Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med 2015;373:1329-39. DOI: 10.1056/NEJMoa1412679

SUPPLEMENTARY APPENDIX

Supplement to: Mease et al. Secukinumab Interleukin-17A Inhibition in Patients With Psoriatic Arthritis.

Table of Contents

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Supplementary Methodological Text

Inclusion Criteria

Patients aged at least 18 years, who were seronegative, had a diagnosis of psoriatic arthritis fulfilling the ClASsification criteria for Psoriatic ARthritis (CASPAR), had experienced symptoms for at least 6 months, and who had ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit counts as one joint each) at baseline were eligible. A diagnosis of active plaque psoriasis, with at least one psoriatic plaque of ≥2 cm diameter (but not in intertriginous areas such as armpits, or chest between breasts, or groin) or nail changes consistent with psoriasis or a documented history of plaque psoriasis was required. Patients should have been on non-steroidal anti-inflammatory drugs (NSAIDs) for at least 4 weeks prior to randomization with inadequate control of symptoms or intolerance to NSAIDs. Concomitant oral corticosteroids (≤10 mg per day prednisone or equivalent) and methotrexate (≤25 mg per week) were permitted, provided the dose was stable for at least 2 and 4 weeks before randomization, respectively, and throughout the study period (or to week 24 in the case of corticosteroids). Disease-modifying anti-rheumatic drugs other than methotrexate were not allowed during the study and required appropriate washout periods. Patients who had previously received a tumor necrosis factor (TNF) inhibitor were eligible provided they had experienced an inadequate response after receiving an approved dose for at least 3 months or had stopped treatment for safety or tolerability reasons. TNF inhibitors required a washout period of 4 to 10 weeks prior to randomization, dependent upon agent (≥4 weeks for etanercept; ≥8 weeks for infliximab; ≥10 weeks for adalimumab, golimumab, and certolizumab).

Exclusion Criteria

Patients who had previously received biologic immunomodulating agents, except for those targeting TNF, and patients who had previously been treated with more than 3 different TNF inhibitors were excluded from the study. Other key exclusion criteria included: active,

ongoing inflammatory diseases other than psoriatic arthritis; history of ongoing, chronic, or recurrent infections, or evidence of active tuberculosis infection; history of malignancy within the past 5 years (except for basal cell carcinoma or actinic keratosis that has been treated with no evidence of recurrence in the past 3 months, in situ cervical cancer or non-invasive malignant colon polyps that have been removed).

Randomization

Randomization, accomplished using an interactive voice or web response system, was stratified by prior therapy with TNF inhibitors; approximately 30% of patients were required to have an inadequate response or intolerance to TNF inhibitors to ensure a representative patient population for the assessment of efficacy and safety.

Study Agents

Secukinumab and placebo were supplied by Novartis Pharma AG (Basel, Switzerland) as lyophilized powders in glass vials for reconstitution. 100 mL 0.9% NaCl solution was used as placebo for intravenous secukinumab and was provided locally by study site.

Study Assessments

To meet American College of Rheumatology 20 (ACR20) response criteria, patients had to have a ≥20% improvement in the number of tender joints (based on 78 joints), the number of swollen joints (based on 76 joints), and in at least three of the following five domains: patient global assessment of disease activity (measured on a visual analog scale of 0 to 100 mm); physician global assessment of disease activity (measured on a visual analog scale of 0 to 100 mm); patient's assessment of psoriatic arthritis pain (measured on a visual analog scale of 0 to 100 mm); disability (measured by HAQ-DI score); acute-phase reactant (measured by high-sensitivity C-reactive protein [hsCRP] or erythrocyte sedimentation rate [ESR]).[1]

Presence of enthesitis was evaluated using a four-point enthesitis index: lateral epicondyle humerus left and right, and proximal achilles left and right. Tenderness on examination was recorded as either present (1) or absent (0) for each site, for an overall score range of 0 to 4. Higher count represented greater enthesitis burden.

Immunogenicity Assay

Immunogenicity to secukinumab was assessed by a sensitive, homogenous bridging immunogenicity assay on an enzyme-linked immunosorbent assay (ELISA)-based Meso Scale Discovery (MSD) platform. Anti-secukinumab antibodies were captured in solution by a combination of biotinylated and ruthenylated forms of secukinumab. An acid dissociation step was built into the assay to improve drug tolerance. Formed complexes were subsequently detected via electrochemiluminescence by capturing complexes on an electroactive surface of the MSD streptavidin-coated plates.

Planned Sample Size

The planned sample size of 200 patients per group (600 in total) was estimated to provide 99% power to detect a treatment difference of 27% (Fisher's exact test; α=0.05) in ACR20 response at week 24, assuming ACR20 responses rates of 22% and 49% for placebo and secukinumab, respectively. A placebo response rate of approximately 25% after 24 weeks was reported for the biologic-naïve population in the PSUMMIT I study,[2] and 15% was reported for the biologic-experienced population in the PSUMMIT II study.[3] Based on the weighted average, the overall placebo rate is expected to be 22%. The response on secukinumab is expected to be 55% in the biologic-naïve population and 35% in the biologic-experienced population. Based on the weighted average, the overall rate on a dose of secukinumab was expected to be 49%.

