Efficacy and Safety of Subcutaneous and Intravenous Loading Dose Regimens of Secukinumab in Patients with Active Rheumatoid Arthritis: Results from a Randomized Phase II Study

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ABSTRACT. ***Objective.*** To evaluate the efficacy and safety of secukinumab, a fully human antiinterleukin-17A monoclonal antibody, administered with an intravenous (IV) or subcutaneous (SC) loading regimen versus placebo, in patients with active rheumatoid arthritis (RA).

Methods. In this phase II, double-blind, double-dummy, 52-week study (ClinicalTrials.gov NCT01359943), 221 patients with inadequate response to methotrexate were randomized (2:2:1) to secukinumab, IV loading 10 mg/kg at baseline, Weeks 2 and 4, then SC 150 mg every 4 weeks (n = 88); secukinumab SC loading 150 mg once weekly for 5 weeks, then every 4 weeks (n = 89); or a matching placebo (followed by secukinumab 150 mg every 4 weeks starting Week 16; n = 44). The primary endpoint was superior efficacy of pooled secukinumab versus placebo using American College of Rheumatology 20% response (ACR20) at Week 12.

Results. The primary efficacy endpoint was not met: ACR20 response at Week 12 was 49.2% for pooled secukinumab versus 40.9% for placebo ($p = 0.3559$). These variables improved significantly with pooled secukinumab versus placebo at Week 12 (all $p < 0.05$): the 28-joint Disease Activity Score (DAS28), patient's and physician's global assessment of disease activity, patient's assessment of RA pain, and high-sensitivity C-reactive protein levels. Results of continuous efficacy outcomes were similar between the IV and SC loading regimens. The most frequent adverse events were infections, with similar rates across secukinumab and placebo.

Conclusion. Although the primary endpoint (ACR20) was not met, secukinumab demonstrated improved efficacy in reducing disease activity over placebo as measured by DAS28 and other secondary endpoints. (J Rheumatol First Release February 1 2016; doi:10.3899/jrheum.150117)

Key Indexing Terms:

SECUKINUMAB	RHEUMATOID ARTHRITIS	INTERLEUKINS
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Rheumatoid arthritis (RA) is a progressive, chronic, inflammatory, autoimmune disease characterized by synovial inflammation and destruction of joint cartilage and bone. RA affects around 0.5% to 1.0% of the population of developed countries and is associated with decline of functional status, significant morbidity, reduced health-related quality of life, and premature mortality[1,2].

Recently, Th17 cells have been identified as prominent in RA pathology[3,4]. Interleukin 17A (IL-17A), the principal effector cytokine of Th17 cells, has been shown to play a direct pathogenic role in both inflammatory and destructive joint tissue manifestations of RA[5,6,7]. It has been implicated in the promotion of osteoclastogenesis[8], cartilage breakdown[9], and bone erosion[10]. On the basis of experimental and clinical evidence[10,11,12,13,14,15,16,17], IL-17A has emerged as a potential therapeutic target for the treatment of RA.

Secukinumab, a fully human IgG1κ anti–IL-17A monoclonal antibody, has been shown to be well tolerated with preliminary evidence of efficacy in patients with active RA[14,15,16]. In a proof-of-concept trial, the American College of Rheumatology 20% response (ACR20) rates were significantly higher with secukinumab infusions than with placebo at Week 6, and the response was observed as early as Week 4 and maintained at Week 16[14]. In a 1-year, phase II, dose-finding trial in patients with active RA responding inadequately to disease-modifying antirheumatic drugs or biologics, patients who were receiving subcutaneous (SC) secukinumab had sustained or improved ACR responses and 28-joint Disease Activity Score (DAS28) C-reactive protein (CRP) scores for up to 1 year; the improvements were highest with the 150 mg and the 300 mg doses compared with the 25 mg and 75 mg doses[15,16].

In proof-of-concept trials in other indications, secukinumab rapidly improved the signs and symptoms of ankylosing spondylitis[18] and showed therapeutic potential in psoriatic arthritis[19]. Recent phase III trials with secukinumab in moderate to severe plaque psoriasis have shown significant efficacy compared with placebo and etanercept[20].

Our phase II study was conducted to assess the efficacy, safety, and tolerability of secukinumab (150 mg SC maintenance dosing) administered following either intravenously (10 mg/kg IV, given every 2 weeks for a total of 3 doses) or SC (150 mg, 4 loading doses at baseline and Weeks 1, 2, and 3, with every-4-week dosing starting at Week 4) secukinumab loading regimens, compared with placebo (at Week 12), in patients with active RA despite stable treatment with methotrexate (MTX). The study also assessed maintenance therapy with secukinumab 150 mg SC until Week 52.

MATERIALS AND METHODS

Study design and patient population. This phase II, multicenter, double-blind, double-dummy, randomized, parallel-group, placebo-controlled study (ClinicalTrials.gov identifier: NCT01359943) was conducted at 38 centers across Bulgaria, Canada, Hungary, Italy, Poland, Slovakia, and the United States between October 2011 (first patient first visit) and December 2013 (last patient last visit). The study consisted of a 4-week screening period, a 16-week double-blind treatment period, a 36-week open-label maintenance period, and an 8-week followup period (Figure 1). The study protocol was approved by the institutional review board or ethics committee at each participating site. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and patients provided written informed consent before enrollment.

