A Randomized Placebo-Controlled Trial of Secukinumab on Aortic Vascular Inflammation in Moderate-to-Severe Plaque Psoriasis (VIP-S)

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Psoriasis, a chronic immune-mediated disease, is associated with an increased risk of cardiovascular events and mortality. Secukinumab selectively neutralizes IL-17A and has reported high efficacy with a favorable safety profile in various psoriatic disease manifestations. Subsequent to the 12-week randomized, placebo-controlled, double-blind treatment period, patients with moderate-to-severe psoriasis received secukinumab for 40 weeks. Vascular inflammation using ^{18}F-2-fluorodeoxyglucose–positron emission tomography/computed tomography imaging and blood-based cardiometabolic was assessed at week 0, 12, and 52. The difference in change in aortic inflammation from baseline to week 12 for secukinumab (n = 46) versus placebo (n = 45) was −0.053 (95% confidence interval = −0.169 to 0.064; P = 0.37). Small increases in total cholesterol, low-density lipoprotein, and low-density lipoprotein particles, but no changes in markers of inflammation, adiposity, insulin resistance, or predictors of diabetes, were observed with secukinumab treatment compared with placebo. At week 52, reductions in TNF-α (P = 0.0063) and ferritin (P = 0.0354), and an increase in fetuin-A (P = 0.0024), were observed with secukinumab treatment compared with baseline. No significant changes in aortic inflammation or markers of advanced lipoprotein characterization, adiposity, or insulin resistance were observed with secukinumab treatment compared with baseline. Secukinumab exhibited a neutral impact on aortic vascular inflammation and biomarkers of cardiometabolic disease after 52 weeks of treatment.

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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 inflammatory pathways that are upregulated in psoriasis are also important factors in the development of cardiometabolic diseases (Hawkes et al., 2017; Nestle et al., 2009), including dyslipidemia, insulin resistance, major adverse cardiovascular (CV) events, and mortality (Gelfand et al., 2007, 2006; Noe et al., 2018; Wan et al., 2018). Recognizing the clinical importance of CV risk in inflammatory diseases, recent CV guidelines now define psoriasis as a risk-enhancing condition warranting early initiation of therapy (e.g., statins) (Elmets et al., 2019; Grundy et al., 2018). Moreover, the presence of CV risk factors and disease is often an important factor when selecting psoriasis treatment (Kaushik and Lebwohl, 2019). The biologic mechanisms linking psoriasis to adverse cardiometabolic outcomes are complex and incompletely understood, given the multiple pathways involved in atherosclerotic disease–related CV events (Sajja et al., 2018). In recent years, psoriasis has been increasingly recognized as a disease driven by IL-23/IL-17 on the basis of response to treatments targeting these cytokines, including IL-17A (Menter et al., 2019), the IL-17 receptor (Lebwohl et al., 2015; Menter et al., 2019; Papp et al., 2012), and IL-23 (Blauvelt et al., 2017; Reich et al., 2019). The role that IL-17 plays in the pathogenesis of CV disease (CVD) is controversial (Ait-Oufella et al., 2019). Mouse models suggest both pro- and anti-atherosclerotic effects of IL-17. In the *Apoe*$^{-/-}$ mouse model, administration of IL-17A–neutralizing antibodies resulted in attenuation of aortic root lesions (Erbel et al.,

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Abbreviations: AE, adverse event; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; CVD, cardiovascular disease; CV, cardiovascular; ^{18}F-FDG, ^{18}F-2-fluorodeoxyglucose; IGA mod 2011, Investigator's Global Assessment modified 2011; PET, positron emission tomography; TBR, target-to-blood pool ratio

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2009), whereas opposite effects were observed in *Ldlr*$^{-/-}$ mice (Danzaki et al., 2012; Erbel et al., 2009; Ge et al., 2013; Smith et al., 2010; van Es et al., 2009). In humans, higher IL-17 expression has been associated with stability of advanced carotid artery plaques (Gisterå et al., 2013). Furthermore, in patients with acute coronary syndrome, those with higher IL-17 levels at the time of event had a lower risk of future CV events (Simon et al., 2013), suggesting that IL-17 may modulate tissue responses to myocardial injury. A recent pilot study demonstrated that treatment with IL-17A inhibitors was associated with a reduction in coronary plaque after one year of treatment. However, this was an open-label, observational study (Elnabawi et al., 2019). Initial studies of IL-17A inhibitors in patients with psoriasis have shown no impact (with large confidence intervals [CIs]) on major adverse CV events (OR 1.00, 95% CI = 0.09−11.09) during the placebo-controlled portion of clinical studies (Strober et al., 2017). However, much larger and long-term studies in humans will be necessary to determine the true impact of IL-17 inhibition on CVD (Gelfand, 2018; Rungapiromnan et al., 2017). Thus, how inhibition of IL-17 modulates CV risk in humans with psoriasis also remains uncertain.

In contrast to IL-17 and its isoforms, the role of other proinflammatory cytokines in accelerating CVD is more defined. For example, IL-1 and IL-6 have been causally linked to CVD through clinical studies and Mendelian randomization studies, respectively (Interleukin-6 Receptor Mendelian Randomisation Analysis [IL6R MR] Consortium et al., 2012; Ridker et al., 2017). It should be noted that IL-6 can promote differentiation of naive $CD4^+$ T lymphocytes into T helper type 17 cells, demonstrating the complex interplay between inflammatory pathways in the skin and blood (Stockinger and Omenetti, 2017).

To better dissect the impact of anticytokine treatments on cardiometabolic diseases in humans, we have conducted a series of randomized, double-blinded, placebo-controlled studies in patients with moderate-to-severe psoriasis to determine the impact of biologics on subclinical vascular disease. These studies assessed vascular inflammation by ^{18}F-2-fluorodeoxyglucose (^{18}F-FDG)—positron emission tomography (PET)/computed tomography (CT) (Dey et al., 2017; Hjuler et al., 2017; Kaur et al., 2018; Gelfand et al., 2020) as a marker of subclinical vascular disease, which, although not a direct marker of coronary heart disease, is known to be predictive of future major CV events and improves rapidly (i.e., within 4−12 weeks) with treatments (i.e., statins) proven to prevent CVD, and therefore, is a well-accepted surrogate marker for early trials of novel therapies for CVDs (Figueroa et al., 2013; Lee et al., 2008; Mehta et al., 2012; Tahara et al., 2006; Tawakol et al., 2013). Simultaneously, we measured blood markers of inflammation, lipids, and glucose metabolism. In the first vascular inflammation in psoriasis study, blockade of TNF-α with adalimumab had a neutral impact on aortic vascular inflammation, lipids, and glucose metabolism and a beneficial effect on markers of inflammation, such as C-reactive protein (CRP), TNF-α, IL-6, and glycoprotein acetyls compared with placebo (Mehta et al., 2018). In this trial, narrow band UVB phototherapy was used as a nonsystemic treatment control, which demonstrated a neutral impact on aortic vascular inflammation and glucose metabolism, decreased levels of CRP and IL-6, and an increase in high-density lipoprotein-P. Compared with placebo in the vascular inflammation in psoriasis-Ustekinumab study, blockade of IL-12 and IL-23 for 12 weeks resulted in reductions in aortic vascular inflammation and serum vascular cell adhesion molecule-1, with no effects on CRP, TNF-α, IL-6, glycoprotein acetyls, and glucose metabolism. There was also a slight increase in cholesterol levels, possibly owing to an increase in apolipoprotein-B lipoproteins (Gelfand et al., 2020). Here, in a prospective randomized, double-blinded, placebo-controlled study, we determined the effect of secukinumab, an antibody selectively targeting IL-17A, on aortic vascular inflammation and blood-based markers of inflammation, lipids, and glucose metabolism compared with placebo in patients with moderate-to-severe psoriasis.

