Published in final edited form as:

J Invest Dermatol. 2020 January ; 140(1): 85–93.e2. doi:10.1016/j.jid.2019.07.679.

A PHASE IV, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CROSSOVER STUDY OF THE EFFECTS OF USTEKINUMAB ON VASCULAR INFLAMMATION IN PSORIASIS (the VIP-U trial)

JM Gelfand[1,2], **DB Shin**[1], **A Alavi**[3], **DA Torigian**[3], **T Werner**[3], **M Papadopoulos**[1], **J Takeshita**[1,2], **MH Noe**[1,2], **AK Dey**[4], **MP Playford**[4], **NN Mehta**[4]

[1:]Department of Dermatology University of Pennsylvania Perelman School of Medicine, Philadelphia PA USA

[2:]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania Perelman School of Medicine, Philadelphia PA USA

[3:]Department of Radiology (Nuclear Medicine), University of Pennsylvania Perelman School of Medicine, Philadelphia PA USA

[4:]Section of Inflammation and Cardiometabolic Diseases, National Heart Lung Blood Institute, Bethesda MD USA

Corresponding author: Joel M Gelfand MD MSCE, 730 South Tower, 3600 Civic Center Boulevard, Philadelphia PA 19104, 215-614-0635, Joel.Gelfand@pennmedicine.upenn.edu, Twitter: @DrJoelGelfand.

CRediT statement
Conceptualization: JG, AA, NM
Data curation: DS, TW, AD, MPP
Formal analysis: JG, DS, NM
Funding acquisition: JG, NM
Investigation: JG, DT, MP, JT, MN, AD, MPP, NM
Methodology: JG, DS, AA, DT, TW, NM
Project administration: JG, AA, TW, MP, NM
Resources: JG, AA, NM
Software: DS, TW
Supervision: JG, AA, DT, TW, MP, JT, MN, NM
Validation: DS, AA, AD, MPP
Visualization: DS
Writing original draft: JG
Writing – review and editing: DS, AA, DT, TW, MP, JT, MN, MPP, AD, NM

Study ethics: Study approval was obtained from the Institutional Review Board (IRB) of the University of Pennsylvania in accordance with the principles of Declaration of Helsinki. All guidelines for good clinical practice and those set forth by the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research) were followed. All study participants in the study provided written informed consent.

Role of the sponsors: The sponsors (NHLBI and Janssen) had no role in the analysis or reporting of the results. Janssen reviewed the manuscript and provided non-binding input for compliance purposes.

Data Availability Statement: De-identified individual participant data that underlie the results reported in this article will be made available by the corresponding author beginning 9 month and ending 36 months following article publication to researchers who provide a methodologically sound proposal for the purpose of individual data meta-analysis. Proposals should be directed to Joel.Gelfand@pennmemdicine.upenn.edu. To gain access, requestors will need to sign a data use agreement.

Abstract

Background: Psoriasis is a Th17 autoimmune disease associated with an increased risk cardiovascular events and mortality. Ustekinumab, an antibody to p40, blocks cytokines IL12 and IL23, and is a highly effective and safe treatment for psoriasis.

Trial Design and Methods: We conducted a randomized double blinded placebo-controlled trial to determine the effect of ustekinumab on aortic vascular inflammation measured by imaging, and key biomarkers of inflammation, lipid and glucose metabolism in the blood of patients with moderate to severe psoriasis.

Results: 43 patients were randomized and at week 12, ustekinumab treated patients had an −18.65% (95% CI: −29.45% to −7.85%) reduction in aortic vascular inflammation at week 12, a reduction in inflammatory biomarkers, and an increase in apolipoprotein-B lipoproteins compared to placebo. At week 12, placebo patients crossed over such that all patients received ustekinumab for a total of 52 weeks. At the end of 52 weeks of ustekinumab treatment there was no change in aortic vascular inflammation compared to baseline, inflammatory markers were reduced and there were increases in selected measures of lipids and leptin.

Conclusions: These results demonstrate blockade of IL12/23 may transiently reduce aortic vascular inflammation with more durable reduction in inflammatory cytokines associated with cardiovascular disease.

Introduction:

Psoriasis is a chronic inflammatory disease affecting over 125 million people worldwide (Kurd and Gelfand, 2009, Parisi et al., 2013). The cause of psoriasis is unknown but is believed to be the result of genetic susceptibility and environmental factors (such as obesity, smoking, and infection with Streptococcus pyogenes) that result in auto-reactive T cells targeting keratinocyte and melanocyte derived peptides (Hawkes et al., 2017). Once disease is established, the pathophysiology is characterized by upregulation of antigen presentation, inflammatory cytokines, epidermal proliferation, and angiogenesis (Nestle et al., 2009). Clinically, increasing psoriasis severity, as assessed by treatment patterns or body surface area affected is associated with an increased risk of diabetes mellitus, major cardiovascular events, and mortality independent of traditional risk factors for these outcomes (Gelfand et al., 2006, Gelfand et al., 2007, Noe et al., 2018, Wan et al., 2018). As a result, present guidelines from major dermatology and cardiology organizations define psoriasis as a disease associated with increased risk for cardiovascular disease warranting more intense screening and treatment of traditional cardiovascular risk factors (Elmets et al., 2019, Grundy et al., 2018).

The biologic mechanisms linking psoriasis to adverse cardiometabolic outcomes is multifactorial and complex given multiple pathways involved in atherosclerotic-disease related cardiovascular events (Sajja et al., 2018). These phenotypically distinct clinical states share many immune (such as increases in interleukin (IL)-1), IL-6, tumor necrosis factor (TNF), C-reactive protein (CRP) and metabolic (dyslipidemias and insulin resistance) abnormalities (Azfar and Gelfand, 2008, Mehta et al., 2012a, Sajja et al., 2018). Indeed, IL-1

and IL-6 have been causally linked to cardiovascular disease through clinical trials and Mendelian randomization studies, respectively(Consortium, 2012, Ridker et al., 2017).

Furthermore, we and others have demonstrated that psoriasis and its severity are associated with increased aortic vascular inflammation as measured by 18F-2-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT)(Dey et al., 2017, Hjuler et al., 2017, Kaur et al., 2018, Mehta et al., 2011). In this cardiovascular imaging modality, radiolabeled glucose (i.e., FDG) taken up by CD68+ macrophages in early, inflamed, wall of the aorta is measured by PET/CT(Bural et al., 2008, Chen et al., 2009). The quantity of uptake of FDG throughout the aorta has been referred to as aortic vascular inflammation. FDG uptake in the aorta has been shown to be associated with future cardiovascular events independent of traditional risk factors and there is evidence to suggest that FDG activity changes (as early as 4-12 weeks) with initiation of treatments (such as statins) known to lower the risk of major cardiovascular events (Lee et al., 2008). These characteristics make aortic vascular inflammation an attractive surrogate for early stage clinical trials of treatments for the prevention of CV events(Lee et al., 2008, Mehta et al., 2012b, Tahara et al., 2006).

