

One-year Efficacy and Safety Results of Secukinumab in Patients With Rheumatoid Arthritis: Phase II, Dose-finding, Double-blind, Randomized, Placebo-controlled Study

Mark C. Genovese, Patrick Durez, Hanno B. Richards, Jerzy Supronik, Eva Dokoupilova, Jacob A. Aelion, Sang-Heon Lee, Christine E. Coddling, Herbert Kellner, Takashi Ikawa, Sophie Hugot, Gregory Ligozio, and Shephard Mpofu

ABSTRACT. Objective. To evaluate the longer-term safety and efficacy of secukinumab, a fully human monoclonal antiinterleukin-17A antibody, in patients with rheumatoid arthritis.

Methods. In this 52-week, double-blind, placebo-controlled (up to Week 20) study (NCT00928512), patients responding inadequately to disease-modifying antirheumatic drugs (DMARD) or biologics were randomized to receive monthly subcutaneous injections of secukinumab (25, 75, 150, or 300 mg), or placebo. The efficacy and safety results up to Week 20 have been reported previously. Here, efficacy results from Week 20 to 52 and safety results from Week 20 to 60 are presented.

Results. Of 237 patients randomized, 174 (73.4%) completed the study. Patients with improved American College of Rheumatology (ACR) and 28-joint Disease Activity Score (DAS28) C-reactive protein (CRP) responses at Week 16 sustained their responses through Week 52. In patients taking 150 mg of secukinumab, responses were improved through Week 52 (ACR50: Week 16 = 45%, Week 52 = 55%; DAS28-CRP \leq 2.6: Week 16 = 25%, Week 52 = 40%). The rate of adverse events (AE) from weeks 20 to 60 was 64.8%, with most AE being mild to moderate in severity. The overall rate of infections was 31.9%, most being mild. The most predominant infection was nasopharyngitis, and was not associated with dose or concurrent neutropenia. Serious AE were reported in 21 patients (8.9%). There were 3 reports of malignancies (ovarian, lung, basal cell), and no deaths between weeks 20 and 60.

Conclusion. Patients with active RA who failed to respond to DMARD and other biologics showed an improvement after longterm treatment with 150 mg of secukinumab. The frequency of AE remained stable over time and secukinumab had a consistent safety profile over 60 weeks. (J Rheumatol First Release Jan 15 2014; doi:10.3899/jrheum.130637)

Key Indexing Terms:

AUTOIMMUNE DISEASES
INTERLEUKINS

METHOTREXATE
MONOCLONAL ANTIBODIES

RHEUMATOID ARTHRITIS
SECUKINUMAB

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic, autoimmune disease of unknown etiology characterized by synovitis leading to joint damage¹. The pathogenesis of RA involves a cascade of inflammatory

processes of invading and resident cells along with inflammatory mediators such as cytokines, which ultimately leads to the destruction of joints². A number of novel cytokines have been implicated in the pathogenesis of RA³. There is

From Stanford University, Palo Alto, California, USA; Pôle de Recherche en Rhumatologie, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain and Cliniques Universitaires Saint-Luc, Brussels, Belgium; Novartis Pharma AG, Basel, Switzerland; NZOZ Centrum Medyczne Artur Racewicz, Białystok, Poland; Medical Plus, Uherske Hradiste, Czech Republic; Arthritis Clinic, Jackson, Tennessee, USA; Konkuk University Medical Center, Seoul, South Korea; Health Research of Oklahoma, Oklahoma City, Oklahoma, USA; Centre for Inflammatory Joint Diseases, Munich, Germany; Kobe-Konan Yamate Clinic, Kobe, Japan; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA.

Supported by an unrestricted grant from Novartis Pharma AG, Basel, Switzerland.

M.C. Genovese, MD, Stanford University; P. Durez, MD, Pôle de Recherche en Rhumatologie, Institut de Recherche Expérimentale et

Clinique, Université catholique de Louvain and Cliniques Universitaires Saint-Luc; H.B. Richards, MD, PhD, Novartis Pharma AG; J. Supronik, MD, PhD, NZOZ Centrum Medyczne Artur Racewicz; E. Dokoupilova, MD, Medical Plus; J.A. Aelion, MD, Arthritis Clinic; S.-H. Lee, MD, Konkuk University Medical Center; C.E. Coddling, MD, Health Research of Oklahoma; H. Kellner, MD, Centre for Inflammatory Joint Diseases; T. Ikawa, MD, Kobe-Konan Yamate Clinic; S. Hugot, MSc, Novartis Pharma AG; G. Ligozio, MS, Novartis Pharmaceuticals Corporation; S. Mpofu, MD, FRCP, Novartis Pharma AG.