RESULTS

A total of 139 patients were screened and 91 were randomized, 46 to secukinumab and 45 to placebo (Supplementary Figure S1). A total of 44 patients randomized to secukinumab completed the study through week 12 (two patients [4.3%] discontinued owing to adverse events [AEs]), and 42 initially assigned to placebo completed up to week 12 (three patients [6.7%] discontinued, two for AEs and one for patient and/or guardian decision). A total of 86 patients entered the double-blinded treatment phase (second phase) of the study, of whom 78 completed the study (eight patients [8.8%] discontinued, two for AEs, one for lack of efficacy, two lost to follow-up, one for protocol deviation, and two for patient and/or guardian decision). The average age of patients was 47 years (SD = 13.7 years), 67% were male, and 79% were Caucasian; average body mass index was 32, mean body surface area was 29%, and the mean PASI score was 22 (Table 1). The baseline characteristics were similar between the two treatment groups, but those assigned to placebo were numerically more likely to have a prior diagnosis of psoriatic arthritis and a prior diagnosis of conditions related to CVD (Table 1).

As anticipated, secukinumab was highly efficacious in treating psoriasis (Table 2). At week 12, secukinumab-treated patients had 74% and 78% greater differences in achieving PASI 90 and Investigator's Global Assessment modified 2011 (IGA mod 2011) 0 or 1 responses, respectively, compared with placebo ($P < 0.0001$ for all). At week 52, PASI 90 and IGA mod 2011 0 or 1 response rates were 53% and 57%, respectively.

Patients assigned to secukinumab had a 2.6% (95% CI = −2.5% to 7.6%) increase in target-to-blood pool ratio (TBR) at week 12 compared with baseline, whereas patients assigned to placebo had a 3.3% (95% CI = −0.8% to 7.5%) increase during the same time period; however, neither of these numbers nor the differences were statistically significant (Table 3). The difference in least squares means change in TBR from baseline to week 12 of secukinumab compared with placebo was −0.053 (95% CI = −0.169 to 0.064; $P = 0.37$) (primary efficacy variable). An analysis based on percent change found that patients treated with secukinumab experienced a non−statistically significant −0.75% reduction (95% CI = −7.2% to 5.7%) in TBR at week 12 compared

Table 1. Demographics and Background Characteristics (Randomized Set)

Characteristic	Secukinumab n = 46	Placebo n = 45	Total N = 91
Age			
Mean years (SD)	47.9 (12.7)	47.0 (14.7)	47.4 (13.7)
Gender, n (%)			
Female	13 (28.3)	17 (37.8)	30 (33.0)
Male	33 (71.7)	28 (62.2)	61 (67.0)
Race, n (%)			
Caucasian	36 (78.3)	36 (80.0)	72 (79.1)
Black	1 (2.2)	3 (6.7)	4 (4.4)
Asian	6 (13.0)	2 (4.4)	8 (8.8)
Other	3 (6.5)	4 (8.9)	7 (7.7)
Ethnicity, n (%)			
Hispanic	15 (32.6)	15 (33.3)	30 (33.0)
Not Hispanic or Latino	31 (67.4)	30 (66.7)	61 (67.0)
Unknown/missing	0 (0.0)	0 (0.0)	0 (0.0)
BMI, kg/m^2			
Mean (SD)	31.09 (6.8)	32.75 (7.8)	31.91 (7.3)
Medical history, n (%)			
Coronary artery Disease	1 (2.2)	4 (8.9)	5 (5.5)
Depression	3 (6.5)	7 (15.6)	10 (11.0)
Diabetes mellitus	0 (0.0)	5 (11.1)	5 (5.5)
Hyperlipidemia	8 (17.4)	11 (24.4)	19 (20.9)
Hypertension	11 (23.9)	16 (35.6)	27 (29.7)
Stroke	(0.0)	1 (2.2)	1 (1.1)
Statin use	0 (0.0)	1 (2.2)	1 (1.1)
Baseline total % BSA			
Mean (SD)	27.6 (19.3)	30.1 (18.7)	28.8 (19.0)
Median (p25, p75)	21.5 (13.9, 36.0)	21.4 (18.0, 40.6)	21.4 (15.0, 37.4)
Baseline PASI			
Mean (SD)	22.5 (12.0)	21.4 (9.9)	22.0 (11.0)
Median (p25, p75)	17.9 (14.2, 26.7)	18.6 (14.9, 22.8)	18.0 (14.7, 24.4)
Baseline IGA mod 2011 n (%)			
3 = Moderate disease	31 (67.4)	28 (62.2)	59 (64.8)
4 = Severe disease	15 (32.6)	17 (37.8)	32 (35.2)
Psoriasis duration (years)			
N	45	45	90
Mean (SD)	16.3 (12.3)	15.4 (12.5)	15.9 (12.4)
Median (p25, p75)	14.0 (5.0, 25.0)	14.0 (6.0, 20.0)	14.0 (5.0, 24.0)
Treatment history, n (%)			
Biologics	20 (43.5)	16 (35.6)	36 (39.6)
Nonbiological systemic therapy	13 (28.3)	14 (31.1)	27 (29.7)
Phototherapy	14 (30.4)	13 (28.9)	27 (29.7)
PsA present (%)			
Yes	6 (13.0)	11 (24.4)	17 (18.7)

Abbreviations: BMI, body mass index; BSA, body surface area; IGA mod 2011, Investigator Global Assessment modified 2011; PsA, psoriatic arthritis; p25, 25th percentile; p75, 75th percentile.

with percentage changes in the placebo group. At week 52, there was no statistically significant change in TBR compared with baseline for those initially assigned to secukinumab (n = 37, −2.6%, 95% CI = −11.9% to 6.8%) and those initially assigned to placebo who then started secukinumab at week 12 (n = 35, 3.4%, 95% CI: −6.1% to 2.8%) (Figure 1). A post hoc sensitivity analysis was conducted in patients with a TBR > 1.6 at baseline (a previously utilized entry criteria for a CV drug development trial [Fayad et al., 2011]). Within-group changes demonstrated a −0.11 (95% CI = −0.20 to 0.02) reduction in aortic vascular inflammation ($P = 0.02$) at week 12 compared with baseline for those initially assigned secukinumab; however, those initially assigned to placebo and then crossed over to secukinumab at week 12 experienced a non−statistically significant within-group TBR increase of +0.11 (95% CI = −0.02 to 0.24) at week 52 compared with week 12 (Supplementary Table S1). No other statistically significant changes were observed at other time points for those were initially assigned secukinumab or for those individuals who initially received placebo followed by secukinumab from week 12 to week 52. Additional post hoc sensitivity analyses evaluating different subgroups based on PASI responses, body mass index, age, and cardiovascular risk status are shown in Supplementary Table S2 and did not change the primary results.

