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Phase 3 Trial of Secukinumab in Polymyalgia Rheumatica

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ABSTRACT

BACKGROUND

Polymyalgia rheumatica is a common inflammatory disease characterized by pain and stiffness in the shoulders and hips. Glucocorticoids are the first-line treatment, but relapses and glucocorticoid-related toxic effects are common, which underscores the need for effective alternatives. Secukinumab is a fully human monoclonal antibody that selectively inhibits interleukin-17A.

METHODS

We enrolled patients with recently relapsed polymyalgia rheumatica and randomly assigned them, in a 1:1:1 ratio, to receive secukinumab at a dose of 300 mg (SEC-300 group), secukinumab at a dose of 150 mg (SEC-150 group), or placebo for 52 weeks. Patients in all the groups also received prednisone on a tapering schedule for 24 weeks. The primary outcome was sustained remission at week 52, defined as remission (the absence of signs or symptoms attributable to polymyalgia rheumatica and no new diagnosis of giant-cell arteritis that warranted escape or rescue treatment) that was sustained from week 12 until week 52. The annual cumulative glucocorticoid dose was a secondary outcome. Safety was also assessed.

RESULTS

A total of 381 patients underwent randomization, and 127 were assigned to each group. At 52 weeks, sustained remission was observed in 41.2% (95% confidence interval [CI], 32.8 to 49.7) of the patients in the SEC-300 group, in 40.6% (95% CI, 32.2 to 49.0) of those in the SEC-150 group, and in 20.4% (95% CI, 13.6 to 27.2) of those in the placebo group ($P<0.001$ for the comparison of each secukinumab dose with placebo). The mean adjusted annual cumulative glucocorticoid dose was 1603.7 mg in the SEC-300 group, 1683.2 mg in the SEC-150 group, and 2093.0 mg in the placebo group. Serious adverse events occurred in 13.5% of the patients in the SEC-300 group, in 15.9% in the SEC-150 group, and in 14.2% in the placebo group. Nasopharyngitis, hypersensitivity reactions, urinary tract infections, fungal infections, and back pain were more common in the secukinumab groups than in the placebo group.

CONCLUSIONS

Among patients with relapsed polymyalgia rheumatica, treatment with secukinumab plus a 24-week glucocorticoid taper resulted in a higher percentage of patients with remission and in lower cumulative glucocorticoid doses than a glucocorticoid taper alone. (Funded by Novartis; REPLENISH ClinicalTrials.gov number, NCT05767034.)

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Polymyalgia rheumatica is the second most common idiopathic inflammatory rheumatic disease after rheumatoid arthritis.[1] Polymyalgia rheumatica occurs nearly exclusively in adults who are 50 years of age or older and is predominantly seen in women.[2,3] It is characterized by bursitis and tendinitis that is associated with intense pain and stiffness in the neck, shoulders, and pelvic girdle, negatively affecting quality of life and physical function.[2-5] Polymyalgia rheumatica is associated with giant-cell arteritis in approximately 16 to 21% of patients.[6] Although the pathogenesis of polymyalgia rheumatica is not fully understood, elevated acute-phase reactants,[7] increased interleukin-17A levels, and an imbalance between proinflammatory type 17 helper T (Th17) cells and regulatory T cells have been reported.[8-10] Interleukin-17A contributes to articular and periarticular inflammation, which is typical of polymyalgia rheumatica.[11-13]

Glucocorticoids, an effective first-line treatment for polymyalgia rheumatica, are recommended by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR).[14-16] These guidelines recommend progressive tapering of glucocorticoids toward complete discontinuation because these agents increase the risk of adverse events such as infections, diabetes mellitus, osteoporosis, pathologic fractures, cardiovascular events (e.g., hypertension and heart failure), and neuropsychiatric conditions (e.g., depression and anxiety).[17-22] Such adverse events are more likely to occur among older persons and women, the persons who are most affected by polymyalgia rheumatica.[18] Even 5 years after diagnosis, 25% of patients with polymyalgia rheumatica continue to receive glucocorticoid treatment.[23] Relapse occurs in 43% of patients within the first year of treatment,[23] resulting in a longer duration of glucocorticoid use.[24] Sarilumab, an interleukin-6 receptor inhibitor, is currently the only biologic agent approved for use in polymyalgia rheumatica.[25] Therefore, there is a need for additional treatments that can induce sustained remission while sparing the side effects of glucocorticoids.