Address correspondence to Dr. M.C. Genovese, Professor of Medicine, Co-Chief, Division of Immunology and Rheumatology, Stanford University, 1000 Welch Road #203, Palo Alto, California 94304, USA. E-mail: genovese@stanford.edu

Accepted for publication November 8, 2013.

consistent evidence that demonstrates the important role of interleukin 17 (IL)-17^{4,5,6,7,8,9,10}. IL-17 comprises 6 subtypes (IL-17A-F), of which IL-17A appears to play an important role in the immunopathogenesis of RA^{4,11}. Several clinical approaches have been developed targeting the IL-17 ligand, its receptor, or associated pathways, such as IL-23, IL-6, and IL-1^{12,13,14,15,16,17}. Another important approach involves antagonizing the transcriptional activity of the key factor retinoic acid-related orphan receptor γ for Th17 differentiation by small molecules¹⁸.

Secukinumab is a high-affinity fully human monoclonal antibody that selectively neutralizes IL-17A and might be effective in RA¹⁹ while preserving other Th17 and innate immune cell functions^{20,21}. Moreover, LY2439821 (ixekizumab), a humanized anti-IL-17 monoclonal antibody, is known to improve signs and symptoms of RA when compared with placebo²², further validating IL-17A neutralization as a potentially valuable target in the treatment of RA. Our study was conducted on patients with active RA despite stable treatment with methotrexate (MTX) to evaluate the efficacy and safety of subcutaneous secukinumab at different doses up to Week 52. The results of the data analyzed for up to Week 20 have been presented²³. Herein, we report the longer-term efficacy and safety.

MATERIALS AND METHODS

Study design and patient population. This was a phase II, dose-finding, double-blind, randomized, placebo-controlled study conducted in 11 countries (Belgium, the Czech Republic, Germany, Hungary, Japan, the Republic of Korea, Poland, Russia, Slovakia, Taiwan, and the United States) at 54 centers (NCT00928512).

Regulatory and ethical review board approvals from authorities in each country were obtained for the study protocol. All patients signed an informed consent document and the study was conducted in accordance with the Declaration of Helsinki and followed good clinical practice guidelines.

Key inclusion criteria were diagnosis of RA [American College of Rheumatology (ACR) 1987 revised criteria] with active disease (≥ 6 of 28 tender and ≥ 6 of 28 swollen joints) and failure of patients to respond to disease-modifying antirheumatic drugs (DMARD) and other biologics. Key exclusion criteria were severe ongoing uncontrolled medical conditions, positive tuberculosis screening, evidence of ongoing inflammatory diseases other than RA, active infections, history of malignancy, or use of prednisone > 10 mg/day. Patients taking current biologic therapy were excluded, but those with a history of use of any biologics were included after an appropriate washout period ranging from 1 week to 26 weeks depending on their half-life.

Adult patients ($n = 237$) taking MTX were randomized (1:1:1:1) to receive subcutaneous injections of secukinumab (25, 75, 150, and 300 mg), or placebo every 4 weeks for 48 weeks. All patients received treatment as initially randomized up to 16 weeks. Based on the assessment of ACR20 response at Week 16, doses of secukinumab were reassigned at Week 20. Patients achieving ACR20 response continued on the same dose while nonresponders taking 25- and 75-mg doses were increased to 150 mg; nonresponders taking 150 mg were increased to 300 mg, patients taking 300 mg of secukinumab continued the same dose regardless of their response, and those on placebo were given 150 mg of secukinumab (Figure 1). There was no placebo arm after Week 20. Stable doses of MTX (≥ 7.5 mg/week to ≤ 25 mg/week) during the trial and for at least 4 weeks prior to

randomization were required. Stable doses of corticosteroids (≤ 10 mg/day prednisone or equivalent) were permitted²³.

