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Sarilumab and Nonbiologic Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Tumor Necrosis Factor Inhibitors

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Objective. **To evaluate the efficacy and safety of sarilumab plus conventional synthetic disease-modifying antirheumatic drugs (DMARDs) in patients with active moderate-to-severe rheumatoid arthritis (RA) who had an inadequate response or intolerance to anti–tumor necrosis factor (anti-TNF) therapy.**

Methods. **Patients were randomly allocated to receive sarilumab 150 mg, sarilumab 200 mg, or placebo every 2 weeks for 24 weeks with background conventional synthetic DMARDs. The co-primary end points were the proportion of patients achieving a response according to the American College of Rheumatology 20% criteria for improvement (ACR20) at week 24, and change from baseline in the Health Assessment Questionnaire disability index (HAQ DI) at week 12. Each sarilumab dose was evaluated against placebo; differences between the 2 sarilumab doses were not assessed.**

Results. **The baseline characteristics of the treatment groups were similar. The ACR20 response rate at week 24 was significantly higher with sarilumab 150 mg and sarilumab 200 mg every 2 weeks compared with placebo (55.8%, 60.9%, and 33.7%, respectively; $P < 0.0001$). The mean change from baseline in the HAQ DI score at week 12 was significantly greater for sarilumab (least squares mean change: for 150 mg, −0.46 [$P = 0.0007$]; for 200 mg, −0.47 [$P = 0.0004$]) versus placebo (−0.26). Infections were the most frequently reported treatment-emergent adverse events. Serious infections occurred in 1.1%, 0.6%, and 1.1% of patients receiving placebo, sarilumab 150 mg, and sarilumab 200 mg, respectively. Laboratory abnormalities included decreased absolute neutrophil count and increased transaminase levels in both sarilumab groups compared with placebo. In this study, reductions in the absolute neutrophil count were not associated with an increased incidence of infections or serious infections.**

Conclusion. **Sarilumab 150 mg and sarilumab 200 mg every 2 weeks plus conventional synthetic DMARDs improved the signs and symptoms of RA and physical function in patients with an inadequate response or intolerance to anti-TNF agents. Safety data were consistent with interleukin-6 receptor blockade and the known safety profile of sarilumab.**

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Conventional synthetic disease-modifying antirheumatic drugs (DMARDs) are the core treatment regimen for patients with rheumatoid arthritis (RA) (1,2). Biologic agents, such as tumor necrosis factor (TNF) inhibitors, are indicated for RA management in patients who have an insufficient response to methotrexate (MTX) and/or other conventional synthetic DMARDs (1,2). However, an estimated 12–30% of patients receiving anti-TNF therapy discontinue treatment due to lack of efficacy or intolerance (3,4). Subsequent treatment with other biologic DMARDs may not result in an optimal response in all of these patients, which makes effective treatment in this population challenging (5). In those patients with an inadequate response, recommendations from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) suggest that switching from 1 class of biologic DMARDs to another with a different mechanism of action may provide better clinical benefit (1,2). As a result, alternative therapies that effectively reduce RA disease activity are needed for these patients.

Interleukin-6 (IL-6) is a pleiotropic cytokine with functions related to immune regulation, B cell and T cell development, and chronic inflammation (6). Expression of IL-6 is increased in several inflammatory disorders, and IL-6 blockade reverses signs of systemic inflammation, including fever and increased production of acute-phase proteins (6,7). IL-6 has been identified in the pathophysiology of RA (6,8,9), and IL-6 expression has been shown to be elevated in the serum and synovial fluid of patients with RA (10–12). Additionally, attenuation of IL-6 signaling reduces osteoclast formation and bone erosion, both of which are characteristic features of RA (13,14). Tocilizumab, a humanized inhibitor of IL-6 receptor (IL-6R) activity, administered as monotherapy or combined with MTX or other conventional synthetic DMARDs, has demonstrated efficacy in patients with moderate-to-severe RA (15–19).

Sarilumab is an investigational human monoclonal antibody directed against IL-6R that has been studied in phase IIb−III clinical trials (20,21). In the phase III, 24-week TARGET study, the efficacy and safety of sarilumab in combination with conventional synthetic DMARDs was evaluated in patients with active moderate-to-severe RA who had a previous inadequate response to or intolerance to anti-TNF therapies.