The REPLENISH trial was based on evidence of Th17 pathway activation in polymyalgia rheumatica, the efficacy of secukinumab in ankylosing spondylitis and psoriatic arthritis,[26] and preliminary evidence of efficacy from a phase 2 trial in giant-cell arteritis.[27] Secukinumab, a fully human monoclonal antibody that selectively neutralizes interleukin-17A, has well-established efficacy and a known safety profile across multiple indications.[26,28-30] Here, we describe the efficacy and safety of secukinumab treatment, in combination with a 24-week tapering course of glucocorticoids, in patients with recently relapsed polymyalgia rheumatica.

METHODS

TRIAL DESIGN AND OVERSIGHT

This phase 3, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of 300 mg and 150 mg of secukinumab in patients with recently relapsed polymyalgia rheumatica. The sponsor (Novartis) and steering committee were involved in the design of the trial. The trial investigators were responsible for data collection, and the sponsor performed site monitoring and collation and analysis of the data. The first draft of the manuscript was prepared by the first and last authors, with input from all the authors. All the authors participated in data interpretation and critical revisions of an earlier version of the manuscript. Medical writing support was funded by Novartis. The trial was conducted at 148 sites in 28 countries and was performed in accordance with applicable local regulations, Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki. Approval was obtained from the institutional review board or ethics committee at each of the participating sites. All the patients provided written informed consent. The steering committee provided scientific input and oversaw the trial design, providing counsel on trial conduct and manuscript submission. The sponsor and the authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org).

PATIENTS

Eligible patients were 50 years of age or older, met the EULAR–ACR classification criteria for polymyalgia rheumatica,[15] had a history of pain in both shoulders, and had an elevated C-reactive protein level (≥10 mg per liter) or an elevated erythrocyte sedimentation rate (≥30 mm per hour). Patients had to have had at least one polymyalgia rheumatica relapse while tapering prednisone or prednisone equivalent (while receiving a dose of

≥5 mg per day) within the 12 weeks before the baseline visit. Patients also had to have received prednisone or equivalent (≥10 mg per day) for at least 8 consecutive weeks at any time before screening to confirm adequate historical glucocorticoid exposure. Patients with a history or evidence of giant-cell arteritis, rheumatoid arthritis, or other inflammatory arthritis were excluded. Details regarding eligibility criteria are provided in the Supplementary Appendix (available at NEJM.org).

TRIAL REGIMENS

Patients were randomly assigned to receive secukinumab at a dose of 300 mg (SEC-300 group), secukinumab at a dose of 150 mg (SEC-150 group), or placebo for 52 weeks (Fig. S1 in the Supplementary Appendix). Patients in the secukinumab groups received secukinumab subcutaneously once a week until week 4, and then every 4 weeks thereafter. The patients in all three groups received the same protocol-specified 24-week tapering course of prednisone, starting at either 15 mg per day or 10 mg per day. The selection of the baseline prednisone dose was based on the glucocorticoid dose that the patient was receiving before baseline at the time of relapse and on investigator-assessed disease activity (Table S1). Randomization was stratified according to region (Japan or non-Japan) to ensure balance within the strata. In the non-Japan population, the patients were further stratified according to baseline glucocorticoid dose (10 mg per day or 15 mg per day).

The prednisone tapering regimen permitted limited adjustments before week 12, but subsequent alterations were not allowed. Patients who exhibited insufficient clinical response to polymyalgia rheumatica therapy or who had relapse were eligible for escape or rescue treatment (details are provided in the Supplementary Appendix). Escape treatment involved increasing the glucocorticoid dose or restarting a glucocorticoid according to the judgment of the investigator. Patients who received escape treatment continued to receive the assigned dose of secukinumab or placebo. Patients who received rescue treatment (any alternative therapy, according to the judgment of the investigator) to control polymyalgia rheumatica discontinued secukinumab or placebo. Relapse occurrence was determined on the basis of the investigator's overall assessment of the signs and symptoms of polymyalgia rheumatica or a new diagnosis of giant-cell arteritis.

OUTCOMES

Remission was defined as the absence of signs or symptoms attributable to polymyalgia rheumatica and no new diagnosis of giant-cell arteritis that warranted escape or rescue treatment. The primary outcome was sustained remission at week 52, defined as remission that occurred by week 12 and was sustained until week 52, without recurrence of polymyalgia rheumatica and with no new diagnosis of giant-cell arteritis that warranted treatment.