The objective of this trial was to determine the effect of ustekinumab, an antibody to the p40 subunit shared by cytokines IL-12 and IL-23, on aortic vascular inflammation, and blood-based markers of inflammation, lipid, and glucose metabolism compared to placebo in patients with moderate to severe psoriasis.

Results:

Sixty-three patients were assessed for eligibility of whom 43 were randomized, 22 to ustekinumab and 21 to placebo (Supplemental Figure 2). All patients randomized to ustekinumab completed the study through week 12 whereas 19 (86%) initially assigned to placebo completed until week 12. Thirty-four (79%) patients completed the study throughout the open label extension period. Recruitment started on August 14, 2014 and the last patient last visit occurred on September 10, 2018. Patients were an average age of 42 years (SD 13.38), 70% male, predominantly white (72%), had an average body mass index (BMI) of 33, and an average body surface area (BSA) and psoriasis area and severity index (PASI) of 25% and 20, respectively (Table 1). The baseline characteristics were similar between the two groups but those assigned to placebo were numerically older, less likely to be white or have hyperlipidemia, and more likely to have hypertension and a prior diagnosis of psoriatic arthritis.

As expected, ustekinumab was highly effective in treating psoriasis (Table 2). At week 12, ustekinumab treated patients had 67%, 41%, and 53% greater differences in achieving PASI75, PASI90, and physician global assessment (PGA) clear/almost clear responses, respectively, compared to placebo ($p<0.01$ for all). At end of study, PASI75, PASI90, and PGA clear/almost clear response rates were 72% (95%CI 55%, 85%), 49% (95%CI 24%, 65%), 46% (95%CI 30%, 63%), respectively. At week 12, there was no change in MEDFICTS dietary assessment questionnaire ($p=0.19$) or international physical activity questionnaire metabolic equivalent task (IPAQ MET) ($p=0.46$) between placebo and

ustekinumab. At the end of study compared to baseline for both groups combined, there was a reduction in MEDFICTS score of 12.325 (p=0.001) suggesting improved eating habits (e.g. of meats, eggs, dairy, fried foods, in baked goods, convenience foods, table fats, snacks) and no change in IPAQ MET (p=0.221).

Patients assigned to ustekinumab had a −6.58% (95%CI: −13.64% to 0.47%) reduction in aortic vascular inflammation at week 12 compared to baseline, while patients assigned placebo had a 12.07% (95%CI: 3.26% to 20.88%) increase in aortic vascular inflammation during the same time period (Table 3). Compared to changes in the placebo group, patients treated with ustekinumab experienced a −18.65% (95% CI: −29.45% to −7.85%) reduction in aortic vascular inflammation at week 12. The findings were similar when adjusted for age, sex, hypertension, hyperlipidemia, and psoriatic arthritis (−21.1%, 95% CI: −33.52—8.69)). At the end of the open label extension (week 52 for those initially assigned to ustekinumab and week 64 for those initially assigned to placebo), there was no change in aortic vascular inflammation compared to baseline (percent change 0.84%, 95% CI: −4.38% to 6.07%) (Table 4). Similarly, there was no change in aortic vascular inflammation (percent change −0.38% 95% CI: −5.02% to 4.25%) during the 52-week period of ustekinumab treatment (i.e., week 52 compared to baseline for those randomized to ustekinumab and week 64 to week 12 in those initially randomized to placebo). The results were similar when the scans were re-read at NIH and when they were independently read at PENN (data not shown).

Changes in blood biomarkers of inflammation, advanced lipoprotein characterization, and glucose metabolism are shown in Table 5. At week 12, patients randomized to ustekinumab had a decrease in vascular cell adhesion molecule-1 (VCAM-1), interleukin-2 receptor alpha (IL-2ra), and IL-17a, and an increase in IL-12/23; a small, but statistically significant increase in total cholesterol mostly driven by apolipoprotein-B lipoproteins [e.g., low density lipoprotein (LDL) cholesterol (ldl-c), LDL particle number (ldl-p), very low density lipoprotein (VLDL) particle number (vldl-p), and intermediate density lipoprotein (IDL) particle number (idl_p)] with a small reduction in VLDL particle number (vldl-p) and small vldl-p (s-vldl-p). There were no changes in high density lipoprotein (HDL) particle size (hdl-z) and number (hdl-p), or markers of glucose metabolism. At the end of the open label extension (week 52 for those initially assigned to ustekinumab and week 64 for those initially assigned to placebo), there was a decrease in IL-1b, IL-17a, and IL-18; an increase in IL-12/23 compared to baseline; and a small, statistically significant increase in hdl-z, large vldl-p (l-vldl-p) and leptin. During the 52-week period of ustekinumab treatment (i.e., week 52 compared to baseline for those randomized to ustekinumab and week 64 to week 12 in those initially randomized to placebo), there was a statistically significant decrease in TNF-alpha, IL-1b, IL-17a, IL-18, and IL-6; an increase in IL-12/23; and a statistically significant increase in hdl-p, l-vldl-p, and leptin.

Safety data are presented in Supplemental Tables 1 and 2, listing non-serious adverse events that occurred in more than 5% of patients in any randomized arm. During the randomized controlled trial period, there were 7 adverse events in those treated with ustekinumab and 5 adverse events in those treated with placebo (none of which were serious). During the open label period, there were 38 adverse events, 4 of which were serious. The serious adverse events all occurred in those initially randomized to placebo, occurred after cross-over to

ustekinumab, and included one case each of endometritis, hypotension, stroke (thromboembolic), and vasovagal reaction. The stroke occurred in a male subject in his sixties with a history of hypertension and coronary artery disease. The patient made a complete recovery without residual deficit.