Patients with RA (≥ 3 mos, ACR 1987 revised criteria) were eligible to enter the study if they were aged ≥ 18 years with active disease (≥ 6 tender joints out of 68 and ≥ 6 swollen joints out of 66 at baseline), presence of rheumatoid factor and/or anticyclic citrullinated peptide antibodies, and high-sensitivity CRP (hsCRP) ≥ 10 mg/l and/or erythrocyte sedimentation rate (ESR) ≥ 28 mm at screening. Patients were required to have received MTX treatment (7.5–25 mg/wk) at least 3 months before randomization and to have had an inadequate response to treatment. Patients taking MTX, systemic corticosteroids, or nonsteroidal antiinflammatory drugs had to be taking a stable dose for at least 4 weeks before randomization.

The major exclusion criteria included ongoing rheumatic or inflammatory joint diseases other than RA, any active infections, history of malignancy, history of hepatitis B or hepatitis C, severe ongoing uncontrolled medical conditions, active tuberculosis, previous exposure ever to an anti-tumor necrosis factor-α (TNF-α) agent or any other immunomodulatory biologic agent (experimental or approved), or live vaccination within 6 weeks before randomization.

Patients were randomized in a 2:2:1 ratio to one of the 3 treatment groups: secukinumab 10 mg/kg IV at baseline and Weeks 2 and 4, followed by secukinumab 150 mg SC every 4 weeks starting at Week 8 through Week 48 (secukinumab IV loading group); secukinumab 150 mg SC at baseline and Weeks 1, 2, 3, and 4, followed by 150 mg SC every 4 weeks starting at Week 8 through Week 48 (secukinumab SC loading group); or a matching IV and SC placebo, followed by secukinumab 150 mg SC every 4 weeks starting at Week 16 through Week 48 (placebo–secukinumab group). The secukinumab IV and SC groups received placebo injections corresponding to the other treatment groups to maintain a double-blind, double-dummy design. The placebo-controlled period was through Week 16.

Study outcomes and assessments. The primary outcome was to assess the superiority of the pooled secukinumab (IV and SC) loading dose regimens compared with placebo with respect to the proportion of patients achieving the ACR20 response at Week 12. The secondary outcomes were to compare the 2 secukinumab regimens (IV and SC) with placebo and each other at Week 12 and over time using the ACR20/50/70 response, DAS28 response (using hsCRP or ESR), and improvements in the ACR core components [patient's global assessment (PtGA) and physician's global assessment (PGA) of disease activity, patient's assessment of RA pain, serum levels of hsCRP, and Health Assessment Questionnaire-Disability Index (HAQ-DI)].

Safety was evaluated by assessing adverse events (AE) including severity, regular monitoring of hematologic and serum chemistry laboratory values, and assessments of vital signs, physical examination and body weight. Immunogenicity assessments to detect anti-secukinumab antibodies were performed using the Meso Scale Discovery bridging assay[20] following a 3-tier approach (screening, confirmation, and titration)[21].

Statistical analyses. The demographic data and baseline characteristics were summarized for all patients who underwent randomization (randomized set; 1 misrandomized patient was excluded). P values were generated using Cochran-Mantel-Haenszel test for discrete variables, and k-sample version (e.g., Kruskal-Wallis test) of the Wilcoxon rank-sum test for continuous variables. The analysis of efficacy variables was performed on data from all patients to whom the study treatment was assigned (full analysis set), according to the intention-to-treat principle. Analyses of safety endpoints were performed on all patients who received at least 1 dose of the study drug (safety set); safety endpoints were summarized descriptively.

The primary efficacy variable was response to treatment according to the ACR20 criteria at Week 12. The ACR20 response was evaluated using logistic regression, with treatment as a factor and baseline weight as a covariate. OR were computed for comparisons of the secukinumab regimens versus the placebo regimen using a logistic regression model. The primary comparison pooled the 2 secukinumab doses compared with placebo, and then each dose of secukinumab was compared separately with placebo. Each comparison with placebo was done at a 5% 2-sided type I error rate; no adjustment for multiplicity of testing was made. For secondary endpoints, the treatment groups were compared with placebo at both Week 12 and other timepoints.

Sample size calculations were performed using NQuery software (advisor 6.01, PTT2). For the primary comparison of the pooled secukinumab doses versus placebo, 86 patients per each of the 2 secukinumab arms and 43 patients receiving placebo were required to yield about 81% power to detect a 25% treatment difference with a 5% 2-sided type I error rate (assuming that all patients have postrandomization data). For the tests of each individual secukinumab group (n = 86) versus placebo (n = 43), the study would have roughly 72% power to show a significant difference between each of the secukinumab dose regimens and placebo at a 5% significance level in a 2-sided Fisher's exact test.