The secondary outcomes were tested hierarchically in the following order: complete sustained remission, defined as sustained remission plus no elevation in inflammatory markers (an erythrocyte sedimentation rate of ≥40 mm per hour and a high-sensitivity C-reactive protein level of ≥10 mg per liter at two or more consecutive visits) at week 52; the adjusted annual cumulative glucocorticoid dose; the time to first use of escape or rescue treatment through week 52; the change from baseline in the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) score (on a scale from 0 to 52, with higher scores indicating less fatigue); and the score on the Health Assessment Questionnaire Disability Index (HAQ-DI) at week 52 (on a scale from 0 to 3, with higher scores indicating worse functioning) (Fig. S2). Details regarding the quality-of-life measures are provided in the Supplementary Appendix. Safety was also assessed. Exploratory outcomes were glucocorticoid-induced toxic effects at week 52 according to the Glucocorticoid Toxicity Index (GTI) (excluding the bone mineral density domain and measured by both the Aggregate Improvement Score [GTI-AIS], on a scale from −317 to 410, and the Cumulative Worsening Score [GTI-CWS], on a scale from 0 to 410; on both scales, higher scores indicate greater severity of toxic effects).[31]

STATISTICAL ANALYSIS

On the basis of Fisher's exact test, we calculated that the enrollment of at least 120 patients per group would give the trial 90% power at a two-sided 5% type I error rate, assuming that 50% of the patients in the secukinumab group and 29% in the placebo group would have a sustained remission. All the P values were calculated on the basis of two-sided tests and were adjusted for multiplicity. A sequential testing strategy[32] was used to maintain a family-wise error rate of 5%

across the outcomes. The estimand framework was applied to the primary and secondary outcomes as well as the exploratory outcomes of the GTI-AIS score and GTI-CWS score (details are provided in the Supplementary Appendix). For the primary estimand of the primary outcome, intercurrent events of trial-regimen discontinuation or prohibited medication use before week 52 were addressed with a composite strategy by classifying these events as nonresponses. The primary analysis used logistic regression, adjusted for baseline prednisone dose, region, and sex. Sensitivity analyses, including a tipping-point analysis, and supplementary estimands were used to assess the robustness of the results of the primary analysis. For the supplementary estimand, we used a treatment-policy strategy for these same intercurrent events in which outcomes were evaluated regardless of the occurrence of such events, and the data collected after the occurrence of the events were included in the analysis. Safety outcomes were assessed in all the patients who received at least one dose of secukinumab or placebo; these outcomes were summarized descriptively on the basis of adverse events that occurred during treatment. Definitions and additional information regarding the statistical analysis, estimands, and handling of missing data are provided in the Supplementary Appendix.

RESULTS

DEMOGRAPHIC AND DISEASE CHARACTERISTICS AT BASELINE

Among the 474 patients who were screened from March 2023 through July 2024, a total of 381 underwent randomization, and 127 were assigned to each group. Two patients (1 in each secukinumab group) who did not meet eligibility criteria but underwent randomization in error did not receive treatment. Of the 379 patients who started treatment, 289 (76.3%) completed the treatment period. More patients in the placebo group than in either of the secukinumab groups discontinued the trial regimen (Fig. S3).

The characteristics of the patients at baseline were similar in all the groups and were representative of the broader population of persons with polymyalgia rheumatica. The mean age was 70 years, 70.3% were women, and 70.0% were White (Table 1 and Tables S2 and S3). The median time since diagnosis of polymyalgia rheumatica was 1.2 years. Notable coexisting conditions included hypertension (in 56.4% of the patients), hypercholesterolemia (in 16.5%), diabetes (in 16.5%), and history of fractures (in 11.3%). Previous medications and concomitant therapies are summarized in the Supplementary Appendix.

PRIMARY OUTCOME

Sustained remission at week 52 was observed in 41.2% (95% confidence interval [CI], 32.8 to 49.7) of the patients in the SEC-300 group, 40.6% (95% CI, 32.2 to 49.0) in the SEC-150 group, and 20.4% (95% CI, 13.6 to 27.2) in the placebo group ($P<0.001$ for the comparison of each secukinumab dose with placebo) (Fig. 1A). The results among men (38.4% in the SEC-300 group, 38.9% in the SEC-150 group, and 24.6% in the placebo group) and among women (42.2% in the SEC-300 group, 41.2% in the SEC-150 group, and 18.6% in the placebo group) were similar to those in the total trial population. Results of the sensitivity analyses are reported in Figure S4 and Table S4.

