ORIGINAL ARTICLE

Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis

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ABSTRACT

BACKGROUND

Secukinumab is an anti–interleukin-17A monoclonal antibody that has been shown to control the symptoms of ankylosing spondylitis in a phase 2 trial. We conducted two phase 3 trials of secukinumab in patients with active ankylosing spondylitis.

METHODS

In two double-blind trials, we randomly assigned patients to receive secukinumab or placebo. In MEASURE 1, a total of 371 patients received intravenous secukinumab (10 mg per kilogram of body weight) or matched placebo at weeks 0, 2, and 4, followed by subcutaneous secukinumab (150 mg or 75 mg) or matched placebo every 4 weeks starting at week 8. In MEASURE 2, a total of 219 patients received subcutaneous secukinumab (150 mg or 75 mg) or matched placebo at baseline; at weeks 1, 2, and 3; and every 4 weeks starting at week 4. At week 16, patients in the placebo group were randomly reassigned to subcutaneous secukinumab at a dose of 150 mg or 75 mg. The primary end point was the proportion of patients with at least 20% improvement in Assessment of Spondyloarthritis International Society (ASAS20) response criteria at week 16.

RESULTS

In MEASURE 1, the ASAS20 response rates at week 16 were 61%, 60%, and 29% for subcutaneous secukinumab at doses of 150 mg and 75 mg and for placebo, respectively ($P<0.001$ for both comparisons with placebo); in MEASURE 2, the rates were 61%, 41%, and 28% for subcutaneous secukinumab at doses of 150 mg and 75 mg and for placebo, respectively ($P<0.001$ for the 150-mg dose and $P=0.10$ for the 75-mg dose). The significant improvements were sustained through 52 weeks. Infections, including candidiasis, were more common with secukinumab than with placebo during the placebo-controlled period of MEASURE 1. During the entire treatment period, pooled exposure-adjusted incidence rates of grade 3 or 4 neutropenia, candida infections, and Crohn's disease were 0.7, 0.9, and 0.7 cases per 100 patient-years, respectively, in secukinumab-treated patients.

CONCLUSIONS

Secukinumab at a subcutaneous dose of 150 mg, with either subcutaneous or intravenous loading, provided significant reductions in the signs and symptoms of ankylosing spondylitis at week 16. Secukinumab at a subcutaneous dose of 75 mg resulted in significant improvement only with a higher intravenous loading dose. (Funded by Novartis Pharma; ClinicalTrials.gov numbers, NCT01358175 and NCT01649375.)

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Ankylosing spondylitis is a chronic, immune-mediated disease that is characterized by inflammation and new bone formation in the axial skeleton[1,2] and that often results in progressive, irreversible structural damage, disability, deterioration of functioning, and a reduced quality of life.[3,4] Therapy with nonsteroidal antiinflammatory drugs (NSAIDs) is often insufficient to control symptoms, and there is no evidence that conventional disease-modifying antirheumatic drugs (DMARDs) are efficacious in axial disease.[5] Anti–tumor necrosis factor (TNF) therapy is currently recommended for patients with persistent disease activity despite conventional treatment.[5] In some patients, however, such therapy fails to achieve adequate disease control or has unacceptable side effects.[6-10]

Several lines of evidence have identified the interleukin-17 pathway as a promising therapeutic target in spondyloarthritis.[11-17] Indeed, numbers of interleukin-17–producing cells are elevated in the circulation and target tissues in patients with ankylosing spondylitis.[14-18]

Secukinumab is a fully human, anti–interleukin-17A monoclonal antibody with proven efficacy in psoriasis.[19] In a phase 2 study, intravenous secukinumab significantly suppressed the symptoms of ankylosing spondylitis.[9] We present the results of two phase 3 trials, MEASURE 1 and MEASURE 2, investigating the efficacy and safety of secukinumab in patients with active ankylosing spondylitis.

METHODS

STUDY DESIGN AND OVERSIGHT

These randomized, double-blind, placebo-controlled phase 3 trials, which are ongoing, are being conducted at 106 centers across Asia, Europe, North America, and South America. MEASURE 1 is a 2-year study followed by a 3-year extension study, and MEASURE 2 is a 5-year study (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Data from the primary analysis at week 16 and the 1-year follow-up analysis (after all patients had completed the visit at week 52) of both studies are presented here.

Each study was designed by the sponsor, Novartis, in collaboration with the authors. The institutional review board at each participating center approved the protocols. Data were collected according to Good Clinical Practice guidelines by the study investigators and were analyzed by the sponsor. All the authors contributed to the interpretation of the data and had access to the full data sets. The statistical analyses were performed by statisticians employed by the sponsor and were reviewed by all the authors. Agreements between the sponsor and the investigators included provisions relating to confidentiality of the study data. The initial draft of the manuscript was written by a medical writer from Seren Communications, funded by the sponsor. All the authors vouch for the accuracy and completeness of the data and analyses, as well as for the fidelity of this report to the trial protocols, which are available at NEJM.org.

PATIENTS

Eligible patients were 18 years of age or older and had ankylosing spondylitis fulfilling the modified New York criteria.[20] They also had a score of 4 or higher on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; scores range from 0 to 10, with higher scores indicating more severe disease activity)[21] and a score for spinal pain of 4 cm or more on a 10-cm visual-analogue scale (with higher numbers indicating greater disease activity), despite treatment with the maximum doses of NSAIDs that were associated with an acceptable side-effects profile.

Previous use of DMARDs and anti-TNF agents was allowed. Washout periods for these agents, other than sulfasalazine and methotrexate, were required before initiation of the study treatment. Patients previously treated with not more than one anti-TNF agent could participate if they had an inadequate response to an approved dose for 3 months or more or had unacceptable side effects with at least one dose (hereafter collectively referred to as patients with an inadequate response to anti-TNF agents). Patients could continue to receive the following medications at a stable dose: sulfasalazine (≤3 g per day), methotrexate (≤25 mg per week), prednisone or equivalent (≤10 mg per day), and NSAIDs.

Key exclusion criteria were total spinal ankylosis, evidence of infection or cancer on chest radiography, active systemic infection within 2 weeks before baseline, and previous treatment with cell-depleting therapies or biologic agents other than anti-TNF agents. Written informed consent was obtained from all the patients.

