A Phase IV, Randomized, Double-Blind, Placebo-Controlled Crossover Study of the Effects of Ustekinumab on Vascular Inflammation in Psoriasis (the VIP-U Trial)

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Psoriasis is a T helper type 17 autoimmune disease associated with an increased risk cardiovascular events and mortality. Ustekinumab, an antibody to p40, blocks cytokines IL-12 and IL-23, and is a highly effective and safe treatment for psoriasis. We conducted a randomized double-blinded placebo-controlled trial to determine the effect of ustekinumab on aortic vascular inflammation (AVI) measured by imaging, and key biomarkers of inflammation, lipid, and glucose metabolism in the blood of patients with moderate-to-severe psoriasis. A total of 43 patients were randomized, and at week 12, ustekinumab-treated patients had a −18.65% (95% confidence interval = −29.45% to −7.85%) reduction in AVI, a reduction in inflammatory biomarkers, and an increase in apolipoprotein B lipoproteins compared with placebo. At week 12, placebo patients were crossed over such that all patients received ustekinumab for 52 weeks. At the end of 52 weeks of ustekinumab treatment, there was no change in AVI compared with baseline, inflammatory markers were reduced, and there were increases in selected measures of lipids and leptin. These results show that blockade of IL-12 and/or IL-23 may transiently reduce AVI, with more durable reduction in inflammatory cytokines associated with cardiovascular disease.

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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 the 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, current 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 and Stone., 2019; Grundy et al., 2019).

The biologic mechanisms linking psoriasis to adverse cardiometabolic outcomes are 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 (e.g., increases in IL-1, IL-6, tumor necrosis factor [TNF], C-reactive protein) 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 showed that psoriasis and its severity are associated with increased aortic vascular inflammation (AVI), 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).

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Abbreviations: AVI, aortic vascular inflammation; CI, confidence interval; FDG-PET/CT, 18F-2-fluorodeoxyglucose-positron emission tomography/computed tomography; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PASI, psoriasis area and severity index; SD, standard deviation; SUV, standardized uptake value; TBR, target-to-background ratio; TNF, tumor necrosis fator; VLDL, very low-density lipoprotein

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Table 1. Baseline Demographics and Clinical Characteristics

Characteristics	Ustekinumab	Placebo	Total
N[1]	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)
BMI (kg/m^2)			
Mean (SD)	33.24 (7.95)	33.32 (6.29)	33.28 (7.1)
Medical History			
Coronary Artery Disease	1 (4.55)	1 (4.76)	1 (4.65)
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, years			
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			
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)

Abbreviations: BMI, body mass index; BSA, body surface area; PASI, psoriasis area and severity index; PGA, physician global assessment; SD, standard deviation.
[1]Values are n (%) unless indicated otherwise.

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 AVI. 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 (e.g., statins) known to lower the risk of major cardiovascular events (Lee et al., 2008). These characteristics make AVI an attractive surrogate for early stage clinical trials of treatments for the prevention of cardiovascular 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 AVI and blood-based markers of inflammation, lipid, and glucose metabolism compared with placebo in patients with moderate-to-severe psoriasis.

RESULTS

A total of 63 patients were assessed for eligibility, of which 43 were randomized, 22 to ustekinumab and 21 to placebo (Supplementary Figure S1). All patients randomized to ustekinumab completed the study through week 12, whereas 19 (86%) initially assigned to placebo completed until week 12. A total of 34 (79%) patients completed the study throughout the open-label extension period. Recruitment started on August 14, 2014, and the last patient visit occurred on September 10, 2018. Patients were an average age of 42 years (standard deviation [SD] 13.38), 70% male, predominantly white (72%), had an average body mass index of 33, and an average body surface area 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, patients treated with ustekinumab had 67%, 41%, and 53% greater differences in achieving PASI75, PASI90, and physician global assessment clear/almost clear responses, respectively, compared with placebo ($P < 0.01$ for all). At the end of study, PASI75, PASI90, and physician global assessment clear/almost clear response rates were 72% (95% confidence interval [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 ($P = 0.46$) between placebo and ustekinumab. At the end of study, compared with baseline for both groups combined, there was a reduction in MEDFICTS score of 12.325 ($P = 0.001$), suggesting improved eating habits (e.g., meats, eggs, dairy, fried foods, baked goods, convenience foods, table fats, and snacks), and no change in international physical activity questionnaire metabolic equivalent task ($P = 0.221$).

