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ORIGINAL ARTICLE

Secukinumab and Sustained Improvement in Signs and Symptoms of Patients With Active Ankylosing Spondylitis Through Two Years: Results From a Phase III Study

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Objective. **Secukinumab improved the signs and symptoms of ankylosing spondylitis (AS) over 52 weeks in the phase III MEASURE 2 study. Here, we report longer-term (104 weeks) efficacy and safety results.**

Methods. **Patients with active AS were randomized to subcutaneous secukinumab 150 mg, 75 mg, or placebo at baseline; weeks 1, 2, and 3; and every 4 weeks from week 4. The primary end point was the Assessment of SpondyloArthritis international Society criteria for 20% improvement (ASAS20) response rate at week 16. Other end points included ASAS40, high-sensitivity C-reactive protein, ASAS5/6, Bath Ankylosing Spondylitis Disease Activity Index, Short Form 36 health survey physical component summary, ASAS partial remission, EuroQol 5-domain measure, and Functional Assessment of Chronic Illness Therapy fatigue subscale. End points were assessed through week 104, with multiple imputation for binary variables and a mixed-effects model repeated measures for continuous variables.**

Results. **Of 219 randomized patients, 60 of 72 (83.3%) and 57 of 73 (78.1%) patients completed 104 weeks of treatment with secukinumab 150 mg and 75 mg, respectively; ASAS20/ASAS40 response rates at week 104 were 71.5% and 47.5% with both secukinumab doses, respectively. Clinical improvements with secukinumab were sustained through week 104 across all secondary end points. Across the entire treatment period (mean secukinumab exposure 735.6 days), exposure-adjusted incidence rates for serious infections and infestations, Crohn's disease, malignant or unspecified tumors, and major adverse cardiac events with secukinumab were 1.2, 0.7, 0.5, and 0.7 per 100 patient-years, respectively. No cases of tuberculosis reactivation, opportunistic infections, or suicidal ideation were reported.**

Conclusion. **Secukinumab provided sustained improvement through 2 years in the signs and symptoms of AS, with a safety profile consistent with previous reports.**

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by new bone formation in the axial skeleton, progressive and irreversible structural damage of the spinal, sacroiliac, and/or peripheral joints, as well as possible extraarticular manifestations such as uveitis, psoriasis, inflammatory bowel disease, and cardiovascular and

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Significance & Innovations

- Secukinumab, a fully human monoclonal IgG1κ antibody to interleukin-17A, has shown efficacy in treating inflammatory diseases such as psoriasis, psoriatic arthritis, and ankylosing spondylitis.
- This article presents the 2-year efficacy and safety clinical trial data on subcutaneous loading and maintenance dosing of secukinumab in ankylosing spondylitis.
- These data show that secukinumab provides sustained improvements at 2 years across multiple clinical domains in patients with active ankylosing spondylitis.

pulmonary abnormalities (1,2). The first-line therapy in AS consists of nonsteroidal antiinflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs), which are often inefficacious in controlling disease symptoms (2). Anti-tumor necrosis factor (anti-TNF) agents are the biologic therapies currently approved for the treatment of AS, and have shown effectiveness in inducing clinical remission for up to 8 years (3–5). However, many patients experience an inadequate response or intolerance, relapse of disease upon discontinuation, and unacceptable safety concerns with anti-TNF therapy; thus, there remains an unmet medical need in the treatment of AS (6–12).

Interleukin (IL)-17A, the predominant proinflammatory cytokine of helper Th17 cells, has recently emerged as one of the key therapeutic targets for the treatment of AS (13,14). Secukinumab, a high-affinity fully human monoclonal IgG1κ antibody that selectively binds and neutralizes IL-17A activity (15), has demonstrated efficacy in the treatment of psoriasis (16), psoriatic arthritis (17–19), and AS (15) and is approved for the treatment of these conditions in Europe, the US, and numerous other countries. Secukinumab provided significant reductions in the signs and symptoms of active AS through 52 weeks of treatment in 2 phase III trials (MEASURE 1: NCT01358175 and MEASURE 2: NCT01649375) (20).

In MEASURE 2, the Assessment of SpondyloArthritis international Society criteria for 20% improvement (ASAS20) response rate at week 16 (primary end point) was significantly higher in patients who received secukinumab 150 mg compared with placebo (20). Additionally, secukinumab 150 mg demonstrated significant improvements across all end points at week 16 compared with placebo, except the ASAS partial remission (20). Prespecified subgroup analyses showed that efficacy was demonstrated in patients who were naive to anti-TNF therapy and those who have had an inadequate response or intolerance to prior anti-TNF therapy (21). Here, we report the longer-term (104 weeks) efficacy and safety outcomes of secukinumab treatment in patients with AS from the MEASURE 2 study.

and UCB (less than $10,000 each). A. Readie and Drs. Richards and Porter own stock or stock options in Novartis.