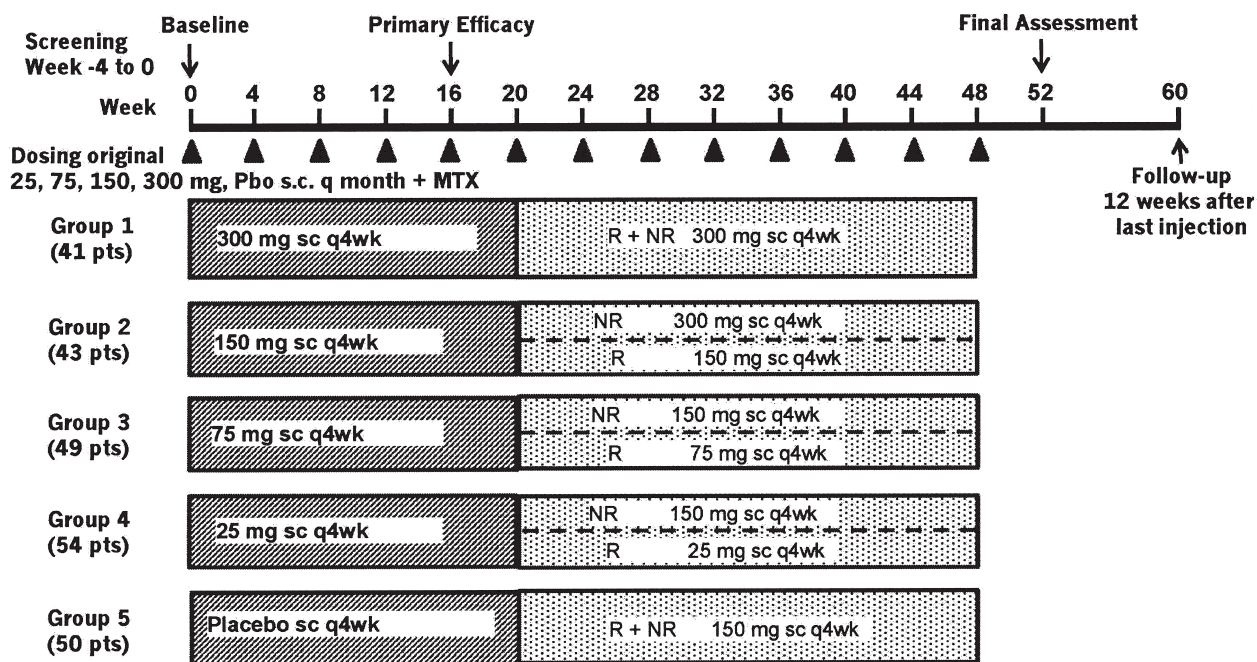
Study endpoints. The primary endpoint was proportion of patients achieving ACR20 response at Week 16. Other efficacy endpoints after Week 20 reported here are the proportion of patients achieving ACR 20, 50, and 70 response; 28-joint Disease Activity Score (DAS28) C-reactive protein (CRP); serum levels of high-sensitivity CRP (hsCRP); erythrocyte sedimentation rate (ESR); and Health Assessment Quality-Disability Index (HAQ-DI) scores. No radiographic data were obtained. Safety is reported here through the safety followup at Week 60.

Statistical analysis. All patients who continued the treatment at Week 20 at the same or reassigned dose regimen were included in the full analysis set and safety set from Week 20 to the end of the study. The proportion of patients achieving ACR20 response at Week 16 was compared with placebo for each of the secukinumab-treated groups based on a logistic regression model with treatment, center, baseline weight, and baseline DAS28 as covariates. Adverse events (AE) and serious AE (SAE) were summarized by absolute and relative frequencies, and by treatment group. A last observation carried forward approach was used for imputing missing values.

RESULTS

Patient demographics and baseline characteristics were comparable across all treatment groups as published²³, with 18.4% to 22.2% of patients previously exposed to biologics. Of a total of 290 patients screened, 237 were randomized to 1 of the 5 treatment groups, and 174 (73.4%) of those completed the study up to Week 60, regardless of the assigned dose. In total, 63 patients (26.6%) discontinued the study: 16 (6.75%) before Week 16²³, 5 (2.1%) between Week 16 and Week 20, and 42 (17.72%) between Week 20 and Week 60 (Figure 2). The reasons for study discontinuation between Week 20 and Week 60 were comparable between the treatment groups, with the exception of discontinuation due to AE (11.1%) and unsatisfactory therapeutic effect (16.7%), which was more frequent in patients receiving 25 mg of secukinumab throughout the study. None of the patients receiving 150 mg of secukinumab for the entire treatment period discontinued the study, neither because of unsatisfactory therapeutic effect nor because of withdrawal of consent (Figure 2).

As reported, statistical significance for the primary efficacy endpoint of ACR20 response at Week 16 was not achieved. ACR20 responses after 16 weeks taking secukinumab (25, 75, 150 and 300 mg dose groups) compared with placebo were 34%, 46.9%, 46.5%, and 53.7% versus 36.0%, respectively²³. After Week 16, patients who responded to secukinumab treatment sustained their response through Week 52 (Figures 3 and 4). Responders who kept taking 150 mg of secukinumab had the greatest improvement in response over time, with 55% and 40% of patients achieving ACR50 and ACR70 response, respectively, at Week 52 (Figure 3). Among patients taking the placebo who had achieved ACR20 response by Week 16 and were reassigned to 150 mg of secukinumab at Week 20, 50% achieved ACR50 response (Figure 3) and 22.2% achieved ACR70 response by Week 52. Additionally, the improvement in DAS28-CRP was sustained up to Week 52 in



R, responder; NR, non-responder; Pbo, placebo; N, number of patients; MTX, methotrexate; s.c., subcutaneous