Changes in blood biomarkers of advanced lipoprotein characterization, inflammation, adiposity, insulin resistance, and predictors of diabetes are shown in Tables 4 and 5. At week 12, patients randomized to secukinumab had a small but statistically significant increase in total cholesterol, low-density lipoprotein, and low-density lipoprotein particles compared with placebo, with no statistically significant changes in biomarkers of inflammation, adiposity, insulin resistance, and predictors of diabetes (Table 4). At week 52, there were no statistically significant changes in markers of advanced lipoprotein characterization compared with baseline and no statistically significant changes in markers of adiposity or insulin resistance. There were statistically significant reductions in TNF-α ($P = 0.0063$) and ferritin ($P = 0.0354$) and an increase in fetuin-A at week 52 ($P = 0.0024$) (Table 5).

Safety data are presented in Supplementary Table S3, with a listing of nonserious AEs that occurred in more than 5% of patients in any randomized arm. During the randomized double-blinded treatment period, there were 26 AEs (56.5%) in those treated with secukinumab (two of which were serious [4.3%]) and 16 AEs (35.6%) in those treated with placebo (none of which were serious). The two serious AEs in the first treatment period occurred in two patients and were rib fracture and upper limb fracture. Over the entire treatment period (52 weeks), when all patients received secukinumab, there were 37 AEs (80.4%), of which five were serious (10.9%). The serious AEs over the 52 weeks occurred in five patients and included abdominal pain, rib fracture, upper limb fracture, muscular weakness, and aortic stenosis.

DISCUSSION

We conducted a randomized, double-blinded, placebo-controlled study to determine the impact of secukinumab, an anti−IL-17A antibody, on important markers of vascular disease risk compared with placebo in patients with moderate-to-severe psoriasis. As anticipated, secukinumab resulted in excellent reduction in the signs and symptoms of psoriasis. At week 12, there was no change in aortic inflammation, that is,

Table 2. Physician-Reported Psoriasis Variables: Weeks 12 and 52

	Wk 12[1]		Difference in Percentage			Wk 52[2]
Variables n (%)	Secukinumab n = 46	Placebo n = 45	Estimated Value	95% CI	*P*-value	Secukinumab n = 78
PASI 90	34 (74)	0	73.9	(61.22–86.60)	<0.0001	53 (68)
IGA mod 2011 0/1 (clear/almost clear)	36 (78.3)	0	78.3	(66.34–90.18)	<0.0001	57 (73)

P-values at week 12 are for comparison of secukinumab with placebo.
Abbreviations: CI, confidence interval; IGA mod 2011, Investigator's Global Assessment modified 2011.
[1]Nonresponder imputation.
[2]Observed cases.

TBR, in secukinumab-treated patients compared with placebo. On the basis of the 95% CI of this observation (95% CI = −7.2% to 5.7%), it is likely that short-term exposure to secukinumab has no clinically significant impact on aortic vascular inflammation as assessed by ^{18}F-FDG–PET/CT (Gelfand et al., 2020; Mehta et al., 2018). Moreover, long-term exposure to secukinumab (52 weeks for those originally assigned to secukinumab or 40 weeks for those initially assigned placebo) also showed no discernible effects on aortic vascular inflammation, reinforcing the primary outcome finding. The results were robust in a number of sensitivity analyses. Patients who had higher aortic vascular inflammation at baseline and received secukinumab showed evidence of TBR improvement at week 12. This finding, however, was not replicated when patients initially assigned to placebo were crossed over to secukinumab. Other trials evaluating the impact of biologics on vascular inflammation in psoriasis have required patients to have higher vascular inflammation by entry TBR value > 1.6 (Bissonnette et al., 2017); however, this approach limits the generalizability of the results; may mask paradoxical effects of targeted biologic treatment on inflammation; and, as previously demonstrated, is not necessary to demonstrate a reduction in aortic vascular inflammation in patients with psoriasis treated with a biologic (i.e., ustekinumab) compared with placebo (Gelfand et al., 2020). Results in this study are largely similar to a recently published trial, which found that secukinumab had minimal effect on flow-mediated dilatation (a marker of early vascular disease, e.g., endothelial dysfunction) compared with placebo (von Stebut et al., 2019). The results are in contrast to a study that demonstrated an improvement in left ventricle global longitudinal strain, left ventricle twisting and untwisting, coronary flow reserve, and pulse wave velocity in patients treated with secukinumab compared with methotrexate or cyclosporine; however, this study was not placebo-controlled and did not evaluate extensive CV biomarkers of inflammation, lipid, and glucose metabolism (Makavos et al., 2020).

We also evaluated the effect of secukinumab on markers of inflammation, lipoproteins, adiposity, and insulin resistance, which are dysregulated in patients with psoriasis and associated with adverse atherosclerotic outcomes and/or incident diabetes mellitus (Sajja et al., 2018). After 12 weeks of therapy, patients treated with secukinumab had a small increase in total cholesterol driven by increases in low-density lipoprotein and low-density lipoprotein particles, but these changes were transient and not sustained at 52 weeks. In addition, there were no differences in markers of inflammation, adiposity, insulin resistance, or predictors of diabetes at 12 weeks between the secukinumab and placebo groups. At 52 weeks, there were reductions in TNF-α and ferritin and an increase in fetuin-A. Thus, despite rapid and sustained improvement in psoriasis observed with secukinumab treatment, there were no impacts on aortic vascular inflammation and biomarkers of cardiometabolic disease.

Strengths of our study include its rigorous placebo-controlled design, plus the comprehensive evaluation of imaging and serum biomarkers of inflammation, lipids, and glucose metabolism. Limitations include a relatively small sample size, which limited our ability to fully investigate a post hoc analysis such as evaluating the effect of secukinumab in patients with higher levels of aortic vascular inflammation at baseline and which possibly resulted in insufficient statistical power for some biomarkers. For example, pooled results from larger studies have shown statistically significant improvements in high-sensitivity CRP in moderate-to-severe patients with psoriasis with comorbid psoriatic arthritis treated with secukinumab compared with placebo (Gottlieb, 2015). We also evaluated a number of biomarkers, which can lead to type 1 errors. Furthermore, other pathways that may be important links between

Table 3. ^{18}F-FDG–PET/CT Primary Assessment: Total Aortic Vascular Inflammation at Week 12

Variables	Secukinumab n = 43	Placebo n = 42	Difference (Secukinumab − Placebo)
Change from baseline (primary efficacy variable), LSM	0.017	0.070	−0.053 (95% CI = −0.169 to 0.064); *P* = 0.37
% change from baseline, mean	2.6% (95% CI = −2.5 to 7.6); *P* = 0.31	3.3% (95% CI = −0.8 to 7.5); *P* = 0.12	−0.75% (95% CI = −7.2 to 5.7); *P* = 0.82

Abbreviations: ^{18}F-FDG–PET/CT, ^{18}F-2-fluorodeoxyglucose–positron emission tomography with computer assisted tomography; CI, confidence interval; LSM, least squares mean.

