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ORIGINAL ARTICLE

Secukinumab for Giant Cell Arteritis

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Abstract

BACKGROUND Glucocorticoids (GCs) are standard treatment for giant cell arteritis (GCA). Many patients experience relapses or GC-related toxicity. Secukinumab, a fully human monoclonal antibody that selectively inhibits interleukin-17A, is being studied as additional therapy for GCA.

METHODS GCAptAIN was a randomized, parallel-group, double-blind, placebo-controlled, multicenter phase 3 trial. Patients with new-onset or relapsing GCA were initially randomly assigned (2:1) to either 300 mg of secukinumab (SEC-300) or placebo for 52 weeks. After a protocol amendment, patients were randomly assigned (1:1:1) to either SEC-300, 150 mg of secukinumab (SEC-150), or placebo. Patients in the SEC-300 and SEC-150 groups received a 26-week GC taper. Patients in the placebo group received a 52-week GC taper. The primary outcome was the proportion of patients experiencing sustained remission in the SEC-300 versus placebo groups at week 52. Sustained remission in patients in the SEC-150 group versus patients in the placebo group enrolled after the protocol amendment was a secondary outcome. Adverse events (AEs) and serious AEs (SAEs) were assessed.

RESULTS A total of 140 patients in the SEC-300 group, 98 in the SEC-150 group, and 115 in the placebo group (19 patients were enrolled in the placebo group before and 96 after the protocol amendment) were analyzed for efficacy and safety. The proportion of patients achieving sustained remission at week 52 was 25.6% for SEC-300 versus 16.9% for placebo (marginal difference: 8.7 percentage points; 95% confidence interval [CI], −1.3 to 18.8; P=0.09) and 19.4% for SEC-150 versus 17.7% for placebo (marginal difference, 1.6 percentage points; 95% CI, −9.2 to 12.4). AEs occurred in 92.9%, 95.9%, and 97.4% of patients in the SEC-300, SEC-150, and placebo groups, respectively. SAEs occurred in 20.0%, 27.6%, and 32.2% of patients in the SEC-300, SEC-150, and placebo groups, respectively. Serious infections occurred in 5.0%, 9.2%, and 6.1% of patients in the SEC-300, SEC-150, and placebo groups, respectively.

CONCLUSIONS Sustained remission at week 52 did not differ significantly between patients with GCA randomly assigned to receive SEC-300 with a 26-week GC taper versus placebo with a 52-week GC taper. (Funded by Novartis Pharma; EudraCT number, 2020-004809-31; ClinicalTrials.gov number, NCT04930094.)

**A complete list of GCAptAIN investigators is provided in the Supplementary Appendix, available at evidence.nejm.org.*

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Introduction

Giant cell arteritis (GCA) is the most common form of vasculitis in older adults.[1] GCA typically afflicts people 50 years of age or older, with peak incidence in the age group from 70 to 79 years, and up to 75% of patients with GCA are female.[2-5] Approximately half of all patients with GCA may also have polymyalgia rheumatica (PMR).[6,7]

Glucocorticoids (GCs), the mainstay of GCA treatment, are associated with well-known adverse effects.[8,9] Many patients relapse when GC therapy is discontinued, following which the renewal of GC therapy heightens the risk of GC toxicity.[9-11] Currently, two approved therapies for GCA are available: tocilizumab, an interleukin (IL)-6 receptor inhibitor, and upadacitinib, an oral Janus kinase inhibitor.[12-14] GCs are administered with both. Relapses are observed with tocilizumab and upadacitinib, and both approved treatments have potential adverse effects that are particularly challenging in older adults.[13,15-17]

Interleukin-17A (IL-17A) plays an important role in GCA pathophysiology.[18,19] Secukinumab, a fully human monoclonal antibody that selectively inhibits IL-17A, has demonstrated efficacy and a well-known safety profile in other immune-mediated inflammatory diseases.[20] In a phase 2 trial (TitAIN), patients with GCA receiving secukinumab plus a 26-week GC taper had a significantly higher sustained remission rate at weeks 28 and 52 compared to those receiving placebo plus a 26-week GC taper.[21] We report the efficacy and safety results from the phase 3 GCAptAIN trial, which evaluated secukinumab combined with a 26-week prednisone taper versus placebo combined with a 52-week prednisone taper, for GCA treatment.

Methods

TRIAL DESIGN AND PATIENT POPULATION

The trial was conducted October 6, 2021–May 12, 2025, across 27 countries and included a screening period of up to 6 weeks followed by a 56-week treatment period (Fig. 1 and Table S1 in the Supplementary Appendix). Eligible patients were 50 years of age or older and had a diagnosis of GCA defined by meeting both of the following criteria: (1) unequivocal cranial symptoms of GCA and/or PMR and/or symptoms of limb ischemia and (2) a temporal artery biopsy and/or an imaging study demonstrating vasculitis. Patients also had to have active GCA defined by meeting both of the following within 6 weeks of baseline: (1) presence of signs/symptoms attributed to active GCA and (2) elevated levels of acute phase reactants (erythrocyte sedimentation rate [ESR]≥30 mm/h or C-reactive protein [CRP]≥10 mg/l) attributed to active GCA or active GCA on temporal artery biopsy or imaging study. Patients could have new-onset or relapsing GCA. The screening period and time period defining new-onset GCA and presence of active disease could be extended up to 8 weeks. Key exclusion criteria included prior exposure to IL-17–targeting biologics and prior treatment failure while being treated with an anti–IL-6/anti–IL6-R inhibitor or a Janus kinase inhibitor. Additional information is included in the Supplementary Appendix in the Eligibility criteria section.

The trial was conducted according to the International Council for Harmonisation E6 Guideline for Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each patient.

ROLE OF THE FUNDING SOURCE

This trial (NCT04930094) was sponsored and funded by Novartis Pharma AG, Basel, Switzerland. Novartis was involved in designing the trial, analysis and interpretation of the data, supported the authors in the manuscript development, and funded the medical writing assistance. The first draft of the manuscript was written by Drs. Stone and Mendelson, with contributions from all authors. All authors approved the content of the submitted manuscript and were involved in the decision to submit the manuscript for publication.

RANDOMIZATION, BLINDING, AND PROCEDURES

Patients enrolled under the original protocol were randomly assigned in a 2:1 ratio to receive 300 mg of subcutaneous secukinumab (SEC-300) or placebo, with prednisone. The 150 mg of secukinumab (SEC-150) group was added as a protocol amendment (Table S2). This amendment was undertaken to characterize the dose–response relationship further and to explore whether a lower dose could provide clinically meaningful efficacy with a potentially differentiated benefit–risk profile. Patients enrolled under the protocol amendment were randomly assigned 1:1:1 to SEC-300, SEC-150, or placebo.