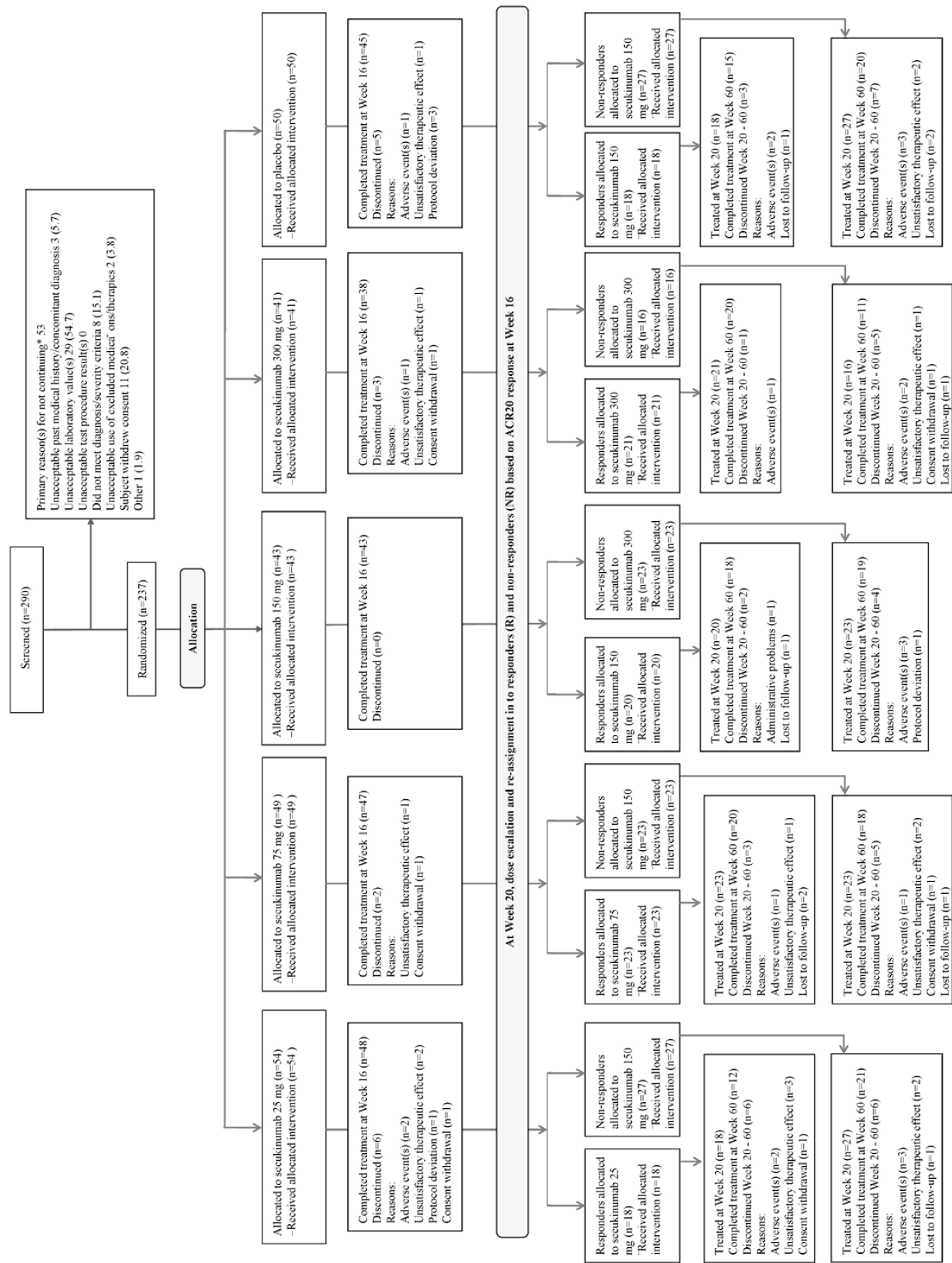
Figure 1. Study design with dosing regimen.

responders across the dose groups, with the greatest improvement observed with the 150 mg dose of secukinumab (Figure 4). The decrease in serum hsCRP levels until Week 16²³ was sustained over time up to Week 52; similarly, the decrease in ESR was sustained over time up to Week 52. Slight improvements in HAQ-DI scores over time were observed through Week 52 in responders who continued taking 150 mg of secukinumab (−0.6 at Week 24 vs −0.7 at Week 52). In our study population, nonresponders taking secukinumab in all dose cohorts up to Week 16 did not appear to gain benefit after dose escalation at Week 20, as assessed by ACR20/50/70 scores and DAS28-CRP (Figures 3 and 4). The greatest percentage of patients achieving DAS28-CRP ≤ 2.6 was with 150 mg of secukinumab and increased over time (Week 24 = 30%, Week 52 = 40%). Patients who responded to placebo but switched to 150 mg of secukinumab at Week 20 had a similar proportion of patients achieving DAS28 CRP ≤ 2.6 (Week 24 = 27.8%, Week 52 = 38.9%). At Week 52, 62% (n = 8 of 13) and 38% (n = 5 of 13) of patients with a previous history of failure to respond to biologics who received 150 mg of secukinumab after Week 20, achieved ACR20 and 50 responses, respectively.