Discussion:

We conducted a randomized, double-blind, placebo controlled, trial to determine the impact of systemic anti-IL-12/23 immune targeted (i.e., ustekinumab) treatment on key markers of vascular disease risk compared with placebo in patients with moderate to severe psoriasis. As expected, ustekinumab resulted in a dramatic reduction in psoriasis activity(Menter et al., 2019). At week 12, there was a significant (i.e. similar to statin effects) 18.65% decrease in aortic vascular inflammation in ustekinumab treated patients compared to placebo(Tawakol et al., 2013). This finding is proof of principle that antibody-based therapies can causally decrease aortic vascular inflammation, and advances observations from prior uncontrolled studies which demonstrated an improvement in aortic vascular inflammation in Korean psoriasis patients treated with ustekinumab(Kim et al., 2018). Moreover, this finding appears specific to the IL-12/23 pathway as similar trials by our group and others have shown a neutral effect of biologics which target TNF (adalimumab) and IL-17 (secukinumab), respectively(Bissonnette et al., 2017, Gelfand et al., 2019, Mehta et al., 2018). The week 12 results, however, were not maintained, with a neutral effect on aortic vascular inflammation observed at week 52 (for those initially randomized to ustekinumab), and no evidence of change in aortic vascular inflammation when patients were crossed over to ustekinumab at week 12 and imaged again 52 weeks later. These findings combined suggest that the improvement in aortic vascular inflammation after 12 weeks of ustekinumab is transient.

We also evaluated the effect of ustekinumab on key markers of inflammation, lipid and glucose metabolism, most known to be dysregulated in patients with psoriasis, associated with adverse atherosclerotic outcomes and/or incident diabetes mellitus(Sajja et al., 2018). After 12 weeks of therapy, those treated with ustekinumab had an increase in LDL (on average 20mg/dL) and LDL-particle number (on average 200), but these changes were transient and were not sustained at 52 weeks. Treatment with IL12/23 inhibition was associated with a reduction in IL-17a, a key cytokine in cutaneous manifestations of psoriasis(Hawkes et al., 2017). Additionally, we observed an increase in IL 12/23 levels following treatment with ustekinumab. Likely, this reflects detection of the p40 subunit of the monoclonal antibody by the sandwich protein of the ELISA and reflects receipt of active drug. At the end of study, there was a statistically significant decrease in TNF-alpha, IL-1b, IL-17a, and IL-6, markers associated with modulation of atherosclerotic cardiovascular diseases(Ridker et al., 2017). Of particular interest was the reduction of VCAM-1. The VCAM-1 protein mediates the adhesion of lymphocytes to vascular endothelium where leukocyte-endothelial cell signal transduction plays a role in the development of atherosclerosis under oxidative stress(Schmidt et al., 1995). Upregulation of VCAM-1 in endothelial cells occurs in states of increased TNF-alpha and IL-1. The reduction of VCAM-1 at 12 weeks suggests reduction in endothelial cell activation early which may potentially impart benefit at later time points despite a lack of sustained decrease at 52 weeks since the benefit of blocking leukocyte transmigration had already occurred.. Future

studies should incorporate other key vascular beds (e.g. coronary arteries) where this VCAM-1 mediated endothelial-myeloid cell interaction may lead to detrimental occlusive disease (e.g., myocardial infarction). Indeed, biologic therapy (anti-TNF, anti-IL-17, and anti-IL-12/23 therapies) was recently shown to be associated with a reduction in coronary artery plaque burden following one-year of treatment in an observational study(Elnabawi et al., 2019).

Strengths of our study include its rigorous design, validation of imaging findings by an independent lab, and comprehensive evaluation of biomarkers of inflammation, lipid and glucose metabolism. Limitations include a relatively small sample size which may have resulted in a failure to observe changes in imaging at weeks 52 and 64 due to variability inherent to measurement of aortic vascular inflammation. Despite the well-established methods for quantification that we used, PET imaging itself has limitations which include the selection of background tissue for correction (e.g. blood pool), as well as which aortic segments were analyzed (e.g. arch versus entire aorta). Moreover, aortic vascular inflammation is not a direct measure of coronary disease but has been shown to correlate with presence of non-calcified plaque burden in the coronary artery, supporting the notion that extending these imaging studies to additionally phenotype the coronary artery tree is important (Joshi et al., 2018). While our study provides important biologic insights into the effects of targeting IL-12/23 in humans on key cardiovascular pathways, we are unable to determine if the effects were mediated by IL-12 or IL-23 blockade or both. Moreover, we evaluated a number of biomarkers and thus type 1 error may have impacted the statistical findings. Furthermore, we did not evaluate other pathways that may be important links between psoriasis and cardiovascular events including platelet function and immune-cell populations by flow (Takeshita et al, 2014).

In conclusion, we demonstrated that IL12/23 may transiently reduce aortic vascular inflammation (i.e., improvements seen at week 12, no difference at 12 months) with more durable reduction in inflammatory cytokines associated with cardiovascular disease. It is important to emphasize that we evaluated blood and imaging biomarkers of cardiovascular events, and thus, ultimately large-scale, long-term, event-driven trials will be necessary to determine the clinical benefits of treatments for psoriasis on cardiovascular disease.

Methods:

Trial design:

The study was a randomized, double-blind, placebo-controlled trial designed to enroll 42 patients with 1:1 allocation to ustekinumab subcutaneous injections or placebo injections at baseline and week 4. At week 12, patients initially assigned to ustekinumab continued this treatment every 12 weeks for 52 weeks and patients initially assigned placebo received ustekinumab at week 12, 16, and then every 12 weeks thereafter until week 64 (Supplemental Figure 1). (The study was registered on July 10, 2014 at www.clinicaltrials.gov ().

Participants:

To be included in the study, participants had to be 18 years of age or older with a diagnosis of psoriasis for at least 6 months and with stable plaque psoriasis for at least 2 months. Moderate to severe psoriasis skin disease severity was defined as body surface area ≥10% and psoriasis area severity index score ≥12 at baseline visit. Women of child-bearing potential and men were required to use contraception during the study period, and subjects were required to be in good health based on medical history, screening laboratory testing, and physical examination performed at screening. Patients were excluded for any of the following reasons: a previous adverse event or lack of response to an IL-12/23 inhibitor that led to treatment discontinuation; diagnoses of alternate forms of psoriasis or other active skin conditions that may interfere with evaluation of psoriasis; use of any of the following psoriasis treatments: ultraviolet B phototherapy or topical prescription psoriasis treatments within 14 days of baseline (patients were allowed to use low-potency steroids up to twice daily to the groin, underarms or face), psoralen-ultraviolet A phototherapy within 30 days of baseline, oral psoriasis treatments within 30 days of baseline, biologics within 90 days of baseline (or 180 days for ustekinumab); use of investigational agents within 30 days or 5 half-lives (whichever is longer) of baseline; required oral or injectable corticosteroids; poorly controlled medical condition including history of diabetes mellitus (unless the duration of type 2 diabetes was <10 years and hemoglobin A1c level was <7.0%) and uncontrolled hypertension, with measured systolic blood pressure >180 mm Hg or diastolic blood pressure >90 mm Hg; history of demyelinating diseases, photosensitivity, or lupus; active infection or risk factors for severe infection, untreated latent tuberculosis, or use of a live vaccine; history of hematological or solid malignancy within the past five years other than successfully treated basal cell carcinoma, non-metastatic cutaneous squamous cell carcinoma or cervical carcinoma in situ; among female subjects, pregnant or breast-feeding or considering becoming pregnant during the study; hemoglobin < 10 g/dL in females or <12 g/dL in males; white blood cell (WBC) count $<2.5 \times 10^9$/L or $> 15 \times 10^9$/L; platelet count $< 100 \times 10^9$/L; serum aspartate transaminase (AST) or alanine transaminase (ALT) >2.5 upper limits of normal; serum total bilirubin ≥2 mg/dL; serum creatinine >1.6 mg/dL; recent history of substance abuse or psychiatric illness that could preclude compliance with the protocol; history of any substance abuse within 365 days of screening visit; alcohol use >14 drinks per week at the screening visit or within 30 days of the screening period; use of cholesterol-lowering medication (e.g., statin) if dose and form of medication was not stable for 90 days prior to week 0 and would not remain stable throughout the duration of the study. The study was conducted at the University of Pennsylvania Health System.