Until the time of unblinding, random assignment was kept strictly confidential and was not known to anyone involved in the trial except the bioanalyst, Interactive Response

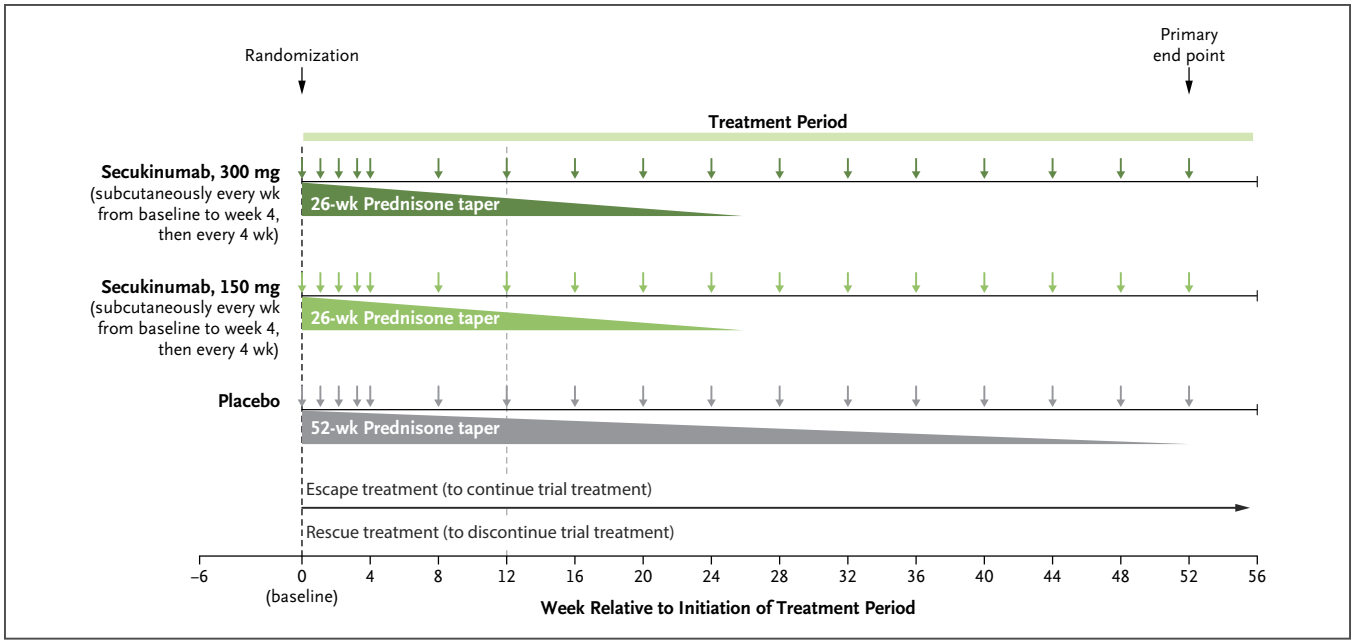

Figure 1. Trial Design.

Patients were randomly assigned at baseline in a 2:1 ratio to 300 mg of secukinumab or placebo. After trial initiation, a protocol amendment introduced the 150-mg secukinumab group, and subsequent patients were randomly assigned at baseline in a 1:1:1 ratio to 300 mg of secukinumab, 150 mg of secukinumab, or placebo. The trial included a screening period of up to 6 weeks (could be increased to 8 weeks). Patients were allowed to have their GC dose modified as determined by the investigator while staying on blinded trial treatment. If such a determination was made, the prednisone supplied for the taper regimen was stopped, and further prednisone "escape" treatment was prescribed at the investigator's discretion, after which GCs were administered open-label. Patients on escape treatment remained in the trial and continued to attend all subsequent scheduled visits. Patients could receive an alternative GCA treatment at the investigator's discretion (i.e., "rescue" treatment). Patients on escape treatment could transition to rescue treatment. If rescue treatment was implemented, concomitant GCs were administered as determined by the site investigator based on clinical assessment. Trial treatment was discontinued before starting the rescue treatment. Vertical arrows indicate administration of a dose of secukinumab. GC denotes glucocorticoid; and wk, week.

Technology vendor, and sponsor group responsible for trial drug supply. After baseline, CRP data were blinded and ESR results were communicated as ranges to the investigator by an unblinded laboratory result reviewer designated at the site. Random assignment was stratified by baseline GCA status (new-onset or relapsing GCA) and baseline prednisone dose (≤30 mg/day or >30 mg/day prednisone). The prednisone taper regimen was 26 weeks for patients in the SEC-300 and SEC-150 groups and 52 weeks for patients in the placebo group (Table S3). Starting baseline prednisone dosages could range from 20 to 60 mg/day, as deemed medically appropriate by the investigator. Patients received open-label prednisone when dosage was 20 mg/day or higher and double-blind prednisone for dosages less than 20 mg/day.

Patients who did not achieve clinical remission by week 12 (Supplementary Appendix, Definitions section) or who experienced a clinical relapse were allowed to have their GC dose modified as determined by the investigator while staying on blinded trial treatment (escape treatment) or could receive an alternative GCA treatment at the investigator's discretion with discontinuation of trial treatment (rescue treatment). Additional details are provided in the Definitions section of the Supplementary Appendix and in section 6.2.3 of the Supplementary Protocol, provided with the full text of this article at evidence.nejm.org.

Baseline demographic and clinical characteristics were collected by site investigators or qualified designees during screening and at the baseline visit based on history and physical examination.

OUTCOMES

The primary endpoint was sustained remission at week 52, comparing the SEC-300 group with placebo. Sustained remission was defined as meeting all the following

criteria: remission achieved by week 12 (Definitions section of the Supplementary Appendix) and sustained from week 12 to week 52, with no (1) recurrence of GCA signs or symptoms requiring an increase in GC dose or rescue therapy, (2) increase in ESR to 30 mm/h or greater attributable to GCA and requiring an increase in GC dose or rescue therapy, (3) CRP elevation to 10 mg/l or greater at two consecutive scheduled visits, or (4) non adherence to prednisone taper characterized by an increase in prednisone dose. All patients who needed escape or rescue treatment were considered not adherent to the prednisone taper.