Additional Statistical Information

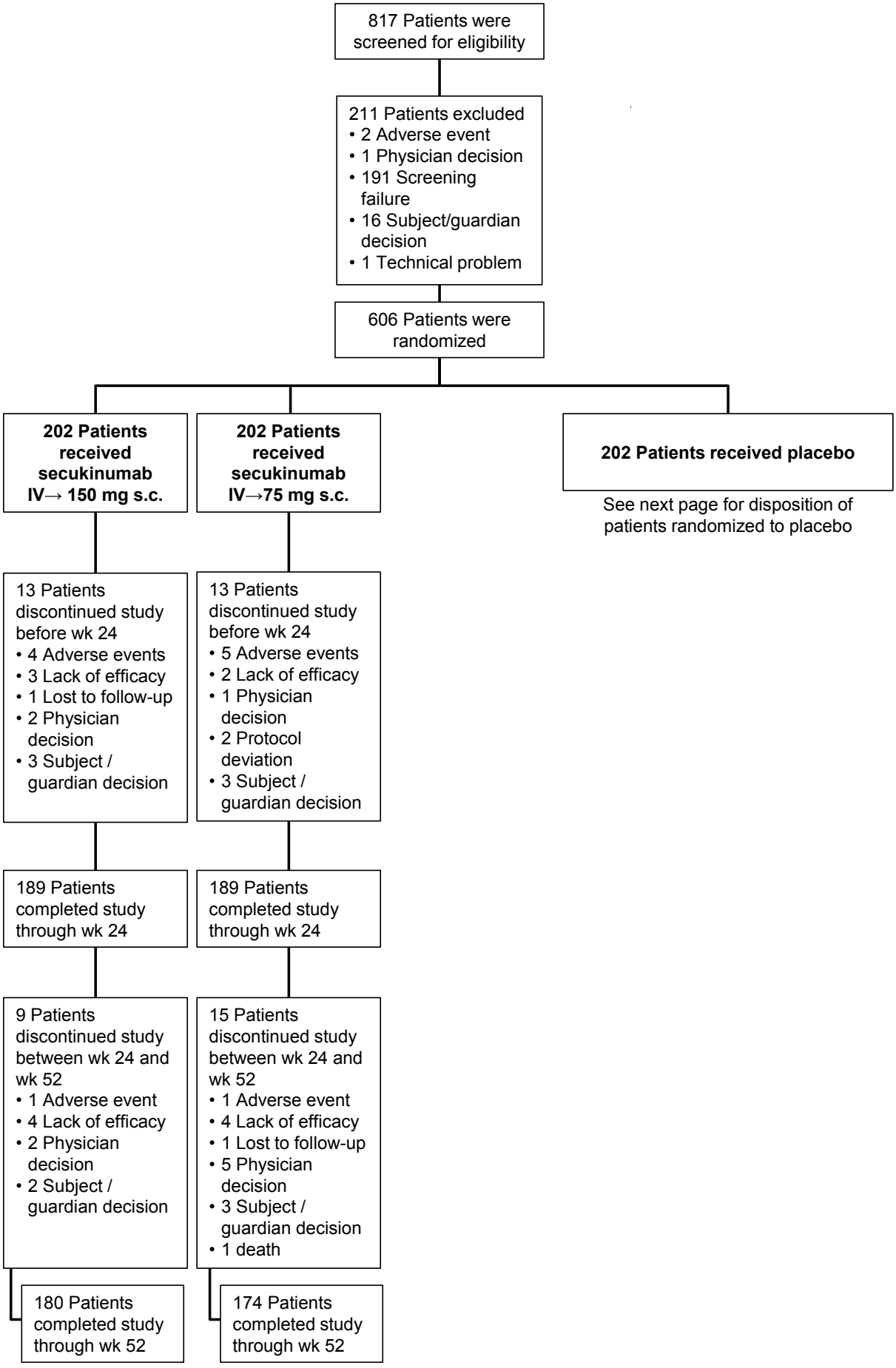
Efficacy assessments at week 24 used the following data-handling rules. For binary variables, week 16 non-responders (≤20% improvement in tender and swollen joint counts) were imputed as non-responders for each categorical variable at week 24. Patients who had prematurely discontinued or who had missing data at week 16 were imputed as non-responders for each categorical variable at week 24. For week 24 analysis of continuous variables, data from non-responders in the placebo group collected after week 16 were treated as missing. Actual values were used for patients in the secukinumab treatment groups. If all post-baseline values were missing then the patient was removed from the analysis. Missing values at week 24 for mean change from baseline in mTSS were imputed by linear extrapolation. Both inferential analyses (with imputation) and descriptive summaries (on observed data) were performed on data from week 28 to week 52. In the inferential analysis of binary variables over this period, a non-responder imputation was applied when patients who withdrew from the trial were considered non-responders from the time of withdrawal. Patients for whom responses could not be calculated at a specific timepoint were classified as non-responders. Since the week 28 to week 52 period had no placebo-comparator, the penalty for early escape used in the primary (baseline to week 24) analysis was lifted (i.e. no imputation was applied on the basis of responder status at week 16 [responder/non-responder]).

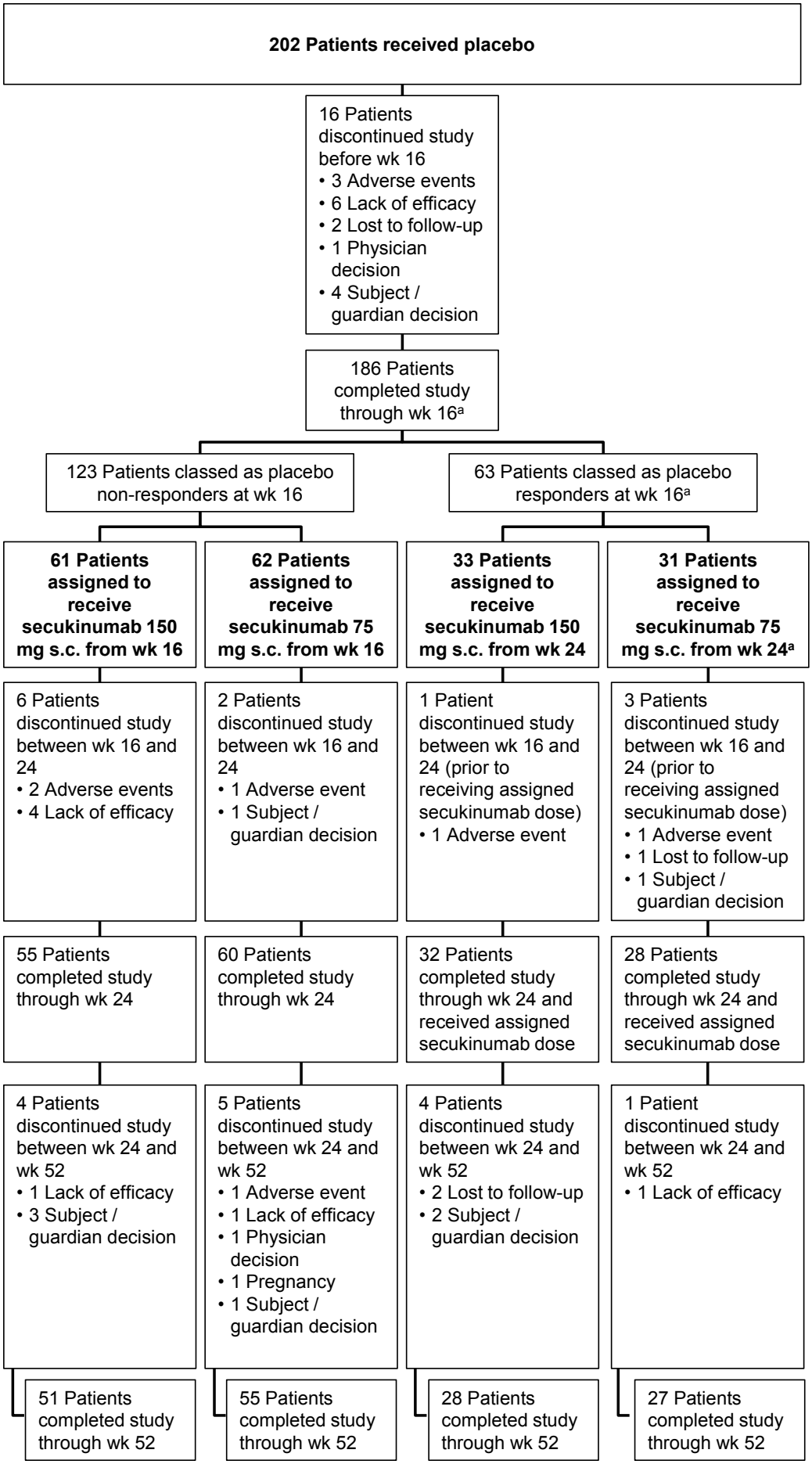
For binary variables (proportion of responders), P-values are from a logistic regression model with treatment and prior TNF inhibitor use as factors and baseline weight as a covariate. Baseline score was also a covariate in the analysis of some endpoints. For continuous variables (change from baseline), P-values are from a repeated measures mixed model with treatment regimen, analysis visit, and prior TNF inhibitor use as factors, and weight and baseline score as continuous covariates. Treatment by analysis visit and baseline score by analysis visit were used as interaction terms, and an unstructured covariance structure was assumed. The change at week 24 from baseline in van der Heijde

total modified Sharp score was evaluated using a non-parametric ANCOVA model with treatment regimen and prior TNF inhibitor use as factors, and weight and baseline score as covariates. For patients who met the criteria for early escape at week 16 and patients who discontinued the study prior to week 24, linear extrapolation was used to impute the value at week 24. Variables such as hsCRP, for which the distribution was not anticipated to be normal, were transformed and analyzed on the $\log_e$ scale.