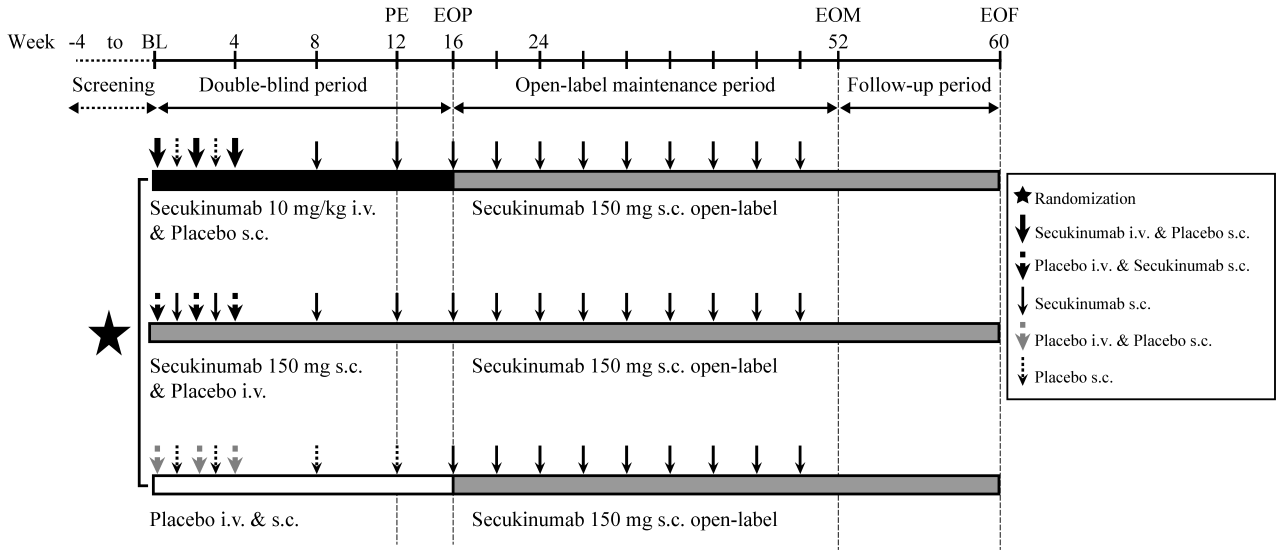

Figure 1. The study design. BL: baseline; PE: primary endpoint; EOP: end of placebo-controlled period; EOM: end of open-label maintenance period; EOF: end of followup period; i.v.: intravenous; s.c.: subcutaneously.

RESULTS

Demographics and baseline characteristics. The patient demographics and baseline characteristics were comparable across the treatment groups (Table 1). There was no statistically significant difference between the treatment groups for any of the variables. Of the 221 randomized patients, 215 patients (97.3%) completed the 12-week treatment period. Discontinuations (2.7%) were primarily due to AE, abnormal laboratory values, and withdrawal of consent. One patient did not receive the study treatment at Week 16 and was excluded from post-Week 16 analyses. Of 214 patients who entered the open-label period, 185 (86.4%) completed the 52-week treatment period and 29 (13.6%) discontinued, primarily because of AE, unsatisfactory effect, and withdrawal of consent (Figure 2).

Efficacy outcomes. The primary objective of achieving

Table 1. Demographic data and baseline characteristics of study patients. Plus/minus values are mean ± SD.

Variables	Secukinumab IV Loading, n = 88	Secukinumab SC Loading, n = 89	Placebo, n = 44
Age, yrs	53.8 ± 11.81	54.5 ± 12.26	53.5 ± 9.33
Female, n (%)	67 (76.1)	72 (80.9)	37 (84.1)
Race, n (%)			
White	86 (97.7)	85 (95.5)	44 (100)
Black	0	2 (2.2)	0
Other	2 (2.3)	2 (2.2)	0
Body weight, kg	74.4 ± 15.15	76.6 ± 19.15	71.3 ± 13.62
Duration of RA, yrs	7.7 ± 7.91	7.6 ± 7.14	7.5 ± 7.72
Adjusted swollen 66-joint count†	14.3 ± 7.39	15.0 ± 10.50	13.3 ± 5.82
Adjusted tender 68-joint count†	23.6 ± 12.93	23.0 ± 12.37	22.2 ± 10.26
DAS28-CRP	5.6 ± 1.06	5.5 ± 0.97	5.7 ± 0.82
DAS28-ESR	6.4 ± 0.97	6.4 ± 0.96	6.4 ± 0.78
Patient's global assessment of disease activity, VAS, mm	60.0 ± 23.27	60.8 ± 22.05	60.3 ± 16.21
Physician's global assessment of disease activity, VAS, mm	62.9 ± 15.15	63.5 ± 16.85	61.9 ± 14.20
Patient's assessment of RA pain, VAS, mm	54.9 ± 23.86	59.1 ± 21.23	55.9 ± 18.62
hsCRP, mg/l	11.6 ± 14.26	13.7 ± 19.50	10.3 ± 9.32
HAQ-DI	1.5 ± 0.64	1.5 ± 0.65	1.5 ± 0.61
RF, U/ml	129.2 ± 124.75	142.9 ± 207.48	170.3 ± 187.05
RF-positive (≥ 14 U/ml), n (%)	84 (95.5)	85 (95.5)	44 (100)
Anti-CCP antibody-positive, n (%)	77 (87.5)	71 (79.8)	35 (79.5)

†If the number of joints for which data were available (e.g., T) was < 66 for the swollen joint assessment or < 68 for the tender joint assessment, the number of swollen or tender joints (e.g., t) was scaled up proportionately (i.e., 66*[t/T] for swollen joint or 68*[t/T] for tender joint). IV: intravenous; SC: subcutaneous; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; RF: rheumatoid factor; hsCRP: high-sensitivity CRP; RA: rheumatoid arthritis; VAS: visual analog scale.