Safety. The frequency of AE was 55.1% up to Week 20²³ and 64.8% from weeks 20 to 60 (Table 1); however, this is not adjusted for the longer time of exposure between Week 20 and Week 60 compared with the initial 20-week period. Infections were the most common AE (n = 69, 31.9%), akin

to AE seen up to Week 20 (n = 52, 21.9%). Most AE were mild to moderate in severity and comprised mostly of nasopharyngitis (n = 28, 13.0%), rheumatoid arthritis (n = 12, 5.6%), or urinary tract infections (n = 10, 4.6%). The incidence of AE in patients who were taking the placebo up to Week 20 was 58.0%. The incidence of AE in this same patient cohort, in which all patients were given 150 mg of secukinumab at Week 20, was 53.3% between Weeks 20 and 60. Between Weeks 20 and 60, 18 patients (8.3%) discontinued the treatment because of AE, with infections and infestations being the most commonly reported AE that led to study discontinuations (3 patients in the 150-mg arm and 1 patient in the 300-mg arm). This includes 3 patients who reported an AE before Week 20, but did not discontinue until after Week 20. Notably, infections were not dose-dependent and none of the reported infections were associated with neutropenia.

A total of 29 SAE were reported in 21 patients [25 mg, n = 1 (5.6%); 75 mg, n = 3 (13.0%); 150 mg, n = 9 (7.8%); and 300 mg, n = 8 (13.3%)] between Weeks 20 and 60, of which 6 SAE were due to infections (lung abscess with no defined pathogen, bronchitis with no defined pathogen, herpes zoster, *Klebsiella pneumonia* bacteremia, *Escherichia coli* urinary tract infection, and chronic cholecystitis with no defined pathogen). Based on exposure-adjusted analysis, this corresponds to an incidence rate of 2.5 serious infections per 100 patient-years. There were 3 reports of malignancy (ovarian, 150 mg, n = 1; lung, 300 mg, n = 1; and



*Subject could have more than one reason for not continuing

Figure 2. Patient disposition (randomization set). ACR: American College of Rheumatology.

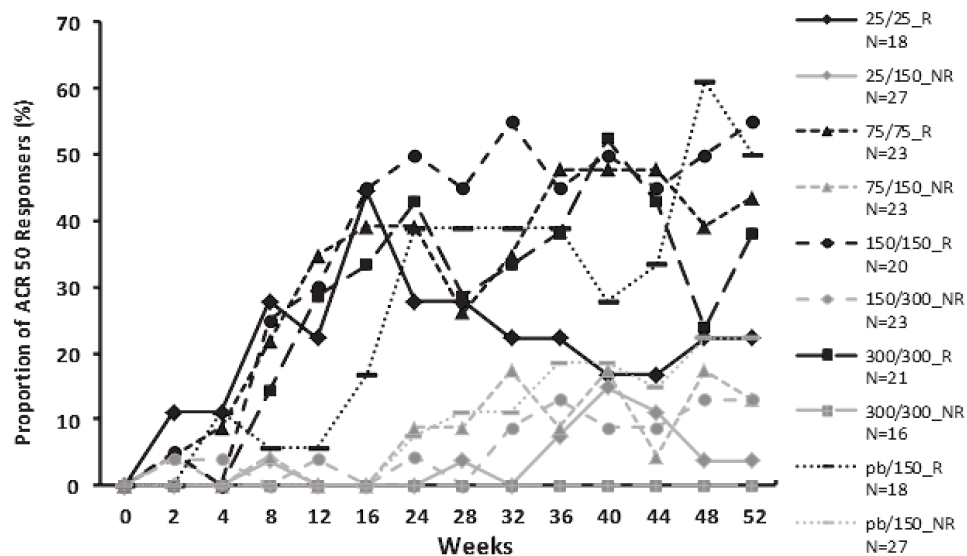


Figure 3. Proportion of patients achieving ACR50 response over time through Week 52 by responders (R) and nonresponders (NR) (full analysis set). ACR: American College of Rheumatology.