Supplementary Figure S1. Patient Disposition and Flow Through the Trial from Screening to Week 52.

The secukinumab groups received intravenous secukinumab 10 mg/kg at baseline, week 2, and week 4, followed by subcutaneous secukinumab at 150 or 75 mg starting at week 8 and then every 4 weeks. The placebo group received intravenous placebo at baseline, week 2, and week 4, followed by subcutaneous placebo at weeks 8 and 12. At week 16, all patients were classified (in a blinded manner) as responders, defined as at least a 20% improvement from baseline in tender and swollen joint counts, or non-responders. Placebo-treated patients treated with placebo were re-randomized (1:1) to receive subcutaneous secukinumab 150 mg or 75 mg every 4 weeks from either week 16 (non-responders) or week 24 (responders).


817 Patients were screened for eligibility
211 Patients excluded
• 2 Adverse event
• 1 Physician decision
• 191 Screening failure
• 16 Subject/guardian decision
• 1 Technical problem
606 Patients were randomized
202 Patients received secukinumab IV→ 150 mg s.c.
202 Patients received secukinumab IV→75 mg s.c.
202 Patients received placebo
See next page for disposition of patients randomized to placebo
13 Patients discontinued study before wk 24
• 4 Adverse events
• 3 Lack of efficacy
• 1 Lost to follow-up
• 2 Physician decision
• 3 Subject / guardian decision
13 Patients discontinued study before wk 24
• 5 Adverse events
• 2 Lack of efficacy
• 1 Physician decision
• 2 Protocol deviation
• 3 Subject / guardian decision
189 Patients completed study through wk 24
189 Patients completed study through wk 24
9 Patients discontinued study between wk 24 and wk 52
• 1 Adverse event
• 4 Lack of efficacy
• 2 Physician decision
• 2 Subject / guardian decision
15 Patients discontinued study between wk 24 and wk 52
• 1 Adverse event
• 4 Lack of efficacy
• 1 Lost to follow-up
• 5 Physician decision
• 3 Subject / guardian decision
• 1 death
180 Patients completed study through wk 52
174 Patients completed study through wk 52


202 Patients received placebo
16 Patients discontinued study before wk 16
• 3 Adverse events
• 6 Lack of efficacy
• 2 Lost to follow-up
• 1 Physician decision
• 4 Subject / guardian decision
186 Patients completed study through wk 16[a]
123 Patients classed as placebo non-responders at wk 16
63 Patients classed as placebo responders at wk 16[a]
61 Patients assigned to receive secukinumab 150 mg s.c. from wk 16
62 Patients assigned to receive secukinumab 75 mg s.c. from wk 16
33 Patients assigned to receive secukinumab 150 mg s.c. from wk 24
31 Patients assigned to receive secukinumab 75 mg s.c. from wk 24[a]
6 Patients discontinued study between wk 16 and 24
• 2 Adverse events
• 4 Lack of efficacy
2 Patients discontinued study between wk 16 and 24
• 1 Adverse event
• 1 Subject / guardian decision
1 Patient discontinued study between wk 16 and 24 (prior to receiving assigned secukinumab dose)
• 1 Adverse event
3 Patients discontinued study between wk 16 and 24 (prior to receiving assigned secukinumab dose)
• 1 Adverse event
• 1 Lost to follow-up
• 1 Subject / guardian decision
55 Patients completed study through wk 24
60 Patients completed study through wk 24
32 Patients completed study through wk 24 and received assigned secukinumab dose
28 Patients completed study through wk 24 and received assigned secukinumab dose
4 Patients discontinued study between wk 24 and wk 52
• 1 Lack of efficacy
• 3 Subject / guardian decision
5 Patients discontinued study between wk 24 and wk 52
• 1 Adverse event
• 1 Lack of efficacy
• 1 Physician decision
• 1 Pregnancy
• 1 Subject / guardian decision
4 Patients discontinued study between wk 24 and wk 52
• 2 Lost to follow-up
• 2 Subject / guardian decision
1 Patient discontinued study between wk 24 and wk 52
• 1 Lack of efficacy
51 Patients completed study through wk 52
55 Patients completed study through wk 52
28 Patients completed study through wk 52
27 Patients completed study through wk 52

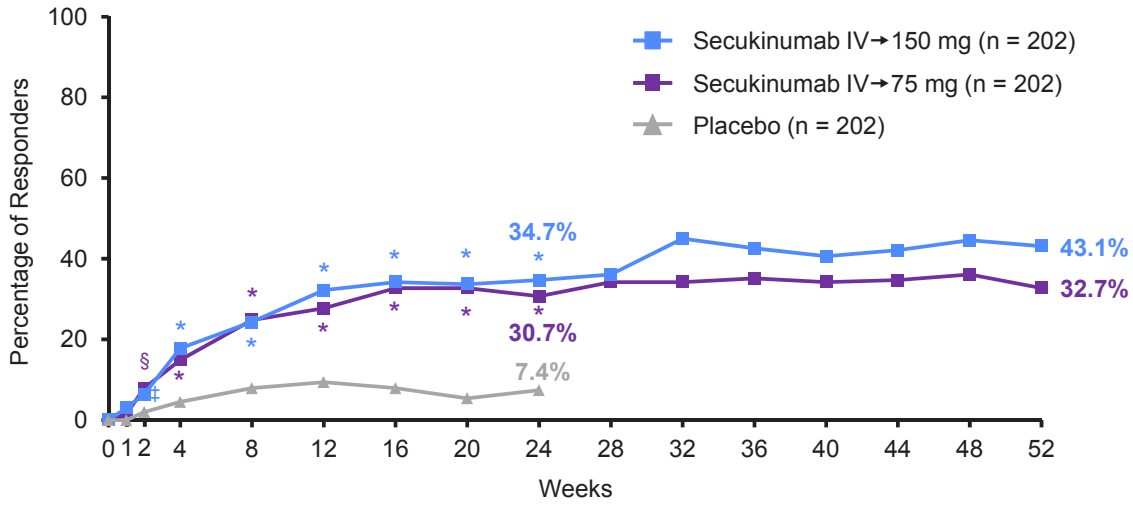
[a]One patient was dosed up to week 12, attended the week 16 visit, and was re-randomized as a placebo responder. However, this patient discontinued the same day, and did not receive active treatment (i.e., reached but did not complete week 16).

Supplementary Figure S2. American College of Rheumatology (ACR) Responses Through Week 52 for Patients Randomized to Secukinumab at Baseline (Non-responder Imputation).

