participation.

3.4 Sample size and source of subjects

A total of **35 analyzable patients** will be recruited for participation and the study will be performed at a single-center institution, Brigham and Women's Hospital (BWH). BWH Faulkner Hospital, Newton Wellesley Hospital, and Massachusetts General Hospital, MGH (PI: Michael Osborne, MD) will participate as feeder sites. All dermatology clinical assessments will be conducted through the Center for Clinical Investigation (CCI) at the BWH or at the 221 Longwood dermatology clinics. All patients will be referred for cardiac PET imaging to BWH, with BWH serving as the Core Imaging Lab and Data Coordinating Center.

4. SUBJECT ENROLLMENT

4.1. Procedures for obtaining informed consent

The Lead Investigator or one of the co-investigators/research assistants will obtain consent during the study-related hospital visit prior to any study-related procedures. Consent of subjects who do not speak English will be obtained and documented following the procedures outlined by IRB policy. The informed consent process will also be documented and added to the patient information for this study.

4.2. Methods of Enrollment

Potential study subjects will be recruited from the dermatology clinic at BWH with external advertising at the Dermatology sites throughout New England. We will include de novo external advertising and social media advertisements, such as the Rally research advertising website through Partners Healthcare.

Screening procedures will include queries for potentially eligible subjects from lists of patients who are followed by BWH Dermatology. BWFH and MGH will also be added as referring sites. This will NOT include any patients who have OPT-OUT of the new RODY program at MGB. We will perform an RPDR query for patients who are eligible for this RODY program at BWH, BWFH, and MGH. The RPDR query will be performed by searching for patients with at least 2 ICD codes for psoriasis in the last 24 months. Exclusion criteria will include ICD diagnosis codes for rheumatoid arthritis, which is a common autoimmune disease that is an exclusion for the study, and known coronary artery disease. We will then screen these MRNs by chart review to further filter and only send to eligible patients after review of the clinical record. All visits will still occur at BWH.

If patients are deemed eligible, we will use two mechanisms to contact. The primary method that we will use the OPT OUT RODY program upon which after obtaining the necessary regulatory approval patients will be contacted with an IRB letter through Patient Gateway or mail. The second method is physicians at MGB will be contacted personally and/or via e-mail to explain the purpose of the study, review its potential risks and discomforts, and the evaluation of whether a patient might be a candidate for the study. After a patient's physician agrees to have a patient participate in the study, the physician will initially introduce the study to the patient in order to obtain the patient's permission to be contacted by study staff. If the patient agrees, the referring physician will provide the study staff with the patient's contact information. This will allow the study staff to call the patient to explain the study and provide the patient a copy of the informed consent form.

Patients who agree to participate will be scheduled for the screening visit, at which point the PI or a qualified member of the research team will review the informed consent form with the patient and answer any additional question the patient may have. Treatment assignment and monitoring will be

performed at the BWH Dermatology clinic. All cardiovascular imaging-related procedures will take place at BWH.

4.3. Treatment assignment

Study subjects will receive a total of three doses of 100mg of SC Tildrakizumab. Each dose will occur on weeks 0, 4 and 16, respectively.

3. STUDY PROCEDURES

5.1. Study visits and parameters to be measured

A detailed description of the assessments that will occur at each visit is presented in Table 1.

Table 1. Schedule of Assessments

Procedure	Screening (-60 to -1 days)	Baseline Dermatology visit (day 0)	Baseline Cardiac PET/Echo (day 0)	Dermatology Visit #2 (week 4)	Dermatology Visit #3 (week 16)	End of Treatment Cardiac PET/Echo and Derm visit #4 (week 24)
Informed Consent	X					
Inclusion/Exclusion Criteria	X		X			
TB Screening	X					
Demographics	X					
Medical History	X		X	X	X	X
Medication History	X		X	X	X	X
Vital Signs	X		X	X	X	X
Physical Exam	X		X			X
Full skin exam	X	X		X	X	X
Pregnancy Test	X		X			X
Lab Tests	X		X			X
ECG			X			X
PET/CT			X			X
Echocardiogram			X			X
Study Drug Dispensed		X		X	X	

AE Monitoring		X	X	X	X	X

*NOTE: The baseline visit (Day 0) and the End of Treatment Visits (Week 24) can be combined into one visit or separated into two visits each within a week period.