PATIENTS AND METHODS

Study design. TARGET was a 3-arm, multicenter, randomized, double-blind, placebo-controlled, phase III study. The first patient was enrolled in October 2012, and the last patient completed the trial in March 2015. The study duration was 34 weeks, consisting of up to 4 weeks of screening, 24 weeks of treatment, and 6 weeks of posttreatment follow-up. Randomization was performed centrally; patients were allocated 1:1:1 to receive subcutaneous sarilumab 150 mg, sarilumab 200 mg, or placebo every 2 weeks in combination with background conventional synthetic DMARD(s) for 24 weeks. Patients were stratified according to the number of previous anti-TNF agents (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39944/abstract) and region. The protocol was approved by the appropriate ethics committees/institutional review boards (see Appendix A), and each patient provided written informed consent before participation in the study. The study was conducted in compliance with institutional review board regulations, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki. The study (Trial ID: EFC10832) is registered with ClinicalTrials.gov (NCT01709578).

Patient population. Eligible patients were ≥18 years of age and fulfilled the 2010 ACR/EULAR classification criteria for RA (22). Patients were included if they had active disease (defined as a swollen joint count [SJC] of ≥6 [66 joints assessed], a tender joint count [TJC] of ≥8 [68 joints assessed], and a high-sensitivity C-reactive protein [hsCRP] level of ≥8 mg/liter at screening), with a disease duration of ≥6 months, and an inadequate response or intolerance to ≥1 anti-TNF therapy as defined by the investigator. Study inclusion also required continuous treatment with standard dose(s) of 1 or a combination of background conventional synthetic DMARD(s) including MTX, leflunomide, sulfasalazine, or hydroxychloroquine for ≥12 weeks before baseline and a stable dose for ≥6 weeks before screening (simultaneous treatment with MTX and leflunomide was not allowed). Patients were excluded if they had uncontrolled concomitant disease, significant extraarticular manifestations of RA, functional class IV RA, other inflammatory diseases, current/recurrent infections, or were receiving prednisone (or equivalent) at a dosage of >10 mg/day (see Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39944/abstract).

Study treatment. Patients received subcutaneous sarilumab 150 mg, sarilumab 200 mg, or placebo every 2 weeks in combination with background conventional synthetic DMARD(s) for 24 weeks. Subcutaneous injections of sarilumab or matching placebo were self-administered or administered by a caregiver. From week 12 onward, patients with <20% improvement from baseline in the SJC or TJC for 2 joint assessments ≥4 weeks apart were offered rescue treatment with open-label sarilumab 200 mg every 2 weeks.

Assessments. ACR core set components (23) were assessed to measure disease activity at randomization, weeks 2 and 4, and every 4 weeks thereafter. Investigators were blinded with regard to the patients' CRP level, serum sarilumab levels, and anti−sarilumab antibody positivity, except at screening and baseline; an independent assessor of joints, with no access to patient data, performed SJC and TJC measurements. Safety parameters were assessed at each visit.

Primary efficacy end points. Two co-primary end points were investigated: the proportion of patients achieving ACR 20% criteria for improvement (ACR20) response (24) at week 24, and change from baseline in physical function as assessed by the Health Assessment Questionnaire disability index (HAQ DI) (25) at week 12.

Secondary efficacy end points. Secondary efficacy end points included change from baseline in the Disease Activity