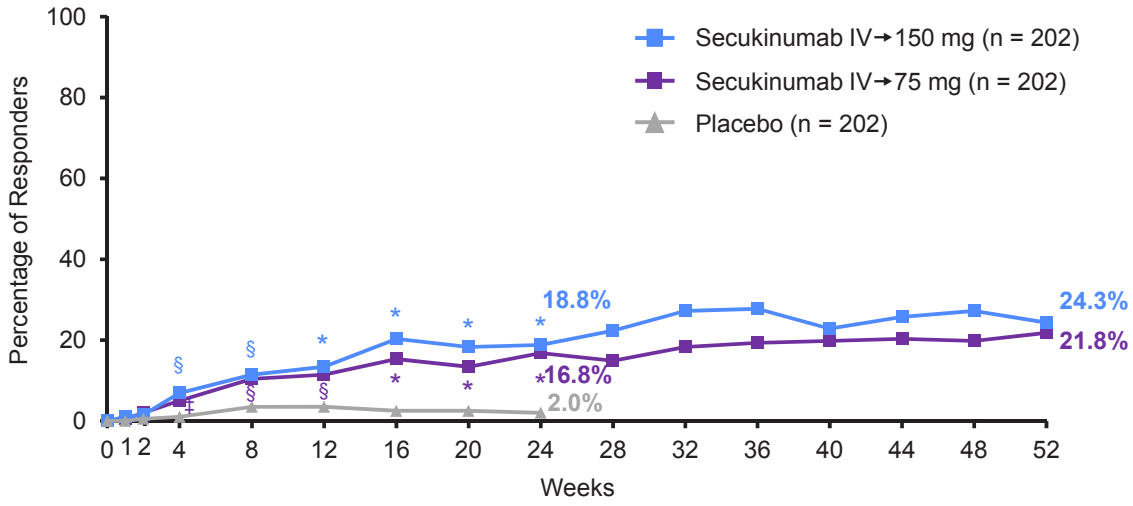
The proportion of patients with at least a 50% and 70% improvement in American College of Rheumatology response criteria (ACR50 [a], ACR70 [b], respectively) through week 52 is shown. Missing data were imputed as non-responses through week 52. P-values for ACR50 response at week 24 were tested as part of the statistical hierarchy and adjusted for multiplicity. Data to week 52 represent those patients randomized to secukinumab at baseline only.

*P<0.001, §P<0.01, ‡P<0.05 versus placebo.

(a) ACR50



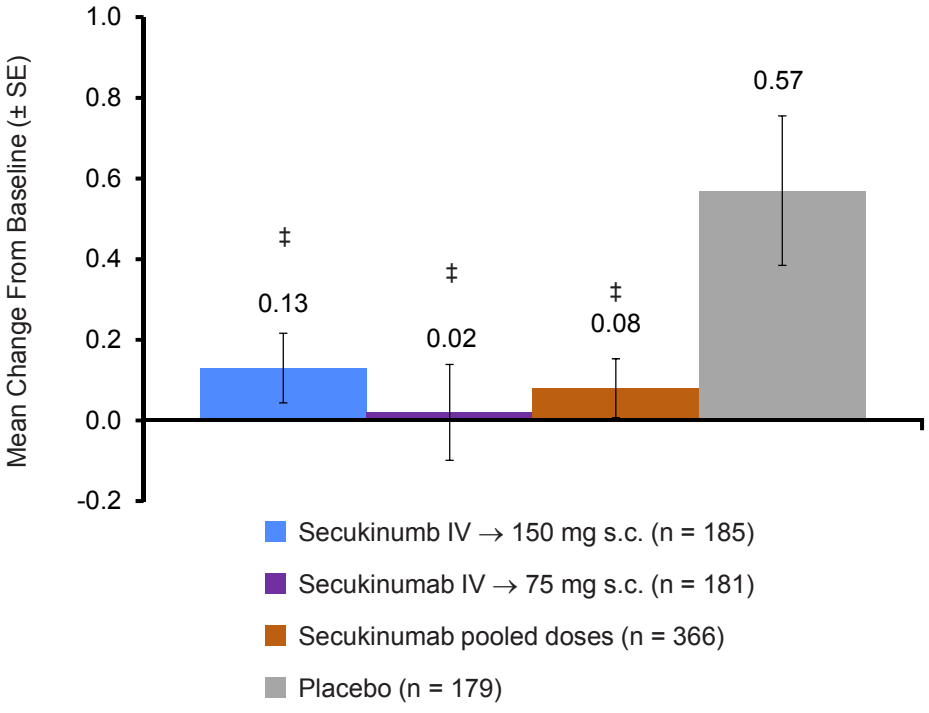
(b) ACR70


Secukinumab IV→150 mg (n = 202)
Secukinumab IV→75 mg (n = 202)
Placebo (n = 202)
Percentage of Responders
100
80
60
40
20
0
0 1 2 4 8 12 16 20 24 28 32 36 40 44 48 52
Weeks
18.8%
24.3%
21.8%
16.8%
2.0%

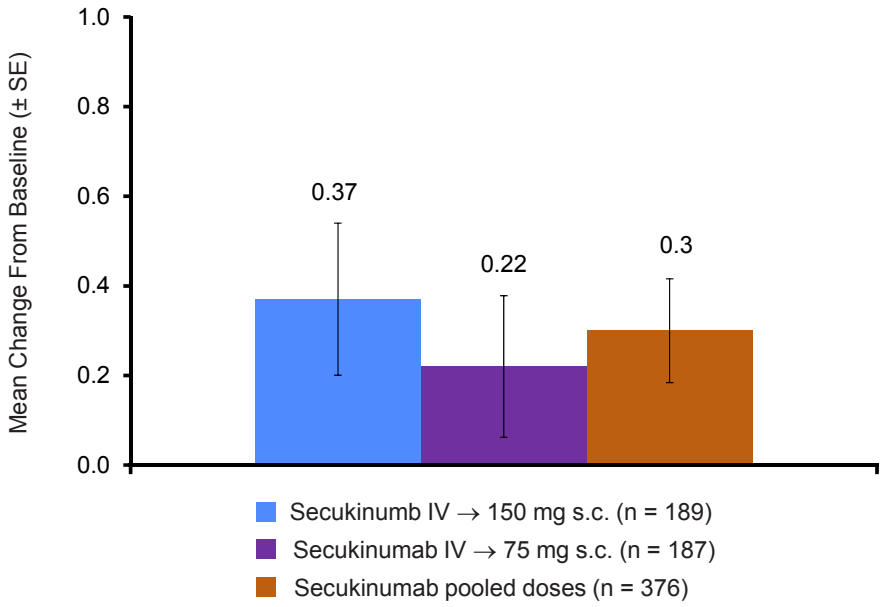
Supplementary Figure S3. Mean Change from Baseline in Modified Total Sharp Score at Week 24 (Placebo-controlled Period), and at Week 52 for Patients Randomized to Secukinumab at Baseline.

The mean change from baseline in modified total Sharp score at week 24 (a) and week 52 (b) is shown. Statistical analyses at week 24 were evaluated using a non-parametric ANCOVA model, with linear extrapolation for missing data. Data to week 52 represent those patients randomized to secukinumab at baseline only. Error bars represent standard error. ‡P<0.05 versus placebo. van der Heijde modified total Sharp score (mTSS) ranges from 0 to 528, with higher scores indicating more articular damage.

(a) Mean Change from Baseline in Modified Total Sharp Score at Week 24



(b) Mean Change from Baseline in Modified Total Sharp Score at Week 52



Supplementary Figure S4. ACR20 Responses at Week 24 by Concomitant Methotrexate (MTX) Use at Randomization (Non-responder Imputation).

The proportion of patients with at least a 20% improvement in American College of Rheumatology response criteria (ACR20) at week 24 is shown for patients with and without concomitant methotrexate use. Missing data were imputed as non-responses through week 24.

*P<0.001 versus placebo.