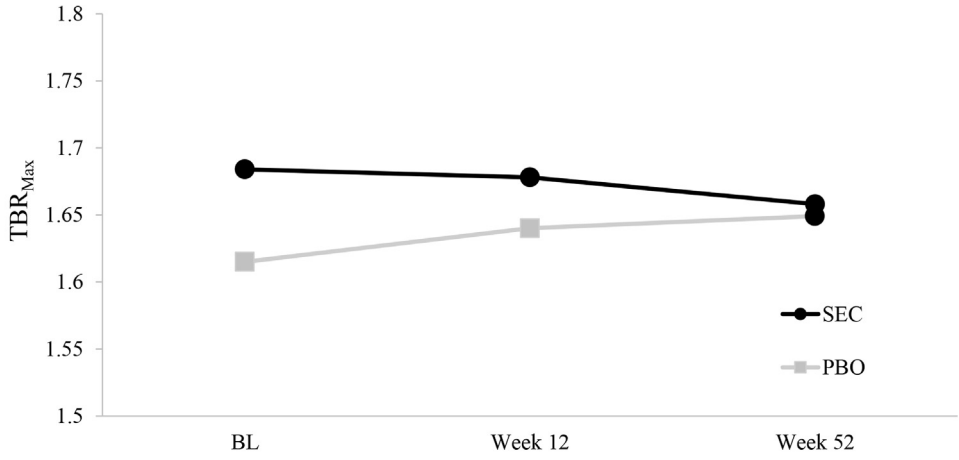

Figure 1. Whole aorta TBR_{max} in week 52 completers. BL, baseline; CI, confidence interval; NA, not applicable; PBO, placebo; SEC, secukinumab; TBR, target-to-blood pool ratio.

Change in TBR vs. baseline

Secukinumab (n=37)	**NA**	**−0.006 (95% CI, −0.081, 0.068)**	**−0.026 (95% CI, −0.119, 0.068)**
Placebo to Secukinumab (n=35)	NA	0.025 (95% CI, −0.043, 0.093)	0.034 (95% CI, −0.061, 0.128)

psoriasis and CV events, including platelet function and immune cell populations by flow cytometry, were not evaluated (Takeshita et al., 2014). In addition, the CV markers tested here have primarily been evaluated in older patients, often with established CVD, or restricted to those with higher levels of a CV biomarker of interest at baseline. Thus, additional studies may be warranted in higher risk and more CVD-enriched populations. Finally, our primary outcome, aortic vascular inflammation, may not fully capture impacts on vascular beds of coronary arteries, the primary sites involved in myocardial infarction. To this point, in a small pilot study in psoriasis, we recently demonstrated that one year of treatment with anti—IL-17A therapy was associated with a reduction in total coronary plaque burden, with no worsening of atherosclerotic plaque features, compared with patients with psoriasis not treated with biologic therapy (Elnabawi et al., 2019). Therefore, it is possible that measuring ^{18}F-FDG uptake in the aorta is not as sensitive as coronary artery plaque characterization by coronary CT with angiography when studying possible CV changes associated with anti-inflammatory treatment. In addition, it is possible that reduction of bioavailable IL-17A modulates immune cells associated more with early coronary artery plaque formation than cells associated with early aortic inflammation. Multimodal imaging studies performed simultaneously are needed to better address this issue.

In summary, treatment of moderate-to-severe psoriasis with secukinumab resulted in rapid and sustained improvement in psoriasis but had a neutral impact on aortic vascular inflammation and biomarkers of cardiometabolic disease. Additional studies evaluating the effects of IL-17A inhibition in patients with higher CV risk that incorporate direct measures of coronary artery disease and major adverse CV events are necessary to more fully understand the CV effects of IL-17A in humans.

MATERIALS AND METHODS

Study design

This was a randomized, double-blinded, placebo-controlled, parallel-group, multicenter study in adult patients (age ≥ 18 years) with moderate-to-severe chronic plaque psoriasis (Supplementary Figure S2). A total of 12 investigative sites in the USA participated between 10 February 2016 and 19 February 2018 (NCT02690701; clinical trials.gov) and consisted of a screening period (≤4 weeks) and a double-blinded treatment period (12 weeks), followed by a double-blinded induction period (4 weeks) and an open-label treatment period (36 weeks). At the beginning of the double-blinded treatment period, eligible patients were randomized (1:1) to either secukinumab 300 mg or placebo. Patients on secukinumab 300 mg who completed the double-blinded treatment phase were sham-induced to placebo injections at weeks 13, 14, and 15, whereas patients who were on placebo were switched to secukinumab at week 12 and received the loading dose of active drug at weeks 13, 14, 15, and 16. At the end of the double-blinded induction period, all patients were switched to open-label secukinumab 300 mg for the remainder of the study.

Protocol

Three protocol amendments were carried out (after 5, 26, and 107 weeks) after the initiation of the study. Of the amendments carried out, the notable ones were the inclusion of HbA1c ≥ 7% as an exclusionary laboratory value and revision of the list of cardiometabolic biomarkers under investigation in the study.

Participants

Adult patients diagnosed with moderate-to-severe chronic plaque psoriasis (≥6 months before randomization) with ≥10% body

Table 4. Effect of Secukinumab on Cardiometabolic Biomarkers: Changes from Baseline at Week 12

Variable, LSM	SEC 300 mg n = 46	Placebo n = 45	LSM Difference (Secukinumab − Placebo)	95% CI for Treatment Difference	*P*-value[1]
Advanced lipoprotein characterization					
Cholesterol (mg/dl)	**10.8**	**−8.4**	**19.2**	**(6.2−32.2)**	**0.0043**
HDL cholesterol (mg/dl)	−0.8	−1.6	0.8	(−2.6 to 4.2)	0.6367
HDL function (cholesterol efflux)	0.1	0.1	0.05	(−0.05 to 0.1)	0.3086
HDL particle total (µmol/L)	−0.2	0.4	0.2	(−1.8 to 2.2)	0.8651
HDL Size (nm)	0.042	−0.002	0.05	(−0.1 to 0.2)	0.5904
IDL particle total (nmol/L)	52.4	6.2	46.2	(−12.1 to 104.4)	0.1188
LDL cholesterol (mg/dl)	**10.5**	**−5.8**	**16.3**	**(3.4−29.2)**	**0.0137**
LDL particle total (nmol/L)	**112.0**	**−94.8**	**206.7**	**(77.9−335.6)**	**0.0020**
LDL size (nm)	0.01	0.1	−0.1	(−0.3 to 0.2)	0.4464
Triglycerides (mg/dl)	11.2	−9.2	20.4	(−2.0 to 42.8)	0.0741
VLDL particle total (nmol/L)	2.8	3.5	-0.7	(−11.0 to 9.6)	0.8917
VLDL size (nm)	0.1	−1.1	1.2	(−1.6 to 4.0)	0.3919
Inflammation					
TNF-α (pg/ml)	−0.5	−0.8	0.3	(−0.2 to 0.7)	0.2577
IL-6 (pg/ml)	2.0	−2.1	4.1	(−2.7 to 10.9)	0.2331
CRP (mg/L)	−1.6	1.5	−3.1	(−8.3 to 2.1)	0.2413
GlycA	−3.7	2.9	−6.6	(−28.0 to 14.8)	0.5410
Adiposity					
Leptin (pg/ml)	−3,741.1	−3,097.8	−643.3	(−4,801.1 to 3,514.6)	0.7590
Adiponectin total (ng/ml)	1,424.9	−1,080.3	2,505.2	(−3,359.5 to 8,369.9)	0.3979
Insulin resistance					
HOMA-IR	0.5	−0.7	1.2	(−0.2 to 2.6)	0.0878
Predictive of diabetes					
Apolipoprotein B (ng/ml)	0.002	0.002	-0.001	(−0.02 to 0.02)	0.9347
Ferritin (ng/ml)	−7.2	−14.8	7.5	(−15.9 to 30.9)	0.5248
IL-2 receptor A (pg/ml)	−3.1	−2.1	−1.0	(−11.9 to 9.9)	0.8608
IL-18 (pg/ml)	32,925.3	−3,763.0	36,688.3	(−34,807 to 108,183)	0.3103
Fetuin-A (ng/ml)	56,948.5	79,453.7	−22,505	(−205,030 to160,020)	0.8068