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MATERIALS AND METHODS

Study design. The MEASURE 2 study design, methodology, and statistical analysis have been described previously (20). This 5-year, phase III trial uses a randomized, double-blind, double-dummy, parallel-group placebo-controlled design to evaluate the efficacy, safety, and tolerability of subcutaneous (SC) loading and maintenance dosing of secukinumab in patients with active AS. After prescreening, eligible patients with active AS were randomized to receive SC secukinumab 150 mg, 75 mg, or placebo at baseline; weeks 1, 2, and 3; and then every 4 weeks starting at week 4. At week 16, placebo-treated patients were re-randomized to SC secukinumab 150 mg or 75 mg every 4 weeks, regardless of clinical response.

Patients. Patients included in the study were age ≥18 years, with active AS fulfilling the Modified New York Criteria (22), with a score of 4 or higher (scores range from 0 to 10, with higher scores indicating more severe disease activity) on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (23), and a spinal pain score ≥4 cm on a 10-cm visual analog scale (with higher numbers indicating greater disease activity), despite treatment with the maximum tolerated doses of NSAIDs. Patients previously treated with DMARDs and anti-TNF agents were included with prior washout periods. Patients were included if they had an inadequate response to an approved dose of no more than 1 anti-TNF agent for 3 months or more, or had experienced unacceptable side effects. Concomitant sulfasalazine (≤3 gm/day), methotrexate (≤25 mg/week), prednisone or equivalent (≤10 mg/day), and NSAIDs were permitted. Key exclusion criteria were total spinal ankylosis, evidence of infection or malignancy on chest radiograph, known human immunodeficiency virus or hepatitis B or C infection at screening, active systemic infection within 2 weeks before baseline, and previous treatment with cell-depleting therapies or biologic agents other than anti-TNF agents.

The study was conducted in accordance with the Declaration of Helsinki (as revised in Brazil 2013; available at http://www.wma.net/en/30publications/10policies/b3/index.html) and was approved by the institutional review boards or independent ethics committees. Written informed consent was provided by all enrolled patients.

Outcome measures. The primary end point was the ASAS20 response rate at week 16 (24). The ASAS20 response was defined as an improvement of ≥20% and ≥1 unit (on a 10-unit scale) in at least 3 of the 4 main ASAS domains (patients' global assessments of disease activity, pain, physical function, and inflammation), and no worsening of ≥20% and ≥1 unit (on a 10-unit scale) in the remaining domain. The ASAS20 response was assessed through week 104.

Other efficacy end points at week 104 included an ASAS40 response (improvement of ≥40% and ≥2 units [on

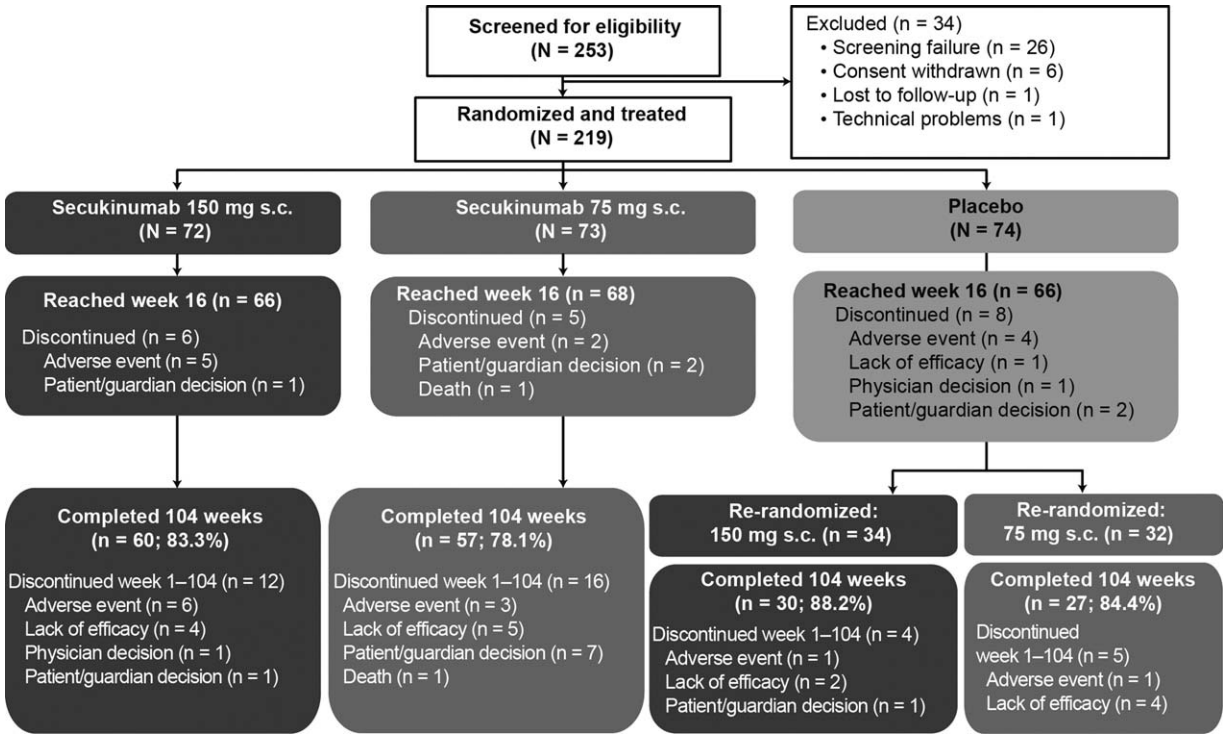

Figure 1. Patient disposition through 104 weeks of secukinumab treatment. s.c. = subcutaneous.