Screening Visit (-60 to -1 days)

- All screening assessments will occur within 30 days prior to start of medication
- Obtain informed consent
- Obtain medical history, including demographics, overview of significant past or present illnesses by body system, as well as a complete cardiac and surgical history
- Obtain concomitant medications review
- Obtain vital signs, including weight and height, systolic and diastolic blood pressure (BP), heart rate (HR), and oxygen saturation (O_2 sat)
- Complete physical exam
- Skin assessment: PGA, BSA, PASI)
- Perform laboratory tests, including serum pregnancy test
- TB screening performed per protocol as discussed in Appendix 2

Study Visit 1: Baseline (Day 0, prior to first dose)

- Verify clinical stability
- Confirm that subjects have withheld caffeine for 12 hours and fasted for 4 hours prior to imaging tests
- Confirm that subjects have withheld beta blockers, calcium channel blockers and arterial vasodilators for 24 hours prior to the PET scan
- Obtain interim medical history and concomitant medications review
- Obtain vital signs, including weight and height, systolic and diastolic blood pressure (BP), heart rate (HR), and oxygen saturation (O_2 sat)
- Obtain 12-lead ECG
- Complete physical exam clinical stability since screening evaluation
- Perform laboratory tests, including serum pregnancy test prior to any imaging
- Perform PET/CT scan
- Perform echocardiogram
- Dermatology Psoriasis baseline clinical visit with full skin assessment (PGA, BSA, PASI)
- Remind patients on most common side effects of the new drug. They are encouraged to immediately contact study investigators/staff by email and/or phone for any new or concerning symptoms.
- Provide first dose of Tildrakizumab 100mg sc

Study Visit 2: Week 4 (study visit #2)

- Verify clinical stability
- Obtain interim medical history and concomitant medications review

- Obtain vital signs, including weight and height, systolic and diastolic blood pressure (BP), heart rate (HR), and oxygen saturation (O_2 sat)
- Full psoriasis skin assessment, including PASI, BSA and PGA scores
- Monitor for AE; subjects are again educated about the most common side effects. They are encouraged to immediately contact study investigators/staff by email and/or phone for any new or concerning symptoms.
- Provide second dose of Tildrakizumab 100mg sc

Study Visit 3: Week 16 (study visit #3)

- Verify clinical stability
- Obtain interim medical history and concomitant medications review
- Obtain vital signs, including weight and height, systolic and diastolic blood pressure (BP), heart rate (HR), and oxygen saturation (O_2 sat)
- Full psoriasis skin assessment, including PASI, BSA and PGA scores
- Monitor for AE; subjects are again educated about the most common side effects. They are encouraged to immediately contact study investigators/staff by email and/or phone for any new or concerning symptoms.
- Provide third dose of Tildrakizumab 100mg sc

Study Visit 4: Week 24 (End of Treatment, study visit #4)

- Verify clinical stability
- Obtain interim medical history and concomitant medications review
- Obtain vital signs, including weight and height, systolic and diastolic blood pressure (BP), heart rate (HR), and oxygen saturation (O_2 sat)
- Complete physical exam
- Full psoriasis skin assessment, including PASI, BSA and PGA scores
- Monitor for AE; subjects are again educated about the most common side effects. They are encouraged to immediately contact study investigators/staff by email and/or phone for any new or concerning symptoms.
- Perform laboratory tests, including serum pregnancy test prior to any cardiovascular imaging
- Perform Cardiac PET/CT scan
- Perform echocardiogram

Telephone follow-up call

Contact all subjects by telephone approximately 2-3 days after the Study Visit 4 to ensure no adverse events have occurred since the study visit.

5.2. Concomitant medications

Only patients with moderate-to-severe psoriasis will be included in the study. Because concurrent medications can potentially affect coronary blood flow and flow reserve (e.g., antihypertensive and oral hypoglycemic agents), only patients on stable treatment for hypertension and diabetes will be included in the study. The following medications will be allowed provided they are neither initiated nor discontinued during the study period:

- Aspirin;
- Angiotensin-converting enzyme inhibitors and/or Angiotensin Receptor Blockers;
- β-blockers;
- Nitroglycerin and long-acting nitrates;
- Oral anti-diabetic medications and Insulin;
- Stable hormone replacement therapy