Interventions:

Ustekinumab (or corresponding placebo) therapy was administered in a double-blind manner as subcutaneous injections. The dose was based on body weight (≤100kg 45 mg, >100kg 90 mg) at the interval described in the trial design above.

Primary Outcomes:

The primary imaging outcome for our study was change in total vascular inflammation of five aortic segments as assessed on FDG-PET/CT between baseline and weeks 12, 52 (only

subjects initially randomized to ustekinumab), and 64 (only crossover subjects). FDG-PET/CT scans were analyzed to derive target-to-background ratio (TBR) values to quantify vascular inflammation by previously published methods. Patients underwent FDG-PET/CT scans using the standard protocol below (Bural et al., 2008, Chen et al., 2009) following overnight fast. Serum glucose levels were checked to ensure a glucose level <200 mg/dL prior to FDG administration. Standard bed positions of three minutes each were obtained for each patient from the vertex of the skull to the toes. All images were acquired by employing integrated PET/CT systems (Gemini TF and Ingenuity TF; Philips Medical Systems, Bothell, Washington, USA with the same scanner being used for individual subjects) about 60 minutes after intravenous administration of 15 mCi of FDG with 1.5-4 mm axial slices of the aorta obtained. After qualitative review of PET and CT images, the extent of FDG uptake within the aorta was measured by using dedicated image analysis software (OsiriX MD, Pixmeo SARL, Bernex, Switzerland) to measure vascular inflammation calculated as a TBR to blood pool activity. Each region of interest produced two measures of metabolic activity: mean standardized uptake value (SUV_{mean}) and maximum standardized uptake value (SUV_{max}), and these were obtained in the entire aorta from the aortic outflow tract to the abdominal aorta. Moreover, regions of interest were also placed on 6 contiguous slices over the superior vena cava to obtain background activity of the FDG radiotracer. The SUV_{mean} from each of the superior vena cava slices were then averaged to produce one venous value. To account for background blood activity, SUV_{max} values from each aortic slice were divided by the average venous SUV_{mean} value yielding TBR_{max} values, the primary outcome measure(Bural et al., 2006, Mehta et al., 2011, Naik et al., 2015). Image analysis was completed at NIH as the primary analysis with a second independent assessment conducted at Penn for quality assurance. All scans were read at two time points at NIH and Penn, first after collection of all week 12 data, and again after end of study (repeating baseline and week 12) in order to eliminate batch effects. We also evaluated change in inflammatory, lipid, and metabolic biomarker levels between baseline and weeks 12, 52 (only subjects initially randomized to ustekinumab), and 64 (only crossover subjects). Biomarkers were analyzed using automated technology where possible. Inflammatory biomarkers CRP, TNF-alpha, IL-6, IL-2ra, IL-18, IL-17a, and VCAM-1 were measured using multiplex ELISA technology (MSD, Maryland). Lipid particle size and number were assessed using nuclear magnetic resonance spectroscopy (LipoScience, USA) and HDL cholesterol efflux capacity using an in-house assay(Mehta et al., 2012a, Salahuddin et al., 2015). Metabolic markers including insulin, leptin and adiponectin were assayed using MSD ELISA. Apolipoproteins were measured using turbidmetry.

Secondary outcomes:

Secondary endpoints included change in physician reported measures of psoriasis activity (PASI and PGA), adverse events, and change in patient-reported dietary and physical activity assessments (e.g. MEDFICTS, and IPAQ MET) from baseline to weeks 12, 52 (only subjects initially randomized to ustekinumab), and 64 (only crossover subjects).

Sample size:

Sample size calculations were based on the primary outcome of changes in standardized uptake value (SUV) of FDG measured by PET/CT. Based on prior work and published

literature, we sought to detect a difference in SUV between ustekinumab-treated and placebo-treated groups of 0.1 (which is similar to the change in SUV observed over one decade of aging).(Mehta et al., 2011) 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 planned to accrue 21 subjects per arm. Regarding biomarkers, 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.

Randomization:

Study group assignment was performed via block randomization (of 4 and 8), using a computerized system at the Investigational Drug Services (IDS), University of Pennsylvania.

Blinding:

Study investigators, staff, and patients were blinded to ustekinumab or placebo status during the placebo-controlled period. All scans were read in a blinded fashion to patient characteristics, treatment allocation, and visit dates (i.e., baseline, week 12, or end of study).

Statistical methods:

Stata 15 (StataCorp, College Station, TX) was used for analysis. All data were summarized using descriptive statistics (mean, SD, range for continuous variables; frequencies for categorical variables) and graphical techniques; missing data were summarized using frequencies for each outcome measure.

Subjects were analyzed based on the group they were assigned to for the primary analyses. There are two primary analyses, the first consisting of pairwise comparisons of the two arms during the placebo-controlled period and the second consisting of comparisons between baseline and end of study. For the first primary analysis, changes in TBR_{max} and biomarker values were calculated for each subject and compared across groups using linear regressions and Wilcoxon rank-sum tests. The primary analyses were restricted to subjects who completed the trial (i.e., had primary outcome measures assessed at baseline and week 12). For TBR_{max}, additional multivariate linear regression models were fitted to assess sensitivity to potential imbalance of covariates (which may occur by chance in smaller randomized controlled trials), such as age, sex, major cardiovascular disease risk factors (serum glucose, systolic and diastolic blood pressure, tobacco use, family history, serum LDL, HDL, and total cholesterol, BMI, psoriatic arthritis, and PASI). For binary outcomes, the treatment group comparisons were assessed using logistic regression models.