STUDY PROCEDURES

After a 4-week screening period, patients were randomly assigned in a 1:1:1 ratio to one of two secukinumab groups or the placebo group. In MEASURE 1, patients received an intravenous loading infusion of secukinumab at a dose of 10 mg per kilogram of body weight at baseline and weeks 2 and 4, followed by subcutaneous injections of secukinumab at a dose of 150 mg or 75 mg every 4 weeks starting at week 8; patients in the placebo group were treated according to the same schedule of intravenous and subcutaneous doses. In MEASURE 2, patients received subcutaneous injections of secukinumab (at a dose of 150 mg or 75 mg) or placebo at baseline; at weeks 1, 2, and 3; and every 4 weeks starting at week 4. At week 16 in both studies, patients in the placebo group were randomly reassigned to receive secukinumab at a dose of 150 mg or 75 mg, according to the schedule outlined in the Supplementary Appendix. Patients who met Assessment of Spondyloarthritis International Society 20 (ASAS20) response criteria (i.e., improvement of ≥20% and absolute improvement of ≥1 unit [on a 10-unit scale] in at least three of the four main ASAS domains, with no worsening by ≥20% in the remaining domain) at week 16 switched to secukinumab at week 24 in MEASURE 1. In both MEASURE 1 and MEASURE 2, patients continued to receive subcutaneous secukinumab at a dose of 150 mg or 75 mg every 4 weeks from week 16 until the end of the study.

Disease activity and efficacy assessments were conducted at baseline and throughout the study, with key assessments at week 16 (primary analysis) and week 52 (follow-up analysis). Blood samples were collected at baseline and immediately before dose administration at weeks 4, 16, 24, and 52 for assessment of secukinumab immunogenicity with the use of a bridging immunoassay (Meso Scale Discovery).[22]

OUTCOME MEASURES

In each study, the primary efficacy end point was the proportion of patients who met ASAS20 response criteria at week 16.[23] Secondary end points assessed at week 16 included ASAS40 response criteria (improvement of ≥40% and absolute improvement of ≥2 units [on a 10-unit scale] in at least three of the four main ASAS domains, with no worsening in the remaining domain), change from baseline in the high-sensitivity C-reactive protein (CRP) level, ASAS5/6 response (≥20% improvement in five of the six ASAS response domains), and changes from baseline in the following scores: total BASDAI score, the summary score for the physical component in version 2 of the Medical Outcomes Study 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),[24] and the score on the Ankylosing Spondylitis Quality of Life (ASQoL) scale (scores range from 0 [best quality] to 18 [poorest quality])[25]; ASAS partial remission (a score of ≤2 units in each of the four core ASAS domains) and overall safety were also assessed.

In each study, a preplanned follow-up analysis was performed after all patients had completed the visit at week 52. Safety analyses, performed with the use of the Common Terminology Criteria for Adverse Events, version 4.03,[26] included all safety data reported up to the cutoff date after all patients had completed at least 52 weeks of treatment in either study. Exploratory analyses of efficacy were performed at week 52.

STATISTICAL ANALYSIS

We calculated that for MEASURE 1 to have 90% power with a 2.5% type I error rate, assuming an ASAS20 response rate of 60% for the secukinumab groups and 20% for the placebo group,[27] we would need to assign at least 39 patients to each study group, on the basis of Fisher's exact test. The target population was increased to 116 patients per group to ensure sufficient safety data, providing 94 to 99% power to detect significant differences between the secukinumab and placebo groups for each of the secondary end points. We used the same power calculations in MEASURE 2. The target sample of 74 patients per group provided 99% power to detect significant between-group differences for the ASAS20 response rate and 79 to 99% power for the secondary end points.

In each study, analyses of primary and secondary efficacy end points at week 16 included all patients according to the treatment assigned at randomization. Closed testing procedures[28] were used to maintain a familywise error rate of 5% across the secukinumab groups and end points. The hypotheses for the primary objective

in either secukinumab treatment group versus the placebo group were tested simultaneously at the 0.025 level. On the basis of the rejection of one or both of these hypotheses, analysis of the secondary end points was completed according to a prespecified hierarchy in the sequence described in Figure S2 in the Supplementary Appendix.

The primary end point and other binary end points were evaluated by means of logistic regression with treatment and anti-TNF response status as factors and weight as a covariate. Missing values, including those due to discontinuation of the study treatment, were imputed as nonresponses. Between-group differences in continuous variables were evaluated with the use of a mixed-model repeated-measures (MMRM) approach, with missing data assumed to be missing at random and with study group, assessment visit, and anti-TNF response status as factors. Weight and baseline values of the end points were included in the model as continuous covariates. Interaction terms included study group and baseline value according to assessment visit. For the change in the high-sensitivity CRP level, the $\log_e$ ratio of the post-baseline value to the baseline value was used to normalize the distribution of the high-sensitivity CRP level at each assessment. The end points assessed at week 16 were analyzed descriptively with the use of observed values from week 20 onward. In a separate analysis of these end points from week 20 onward, missing values for binary variables were imputed as nonresponses, and missing values for continuous variables were imputed with the use of MMRM analysis.

Safety end points were evaluated for all patients who received at least one dose of the study drug; these end points were summarized descriptively. A data and safety monitoring committee reviewed unblinded safety data at regular intervals.

RESULTS

STUDY PARTICIPANTS

In MEASURE 1, from November 9, 2011, through January 21, 2013, we randomly assigned 371 patients to receive an intravenous loading dose of secukinumab (10 mg per kilogram) followed by subcutaneous secukinumab at a dose of 150 mg (125 patients), an intravenous loading dose of secukinumab (10 mg per kilogram) followed by subcutaneous secukinumab at a dose of 75 mg (124), or placebo (122). At week 16, a total of 351 patients (95%) remained in the study; 20 patients discontinued the study for the reasons outlined in Figure 1. In MEASURE 2, from October 28, 2012, through July 29, 2013, we randomly assigned 219 patients to receive subcutaneous secukinumab at a dose of 150 mg (72 patients), subcutaneous secukinumab at a dose of 75 mg (73), or placebo (74). At week 16, a total of 200 patients (91%) remained in the study; 19 patients discontinued the study for the reasons outlined in Figure 2.

Baseline demographic and disease characteristics were similar between studies and among the groups within each study (Table 1, and Table S1 in the Supplementary Appendix). The mean time since diagnosis was 6.5 to 8.3 years in MEASURE 1 and 5.3 to 7.0 years in MEASURE 2; the total BASDAI score was 6.1 to 6.5 and 6.6 to 6.8, respectively; 69 to 80% and 73 to 79% of patients were positive for HLA-B27, respectively; and approximately 26 to 39% of patients in each group had inadequate responses to anti-TNF agents in the two studies. Approximately 3% of patients in MEASURE 1 and 2% of those in MEASURE 2 had a history of inflammatory bowel disease at baseline.