Secondary endpoints (Table S4) at week 52 included sustained remission with SEC-150 compared with placebo and the following measures at 52 weeks compared between SEC-300 and placebo and SEC-150 and placebo: cumulative GC dose, time to first escape or rescue treatment, Aggregate Improvement Score (AIS) of the Glucocorticoid Toxicity Index (GTI) (not including bone mineral density domain) (higher index indicates more toxicity),[22] change in 36-item Short Form (SF-36) score[23] (Physical Component Score [PCS]; higher scores indicate better health-related quality of life), and change in Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue score (higher scores indicate less fatigue).[24,25] Cumulative GC dose was obtained from drug administration records. Data to compute the GTI were obtained from laboratory results and the site investigator's clinical assessment. The SF-36 and FACIT-Fatigue questionnaires were completed by the patients.

Prespecified subgroup analyses were conducted for patients with GCA who had PMR (based on history of or reported signs and symptoms) and stratified by sex. A post hoc exploratory analysis adding sex as a covariate was undertaken because a baseline sex imbalance across treatment groups was observed (Table 1). Additional prespecified exploratory analyses for sustained clinical remission and GTI-cumulative worsening score were conducted. Sustained clinical remission was defined using all of the above-mentioned components for sustained remission except CRP elevation.

Safety and tolerability were evaluated by assessing treatment-emergent adverse events (AEs) and serious AEs (SAEs) over the 56-week treatment period. Safety topics of interest were also evaluated, including infections, hypersensitivity, malignancies, major adverse cardiovascular events, neutropenia, suicidal ideation, inflammatory bowel disease, and hepatitis B reactivation.

SAMPLE SIZE

With 96 patients per group to be enrolled after protocol amendment, the expected sample sizes of 137 patients in the SEC-300 group and 116 patients in the placebo group and 96 patients in the SEC-150 group and 96 patients in the placebo group (enrolled after the amendment) were projected to provide over 99% and 98% power to reject the null hypothesis of no difference in sustained remission rates between SEC-300 versus placebo and SEC-150 versus placebo, respectively.

STATISTICAL ANALYSIS

The SEC-300 group was compared to all randomly assigned patients in the placebo group enrolled before and after the protocol amendment with a binary time period variable added to the models. The SEC-150 group was compared only to those patients in the placebo group enrolled after the protocol amendment. In the subgroup analyses, SEC-300 and SEC-150 arms were compared with all patients in the placebo arm (enrolled before and after the protocol amendment).

The primary endpoint analysis was performed when all patients completed the week-56 visit or discontinued prior to week 56, using the Full Analysis Set. All tests were two-sided with a familywise type I error rate of 5%, controlled by a prespecified sequential testing hierarchy (Fig. S1). Results for secondary endpoints that were not adjusted for multiplicity were reported with point estimates and 95% confidence intervals (CIs), the widths of which should not be used in place of hypothesis testing. Subgroup and post hoc exploratory analyses were not multiplicity-adjusted.

For the analyses examining sustained remission at week 52, the difference in response proportion was estimated using logistic regression adjusted for baseline prednisone dose (≤30 mg/day or >30 mg/day) and baseline GCA status (new-onset or relapsing).

Continuous variables were analyzed using an analysis of covariance (ANCOVA) model with Huber–White "sandwich" standard error,[26,27] including treatment group, baseline prednisone dose (≤30 mg/day or >30 mg/day) and baseline GCA status (new onset or relapsing GCA) and a binary time period variable (before and after the protocol amendment for the comparison of SEC-300 vs. placebo only). Baseline scores for SF-36 and FACIT-Fatigue were included as covariates in the analyses for these endpoints. Further details on the ANCOVA model are available in the

Table 1. Demographics and Baseline Clinical Characteristics.*

Characteristic	Secukinumab 300 mg (N=140)	Secukinumab 150 mg (N=98)	All Placebo (N=116)†	Subset of placebo group after protocol change adding secukinumab 150 mg group (N=97)†
Age (years) — mean (SD)	72.2 (7.34)	72.3 (7.37)	71.4 (7.46)	72.2 (7.38)
Female sex — n (%)	101 (72.1)	66 (67.3)	65 (56.0)	57 (58.8)
Race — n (%)‡				
White	139 (99.3)	96 (98.0)	113 (97.4)	95 (97.9)
Other	1 (0.7)	2 (2.0)	3 (2.6)	2 (2.1)
Ethnicity — n (%)				
Hispanic or Latino	19 (13.6)	10 (10.2)	11 (9.5)	10 (10.3)
Non-Hispanic or Latino	120 (85.7)	87 (88.8)	103 (88.8)	86 (88.7)
Not reported/unknown	1 (0.7)	1 (1.0)	2 (1.7)	1 (1.0)
Weight (kg) — mean (SD)§	n=140 68.9 (14.3)	n=98 70.5 (18.6)	n=115 71.8 (16.0)	n=96 71.7 (16.2)
BMI — mean (SD)§	n=138 25.6 (4.5)	n=97 25.9 (5.4)	n=114 25.8 (5.0)	n=95 25.9 (5.1)
Smoking status at baseline — n (%)				
Current	13 (9.3)	9 (9.2)	16 (13.8)	9 (9.3)
Former	47 (33.6)	40 (40.8)	40 (34.5)	35 (36.1)
GCA status — n (%)				
New-onset	91 (65.0)	66 (67.3)	78 (67.2)	65 (67.0)
Relapsing	49 (35.0)	32 (32.7)	38 (32.8)	32 (33.0)
Time since first diagnosis of GCA (weeks, for new-onset patients) — mean (SD)¶	n=91 4.9 (1.4)	n=66 5.0 (1.7)	n=78 5.0 (1.5)	n=65 5.0 (1.5)
Time since first diagnosis of GCA (weeks, for relapsing patients) — mean (SD)¶	n=49 123.0 (150.3)	n=32 132.8 (109.1)	n=38 128.0 (181.3)	n=32 124.0 (186.1)
Signs and symptoms of GCA at baseline — n (%)‖				
Cranial signs and symptoms	36 (25.7)	37 (37.8)	35 (30.2)	29 (29.9)
Ischemia-related visual symptoms	8 (5.7)	11 (11.2)	11 (9.5)	9 (9.3)
PMR signs and symptoms	17 (12.1)	13 (13.3)	9 (7.8)	8 (8.2)
Signs and symptoms of limb ischemia	5 (3.6)	1 (1.0)	4 (3.4)	2 (2.1)
Assigned prednisone dose at baseline (mg/day) — mean (SD)	n=140 35.7 (12.0)	n=98 36.7 (13.6)	n=115 35.0 (12.1)	n=96 34.9 (12.6)
Prednisone dose at baseline — n (%)				
>30 mg/day	77 (55.0)	54 (55.1)	63 (54.3)	52 (53.6)
ESR at baseline — n (%)				
≥30 mm/h	33 (23.6)	17 (17.3)	22 (19.0)	18 (18.6)
CRP at baseline — n (%)				
≥10 mg/l	16 (11.4)	13 (13.3)	17 (14.7)	15 (15.5)
Methotrexate use at baseline — n (%)	7 (5.0)	5 (5.1)	6 (5.2)	—

* CRP denotes C- reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; and SD, standard deviation.