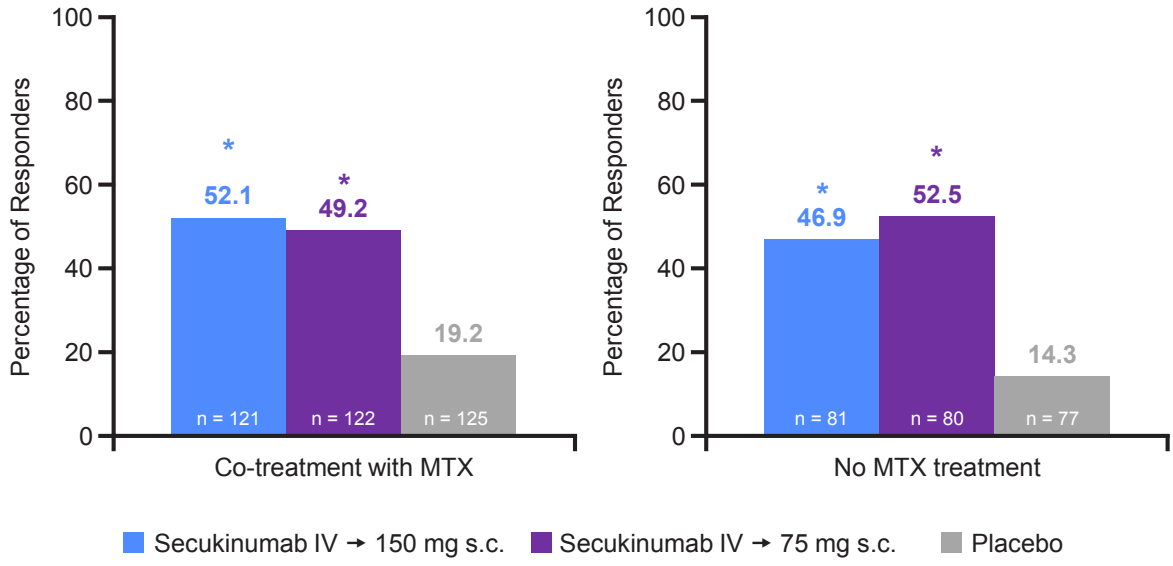
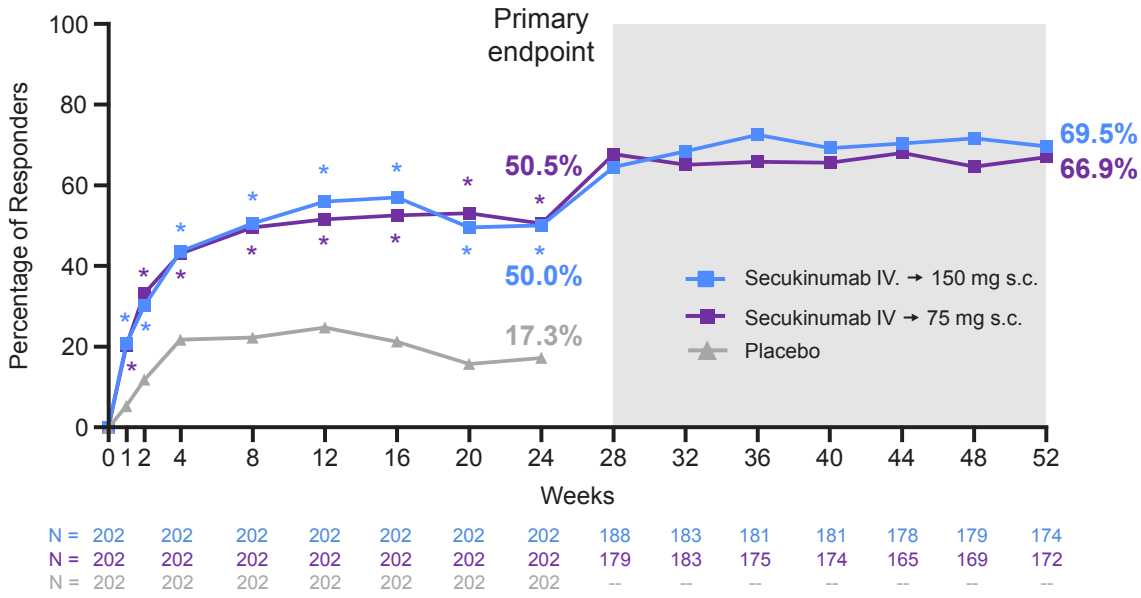


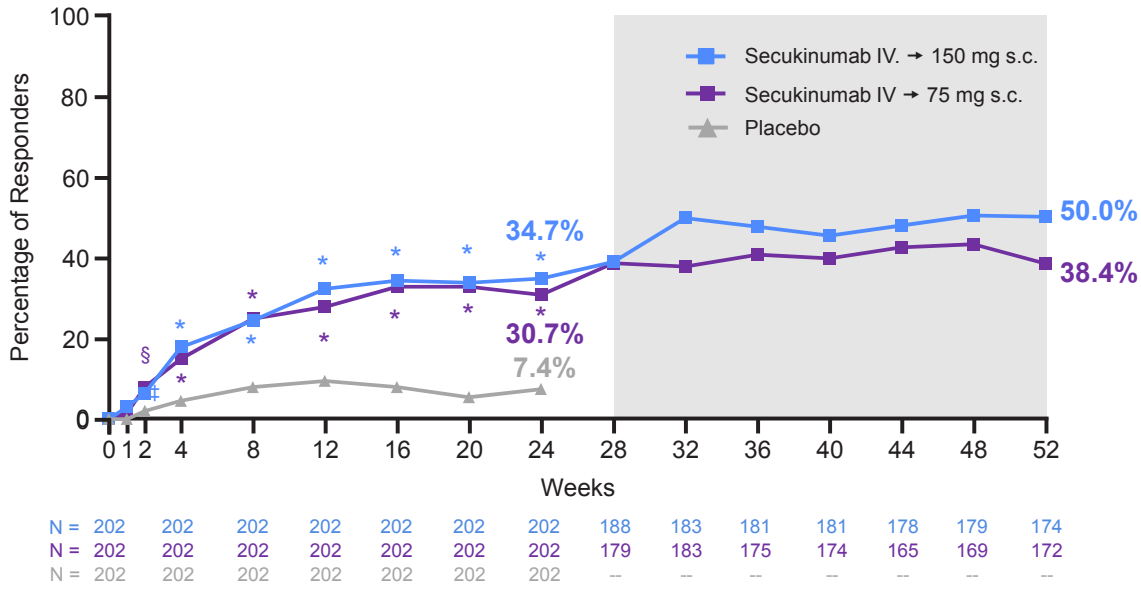
Figure S5. ACR Responses from Baseline to Week 24 (Placebo-controlled Period), and Through Week 52 (Observed) for Patients Randomized to Secukinumab at Baseline.

The proportion of patients with at least a 20%, 50%, and 70% improvement in American College of Rheumatology response criteria (ACR20 [a], ACR50 [b] and ACR70 [c], respectively) over time is shown. Missing data were imputed as non-responses through week 24; observed data are reported from week 28 to week 52 (gray box). Data to week 52 represent those patients randomized to secukinumab at baseline only. N represents the number of patients included in the analysis at each timepoint. P-values at week 24 for ACR20 and ACR50 were adjusted for multiplicity of testing. *P<0.001, §P<0.01, ‡P<0.05 versus placebo.