Patients assigned to ustekinumab had a −6.58% (95% CI = −13.64% to 0.47%) reduction in AVI at week 12 compared with baseline, whereas patients assigned to placebo had a 12.07% (95% CI = 3.26% to 20.88%) increase in AVI during the same time period (Table 3). Compared with changes in the placebo group, patients treated with ustekinumab experienced a −18.65% (95% CI = −29.45% to −7.85%) reduction in AVI at week 12. The findings were

Table 2. Changes in Psoriasis Activity by Treatment Group during Trial Period

Changes	Ustekinumab (n = 22)	Placebo (n = 19)	Combined (n = 39)
Changes between	Baseline and Week 12		Baseline and EOS
PASI75[1]	0.773 (0.546, 0.922)	0.105 (0.013, 0.331)	0.718 (0.551, 0.850)
PASI90[1]	0.409 (0.207, 0.637)	0 (0, 0.177)	0.487 (0.24, 0.652)
PGA (clear/almost clear)[1]	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[2]	−0.668 (<0.001)[3]	—	—
PASI90[2]	−0.409 (0.002)[3]	—	—
PGA[2]	−0.531 (<0.001)[3]	—	—

Abbreviations: CI, confidence interval; EOS, end of study; PASI, psoriasis area severity index score; PGA, physician global assessment.
[1]Proportion (95% CI).
[2]Difference of proportions (*P*-value).
[3]Statistically significant findings.

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 AVI compared with baseline (percent change 0.84%, 95% CI = −4.38% to 6.07%; Table 4). Similarly, there was no change in AVI (percent change −0.38%, 95% CI = −5.02% to 4.25%) during the 52-week period of ustekinumab treatment (i.e., week 52 compared with baseline for those randomized to ustekinumab, and week 12 to week 64 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 VCAM-1, IL-2 receptor alpha, and IL-17a, and an increase in IL-12 and IL-23; a small, but statistically significant increase in total cholesterol mostly driven by apolipoprotein B lipoproteins (e.g., low-density lipoprotein [LDL] cholesterol, LDL particle number, very low-density lipoprotein [VLDL] particle number, and intermediate-density lipoprotein particle number), with a small reduction in VLDL particle number and small VLDL particle number. There were no changes in high-density lipoprotein (HDL) particle size and number, 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 and IL-23 compared with baseline; and a small, statistically significant increase in HDL particle size, large VLDL particle number, and leptin. During the 52-week period of ustekinumab treatment (i.e., week 52 compared with 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-α, IL-1b, IL-17a, IL-18, and IL-6; an increase in IL-12 and IL-23; and a statistically significant increase in HDL particle number, large VLDL particle number, and leptin.

Safety data are presented in Supplementary Tables S1 and S2, 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 seven adverse events in those treated with ustekinumab and five adverse events in those treated with placebo (none of which were serious). During the open-label period, there were 38 adverse events, four of which were serious. All serious adverse events occurred in those initially randomized to placebo, occurred after crossover to ustekinumab, and included one case each of endometritis, hypotension, stroke (thromboembolic), and vasovagal reaction. The stroke occurred in a male subject in his 60s with a history of hypertension and coronary artery

Table 3. Changes in TBR_{max} by Treatment Group during Randomized Controlled Trial Period

Changes	Ustekinumab (n = 22)	Placebo (n = 19)
Global change compared with baseline within group		
Mean difference[1]	−0.102 (0.041)[2]	0.144 (0.014)[2]
Mean % of change (95% CI)[1]	−6.58% (−13.64% to 0.47%); (0.066)	12.07% (3.26% to 20.88%); (0.010)[2]
Global change compared with placebo (n = 41)		
Difference of differences[3]	−0.246 (0.001)[2]	—
Difference of % change[3]	−18.65% (−29.45% to −7.85%); (0.001)[2]	—

Results with NIH-read images (primary analysis).
Abbreviations: CI, confidence interval; TBR_{max}, maximum target-to-background ratio.
[1]One sample test (*P*-value).
[2]Statistically significant findings.
[3]Difference of differences (*P*-value).