† The initial protocol used a 2:1 randomization scheme to allocate patients to 300 mg of secukinumab or placebo. After trial initiation, a protocol amendment added a 150-mg secukinumab group, with 1:1:1 random assignment to 300 mg of secukinumab, 150 mg of secukinumab, or placebo. A total of 116 patients were randomly assigned to the placebo group before and after the protocol change, and 97 patients were randomly assigned to the placebo group after the protocol change.

‡ Race was reported by the participants.

§ For BMI (body-mass index), height, and body weight, the last value prior to random assignment was used. The BMI is the weight in kilograms divided by the square of the height in meters.

¶ Time since first diagnosis of GCA indicates the time from the first diagnosis to the randomization date. For new-onset patients, the date of first clinical diagnosis was the date when glucocorticoids were started for suspected GCA diagnosis.

‖ A patient could be counted under more than one category of signs or symptoms. All patients had signs and/or symptoms for the current episode. However, percentages at baseline may not add to 100% because the treatment for GCA was expected to have been initiated prior to baseline, and there were patients who no longer had signs and/or symptoms at baseline.

Supplementary Appendix in the Detailed statistical analysis section.

Between-treatment differences in time to first use of escape or rescue treatment due to GCA through week 52 were evaluated using a stratified log-rank test, adjusting for randomization factors (GCA status and baseline prednisone dose) and a binary time period variable (before and after the protocol amendment for the comparison of SEC-300 vs. placebo only).

For the primary estimand, trial treatment discontinuation for any reason, use of prohibited medication, and prednisone non-adherence not due to GCA were defined as intercurrent events and handled using a composite estimand strategy. Patients were classified as nonresponders from the time of event occurrence. Intermittent missing GCA remission assessments were imputed as remission if remission status was observed at both the preceding and subsequent visits. All other missing data were handled using nonresponder imputation. Patients with accidental treatment unblinding were considered nonresponders from the time of unblinding through week 56. Handling of intercurrent events and missing values for secondary estimands is detailed in Table S5.

Results

PATIENT BASELINE CHARACTERISTICS AND DISPOSITION

Prior to the protocol amendment, 42 patients were randomly assigned (2:1) to SEC-300 and 19 to placebo. Following the protocol amendment introducing the SEC-150 treatment group, 98, 98, and 97 patients were randomly assigned to SEC-300, SEC-150, and placebo (1:1:1), respectively. Consequently, a total of 140, 98, and 116 patients were randomly assigned to SEC-300, SEC-150, and placebo, respectively. A total of 354 patients were included in the randomized set. After excluding one patient who was incorrectly randomly assigned, 353 patients were included in both the Full Analysis Set and Safety Set, with 140, 98, and 115 in SEC-300, SEC-150, and placebo groups, respectively (Fig. 2). Overall, 292/354 patients (82.5%) completed participation (Table S6).

Baseline characteristics, except for sex, were comparable across treatment groups and were representative of the general population with GCA (Table S7). The proportion of female patients in each group was as follows: SEC-300, 72.1%; SEC-150, 67.3%; and placebo, 56.0%. Most patients (98.3%) were White, with a mean age of 72 years. Overall, 66.4% of patients had new-onset GCA, with a mean time since first diagnosis of 5.0 weeks. The relapsing GCA subgroup (33.6%) had a mean time since diagnosis of 127.2 weeks (Table 1 and Table S8).

EFFICACY

Primary Outcome

The proportion of patients achieving sustained remission at week 52 was 25.6% in the SEC-300 group compared with 16.9% in the placebo group (marginal difference: 8.7 percentage points; 95% CI, −1.3 to 18.8; P=0.09) (Table 2 and Fig. S2). Table S9 summarizes nonresponders on account of relapse.

Secondary Outcomes

The proportion of patients in sustained remission at week 52 was 19.4% in the SEC-150 versus 17.7% in the placebo group (marginal difference, 1.6 percentage points; 95% CI, −9.2 to 12.4). The cumulative GC dose (least-squares mean) was 3158.0 mg in the SEC-300 group versus 3941.4 mg in the placebo group (difference, −783.39 mg; 95% CI, −1323.62 to −243.16). The cumulative GC dose was 3988.1 mg in the SEC-150 group and 3952.2 mg in the placebo group (difference, 35.91 mg; 95% CI, −1002.82 to 1074.64) (Table 2 and Table S10).

GTI-AIS values (least-squares mean) at week 52 in the SEC-300 and placebo group were 23.2 and 73.1, respectively (least-squares mean difference, −49.92; 95% CI, −81.95 to −17.89) and 88.7 and 69.4 in the SEC-150 and placebo group, respectively (least-squares mean difference, 19.21, 95% CI, −25.03 to 63.44). Median time to first use of escape or rescue treatment due to GCA through week 52 was 309 days for SEC-300 versus 326 days for placebo. For SEC-150, time to first use of escape or rescue treatment was 254 days versus 290 days for placebo (Table 2 and Fig. 3). Results for the SF-36 scores and FACIT-Fatigue scores at week 52 are shown in Table 2.