PRIMARY END POINT

The primary end point was met in both secukinumab groups in MEASURE 1 and in the group that received 150 mg of secukinumab subcutaneously in MEASURE 2. In MEASURE 1, ASAS20 response rates at week 16 were 61% with subcutaneous secukinumab at a dose of 150 mg, 60% with subcutaneous secukinumab at a dose of 75 mg, and 29% with placebo ($P<0.001$ for both comparisons with placebo). In MEASURE 2, ASAS20 response rates at week 16 were 61% with subcutaneous secukinumab at a dose of 150 mg, 41% with subcutaneous secukinumab at a dose of 75 mg, and 28% with placebo ($P<0.001$ and $P=0.10$ for comparisons of the higher and lower doses, respectively, with placebo) (Fig. 3).

SECONDARY END POINTS

In MEASURE 1, all predefined secondary end points were met in both secukinumab groups (Table 2, and Fig. S5 in the Supplementary Appendix). ASAS40 response rates at week 16 were

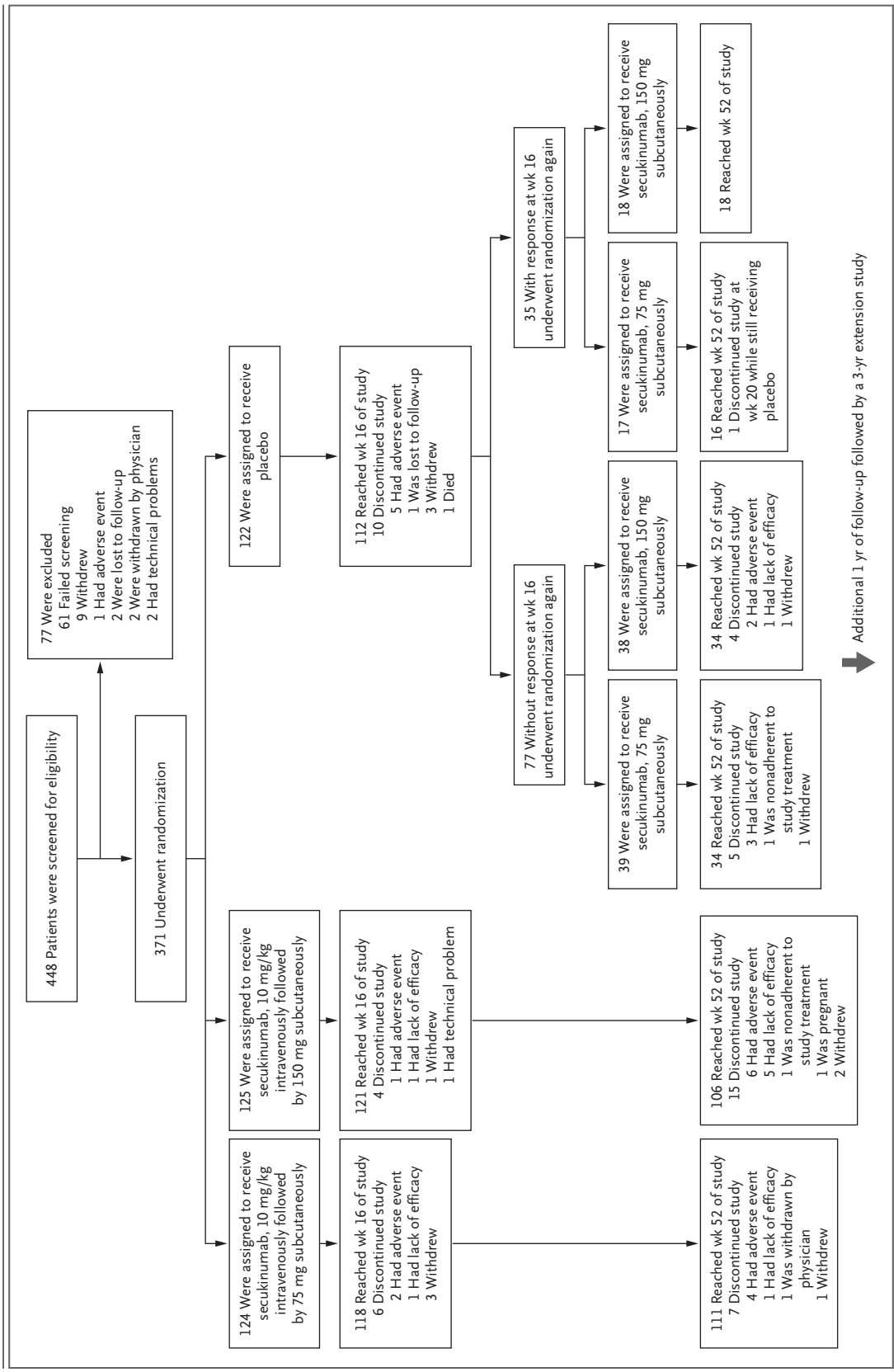

Figure 1. Numbers of Patients in MEASURE 1 Who Were Screened, Underwent Randomization, and Completed 52 Weeks of the Study.

In MEASURE 1, the secukinumab groups received intravenous secukinumab at a dose of 10 mg per kilogram of body weight at baseline, week 2, and week 4, followed by subcutaneous secukinumab at a dose of 150 mg or 75 mg, starting at week 8 and then every 4 weeks. The placebo group received intravenous placebo at baseline, week 2, and week 4, followed by subcutaneous placebo every 4 weeks starting at week 8. Patients initially assigned to receive placebo were randomly reassigned at week 16 to receive secukinumab, with active treatment starting either at week 16 (for those without a response to placebo) or at week 24 (for those with a response to placebo). Analyses of primary and secondary efficacy end points at week 16 included all patients according to the assigned study treatment at baseline.