The second primary analysis involved the changes in outcome measures from baseline to the end of the open label period and were restricted to subjects whose outcome measures were assessed at the end of study or at early termination. The mean changes and proportions were calculated along with their respective 95% confidence intervals (CIs).

Secondary analyses consist of pairwise comparisons during the placebo-controlled period and comparisons between baseline and end of study for clinical disease severity and patient-reported outcomes. Group-level summary measures of clinical disease severity and patient-reported outcomes were also plotted longitudinally along with their respective 95% CIs. Finally, a sensitivity analysis was conducted restricting the analysis to the period in which patients were taking ustekinumab, thus excluding the period patients were taking placebo (i.e., baseline to week 52 for those assigned ustekinumab, and week 12 to week 64 for those assigned placebo initially).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We are grateful to the patients who volunteered for this study and for the expertise of Suzette Baez Vanderbeek, MPH for her project management expertise.

Funding: This study was funded by a grant to the Trustees of the University of Pennsylvania from Janssen Pharmaceuticals (JMG). Dr. Gelfand received additional funding from NIAMS K24AR064310. Dr Takeshita is funded in part by K23 AR068433. Dr. Mehta received additional funding from NHLBI Intramural Research Program (HL006193-05)

Conflict of Interest

Dr. Gelfand served as a consultant for BMS, Boehringer Ingelheim, Janssen Biologics, Novartis Corp, UCB (DSMB), Sanofi, and Pfizer Inc., receiving honoraria; and receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Boehringer Ingelheim, Janssen, Novartis Corp, Celgene, Ortho Dermatologics, and Pfizer Inc.; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly, Ortho Dermatologics and Novartis. Dr. Gelfand is a co-patent holder of resiquimod for treatment of cutaneous T cell lymphoma. Dr. Gelfand is a Deputy Editor for the Journal of Investigative Dermatology receiving honoraria from the Society for Investigative Dermatology. Dr. Torigian is a co-founder of Quantitative Radiology Solutions LLC. Megan Noe receives a research grant via the Trustees of the University of Pennsylvania from Boehringer Ingelheim, and she is supported by a K23-AR073932 career development Award from the National Institute of Arthritis and Musculoskeletal and Skin Diseases. She has also received payments for work done as in independent contractor from UptoDate and Derm101. Dr. Takeshita receives a grant from NIAMS K23-AR068433 (to the Trustees of the University of Pennsylvania) and a research grant (to the Trustees of the University of Pennsylvania) from Pfizer Inc. and has received payment for continuing medical education work related to psoriasis that was supported indirectly by Eli Lilly and Novartis. Dr Mehta is a full time US government employee. Dr. Mehta has served as a consultant for Amgen, Eli Lilly, and Leo Pharma receiving grants/other payments; as a principal investigator and/or investigator for AbbVie, Celgene, Janssen Pharmaceuticals, Inc, and Novartis receiving grants and/or research funding; and as a principal investigator for the National Institute of Health receiving grants and/or research funding. All other authors declare no conflicts of interests in relation to the work presented in this manuscript.

Abbreviations:

BSA	body surface area
PASI	psoriasis area and severity index
PGA	physician global assessment
IPAQ MET	international physical activity questionnaire metabolic equivalent task
CRP	C-reactive protein

FDG-PET/CT	18F-2-fluorodeoxyglucose-positron emission tomography/ computed tomography
TBR	target-to-background ratio
SUV	standardized uptake value
HDL	high-density lipoprotein
hdl-c	high-density lipoprotein cholesterol
hdl-p	high-density lipoprotein particle number
hdl-s	high-density lipoprotein particle size
LDL	low-density lipoprotein
ldl-c	low-density lipoprotein cholesterol
ldl-p	low-density lipoprotein particle number
ldl-s	low-density lipoprotein particle size
IDL	intermediate-density lipoprotein
idl-p	intermediate-density lipoprotein particle number
VLDL	very low-density lipoprotein
vldl-p	very low-density lipoprotein particle number
l-vldl-p	large very low-density lipoprotein particle number
HOMA-IR	homeostasis model assessment of insulin resistance
ICAM-1	intercellular adhesion molecule-1
VCAM-1	vascular cell adhesion molecule
IFN-gamma	interferon-gamma
TNF-alpha	tumor necrosis factor-alpha
SAA	serum amyloid A
IL	interleukin
IL-2ra	interleukin-2 receptor alpha
MCP-1	monocyte chemoattractant protein-1

References:

(Interleukin-6 Receptor Mendelian Randomisation Analysis et al., 2012)Azfar RS, Gelfand JM. Psoriasis and metabolic disease: epidemiology and pathophysiology. Curr Opin Rheumatol 2008;20(4):416–22. [PubMed: 18525354]

Bissonnette R, Harel F, Krueger JG, Guertin MC, Chabot-Blanchet M, Gonzalez J, et al. TNF-alpha Antagonist and Vascular Inflammation in Patients with Psoriasis Vulgaris: A Randomized Placebo-Controlled Study. J Invest Dermatol 2017;137(8):1638–45. [PubMed: 28286061]

Bural GG, Torigian DA, Chamroonrat W, Alkhawaldeh K, Houseni M, El-Haddad G, et al. Quantitative assessment of the atherosclerotic burden of the aorta by combined FDG-PET and CT image analysis: a new concept. Nuclear medicine and biology 2006;33(8):1037–43. [PubMed: 17127178]

Bural GG, Torigian DA, Chamroonrat W, Houseni M, Chen W, Basu S, 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 2008;35(3):562–9. [PubMed: 17957367]

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 2009;36(1):144–51. [PubMed: 18982324]

Consortium TI-RMRAIRM. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. The Lancet 2012;379(9822):1214–24.

Dey AK, Joshi AA, Chaturvedi A, Lerman JB, Aberra TM, Rodante JA, et al. Association Between Skin and Aortic Vascular Inflammation in Patients With Psoriasis: A Case-Cohort Study Using Positron Emission Tomography/Computed Tomography. JAMA cardiology 2017;2(9):1013–8. [PubMed: 28564678]

Elmets CA, Leonardi CL, Davis DMR, Gelfand JM, Lichten J, Mehta NN, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol 2019;80(4):1073–113. [PubMed: 30772097]

Elnabawi YA, Dey AK, Goyal A, Groenendyk JW, Chung JH, Belur AD, et al. Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study. Cardiovascular research 2019;115(4):721–8. [PubMed: 30721933]

Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA 2006;296(14):1735–41. [PubMed: 17032986]

Gelfand JM, Shin DB, Mark E, Steadman J, Kianifard F, Sarkar R, et al. The VIP-S Trial: Study to Evaluate the Effect of Secukinumab Compared to Placebo on Aortic Vascular Inflammation in Subjects with Moderate to Severe Plaque Psoriasis (NCT02690701). American Academy of Dermatology Late Breaking Clinical Trials Research Washington DC 2019.

Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol 2007;143(12):1493–9. [PubMed: 18086997]

Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018:25709.

Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. J Allergy Clin Immunol 2017;140(3):645–53. [PubMed: 28887948]

Hjuler KF, Gormsen LC, Vendelbo MH, Egeberg A, Nielsen J, Iversen L. Increased global arterial and subcutaneous adipose tissue inflammation in patients with moderate-to-severe psoriasis. Br J Dermatol 2017;176(3):732–40. [PubMed: 27787888]

Interleukin-6 Receptor Mendelian Randomisation Analysis C, Swerdlow DI, Holmes MV, Kuchenbaecker KB, Engmann JE, Shah T, et al. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. Lancet 2012;379(9822):1214–24. [PubMed: 22421340]

Kaur S, Shafiq N, Dogra S, Mittal BR, Attri SV, Bahl A, et al. 18F-fluorodeoxyglucose positron emission tomography-based evaluation of systemic and vascular inflammation and assessment of the effect of systemic treatment on inflammation in patients with moderate-to-severe psoriasis: A randomized placebo-controlled pilot study. Indian J Dermatol Venereol Leprol 2018;84(6):660–6. [PubMed: 29893297]

Kim BS, Lee WK, Pak K, Han J, Kim GW, Kim HS, et al. Ustekinumab treatment is associated with decreased systemic and vascular inflammation in patients with moderate-to-severe psoriasis: Feasibility study using (18)F-fluorodeoxyglucose PET/CT. J Am Acad Dermatol 2018.

Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003–2004. J Am Acad Dermatol 2009;60(2):218–24. [PubMed: 19022533]

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 2008;49(8):1277–82. [PubMed: 18632820]

Mehta NN, Li R, Krishnamoorthy P, Yu Y, Farver W, Rodrigues A, et al. Abnormal lipoprotein particles and cholesterol efflux capacity in patients with psoriasis. Atherosclerosis 2012a;224(1): 218–21. [PubMed: 22858285]

Mehta NN, Shin DB, Joshi AA, Dey AK, Armstrong AW, Duffin KC, et al. Effect of 2 Psoriasis Treatments on Vascular Inflammation and Novel Inflammatory Cardiovascular Biomarkers: A Randomized Placebo-Controlled Trial. Circulation Cardiovascular imaging 2018;11(6):e007394. [PubMed: 29776990]

Mehta NN, Torigian DA, Gelfand JM, Saboury B, Alavi A. Quantification of atherosclerotic plaque activity and vascular inflammation using [18-F] fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). J Vis Exp 2012b;2(63):e3777.

Mehta NN, Yu Y, Saboury B, Foroughi N, Krishnamoorthy P, Raper A, 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 2011;147(9):1031–9. [PubMed: 21576552]

Menter A, Strober BE, Kaplan DH, Kivelevitch D, Prater EF, Stoff B, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol 2019;80(4):1029–72. [PubMed: 30772098]

Naik HB, Natarajan B, Stansky E, Ahlman MA, Teague H, Salahuddin T, 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;35(12): 2667–76. [PubMed: 26449753]

Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med 2009;361(5):496–509. [PubMed: 19641206]

Noe MH, Shin DB, Wan MT, Gelfand JM. Objective Measures of Psoriasis Severity Predict Mortality: A Prospective Population-Based Cohort Study. J Invest Dermatol 2018;138(1):228–30. [PubMed: 28843488]

Parisi R, Symmons DP, Griffiths CE, Ashcroft DM, Identification, Management of P, et al. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol 2013;133(2):377–85. [PubMed: 23014338]

Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 2017;377(12):1119–31. [PubMed: 28845751]

Sajja AP, Joshi AA, Teague HL, Dey AK, Mehta NN. Potential Immunological Links Between Psoriasis and Cardiovascular Disease. Front Immunol 2018;9(1234):1234. [PubMed: 29910818]

Salahuddin T, Natarajan B, Playford MP, Joshi AA, Teague H, Masmoudi Y, et al. Cholesterol efflux capacity in humans with psoriasis is inversely related to non-calcified burden of coronary atherosclerosis. Eur Heart J 2015;36(39):2662–5. [PubMed: 26188212]

Schmidt AM, Hori O, Chen JX, Li JF, Crandall J, Zhang J, et al. Advanced glycation endproducts interacting with their endothelial receptor induce expression of vascular cell adhesion molecule-1 (VCAM-1) in cultured human endothelial cells and in mice. A potential mechanism for the accelerated vasculopathy of diabetes. J Clin Invest 1995;96(3):1395–403. [PubMed: 7544803]

Tahara N, Kai H, Ishibashi M, Nakaura H, Kaida H, Baba K, et al. Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. J Am Coll Cardiol 2006;48(9):1825–31. [PubMed: 17084257]

Tawakol A, Fayad ZA, Mogg R, Alon A, Klimas MT, Dansky H, et al. Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter

fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study. J Am Coll Cardiol 2013;62(10):909–17. [PubMed: 23727083]

Wan MT, Shin DB, Hubbard RA, Noe MH, Mehta NN, Gelfand JM. Psoriasis and the risk of diabetes: A prospective population-based cohort study. J Am Acad Dermatol 2018;78(2):315–22 e1. [PubMed: 29128465]

Joshi AA, Lerman JB, Dey AK, Sajja AP, Belur AD, Elnabawi YA, et al. Association Between Aortic Vascular Inflammation and Coronary Artery Plaque Characteristics in Psoriasis. JAMA cardiology 2018;3(10):949–56 [PubMed: 30208407]

Takeshita J, Mohler ER, Krishnamoorthy P, Moore J, Rogers WT, Zhang L, et al. Endothelial cell-, platelet-, and monocyte/macrophage-derived microparticles are elevated in psoriasis beyond cardiometabolic risk factors. Journal of the American Heart Association 2014;3(1):e000507. [PubMed: 24584739]

Table 1.

Baseline Demographics and Clinical Characteristics.