a 10-unit scale] in at least 3 of the 4 main ASAS domains and no worsening at all in the remaining domain) (24); changes from baseline in high-sensitivity C-reactive protein (hsCRP) level; ASAS5/6 response (≥20% improvement in 5 of the 6 ASAS response domains: patients' global assessments of disease activity, pain, physical function, inflammation, hsCRP, and spinal mobility); changes from baseline in the total BASDAI score (questions on a 0–10 scale captured as a continuous visual analog scale, pertaining to the 5 major symptoms of AS: fatigue, spinal pain, joint pain/swelling, areas of localized tenderness [called enthesitis, or inflammation of tendons and ligaments], and morning stiffness duration and severity) (24); physical component summary (PCS) score for the 36-Item Short-Form health survey (SF-36; scores range from 0 [maximum disability] to 100 [no disability] for individual domains, with a normative composite summary score of 50) (25); ASAS partial remission (a score of ≤2 units [on a 10-unit scale] in each of the 4 core ASAS domains); EuroQoL 5-domain (EQ-5D) health status questionnaire (5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) (26,27); and the Functional Assessment of Chronic Illness Therapy fatigue questionnaire (FACIT-fatigue; 13-item questionnaire evaluated on a 5-point scale) (28).

The overall safety and tolerability of secukinumab was reported through week 104. Safety was assessed by evaluation of all adverse events (AEs) and serious AEs (SAEs), as well as physical examinations, vital signs, electrocardiograms, injection site reactions, laboratory evaluations, and assessments of tolerability and immunogenicity (anti-secukinumab antibody development).

Statistical analysis. The details of sample size calculation and analysis of the primary and other efficacy end points have been reported previously (20). A sample of 74 patients per group provided 99% power to detect significant differences between groups for the ASAS20 response rate, and 79% to 99% power for the secondary end points. The predefined hierarchical hypothesis testing strategy was used to control the family-wise (2-sided) Type I error $\alpha = 5\%$. Statistical analyses used a logistic regression model that considered missing values as nonresponse (nonresponder imputation) during the 16-week placebo-controlled period and multiple imputation during the long-term followup (up to 104 weeks) for binary variables, with treatment and anti-TNF response status as factors and weight as a covariate. Mixed-effects model repeated measures analysis was used for continuous variables through week 104, with study group, assessment visit, and anti-TNF response status as factors and weight and baseline values as continuous covariates. EQ-5D and FACIT-fatigue score changes from baseline at week 104 were reported as observed. Analyses stratified by anti-TNF history (anti–TNF-naive or inadequate response or intolerance to an anti-TNF agent [anti–TNF-IR]) were prespecified and reported as observed at week 104. The ASAS20 and ASAS40 response rates in patients who were originally randomized to placebo and subsequently switched to secukinumab at week 16 were reported as observed through week 104. Safety analyses included all patients who received ≥1 dose of the study treatment during the treatment period, with patients evaluated according to the treatment received.

RESULTS

Patients. A total of 219 patients with active AS were randomized at baseline to SC secukinumab 150 mg (72