EXPLORATORY AND POST HOC ENDPOINTS

GTI-CWS scores (least-squares mean) at week 52 were 53.0 in the SEC-300 versus 100.4 in the placebo group and 114.3 in the SEC-150 versus 99.0 in the placebo group enrolled after the protocol change. In the female subgroup, the proportion of patients achieving sustained remission at week 52 in the SEC-300 group was 23.8% (95% CI: 15.5 to 32.0) and 6.3% (95% CI: 0.3 to 12.2) in the placebo group. A total of 22.6% (95% CI: 13.1 to 32.1) of female patients

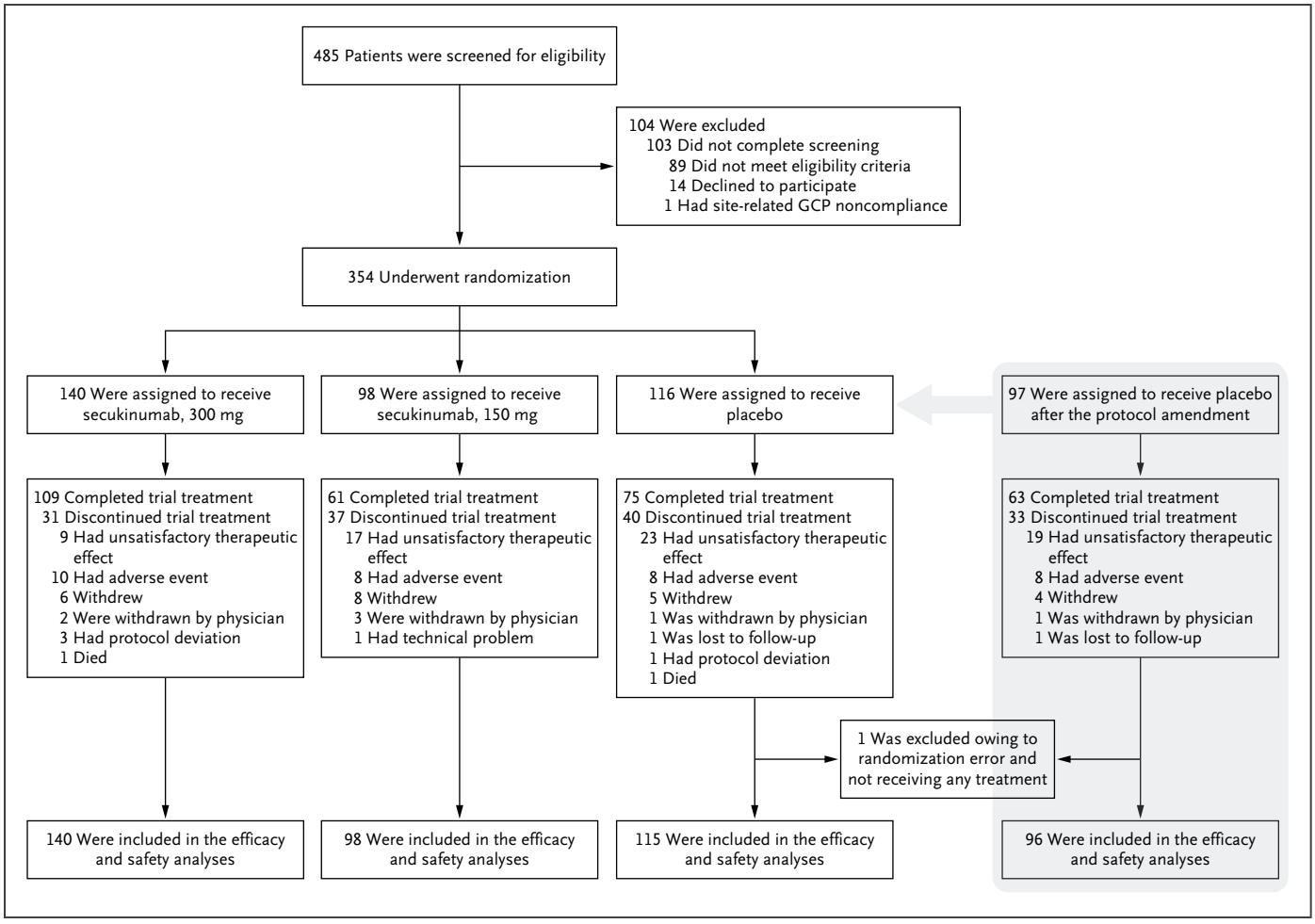

Figure 2. Patient Disposition.

Under the original protocol (2:1 randomization), 42 patients were randomly assigned to SEC-300 and 19 to placebo. Following the protocol amendment to introduce the SEC-150 treatment group (1:1:1 randomization), 98, 98, and 97 patients were randomly assigned to SEC-300, SEC-150, and placebo, respectively. Consequently, a total of 140, 98, and 116 patients were assigned to SEC-300, SEC-150, and placebo groups, respectively. GCP denotes Good Clinical Practice.

in the SEC-150 group and 6.3% (95% CI: 0.4 to 12.2) in the placebo group achieved sustained remission (Table S11). In female patients, the mean cumulative GC dose in SEC-300 was 3133 mg and 4232 mg in the placebo group, and the mean GTI-AIS score was 32.0 in the SEC-300 and 73.3 in the placebo group. Additional female subgroup results are presented in Table S11. The sustained remission rates among male patients randomly assigned to the SEC-300 versus placebo groups were 28.8% and 30.9%, respectively. The sustained remission rate among male patients randomly assigned to SEC-150 group was 12.6% versus 31.3% in the placebo group. In an exploratory analysis that included sex as a covariate, the proportion of patients with sustained remission was 26.8% (95% CI, 19.3 to 34.3) in the SEC-300 group and 15.9% (95% CI, 9.8 to 22.0) in the placebo group (marginal difference: 10.9 percentage points; 95% CI, 1.3 to 20.5) (Table 2). Results for the PMR subgroup analysis are found in Table S12.

SAFETY

The proportion of patients experiencing AEs were as follows: SEC-300, 92.9%; SEC-150, 95.9%; and placebo, 97.4%. AEs leading to treatment discontinuation occurred in 7.1%, 11.2%, and 13.9% of patients in the SEC-300, SEC-150, and placebo groups, respectively (Table 3). The most common AEs across treatment groups were Covid-19, arthralgia, and headache (Table S13). Most AEs in all

Table 2. Primary, Secondary, and Exploratory Endpoints through Week 52 (Full Analysis Set).*