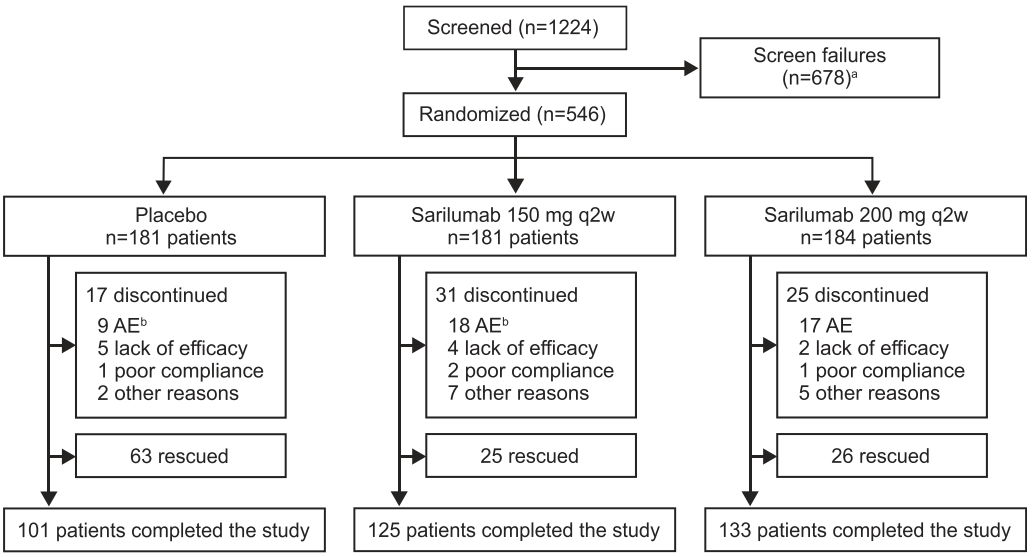

Figure 1. Patient disposition. a = Screen failures mainly resulted from failure to meet the inclusion criterion for disease severity (53%), for not having a high-sensitivity C-reactive protein level of ≥8 mg/liter, or because of tuberculosis (21%). b = A total of 5 patients (1 in the placebo group and 4 in the sarilumab 150 mg group) discontinued from the study because their laboratory values measured at baseline were abnormal and precluded them from study inclusion before treatment initiation. AE = adverse event; q2w = every 2 weeks.

Score in 28 joints using the CRP level (DAS28-CRP) (26) at week 24, ACR50 and ACR70 response rates at week 24, DAS28-CRP level of <2.6 at week 24, and change from baseline in the HAQ DI at week 24. For a full list of secondary end points, see Supplementary Table 3 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39944/abstract).

Safety assessments. Safety assessments included the incidence of treatment-emergent adverse events (AEs), treatment-emergent serious AEs (SAEs), and laboratory test results. Treatment-emergent AEs, SAEs, and AEs of special interest were reported by investigators, and laboratory parameters were measured. AEs were described at the Medical Dictionary for Regulatory Activities (MedDRA; version 17.1) preferred term level, whereas AEs of special interest were identified using prespecified search criteria. Anti-sarilumab antibody positivity at ≥2 consecutive samplings during the treatment-emergent AE period was classified as persistent.

Statistical analysis. A sample size of 174 patients per treatment group was calculated to detect a statistically significant difference with 90% power in change in HAQ DI from baseline between either dose of sarilumab plus conventional synthetic DMARDs and placebo plus conventional synthetic DMARDs, assuming that the change in the HAQ DI from baseline to week 24 was −0.05 in the placebo group and −0.35 in the sarilumab groups, with a common SD of 0.79 (15). This sample size provided 99% power for the co-primary end point, the ACR20 response at week 24, based on the assumption of a 20% response rate in the placebo group and a 50% response rate in the sarilumab groups. Each sarilumab dose was evaluated against placebo; differences between the 2 sarilumab doses were not assessed. Primary efficacy and safety analyses were conducted in the intent-to-treat population, which consisted of all randomized patients who received ≥1 dose of sarilumab.

ACR20 responses at week 24 were analyzed using the Cochran-Mantel-Haenszel 2-sided test, adjusted for region and number of previous anti-TNF agents. Patients who received rescue medication or discontinued treatment were considered nonresponders in the primary analysis. In a sensitivity analysis, the last observation carried forward (LOCF) procedure from point of treatment discontinuation was applied to impute missing data.

Change from baseline in the HAQ DI at week 12 was analyzed using a mixed model for repeated measures adjusted for previous anti-TNF agents, region, visit, treatment-by-visit interaction, and baseline score as covariates. In the primary analysis, data collected after treatment discontinuation or rescue were classified as missing. A clinically meaningful HAQ DI response, defined as ≥0.22 units of improvement from baseline, is presented (27). The higher HAQ DI threshold of ≥0.30 units of improvement is also reported. Sensitivity analyses for change in the HAQ DI included LOCF and multiple imputation procedures; both were used to impute missing data after rescue or treatment discontinuation.

Categorical secondary efficacy end points were analyzed using the Cochran-Mantel-Haenszel 2-sided test stratified by region and number of previous anti-TNF agents, and change from baseline in continuous variables was analyzed using the mixed model for repeated measures as described above.

To adjust for multiplicity, a Bonferroni correction together with a hierarchical testing procedure was used to control the Type I error rate at a significance level of 0.05. A nominal *P* value of less than 0.025 was considered significant when all preceding end points in the predefined hierarchy were statistically significant. Statistical significance could not be claimed for end points outside of the hierarchy (for the complete hierarchy, see Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39944/abstract).