5.3. Procedures

Positron Emission Tomography (PET): Regional and global myocardial blood flow will be assessed using PET imaging. Clinical and research cardiac PET studies are routinely performed at BWH. The PET imaging team at BWH under Dr. Di Carli's leadership consist of experienced imaging specialists and have a track record in research studies using PET. Di Carli has extensive experience in performing these procedures, quantifying myocardial blood flow and flow reserve, has published extensively on this topic, and runs an active core laboratory with experience in multi-center trials using imaging endpoints. PET scans will be performed using a whole-body PET/CT scanner. Study participants will be asked to refrain from drinking caffeine-containing beverages and taking theophylline-containing medications for 12 hours before the PET study. Calcium channel blockers, beta blockers, and arterial vasodilators will be withheld for 24 hours prior to the PET scan. Studies will be performed after 4 hours of fasting.

Assessment of myocardial blood flow and CFR: Regional myocardial blood flow (MBF) will be measured at rest and during vasodilator-stress with adenosine using ^{13}N-ammonia or ^{82}Rubidium as the flow tracer. ^{13}N-ammonia and ^{82}Rubidium is used in clinical and research studies and has been validated for the quantification of myocardial blood flow and CFR. After transmission imaging and beginning with the intravenous bolus administration of ^{13}N-ammonia (~5 mCi) or ^{82}Rubidium (15-20 mCi), list mode images will be acquired for 6-10 minutes. The patient will then undergo a standard infusion of adenosine (140 mcg/kg/min) for 4 mins or regadenoson bolus injection (0.4 mg). Two mins into the adenosine infusion or one minute after the regadenoson bolus, a second dose of ^{13}N-ammonia (~20 mCi) or ^{82}Rubidium (15-20 mCi) will be administered, and PET imaging collected in the same manner. Heart rate, blood pressure, and 12-lead electrocardiogram will be recorded at baseline, every minute during the infusion, and during 5 minutes after completion of the adenosine infusion or regadenoson injection. The calcium score (CAC) CT is acquired in axial mode with 120 kVp, 90 mAs, 32x0.625 mm collimation with approximately 5 s acquisition time, and still falls within the 1–2 mSv radiation dose approved for this study. All CT images were reconstructed with 2.5 mm thickness. CAC is scored using the Agatston method.

Analysis of PET data: Absolute MBF (in ml/g/min) will be computed from the dynamic rest and stress images using commercially available software (Corridor4DM; Ann Arbor, Michigan) and previously validated methods[52,53]. Automated factor analysis will be used to generate blood pool (arterial input function) and tissue time-activity curves. Regional and global rest and vasodilator-stress MBF will be calculated by fitting the ^{13}N-ammonia or ^{82}Rubidium time-activity curves to a two-compartment tracer kinetic model as described previously [52,53]. Per-patient global CFR will be calculated as the ratio of MBF at peak vasodilator-stress over that at rest for the entire left ventricle. This method for quantitation of MBF

is highly reproducible. In the PET core laboratory at BWH, the intra-class correlation coefficient for CFR among four readers is 0.94 (95%CI 0.88-0.98), indicating excellent reproducibility[24].

Echocardiographic Images

Quantitative analysis of echocardiograms: All echocardiograms will be analyzed by cardiologists blinded to randomized treatment assignment. LV volumes will be determined by the modified Simpson's method in the apical 4 and 2 chamber views, and LVEF will be calculated from volumes in the standard manner.[69] Peak early mitral annular relaxation velocity (E') will be measured from both the septal and lateral aspects of the mitral annulus. Mitral flow velocity will be assessed by pulsed wave Doppler from the apical 4-chamber view by positioning the sample volume at the tip of the mitral leaflets. The deceleration time of the E wave is measured as the interval from the peak E wave to its extrapolation to the baseline[70]. LV mass will be calculated by the ASE recommended formula for estimation of LV mass from LV linear dimensions and indexed to body surface area, and relative wall thickness (RWT) will similarly be calculated as recommended by ASE guidelines[69]. LA volume will be assessed by the biplane area-length method from apical 2- and 4-chamber views at end-systole from the frame preceding mitral valve opening and indexed to body surface area (LA volume index, LAVi). In our laboratory, the intra-class correlation for E' is 0.98 (CV 5.8%), indicating excellent reproducibility.