Endpoint	Secukinumab 300 mg (N=140)	Placebo compared to secukinumab 300 mg (enrolled before and after protocol change)† (N=115)	Secukinumab 150 mg (N=98)	Subset of placebo group compared to secukinumab 150 mg group (enrolled after protocol change)† (N=96)
Sustained remission at week 52 — n/m (%)‡	35/140 (25.0)	20/115 (17.4)	19/98 (19.4)	17/96 (17.7)
Estimated response proportion (95% CI)	25.6 (18.3 to 32.9)	16.9 (10.1 to 23.7)	19.4 (11.8 to 26.9)	17.7 (10.0 to 25.5)
Marginal difference (95% CI)	8.7 (−1.3 to 18.8)		1.6 (−9.2 to 12.4)	
P value	0.09			
Cumulative GC dose through week 52 (mg)§				
Within treatment LS means (SE)	3158.0 (193.68)	3941.4 (195.82)	3988.1 (483.90)	3952.2 (212.18)
LS means difference (95% CI)	−783.39 (−1323.62 to −243.16)		35.91 (−1002.82 to 1074.64)	
Escape treatment or rescue treatment				
Patients initiating first use of escape/rescue treatment by week 52 — n (%)	73 (52.1)	61 (53.0)	52 (53.1)	54 (56.3)
Median time to initiation, days (95% CI)	309.0 (231.0 to NC)	326.0 (226 to NC)	254.0 (174.0 to NC)	290.0 (225.0 to 365.0)
Change in SF-36 score (PCS) at week 52§				
Within treatment LS means (SE)	−16.0 (1.35)	−17.8 (1.35)	−17.7 (1.49)	−19.4 (1.40)
LS means difference (95% CI)	1.83 (−1.97 to 5.62)		1.67 (−2.36 to 5.71)	
GTI-AIS at week 52§				
Within treatment LS means (SE)	23.2 (8.33)	73.1 (14.02)	88.7 (16.55)	69.4 (15.13)
LS means difference (95% CI)	−49.92 (−81.95 to −17.89)		19.21 (−25.03 to 63.44)	
Change in FACIT-Fatigue score at week 52§				
Within treatment LS means (SE)	−19.5 (1.60)	−20.9 (1.71)	−22.0 (1.74)	−22.9 (1.81)
LS means difference (95% CI)	1.39 (−3.26 to 6.03)		0.91 (−4.04 to 5.85)	
Sustained clinical remission (excluding CRP) at week 52	51/140 (36.4)	38/115 (33.0)	36/98 (36.7)	28/96 (29.2)
Estimated response proportion (95% CI)	36.4 (28.4 to 44.4)	33.0 (24.4 to 41.7)	36.7 (27.5 to 45.9)	29.2 (20.0 to 38.4)
Marginal difference (95% CI)	3.4 (−8.6 to 15.4)		7.5 (−5.5 to 20.5)	
Exploratory analysis including sex as a covariate				
Sustained remission at week 52 — (%)¶	35/140 (25.0)	20/115 (17.4)	19/98 (19.4)	17/96 (17.7)
Estimated response proportion (95% CI)	26.8 (19.3 to 34.3)	15.9 (9.8 to 22.0)	19.7 (12.0 to 27.4)	17.4 (10.1 to 24.7)
Marginal difference (95% CI)	10.9 (1.3 to 20.5)		2.3 (−8.1 to 12.8)	
Cumulative GC dose through week 52				
Within treatment LS means (SE)	3137.0 (195.92)	3966.9 (197.24)	3976.8 (484.72)	3963.7 (212.59)
LS means difference (95% CI)	−829.83 (−1381.60 to −278.05)		13.05 (−1030.65 to 1056.74)	

(*Continued*)

Table 2. (*Continued*)

Endpoint	Secukinumab 300 mg (N=140)	Placebo compared to secukinumab 300 mg (enrolled before and after protocol change)† (N=115)	Secukinumab 150 mg (N=98)	Subset of placebo group compared to secukinumab 150 mg group (enrolled after protocol change)† (N=96)
GTI-AIS at week 52				
Within treatment LS means (SE)	22.0 (8.09)	74.5 (14.00)	88.7 (16.54)	69.5 (15.02)
LS means difference (95% CI)	−52.57 (−84.02 to −21.11)		19.14 (−24.73 to 63.01)	

* Confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing. ANCOVA denotes analysis of covariance; BMD, bone mineral density; CI, confidence interval; CRP, C-reactive protein; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue scale; GC, glucocorticoid; GCA, giant cell arteritis; GTI-AIS, Glucocorticoid Toxicity Index Aggregate Improvement Score; LS, least-squares; m, number of patients in the treatment group with evaluation; N, total number of patients in the treatment group based on the Full Analysis Set; NC, non-calculable; PCS, Physical Component Summary; SE, standard error; and SF-36, 36-Item Short Form Survey.

† The initial protocol used a 2:1 randomization scheme to allocate patients to 300 mg of secukinumab or placebo. After trial initiation, a protocol amendment added a 150-mg secukinumab group, with 1:1:1 random assignment to either 300 mg of secukinumab, 150 mg of secukinumab, or placebo. The 300-mg secukinumab group is compared to placebo patients enrolled before and after the protocol change (N=116; one patient was incorrectly randomly assigned, resulting in N=115). The 150-mg secukinumab group is compared to only placebo patients enrolled after the protocol change (N=96).

‡ Estimated mean, marginal difference, and 95% CI are from a logistic regression model with treatment and stratification factor (baseline GCA status and baseline prednisone dose) and a binary time period variable (before and after protocol change for the comparison of SEC-300 versus placebo only) as factors using marginal standardization method.

§ The ANCOVA model with Huber–White "sandwich" standard error was used. The model includes treatment group, baseline prednisone dose (≤ 30 mg/day or >30 mg/day) and baseline GCA status (newly onset or relapsing GCA), and a binary time period variable (before and after the protocol change for the comparison of secukinumab 300 mg versus placebo only). Baseline scores for SF-36 and FACIT-Fatigue were included as covariates in the analyses for these endpoints. Both total commercial GC dose and trial prednisone are considered for calculating the GC dose. Cumulative GC dose exposure is based on observed data from Day 1 up to Day 364.

¶ Estimated mean, marginal difference, and 95% CI are from a logistic regression model with treatment, sex, and stratification factor (baseline GCA status and baseline prednisone dose) and a binary time period (before and after the protocol change) for comparison of 300 mg of secukinumab versus placebo as factors using the marginal standardization method.

treatment groups were mild or moderate in severity. SAEs occurred in 20.0%, 27.6%, and 32.2% of patients in the SEC-300, SEC-150, and placebo groups, respectively (Table S14).

Three deaths in the SEC-300 group (cardiac arrest, pulmonary sepsis, and Covid-19) and one death in the placebo group (unknown cause) were reported (Supplementary Appendix, p. 21). The most common safety topics of interest were infections/infestations and hypersensitivity. Infections/infestations occurred in each group as follows: SEC-300, 63.6%; SEC-150, 62.2%; and placebo 74.8% (Table S15). Serious infections occurred in 5.0%, 9.2%, and 6.1% of patients in the SEC-300, SEC-150, and placebo groups, respectively. Most infections in both secukinumab groups were of mild to moderate severity and did not lead to treatment discontinuation. Hypersensitivity reactions occurred in 14.3%, 12.2%, and 9.6% of patients in the SEC-300, SEC-150, and placebo groups, respectively (Table 3). The most common hypersensitivity events were rash (SEC-300, 3.6%; SEC-150, 5.1%; and placebo, 3.5%), eczema (SEC-300, 2.1%; SEC-150, 1.0%; and placebo, 0.9%), and cutaneous vasculitis (SEC-300, 1.4%; SEC-150, 0%; and placebo, 0%). All hypersensitivity reactions were nonserious and nonsevere.