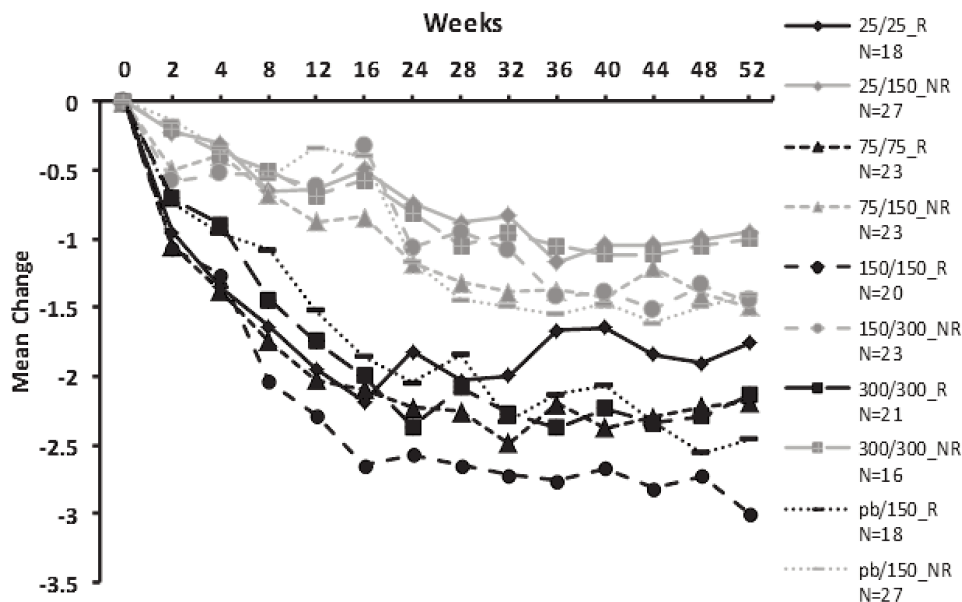


Figure 4. Mean change in 28-joint Disease Activity Score-C-reactive protein response from baseline through Week 52 by responders (R) and nonresponders (NR; full analysis set).

basal cell, 300 mg, n = 1) and no report of death up to Week 60. Treatment with secukinumab did not affect lipid profiles [triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and HDL/LDL ratio] and no notable elevations in liver enzymes or total bilirubin were observed between weeks 20 and 60. A decrease in white blood cells and absolute neutrophils was observed in a few patients between weeks 20 and 60, although those cases were transient and did not lead to study discontinuation (Table 2).

DISCUSSION

Results from this phase II trial constitute the first longer-term efficacy and safety data for secukinumab in patients with RA. The safety and tolerability profile of secukinumab was consistent with the profile observed through Week 20²³ and there was no indication of dose-dependent adverse effects. In our study, AE rates occurring during Weeks 20 to 60 in patients receiving 25 to 300 mg of secukinumab were comparable to those observed in patients receiving placebo until Week 20 (secukinumab

Table 1. Safety profile showing any adverse events from Week 20 through to the end of the study (safety set).

Adverse Events*	Secukinumab				
	25 mg n = 18, n (%)	75 mg n = 23, n (%)	150 mg n = 115, n (%)	300 mg n = 60 n (%)	Total n = 216, n (%)
Any adverse event	11 (61.1)	15 (65.2)	73 (63.5)	41 (68.3)	140 (64.8)
Infections and infestations	6 (33.3)	6 (26.1)	40 (34.8)	17 (28.3)	69 (31.9)
Nasopharyngitis	1 (5.6)	4 (17.4)	15 (13.0)	8 (13.3)	28 (13.0)
Pharyngitis	0	0	1 (0.9)	5 (8.3)	6 (2.8)
Urinary tract infection	2 (11.1)	1 (4.3)	5 (4.3)	2 (3.3)	10 (4.6)
Upper respiratory tract infection	2 (11.1)	0	6 (5.2)	1 (1.7)	9 (4.2)
Bronchitis	0	0	6 (5.2)	2 (3.3)	8 (3.7)
Gastrointestinal infection	1 (5.6)	0	0	0	1 (0.5)
Gastrointestinal disorders	0	3 (13.0)	14 (12.2)	5 (8.3)	22 (10.2)
Musculoskeletal and connective tissue disorders	3 (16.7)	2 (8.7)	24 (20.9)	11 (18.3)	40 (18.5)
Rheumatoid arthritis	2 (11.1)	0	6 (5.2)	4 (6.7)	12 (5.6)
General disorders and administration site conditions	2 (11.1)	1 (4.3)	4 (3.5)	4 (6.7)	11 (5.1)
Blood and lymphatic system disorders	1 (5.6)	3 (13.0)	8 (7.0)	5 (8.3)	17 (7.9)
Investigations	2 (11.1)	1 (4.3)	6 (5.2)	3 (5.0)	12 (5.6)
Nervous system disorders	2 (11.1)	1 (4.3)	4 (3.5)	6 (10.0)	13 (6.0)
Reproductive system and breast disorders	2 (11.1)	0	0	0	2 (0.9)
Skin and subcutaneous tissue disorders	0	2 (8.7)	8 (7.0)	7 (11.7)	17 (7.9)

* Listed affected system organ classes are those reported in at least 10% of patients; listed infections are those reported in at least 5% of patients.

Table 2. Grades of newly occurring clinically notable abnormalities in white blood cells and absolute neutrophils from Week 20 through to the end of the study, by laboratory test and treatment (safety set).

Laboratory Test	Secukinumab, n (%)			
	25 mg, n = 18	75 mg, n = 23	150 mg, n = 115	300 mg, n = 60
White blood cells (total), 10 ⁹ /l				
Grade 1 (3–LLN)	0	3 (13.0)	6 (5.2)	6 (10.0)
Grade 2 (2–3)	0	1 (4.3)	6 (5.2)	0
Grade 3 (1–2)	0	1 (4.3)	0	0
Grade 4 (< 1)	0	0	0	0
Absolute neutrophils (segments + bands), 10 ⁹ /l				
Grade 1 (1.5–LLN)	0	1 (4.3)	3 (2.6)	0
Grade 2 (1.0–1.5)	0	0	5 (4.3)	1 (1.7)
Grade 3 (0.5–1.0)	0	2 (8.7)	5 (4.3)	0
Grade 4 (< 0.5)	0	0	0	1 (1.7)

LLN: lower limit of normal.