SECONDARY OUTCOMES

Complete sustained remission at week 52 was observed in 28.2% (95% CI, 20.3 to 36.0) of the patients in the SEC-300 group, 24.5% (95% CI, 17.0 to 31.9) in the SEC-150 group, and 4.7% (95% CI, 1.1 to 8.3) in the placebo group ($P<0.001$ for the comparison of each secukinumab dose with placebo) (Fig. 1A). At week 52, the mean adjusted annual cumulative glucocorticoid dose was 1603.7 mg in the SEC-300 group (mean difference vs. placebo, −489.4 mg; 95% CI, −734.47 to −244.25; $P<0.001$), 1683.2 mg in the SEC-150 group (mean difference vs. placebo, −409.9 mg; 95% CI, −661.8 to −157.9; $P=0.002$), and 2093.0 mg in the placebo group (Fig. 1C).

Overall, 50.8% of the patients in the SEC-300 group, 51.6% of those in the SEC-150 group, and 75.6% in the placebo group received escape or rescue treatment. The median time to first use of escape or rescue treatment was 337 days (95% CI, 169 to not calculable) in the SEC-300 group, 282 days (95% CI, 170 to not calculable) in the SEC-150 group, and 157 days (95% CI, 141 to 169) in the placebo group (Fig. 2). The curves for the time to first use of escape or rescue treatment showed a significant difference between the secukinumab groups and the placebo group. The hazard ratio for the use of escape or rescue treatment was 0.5 (95% CI, 0.4 to 0.7; $P<0.001$)

Table 1. Demographic and Disease Characteristics at Baseline.*

Characteristic	Secukinumab, 300 mg (N=127)	Secukinumab, 150 mg (N=127)	Placebo (N=127)
Age — yr	69.9±8.04	70.3±7.57	69.8±9.03
Female sex — no. (%)	96 (75.6)	86 (67.7)	86 (67.7)
Weight — kg	76.0±16.2	75.7±17.2	73.6±17.2
Body-mass index†	28.7±5.7	28.2±5.2	27.3±5.7
Race or ethnic group — no. (%)‡			
White	92 (72.4)	88 (69.3)	85 (66.9)
Asian	16 (12.6)	16 (12.6)	17 (13.4)
Other	19 (15.0)	23 (18.1)	25 (19.7)
Hispanic or Latino ethnic group — no. (%)‡			
Yes	18 (14.2)	16 (12.6)	19 (15.0)
No	90 (70.9)	98 (77.2)	87 (68.5)
Not reported or unknown	19 (15.0)	13 (10.2)	21 (16.5)
Signs and symptoms of active polymyalgia rheumatica — no. (%)	107 (84.3)	111 (87.4)	110 (86.6)
Previous polymyalgia rheumatica relapses — no. (%)			
1	64 (50.4)	51 (40.2)	54 (42.5)
>1	62 (48.8)	76 (59.8)	73 (57.5)
Missing data	1 (0.8)	0	0
Starting prednisone dose at baseline — no. (%)			
10 mg	88 (69.3)	87 (68.5)	92 (72.4)
15 mg	38 (29.9)	39 (30.7)	35 (27.6)
Missing data	1 (0.8)	1 (0.8)	0
High-sensitivity C-reactive protein level — mg/liter§	9.8±17.8	8.2±13.1	7.1±12.2
Erythrocyte sedimentation rate — mm/hr§	29.0±21.6	29.4±25.2	27.9±22.9

* Plus–minus values are means ±SD. The glucocorticoid dose (prednisone or prednisone equivalent) at the time of relapse before trial enrollment ranged from 5 to 15 mg per day; 4% of the patients had a relapse while receiving doses of 20 to 35 mg per day, and more than 63% had relapses while receiving less than 10 mg per day.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for one patient in each group.
‡ Race and ethnic group were reported by the patients. Asian included Japanese and Indian. Other race or ethnic group included Black or African American, American Indian, Alaska Native, multiple, or unknown.
§ Data were missing for one patient in each secukinumab group.

in the SEC-300 group and 0.5 (95% CI, 0.4 to 0.7; P=0.002) in the SEC-150 group.