Assessment of LV Strain: B-mode speckle-tracking analysis will be performed off-line using validated vendor-independent software (Cardiac Performance Analysis, Tomtec system, Munich, Germany),[71] which has demonstrated excellent reproducibility in our laboratory[72–75]. The endocardial border is traced at an end-diastolic frame in apical 4- and 2- chamber views and at an end-systolic frame in short axis view, where end-diastole is defined by the QRS complex or the frame just before mitral valve opening. Adequate tracking of speckles along the endocardial and epicardial borders throughout the cardiac cycle is visually assessed. Peak longitudinal, radial and circumferential strain and strain rate curves are then computed automatically and provided as global and segmental data including 6 segments in each view[76]. In our laboratory, the intra-class correlation for peak global longitudinal strain (GLS) is 0.87 (CV 8.0%), indicating excellent reproducibility

Coordination of ancillary study and central imaging analyses. BWH will serve as the coordinating center and central imaging core laboratory for the proposed PET scans in the pilot study. Dr. Di Carli runs a very active core laboratory and, as mentioned above, has extensive experience in managing multi-site imaging trials. For the central analysis of the PET images, all imaging data will be stripped of patient identifiers and assigned a trial-specific identifier to maintain compliance with US regulatory requirements regarding protection of patient privacy. Drs. Weber and Merola will organize a bi-monthly teleconference including investigators and research coordinators from each clinical site to monitor, discuss, and troubleshoot recruitment and other issues that may arise during the conduct of the clinical trial.

5.4. Data to be collected and timing of data collection

At each of the study visits, a medical history with symptom assessment, medication review, vital signs, and physical exam will be obtained. As described above, additional data from the PET/CT scan and echocardiogram will be obtained at baseline and at the end of treatment period. One week after completion of the trial, telephone follow-up will be conducted to assess for any adverse events.

Laboratory analysis: Routine labs required for initiation and monitoring of biologic therapy will be collected at the baseline and follow-up cardiovascular visit. At the Baseline and End of Treatment visit, hs-CrP, Hs-troponin, BMP, CBC, lipid panel, and a pregnancy test (women of child-bearing potential before

each PET scan) will be obtained. Inclusion criteria will include TB screening per protocol. Blood samples will also be collected and stored for future analysis of biomarkers of inflammation and myocyte injury.

6. BIOSTATISTICAL ANALYSIS

6.1. Identification of clinical sites participating in the proposed ancillary study. BWH will be the primary site with extrenal adversiting and recruitment from hospitals in the surrounding New England area. Based on the power calculations below and assuming a 15% effect size, the study will need to recruit approximately 35 patients which includes a 20% attrition rate. We will perform an interim analysis at 20 patients where a conditional power analysis will be performed for futility of the paired t-test to be performed at the end of the study . This analysis will be computed using PASS Sample Size Software (Version 15) with the observed data from these 20 patients[80]. If the conditional power is less than 15%, the study will curtailed**.** We believe that the proposed study is reasonable and attainable. Dr. Merola is an experienced clinical investigator with a successful track record in psoriasis clinical trials[81–85]. Di Carli is a recognized expert in quantitative PET and nuclear cardiology imaging, has published widely on these topics, and has extensive experience in conducting clinical trials using imaging endpoints[86–89]. With external advertising throughout the New England area and social-media, we estimate recruitment rates of 2-4 patients/month and estimate a trial length of ~2.5 years.

6.2. Power Analysis:

Table 2 shows the sample size needed to reach 90% power for an effect size of 15-25% relative improvement in CFR from baseline using a standard deviation of 0.7 at baseline and follow-up and a correlation of 0.7 between baseline and follow-up measurements. Effect sizes were calculated from a baseline mean CFR of 2.4, which is a conservative value derived from a prior study which examined CFR by doppler echocardiography in patients with psoriasis without coronary artery disease[90]. Although data from our retrospective registry demonstrate lower CFR values in patients with psoriasis, this was a selected high-risk population who were clinically referred for PET without objective data on the degree of severity of psoriasis. Thus, we chose to use the conservative estimate of 2.4 for the power calculations.