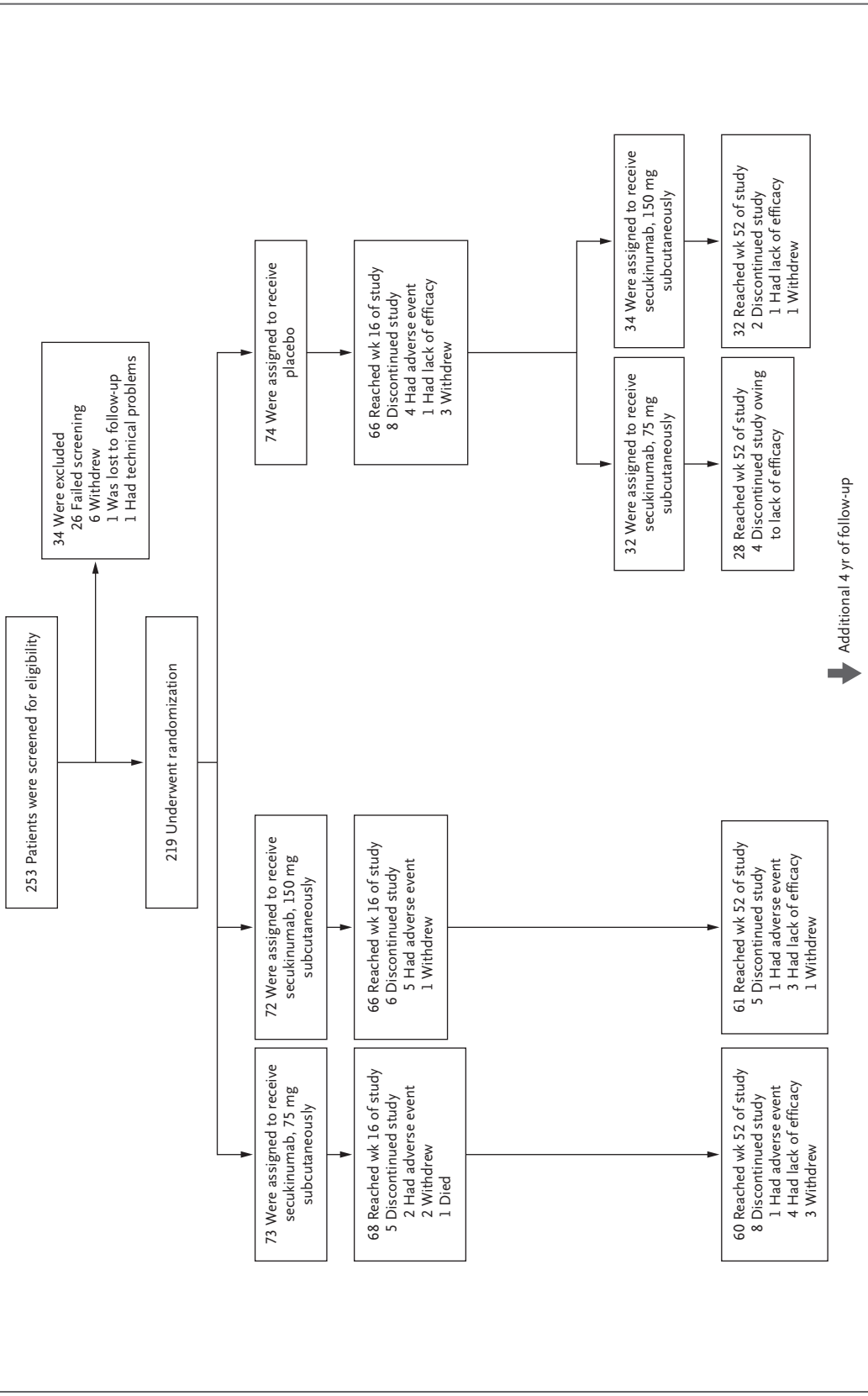

Figure 2. Numbers of Patients in MEASURE 2 Who Were Screened, Underwent Randomization, and Completed 52 Weeks of the Study.

In MEASURE 2, the patients received subcutaneous secukinumab, at a dose of 150 mg or 75 mg, or placebo at baseline; at weeks 1, 2, and 3; and every 4 weeks thereafter. Patients initially assigned to receive placebo were randomly reassigned at week 16 to receive secukinumab. Analyses of primary and secondary efficacy end points at week 16 included all patients according to the assigned study treatment at baseline.

Table 1. Demographic and Baseline Characteristics of the Patients in MEASURE 1 and MEASURE 2 (Full Analysis Set).*

Characteristic	MEASURE 1			MEASURE 2		
	Secukinumab, 150 mg SC (N=125)	Secukinumab, 75 mg SC (N=124)	Placebo (N=122)	Secukinumab, 150 mg SC (N=72)	Secukinumab, 75 mg SC (N=73)	Placebo (N=74)
Age — yr	40.1±11.6	42.3±13.2	43.1±12.4	41.9±12.5	44.4±13.1	43.6±13.2
Male sex — no. (%)	84 (67)	88 (71)	85 (70)	46 (64)	51 (70)	56 (76)
Weight — kg	74.7±16.2	77.7±19.6	76.7±14.4	82.3±18.0	81.5±17.4	80.3±15.2
Race — no. (%)†						
White	69 (55)	76 (61)	81 (66)	69 (96)	70 (96)	70 (95)
Asian	21 (17)	23 (19)	19 (16)	2 (3)	3 (4)	4 (5)
Other	35 (28)	25 (20)	22 (18)	1 (1)	0	0
Time since diagnosis of ankylosing spondylitis — yr	6.5±6.9	7.9±9.7	8.3±8.9	7.0±8.2	5.3±7.4	6.4±8.9
Positive for HLA-B27 — no. (%)	86 (69)	99 (80)	90 (74)	57 (79)	53 (73)	58 (78)
Previous disorders — no. (%)						
Psoriasis	8 (6)	4 (3)	7 (6)	6 (8)	6 (8)	8 (11)
Inflammatory bowel disease	2 (2)	6 (5)	2 (2)	3 (4)	0	2 (3)
Uveitis	15 (12)	25 (20)	22 (18)	11 (15)	10 (14)	13 (18)
No previous anti-TNF therapy — no. (%)	92 (74)	90 (73)	89 (73)	44 (61)	45 (62)	45 (61)
Medication use — no. (%)						
Methotrexate	17 (14)	22 (18)	16 (13)	8 (11)	9 (12)	9 (12)
Sulfasalazine	42 (34)	40 (32)	42 (34)	10 (14)	12 (16)	9 (12)
Glucocorticoid	19 (15)	15 (12)	16 (13)	4 (6)	7 (10)	7 (9)
Median hsCRP (range) — mg/liter	7.4 (0.2–147.7)	9.2 (0.4–139.7)	7.9 (0.2–146.8)	7.5 (0.4–237.0)	5.7 (0.5–86.2)	8.3 (0.5–84.6)
BASDAI, total score	6.4±1.6	6.1±1.4	6.5±1.5	6.6±1.5	6.6±1.3	6.8±1.3
Total score for back pain (0–100 mm scale)‡	64.0±18.6	61.7±18.9	66.7±16.5	66.2±16.7	65.1±17.7	69.2±18.8
Patient's global assessment of disease activity (0–100 mm scale)§	64.0±19.4	60.5±18.3	66.3±18.6	67.5±16.8	64.6±17.9	70.5±15.8

* In MEASURE 1, subcutaneous (SC) doses of secukinumab were preceded by an intravenous loading dose of 10 mg per kilogram of body weight. Plus–minus values are means ±SD. There were no significant between-group differences in the baseline characteristics listed in either study. BASDAI denotes Bath Ankylosing Spondylitis Disease Activity Index (scores range from 0 to 10, with higher scores indicating more severe disease activity), hsCRP high-sensitivity C-reactive protein, and TNF tumor necrosis factor.
† Race was self-assessed. Additional data are provided in Table S1 in the Supplementary Appendix.
‡ Back pain was scored on a visual-analogue scale from 0 mm (no pain) to 100 mm (the most severe pain).
§ Disease activity was scored on a visual-analogue scale from 0 mm (no disease activity) to 100 mm (the most severe disease activity).