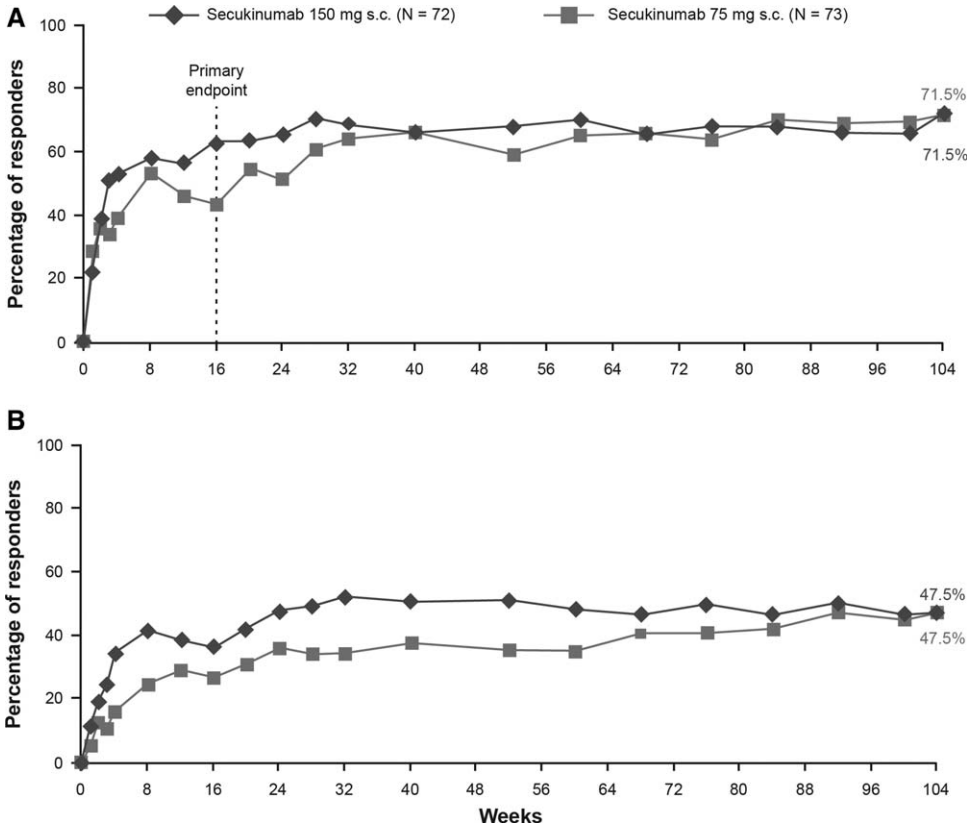

Figure 2. Assessment of SpondyloArthritis international Society criteria for 20% improvement (ASAS20) (**A**) and ASAS40 (**B**) response rates from baseline by treatment groups over 104 weeks. All data through week 104 calculated with multiple imputation for patients originally randomized to secukinumab. s.c. = subcutaneous.

patients), 75 mg (73 patients), or placebo (74 patients) (20). At week 16, 66 placebo-treated patients were re-randomized to SC secukinumab 150 mg or 75 mg (8 placebo-treated patients discontinued the study before week 16). In total, 200 patients (91.3%) remained in the study after the 16-week placebo-controlled period, and 174 patients (79.5%) completed all 104 weeks. This included 117 of the 145 patients (80.7%) initially randomized to secukinumab, who received 104 weeks of secukinumab treatment, and 57 of the 74 patients (77.0%) originally randomized to placebo, who received 88 weeks of secukinumab treatment as the 2 respective doses. Details of patient randomization and discontinuation through week 104 are presented in Figure 1.

Baseline characteristics. There were no clinically meaningful differences in demographic and other baseline characteristics across the treatment groups. Of the total 219 randomized patients, the majority were male (153, 69.9%),

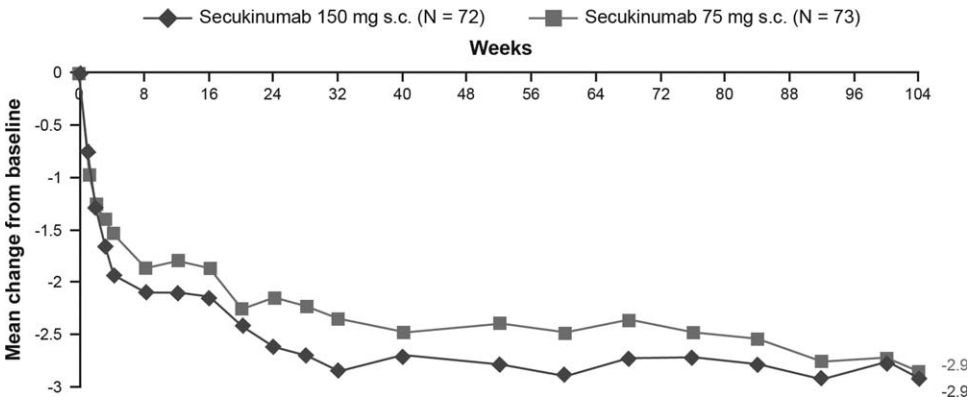

Figure 3. Mean change in Bath Ankylosing Spondylitis Disease Activity Index score from baseline by treatment groups through week 104. Least squares mean change using mixed-effects model repeated measures through week 104 for patients originally randomized to secukinumab. s.c. = subcutaneous.

Table 1. Clinical improvement with secukinumab at weeks 16 and 104*

End points	Secukinumab 150 mg (SC) (n = 72)	Secukinumab 75 mg (SC) (n = 73)	Placebo (n = 74)
ASAS20 response, no. (%)			
Week 16	44 (61.1)†	30 (41.1)	21 (28.4)
Week 104	51 (71.5)	52 (71.5)	–
ASAS40 response, no. (%)			
Week 16	26 (36.1)†	19 (26.0)	8 (10.8)
Week 104	34 (47.5)	35 (47.5)	–
hsCRP (mg/liter), LS mean change ± SE			
Week 16	0.6 ± 1.1†	0.6 ± 1.1	1.1 ± 1.1
Week 104	0.5 ± 1.1	0.6 ± 1.1	–
ASAS5/6 response rate, no. (%)			
Week 16	31 (43.1)†	25 (34.2)	6 (8.1)
Week 104	36 (50.2)	30 (41.0)	–
BASDAI, LS mean change ± SE			
Week 16	−2.2 ± 0.2†	−1.9 ± 0.2	−0.9 ± 0.3
Week 104	−2.9 ± 0.3	−2.9 ± 0.3	
SF-36 PCS, LS mean change ± SE			
Week 16	6.1 ± 0.8†	4.8 ± 0.8	1.9 ± 0.8
Week 104	7.3 ± 1.0	6.6 ± 1.0	–
ASAS partial remission, no. (%)			
Week 16	10 (13.9)	11 (15.1)	3 (4.1)
Week 104	14 (19.9)	10 (13.7)	–
EQ-5D measure, LS mean change ± SE‡			
Week 16	11.5 ± 2.4	12.6 ± 2.5	5.9 ± 2.5
Week 104	21.2 ± 26.0	14.1 ± 21.0	–
FACIT-fatigue, LS mean change ± SE‡			
Week 16	8.1 ± 1.1§	6.7 ± 1.1¶	3.3 ± 1.1
Week 104	11.2 ± 10.0	9.8 ± 8.2	–