The patients in the secukinumab groups had less fatigue and better scores for physical function than those in the placebo group. The least-squares mean change from baseline in the FACIT-Fatigue score was –13.7 points in the SEC-300 group (difference in change vs. placebo, 6.14 points; 95% CI, 2.48 to 9.81; P=0.002), –13.8 points in the SEC-150 group (difference in change vs. placebo, 5.99 points; 95% CI, 2.28 to 9.70; P=0.002), and –19.8 points in the placebo group. At week 52, the least-squares mean change from baseline in the HAQ-DI score was 1.1 points in the SEC-300 group (difference in change vs. placebo, −0.44 points; 95% CI, −0.70 to −0.18; P=0.002), 1.1 points in the SEC-150 group (difference in change vs. placebo, −0.44 points; 95% CI, −0.71 to −0.18; P=0.002), and 1.5 points in the placebo group (Table S5).

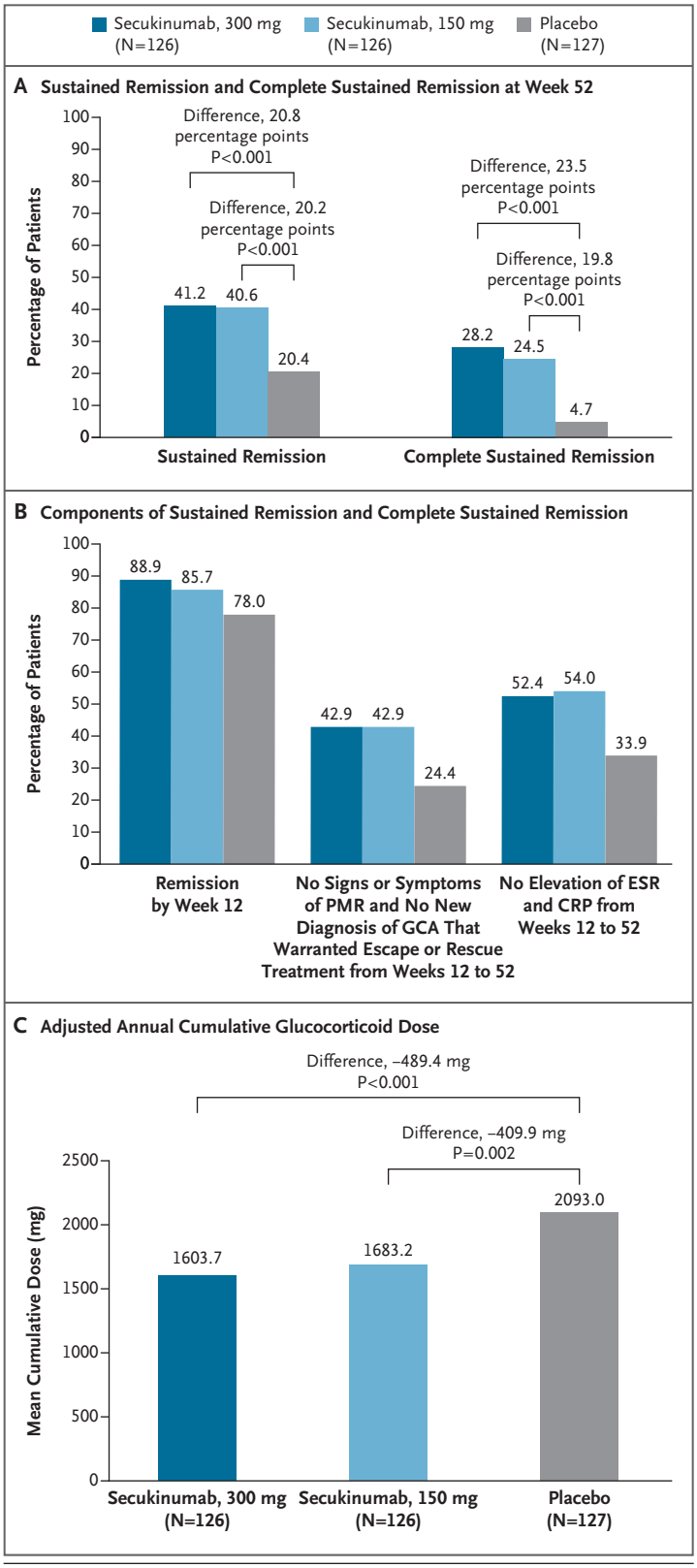


Figure 1. Remission and Cumulative Glucocorticoid Dose at Week 52.