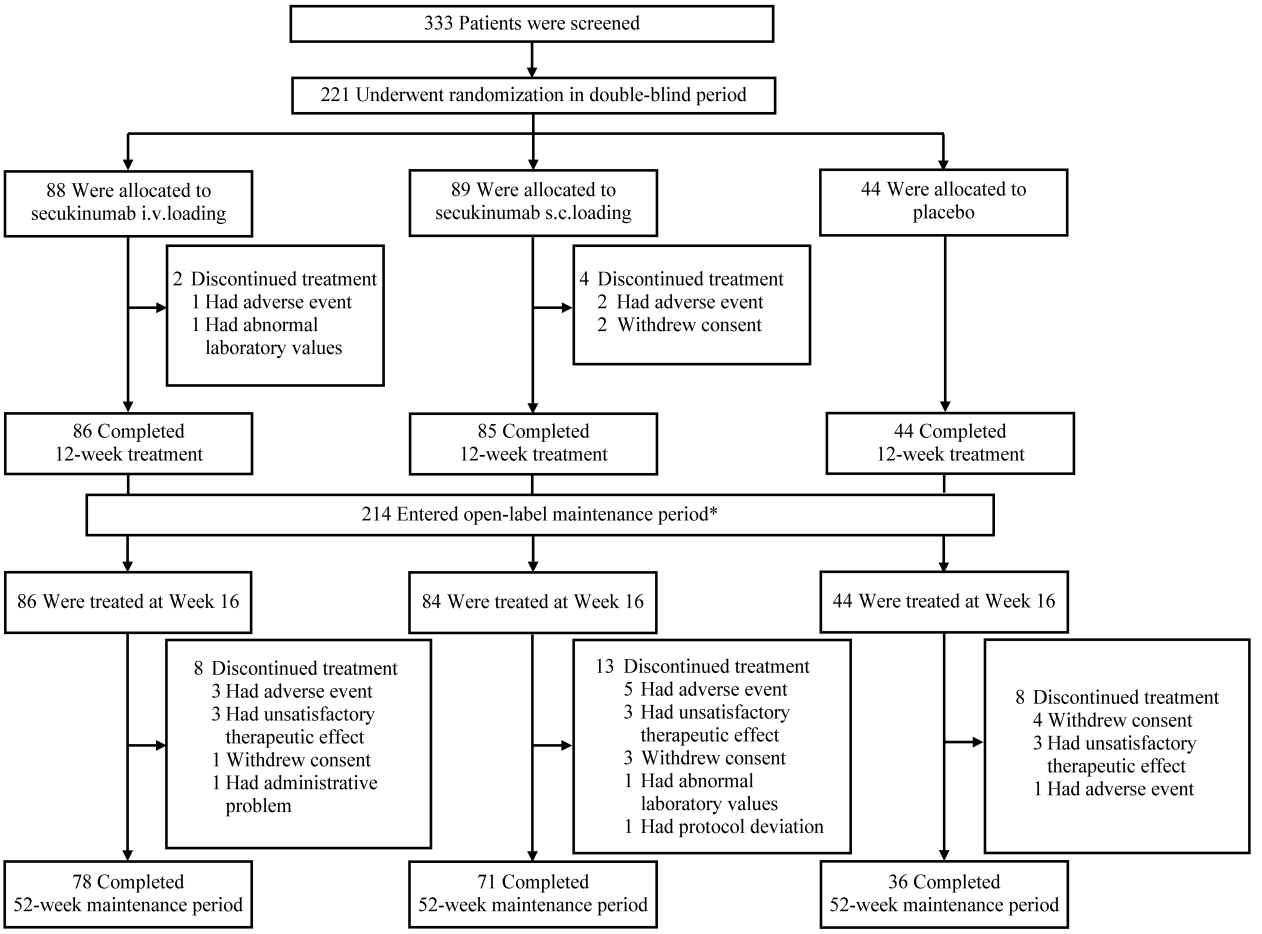

Figure 2. Patient disposition. *Starting from Week 16, all patients received open-label secukinumab 150 mg subcutaneously (s.c.) after completing all Week 16 assessments. One patient from the secukinumab s.c. loading group did not receive the study drug at Week 16. i.v.: intravenously.

superior ACR20 response at Week 12 with pooled secukinumab versus placebo was not met. At Week 12, ACR20 response rate was 49.2% in the pooled secukinumab group compared with 40.9% in the placebo group [OR 1.37 (95% CI 0.70, 2.69); p = 0.3559; Table 2]. ACR50 and ACR70 responses at Week 12 were 19.2% and 6.8%, respectively, in the pooled secukinumab group compared with 11.4% and 0% in the placebo group. At Week 12, reductions of DAS28-CRP and DAS28-ESR were significantly greater for the pooled secukinumab group compared with the placebo group ($p < 0.05$; Table 2).