* SC = subcutaneous; ASAS = Assessment of SpondyloArthritis international Society criteria for 20% improvement; hsCRP = high-sensitivity C-reactive protein; LS = least squares; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; SF-36 = Short-Form 36 health survey; PCS = physical component summary; EQ-5D = EuroQol 5-domain measure; FACIT-fatigue = Functional Assessment of Chronic Illness Therapy fatigue subscale.
† $P < 0.001$.
‡ EQ-5D and FACIT-fatigue scores are reported as LS mean change ± SE using mixed-effects model repeated measures (MMRM) at week 16, and as observed (mean ± SD) in n = 59, 54 (EQ-5D) and 59, 55 (FACIT-fatigue) in the secukinumab 150 mg and 75 mg groups, respectively, at week 104.
§ $P < 0.01$.
¶ $P < 0.05$ versus placebo (P values at week 16 adjusted for multiplicity of testing, except FACIT-fatigue); continuous variables are reported as LS mean change ± SE using MMRM through week 104, and binary variables are reported using nonresponder imputation at week 16 and multiple imputation at week 104.

and the mean ± SD age was 43.3 ± 12.89 years. Disease history at baseline was well-balanced across the treatment groups and reflected a study population with moderate to severe active AS. The mean ± SD time since the first diagnosis of AS was 6.2 ± 8.2 years. The total mean ± SD BASDAI score was 6.7 ± 1.3, and the median (range) hsCRP level was 7.3 (2.4–10.0) mg/liter. Additionally, 168 patients (76.7%) were human leukocyte antigen-B27 positive at randomization. At baseline, 85 patients (38.8%) previously had an inadequate response to an anti-TNF agent, while the remainder had not been exposed to any anti-TNF agent. Detailed demographic and baseline characteristics are presented in Supplementary Table 1 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23233/abstract).

Efficacy. *Week 16 results.* As reported previously, secukinumab 150 mg significantly improved all prespecified end points at week 16 versus placebo, except ASAS partial remission; the 75-mg dose did not reach statistical significance at week 16 for the primary end point or any prespecified secondary end points based on hierarchical hypothesis testing (20). ASAS20 response rates at week 16 were 61.1%, 41.1%, and 28.4% with secukinumab 150 mg, 75 mg, and placebo, respectively ($P < 0.001$ and $P = 0.10$, respectively, versus placebo) (Figure 2A). All 5 individual ASAS components were also significantly improved versus placebo at week 16 with secukinumab 150 mg (see Supplementary Table 2, available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23233/abstract).

Long-term efficacy. Clinical improvements observed with secukinumab at week 16 were sustained through week 104 across all end points in patients originally randomized to secukinumab. ASAS20 and ASAS40 response rates at week 104 were 71.5% and 47.5% with both secukinumab doses (Figure 2A and B). At week 104, the least squares mean change from baseline in BASDAI score was −2.9 with