Table 2. Power calculation

Effect Size	Mean CFR difference (24 weeks – Baseline)	SD	Total Sample Size (85% power)	Total Sample Size (90% power)	Total Sample Size (99% power)
15%	0.36	0.7	23	26	44
20%	0.48	0.7	14	16	26
25%	0.6	0.7	10	11	18

Using a total sample size of 35 evaluable patients and a two-tailed alpha of 0.05, there will be 90% power to detect an effect size of 15% relative improvement in CFR from baseline, estimating a ~20% attrition rate between time of baseline and final PET.

6.3. Study endpoints

Primary Endpoint: Change (from baseline) in CFR, as measured by PET imaging at 24 weeks after initiation of Tildrakizumab

Secondary Endpoints:

(1) Correlation between the change (from baseline) in global CFR and psoriasis skin severity score (PGA, BSA PASI) at 24 weeks after initiation of Tildrakizumab;
(2) Change (from baseline) in peak-stress global myocardial blood flow (in mL/min/g) at 24 weeks after initiation of Tildrakizumab;
(3) Change (from baseline) in peak-stress global coronary vascular resistance (in mm Hg/mL/min/g) at 24 weeks after initiation of Tildrakizumab;
(4) Change (from baseline) in LV peak GLS and E' at 24 weeks after initiation of Tildrakizumab
(5) Correlation of the change (from baseline) in LV peak GLS and E' with the global CFR at 24 weeks after initiation of Tildrakizumab
(6) Change in serum biomarkers of inflammation (hs-CRP), myocyte injury and strain (hs-Troponin, NT-proBNP) at baseline and 24 weeks after initiation of Tildrakizumab.
(7) If the primary endpoint is positive, secondary exploratory analyses will use stored aliquots of plasma and serum to IL-6, TNFRII, ICAM, Glyc-A, p-selectin, e-selectin, sCD40L, adiponectin, and MCP-1.

6.4. Statistical methods

To test *the central hypothesis*, that reducing endothelial cell activation and dysfunction by treatment with Tildrakizumab will quantitatively improve CFR as measured by PET over 24 weeks, we will perform a paired t-test to assess the ΔCFR between baseline and follow-up for each subject.

If a significant change in CFR after the initiation of Tildrakizumab is observed, we will perform secondary analyses of association between other markers of inflammation also implicated in atherosclerosis with ΔCFR. Significance of associations with other inflammatory markers and ΔCFR will be adjusted using the Bonferroni correction.

7. RISKS AND DISCOMFORTS

7.1. Blood sampling and intravenous catheter

There are minor risks and discomforts associated with placement of an intravenous line, including the possibility of bleeding, pain, inflammation (redness and swelling), and leaking of contrast agent outside of the vein at the site of the IV. These problems are usually self-limited or require only minor treatments, such as application of an ice-pack or slight pressure for a few minutes.

7.2. Vasodilator stress

Vasodilator-stress with regadenoson and adenosine, as will be performed in this study, has been used routinely for many years for evaluation of known or suspected coronary artery disease in conjunction with myocardial perfusion imaging. During the infusion of the vasodilator stress agent, the patient may experience flushing, chest pain/pressure, nausea, or lightheadedness. If significant symptoms are present, patients will be given aminophylline (reversal agent) IV to relieve these symptoms. There will be continuous monitoring of heart rate, blood pressure, and 12-lead ECG throughout the infusion and recovery. These procedures are routinely performed in patients with CAD, as those in the CIRT trial, and are considered safe.

Regadenoson stress as performed in this study has been used routinely for many years for evaluating patients with known or suspected CAD. The most common side effects associated with the regadenoson bolus include: flushing, chest pain/pressure, shortness of breath, palpitations, headache, mild

hypotension and heart block. These side effects are usually mild and self-limiting. If they are severe in intensity, aminophylline IV (1 mg/kg) will be given as per standard protocol.

Subjects with a history of seizures may receive adenosine. The side effects associated with this product include: facial flushing, headache, sweating, palpitations, chest pain, hypotension, shortness of breath/dyspnea, chest pressure, hyperventilation, head pressure, lightheadedness, dizziness, tingling in arms, numbness, apprehension, blurred vision, burning sensation, heaviness in arms, neck and back pain, nausea, metallic taste, tightness in throat, and pressure in groin. Adenosine is administered as a continuous infusion over 4 minutes and administered in a dose of 0.14mg/kg/min. The half-life of adenosine is less than 10 seconds. If the patient is having symptoms the infusion can be stopped, no further medication is administered, and the symptoms would stop within seconds because the medication would already be cleared from the heart. Therefore, no reversal medication is needed.