The treatment differences in terms of change in ACR20 response rate from baseline were statistically significant at Weeks 1, 2, 3, 4, and 16 for the pooled secukinumab group compared with the placebo group ($p < 0.05$). At all timepoints through Week 16, ACR50 and ACR70 responses were low in all the treatment groups, but these responses were numerically greater for the pooled secukinumab group compared with the placebo group (ACR50 at Week 16: 19.2% vs 9.1%; ACR70 at Week 16: 7.9% vs 2.3%). The reductions in DAS28-CRP and DAS28-ESR were significantly greater for the pooled secukinumab group compared with the placebo group at all timepoints from Week 1 to Week 16 (all $p < 0.05$). At Week 16, the least-squares mean difference in DAS28-CRP and DAS28-ESR between pooled secukinumab and placebo were –0.53 (95% CI –0.90, –0.17) and –0.55 (95% CI –0.95, –0.14), respectively.

ACR20 response rates in the secukinumab IV and SC loading groups were comparable, with no statistical differences through Week 12, except at Week 16 ($p < 0.05$ for the IV loading group compared with the SC loading group). Similarly, ACR50 and ACR70 response rates of secukinumab IV and SC loading groups were comparable, with no statistical differences at any timepoint through Week 16 (Figure 3A-3C). Reductions of the DAS28-CRP (Figure 3D) and DAS28-ESR in the secukinumab IV and SC loading groups were similar, with no statistical differences between the 2 regimens for either DAS28-CRP or DAS28-ESR through Week 16.

During the open-label period post-Week 16 through Week

Table 2. Efficacy outcomes at Week 12 (primary and secondary endpoints).

Variables	Secukinumab IV Loading, n = 88	Secukinumab SC Loading, n = 89	Secukinumab Pooled, n = 177	Placebo, n = 44
ACR20 responders, n (%)	47 (53.4)	40 (44.9)	87 (49.2)	18 (40.9)
ACR50 responders, n (%)	18 (20.5)	16 (18.0)	34 (19.2)	5 (11.4)
ACR70 responders, n (%)	7 (8.0)	5 (5.6)	12 (6.8)	0 (0.0)
DAS28-CRP				
LS mean of change (SE)	−1.7 (0.12)	−1.7 (0.12)	−1.7 (0.08)	−1.2 (0.17)
LS mean difference (SE) vs placebo	−0.5 (0.20)*	−0.4 (0.21)*	−0.5 (0.19)*	
DAS28-ESR				
LS mean change from baseline (SE)	−2.0 (0.13)	−1.8 (0.13)	−1.9 (0.09)	−1.5 (0.18)
LS mean difference (SE) vs placebo	−0.5 (0.22)*	−0.4 (0.22)	−0.4 (0.20)*	
Patient's global assessment of disease activity, VAS, mm				
LS mean change from baseline (SE)	−18.6 (2.04)	−15.3 (2.06)	−16.9 (1.45)	−9.9 (2.88)
LS mean difference (SE) vs placebo	−8.7 (3.53)*	−5.4 (3.55)	−7.0 (3.23)*	
Physician's global assessment of disease activity, VAS, mm				
LS mean change from baseline (SE)	−27.1 (1.93)	−29.0 (1.95)	−28.0 (1.37)	−18.9 (2.73)
LS mean difference (SE) vs placebo	−8.2 (3.34)*	−10.1 (3.36)*	−9.2 (3.05)*	
Patient's assessment of RA pain, VAS, mm				
LS mean change from baseline (SE)	−14.4 (2.06)	−12.6 (2.07)	−13.5 (1.46)	−6.7 (2.90)
LS mean difference (SE) vs placebo	−7.8 (3.56)*	−6.0 (3.57)	−6.9 (3.25)*	
hsCRP				
LS mean change from baseline (SE)	−6.0 (0.94)	−5.7 (0.95)	−5.9 (0.67)	−1.7 (1.34)
LS mean difference (SE) vs placebo	−4.3 (1.63)*	−4.0 (1.64)*	−4.2 (1.50)*	
HAQ-DI				
LS mean change from baseline (SE)	−0.4 (0.05)	−0.3 (0.05)	−0.3 (0.04)	−0.2 (0.07)
LS mean difference (SE) vs placebo	−0.2 (0.09)	−0.1 (0.09)	−0.1 (0.08)	

*p < 0.05 for comparison with placebo. ACR: American College of Rheumatology; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire–Disability Index; hsCRP: high-sensitivity C-reactive protein; IV: intravenous; LS: least-square; RA: rheumatoid arthritis; SE: standard error; SC: subcutaneous; VAS: visual analog scale.

52, ACR20, ACR50, and ACR70 response rates were maintained in the secukinumab IV and SC loading groups (Figure 3 A-C). For all the placebo patients who switched to secukinumab 150 mg SC at Week 16 without a loading regimen, that is, the placebo–secukinumab group, ACR20 response rates increased from 29.5% at Week 16 to 52.3% at Week 52. ACR50 and ACR70 response rates were 9.1% and 2.3% at Week 16 and 13.6% and 4.5% at Week 52, respectively, in the placebo–secukinumab group.