(a) ACR20



(b) ACR50



(c) ACR70

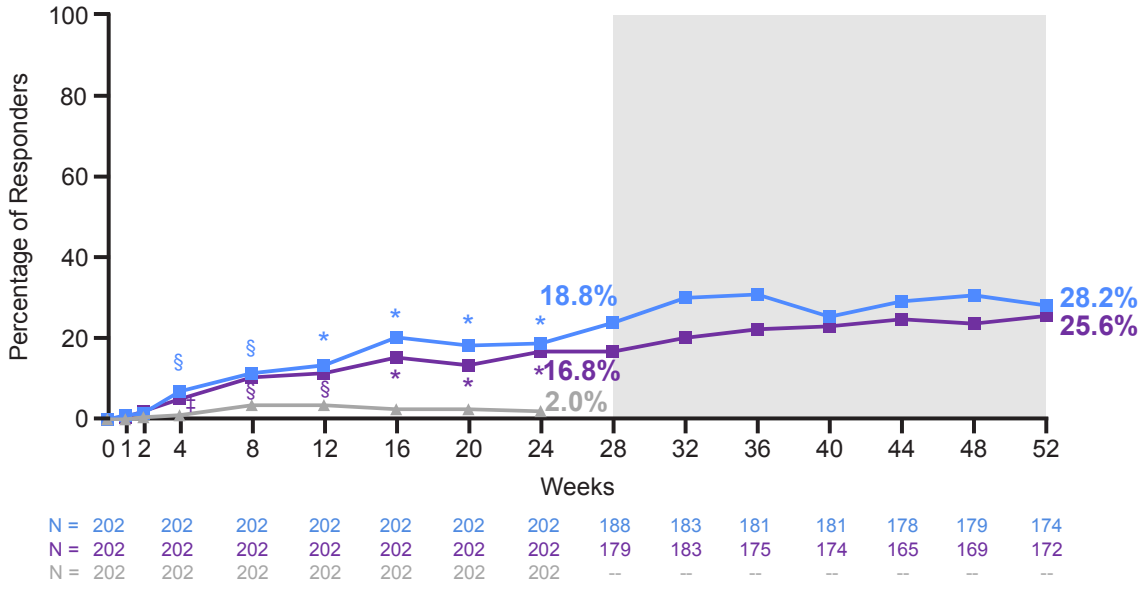
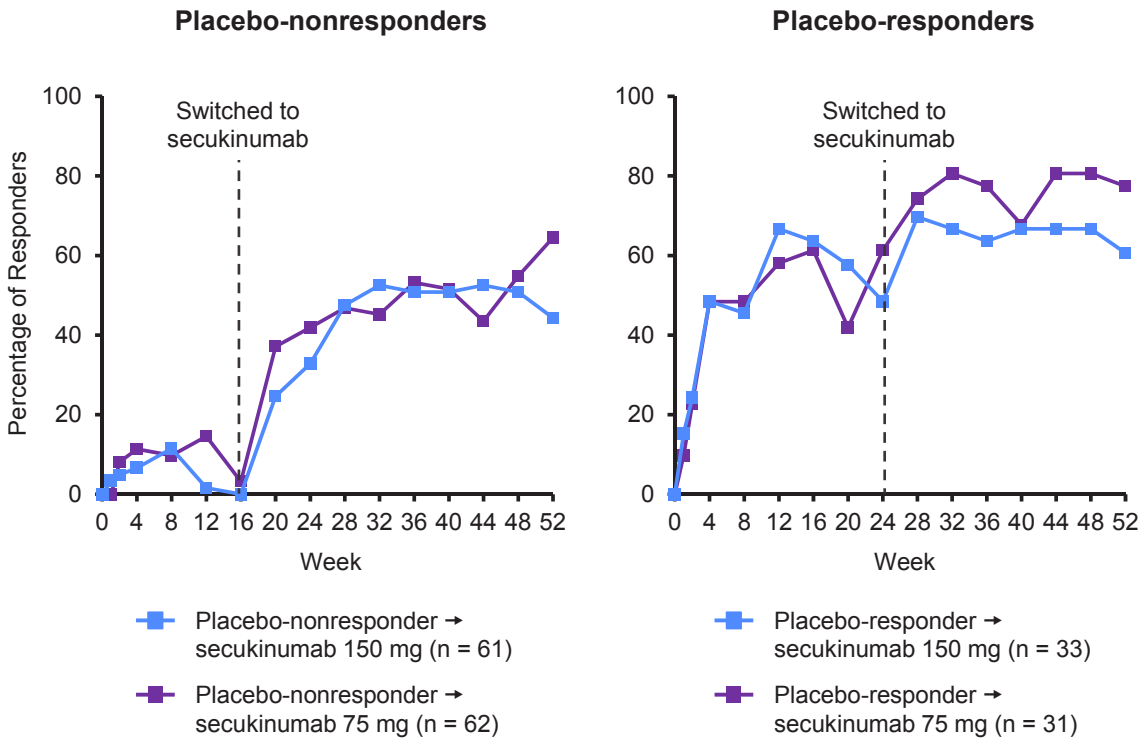


Figure S6. ACR20 Responses Through Week 52 in Placebo-treated Patients Switched to Secukinumab at Week 16 or Week 24 (Non-responder Imputation).

The proportion of placebo-treated patients with at least a 20% improvement in American College of Rheumatology response criteria through week 52 is shown. At week 16, patients were classified as responders, defined as ≥20% improvement from baseline in tender and swollen joint counts, or non-responders. Placebo-treated patients were re-randomized (1:1) to receive subcutaneous secukinumab 150 mg or 75 mg every 4 weeks from either week 16 (responders) or week 24 (non-responders). Missing data were imputed as non-responses through week 52.



Supplementary Table S1. Comparison of Efficacy at Week 24 (Placebo-controlled Phase) in Anti-TNF–naïve and Anti-TNF–experienced Patients.

Efficacy Endpoint	Secukinumab IV→150 mg	Secukinumab IV→75 mg	Placebo
Anti-TNF–naïve patients[a]			
ACR20 response, n/N (%)	78/143 (54.5)[†]	79/142 (55.6)[†]	25/143 (17.5)
ACR50 response, n/N (%)	57/143 (39.9)[†]	52/142 (36.6)[†]	12/143 (8.4)
ACR70 response, n/N (%)	32/143 (22.4)[†]	27/142 (19.0)[†]	4/143 (2.8)
DAS28-CRP, LS mean change from baseline (SE)[¥]	–1.68 (0.093)[†]	–1.73 (0.094)[†]	–0.75 (0.130)
Anti-TNF–experienced patients			
ACR20 response, n/N (%)	23/59 (39.0)[§]	23/60 (38.3)[§]	10/59 (16.9)
ACR50 response, n/N (%)	13/59 (22.0)[‡]	10/60 (16.7)[‡]	3/59 (5.1)
ACR70 response, n/N (%)	6/59 (10.2)[‡]	7/60 (11.7)[‡]	0/59 (0)
DAS28-CRP, LS mean change from baseline (SE)[§]	–1.52 (0.179)	–1.59 (0.176)	–0.92 (0.301)

[‡]P<0.05, [§]P<0.01, [†]P<0.001 versus placebo. P-values for the responses stratified by prior exposure to anti-TNF therapy are unadjusted for multiplicity. Non-responder imputation applied to binary variables; mixed model repeated measures for continuous variables.

[a]Note, 1 patient received one dose of infliximab which was subsequently discontinued for logistical reasons, rather than due to inadequate response. This patient was reported as biologic-naïve.