Rarely, an aminophylline IV injection may be used to reverse side effects of regadenoson infusion. Aminophylline is generally well tolerated; possible side effects of aminophylline may include nausea, headache, restlessness, convulsions, rapid breathing, a rapid heart rate, and allergic reactions such as rash.

7.3. Radiation risk

The estimated whole body effective radiation dose from each of the ^{13}N-ammonia or ^{82}Rubidium PET scan is ~3-4 mSv[55], comparable to the annual radiation dose from background radiation sources in North America. Each subject will undergo 2 PET studies during the trial for a total dose of ~6-7 mSv, significantly lower than the average radiation exposure associated with a single conventional myocardial perfusion imaging study using single-photon emission computed tomography (SPECT)[55].

7.4. Drug side effects and toxicities

There are three adverse reactions >1% that occurred more frequently with Tildrakizumab as compared to placebo in the phase 1 and 2 clinical trials (resurface 1 and 2) which were: upper respiratory infection (14% versus 12% in placebo), injection site reactions (3% versus 2%) and diarrhea (2% versus 1% (Appendix 3) This drug has demonstrated safety over three years (Appendix 4).

7.4.1 Allergic reactions

Symptoms of an allergic reaction to Tildrakizumab may include headache, rash, itching, flushing, swelling, shortness of breath, nausea and sometimes vomiting. Severe allergic reactions can cause dizziness, severe skin reactions, difficulty breathing or swallowing, a decrease in blood pressure, and could be life threatening.

7.5. Echo Contrast (Definity)

In the event of suboptimal imaging windows on echocardiogram, echo contrast (e.g. Definity) may be injected into a vein through the IV prior to conducting the rest and stress echocardiograms. Definity is a perflutren lipid microsphere suspension that is non-iodinated and usually well-tolerated. Rare adverse events, including serious cardiopulmonary or anaphylactoid reactions, have been reported in association with this agent. It will not be administered to patients with known or suspected intracardiac shunts or to patients with known hypersensitivity to echo contrast agents.

7.6. Reproductive risks

Pregnant or breastfeeding patients will be excluded from this study.

7.7. Unknown Risks:

There may be other risks and side effects that are not known at this time.

8. POTENTIAL BENEFITS

8.1. Potential benefits to participating individuals

There are no direct benefits for the patient from taking part in this study. The proposed study will test the important question of whether reducing endothelial cell activation and dysfunction using Tildrakizumab will quantitatively improve coronary flow reserve, a sensitive measure of myocardial ischemia. Thus, this pilot study will provide important and unique mechanistic insights of the capabilities of novel psoriasis therapies to improve key determinants of clinical risk (improve coronary blood flow and reduce ischemia) and, in so doing, improve patient symptoms and quality of life, as well as outcomes.

8.2. Potential benefits to society

Data collected in this trial may provide important mechanistic insights into presumed cardiovascular benefits from novel psoriasis therapies, as well as into the pathophysiology of microvascular dysfunction in psoriasis.

9. MONITORING AND QUALITY ASSURANCE

9.1. Safety monitoring

The PI of the study will monitor the overall safety of the study and will report any adverse effect to the IRB immediately. The PI will also monitor this study to ensure that subjects' human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol, and study data reported by the investigator/subinvestigator are accurate, complete and verifiable with study-related records such as source documents.

Safety data will be obtained at each study visit from the spontaneous reports by patients of adverse events, vital sign monitoring, physical examinations, 12-lead ECGs and clinical laboratory tests. In addition, telephone follow-up will be conducted to assess for any adverse events. All safety data will be reviewed by the principle investigators of the study (which includes to clinical cardiologists and two clinical dermatologists)

Patients with unexpected abnormalities on the baseline PET scan will be discussed with the patient's PCP/Dermatology physician to decide whether the patient should participate in this pilot trial. The findings will be discussed with the patient and the patient's primary physician in order to facilitate an appropriate management plan. If a patient is excluded on safety grounds, we do not think that this will affect our ability to determine the effect of Tildrakizumab on myocardial blood flow.