Reductions of the DAS28-CRP and DAS28-ESR were comparable between the secukinumab IV loading, secukinumab SC loading, and placebo–secukinumab groups throughout the maintenance period. At Week 52, the mean changes in DAS28-CRP and DAS28-ESR from baseline were −2.24 and −2.59 (secukinumab IV loading), −2.14 and −2.45 (secukinumab SC loading), and −2.38 and −2.77 (placebo–secukinumab), respectively. The mean change from baseline to post-Week 16 through Week 52 with secukinumab (all 3 groups included) ranged from −1.77 to −2.23 for DAS28-CRP and −2.04 to −2.59 for DAS28-ESR.

Improvements in the ACR core components (PtGA, PGA, and patient's assessment of RA pain) were also significantly greater at Week 12 in the pooled secukinumab group compared with the placebo group ($p < 0.05$; Table 2). The improvements were significant at Weeks 2, 4, 8, 12, and 16 for PtGA; starting at Week 1 through Week 16 for PGA; and starting at Week 2 through Week 16 for patient's assessment of RA pain ($p < 0.05$). During the open-label period post-Week 16 through Week 52, the ACR core components further improved across the treatment groups.

Serum hsCRP levels decreased significantly by Week 12 in the pooled secukinumab group compared with the placebo group ($p < 0.05$; Table 2). The decreases in hsCRP levels were also significantly greater for the pooled secukinumab group compared with the placebo group at Weeks 1, 2, 3, and 16 ($p < 0.05$). The decreases in hsCRP levels in the secukinumab IV and SC loading groups were comparable, with no statistical differences through Week 16.

The HAQ-DI scores showed a greater decrease in the pooled secukinumab group versus the placebo group at all timepoints, but statistical significance was only achieved at Weeks 3 (least-square mean difference −0.17, $p = 0.0097$) and 16 (least-square mean difference −0.18, $p = 0.0410$).

Safety outcomes. No deaths were reported during our study. During the 16-week placebo-controlled treatment period, the proportion of patients who experienced an AE was higher in the secukinumab SC loading group (50.6%) compared with the secukinumab IV loading (40.9%) and placebo groups (43.2%; Table 3). The majority of AE across the study population were mild to moderate in severity (27.1% mild,