Discussion

GCA remains a condition with a substantial unmet clinical need in terms of treatment efficacy and treatment-related adverse effects. The GCAptAIN study found that among patients with new-onset or relapsing GCA, sustained remission at week 52 (primary outcome) did not differ significantly between those randomly assigned to receive SEC-300 with a 26-week GC taper and those receiving placebo with a 52-week GC taper. The lower cumulative GC exposure and GC-related toxicity (as measured by GTI-AIS) among patients in the SEC-300 compared to placebo group needs to be interpreted in relation to the fact that the prednisone taper was 26 weeks in the SEC-300 group and 52 weeks in the placebo group. Results for all other prespecified secondary endpoints appeared consistent with that of the primary outcome showing a lack of benefit of SEC-300 or SEC-150 versus placebo. No safety findings of concern were identified, consistent with the safety profile of secukinumab observed over the past 10 years across its approved indications.[20]

The GCAptAIN results add to the findings of other trials of other treatments for GCA and PMR; however, various differences in trial designs limit direct comparisons. In

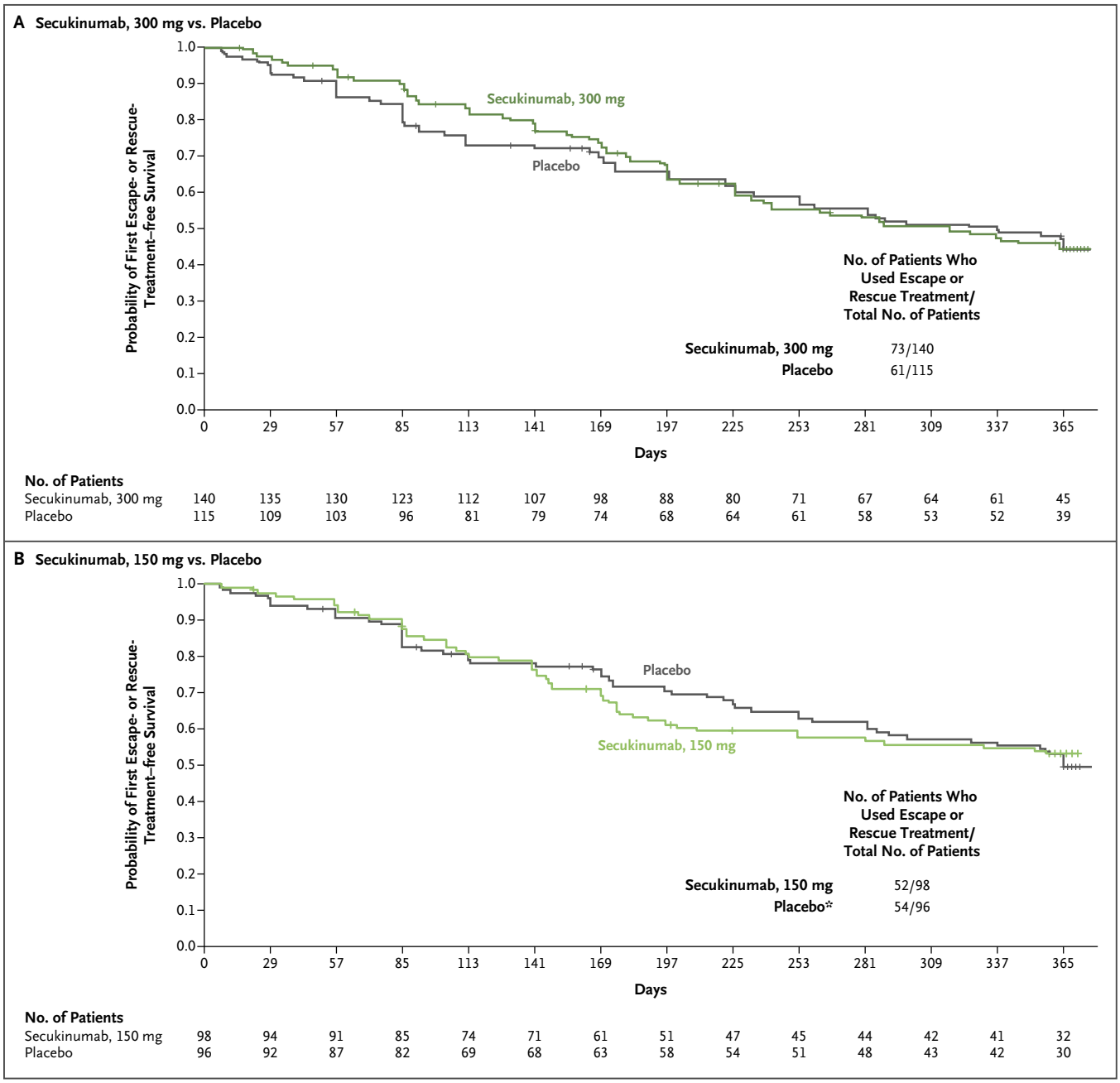

Figure 3. Time to First Escape or Rescue Treatment through Week 52 for (Panel A) 300 mg of Secukinumab and (Panel B) 150 mg of Secukinumab, versus Placebo.

*Only patients in the placebo group enrolled after protocol amendment were included. For the intercurrent event of prohibited medication use, the start date of the medication was considered as the onset of the event. Between-treatment differences are evaluated using a log-rank test with the two stratification factors applied at random assignment: (1) baseline patient's GCA status (new onset or relapsing) and (2) baseline prednisone dose (≤30 mg/day or >30 mg/day), and a binary time period variable (before and after protocol change) for the comparison of 300 mg of secukinumab versus placebo. The initial protocol used a 2:1 randomization scheme to allocate patients to 300 mg of secukinumab or placebo. After trial initiation, a protocol amendment added a 150-mg secukinumab group, with 1:1:1 random assignment to either 300 mg of secukinumab, 150 mg of secukinumab, or placebo. The 300-mg secukinumab group is compared to placebo patients enrolled before and after the protocol change (N=115). The 150-mg secukinumab group is compared to only placebo patients enrolled after the protocol change (N=96).