Table 4. Changes in TBR_{max} Open-Label Extension

Changes	Mean (*P*-Value[1])
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)

Results with NIH-read images.

Abbreviations: CI, confidence interval; TBR_{max}, maximum target-to-background ratio.

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

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 and -IL-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 AVI in patients treated with ustekinumab compared with placebo (Tawakol et al., 2013). This finding is proof of principle that antibody-based therapies can causally decrease AVI, and advances observations from prior uncontrolled studies, which showed an improvement in AVI in Korean patients with psoriasis treated with ustekinumab (Kim et al., 2019). Moreover, this finding appears specific to the IL-12 and IL-23 pathway, as similar trials by our group and others have shown a neutral effect of biologics that 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 AVI observed at week 52 (for those initially randomized to ustekinumab), and no evidence of change in AVI when patients were crossed over to ustekinumab at week 12 and imaged again 52 weeks later. These findings combined suggest that the improvement in AVI 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 (20 mg/dl on average) and LDL particle number (200 on average), but these changes were transient and were not sustained at 52 weeks. Treatment with IL-12 and IL-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 and IL-23 levels after treatment with ustekinumab. Likely, this reflects detection of the p40 subunit of the monoclonal antibody by ELISA (sandwich protein format), and reflects receipt of active drug. At the end of the study, there was a statistically significant decrease in TNF-α, 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-α 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, anti-IL-12 and -IL-23 therapies) was recently shown to be associated with a reduction in coronary artery plaque burden after one-year 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 because of variability inherent to measurement of AVI. Despite the well-established methods used for quantification, PET imaging itself has limitations, which include the selection of background tissue for correction (e.g., blood pool) and which aortic segments were analyzed (e.g., arch vs. entire aorta). Moreover, AVI is not a direct measure of coronary disease, but it 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). Although, our study provides important biologic insights into the effects of targeting IL-12 and IL-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 affected the statistical findings. Furthermore, we did not evaluate other pathways that might be important links between psoriasis and cardiovascular events, including platelet function and immune-cell populations by flow (Takeshita et al., 2014).

In conclusion, we showed that IL-12 and IL-23 may transiently reduce AVI (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.

Table 5. Change in Advanced Lipoprotein Characterization, Glucose Metabolism, and Inflammation