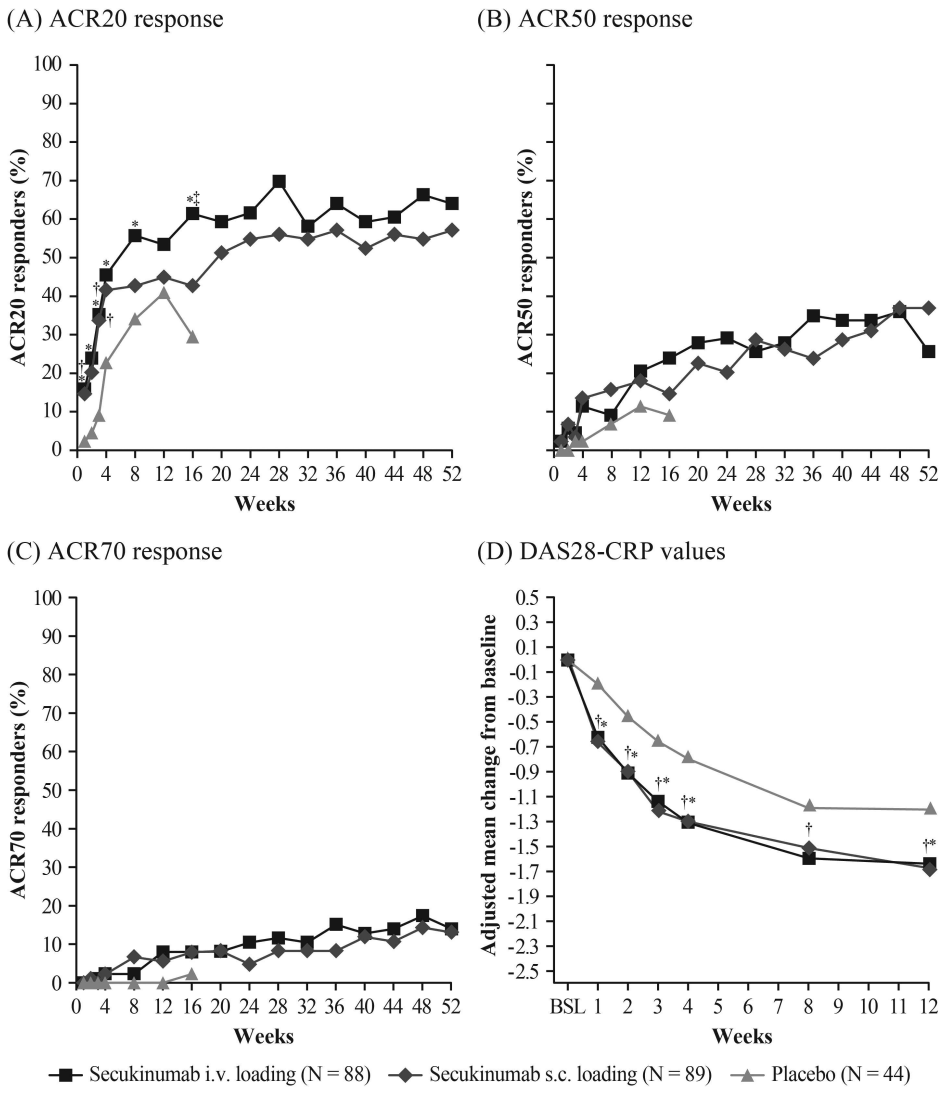

Figure 3. ACR20 (A), ACR50 (B), ACR70 (C) responses, and DAS28- CRP values (D) over time. Missing ACR responses were considered nonresponders. Moreover, for patients who discontinued the study before Week 16, any ACR responses from the time of discontinuation were set as nonresponders. All patients who entered the maintenance phase and dosed at Week 16 were given open-label secukinumab 150 mg s.c. (subcutaneously) every 4 weeks through Week 48. Panel D shows the mean DAS28-CRP over time from baseline to Week 12 for the 3 different treatment groups. *$p < 0.05$ for secukinumab i.v. (intravenous) loading group in comparison with placebo; †$p < 0.05$ for secukinumab s.c. loading group in comparison with placebo; ‡$p < 0.05$ for secukinumab i.v. loading group in comparison with s.c. loading group. ACR: American College of Rheumatology; BSL: baseline; DAS28: 28-joint Disease Activity Score; CRP: C-reactive protein.

16.3% moderate, and 1.8% severe). The proportion of patients with infections and infestations was 21.6% in the secukinumab IV loading group, 18.0% in the secukinumab SC loading group, and 22.7% in the placebo group. The most frequently reported AE across the treatment groups were nasopharyngitis (6.3%), headache (3.2%), and worsening of RA (3.2%). Serious AE were reported by 6 (2.7%) patients: 2 (2.3%) in the secukinumab IV loading group, 3 (3.4%) in the secukinumab SC loading group, and 1 (2.3%) in the placebo group. During the placebo-controlled period, there was 1 patient in the placebo group who had a myocardial infarction, with baseline risk factors of hyperlipidemia and a 40 pack-year smoking history (Supplementary Table 1, available from the authors on request). In total, 4 patients (1.8%) discontinued the study treatment owing to an AE (acute tonsillitis, herpes zoster, brain neoplasm, and increased hepatic enzymes; Supplementary Table 2, available from the authors on request).

During the open-label period post-Week 16 through Week 52 when all patients had been switched to secukinumab

Table 3. Adverse events during the double-blind period and open-label period. Affected system organ classes listed here are those reported in at least 10% of patients; preferred terms are those reported in at least 5% of patients within the affected system organ class. Data are n (%).

Variables	Adverse Events up to Week 16				Adverse Events during Open-label Period			
	Secukinumab IV Loading, n = 88	Secukinumab SC Loading, n = 89	Any Secukinumab, n = 177	PBO, n = 44	Secukinumab IV Loading, n = 86	Secukinumab SC Loading, n = 84	PBO–Secukinumab, n = 44	Any Secukinumab, n = 214
Any adverse event	36 (40.9)	45 (50.6)	81 (45.8)	19 (43.2)	51 (59.3)	52 (61.9)	21 (47.7)	124 (57.9)
Deaths	0	0	0	0	0	0	0	0
Any serious adverse event	2 (2.3)	3 (3.4)	5 (2.8)	1 (2.3)	6 (7.0)	10 (11.9)	2 (4.5)	18 (8.4)
Discontinuations because of adverse event	1 (1.1)	3 (3.4)	4 (2.3)	0	3 (3.5)	4 (4.8)	2 (4.5)	9 (4.2)
Infections and infestations	19 (21.6)	16 (18.0)	35 (19.8)	10 (22.7)	28 (32.6)	29 (34.5)	13 (29.5)	70 (32.7)
Nasopharyngitis	5 (5.7)	5 (5.6)	10 (5.6)	4 (9.1)	3 (3.5)	4 (4.8)	4 (9.1)	11 (5.1)
Upper respiratory tract infection	1 (1.1)	1 (1.1)	2 (1.1)	0	8 (9.3)	7 (8.3)	2 (4.5)	17 (7.9)
Pharyngitis	0	1 (1.1)	1 (0.6)	0	1 (1.2)	5 (6.0)	0	6 (2.8)
Oral herpes	0	1 (1.1)	1 (0.6)	3 (6.8)	2 (2.3)	3 (3.6)	0	5 (2.3)
Musculoskeletal and connective tissue disorders	3 (3.4)	11 (12.4)	14 (7.9)	3 (6.8)	14 (16.3)	14 (16.7)	6 (13.6)	34 (15.9)
Rheumatoid arthritis	0	5 (5.6)	5 (2.8)	2 (4.5)	7 (8.1)	4 (4.8)	2 (4.5)	13 (6.1)
Gastrointestinal disorders	8 (9.1)	7 (7.9)	15 (8.5)	1 (2.3)	7 (8.1)	10 (11.9)	2 (4.5)	19 (8.9)
Respiratory, thoracic, and mediastinal disorders	4 (4.5)	3 (3.4)	7 (4.0)	2 (4.5)	8 (9.3)	4 (4.8)	5 (11.4)	17 (7.9)
Cough	0	1 (1.1)	1 (0.6)	0	2 (2.3)	2 (2.4)	3 (6.8)	7 (3.3)

IV: intravenous; SC: subcutaneous; PBO: placebo.