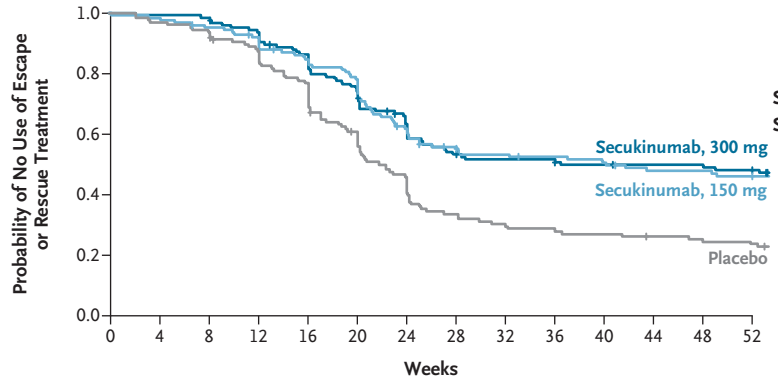
Remission was defined as the absence of signs or symptoms attributable to polymyalgia rheumatica (PMR) and no new diagnosis of giant-cell arteritis (GCA) that warranted escape or rescue treatment. The primary outcome was sustained remission at week 52, defined as remission that occurred by week 12 and was sustained until week 52, without recurrence of PMR and with no new diagnosis of GCA that warranted treatment. Complete sustained remission was defined as remission by week 12 with no elevation in the erythrocyte sedimentation rate (ESR) and high-sensitivity C-reactive protein (CRP) level at two consecutive visits from week 12 to week 52. The P values were adjusted for multiplicity. The adjusted mean annual cumulative glucocorticoid dose was calculated as the total cumulative glucocorticoid dose divided by the total number of days the patient participated in the trial up to the time of discontinuation or week 52 (whichever occurred first), multiplied by 365.25. The total cumulative glucocorticoid dose was calculated by combining the doses included in the prednisone taper, the escape or rescue glucocorticoid, and other glucocorticoid (converted to the prednisone-equivalent dose). Other glucocorticoid was a glucocorticoid other than the prednisone taper or the escape or rescue glucocorticoid.

In both secukinumab groups, the percentage of patients who met the criteria for the individual components of sustained remission and complete sustained remission at week 52 was higher than in the placebo group (Fig. 1B). Giant-cell arteritis developed in two patients (one in the SEC-300 group and one in the placebo group) over the 52-week treatment period; one of these patients received escape treatment.

The patients in the secukinumab groups appeared to have less severe glucocorticoid-related toxic effects than those in the placebo group. At week 52, the mean GTI-AIS score was 32.4 in the SEC-300 group, 54.0 in the SEC-150 group, and 84.3 in the placebo group. The mean GTI-CWS score was 69.0 in the SEC-300 group, 90.1 in the SEC-150 group, and 123.5 in the placebo group (Table S6).

SAFETY

The median duration of exposure to secukinumab was 60.0 weeks in the SEC-300 group and 58.8 weeks in the SEC-150 group, and the median duration of exposure to placebo was 56.1 weeks. At least one adverse event of any grade occurred



No. of Patients														
Secukinumab, 300 mg	126	125	124	117	107	92	76	64	61	61	57	56	56	54
Secukinumab, 150 mg	126	124	119	114	104	96	75	65	61	59	57	53	53	51
Placebo	127	123	119	109	96	74	56	41	37	35	33	31	30	28

No. of Events/Total No. of Patients	
Secukinumab, 300 mg	64/126
Secukinumab, 150 mg	65/126
Placebo	96/127

Hazard ratio for escape or rescue treatment:
Secukinumab, 300 mg vs. placebo, 0.5 (95% CI, 0.4–0.7); P<0.001
Secukinumab, 150 mg vs. placebo, 0.5 (95% CI, 0.4–0.7); P=0.002

Figure 2. Time to First Use of Escape or Rescue Treatment through Week 52.