	Change[1] Ustekinumab versus Placebo (Week 12) (n = 40)	Change[2] EOS compared with baseline (n = 38)	Change[2] EOS compared with 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)[4]	−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-γ	−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-α	−0.90 (−2.27, 0.47)	−0.67 (−1.36, 0.02)	−1.02 (−1.89, −0.14)[4]
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)[4]	−0.61 (−1.01, −0.21)[5]
IL-2ra	−70.76 (−138.42, −3.11)[4]	71.72 (−197.50, 340.93)	71.27 (−198.21, 340.76)
IL-12/23	191.49 (98.18, 284.81)[6]	171.21 (130.08, 212.34)[6]	168.40 (127.79, 209.01)[6]
IL-17a	−2.63 (−4.62, −0.64)[4]	−1.15 (−1.79, −0.51)[6]	−1.13 (−1.72, −0.55)[6]
IL-18	−155.31 (−1548.66, 1238.04)	−407.43 (−773.57, −41.29)[4]	−644.75 (−1170.13, −119.37)[4]
IL-6	−0.47 (−1.25, 0.32)	−0.38 (−0.80, 0.03)	−0.39 (−0.79, −0.00)[4]
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)[4]	−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-p	1.25 (−0.83, 3.34)	0.91 (−0.56, 2.37)	1.38 (0.00, 2.76)[4]
HDL-s	−0.11 (−0.34, 0.11)	0.17 (0.04, 0.31)[4]	0.09 (−0.06, 0.24)
Large-HDL-p	0.12 (−1.09, 1.33)	0.51 (−0.22, 1.24)	0.33 (−0.41, 1.06)
Small-HDL-p	2.49 (−0.94, 5.93)	0.21 (−1.49, 1.91)	1.53 (−0.15, 3.21)
Medium-HDL-p	−1.37 (−4.79, 2.05)	0.17 (−1.80, 2.13)	−0.47 (−2.11, 1.17)
Large medium-HDL-p	−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)[5]	−2.92 (−11.17, 5.33)	0.97 (−6.40, 8.34)
LDL-p	230.77 (89.47, 372.08)[5]	−31.89 (−116.40, 52.61)	15.24 (−60.81, 91.28)
LDL-s	0.04 (−0.30, 0.38)	0.03 (−0.19, 0.24)	−0.03 (−0.22, 0.17)
Small-LDL-p	46.96 (−66.65, 160.57)	4.68 (−63.91, 73.28)	6.14 (−60.97, 73.26)
Large-LDL-p	7.01 (−91.80, 105.81)	−24.74 (−90.78, 41.30)	−30.37 (−95.86, 35.12)
Very large-LDL-p	194.69 (60.61, 328.77)[5]	−29.16 (−106.17, 47.85)	11.63 (−58.44, 81.70)
VLDL-s	3.14 (−2.55, 8.83)	1.50 (−1.36, 4.36)	1.23 (−1.58, 4.05)
VLDL-p	−16.74 (−30.03, −3.45)[4]	−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-p	−15.71 (−27.39, −4.03)[5]	−0.50 (−4.69, 3.70)	−4.53 (−10.50, 1.43)
Medium-VLDL-p	0.34 (−8.91, 9.59)	−1.86 (−6.77, 3.06)	0.43 (−4.96, 5.81)
Large medium-VLDL-p	0.08 (−10.37, 10.53)	0.38 (−4.86, 5.63)	2.25 (−3.29, 7.78)
Large-VLDL-p	−0.28 (−2.91, 2.36)	2.30 (0.12, 4.48)[4]	2.06 (0.10, 4.03)[4]
IDL-particle number	152.65 (64.07, 241.23)[5]	−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)

(*continued*)

MATERIALS AND METHODS

Trial design

The study was a randomized, double-blind, placebo-controlled trial designed to enroll 42 patients with allocation ratio of 1:1 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 (Supplementary Figure S2). The study was registered on July 10, 2014, at www.clinicaltrials.gov (NCT02187172).

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

Table 5. Continued

	Change[1] Ustekinumab versus Placebo (Week 12) (n = 40)	Change[2] EOS compared with baseline (n = 38)	Change[2] EOS compared with start of Ustekinumab (n = 38)
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)[5]	4524.61 (469.82, 8579.41)[4]
Insulin	−68.95 (−335.97, 198.08)	−7.96 (−182.18, 166.26)	−53.02 (−224.40, 118.37)
Glucose[3]	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)

Abbreviations: CI, confidence interval; CRP, C-reactive protein; EOS, end of study; HDL, high-density lipoprotein; HDL-p, HDL particle number; HDL-s, HDL particle size; HOMA-IR, homeostasis model assessment of insulin resistance; ICAM-1, intercellular adhesion molecule-1; IDL, intermediate-density lipoprotein; IFN-γ, interferon-γ; IL-2ra, interleukin-2 receptor alpha; LDL, low-density lipoprotein; LDL-p, LDL particle number; LDL-s, LDL particle size; MCP-1, monocyte chemoattractant protein-1; SAA, serum amyloid A; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; VLDL, very low-density lipoprotein; VLDL-p, VLDL particle number; VLDL-s, VLDL particle size.
[1]Difference of difference (95% CI).
[2]Difference (95% CI).
[3]For glucose, n of 41, 39, and 39 for week 12, baseline to EOS, and start of ustekinumab to EOS analyses, respectively.
[4]$P < 0.05$.
[5]$P < 0.01$.
[6]$P < 0.001$.