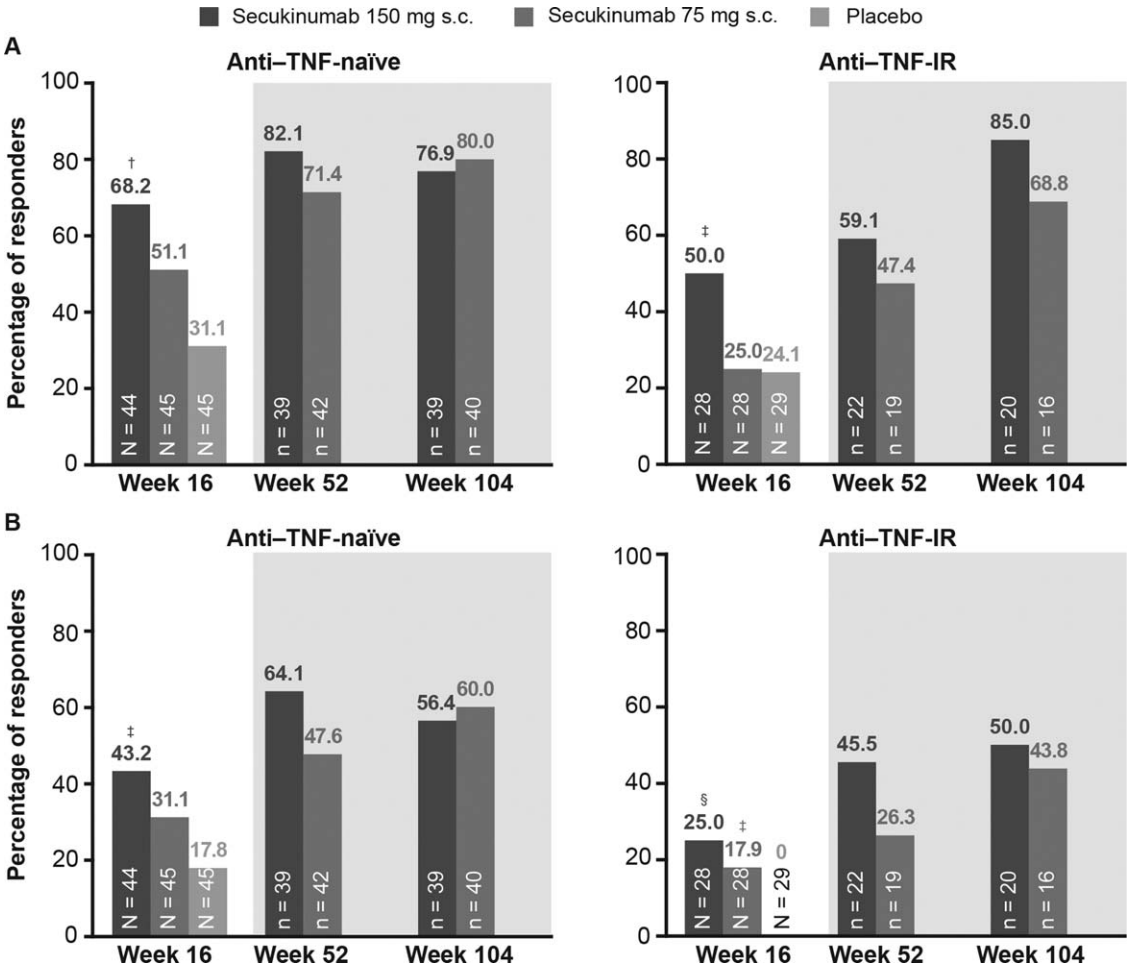

Figure 4. Assessment of SpondyloArthritis international Society criteria for 20% improvement (ASAS20) (**A**) and ASAS40 (**B**) response rates at weeks 16, 52, and 104 by anti–tumor necrosis factor (anti-TNF) status. Missing data were imputed as nonresponses at week 16 (nonresponders imputation). Observed data are shown at weeks 52 and 104 (shaded background). *P* values are versus placebo at week 16. s.c. = subcutaneous; IR = inadequate response; † = $P < 0.001$; ‡ = $P < 0.05$; § = $P < 0.01$.

both secukinumab doses (Figure 3). Improvements were also sustained in hsCRP levels, ASAS5/6, and ASAS partial remission response rates, as well as SF-36 PCS, EQ-5D, and FACIT-fatigue scores through 104 weeks of secukinumab treatment (Table 1).

Improvements in ASAS20 and ASAS40 response rates were also observed in placebo-treated patients switched to either secukinumab 150 mg or 75 mg at week 16. These responses were sustained or further improved through week 104 (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23233/abstract). At week 104, placebo patients switched to either secukinumab 150 mg or 75 mg and had ASAS20/ASAS40 response rates of 85.7%/71.4% and 57.7%/34.6%, respectively.

Clinically meaningful improvement was observed regardless of anti-TNF status at week 16 in patients treated with secukinumab, which was further improved at week 52 (21), and sustained through week 104. In the subgroup of anti–TNF-naive patients, ASAS20/ASAS40 response rates at week 104 (observed data) were 76.9%/56.4% and 80.0%/60.0% with secukinumab 150 mg and 75 mg, respectively; corresponding rates in anti–TNF-IR patients were 85.0%/50.0% and 68.8%/43.8%, respectively (Figure 4A and B).

Safety. The safety profile was consistent with that reported previously (20). The total exposure to at least 1 dose of secukinumab over the entire 104-week safety-reporting period was 424.9 patient-years, with an average per-patient exposure of 735.6 days. The incidence of treatment-emergent AEs and SAEs during the entire safety-reporting period is shown in Table 2. Most of the AEs were mild to moderate in severity. The most frequent treatment-emergent AEs with secukinumab were nasopharyngitis, upper respiratory tract infection, diarrhea, headache, and hypertension. The rate of treatment-emergent serious infections and infestations was low among all patients exposed to secukinumab (i.e., originally randomized patients to secukinumab and those who switched from placebo) over the entire safety-reporting period. No patient discontinued treatment because of a serious infection.