The results for the ESR and CRP level were concealed from the investigators, trial personnel, and the clinical trial team. Data for patients who discontinued the trial early or were lost to follow-up and had not received escape treatment, rescue treatment, or a prohibited medication were censored on the date of discontinuation or the date of the week 52 visit, whichever occurred earlier. One patient (in the placebo group) had a new diagnosis of GCA that warranted escape treatment. The tick marks indicate censored data.

in 91.3% of the patients in the SEC-300 group, in 88.1% in the SEC-150 group, and in 89.8% in the placebo group. Adverse events that led to discontinuation of the trial regimen occurred in 3.2% of the patients in each secukinumab group and in 6.3% in the placebo group (Table 2). The most common adverse events that were more frequent in the secukinumab groups than in the placebo group were nasopharyngitis, urinary tract infections, upper respiratory infections, and back pain (Table 2 and Tables S7 and S8). Among the adverse events of interest, fungal infections and hypersensitivity reactions were more common in the secukinumab groups than in the placebo group. Most of the patients in the trial had mild or moderate adverse events, as determined by the investigators. Mild adverse events occurred in 38.9% of the patients in the SEC-300 group, in 38.9% in the SEC-150 group, and in 36.2% in the placebo group; moderate adverse events occurred in 46.0%, 39.7%, and 42.5% in the three groups, respectively. Severe adverse events occurred in 6.3% of the patients in the SEC-300 group, in 9.5% in the SEC-150 group, and in 11.0% in the placebo group (Table 2).

Serious adverse events occurred in 13.5% of the patients in the SEC-300 group, in 15.9% in the SEC-150 group, and in 14.2% in the placebo group (Table S9). Three deaths were reported: one patient in the SEC-150 group died from cryptococcal meningitis, one patient in the SEC-150 group died from cardiac failure, and one patient in the placebo group completed suicide. The case of cryptococcal meningitis occurred in an older patient who had risk factors that included long-term glucocorticoid treatment and preexisting meningioma and was considered by the investigator to be potentially related to secukinumab. The other two deaths were considered to be unrelated to the trial regimen.

The adverse events of interest for secukinumab included infections and infestations, hypersensitivity, malignant tumors, major adverse cardiovascular events, neutropenia, suicidal ideation, inflammatory bowel disease, and hepatitis B reactivation (no events were reported in the last two categories) (Table S10). The adverse events of interest that were reported most frequently in the secukinumab groups were infections and infestations (in 57.9% of the patients in the SEC-300 group, 61.1% in the SEC-150 group, and 53.5% in the placebo group) and hypersensitivity (in 14.3%

Table 2. Overview of Adverse Events.*

Event	Secukinumab, 300 mg (N=126)	Secukinumab, 150 mg (N=126)	Placebo (N=127)
	number of patients (percent)		
Any adverse event	115 (91.3)	111 (88.1)	114 (89.8)
Mild	49 (38.9)	49 (38.9)	46 (36.2)
Moderate	58 (46.0)	50 (39.7)	54 (42.5)
Severe	8 (6.3)	12 (9.5)	14 (11.0)
Adverse events reported in >10% of patients			
Nasopharyngitis	18 (14.3)	23 (18.3)	11 (8.7)
Urinary tract infection	14 (11.1)	14 (11.1)	7 (5.5)
Arthralgia	17 (13.5)	10 (7.9)	14 (11.0)
Diarrhea	12 (9.5)	7 (5.6)	13 (10.2)
Serious adverse event	17 (13.5)	20 (15.9)	18 (14.2)
Fatal serious adverse event	0	2 (1.6)	1 (0.8)
Adverse event leading to discontinuation of the trial regimen	4 (3.2)	4 (3.2)	8 (6.3)
Adverse event leading to interruption of the trial regimen	16 (12.7)	13 (10.3)	14 (11.0)
Adverse event of interest			
Infection or infestation†	73 (57.9)	77 (61.1)	68 (53.5)
Serious infection	4 (3.2)	3 (2.4)	4 (3.1)
Fungal infection	8 (6.3)	13 (10.3)	4 (3.1)
Hypersensitivity reaction‡	18 (14.3)	18 (14.3)	12 (9.4)

* Shown are adverse events that occurred after the first dose of secukinumab or placebo or events that were present before the first dose but increased in severity according to the preferred term until the date of the last dose plus 84 days. All the adverse events were evaluated according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 28.0. Details regarding the safety outcomes are provided in Tables S7 through S10 in the Supplementary Appendix.
† Infections and infestations were categorized according to system organ class.
‡ Hypersensitivity reactions were identified on the basis of a (narrow) standardized MedDRA query.

in the SEC-300 group, 14.3% in the SEC-150 group, and 9.4% in the placebo group).