psoriasis skin disease severity was defined as body surface area ≥10% and PASI 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 and/or IL-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 5 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 count $<2.5 \times 10^9$/l or $>15 \times 10^9$/l; platelet count $<100 \times 10^9$/l; serum aspartate transaminase or alanine transaminase >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 (<100 kg, 45 mg; >100 kg, 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) after overnight fast. Serum glucose levels were checked to ensure a glucose level <200 mg/dl before FDG administration. Standard bed positions of 3 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, WA), 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 using an 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 the following two measures of metabolic activity: mean standardized uptake value (SUV_{mean}) and maximum SUV (SUV_{max}); these were obtained in the entire aorta from the aortic outflow tract to the abdominal aorta. Moreover, regions of interest were also placed on six 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 the end of study (repeating baseline and week 12) 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 C-reactive protein, TNF-α, IL-6, IL-2 receptor alpha, IL-18, IL-17a, and VCAM-1 were measured using multiplex ELISA technology (MSD, Rockville, MD). Lipid particle size and number were assessed using nuclear magnetic resonance spectroscopy (LipoScience, Morrisville, NC), 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 ELISA (MSD). Apolipoproteins were measured using turbidmetry.

Secondary outcomes. Secondary endpoints included change in physician reported measures of psoriasis activity (PASI and physician global assessment), adverse events, and change in patient-reported dietary and physical activity assessments (e.g., MEDFICTS and international physical activity questionnaire metabolic equivalent task) 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 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 SD of the change in SUV is approximately 0.11. Using a two-sided test with significance level of $\alpha = 0.05$, a total of 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 four and eight), using a computerized system at the Investigational Drug Services, 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 analysis

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. The 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, and major cardiovascular disease risk factors (serum glucose, systolic and diastolic blood pressure, tobacco use, family history, serum LDL, HDL, total cholesterol, body mass index, 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 was 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% 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).

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 months and ending 36 months after 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.

ETHICS STATEMENTS

Study approval was obtained from the Institutional Review Board 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 provided written informed consent.

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CONFLICT OF INTEREST

Outside of the submitted work, JMG served and received honoraria as a consultant for BMS, Boehringer Ingelheim, Janssen Biologics, Novartis Corp, UCB (DSMB), Sanofi, and Pfizer Inc.; and received 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 Eli Lilly, Ortho Dermatologics, and Novartis. JMG is a co-patent holder of resiquimod for treatment of cutaneous T-cell lymphoma, and is a Deputy Editor for the Journal of Investigative Dermatology receiving honoraria from the Society for Investigative Dermatology. DAT is a cofounder of Quantitative Radiology Solutions LLC. MHN 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. MHN has also received payments for work done as in independent contractor from UptoDate and Derm101. JT receives a grant from NIAMS K23-AR068433 and a research grant (both 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. NNM is a full time US government employee. NNM has served as a consultant for Amgen, Eli Lilly, and Leo Pharma receiving grants and/or 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 the other authors state no conflict of interest

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Disclaimer

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.

AUTHOR CONTRIBUTIONS

Conceptualization: JMG, AA, NNM; Data Curation: DBS, TW, AKD, MPP; Formal Analysis: JMG, DBS, NNM; Funding Acquisition: JMG, NNM; Investigation: JMG, DAT, MP, JT, MHN, AKD, MPP, NNM; Methodology: JMG, DBS, AA, DAT, TW, NNM; Project Administration: JMG, AA, TW, MP, NNM; Resources: JMG, AA, NNM; Software: DBS, TW; Supervision: JMG, AA, DAT, TW, MP, JT, MHN, NNM; Validation: DBS, AA, AKD, MPP; Visualization: DBS; Writing - Original Draft Preparation: JMG; Writing - Review and Editing: DBS, AA, DAT, TW, MP, JT, MHN, MPP, AKD, NNM.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2019.07.679.