	Ustekinumab	Placebo	Total
N	22	21	43
Age			
Mean (SD)	39.45(13.6)	45.33(12.76)	42.33(13.38)
Sex (%)			
Female	6 (27.27)	7 (33.33)	13 (30.23)
Male	16 (72.73)	14 (66.67)	30 (69.77)
Race (%)			
Caucasian	19 (86.36)	12 (57.14)	31 (72.09)
Black	2 (9.09)	5 (23.81)	7 (16.28)
Asian	1 (4.55)	2 (9.52)	3 (6.98)
Other	0 (0)	2 (9.52)	2 (4.65)
Ethnicity (%)			
Hispanic	2 (9.09)	2 (9.52)	4 (9.3)
Not Hispanic or Latino	19 (86.36)	19 (90.48)	38 (88.37)
Unknown/Missing	1 (4.55)	0 (0)	1 (2.33)
Body mass index (kg/m^2)			
Mean (SD)	33.24 (7.95)	33.32 (6.29)	33.28 (7.1)
Medical History (%)			
Coronary Artery	1 (4.55)	1 (4.76)	1 (4.65)
Disease			
Depression	2 (9.09)	2 (9.52)	4 (9.3)
Diabetes mellitus	0 (0)	1 (4.76)	1 (2.33)
Hyperlipidemia	5 (22.73)	2 (9.52)	7 (16.28)
Hypertension	2 (9.09)	6 (28.57)	8 (18.6)
Stroke	1 (4.55)	0 (0)	1 (2.33)
Statin Use	3 (13.64)	3 (14.29)	6 (13.95)
Baseline total BSA			
Mean (SD)	26.18 (17.51)	23.71 (15.58)	24.98 (16.45)
Median (p25, p75)	19.75 (14, 31)	19.5 (12, 31)	19.5 (12, 31)
Baseline PASI score			
Mean (SD)	20.03 (7.47)	19.82 (7.64)	19.93 (7.46)
Median (p25, p75)	18 (14.8, 23.2)	17 (13, 26.8)	17.8 (13.4, 23.4)
Baseline PGA			
Mean (SD)	3.5 (0.57)	3.38 (0.8)	3.44 (0.69)
Median (p25, p75)	3.5 (3.3, 4)	3.3 (3, 4)	3.3 (3, 4)
Psoriasis duration (Y)			

	Ustekinumab	**Placebo**	**Total**
N	22	17	39
Mean (SD)	16.45 (11.02)	20.29 (14.41)	18.13 (12.58)
Median (p25, p75)	15 (8, 23)	20 (7, 34)	17 (7, 27)
Treatment history, n (%)			
Biologics	10 (45.45)	9 (42.86)	19 (44.19)
Oral systemic	6 (27.27)	2 (9.52)	8 (18.6)
Phototherapy	10 (45.45)	9 (42.86)	19 (44.19)
Psoriatic arthritis present (%)			
Yes	1 (4.55)	6 (28.57)	7 (16.28)

Table 2.

Changes in Psoriasis Activity by Treatment Group During Trial Period

	Ustekinumab (n=22)	**Placebo (n=19)**	**Combined (n=39)**
Changes between	Baseline and Week 12		Baseline and EOS
PASI75 *	0.773 (0.546, 0.922)	0.105 (0.013, 0.331)	0.718 (0.551, 0.850)
PASI90 *	0.409 (0.207, 0.637)	0 (0, 0.177)	0.487 (0.24, 0.652)
PGA (clear/almost clear) *	0.636 (0.407, 0.828)	0.105 (0.013, 0.331)	0.462 (0.301, 0.628)
	Change compared with placebo (n=41)		
PASI75 **	−0.668 (<0.001) ***	-	
PASI90 **	−0.409 (0.002) ***	-	
PGA **	−0.531 (<0.001) ***	-	

* Proportion (95% CI) PASI: psoriasis area severity index score; PGA: physician global assessment

** Difference of proportions (*P* value)

*** Statistically significant findings

Table 3.

Changes in TBR_{max} by Treatment Group During Randomized Controlled Trial Period

	Ustekinumab (n=22)	**Placebo (n=19)**
Global change compared with baseline within group		
Mean difference *	−0.102 (0.041) **	0.144 (0.014) **
Mean % of change (95% CI) *	−6.58% (−13.64% to 0.47%); (0.066)	12.07% (3.26% to 20.88%);(0.010) **
Global change compared with placebo (n=41)		
Difference of differences ***	−0.246 (0.001) **	…
Difference of % change ***	−18.65% (−29.45% to −7.85%); (0.001) **	…

CI indicates confidence interval; and TBR, target-to-background ratio.

* One sample test (*P* value).

** Statistically significant findings.

*** Difference of differences (*P* value).

Results with NIH-read images (Primary Analysis).

Table 4.

Changes in TBR_{max} Open-Label Extension

	Mean (*P* Value[*])
Global change baseline compared with end of open-label extension (n=38)	
Difference	−0.015 (0.672)
% change (95% CI)	0.84% (−4.38% to 6.07%); (0.746)
Global change start of ustekinumab compared with end of open-label extension (n=38)	
Difference	−0.025 (0.433)
% change (95% CI)	−0.38% (−5.02% to 4.25%); (0.868)

CI indicates confidence interval; and TBR, target-to-background ratio.

[*] One sample test (*P* value).

Results with NIH-read images.

Table 5.

Change in Advanced Lipoprotein Characterization, Glucose Metabolism, and Inflammation