Table 1. Summary of patient demographics and disease characteristics at baseline*

	Placebo plus csDMARD(s) (n = 181)	Sarilumab 150 mg every 2 weeks plus csDMARD(s) (n = 181)	Sarilumab 200 mg every 2 weeks plus csDMARD(s) (n = 184)
Female	154 (85.1)	142 (78.5)	151 (82.1)
Age, mean ± SD years	51.9 ± 12.4	54.0 ± 11.7	52.9 ± 12.9
Race			
White	124 (68.5)	134 (74.0)	130 (70.7)
Black	7 (3.9)	8 (4.4)	5 (2.7)
Asian	1 (0.6)	3 (1.7)	1 (0.5)
Other	49 (27.1)	36 (19.9)	48 (26.1)
Geographic region†			
Region 1	77 (42.5)	77 (42.5)	79 (42.9)
Region 2	74 (40.9)	74 (40.9)	74 (40.2)
Region 3	30 (16.6)	30 (16.6)	31 (16.8)
Background csDMARDs‡			
Methotrexate	158 (87.3)	154 (85.1)	156 (84.8)
Leflunomide	17 (9.4)	17 (9.4)	18 (9.8)
Sulfasalazine	5 (2.8)	12 (6.6)	15 (8.2)
Hydroxychloroquine	10 (5.5)	14 (7.7)	13 (7.1)
Prior exposure to anti-TNF agent	181 (100)	181 (100)	184 (100)
1 exposure	135 (74.6)	143 (79.4)	140 (76.5)
>1 exposure	46 (25.4)	37 (20.6)	43 (23.5)
Concomitant corticosteroids§	112 (61.9)	116 (64.1)	113 (61.4)
Duration of RA, mean ± SD years	12.0 ± 10.0	11.6 ± 8.6	12.7 ± 9.6
Rheumatoid factor positive	142 (78.9)	135 (74.6)	132 (72.9)
Anti-CCP antibody positive	150 (83.3)	135 (75.0)	137 (76.1)
DAS28-CRP, mean ± SD	6.2 ± 0.9	6.1 ± 0.9	6.3 ± 1.0
TJC (68 assessed), mean ± SD	29.4 ± 14.5	27.7 ± 15.6	29.6 ± 15.5
SJC (66 assessed), mean ± SD	20.2 ± 11.3	19.6 ± 11.2	20.0 ± 11.9
HAQ DI score, mean ± SD	1.8 ± 0.6	1.7 ± 0.6	1.8 ± 0.6
CRP, mean ± SD mg/liter¶	26.0 ± 25.2	23.6 ± 23.4	30.8 ± 28.4
Hemoglobin, mean ± SD gm/liter#	126.6 ± 15.3	128.1 ± 15.0	125.7 ± 14.3
Serum albumin, mean ± SD gm/liter**	37.6 ± 3.6	37.7 ± 3.4	37.1 ± 3.7

* Except where indicated otherwise, values are the number (%). Anti-TNF = anti–tumor necrosis factor; RA = rheumatoid arthritis; anti-CCP = anti–cyclic citrullinated peptide; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; TJC = tender joint count; SJC = swollen joint count; HAQ DI = Health Assessment Questionnaire disability index.

† Region 1 = Australia, Canada, Czech Republic, Germany, Greece, Hungary, Israel, Italy, New Zealand, Portugal, Spain, US; region 2 = Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Peru; region 3 = Lithuania, Poland, Russia, South Korea, Taiwan, Thailand, Turkey, Ukraine.

‡ Concomitant use of 2 conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) was reported by 6.4% of patients, and 0.7% of patients reported concomitant use of 3 csDMARDs.

§ Oral corticosteroids were permitted if the daily dose was ≤10 mg prednisone or equivalent and was stable for ≥4 weeks before randomization. No change was permitted unless an adverse event occurred.

¶ Normal range for a 50-year-old woman <3.1 mg/liter.

Normal ranges for a 50-year-old man and a 50-year-old woman 135–175 gm/liter and 120–160 gm/liter, respectively.