25–300 mg: 61.1%–68.3% vs 58.0%). After Week 20, infections and infestations, predominantly nasopharyngitis (range 5.6% to 17.4%), were the most frequently occurring organ class AE across treatment groups, but there was no clear dose dependency. Moreover, there was no increase in the incidence of AE in the cohorts where the dose of secukinumab was increased. The majority of AE were mild or moderate in severity and were not suspected to be related to the study drug.

In our study, the overall completion rate (73.4%) was comparable to those observed in phase II studies of other

biologics. For abatacept 2 and 10 mg/kg, the 1-year completion rates were 70.5% and 78.3%, respectively, with only 59.7% completing 1 year in the placebo cohort²⁴. For 500 mg and 1000 mg rituximab cohorts, the completion rates at 24 weeks were 91% and 86%, respectively, while it was only 65% for the placebo group²⁵. Interestingly, in our study, there were no withdrawals of consent and no discontinuations due to lack of efficacy in patients who were taking the 150-mg dose throughout the study and also those who were initially taking 150 mg and later increased to 300 mg at Week 20, indicating that the 150-mg dose cohort as

originally randomized was associated with the greatest treatment adherence (Figure 2). Discontinuations due to unsatisfactory therapeutic effects were most frequent in the 25-mg dose cohort (Figure 2). After Week 20, no deaths or cases of tuberculosis were reported.

With respect to efficacy, patients who continued taking secukinumab had sustained or improved ACR responses and DAS28 scores for up to 1 year. Patients who received 150 mg of secukinumab or who switched from placebo to 150 mg of secukinumab showed the greatest improvement in ACR responses and DAS28 scores over time up to 1 year, as well as the greatest reduction in CRP levels, improvement in DAS28 CRP < 2.6 rates, and HAQ-DI scores. Patients with a history of failure to biologics (18.4% to 22.2%) who received 150 mg of secukinumab also showed improved ACR responses monthly. These results suggest that the 150-mg dose regimen may be an effective dose regimen for the treatment of RA, including patients with a history of failure to respond to biologics. However, this needs confirmation in larger studies.

In our study, ACR20 nonresponders at Week 16 did not gain any additional benefit after dose escalation, indicating that patients who did not demonstrate a response up to Week 16 were not likely to benefit from higher doses or with continued longterm exposure. Nonresponse at an early timepoint is being further explored in ongoing studies to ascertain characteristics and potential phenotypes that influence efficacy. This paradigm is critical for elucidating a novel approach in identifying the right patients who will benefit from therapeutic intervention along this pathway.

Our study shows that inhibition of IL-17 may have potential as an effective therapeutic approach in the treatment of RA. This is consistent with results from a study in which ixekizumab, a humanized anti-IL-17 monoclonal antibody, added to oral DMARD improved signs and symptoms of RA²². However, brodalumab, a human monoclonal antibody that neutralizes the IL-17A receptor (blocks both IL-17A and F and possibly other ligands as well), had no meaningful clinical efficacy or reduction of CRP in patients with RA²⁶, suggesting that targeting the ligand versus the receptor results in different outcomes, underscoring the need for a greater understanding of the IL-17 pathway in RA.

This phase II study has a number of limitations. The placebo-comparator arm of the study was only for 20 weeks, thus not allowing for longterm comparison between placebo and secukinumab. However, a limited duration of placebo was implemented for ethical reasons to limit the time patients were receiving MTX alone despite active disease. Another limitation was the small number of patients in each treatment arm; this dose-ranging study was designed to test a wide dose range. Notably, this study included patients with and without previous exposure to biologics, which might have had an influence on response rates. However, because

of the small size of the group, further subanalysis of the efficacy in patients previously exposed to biologics (18.4% to 22.2% per cohort as originally randomized) was not powered to assess subgroup effects.

Patients with active RA who had failed to respond to DMARD and other biologics showed an improvement in signs and symptoms of their disease with longterm treatment with 150 mg of secukinumab. Nonresponders taking secukinumab did not gain additional efficacy benefit after dose increase. There were no safety signals with secukinumab related to specific organ class and the frequency of AE remained stable over time. Phase III studies are in progress, which will define the potential clinical utility of inhibition of IL-17A with secukinumab in patients with RA.

ACKNOWLEDGMENT

The authors are grateful to the patients and study personnel who made this study possible. We also thank John Gallagher, Novartis Pharmaceutical Corporation, Basel, Switzerland; Kalyan Pulipaka and Venugopal Madhusudhana, Novartis Healthcare Pvt. Ltd, Hyderabad, India, for their editorial assistance on this manuscript.