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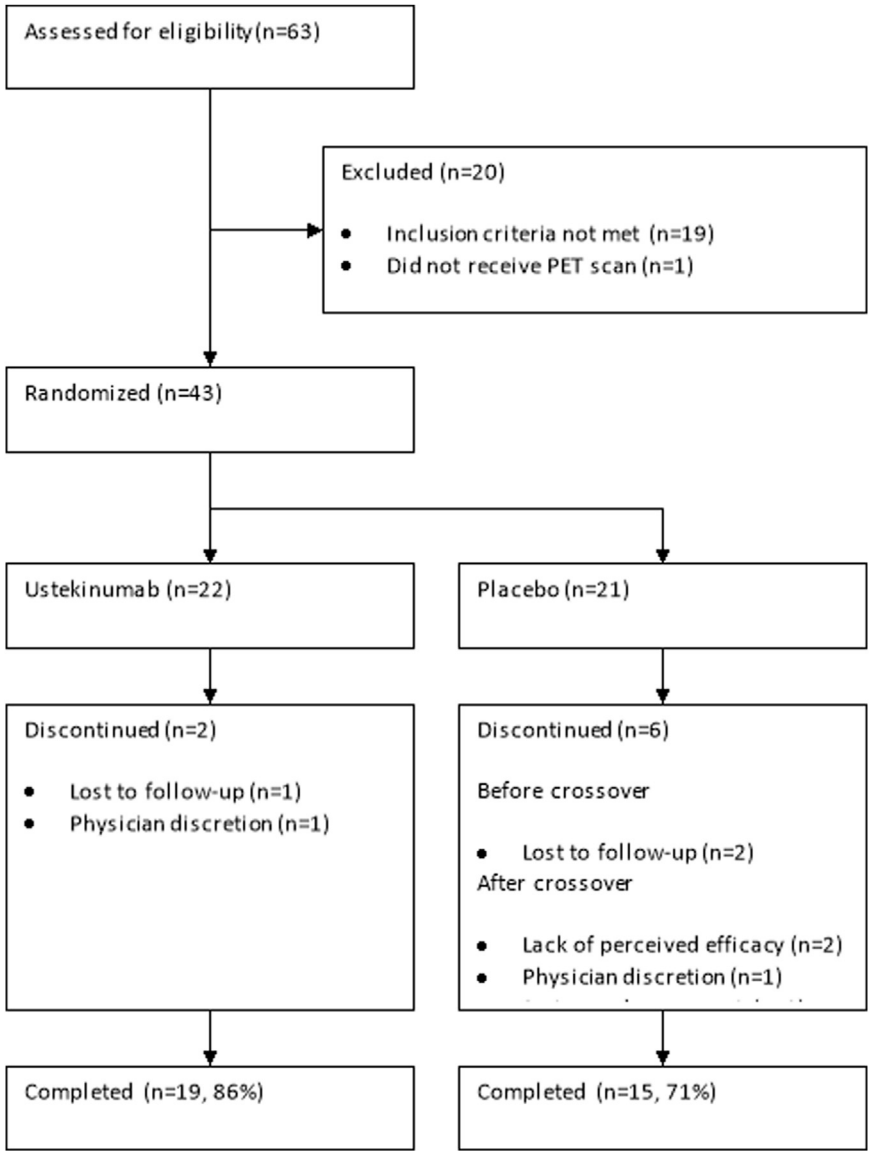
SUPPLEMENTARY MATERIALS