42% and 33% in the groups that received subcutaneous secukinumab at the higher and lower doses, respectively, as compared with 13% in the placebo group (P<0.001 for both comparisons with placebo) (Fig. 3 and Table 2).

In MEASURE 2, all predefined secondary end points except ASAS partial remission were met with subcutaneous secukinumab at a dose of 150 mg; responses with subcutaneous secukinumab at a dose of 75 mg did not differ significantly from responses with placebo on the basis of hierarchical testing (Table 2, and Fig. S5 in the Supplementary Appendix). ASAS40 response rates at week 16 were 36% with subcutaneous secukinumab at a dose of 150 mg and 26% with subcutaneous secukinumab at a dose of 75 mg, as compared with 11% with placebo (P<0.001 and P=0.10 for comparisons of the higher and lower doses, respectively, with placebo) (Fig. 3 and Table 2).

LONG-TERM EFFICACY

At week 52, a total of 319 patients (86%) remained in MEASURE 1, and 181 patients (83%) in MEASURE 2. The clinical responses observed at week 16 were maintained through 52 weeks of treatment among patients randomly assigned to secukinumab at baseline, on the basis of both observed data and a more conservative assessment of efficacy in which missing values were imputed as nonresponses (Fig. 3, and Fig. S3 and Tables S2 and S3 in the Supplementary Appendix). In addition, patients randomly assigned to placebo had improvements in ASAS20 response rates on switching to secukinumab (Fig. S4 in the Supplementary Appendix).

SAFETY

Adverse events during the placebo-controlled periods of both studies are shown in Table 3, as well as in Table S4 in the Supplementary Appendix. The incidence of infection was higher with secukinumab than with placebo (30% vs. 12% in MEASURE 1 and 32% vs. 27% in MEASURE 2).

During the entire safety period of MEASURE 1, exposure-adjusted incidence rates of serious adverse events were 8.0 and 8.6 events per 100 patient-years among patients who received at least one dose of secukinumab at the higher and lower doses, respectively (including patients who were randomly assigned to secukinumab at baseline and those who switched from placebo to active treatment) (Table S5 in the Supplementary Appendix). The rates of infection were 73.5 and 59.4 events per 100 patient-years of exposure for subcutaneous secukinumab at doses of 150 mg and 75 mg, respectively. During the entire safety period of MEASURE 2, exposure-adjusted incidence rates of serious adverse events were 6.6 and 7.7 events per 100 patient-years for subcutaneous secukinumab at doses of 150 mg and 75 mg, respectively (Table S5 in the Supplementary Appendix). Incidence rates of infection in the groups that received subcutaneous secukinumab at the higher and lower doses were 60.5 and 89.1 events per 100 patient-years of exposure, respectively. No patients in either study discontinued treatment because of a serious infection.

Candida infections were reported in three patients treated with subcutaneous secukinumab in MEASURE 1 (genital candidiasis in a patient receiving the 75-mg dose, oral candidiasis in a patient receiving the 75-mg dose, and candida thrush infection in a patient receiving the 150-mg dose) and in three patients treated with subcutaneous secukinumab in MEASURE 2 (one case of candida infection at the 75-mg dose and two cases of oral candidiasis [one each at the lower and higher doses]). The pooled exposure-adjusted incidence of candidiasis in secukinumab-treated patients across the two studies was 0.9 events per 100 patient-years of exposure (Table 4). These events did not lead to study discontinuation and resolved spontaneously or with standard antifungal treatment.

Grade 3 neutropenia was documented at a single visit in each of three patients receiving subcutaneous secukinumab at the 75-mg dose in MEASURE 1 and in one patient receiving subcutaneous secukinumab at the 150-mg dose in MEASURE 2. Grade 4 neutropenia was reported in one patient (receiving subcutaneous secukinumab at the 75-mg dose) at a single visit in MEASURE 1 (pooled incidence of grade 3 or 4 neutropenia in the two studies: 0.7 events per 100 patient-years of exposure [Table 4]). None of these events led to treatment interruption or discontinuation, and only one grade 3 case was associated with infection (a nonserious upper respiratory tract infection).

Adjudicated major adverse cardiac events were recorded in two patients treated with subcutaneous secukinumab in MEASURE 1 (myocardial infarction in a patient receiving the 75-mg dose