	Change [a] Ustekinumab vs. Placebo (Week 12) (n=40)	Change [b] End of study compared to Baseline (n=38)	Change [b] End of study compared to Start of Ustekinumab (n=38)
Inflammatory			
ICAM-1	−64.97 (−155.83, 25.89)	6.65 (−38.41, 51.72)	−27.68 (−81.21, 25.85)
VCAM-1	−80.89 (−142.55, −19.23) *	−1.99 (−30.58, 26.59)	−28.98 (−58.63, 0.67)
SAA	−7884.29 (−23634.67, 7866.10)	−3782.54 (−12035.72, 4470.64)	−3931.92 (−12167.24, 4303.41)
CRP	−3027.21 (−9465.95, 3411.53)	−1974.63 (−5336.30, 1387.04)	−2264.77 (−5579.82, 1050.28)
Ferritin	20.66 (−78.03, 119.34)	47.00 (−25.63, 119.63)	62.45 (−17.47, 142.37)
IFN-g	−0.07 (−5.22, 5.07)	−1.09 (−3.29, 1.11)	−1.13 (−3.26, 1.01)
MCP-1	−14.79 (−55.19, 25.61)	−7.24 (−30.47, 15.99)	−7.83 (−28.97, 13.32)
TNF-a	−0.90 (−2.27, 0.47)	−0.67 (−1.36, 0.02)	−1.02 (−1.89, −0.14) *
GlycA	−4.14 (−27.24, 18.96)	−8.35 (−25.40, 8.69)	−11.19 (−28.85, 6.46)
IL-1b	−0.52 (−1.56, 0.51)	−0.31 (−0.54, −0.08) *	−0.61 (−1.01, −0.21) **
IL-2ra	−70.76 (−138.42, −3.11) *	71.72 (−197.50, 340.93)	71.27 (−198.21, 340.76)
IL-12/23	191.49 (98.18, 284.81) ***	171.21 (130.08, 212.34) ***	168.40 (127.79, 209.01) ***
IL-17a	−2.63 (−4.62, −0.64)	−1.15 (−1.79, −0.51) ***	−1.13 (−1.72, −0.55) ***
IL-18	−155.31 (−1548.66, 1238.04)	−407.43 (−773.57, −41.29) *	−644.75 (−1170.13, −119.37) *
IL-6	−0.47 (−1.25, 0.32)	−0.38 (−0.80, 0.03)	−0.39 (−0.79, −0.00) *
IL-8	−16.87 (−48.48, 14.75)	−2.23 (−5.69, 1.22)	−11.95 (−28.91, 5.02)
Lipid			
Triglyceride	2.06 (−24.09, 28.20)	10.55 (−6.18, 27.29)	12.21 (−3.43, 27.85)
Total cholesterol	19.20 (4.21, 34.20)	−0.79 (−9.19, 7.61)	2.13 (−5.52, 9.78)
Hdl-cholesterol	3.66 (−0.30, 7.62)	1.92 (−0.95, 4.80)	2.39 (−0.42, 5.21)
Hdl-particle number	1.25 (−0.83, 3.34)	0.91 (−0.56, 2.37)	1.38 (0.00, 2.76) *
Hdl-particle size	−0.11 (−0.34, 0.11)	0.17 (0.04, 0.31) *	0.09 (−0.06, 0.24)
Large-hdl-particle number	0.12 (−1.09, 1.33)	0.51 (−0.22, 1.24)	0.33 (−0.41, 1.06)
Small-hdl-particle number	2.49 (−0.94, 5.93)	0.21 (−1.49, 1.91)	1.53 (−0.15, 3.21)
Medium-hdl-particle number	−1.37 (−4.79, 2.05)	0.17 (−1.80, 2.13)	−0.47 (−2.11, 1.17)
Large medium-hdl-particle number	−1.12 (−4.95, 2.71)	0.77 (−1.25, 2.80)	−0.03 (−1.71, 1.64)
Ldl-cholesterol	21.37 (7.86, 34.87) **	−2.92 (−11.17, 5.33)	0.97 (−6.40, 8.34)
Ldl-particle number	230.77 (89.47, 372.08) **	−31.89 (−116.40, 52.61)	15.24 (−60.81, 91.28)
Ldl-particle size	0.04 (−0.30, 0.38)	0.03 (−0.19, 0.24)	−0.03 (−0.22, 0.17)
Small-ldl-particle number	46.96 (−66.65, 160.57)	4.68 (−63.91, 73.28)	6.14 (−60.97, 73.26)
Large-ldl-particle number	7.01 (−91.80, 105.81)	−24.74 (−90.78, 41.30)	−30.37 (−95.86, 35.12)

	Change [a] Ustekinumab vs. Placebo (Week 12) (n=40)	**Change [b] End of study compared to Baseline (n=38)**	**Change [b] End of study compared to Start of Ustekinumab (n=38)**
Very large-ldl-particle number	194.69 (60.61, 328.77) **	−29.16 (−106.17, 47.85)	11.63 (−58.44, 81.70)
Vldl-particle size	3.14 (−2.55, 8.83)	1.50 (−1.36, 4.36)	1.23 (−1.58, 4.05)
Vldl-particle number	−16.74 (−30.03, −3.45) *	−0.11 (−6.93, 6.71)	−2.44 (−9.22, 4.33)
Vldl-triglycerides	−9.21 (−33.03, 14.60)	11.14 (−3.72, 25.99)	10.10 (−3.31, 23.52)
Small-vldl-particle number	−15.71 (−27.39, −4.03) **	−0.50 (−4.69, 3.70)	−4.53 (−10.50, 1.43)
Medium-vldl-particle number	0.34 (−8.91, 9.59)	−1.86 (−6.77, 3.06)	0.43 (−4.96, 5.81)
Large medium-vldl-particle number	0.08 (−10.37, 10.53)	0.38 (−4.86, 5.63)	2.25 (−3.29, 7.78)
Large-vldl-particle number	−0.28 (−2.91, 2.36)	2.30 (0.12, 4.48) *	2.06 (0.10, 4.03) *
Idl-particle number	152.65 (64.07, 241.23) **	−2.97 (−55.04, 49.09)	41.66 (−5.12, 88.44)
Cholesterol Efflux Capacity	0.06 (−0.03, 0.14)	0.04 (−0.03, 0.10)	0.02 (−0.05, 0.08)
Apolipoprotein-B	0.15 (−0.11, 0.41)	0.10 (−0.02, 0.23)	0.13 (−0.01, 0.28)
Fetuin-A	48.43 (−76.31, 173.16)	−49.56 (−105.97, 6.85)	−17.19 (−67.52, 33.15)
Metabolic			
Adiponectin	−0.28 (−2.52, 1.97)	0.38 (−0.65, 1.40)	0.16 (−0.78, 1.10)
Leptin	3320.58 (−3592.51, 10233.67)	6926.25 (2351.43, 11501.07) **	4524.61 (469.82, 8579.41) *
Insulin	−68.95 (−335.97, 198.08)	−7.96 (−182.18, 166.26)	−53.02 (−224.40, 118.37)
Glucose [c]	4.20 (−6.28, 14.68)	3.41 (−3.54, 10.36)	4.08 (−2.37, 10.53)
HOMA-IR	−0.49 (−3.56, 2.59)	−0.07 (−1.88, 1.73)	−0.31 (−2.10, 1.48)

[a] Difference of difference (95% CI)

[b] Difference (95% CI)

[c] For glucose, n of 41, 39, and 39 for Week 12, Baseline to End of Study, and Start of Ustekinumab to End of Study analyses, respectively

* p<0.05

** p<0.01

*** p<0.001

ICAM-1: intercellular adhesion molecule-1, VCAM-1: vascular cell adhesion molecule-1, SAA: serum amyloid A, CRP: C-reactive protein, IFN-g: interferon-gamma, MCP-1: monocyte chemoattractant protein-1, TNF-a, tumor necrosis factor-alpha, IL-interleukin, HDL: high-density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein, IDL: intermediate-density lipoprotein, HOMA-IR: homeostasis model assessment of insulin resistance.