REFERENCES

1. Voulgari PV. Emerging drugs for rheumatoid arthritis. *Expert Opin Emerg Drugs* 2008;13:175-96.
2. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med* 2001;344:907-16.
3. Astry B, Harberts E, Moudgil KD. A cytokine-centric view of the pathogenesis and treatment of autoimmune arthritis. *J Interferon Cytokine Res* 2011;31:927-40.
4. Ziolkowska M, Koc A, Luszczkiewicz G, Ksiezopolska-Pietrzak K, Klimczak E, Chwalinska-Sadowska H, et al. High levels of IL-17 in rheumatoid arthritis patients: IL-15 triggers in vitro IL-17 production via cyclosporin A-sensitive mechanism. *J Immunol* 2000;164:2832-8.
5. Honorati MC, Meliconi R, Pulsatelli L, Cane S, Frizziero L, Facchini A. High in vivo expression of interleukin-17 receptor in synovial endothelial cells and chondrocytes from arthritis patients. *Rheumatology* 2001;40:522-7.
6. Cai L, Yin JP, Starovasnik MA, Hogue DA, Hillan KJ, Mort JS, et al. Pathways by which interleukin 17 induces articular cartilage breakdown in vitro and in vivo. *Cytokine* 2001;16:10-21.
7. Shahrara S, Pickens SR, Dorfleitner A, Pope RM. IL-17 induces monocyte migration in rheumatoid arthritis. *J Immunol* 2009;182:3884-91.
8. Gaffen SL. The role of interleukin-17 in the pathogenesis of rheumatoid arthritis. *Curr Rheumatol Rep* 2009;11:365-70.
9. Metawi SA, Abbas D, Kamal MM, Ibrahim MK. Serum and synovial fluid levels of interleukin-17 in correlation with disease activity in patients with RA. *Clin Rheumatol* 2011;30:1201-7.
10. Zhu S, Qian Y. IL-17/IL-17 receptor system in autoimmune disease: mechanisms and therapeutic potential. *Clin Sci* 2012;122:487-511.
11. Hueber AJ, Asquith DL, Miller AM, Reilly J, Kerr S, Leipe J, et al. Mast cells express IL-17A in rheumatoid arthritis synovium. *J Immunol* 2010;184:3336-40.
12. Nakajima K. Critical role of the interleukin-23/T-helper 17 cell axis in the pathogenesis of psoriasis. *J Dermatol* 2012;39:219-24.
13. Toussiot E. The IL23/Th17 pathway as a therapeutic target in chronic inflammatory diseases. *Inflamm Allergy Drug Targets* 2012;11:159-68.
14. Zoghi D, Krueger GG, Callis Duffin K. Ustekinumab: a review in

- the treatment of plaque psoriasis and psoriatic arthritis. *J Drugs Dermatol* 2012;11:160-7.
15. Krausz S, Boumans MJ, Gerlag DM, Lufkin J, van Kuijk AW, Bakker A, et al. A phase IIa, randomized, double-blind, placebo-controlled trial of apilimod mesylate, an IL-12/IL-23 inhibitor, in patients with rheumatoid arthritis. *Arthritis Rheum* 2012;64:1750-5.
 16. Sebba A. Tocilizumab: The first interleukin-6-receptor inhibitor. *Am J Health Syst Pharm* 2008;65:1413-8.
 17. Mertens M, Singh JA. Anakinra for rheumatoid arthritis: a systematic review. *J Rheumatol* 2009;36:1118-25.
 18. Huh JR, Leung MW, Huang P, Ryan DA, Krout MR, Malapaka RR, et al. Digoxin and its derivatives suppress TH17 cell differentiation by antagonizing ROR γ t activity. *Nature* 2011;472:486-90.
 19. Hueber W, Patel DD, Dryja T, Wright AM, Koroleva I, Bruin G, et al. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. *Sci Transl Med* 2010;2:52ra72.
 20. Garber K. Psoriasis: from bed to bench and back. *Nat Biotechnol* 2011;29:563-6.
 21. Lin AM, Rubin CJ, Khandpur R, Wang JY, Riblett M, Yalavarthi S, et al. Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. *J Immunol* 2010;187:490-500.
 22. Genovese MC, Van den Bosch F, Roberson SA, Bojin S, Biagini IM, Ryan P, et al. LY2439821: A phase I, randomized, double-blind, placebo-controlled, proof-of-concept study. *Arthritis Rheum* 2010;62:929-39.
 23. Genovese MC, Durez P, Richards HB, Supronik J, Dokoupilova E, Mazurov V, et al. Efficacy and safety of secukinumab in patients with rheumatoid arthritis: a phase II, dose-finding, double-blind, randomised, placebo controlled study. *Ann Rheum Dis* 2013;72:863-9.
 24. Kremer JM, Dougados M, Emery P, Durez P, Sibilia J, Shergy W, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase IIb, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;52:2263-71.
 25. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. *Arthritis Rheum* 2006;54:1390-400.
 26. Pavelka K, Chon Y, Newmark R, Erond N, Lin S. A randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety, tolerability, and efficacy of brodalumab (AMG 827) in subjects with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Rheum* 2012;64 Suppl 10:S362.