150 mg SC, the proportion of patients experiencing an AE was lower in the patients who had previously received placebo (47.7%) compared with the secukinumab IV loading group (59.3%) and the secukinumab SC loading group (61.9%; Table 3). The proportion of patients with infections and infestations was 32.6% in the secukinumab IV loading group, 34.5% in the secukinumab SC loading group, and 29.5% in the placebo–secukinumab group. The most frequently reported AE across the treatment groups were upper respiratory tract infection (7.9%), worsening of RA (6.1%), hypertension (5.1%), and nasopharyngitis (5.1%). Serious AE were reported by 18 patients (8.4%; 6 in the secukinumab IV loading group, 10 in the secukinumab SC loading group, and 2 in the placebo–secukinumab group). During the open-label period, 1 patient in the secukinumab IV loading group had a myocardial infarction, with baseline risk factors of diabetes mellitus and hypertension. Serious AE and AE leading to discontinuation of the study drug during the open-label period are presented in Supplementary Tables 3 and 4, available from the authors on request.

One patient each in the secukinumab SC loading group reported grade 2 neutropenia during the 16-week placebo-controlled and open-label treatment periods; neither patient discontinued the study treatment or had associated infections. Grade 3 lymphocytopenia and anemia were reported by 1 patient each in the secukinumab SC loading group during the 16-week placebo-controlled period, and by 1 and 2 patients, respectively, in the secukinumab SC loading group during the open-label treatment. Grade 4 cytopenia was not reported by any patient.

Treatment-emergent anti-drug antibodies (developing on secukinumab treatment in patients negative for anti-drug antibodies at baseline) were detected in 4 patients. None was associated with a loss of efficacy or clinically relevant AE.

DISCUSSION

A statistically significant treatment difference with pooled secukinumab was not achieved at Week 12 in ACR20 response versus placebo, with significant differences observed only at Week 1 through Week 4 and at Week 16 ($p < 0.05$). However, the pooled secukinumab group achieved statistically significant differences ($p < 0.05$) from placebo on several secondary endpoints at most timepoints through Week 16, including DAS28, PtGA, PGA, RA pain, hsCRP, and HAQ-DI.

While secukinumab IV loading demonstrated numerically higher efficacy for ACR20 than SC loading, there was no statistical difference between the 2 regimens. For DAS28-CRP and DAS28-ESR, continuous variables better suited to measure differences in efficacy between smaller cohorts[22], reduction in disease activity was similar over time for the secukinumab IV and SC loading groups (Figure 3D).

In a previous phase II, dose-finding study with secukinumab in patients with active RA who responded inadequately to disease-modifying antirheumatic drugs or biologics, the primary endpoint (ACR20 at Week 16) was also not met. ACR20 responses with secukinumab at doses of 25 mg to 300 mg were not significantly different from placebo at Week 16, but the decrease in DAS28-CRP was significantly higher with secukinumab 75 mg and 150 mg

versus placebo from baseline over the 16-week period[15]. In the current study, the Week 12 timepoint for primary efficacy assessment was chosen. Akin to the previous dose-finding study[15], the primary endpoint was not met in this regimen-finding study. Notably, a significant ACR20 response and improved RA signs and symptoms at Week 12 were observed with another IL-17A inhibitor, ixekizumab, versus placebo, in a phase II study in patients with RA who were either naive to treatment with biologics or had an inadequate response to TNF inhibitors[17]. In general, the ACR response rates observed in the current study are lower than those reported for placebo-controlled studies of anti–TNF-α agents (adalimumab, etanercept) and anti–IL-6 receptor antibodies (tocilizumab, olokizumab), but similar to those of ixekizumab[17,23,24,25,26,27,28]. Results from the ongoing phase III studies with secukinumab in patients with RA are expected to provide more definitive conclusions on its efficacy in these patients.

Secukinumab was well tolerated in our study with an AE profile consistent with that reported in the phase II secukinumab dose-finding study in RA[15,16]. The safety profiles of the secukinumab IV and SC loading groups were comparable. Most of the AE were mild or moderate in severity, with infections and infestations being the most common system organ class, although clinically significant neutropenia was not observed. Immunogenicity was very low.

Limitations of our study include the relatively small sample size that did not allow investigation of subgroups based on particular baseline characteristics that may have been of interest, such as MTX or corticosteroid dose. The sample size may have also contributed to the failure to achieve statistical significance for the primary endpoint, because ACR20 is a binary outcome measure that is less sensitive in detecting therapeutic responses in smaller cohorts. In contrast, DAS28, which is a continuous variable, did reach statistical significance for the pooled secukinumab treatments versus placebo at Week 12.

The efficacy observed with secukinumab in this phase II study did not achieve statistical significance versus placebo for the primary endpoint of ACR20. Numerically higher efficacy responses were observed with both the IV and SC secukinumab loading regimens over time for most of the outcome measures; efficacy particularly regarding ACR50 and ACR70 rates was lower than that observed in phase III trials with currently approved biologics[26,29] and comparable to that of another IL-17 antagonist[17]. The efficacy through Week 12 observed with the secukinumab 10 mg/kg IV loading regimen was comparable to the efficacy observed with the 150 mg SC loading regimen, suggesting that exposure higher than the 150 mg SC loading does not result in greater efficacy. The safety profile of secukinumab was consistent with the known benefit-risk profile of secukinumab in patients with RA, based on earlier phase I and II trials[14,15,16].

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