** Normal range for a 50-year-old woman 35–55 gm/liter.

RESULTS

Patient demographics and baseline characteristics. Of the 1,224 patients screened, 546 patients were randomized and treated in 155 study centers across 27 countries (Figure 1) and comprised the efficacy and safety populations. The baseline demographics and disease characteristics were well balanced among treatment groups (Table 1). The mean RA duration was 12.1 years, and 57.7% of the patients were categorized as being in RA functional class II. MTX, either alone or in combination with other conventional synthetic DMARDs, was the most common background therapy. A majority of patients reported prior use of 1 anti-TNF treatment for RA (79.4%, 76.5%, and 74.6% of patients in the sarilumab 150 mg, sarilumab 200 mg, and placebo groups, respectively) (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39944/abstract); the most commonly

Table 2. Efficacy results in the intent-to-treat population according to treatment group*

		Sarilumab	
	Placebo plus csDMARD(s) (n = 181)	150 mg every 2 weeks plus csDMARD(s) (n = 181)	200 mg every 2 weeks plus csDMARD(s) (n = 184)
Signs and symptoms			
ACR20 at week 24, no. (%)†	61 (33.7)	101 (55.8)‡	112 (60.9)‡
ACR50 at week 24, no. (%)†	33 (18.2)	67 (37.0)‡	75 (40.8)‡
ACR70 at week 24, no. (%)†	13 (7.2)	36 (19.9)§	30 (16.3)¶
ACR core set of disease activity measures, adjusted mean change from baseline at week 24 ± SE			
SJC (66 assessed)#	−8.2 ± 0.72	−11.6 ± 0.69¶	−11.9 ± 0.67‡
TJC (68 assessed)#	−10.6 ± 1.06	−14.4 ± 1.02§	−17.0 ± 0.99‡
Patient's global assessment (0–100 mm VAS)#	−19.8 ± 2.17	−29.6 ± 2.05§	−31.3 ± 2.00‡
Physician's global assessment (0–100 mm VAS)#	−28.6 ± 1.81	−40.7 ± 1.70‡	−43.2 ± 1.65‡
Patient's assessment of pain (0–100 mm VAS)#	−21.3 ± 2.25	−31.9 ± 2.09§	−33.7 ± 2.04‡
HAQ DI#	−0.3 ± 0.05	−0.5 ± 0.05¶	−0.6 ± 0.05§
CRP, mg/liter#	−3.6 ± 1.56	−15.2 ± 1.46‡	−23.3 ± 1.42‡
DAS28-CRP, adjusted mean change from baseline at week 24 ± SE†	−1.4 ± 0.12	−2.4 ± 0.11‡	−2.8 ± 0.11‡
DAS28-CRP response at week 24, no. (%)			
<2.6†	13 (7.2)	45 (24.9)‡	53 (28.8)‡
≤3.2#	25 (13.8)	59 (32.6)‡	74 (40.2)‡
Physical function			
HAQ DI, adjusted mean change from baseline at week 12 ± SE†	−0.26 ± 0.04	−0.46 ± 0.04§	−0.47 ± 0.04§
HAQ DI response at week 24, no. (%)#			
Change ≥0.22	64 (35.4)	86 (47.5)**	103 (56.0)‡
Change ≥0.30	57 (31.5)	78 (43.1)**	87 (47.3)¶

* Each selected sarilumab dose regimen was tested versus placebo at a significance level of 0.025 (with Bonferroni adjustment for multiple comparisons). csDMARD(s) = conventional synthetic disease-modifying antirheumatic drug(s); ACR20 = American College of Rheumatology 20% criteria for improvement; VAS = visual analog scale.
† End point in predefined hierarchy.
‡ $P < 0.0001$ versus placebo plus csDMARD(s).
§ $P < 0.001$ versus placebo plus csDMARD(s).
¶ $P < 0.01$ versus placebo plus csDMARD(s).
# In the 2 sarilumab groups, the benchmark was not included in the predefined hierarchy for the swollen joint count (SJC), tender joint count (TJC), patient's global assessment, physician's global assessment, patient's global assessment of pain, Health Assessment Questionnaire disability index (HAQ DI), C-reactive protein (CRP) level, change from baseline in the Disease Activity Score in 28 joints (DAS28) using the CRP level, DAS28-CRP response at week 24 of ≤3.2, and change in HAQ DI response at week 24. Nominal P values are provided.
** = $P < 0.05$ versus placebo plus csDMARD(s).

used prior anti-TNF agents were adalimumab and etanercept. Most patients discontinued prior anti-TNF therapy because of an inadequate response (92.3%); thus, TARGET is primarily composed of a population with an inadequate response to anti-TNF therapy.