[¥]N = 142 in the secukinumab IV→75 mg group and N = 143 in the other groups; [§]N = 60 in the secukinumab IV→75 mg group and N = 59 in the other groups. Due to the lack of anti-TNF–experienced patients achieving an ACR70 response with placebo, a Fisher exact test was performed for between-treatment statistical analysis for these assessments in these patients.

Anti-TNF–experienced, documented inadequate response or lack of safety/tolerability with TNF inhibitor(s).

ACR 20/50/70, at least a 20%/50%/70% improvement in American College of Rheumatology response criteria. To meet ACR20 response criteria, patients had to have a ≥20% improvement in the number of tender joints (based on 78 joints), the number of swollen joints

(based on 76 joints), and in three of the following five domains: patient global assessment (measured on a visual analog scale of 0 to 100); physician global assessment (measured on a visual analog scale of 0 to100); patient's assessment of psoriatic arthritis pain (measured on a visual analog scale of 0 to100); disability (measured by HAQ-DI score); acute phase reactant (measured by high-sensitivity C-reactive protein [hsCRP] or erythrocyte sedimentation rate [ESR]).

Disease Activity Score for 28-joint counts (DAS28) based on C-reactive protein (CRP) ranges from 2 to 10, with higher scores indicating more severe disease activity (> 5.1 implies active disease, ≤ 3.2 low disease activity, and < 2.6 remission).

Supplementary Table S2. Summary of Observed Efficacy Data and Efficacy Data with Missing Values Imputed at Week 52 Among Patients Randomized to Secukinumab at Baseline.

	Observed		Imputation	
Efficacy Endpoint	**Secukinumab IV→150 mg**	**Secukinumab IV→75 mg**	**Secukinumab IV→150 mg**	**Secukinumab IV→75 mg**
ACR20 response, n/N (%)	121/174 (69.5)	115/172 (66.9)	121/202 (59.9)	115/202 (56.9)
ACR50 response, n/N (%)	87/174 (50.0)	66/172 (38.4)	87/202 (43.1)	66/202 (32.7)
ACR70 response, n/N (%)	49/174 (28.2)	44/172 (25.6)	49/202 (24.3)	44/202 (21.8)
DAS28-CRP, mean change from baseline (SD [observed data], SE [imputed data])	–1.82 (1.16)	–1.90 (1.22)	–1.77 (0.08)	–1.77 (0.08)
Patients with dactylitis, n/N (%)	22/179 (12.3)	18/175 (10.3)	32/104 (30.8)	28/104 (26.9)
Patients with enthesitis, n/N (%)	33/179 (18.4)	36/175 (20.6)	43/126 (34.1)	53/129 (41.1)
PASI75 response, n/N (%)	83/99 (83.8)	71/99 (71.7)	83/108 (76.9)	71/108 (65.7)
PASI90 response, n/N (%)	64/99 (64.6)	52/99 (52.5)	64/108 (59.3)	52/108 (48.1)
SF-36 PCS score, mean change from baseline (SD [observed data], SE [imputed data])	6.79 (7.46)	5.56 (7.43)	5.89 (0.54)	4.95 (0.54)

HAQ-DI score, mean change from baseline (SD [observed data], SE [imputed data])	–0.46 (0.51)	–0.45 (0.61)	–0.41 (0.04)	–0.39 (0.04)

For continuous variables, mean change from baseline is reported for observed data and least-square mean change where mixed model repeated measures analysis was performed.

ACR20/50/70, ≥20%/50%/70% improvement in American College of Rheumatology response criteria; DAS28-CRP, 28-joint Disease Activity Score 28 based on C-reactive protein; HAQ-DI, health assessment questionnaire disability index; n/N, number of patients who are responders/number of patients in each treatment group of the specified analysis set; PASI75/90, ≥75%/90% improvement in psoriasis area-and-severity index; SD, standard deviation; SE, standard error; SF-36 PCS, short form 36 physical component summary.

ACR 20/50/70, at least a 20%/50%/70% improvement in American College of Rheumatology response criteria. To meet ACR20 response criteria, patients had to have a ≥20% improvement in the number of tender joints (based on 78 joints), the number of swollen joints (based on 76 joints), and in three of the following five domains: patient global assessment (measured on a visual analog scale of 0 to 100); physician global assessment (measured on a visual analog scale of 0 to100); patient's assessment of psoriatic arthritis pain (measured on a visual analog scale of 0 to100); disability (measured by HAQ-DI score); acute phase reactant (measured by high-sensitivity C-reactive protein [hsCRP] or erythrocyte sedimentation rate [ESR]).

Disease Activity Score for 28-joint counts (DAS28) based on C-reactive protein (CRP) ranges from 2 to 10, with higher scores indicating more severe disease activity (> 5.1 implies active disease, ≤ 3.2 low disease activity, and < 2.6 remission).

Scores on the psoriasis area-and-severity index (PASI) range from 0 to 72, with higher scores indicating more severe disease.

Scores on the Medical Outcomes 36-Item Short-Form Health Survey physical component summary (SF-36 PCS) range from 0 to 100, with a normative score of 50 (scores lower than 50 reflect less than average health and scores greater than 50 reflect better than average health). Minimally important differences of ≥ 2.5 points and ≥ 5 points were used for analysis.

The Health Assessment Questionnaire–Disability Index (HAQ-DI) consists of 20 questions across 8 categories, scored on a 4-point scale from 0 [no difficulty] to 3 [unable to do.

Supplementary Table S3. Serious Adverse Events Through Entire Safety Data Period†

	Any Secukinumab 75 mg Group N = 292	Any Secukinumab 150 mg Group N = 295	Any Secukinumab Pooled Group N = 587	Placebo Group N = 202
Exposure to study treatment – days, mean (SD)	437.6 (144.8)	439.4 (146.5)	438.5 (145.6)	128.5 (33.9)
Primary system organ class **Preferred term**	**Number of Events (Events per 100 Patient-Years)**			
Total serious adverse events	25 (7.4)	38 (11.5)	63 (9.4)	11 (16.0)
Blood and lymphatic system disorders (total)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Normochromic normocytic anemia	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Cardiac disorders (total)	4 (1.2)	4 (1.1)	8 (1.1)	1 (1.4)
Angina pectoris	1 (0.3)	1 (0.3)	2 (0.3)	0 (0.0)
Coronary artery disease	0 (0.0)	2 (0.6)	2 (0.3)	1 (1.4)
Cardiac failure	1 (0.3)	1 (0.3)	2 (0.3)	0 (0.0)
Palpitations	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Atrial fibrillation	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Myocardial infarction	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Acute myocardial infarction	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Angina unstable	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Ear and labyrinth disorders (total)	2 (0.6)	0 (0.0)	2 (0.3)	0 (0.0)
Vertigo positional	2 (0.6)	0 (0.0)	2 (0.3)	0 (0.0)
Eye disorders (total)	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Ocular myasthenia	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Gastrointestinal disorders (total)	3 (0.9)	6 (1.7)	9 (1.3)	1 (1.4)