Table 3. Adverse Events.*

Adverse Event (AE)	Secukinumab 300 mg (N=140)	Secukinumab 150 mg (N=98)	Placebo (N=115)†
AEs — n (%)	130 (92.9)	94 (95.9)	112 (97.4)
Mild	47 (33.6)	38 (38.8)	35 (30.4)
Moderate	65 (46.4)	45 (45.9)	55 (47.8)
Severe	18 (12.9)	11 (11.2)	22 (19.1)
AEs reported in >10% of patients in secukinumab groups by preferred term — n (%)			
Covid-19	28 (20.0)	9 (9.2)	16 (13.9)
Arthralgia	23 (16.4)	6 (6.1)	23 (20.0)
Headache	20 (14.3)	14 (14.3)	24 (20.9)
Upper respiratory tract infection	18 (12.9)	12 (12.2)	13 (11.3)
Nasopharyngitis	17 (12.1)	11 (11.2)	18 (15.7)
Back pain	16 (11.4)	8 (8.2)	13 (11.3)
Insomnia	13 (9.3)	10 (10.2)	8 (7.0)
Urinary tract infection	11 (7.9)	10 (10.2)	6 (5.2)
Diarrhea	10 (7.1)	15 (15.3)	15 (13.0)
Peripheral edema	10 (7.1)	12 (12.2)	8 (7.0)
Cough	9 (6.4)	10 (10.2)	9 (7.8)
Fatigue	7 (5.0)	11 (11.2)	12 (10.4)
SAEs — n (%)	28 (20.0)	27 (27.6)	37 (32.2)
Fatal SAEs‡	3 (2.1)	0	1 (0.9)
AEs leading to treatment discontinuation — n (%)	10 (7.1)	11 (11.2)	16 (13.9)
AEs leading to treatment dose interruption — n (%)	18 (12.9)	10 (10.2)	23 (20.0)
Selected safety topics of interest			
Infections and infestations (SOC)	89 (63.6)	61 (62.2)	86 (74.8)
Serious infections	7 (5.0)	9 (9.2)	7 (6.1)
Hypersensitivity (SMQ)	20 (14.3)	12 (12.2)	11 (9.6)

* MedDRA version 28.0 has been used for the reporting of AEs. MedDRA denotes Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SMQ, standardized MedDRA query; and SOC, system organ class.
† Overall placebo population (including those enrolled after protocol amendment). AEs started after the first dose of trial treatment (secukinumab/placebo) or events present prior to the first dose of trial treatment (secukinumab/placebo) but increased in severity on or before last trial treatment (secukinumab/placebo) dose date+84 days.
‡ Three deaths in the SEC-300 group were due to cardiac arrest, pulmonary sepsis, and Covid-19. The cause death for one patient in the placebo group was unknown.

GCAptAIN, the primary endpoint of sustained remission rate for secukinumab (25.6%) was lower compared to tocilizumab in the GiACTA (56.0%) and upadacitinib in the SELECT-GCA (46.4%) phase 3 trials.[12,13] However, the definition of sustained remission differed across the trials. "No elevation of CRP at 2 consecutive visits" was part of the primary endpoint definition for sustained remission in GCAptAIN, including during the first 12 weeks of the trial, but not in SELECT-GCA. When "no elevation of CRP at 2 consecutive visits" was included in the definition of the secondary endpoint, sustained complete remission (from weeks 12 to 52) in SELECT-GCA, the response rate for upadacitinib was 37.1%.[13] In the phase 2 TitAIN trial, secukinumab achieved a 59% sustained remission rate at 52 weeks, compared to 8% for placebo. However, TitAIN also did not include "no elevation of CRP at 2 consecutive visits" to define sustained remission. Additionally, TitAIN allowed investigators full access to ESR and CRP values, unlike GCAptAIN. In addition, unlike GCAptAIN, which used a 52-week GC taper in the placebo group, both groups of TitAIN had a 26-week taper.[21] The GCAptAIN results are viewed in the context of the REPLENISH phase 3 trial,[28] which evaluated secukinumab in patients with relapsed PMR. In REPLENISH, secukinumab with 24-week glucocorticoid taper demonstrated superior remission rates and reductions in GC use compared to a 24-week prednisone taper alone. Thus, the GC taper was not the same in the two trials. The lack of significant difference in remission rate in

the GCAptAIN should be interpreted in view of the fact the GC taper was 26 weeks for the secukinumab groups and 52 weeks for the placebo group.

The higher proportion of females in the SEC-300 and SEC-150 groups relative to the placebo groups in the GCAptAIN trial occurred by chance. In post hoc analyses, the marginal difference of sustained remission in the SEC-300 versus placebo group appeared to be higher when sex was included as a covariate (10.9) than in the primary analysis (8.7). In GCAptAIN, the difference in sustained remission rates between the SEC-300 and placebo group among female patients (17.5%) (Table S11) was similar to that reported for the overall cohort in the SELECT-GCA trial between patients randomly assigned to 15 mg of upadacitinib and placebo (17.1%).[13] GCAptAIN also found that female patients in the SEC-300 group appeared to have lower cumulative GC dose and GC toxicity than those in the placebo group and more favorable changes in SF-36 and FACIT-Fatigue scores. These results are notable given that females represent approximately 75% of the GCA population overall and when treated with GCs have increased risk of relapse and GC toxicity resulting in osteoporosis and bone fracture compared with males.[29-32]

This trial has limitations that deserve comment. First, there was a higher proportion of females in the secukinumab groups than in the placebo group. It is notable that the response rate in the placebo group was 30.9% in males and 6.3% in females. Similarly, GiACTA reported a clinical remission rate in the placebo group of 60.8% among males and 18.3% among females.[29] Prior reports suggest a stronger proinflammatory cytokine response, and consequently less potent GC anti-inflammatory effect, in females.[33] Another limitation was the longer GC taper schedule in the placebo versus secukinumab groups, as noted above. Finally, the addition of the SEC-150 group during the trial resulted in unequal sample sizes and a more complex interpretation than would have existed under a single random assignment scheme followed throughout the trial. The amendment aimed to evaluate whether a lower secukinumab dose could achieve efficacy comparable to that of the higher dose while minimizing drug exposure.

In conclusion, the GCAptAIN trial did not demonstrate superiority of SEC-300 plus a 26-week GC taper over placebo plus a 52-week GC taper for sustained remission of GCA at week 52. Safety findings were consistent with the known safety profile for secukinumab.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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