Of the total population, fewer patients in the placebo group (55.8%) completed the study compared with patients in the sarilumab 150 mg and 200 mg groups (69.1% and 72.3%, respectively). More patients in the placebo group received rescue treatment (34.8%) compared with the sarilumab 150 mg and 200 mg groups (13.8% and 14.1%, respectively). Treatment discontinuations due to treatment-emergent AEs occurred in 4.4% of the placebo group compared with 7.7% and 9.2% of the sarilumab 150 mg and 200 mg groups, respectively.

Efficacy. Statistically significant improvements in the co-primary end points of the ACR20 response at week 24 ($P < 0.0001$ each) and change in the HAQ DI at week 12 ($P = 0.0007$ for sarilumab 150 mg versus placebo and $P = 0.0004$ for sarilumab 200 mg versus placebo) were observed in patients receiving either dose of sarilumab compared with those receiving placebo. Treatment with sarilumab 150 mg and 200 mg every 2 weeks produced similar benefits for secondary clinical end points in the hierarchy, including the ACR50 and ACR70 responses and change in the HAQ DI at week 24. Significantly

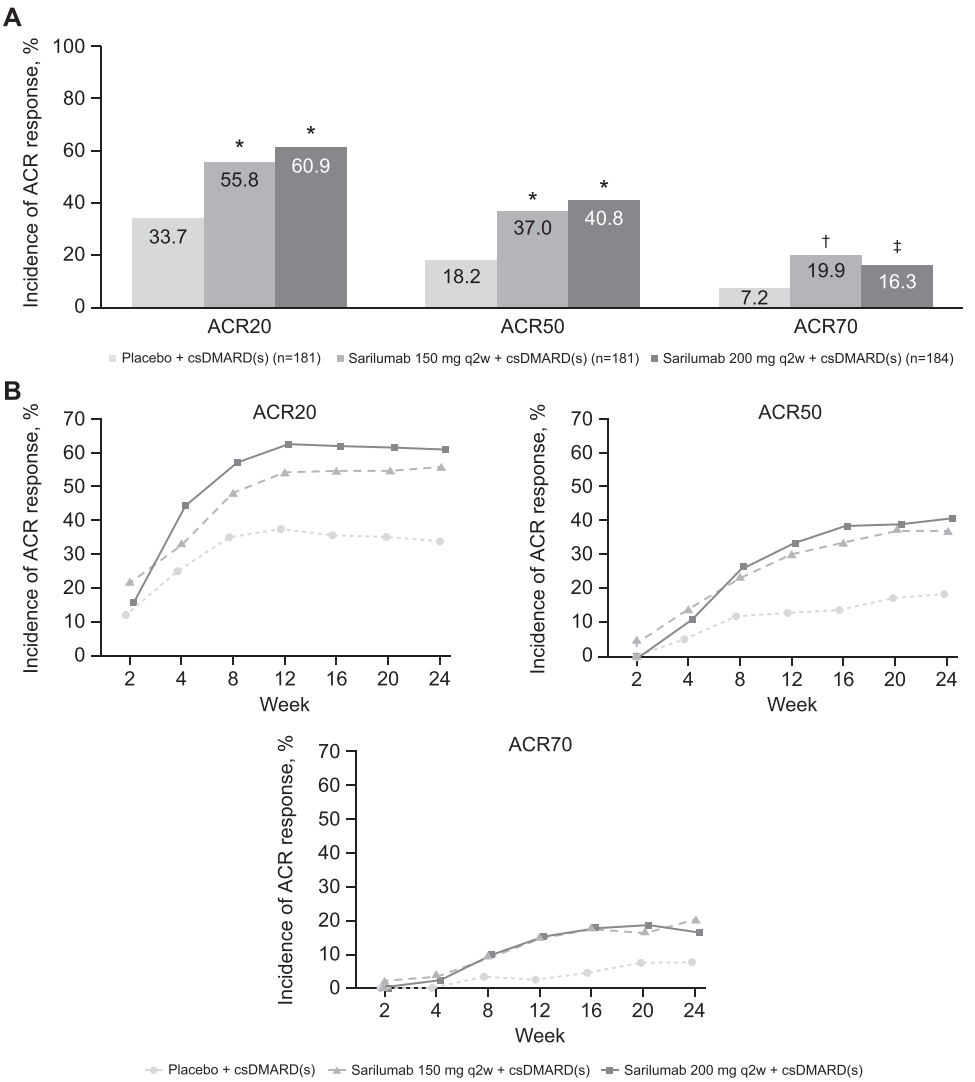

Figure 2. Incidence of American College of Rheumatology 20% criteria for improvement (ACR20), ACR50, and ACR70 responses. **A,** Proportion of patients who had achieved ACR20, ACR50, and ACR70 responses at week 24. Values inside the bars are the response rates. **B,** Proportion of patients who had achieved ACR20, ACR50, and ACR70 responses over time. $* = P < 0.0001$ versus placebo plus conventional synthetic disease-modifying antirheumatic drug(s) (csDMARD[s]); $† = P = 0.0002$ versus placebo plus csDMARD(s); $‡ = P = 0.0056$ versus placebo plus csDMARD(s). q2w = every 2 weeks.

greater improvements in the DAS28-CRP were observed in the sarilumab groups relative to the placebo group. In addition, a larger proportion of sarilumab-treated patients versus those treated with placebo achieved DAS28-CRP scores of <2.6 and DAS28-CRP scores of ≤3.2. Improvements in all ACR components were observed in patients receiving both doses of sarilumab at week 24, including scores for patient's assessment of disease activity and pain (Table 2).

Improvement in signs and symptoms of RA. A significantly greater proportion of patients receiving either dose of sarilumab achieved ACR20 responses at week 24 (for sarilumab 150 mg, 55.8%; for sarilumab 200 mg, 60.9%; for placebo, 33.7% [$P < 0.0001$ versus placebo for both doses]) (Figure 2A and Table 2). A greater proportion of sarilumab-treated patients (48.1% of those receiving 150 mg [nominal $P < 0.05$ versus placebo], and 57.1% of those receiving 200 mg [nominal $P < 0.0001$ versus placebo]) achieved ACR20 responses by week 8 compared with placebo, and the responses persisted throughout the treatment period (Figure 2B). Results from the prespecified sensitivity analysis, in which the LOCF from the point of discontinuation was used to impute missing data, were consistent with those from the primary analyses for