The safety of Tildrakizumab will be assessed with respect to the following end points: (1) death from any cause, (2) the composite of death from any cause or any cardiovascular hospitalization, (3) frequency of symptomatic documented arrhythmia, (4) serious adverse events related to the study drug and clinically significant laboratory abnormalities.

9.2. Treatment Compliance

Subject compliance to treatment regimen will be assessed by confirmation of the full administration of each dose being administered during the four Dermatology clinical assessments.

9.3. Discontinuation criteria for individual subjects

Discontinued subjects are those who are enrolled in the study and for whom study treatment is terminated prematurely for any reason. The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

Subjects will be discontinued if:

- Subject experiences a serious or intolerable adverse event
- Subject has severe disease and has to be intervened upon based on the imaging tests
- In the Investigator's opinion, the subject is non-compliant with the protocol requirements
- Subject's health would be jeopardized by continued participation
- Subject wishes to withdraw consent
- Investigator elects to end the study

9.4. Adverse event reporting guidelines

9.4.1 Definition of Adverse Events (AEs)

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a study drug, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one or more of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator

9.4.2 Definition of Serious Adverse Events (SAEs)

A serious AE is any untoward medical occurrence that, at any dose:

- Results in death,

- Is life threatening (an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe),
- Results in persistent or significant disability/incapacity,
- Results in congenital anomaly, or birth defect,
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability, should also usually be considered serious.

9.4.3 Criteria for Causal Relationship to the Study Drug

Adverse events that fall under either "Possible" or "Probable" should be defined as "adverse events whose relationship to the study drugs could not be ruled out."

Causal relationship to the study drug	**Criteria for causal relationship**
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re-administration (re-challenge) or withdrawal (de-challenge).

9.4.4 Criteria for Defining the Severity of an Adverse Event

The following standard with 3 grades is to be used to measure the severity of adverse events, including abnormal clinical laboratory values.

- Mild: No disruption of normal daily activities
- Moderate: Affect normal daily activities

- Severe: Inability to perform daily activities

9.4.5 Reporting of Serious Adverse Events (SAEs)

In the case of a serious adverse event (SAE), the investigator should submit a report to the IRB within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem as per Partners policy.

9.4.6 Follow-up to Adverse Events

All adverse events occurring during the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during adverse event follow-up, the adverse event progresses to an ″SAE,″ or if a subject experience a new SAE, the investigator must immediately report the information to the sponsor.

9.4.7 Procedure in Case of Pregnancy

If a woman becomes pregnant during the study dosing period or within 30 days from the discontinuation of dosing, the investigator will report the information to the PHRC as if it is an SAE. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result and neonatal data etc., should be included in this information.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below:

- ″Spontaneous abortion″ includes abortion and missed abortion.
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator.
- In the case of a delivery of a living newborn, the ″normality″ of the infant is evaluated at the birth. ″Normality″ of the miscarried fetus is evaluated by visual examination unless test results which indicate a congenital anomaly are obtained prior to miscarriage.

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Appendix

Appendix 1: Therapy-specific washout periods

Therapy	Length of washout period
Systemic Therapy	
Biologics	
Etanercept	30 days
Adalimumab and Infliximab	45 days
Anti-IL17 Biologics (Including Secukinumab, bimekizumab, ixekizumab, brodalumab	60 days
Ustekinumab	60 days
Non-biologics	
Apremilast, cyclosporine, corticosteroids, methotrexate, acitretin, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, fumaric acid esters	30 days
Phototherapy	
Ultraviolet B [UVB], psoralen and ultraviolet A radiation [PUVA]	30 days
Topical Therapy	
Medium and High potency topical corticosteroids, vitamin D analog preparations (calcipotriene, calcitriol), calcineurin inhibitors (pimecrolimus, tacrolimus) -Exceptions: Unmedicated emollients (eg, Eucerin®) for body lesions and non-medicated shampoos for scalp lesions (Subjects should not use these topical treatments within 24 hours prior to the clinic visit.) Mild potency topical steroids** will be permitted for use limited to the face, neck, axilla, and/or genitalia as rescue medication	14 days

* Examples of Medium and High Potency Topical Steroids: Diprolene Cream AF (betamethasone), Halong Ointment (halcinonide), Ultravate Cream (halobetasol), Psorcon (E) Ointment (diflorasone), Vanos Cream (fluocinonide), Cordran Ointment (flurandrenolide), Clobex Lotion/Spray/Shampoo (clobetasol), Cormax Cream/Solution (clobetasol), Temovate Cream/Ointmenet/Solution (clobetasol), Elocon Ointment (mometasone), Tropicort Cream (desoximetasone), Tropicort Gel (desoximetasone), Tropicort LP Cream (desoximetasone).