Abbreviations: ANCOVA, analysis of covariance; CRP, C-reactive protein; GlycA, Glycoprotein acetyls; HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LSM, least squares mean; SEC, secukinumab; VLDL, very-low-density lipoprotein.

Boldface indicates statistical significance at $P < 0.05$.

[1]*P*-values calculated by ANCOVA.

surface area involvement, PASI ≥ 12, and IGA mod 2011 score ≥ 3 (based on a scale of 0 to 4) at baseline and who were eligible for systemic therapy were included in the study. Patients underwent clinical examinations (including ^{18}F-FDG−PET/CT), and their results were required to not meaningfully alter the risk-benefit profile of secukinumab in the investigator's opinion. At baseline, patients with previous exposure to secukinumab or any other biologic drug directly targeting IL-17A or IL-17RA or any investigational drug within 4 weeks (or five half-lives, whichever was longer) before randomization or with other active skin diseases or infections affecting the evaluation of psoriasis were excluded. Patients were also excluded if they did not limit UV exposure; used prohibited psoriasis treatments; used cholesterol-lowering medications (unless the use of cholesterol-lowering medications involved a dose that was stable ≥90 days before randomization and remained stable during the study); had notable current CV or cerebrovascular disease (e.g., uncontrolled diabetes as evidenced by HbA1c ≥ 7%, myocardial infarction, cerebrovascular accident within six months before the screening visit, or unstable ischemic heart disease) in the investigator's opinion; had significant medical problems (uncontrolled hypertension with measured systolic ≥ 180 mmHg and/or diastolic ≥ 95 mm Hg or congestive heart failure [New York Heart Association status of class III or IV]); or had a serum creatinine level of >2.0 mg/dl, a fasting blood glucose ≥ 150 mg/dl, or a total white blood cell count < 2,500/µl, thrombocytes < 100,000/µl, neutrophils < 1,500/µl, or hemoglobin < 8.5 g/dl at screening.

Interventions and follow-up

For the secukinumab group, patients or trained caregivers administered a dose of secukinumab 300 mg (two subcutaneous injections of 150 mg) once weekly for 5 weeks (at randomization and weeks 1, 2, 3, and 4), followed by dosing every 4 weeks, starting at week 8 through week 48. For the placebo group, patients and/or trained caregivers administered a dose of placebo (two injections of the placebo 1 ml prefilled syringe each containing a mixture of inactive excipients, matching the composition of the secukinumab 150 mg dose) once weekly for 5 weeks (at randomization and weeks 1, 2, 3, and 4), followed by a dose after 4 weeks at week 8. From week 12, all patients in the placebo group were switched to treatment with secukinumab 300 mg. Patients received a dose of secukinumab 300 mg once weekly for 5 weeks (at weeks 12, 13, 14, 15, and 16) followed by dosing every 4 weeks, starting at week 20 to week 48. To maintain the blinding during the double-blinded induction period, placebo doses were self-administered by the patients and/or

Table 5. Effect of Secukinumab on Cardiometabolic Biomarkers: Changes from Baseline at Week 52

Variable, LSM	Secukinumab n = 91	*P*-value[1]
Advanced lipoprotein characterization		
Cholesterol (mg/dl)	1.1	0.7380
HDL cholesterol (mg/dl)	−0.6	0.5219
HDL function (cholesterol efflux)	0.04	0.2213
HDL particle total (μmol/L)	−0.2	0.7446
HDL size (nm)	0.06	0.3128
IDL particle total (nmol/L)	22.7	0.1978
LDL cholesterol (mg/dl)	1.4	0.6567
LDL particle total (nmol/L)	−11.3	0.7726
LDL size (nm)	0.07	0.3981
Triglycerides (mg/dl)	5.9	0.4121
VLDL particle total (nmol/L)	0.007	0.9983
VLDL size (nm)	1.3	0.2176
Inflammation		
TNF-α (pg/ml)	**−0.9**	**0.0063**
IL-6 (pg/ml)	−2.4	0.1606
CRP (mg/L)	−1.6	0.0664
GlycA	−4.0	0.4512
Adiposity		
Leptin (pg/ml)	−1,854.4	0.2522
Adiponectin total (ng/ml)	−1,802.7	0.2582
Insulin resistance		
HOMA-IR	−0.2	0.6186
Predictive of diabetes		
Apolipoprotein B (ng/ml)	0.01	0.1264
Ferritin (ng/ml)	**−16.6**	**0.0354**
IL-2 receptor A (pg/ml)	0.002	0.9996
IL-18 (pg/ml)	−47.5	0.4239
Fetuin-A (ng/ml)	**142,675.3**	**0.0024**

Abbreviations: CRP, C-reactive protein; GlycA, Glycoprotein acetyls; HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LSM, least squares mean; VLDL, very low-density lipoprotein.
Boldface indicates statistical significance at $P < 0.05$.
[1]*P*-values calculated by linear regression.

trained caregivers at weeks 13, 14, and 15, who were previously on secukinumab treatment in the double-blinded treatment period.

Outcomes

TBR was used to evaluate aortic vascular inflammation. Patients underwent ^{18}F-FDG–PET/CT scans using the standard protocol (Bural et al., 2008; Chen et al., 2009). Following overnight fast, prescan glucose level was <150 mg/dl before ^{18}F-FDG administration. Standard bed positions of three minutes each scanning whole body were obtained for each patient from the vertex of the skull to the toes 120 minutes after administration of ^{18}F-FDG. After qualitative review of PET and CT images, the extent of ^{18}F-FDG uptake within the aorta was directly measured by OsiriXTM to calculate TBR. Each region of interest produced two measures of metabolic activity, mean standardized uptake value and maximal standardized uptake value, and these were obtained in the entire aorta. Moreover, regions of interest were also placed on six contiguous slices over the superior vena cava to obtain background activity of the ^{18}F-FDG tracer. The mean standardized uptake values from each of the superior vena cava slices were then averaged to produce one venous value. To account for background blood activity, maximal standardized uptake values from each aortic slice was divided by the average venous mean standardized uptake value, yielding a TBR (Bural et al., 2006; Mehta et al., 2018; Naik et al., 2015).