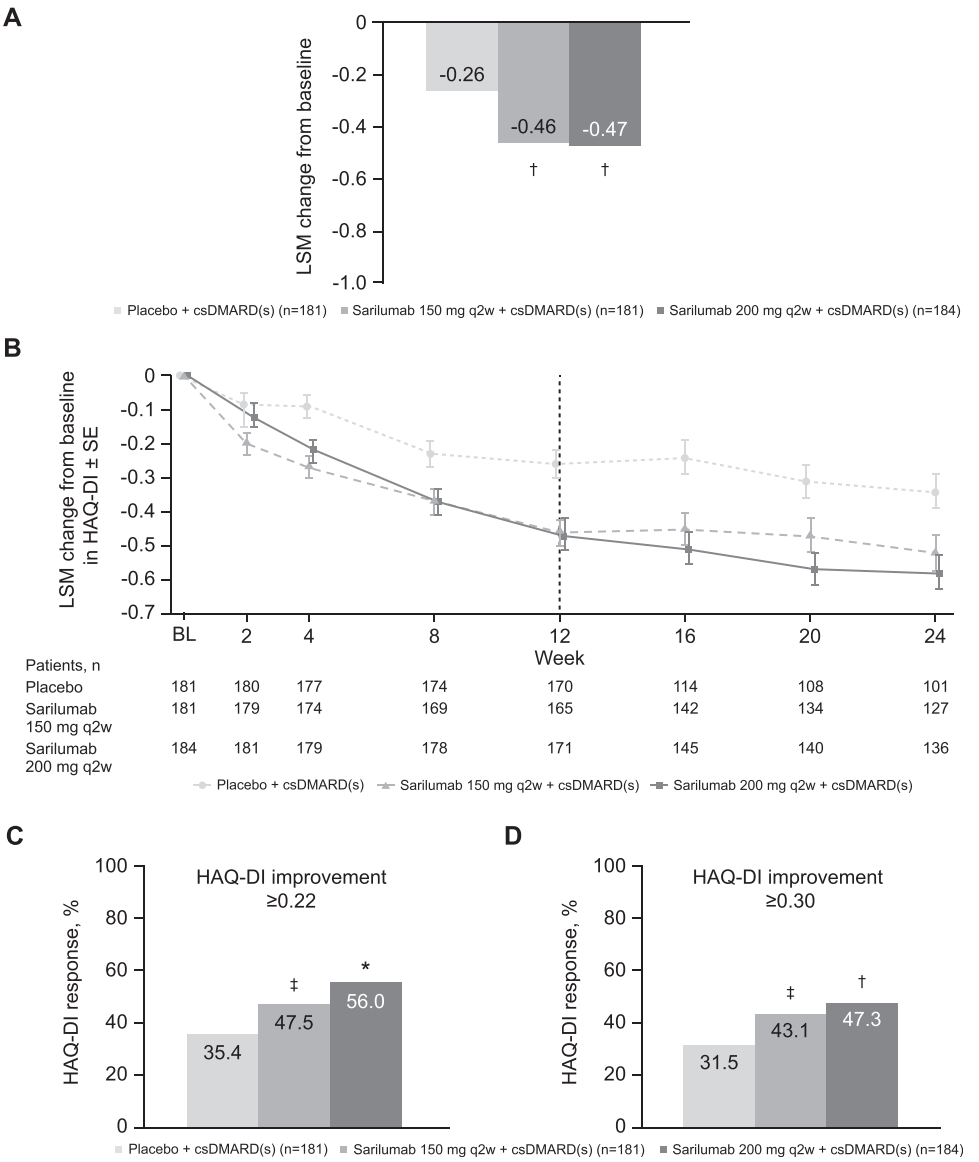

Figure 3. Mean change from baseline in Health Assessment Questionnaire disability index (HAQ DI) scores. **A,** Least squares mean (LSM) change from baseline in HAQ DI scores at week 12. **B,** LSM change from baseline in the HAQ DI over time according to treatment group. **C,** Proportion of patients who had achieved improvement in the HAQ DI of ≥0.22 units at week 24. **D,** Proportion of patients who had achieved improvement in the HAQ DI of ≥0.30 units at week 24. In **C** and **D**, values inside the bars are the response rates. $* = P < 0.0001$ versus placebo plus csDMARDs; $† = P < 0.01$ versus placebo plus csDMARDs; $‡ = P < 0.05$ versus placebo plus csDMARDs. Dotted vertical line indicates the time point after which rescue was permitted. See Figure 2 for other definitions.

ACR20 response. Greater ACR20 response rates with sarilumab compared with placebo were observed regardless of the number of prior anti-TNF agents (see Supplementary Table 4, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39944/abstract). Although the study was not powered to compare sarilumab doses, the ACR20 response rates achieved with sarilumab 200 mg were numerically higher than those achieved with sarilumab 150 mg.

Improvement in physical function. Patients receiving sarilumab 150 mg and those receiving 200 mg every 2 weeks had significantly greater improvements in the HAQ DI than those receiving placebo (least squares mean [LSM] change −0.46, −0.47, and −0.26, respectively [for 150 mg, $P = 0.0007$ versus placebo; for 200 mg, $P = 0.0004$ versus placebo]) (Figure 3A). Results of 2 sensitivity analyses, in which the LOCF method or multiple imputations were used to impute data collected after rescue or treatment