	Any Secukinumab 75 mg Group N = 292	Any Secukinumab 150 mg Group N = 295	Any Secukinumab Pooled Group N = 587	Placebo Group N = 202
Abdominal pain	0 (0.0)	2 (0.6)	2 (0.3)	0 (0.0)
Large intestine polyp	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Oesophagitis	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Hemorrhoids	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Femoral hernia	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Colitis	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Dysphagia	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Crohn's disease	1 (0.3)	0 (0.0)	1 (0.1)	1 (1.4)
Rectal hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
General disorders and administration site conditions (total)	0 (0.0)	3 (0.8)	3 (0.4)	1 (1.4)
Non-cardiac chest pain	0 (0.0)	2 (0.6)	2 (0.3)	1 (1.4)
Local swelling	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Impaired healing	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Hepatobiliary disorders (total)	1 (0.3)	2 (0.6)	3 (0.4)	1 (1.4)
Biliary colic	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Cholecystitis	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Chronic hepatitis	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Cholecystitis acute	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Infections and infestations (total)	9 (2.6)	10 (2.9)	19 (2.7)	1 (1.4)
Sepsis	3 (0.9)	0 (0.0)	3 (0.4)	0 (0.0)
Cellulitis	1 (0.3)	1 (0.3)	2 (0.3)	0 (0.0)
Erysipelas	1 (0.3)	1 (0.3)	2 (0.3)	0 (0.0)
Diverticulitis	0 (0.0)	2 (0.6)	2 (0.3)	0 (0.0)
Pneumonia	2 (0.6)	0 (0.0)	2 (0.3)	0 (0.0)
Septic shock	2 (0.6)	0 (0.0)	2 (0.3)	0 (0.0)
Upper respiratory tract infection	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)

	Any Secukinumab 75 mg Group N = 292	Any Secukinumab 150 mg Group N = 295	Any Secukinumab Pooled Group N = 587	Placebo Group N = 202
Lobar pneumonia	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Lung abscess	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Diarrhea infectious	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Prostatitis *Escherichia coli*	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Oral candidiasis	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Appendiceal abscess	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Dengue fever	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Escherichia urinary tract infection	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Wound infection	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Typhoid fever	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Necrotising fasciitis	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Viral infection	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Urosepsis	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Injury, poisoning and procedural complications (total)	2 (0.6)	3 (0.8)	5 (0.7)	0 (0.0)
Femur fracture	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Tibia fracture	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Sternal fracture	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Excoriation	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Facial bones fracture	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Laceration	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Multiple injuries	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders (total)	1 (0.3)	1 (0.3)	2 (0.3)	0 (0.0)
Hyperglycemia	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Hyponatremia	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)

	Any Secukinumab 75 mg Group N = 292	Any Secukinumab 150 mg Group N = 295	Any Secukinumab Pooled Group N = 587	Placebo Group N = 202
Musculoskeletal and connective tissue disorders (total)	1 (0.3)	7 (2.0)	8 (1.1)	1 (1.4)
Osteoarthritis	0 (0.0)	2 (0.6)	2 (0.3)	1 (1.4)
Psoriatic arthropathy	0 (0.0)	2 (0.6)	2 (0.3)	0 (0.0)
Back pain	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Synovitis	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Osteochondrosis	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Pain in extremity	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps [total])	1 (0.3)	3 (0.9)	4 (0.6)	1 (1.4)
Salivary gland adenoma	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Ovarian germ cell teratoma benign	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Basal cell carcinoma	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Metastases to bone	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Prostate cancer	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Intraductal proliferative breast lesion	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Nervous system disorders (total)	5 (1.4)	2 (0.6)	7 (1.0)	0 (0.0)
Stroke	2 (0.6)	0 (0.0)	2 (0.3)	0 (0.0)
Transient ischemic attack	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Cerebral infarction	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Thrombotic stroke	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Dizziness	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Hemiplegia	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Intracranial venous sinus thrombosis	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)

	Any Secukinumab 75 mg Group N = 292	Any Secukinumab 150 mg Group N = 295	Any Secukinumab Pooled Group N = 587	Placebo Group N = 202
Psychiatric disorders (total)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Renal and urinary disorders (total)	1 (0.3)	1 (0.3)	2 (0.3)	1 (1.4)
Renal failure acute	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Nephrolithiasis	0 (0.0)	1 (0.3)	1 (0.1)	1 (1.4)
Reproductive system and breast disorders (total)	0 (0.0)	2 (0.6)	2 (0.3)	0 (0.0)
Endometriosis	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Metrorrhagia	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders (total)	0 (0.0)	1 (0.3)	1 (0.1)	1 (1.4)
Pulmonary embolism	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Pleural effusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Skin and subcutaneous tissue disorders (total)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Rosacea	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)
Vascular disorders (total)	1 (0.3)	2 (0.6)	3 (0.4)	1 (1.4)
Deep vein thrombosis	0 (0.0)	2 (0.6)	2 (0.3)	0 (0.0)
Hypertension	1 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Hypertensive crisis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)

[†]The safety data period was defined as the period from baseline through week 52 visit of the last patient (maximum secukinumab exposure of 103 weeks and mean and median exposure of 438.5 and 456 days). Patients in the placebo group with less than a 20% improvement from baseline in tender and swollen joint counts at week 16 were re-randomized to secukinumab 150 or 75 mg subcutaneously. The remaining placebo-treated patients were re-randomized to active treatment (secukinumab 150 or 75 mg subcutaneously) at week 24. In the analysis of the entire study period, the placebo group includes all patients who received placebo during the study. The secukinumab groups in this period include any patients who received the stated dose of secukinumab and include those

patients randomized to placebo at baseline who were re-randomized to active treatment at week 16 or 24.

Supplementary Table S4. Overview of Adjudicated Major Adverse Cardiac Events

Study treatment	Day of event	Preferred term	Adjudication Outcome / Event type	Age / Gender / BMI / Medical history and relevant risk factors / Smoking history	Outcome
Secukinumab IV→75 mg	Day 375	Myocardial infarction	Confirmed / Type 1: Spontaneous MI	56 years old / female / 29.9 kg/m^2 / concomitant use of naproxen; elevated cholesterol, LDL, lipoprotein A and hsCRP at randomization / current smoker	Concomitant medication was given and the outcome of the event was recovered at Day 480
Secukinumab IV→75 mg	Day 24	Stroke	Confirmed / Ischemic stroke	65 years old / female / 28.4 kg/m^2 / hypertension and concomitant use of diclofenac / never smoked	Concomitant medication was given and the outcome of the event was recovering / resolving
Secukinumab IV→75 mg	Day 445	Stroke	Confirmed / Ischemic stroke	54 years old / female / 26.6 kg/m^2 / concomitant use of antihypertensive medications and intermittent heart palpitations / never smoked	Concomitant medication was given and the outcome of the event was recovered at Day 449
Secukinumab IV→75 mg	Day 245	Intracranial venous sinus thrombosis	Confirmed / Hemorrhagic stroke	57 years old / female / 35.4 kg/m^2 / atrial fibrillation, hypertension, cardioversion, renal failure, myocarditis / former smoker	Concomitant medication was given and the outcome of the event was death.

Secukinumab IV→75 mg	Day 388	Cerebral infarction	Confirmed / Ischemic stroke	64 years old / female / 22.9 kg/m^2 / uncomplicated diabetes, hypertension / never smoked	Concomitant medication was given and the outcome of the event was recovered at Day 390
Placebo responder switched to secukinumab 150 mg	Day 542	Myocardial infarction	Confirmed / Type 1: Spontaneous MI	61 years old / male / 24.1 kg/m^2 / coronary artery disease, hypertension, hyperlipidemia, myocardial ischemia, hypercholesterolemia / former smoker	Concomitant medication was given and the outcome of the event was recovered at Day 545

BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; LDL, low density lipoprotein; MI, myocardial infarction

Supplementary References

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