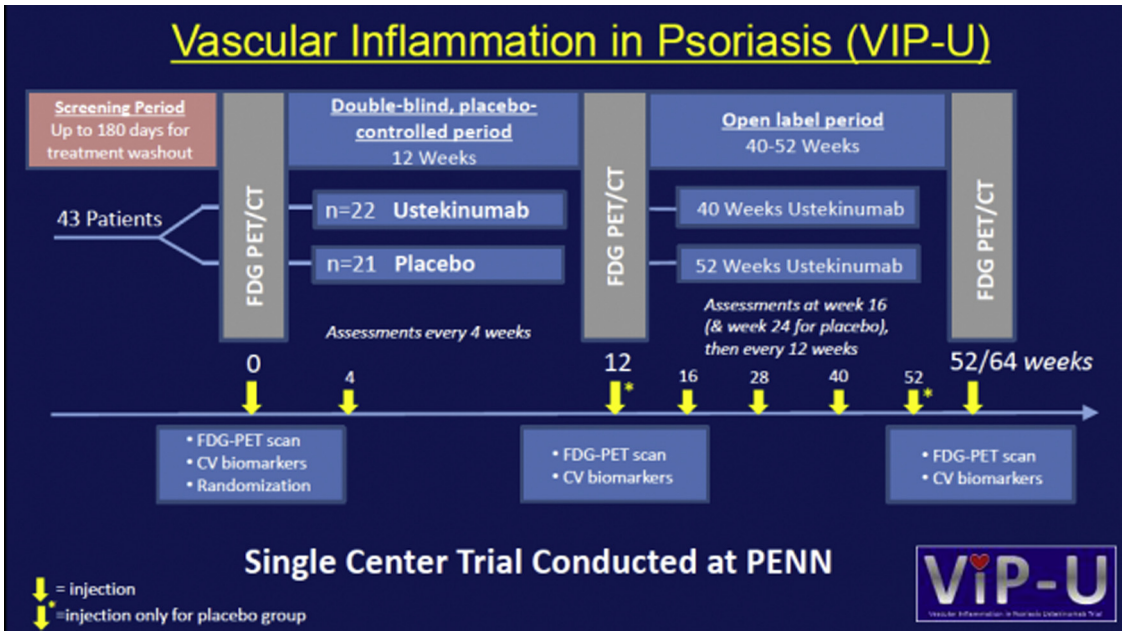
There were no statistically significant or clinically important differences in MEDFICTS and IPAQ at baseline between ustekinumab and placebo groups:

Measures	n	Coef	*P*-Value	95% CI	
Difference in baseline IPAQ MET	39	1619.80	0.2051	−924.77	4164.37
Difference in baseline MEDFICTS	43	−0.39	0.9626	−17.26	16.47

Abbreviations: Coef, coefficient; CI, confidence interval; IPAQ MET, international physical activity questionnaire metabolic equivalent task.

Supplementary Figure S1. Patient recruitment scheme for the study. PET, positron emission tomography.





Supplementary Figure S2. Study schematic. CV, cardiovascular; FDG-PET/CT, 18F-2-fluorodeoxyglucose-positron emission tomography/computed tomography.

Supplementary Table S1. Non-Serious Adverse Events during Trial Period

Adverse Events	Ustekinumab	Placebo	Total
Common cold	3 (13.64)	0	3 (6.98)
External ear pain[1]	0	1 (4.76)	1 (2.33)
Fracture[1]	1 (4.55)	0	1 (2.33)
Pain	0	1 (4.76)	1 (2.33)
Skin and subcutaneous tissue disorders[1]	1 (4.55)	0	1 (2.33)
Upper respiratory infection	1 (4.55)	3 (14.29)	4 (9.30)
Urinary tract infection[1]	1 (4.55)	0	1 (2.33)

[1]Total adverse events greater than 5% throughout the trial.

Supplementary Table S2. Non-Serious Adverse Events during Open-Label Extension Period

Adverse Events	Ustekinumab	Placebo Crossover to Ustekinumab	Total
Allergies to foods, food additives, drugs	0	2 (9.52)	2 (4.65)
Anxiety	2 (9.09)	0	2 (4.65)
Back pain	2 (9.09)	9	2 (4.65)
Common cold	3 (13.64)	2 (9.52)	5 (11.63)
Dizziness	2 (9.09)	0	2 (4.65)
External ear pain[1]	0	1 (4.76)	1 (2.33)
Fracture[1]	1 (4.55)	0	1 (2.33)
Pain[1]	0	1 (4.76)	1 (2.33)
Skin and subcutaneous tissue disorders	1 (4.55)	1 (4.76)	2 (4.65)
Upper respiratory infection	10 (45.45)	4 (19.05)	14 (32.56)
Urinary tract infection	2 (9.09)	0	2 (4.65)

[1]Total adverse events greater than 5% throughout the trial.