A PHASE IV, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CROSSOVER STUDY OF THE EFFECTS OF USTEKINUMAB ON VASCULAR INFLAMMATION IN PSORIASIS

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Study Summary

Title	A Phase IV, Randomized, Double-Blind, Placebo-Controlled Study of the Effects of Ustekinumab on Vascular Inflammation in Psoriasis
Short Title	Vascular Inflammation in Psoriasis – Ustekinumab (VIP-U)
Protocol Number	To be assigned.
Phase	Phase 4
Methodology	Two-arm, randomized, double-blind, placebo-controlled trial
Study Duration	64-100 weeks.
Study Center(s)	University of Pennsylvania
Objectives	The primary objectives of this study are to determine the effect of anti-IL-12/23 therapy vs. placebo on vascular inflammation and cardiometabolic biomarkers in patients with psoriasis. Vascular inflammation will be assessed with multi-volumetric product, tissue-to-background ratio and total atherosclerotic burden using FDG-PET/CT.
Number of Subjects	42
Diagnosis and Main Inclusion 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, Dose, Route, Regimen	Ustekinumab (Stelara) subcutaneous injection 45mg (subject weight ≤100kg) or 90mg (subject weight >100kg) at day 0 and week 4 followed by every 12 week dosing thereafter.
Duration of administration	52 - 64 weeks
Reference therapy	Placebo subcutaneous injection at weeks 0 and 4.
Statistical Methodology	Descriptive statistics, Wilcoxon rank-sum tests, Multivariable linear regression, Exploratory analyses

1 Statistical Plan

1.1 Sample Size Determination

Sample size calculations were based on the primary outcome of changes in standard uptake value (SUV) of the tracer measured by FDG-PET/CT. Based on prior work and published literature, we wish to be able to detect a difference in SUV between ustekinumab- and placebo-treated groups of 0.1 (which is similar to the change in SUV observed over one decade of aging).[49] Prior work also indicates that the standard deviation (SD) of the change in SUV is approximately 0.11. Using a two-sided test with significance level of α=0.05, 19 patients per arm will provide 80% power to detect the clinically significant change of 0.1 SUV between groups stratified by weight. To accommodate potential dropout of up to 10%, we intend to accrue 21 subjects per arm.

Assuming an effective sample size of 21 subjects per arm, we have 80% power to detect clinically relevant differences in biomarker changes between groups of approximately 0.88 SD, well below the general threshold for significance of one SD. Table 1 below shows the detectable difference for several markers for which we have data on the variability of the change over time.

Table 1. Detectable differences for various cardiometabolic biomarkers

Marker	HDL	HOMA	CRP	TNF-α	IL-6
Detectable difference	3.56 mg/dL	0.18 AU	0.13 g/dL	0.36 pg/mL	1.78 pg/mL

1.2 Statistical Methods

Stata 12.0 (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 for Placebo-Controlled 12 Week Period.
The primary analysis will consist of pairwise comparisons of the two arms using the Wilcoxon rank-sum test. This is a non-parametric test that does not require normally distributed outcomes and is appropriate for smaller sample sizes. The change in outcome (SUV, biomarkers) will be calculated for each subject and compared between the two groups. In addition, we will conduct modeling of predictors for change, including indicators of treatment group but also adjusting for clinical and demographic covariates. The association between change in SUV over 12 weeks and psoriasis will be analyzed using multivariable linear regression with SUV as the dependent variable, and covariates in the model being age, sex, major cardiovascular disease risk factors (serum glucose, systolic and diastolic blood pressure, tobacco use, family history, serum LDL, HDL and total cholesterol, body mass index (BMI), and psoriasis activity). Because the primary outcome is a change score, the analysis will be restricted to subjects who complete the trial. Secondary analyses will include multiple imputation to address possible sensitivity to missing data.

Primary Analysis for 52 Week Active Treatment Period.
The primary analysis will consist of comparisons of vascular inflammation and biomarker levels between week 52 of the ustekinumab treatment period and baseline (for those subjects initially randomized to active treatment) or week 64 of the ustekinumab treatment period and week 12 (for those subjects initially randomized to placebo). Appropriate regression analyses will also be performed using the changes in outcome for each subject (SUV, biomarkers) as dependent variables. In addition, we will conduct modeling of predictors for change, including indicators of treatment group (i.e., crossover from placebo or continuation) but also adjusting for clinical and demographic covariates. The association between change in SUV over the active treatment period and psoriasis will be analyzed using multivariable linear regression with SUV as the dependent variable, and covariates in the model being age, sex, major CVD risk factors (serum glucose, systolic and diastolic blood pressure, tobacco, family history, serum LDL, HDL and total cholesterol, BMI and psoriasis activity). We will also conduct exploratory analyses to

determine whether change in SUV over time is predicted by psoriasis activity, CV biomarkers individually, or within subtypes (inflammatory, metabolic and lipoprotein). This modeling will be limited and exploratory due to the sample size, but will inform hypothesis generation and future studies.

Additional analyses will include longitudinal models of vascular inflammation 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.