The primary objective was to evaluate the effect of secukinumab 300 mg compared with placebo with respect to the change in TBR from baseline at week 12. TBR was assessed using vascular inflammation imaging by full-body ^{18}F-FDG–PET/CT at three scheduled visits, baseline, week 12, and week 52.

The secondary objectives included the effect of secukinumab compared with placebo on changes from baseline in cardiometabolic markers and PASI 90 and IGA mod 2011 0 or 1 responses at week 12 and at week 52 (as exploratory objectives). Cardiometabolic biomarkers included measures of advanced lipoprotein characterization, measures of inflammation, insulin resistance, and markers predictive of diabetes. Serum biomarkers and imaging data were analyzed centrally at the National Institutes of Health (Mehta Lab). The advanced lipoprotein characterization biomarkers included lipid particle size and high-density lipoprotein function (cholesterol efflux); inflammatory markers included TNF-α, IL-6, and CRP; and adiposity markers included leptin and adiponectin. Insulin resistance biomarkers included insulin levels and glucose to yield homeostatic model assessment–insulin resistance, and diabetes predictive biomarkers included apolipoprotein B, ferritin, IL-2 receptor A, IL-18, and fetuin-A.

Clinical safety and tolerability of secukinumab was evaluated by monitoring vital signs, clinical laboratory variables, and AEs. Safety assessments consisted of recording all AEs and serious AEs, with their severity and relationship to study drug and pregnancies. The safety assessments also included regular monitoring of hematologic, blood chemistry, and urine tests and regular assessments of vital signs, physical condition, and body weight.

Sample size

The sample size was based on the change from baseline in the TBR from the aorta. Using a *t*-test, a clinically important mean treatment difference of 0.15 in TBR, a (common) SD of 0.196, a 2-sided significance level of 0.05, and a power of 0.90, it was determined that approximately 74 patients (37 in each treatment group) were necessary (Bissonnette et al., 2013; Tawakol et al., 2013). Allowing for a loss to follow-up rate of 0.10, approximately 84 patients (42 in each treatment group) were required to be randomized.

Randomization, assignment, and masking

Eligible patients were randomized via Interactive Response Technology in a 1:1 ratio to either secukinumab 300 mg or placebo. Patients, investigators or site staff, persons performing assessments, and Novartis study personnel remained blinded to individual treatment assignment from time of randomization until the final database lock at week 52.

Statistical methods and analysis

The primary efficacy variable was analyzed by an analysis of covariance model with treatment, baseline, and body weight (<90 kg and ≥90 kg) as explanatory variables. The randomized set included all patients who were randomized to the treatment groups, the safety set included all patients who received at least one dose of study medication, and the full analysis set included all patients to whom study medications were assigned. For the primary efficacy variable, data for patients with missing post-baseline value were not

imputed, and patients were included in the analysis if they had both baseline and post-baseline assessments. The primary analysis was based on the full analysis set. Changes from baseline in each cardiometabolic biomarker were analyzed at each time point using the same analysis of covariance model as the primary efficacy variable; missing data were imputed using the last-observation-carried-forward method. In addition, the primary efficacy variable and changes from baseline in each biomarker were analyzed using the stratified Wilcoxon rank-sum test with modified ridit scores (van Elteren's test), adjusting for body weight. PASI 90 and IGA mod 2011 0 or 1 responses were analyzed at each time point using the Cochran-Mantel-Haenszel test, adjusting for body weight, to compare the effect of secukinumab to placebo.

Exploratory analyses were performed to assess the effect of continuous treatment using secukinumab at week 52 compared with baseline by combining both randomization arms. The primary efficacy variable was analyzed using a linear regression model as well as the Wilcoxon signed-rank test, and PASI and IGA mod 2011 responses were summarized using proportions and 95% CIs. Additionally, TBR was analyzed as percent change from baseline using a linear model with treatment as the only explanatory variable. Sensitivity analyses were performed using linear regression models in subgroups defined by clinical treatment responses, body mass index, age, CVD risk, or baseline aortic inflammation.

Study ethics

The study protocol and all amendments were approved by the independent ethics committee or institutional review board of each center. The study was conducted according to the Declaration of Helsinki, and written informed consent was obtained from each participant.

Role of the sponsor

Novartis served as regulatory sponsor. Dr Mehta's lab provided the analysis of images and biomarkers. Novartis analyzed the primary and secondary efficacy variables.

Dr. Gelfand's lab replicated the Novartis analyses independently and conducted the exploratory analyses.

Data availability statement

Available data are posted on https://clinicaltrials.gov/ct2/show/results/NCT02690701. For further questions regarding the data, please contact the primary/corresponding author.

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CONFLICT OF INTEREST

Gelfand served as a consultant for BMS, Boehringer Ingelheim, Janssen Biologics, Novartis Corp, UCB (DSMB), Sanofi, and Pfizer, receiving honoraria; receives research grants (to the Trustees of the University of Pennsylvania) from AbbVie, Boehringer Ingelheim, Janssen, Novartis, Celgene, Ortho Dermatologics, and Pfizer; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Eli Lilly, Ortho Dermatologics, and Novartis. Gelfand is a deputy editor for the Journal of Investigative Dermatology, receiving honoraria from the Society for Investigative Dermatology. Gelfand's laboratory replicated the Novartis analyses independently and conducted the exploratory analyses. Duffin has received research grants from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, Sienna Biopharmaceuticals, Stiefel Laboratories, and UCB; has received consulting fees from AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Novartis, Ortho Dermatologic, Pfizer, Sienna Biopharmaceuticals, Stiefel Laboratories, and UCB; and is on the speaker's bureau for Novartis. Armstrong has served as investigator, advisor, and/or consultant to Leo, AbbVie, UCB, Janssen, Novartis, Eli Lilly, Sun, Dermavant, BMS, Regeneron Pharmaceuticals, Inc, Sanofi U.S., Dermira, Modmed, and Ortho Dermatologics, Inc. Blauvelt has served as a scientific advisor and/or clinical study investigator for AbbVie, Aclaris, Akros, Allergan, Almirall, Amgen, Arena, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly, FLX Bio, Forte, Galderma, Genentech/Roche, GlaxoSmithKline, Janssen, Leo, Meiji, Merck Sharp & Dohme, Novartis, Ortho, Pfizer, Purdue Pharma, Regeneron, Revance, Sandoz, Sanofi Genzyme, Sienna Pharmaceuticals, Sun Pharma, UCB Pharma, and Vidac and as a paid speaker for AbbVie, Regeneron, and Sanofi Genzyme. Tyring has conducted studies sponsored by the producer of secukinumab. Menter has received compensation from or served as an investigator, consultant, advisory board member, or speaker for Abbott Labs, AbbVie, Allergan, Amgen, Anacor, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Galderma, Janssen, Leo, Merck & Co, Neothetics, Novartis, Pfizer, Regeneron, Sienna, Symbio/Maruho, UCB, Vitae, and Xenoport. Gottlieb is currently serving as consultant, advisory board member, speaker for Janssen, Celgene, Bristol-Myers Squibb, Beiersdorf, AbbVie, UCB, Novartis, Incyte, Lilly, Reddy Labs, Valeant, Dermira, Allergan, Sun Pharmaceutical Industries, Xbiotech, Leo, and Avotres Therapeutics, and has received research/educational grants from Janssen, Incyte, UCB, Novartis, Lilly Xbiotech, and Boeringer Ingelheim. Lockshin reports personal fees from Lilly, Novartis, Janssen, and Abbott; has served as a speaker for Novartis, Eli Lilly, and AbbVie; conducted research for Celgene, AbbVie, Novartis, Eli Lilly, and Strata; and served as a consultant for Novartis, Eli Lilly, AstraZeneca, and AbbVie. Simpson reports grants from Eli Lilly, Kyowa Hakko Kirin, Leo Pharmaceutical, Merck, Pfizer, and Regeneron, and personal fees from Menlo Therapeutics, Valeant, Novartis, Eli Lilly, Galderma, Dermira, Sanofi Genzyme, Pfizer, Regeneron, and Leo Pharmaceuticals. F Kianifard, E Muscianisi, and J Steadman are employees and/or stockholders of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA. R Sarkar is an employee of Novartis Healthcare Private Limited, Hyderabad, India. Mehta is a full-time US Government Employee and receives research grants to NHLBI from AbbVie, Janssen, Celgene and Novartis. Gelfand in the past has served as a consultant for Amgen, Coherus (DSMB), Dermira, Eli Lilly, Janssen Biologics, Leo Pharma, Merck (DSMB), Novartis Corp, Regeneron, Dr. Reddy's labs, Sanofi and Pfizer Inc, receiving honoraria; receives research grants (to the Trustees of the University of Pennsylvania) from AbbVie, Janssen, Novartis Corp, Regeneron, Sanofi, Celgene, and Pfizer; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Eli Lilly and AbbVie. Shin, Ahlman, Playford, Joshi, Dey, Werner, and Alavi have nothing to disclose. This study is funded by Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA.