Table 2. Incidence of treatment-emergent AEs and SAEs during the entire treatment period through week 104*

Variable	Any secukinumab, 150 mg (n = 106)†	Any secukinumab, 75 mg (n = 105)†	Any secukinumab (pooled data) (n = 211)†
Exposure to study treatment, mean ± SD days	745.4 ± 234.6	725.7 ± 246.1	735.6 ± 240.0
Patients with event, no. (%)			
Any AE	90 (84.9)	91 (86.7)	181 (85.8)
Any SAE	11 (10.4)	15 (14.3)	26 (12.3)
Deaths‡	0	1 (1.0)	1 (0.5)
Discontinuation due to AE	8 (7.5)	6 (5.7)	14 (6.6)
Infection and infestation§	62 (58.5)	69 (65.7)	131 (62.1)
Serious infection and infestation	1 (0.9)	4 (3.8)	5 (2.4)
Common AEs, no. (%) patients¶			
Nasopharyngitis	22 (20.8)	24 (22.9)	46 (21.8)
Upper respiratory tract infection	11 (10.4)	13 (12.4)	24 (11.4)
Diarrhea	13 (12.3)	8 (7.6)	21 (10.0)
Headache	11 (10.4)	8 (7.6)	19 (9.0)
Hypertension	11 (10.4)	7 (6.7)	18 (8.5)
Influenza	8 (7.5)	10 (9.5)	18 (8.5)
Bronchitis	7 (6.6)	10 (9.5)	17 (8.1)
Gastroenteritis	6 (5.7)	6 (5.7)	12 (5.7)
Arthralgia	5 (4.7)	6 (5.7)	11 (5.2)
Musculoskeletal pain	6 (5.7)	4 (3.8)	10 (4.7)
Hyperlipidemia	6 (5.7)	3 (2.9)	9 (4.3)
Spinal pain	6 (5.7)	2 (1.9)	8 (3.8)
Pain in extremity	6 (5.7)	1 (1.0)	7 (3.3)
AEs of special interest, no. (EAIR per 100 patient-years)			
Candida infection	2 (0.9)	2 (1.0)	4 (0.9)
Herpes viral infections	4 (1.9)	8 (4.0)	12 (2.9)
Malignant or unspecified tumors	2 (0.9)	0 (0.0)	2 (0.5)
Neutropenia (preferred term)	2 (0.9)	3 (1.5)	5 (1.2)
Crohn's disease	1 (0.5)	2 (1.0)	3 (0.7)
Major adverse cardiac events (adjudicated)	1 (0.5)	2 (1.0)	3 (0.7)

* The safety-reporting period for safety data was from baseline to the week 104 visit of the last patient enrolled; therefore, most patients reported safety data beyond week 104. AE = adverse event; SAEs = serious AEs; EAIR = exposure-adjusted incidence rates.
† Includes patients randomized to secukinumab at baseline and placebo-treated patients re-randomized to secukinumab at week 16.
‡ A 60-year-old male patient (smoker with multiple baseline cardiac risk factors [elevated high-sensitivity C-reactive protein, lipoprotein A, and low-density lipoprotein levels]) died on day 29 (during placebo-controlled period) from acute myocardial infarction adjudicated as major adverse cardiac event, which was considered to be unrelated to the study medication.
§ System organ class category.
¶ AEs with frequency ≥5% of patients during the entire safety-reporting period in either of the 2 secukinumab dose groups; events are listed according to preferred term in the Medical Dictionary for Regulatory Activities, version 17.0, and sorted in descending order of frequency in the pooled secukinumab column.

One death occurred over the entire safety-reporting period owing to acute myocardial infarction, which was not considered by the investigator to be related to study treatment. This occurred in the secukinumab 75-mg dose group during the 16-week, placebo-controlled period, and is the same death as previously reported (20).

The exposure-adjusted incidence rates (EAIRs) for AEs of special interest over the entire safety-reporting period with secukinumab are shown in Table 2. *Candida* infection was reported in 4 patients treated with secukinumab (2 cases of oral candidiasis [1 each with 150 mg and 75 mg], 1 case of *Candida* infection with 75 mg, and 1 case of vulvovaginal candidiasis with 150 mg). These events did not lead to study discontinuation and resolved spontaneously or with standard antifungal treatment.

Grade 3 neutropenia was documented in 1 patient receiving secukinumab 150 mg, and the patient did not discontinue treatment. No grade 4 neutropenia cases were reported. Three cases of adjudicated major adverse cardiac events (MACE) were reported (2 myocardial infarction [1 each with 150 mg and 75 mg] and the 1 death due to myocardial infarction that occurred during the placebo-controlled period with 75 mg). There was a single case of malignant melanoma in a patient receiving the secukinumab 150 mg dose, which led to interruption of the study treatment. Three cases of Crohn's disease (2 patients with 75 mg

[leading to study discontinuation] and 1 patient with 150 mg) were reported, which were considered SAEs. Two cases of uveitis were recorded with secukinumab 150 mg: 1 de novo case occurred during the first 52 weeks (as reported previously [20]), and the other case occurred during the second 52 weeks in a patient with a prior history of uveitis. Both cases were nonserious and did not lead to the discontinuation of study treatment. No cases of tuberculosis reactivation, opportunistic infections, immunogenicity (antidrug antibodies), or suicidal ideation were reported over the entire safety-reporting period.