**Examples of Mild Potency Topical Steroids: Synalar Ointment (flucinolone acetonide), Cutivate Ointment (fluticasone), Verdeso Foam (desonide), Desonate Gel (desonide), DesOwen Lotion (desonide), Aclovate Cream/Ointment (aclometasone), Hydrocortisone Cream

Appendix 2: Assessment and management of TB and TB risk factors

All subjects will be assessed for tuberculosis (TB) at Screening through physical examination for signs and symptoms of TB, laboratory testing (Quatiferon Gold). If laboratory testing is positive, patients will be referred for a chest radiograph. Referral to an infectious disease specialist should be considered on a case-by-case basis. For the purposes of this study, TB definitions are as follows:

A. Known TB Infection

- Active TB infection or clinical signs and symptoms suspicious for TB (pulmonary or extra-pulmonary).
- History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection, unless adequately treated and proven to be fully recovered upon consult with a TB specialist.
- Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the subject's medical history.

B. *High risk of acquiring TB infection*:

- Known exposure to another person with active TB infection within the 3 months prior to screening.
- Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high.

C. *Latent TB infection* (unless appropriate prophylaxis is initiated at least 8 weeks prior to IMP dosing and continued to completion of prophylaxis):

- The absence of signs, symptoms, or physical findings suggestive of TB infection with a positive IGRA test (or 2 indeterminate IGRA test results) and a chest x-ray (or other imaging) without evidence of TB infection. If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be randomized to IMP without further evaluation by a TB specialist and discussion with the Study Physician, if LTB infection is identified. The retest must be done during the protocol-defined Screening window. Note: If available, respiratory or other specimens must also be smear and culture negative for TB (CDC diagnosis of LTB infection) http://www.cdc.gov/TB/topic/testing/default.htm).

D. *NTMB infection* is defined as a clinical infection caused by mycobacterial species other than those belonging to the Mycobacterium tuberculosis complex.

E. *Tuberculosis test conversion*:

- A positive IGRA result for the current test when previous IGRA test results were negative. All subjects with TB test conversion must immediately stop IMP administration and be referred to a TB specialist for further evaluation. Confirmed TB test conversions should be classified as due to LTBI, active TB infection, or NTMB, and documented appropriately.

*Appendix 3. Drug side effects: Data from three placebo-controlled trials[91,92]**

	Tildrakizumab 100mg (n=705) % (n)	**Placebo (n=355) % (n)**
Upper Respiratory Infection	14% (98)	12% (41)
Injection site reactions	3% (24)	2% (7)
Diarrhea	2% (13)	1% (5)

*In clinical trials, a total of 1994 subjects with plaque psoriasis were treated with ILUMYA™, of which 1083 subjects were treated with ILUMYA™ 100 mg. Of these, 672 subjects were exposed for at least 12 months, 587 for 18 months, and 469 for 24 months. Data from three placebo-controlled trials (Trials 1, 2, and 3) in 705 subjects (mean age 46 years, 71% males, 81% white) were pooled to evaluate the safety of ILUMYA™ (100 mg administered subcutaneously at Weeks 0 and 4, followed by every 12 weeks [Q12W]

Appendix 4: Drug side effects: Demonstrated Safety over Three Years [93]

Adverse Events/100 Patient-Years	**Weeks 0-148 Tildrakizumab 100mg (n=872)**	**Weeks 0-12 Placebo (n=543)**
Injection site Reactions	1.94	5.36
Severe Infections	1.14	0.97
Non-melanoma skin cancer	0.5	0.97
Malignancies	0.45	0
Extended MACE*	0.4	0.49
Drug-related hypersensitivity AEs	0.3	0.39
Deaths	0.3	0
Melanoma	0.05	0

Data are in n (%). *Extended MACE includes non-fatal myocardial infarction, non-fatal stroke, unstable angina, coronary revascularization, resuscitated cardiac arrest, and CV deaths that are confirmed as "cardiovascular" or "sudden."