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AUTHOR CONTRIBUTIONS

Conceptualization: JG, AA, NM, FK, JS; Data Curation: DS, AAJ, TW, MP; Formal Analysis: JG, DS, NM, AAJ, RPS, FK; Funding Acquisition: JG, NM; Investigation: JG, KCD, AA, AB, ST, SG, BL, ES, AM, TW, MP; Methodology: JG, DS, MA, EM, FK, AD; Project Administration: JG, JS, TW; Resources: JG, AA, NM, MA, AD; Software: DS, RPS; Supervision: JG, FK, EM; Validation:

DS; Visualization: DS, RPS, FK; Writing - Original Draft: JG; Writing - Review and Editing: DS, KCD, AA, AB, ST, AM, SG, BL, ES, FK, RPS, EM, JS, MA, MP, AJ, AD, TW, AA, NM

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.2020.01.025.

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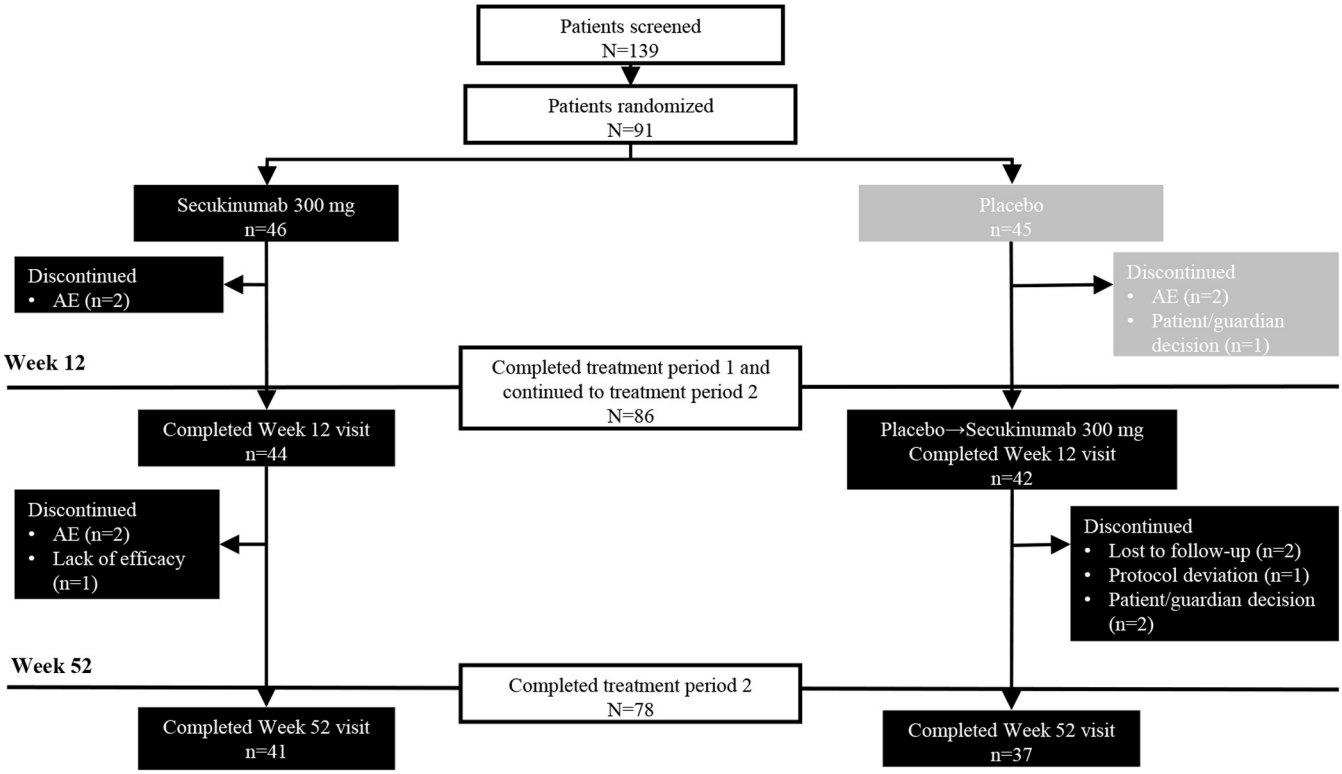
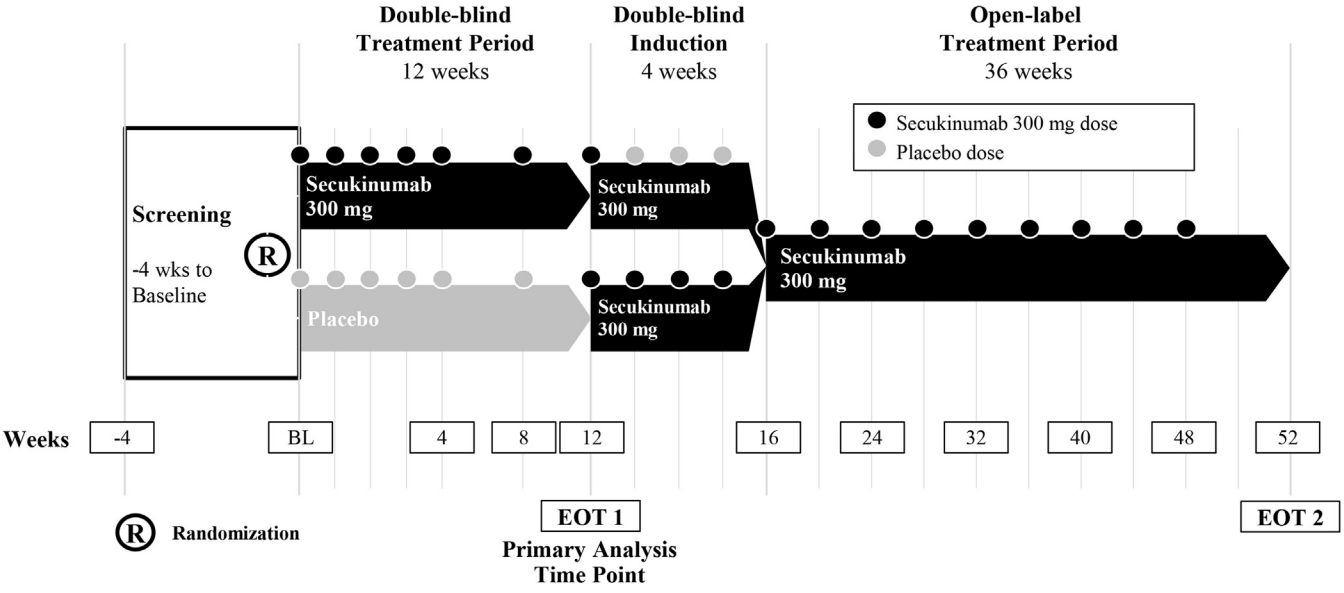