Fungal infections were reported in 6.3% of the patients in the SEC-300 group, 10.3% in the SEC-150 group, and 3.1% in the placebo group. Most infections, including fungal infections, were mild to moderate in severity and did not result in discontinuation of the trial regimen. Hypersensitivity reactions occurred in 14.3% of the patients in each of the secukinumab groups and in 9.4% in the placebo group. The most common hypersensitivity reactions reported in the secukinumab groups were eczema, dermatitis, and rash (none resulted in discontinuation of the trial regimen). All the hypersensitivity reactions were nonserious and nonsevere.

DISCUSSION

The patients enrolled in this trial were highly representative of the larger population of patients with polymyalgia rheumatica with respect to age, sex, and race. The results of the trial showed that among patients with relapsed polymyalgia rheumatica, a strategy of glucocorticoid tapering plus treatment with 300 mg or 150 mg of secukinumab resulted in a significantly higher percentage of patients with remission by week 52. Previous trials in polymyalgia rheumatica have either been shorter in duration or had smaller sample sizes or both.[25,33,34] This trial addressed two critical unmet needs in the management of polymyalgia rheumatica: maintenance of sustained

remission and reduction of glucocorticoid use, which appears to have resulted in less severity in glucocorticoid-related toxic effects, as measured by the GTI.

Elevated C-reactive protein level and erythrocyte sedimentation rate are associated with an increased risk of relapse[24,35] and therefore were included in the classification criteria for polymyalgia rheumatica,[15] as were various relapse and remission definitions.[36] A higher percentage of patients in the secukinumab groups than in the placebo group had complete remission, which included normalization of inflammatory markers (the high-sensitivity C-reactive protein level and erythrocyte sedimentation rate).

Sustained remission remains the treatment target for polymyalgia rheumatica because relapses impair physical function.[14,16] In this trial, secukinumab not only resulted in sustained remission over 1 year but was also associated with better scores for fatigue and physical function as compared with glucocorticoid treatment alone, a finding that reinforces the clinical relevance of targeting interleukin-17A–mediated pathways in polymyalgia rheumatica.

A uniform 24-week glucocorticoid taper regimen was chosen across all the groups to minimize the cumulative glucocorticoid exposure in patients who were already at higher risk for glucocorticoid-related toxic effects owing to previous prolonged glucocorticoid use and to enable balanced comparisons. The annual cumulative glucocorticoid exposure was 20 to 23% less among patients who received secukinumab than among those who received placebo, which underscores its potential as an effective glucocorticoid-sparing agent in this patient population. Despite the short 24-week glucocorticoid taper, glucocorticoid-related toxic effects were less severe in the secukinumab groups than in the placebo group.

Infections and hypersensitivity reactions were more common in the secukinumab groups than in the placebo group, but the incidence of serious infections was similar in the secukinumab groups and the placebo group, and no serious hypersensitivity reactions occurred. These findings, and the overall safety data, are aligned with the safety profile of secukinumab in approved indications.[37] It remains unclear whether the percentage of patients in the placebo group who had remission could have been higher if glucocorticoids were administered for 52 weeks. However, the results of two other trials do not support this hypothesis. The SAPHYR trial[25] in polymyalgia rheumatica showed a sustained remission (in an analysis that did not take the C-reactive protein level and erythrocyte sedimentation rate into consideration) in only 14% of the patients in the placebo group, and the GiACTA trial[38] showed similar results for remission (14% in the 26-week taper group and 18% in the 52-week taper group). Other limitations of this trial were the lack of efficacy data beyond 1 year and a higher rate of discontinuation in the placebo group than in the secukinumab groups, which might have resulted in underdetection of adverse events associated with conventional treatment.

Among patients with relapsed polymyalgia rheumatica, treatment with secukinumab with a 24-week glucocorticoid taper showed superior efficacy with respect to sustained remission over a 24-week glucocorticoid taper alone. This greater efficacy was associated with a significant glucocorticoid-sparing effect. These findings support interleukin-17A inhibition with secukinumab as an effective treatment option with a glucocorticoid-sparing effect in patients with recently relapsed polymyalgia rheumatica.

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