DISCUSSION

Secukinumab significantly reduced the signs and symptoms of AS, with improved physical function and decreased disease activity in the MEASURE 2 study. Of the original 219 patients who entered the study, 79.5% (n = 174) completed 104 weeks of treatment, reflecting a high retention rate of patients in this study. Of patients randomized to secukinumab at baseline, 80.7% were still receiving secukinumab treatment at week 104, while of those switched to secukinumab from placebo at week 16, 86.3% were still receiving secukinumab treatment at week 104.

At week 16, the secukinumab 150 mg dose demonstrated statistically significant and clinically meaningful efficacy compared with placebo across all end points, except ASAS partial remission, whereas the secukinumab 75 mg dose did not reach statistical significance based on hierarchical testing (20). Improvements across all efficacy end points with secukinumab were sustained through 104 weeks, demonstrating the long-term sustainability of the clinically meaningful treatment benefit. At week 104, the ASAS20 and ASAS40 response rates (71.5% and 47.5%) and the BASDAI score changes (−2.9) with secukinumab 150 mg and 75 mg were similar. This similarity in outcomes between the 2 secukinumab doses may be influenced somewhat by survivor bias in patient-reported outcomes during this long-term, uncontrolled treatment phase. Of note, the higher hurdle clinical efficacy end point of ASAS partial remission showed higher response rates for the 150 mg dose compared to the 75 mg dose at week 104. Similar results for secukinumab 150 mg and 75 mg at week 104 were also noted for hsCRP (0.5 and 0.6 mg/liter, respectively); this is consistent with the results of past studies on secukinumab in other indications, where secukinumab doses as low as 25 mg SC monthly demonstrated rapid effects in reducing blood levels of this inflammation marker (29,30). Patients originally randomized to placebo who switched to secukinumab at week 16 also improved the ASAS20 and ASAS40 response rates that were sustained through 104 weeks.

Both secukinumab doses were associated with superior improvements over placebo in all 5 health status domains of the EQ-5D at week 16, which were sustained through 104 weeks. This suggests that secukinumab improves physical function and quality of life in patients with AS. Of note, fatigue is a major complication of AS, and is related to pain, stiffness, and poor sleep quality (31,32). Recent research has confirmed the importance of treating fatigue in people experiencing AS symptoms (33,34). In this study, both secukinumab doses significantly reduced fatigue and its impact on daily activity and function versus placebo at week 16, as measured by the FACIT-fatigue scale. These decreases in the severity of fatigue were sustained through 104 weeks of secukinumab treatment.

Anti-TNF therapy is widely used for the treatment of patients with AS who fail conventional therapy with NSAIDs. With up to 40% of AS patients not responding to, or not tolerating, TNF inhibitors (7–9,35,36), or experiencing a loss of efficacy over time (5), there is a clear unmet medical need for new treatment options that provide sustained efficacy and a good safety profile. It is therefore noteworthy that in this study, secukinumab provided sustained efficacy in both patients naive to anti-TNF therapy and in those who previously had an inadequate response, or were intolerant to anti-TNF agents (Figure 4A and B) (21). Thus, these findings indicate that secukinumab is not only an efficacious first-line biologic therapy for active AS, but is also an important treatment option for the substantial number of patients whose disease is not controlled by anti-TNF therapy.

This article establishes that secukinumab was well-tolerated through 2 years of treatment, with no new safety signals or unexpected safety findings compared with the first 52 weeks (20), and it was consistent with previous reports on psoriasis (16) and psoriatic arthritis (17). AEs in patients receiving secukinumab treatment through week 104 were mostly mild to moderate in severity, and primarily driven by nonserious infections. Serious infections were infrequent in both secukinumab dose groups.

As IL-17A has been implicated in host defense against extracellular infections and fungi (37), as well as in neutrophil homeostasis (38), special interest has been placed on monitoring related AEs during this study. Fungal, and specifically *Candida,* infections were reported in a small number of patients, which were nonserious and either resolved spontaneously or were clinically manageable with antifungal agents. Other AEs of special interest (herpes viral infections, neutropenia, and malignant or unspecified tumors) each occurred in only a few patients.

The EAIR of MACE among patients receiving 150 mg was 0.5 per 100 patient-years, which is consistent with incidence rates reported in other spondyloarthritides (39). The incidence of Crohn's disease (0.5 per 100 patient-years among patients receiving 150 mg) was low and in line with reported incidence rates of Crohn's disease, ranging from 0.2 to 1.8 per 100 patient-years in AS patients receiving different forms of TNF inhibitor therapy (40).

Limitations of this analysis include the lack of a comparator group beyond week 16 and the fact that, although originally randomized treatment groups were blinded in this study up to week 104, the nature of the study design meant that patients and investigators were aware that all patients received secukinumab from week 16 onward, which could have introduced systematic bias in the reporting of results.

In conclusion, SC loading and maintenance dosing of secukinumab 150 mg demonstrated sustained efficacy in the key clinical manifestations of ankylosing spondylitis, through 2 years of treatment. Secukinumab was well-tolerated with no unexpected safety findings.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Marzo-Ortega had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ROLE OF THE STUDY SPONSOR

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