Supplementary Figure S1. CONSORT 2010 flow diagram. AE, adverse event.



Supplementary Figure S2. Study design. Subcutaneous secukinumab 300 mg dose self-administered was matched with placebo. Primary analysis time point was evaluated at week 12. BL, Baseline; EOT1, End of Treatment 1; EOT2, End of Treatment 2; wk, week.

Supplementary Table S1. Subgroup Analyses of Patients with Baseline TBR > 1.6

Period	Secukinumab	Placebo to Secukinumab
Baseline to Week 12	−0.11 (95% CI = −0.20 to 0.02); $P = 0.02$ (n = 22)	0.2 (95% CI = −0.11 to 0.15); $P = 0.77$ (n = 16)
Baseline to Week 52	−0.08 (95% CI = −0.23 to 0.06); $P = 0.24$ (n = 21)	0.13 (95% CI = −0.05 to 0.31); $P = 0.16$ (n = 16)
Week 12 to Week 52	0.01 (95% CI = −0.15 to 0.17); $P = 0.94$ (n = 21)	0.11 (95% CI = −0.02 to 0.24); $P = 0.09$ (n = 16)

Abbreviations: CI, confidence interval; TBR, target-to-blood pool ratio.

Supplementary Table S2. Baseline to Week 12 Sensitivity Analyses on Group Differences in Aortic TBR_{max}

Model	n	LSM Difference (Secukinumab − Placebo)[1]	95% CI		*P*
Primary analysis (ANCOVA)	85	−0.053	−0.169	0.064	0.37
Age & sex adjusted analysis (linear regression)	85	−0.050	−0.165	0.067	0.40
Unadjusted analysis (linear regression)	85	−0.051	−0.167	0.064	0.38
Restricted to PASI 75 responders and controls	80	−0.076	−0.189	0.037	0.18
Restricted to PASI 90 responders and controls	75	−0.087	−0.199	0.026	0.13
Restricted to PASI 100 responders and controls	59	−0.046	−0.188	0.096	0.52
Restricted to BMI $\geq$ 30	45	−0.007	−0.195	0.181	0.94
Restricted to BMI $<$ 30	40	−0.099	−0.235	0.037	0.15
Restricted to age $\geq$ 50	38	−0.062	−0.205	0.082	0.39
Restricted to CVD risk score $\geq$ 2	32	−0.046	−0.219	0.126	0.59
Restricted to CVD risk score $<$ 2	53	−0.070	−0.239	0.098	0.41
Restricted to BMI $\geq$ 30 & CVD risk $\geq$ 2	18	0.0023	−0.239	0.244	0.98
Restricted to BMI $\geq$ 30 & CVD risk $<$ 2	27	−0.030	−0.326	0.265	0.83
Restricted to baseline $TBR_{max} > 1.6$ & imaged at three time points	38	−0.126	−0.271	0.020	0.09
Restricted to baseline $TBR_{max} \leq 1.6$ & imaged at three time points	38	0.063	−0.059	0.186	0.30

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; CVD, cardiovascular disease; LSM, least squares means; TBR, target-to-blood pool ratio.

[1]The minus sign indicates a trend toward reduction in TBR in the secukinumab group compared with the placebo group.

Supplementary Table S3. AEs by Primary System Organ Class and Preferred Term Over 52 Weeks

Primary System Organ Class/ Preferred Term	Secukinumab 300 mg N = 46, n (%)	Placebo to Secukinumab 300 mg N = 45, n (%)	Total N = 91, n (%)
Any AE			
Total	37 (80.4)	30 (66.7)	67 (73.6)
Gastrointestinal disorders			
Total	8 (17.4)	12 (26.7)	20 (22.0)
Diarrhea	3 (6.5)	2 (4.4)	5 (5.5)
Infections and infestations			
Total	25 (54.3)	20 (44.4)	45 (49.5)
Nasopharyngitis	9 (19.6)	7 (15.6)	16 (17.6)
Upper respiratory tract infection	6 (13.0)	4 (8.9)	10 (11.0)
Bronchitis	3 (6.5)	0 (0.0)	3 (3.3)
Sinusitis	0 (0.0)	3 (6.7)	3 (3.3)
Musculoskeletal and connective tissue disorders			
Total	10 (21.7)	6 (13.3)	16 (17.6)
Arthralgia	5 (10.9)	3 (6.7)	8 (8.8)
Nervous system disorders			
Total	4 (8.7)	5 (11.1)	9 (9.9)
Dizziness	1 (2.2)	3 (6.7)	4 (4.4)
Headache	0 (0.0)	4 (8.9)	4 (4.4)
Respiratory, thoracic, and mediastinal disorders			
Total	10 (21.7)	5 (11.1)	15 (16.5)
Cough	1 (2.2)	4 (8.9)	5 (5.5)

AEs starting on or after the first dose of study treatment and until the last dose of study treatment plus 7 days are included. For serious AEs last dose of study treatment plus 30 days are included. Primary system organ classes are sorted alphabetically; preferred terms are sorted within primary system organ class in descending order of frequency in the secukinumab 300 mg column. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A patient with multiple AEs within a primary system organ class is counted only once in the total row. MedDRA version 20.0 was used for reporting (https://www.meddra.org/sites/default/files/guidance/file/intguide_20_0_english.pdf).

Abbreviation: AE, adverse event.