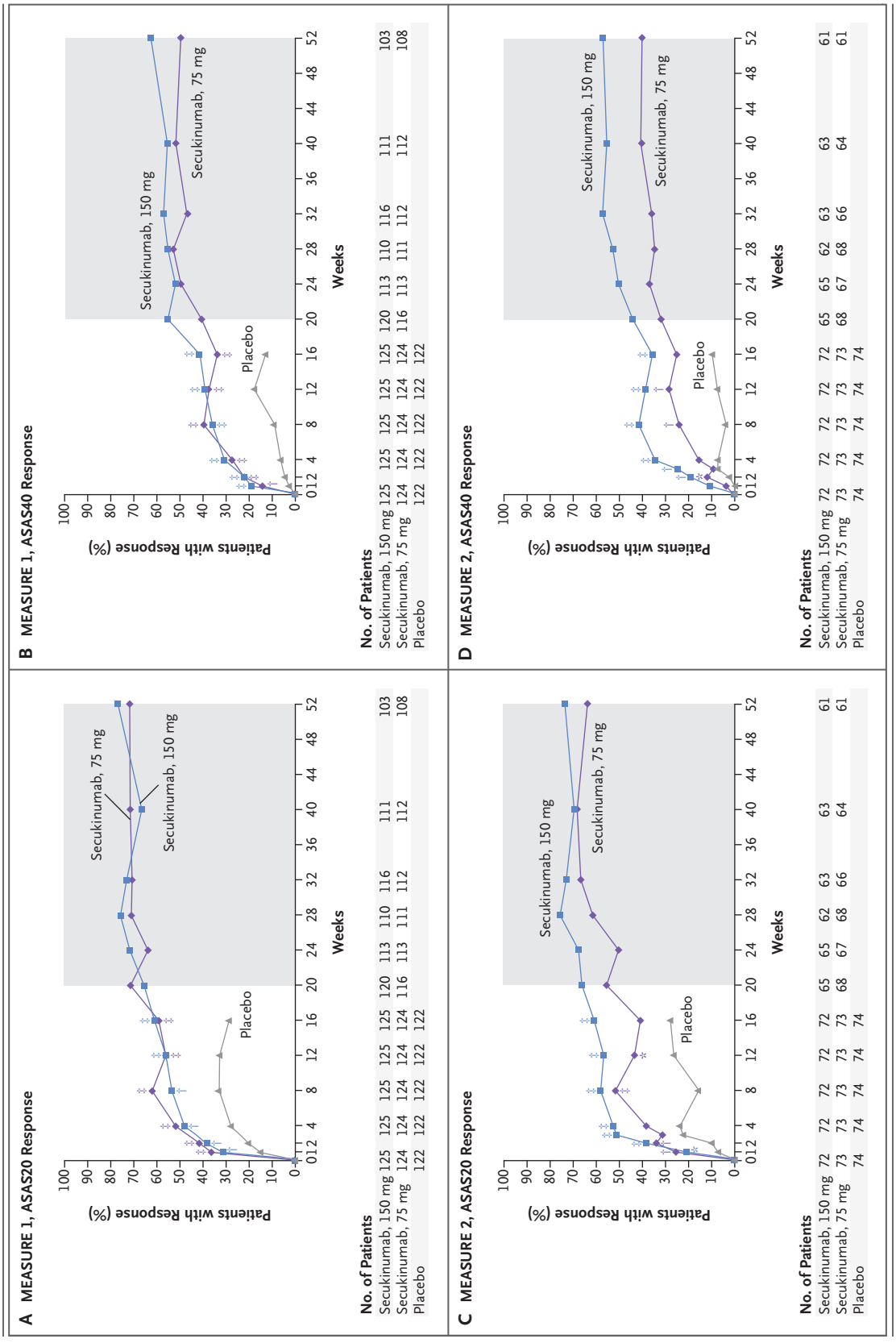

Figure 3 (facing page). Response Rates through Week 16 (Placebo-Controlled Phase) and through Week 52 among Patients Randomly Assigned to Secukinumab or Placebo at Baseline in MEASURE 1 and MEASURE 2.

Shown are the proportions of patients with Assessment of Spondyloarthritis International Society 20 (ASAS20) responses (improvement of ≥20% and absolute improvement of ≥1 unit [on a 10-unit scale] in at least three of the four main ASAS domains, with no worsening by ≥20% in the remaining domain) and the proportion with ASAS40 responses (improvement of ≥40% and absolute improvement of ≥2 units [on a 10-unit scale] in at least three of the four main ASAS domains, with no worsening in the remaining domain) in MEASURE 1 (Panels A and B) and MEASURE 2 (Panels C and D). The predefined statistical hypothesis-testing hierarchy was designed to maintain the family-wise type I error rate at 5% across the primary and ranked secondary end points. Missing data were imputed as nonresponses up to week 16. Observed data are presented from week 20 to week 52 (indicated by the gray box in each panel). P values at week 16 were adjusted for multiple testing. An asterisk denotes $P<0.05$, a dagger $P<0.01$, and a double dagger $P<0.001$ for the comparison with placebo.

and stroke in a patient receiving the 150-mg dose) and in one patient treated with subcutaneous secukinumab in MEASURE 2 (fatal myocardial infarction in a patient receiving the 75-mg dose). The pooled exposure-adjusted incidence rate of adjudicated major adverse cardiac events across both studies was 0.4 events per 100 patient-years of exposure to secukinumab (Table 4).

Four cancers were reported in MEASURE 1: B-cell lymphoma (in a patient receiving subcutaneous secukinumab at the 75-mg dose), breast cancer (in a patient receiving subcutaneous secukinumab at the 150-mg dose), transitional-cell carcinoma of the bladder (in a patient receiving subcutaneous secukinumab at the 150-mg dose), and lymphoma (in a patient receiving placebo). In MEASURE 2, there was a single case of malignant melanoma (in a patient receiving subcutaneous secukinumab at the 150-mg dose). These five events resulted in discontinuation of the study treatment.

Crohn's disease was an adverse event in three patients in the group receiving subcutaneous secukinumab at a dose of 75 mg in MEASURE 1. Two cases were in patients with a history of Crohn's disease, and one was in a patient with a history of a polyp and an adenoma in the colon; all three cases were nonserious. Crohn's disease was a serious adverse event in two patients receiving subcutaneous secukinumab in MEASURE 2 (one each in the 75-mg and 150-mg groups); the patient receiving the lower dose of secukinumab was considered to have an exacerbation of preexisting Crohn's disease related to the study treatment, and this resulted in discontinuation. The pooled exposure-adjusted incidence rate of Crohn's disease across both studies was 0.7 events per 100 patient-years of exposure to secukinumab (Table 4).

Uveitis was reported in six patients receiving secukinumab (five of whom had a history of uveitis) and two patients receiving placebo (one of whom had a history of uveitis) in MEASURE 1, with a single serious case in the 150-mg group that resolved and did not lead to discontinuation of the study treatment (Table S6 in the Supplementary Appendix). A single case of uveitis was reported with subcutaneous secukinumab (at the 150-mg dose) in MEASURE 2, in a patient with no history of uveitis.

There was one death in MEASURE 1 (a suicide in the placebo group) and one death in MEASURE 2 (a fatal myocardial infarction in a patient receiving 75 mg of secukinumab subcutaneously). There were no suicides or adverse events related to suicidality among secukinumab-treated patients.

After treatment was started, antidrug antibodies were detected at week 52 in two patients in MEASURE 1 who were receiving subcutaneous secukinumab at a dose of 150 mg; neutralizing antibodies to secukinumab were detected in one of these patients. Neither patient had a loss of the ASAS20 response or had any immune-related adverse events. No antidrug antibodies were detected after the start of treatment in MEASURE 2.

DISCUSSION

Secukinumab significantly reduced the signs and symptoms of ankylosing spondylitis, as compared with placebo, in both phase 3 trials, extending the positive results of the phase 2 study.[9] An ASAS20 response, the primary end point, was achieved in approximately 60% of patients in both groups receiving intravenous loading followed by subcutaneous secukinumab (150 mg or 75 mg) in MEASURE 1 and in the group receiving 150-mg of subcutaneous secukinumab in MEASURE 2, showing that despite the much

Table 2. Efficacy End Points at Week 16 in the MEASURE 1 and MEASURE 2 Studies (Full Analysis Set).*

End Point	MEASURE 1			MEASURE 2		
	Secukinumab, 150 mg SC (N=125)	Secukinumab, 75 mg SC (N=124)	Placebo (N=122)	Secukinumab, 150 mg SC (N=72)	Secukinumab, 75 mg SC (N=73)	Placebo (N=74)
ASAS20 response — no. (%)†	76 (61)‡	74 (60)‡	35 (29)	44 (61)‡	30 (41)	21 (28)
ASAS40 response — no. (%)§	52 (42)‡	41 (33)‡	16 (13)	26 (36)‡	19 (26)	8 (11)
hsCRP, ratio of postbaseline level to baseline level	0.40±1.09‡	0.45±1.09‡	0.97±1.10	0.55±1.10‡	0.61±1.10	1.13±1.11
ASAS5/6 response — no. (%)¶	61 (49)‡	56 (45)‡	16 (13)	31 (43)‡	25 (34)	6 (8)
BASDAI score, mean change from baseline	−2.32±0.17‡	−2.34±0.18‡	−0.59±0.18	−2.19±0.25‡	−1.92±0.25	−0.85±0.25
SF-36 physical-component summary score, mean change from baseline‖	5.57±0.59‡	5.64±0.60‡	0.96±0.61	6.06±0.78‡	4.77±0.80	1.92±0.79
ASQoL score, mean change from baseline**	−3.58±0.42‡	−3.61±0.42‡	−1.04±0.44	−4.00±0.53††	−3.33±0.54	−1.37±0.53
ASAS partial remission — no. (%)‡‡	19 (15) ††	20 (16) ††	4 (3)	10 (14)	11 (15)	3 (4)

* In MEASURE 1, subcutaneous doses of secukinumab were preceded by an intravenous loading dose of 10 mg per kilogram of body weight. Plus–minus values are least-squares mean (±SE) changes from baseline. A prespecified hierarchical testing strategy was used to account for multiple testing in the overall study population. Missing data for binary variables were imputed as nonresponses. Missing data for continuous variables were imputed with the use of mixed-model repeated-measures analysis.

† ASAS20 response indicates improvement of at least 20% and absolute improvement of at least 1 unit (on a 10-unit scale) in at least three of the four main Assessment of Spondyloarthritis International Society domains, with no worsening by 20% or more in the remaining domain.

‡ P<0.001 for the comparison with placebo.

§ ASAS40 response indicates improvement of at least 40% and absolute improvement of at least 2 units (on a 10-unit scale) in at least three of the four main ASAS domains, with no worsening in the remaining domain.

¶ ASAS5/6 response indicates 20% or more improvement in five of the six ASAS response criteria.

‖ Scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 (maximum disability) to 100 (no disability) for individual domains, with a normative composite summary score of 50.

** Scores on the Ankylosing Spondylitis Quality of Life (ASQoL) scale range from 0 (best quality) to 18 (poorest quality).

†† P<0.01 for the comparison with placebo.

‡‡ ASAS partial remission indicates a score of 2 units or less (on a scale from 0 to 10) in each of the four core ASAS domains.

Table 3. Safety Profile during the 16-Week, Placebo-Controlled Induction Period of the MEASURE 1 and MEASURE 2 Studies.*

Variable	MEASURE 1		MEASURE 2	
	Secukinumab, Pooled Data (N=249)	Placebo (N=122)	Secukinumab, Pooled Data (N=145)	Placebo (N=74)
Exposure to study treatment — days	113.2±13.2	109.2±22.7	110.1±15.8	107.6±22.4
Any adverse event — no. of patients (%)	170 (68)	68 (56)	89 (61)	47 (64)
Death — no. of patients (%)	0	1 (<1)†	1 (<1)‡	0
Serious adverse event — no. of patients (%)‡	5 (2)	5 (4)	8 (6)	3 (4)
Discontinuation of study treatment because of any adverse event — no. of patients (%)	3 (1)	5 (4)	7 (5)	4 (5)
Infection or infestation — no. of patients (%)§	75 (30)	15 (12)	46 (32)	20 (27)
Common adverse events — no. of patients (%)¶				
Nasopharyngitis	30 (12)	9 (7)	14 (10)	3 (4)
Dyslipidemia	24 (10)	6 (5)	2 (1)	1 (1)
Headache	20 (8)	7 (6)	6 (4)	6 (8)
Adverse events of special interest — no. of patients (%)				
Candida infection	1 (<1)	0	1 (<1)	0
Crohn's disease	1 (<1)	0	1 (<1)	0
Major adverse cardiac event, adjudicated	0	0	1 (<1)‡	0
Neutropenia, grade 3 or 4	0	0	0	0

* Plus–minus values are means ±SD.
† The patient had depression and committed suicide.
‡ The patient died from a major adverse cardiac event, adjudicated as myocardial infarction, which was considered to be unrelated to the study medication. The patient was a 60-year-old male smoker with multiple baseline cardiac risk factors (elevated hsCRP, lipoprotein A, and low-density lipoprotein cholesterol levels), who died on day 29 from acute myocardial infarction. An autopsy showed three-vessel cardiac arteriosclerosis, cardiac hypertrophy, recurrent anteroseptal myocardial infarction, chronic pulmonary congestion, and emphysema; coronary heart disease and nicotine abuse were reported as factors that may have contributed to the infarction.
§ Serious adverse events included deaths.
¶ Common adverse events are those that occurred in at least 5% of patients in the combined secukinumab group in either study during the 16-week placebo-controlled period. Events are listed according to the preferred terms in the *Medical Dictionary for Regulatory Activities*.

greater exposure conferred by intravenous loading, no incremental increase in efficacy was observed, as compared with the subcutaneous loading regimen. Benefits over placebo were also observed for most of the secondary efficacy end points at week 16, including the ASAS40 response, high-sensitivity CRP level, ASAS5/6 response, and scores on the BASDAI, the physical component of SF-36, and the ASQoL scale, and were sustained through 52 weeks of therapy. Notably, in MEASURE 1 and MEASURE 2, the rates for ASAS40 and ASAS5/6 responses, which are based on more stringent criteria than those for the ASAS20 response, both reached approximately 60% in the 150-mg dose groups among patients who completed 52 weeks of therapy.

Subcutaneous secukinumab at a dose of 75 mg was shown to be ineffective in MEASURE 2, since there were no significant differences in the hierarchically tested end points, as compared with placebo. These results suggest that the efficacy of secukinumab at the 75-mg dose in MEASURE 1 may have been due to the greater exposure at week 16 as a result of the intravenous loading regimen, not to the 75-mg subcutaneous maintenance dose. Despite the significant results observed with secukinumab at the 75-mg dose in MEASURE 1, a descriptive analysis showed an increasing dose separation between the 150-mg and 75-mg treatment groups with the use of more stringent response criteria (ASAS40 response and ASAS partial remission) as time points approached week 52. Moreover, in MEASURE 2, subcutaneous secukinumab at the 150-mg dose showed consistently greater efficacy than subcutaneous secukinumab at the 75-mg

Table 4. Safety Profile during the Entire Safety Reporting Period in the MEASURE 1 and MEASURE 2 Studies.*

Variable	MEASURE 1	MEASURE 2	MEASURE 1 and MEASURE 2
	Any Secukinumab, Pooled Data (N=360)	Any Secukinumab, Pooled Data (N=211)	Any Secukinumab, Pooled Data (N=571)
Exposure to study treatment — days	451.7±146.5	425.8±135.1	442.1±142.8
Any adverse event — no. of patients (no. of cases/100 patient-yr)	291 (203.2)	175 (212.9)	466 (206.8)
Death — no. of patients (no. of cases/100 patient-yr)†	0	1‡	1‡
Serious adverse event — no. of patients (no. of cases/100 patient-yr)§	35 (8.3)	17 (7.1)	52 (7.9)
Discontinuation of study treatment due to adverse event — no. of patients (no. of cases/100 patient-yr)†¶	15	9	24
Infection or infestation — no. of patients (no. of cases/100 patient-yr)	187 (66.1)	111 (73.7)	298 (68.8)
Common adverse events — no. of patients (no. of cases/100 patient-yr)‖			
Nasopharyngitis	72 (18.8)	35 (16.3)	107 (17.9)
Headache	39 (9.6)	14 (6.0)	53 (8.3)
Diarrhea	39 (9.4)	14 (5.9)	53 (8.1)
Upper respiratory tract infection	35 (8.4)	17 (7.3)	52 (8.0)
Adverse events of special interest — no. of patients (no. of cases/100 patient-yr)			
Candida infection	3 (0.7)	3 (1.2)	6 (0.9)
Crohn's disease	3 (0.7)	2 (0.8)	5 (0.7)
Major adverse cardiac event, adjudicated	2 (0.5)	1 (0.4)	3 (0.4)
Neutropenia, grade 3 or 4	4 (0.9)	1 (0.4)	5 (0.7)

* Plus–minus values are means ±SD. The reporting period for safety data was the period from baseline to the visit at week 52 of the last patient enrolled. The placebo group includes all patients who received placebo during the study. The secukinumab groups in this period include any patients who received the stated dose of secukinumab and include patients randomly assigned to placebo at baseline who were randomly reassigned to active treatment at week 16 or 24.
† Exposure-adjusted incidence rates were not calculated for death or discontinuation of study treatment.
‡ The patient died from a major adverse cardiac event, adjudicated as myocardial infarction, which was considered to be unrelated to the study medication. The patient was a 60-year-old male smoker with multiple baseline cardiac risk factors (elevated hsCRP, lipoprotein A, and low-density lipoprotein levels), who died on day 29 from acute myocardial infarction. An autopsy showed three-vessel cardiac arteriosclerosis, cardiac hypertrophy, recurrent anteroseptal myocardial infarction, chronic pulmonary congestion, and emphysema; coronary heart disease and nicotine abuse were reported as factors that may have contributed to the infarction.
§ Serious adverse events included deaths.
¶ An additional three patients discontinued secukinumab because of an adverse event after week 52.
‖ Common adverse events are those that had an exposure-adjusted incidence rate of at least 7.0 cases per 100 patient-years in the combined secukinumab groups of either study during the entire safety reporting period. Events are listed according to the preferred term in the *Medical Dictionary for Regulatory Activities*.

dose for all primary and secondary end points at week 16 (except ASAS partial remission), as well as at week 52. Thus, 150 mg administered subcutaneously appears to be the more effective dose for secukinumab in patients with ankylosing spondylitis.

Anti-TNF agents are the only approved biologic agents for ankylosing spondylitis, with a number of other therapies failing to show benefits.[29-33] Although head-to-head trials would be required to fully assess the efficacy and safety of secukinumab versus TNF-inhibitors, the ASAS20

response rates achieved with secukinumab at week 16 in our studies were similar to those reported in phase 3 studies of anti-TNF agents in which most of the patients had not received previous anti-TNF therapy (response rates of 58 to 64% at weeks 12 to 24),[6,7,27,34,35] even though 30 to 40% of the patients in our studies had had no response to previous anti-TNF treatment. Thus, secukinumab not only is effective in patients who have not received TNF agents previously but also may be effective in patients in whom previous anti-TNF treatment failed.

The safety profile of secukinumab in the present studies is consistent with that in previous studies of secukinumab for ankylosing spondylitis and moderate-to-severe plaque psoriasis.[9,19] The incidence of infections or infestations was higher with secukinumab than with placebo in MEASURE 1. During the entire treatment period, pooled exposure-adjusted incidence rates of grade 3 or 4 neutropenia, candida infections, and Crohn's disease were 0.7, 0.9, and 0.7 events per 100 patient-years, respectively, among secukinumab-treated patients. In MEASURE 1, increases in serum cholesterol and triglyceride levels were generally mild (grade 1 or 2). Dyslipidemia was not evident in MEASURE 2 or in studies of secukinumab for other indications.[9,19,36,37] Across our two studies, two secukinumab-treated patients had myocardial infarction and one patient had a stroke. One case of myocardial infarction, in a patient receiving subcutaneous secukinumab at the 75-mg dose in MEASURE 2, resulted in death on day 29; the patient was found on autopsy to have extensive preexisting coronary artery disease. One patient, who was receiving placebo, committed suicide. There were no suicides or suicidality-related adverse events among secukinumab-treated patients in either study. The immunogenicity of secukinumab was low, and anti-secukinumab antibodies were not associated with immune reactions or reduced efficacy.

In conclusion, secukinumab showed efficacy in key clinical domains of ankylosing spondylitis. The results suggest that interleukin-17A plays a role in the pathogenesis of ankylosing spondylitis, and they validate inhibition of this cytokine as a potential therapeutic approach.

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