discontinuation, were consistent with those of the primary analyses. Improvements in the HAQ DI were seen in both sarilumab groups by week 4 (nominal $P < 0.01$) and were sustained throughout the 24-week study period (Figure 3B). Greater improvements in the HAQ DI were observed with sarilumab compared with placebo regardless of the number of prior anti-TNF agents (Supplementary Table 4).

Compared with placebo-treated patients, more sarilumab-treated patients had clinically meaningful improvement in the HAQ DI (defined as ≥0.22 units of improvement from baseline [27]) at week 24 (sarilumab 150 mg, 47.5% [nominal $P = 0.0137$] and sarilumab 200 mg, 56.0% [nominal $P < 0.0001$] versus placebo, 35.4%) (Figure 3C). More sarilumab-treated patients also showed ≥0.30 units of improvement in the HAQ DI (sarilumab 150 mg, 43.1% [nominal $P = 0.0165$] and sarilumab 200 mg, 47.3% [nominal $P = 0.0014$] versus placebo, 31.5%) (Figure 3D).

Regional variations. There were some differences in responses to placebo and sarilumab treatment among the 3 regions in the TARGET study. Placebo responses were greater in region 2 relative to regions 1 and 3, and there was a correspondingly higher treatment response for the 2 sarilumab groups in region 2. As a result, treatment differences between the active-treatment and placebo groups were maintained despite the differential responses according to regions, with analyses of interaction tests indicating no significant treatment-by-subgroup effect according to region in the ACR20 response rates at week 24 ($P = 0.7319$) or in the mean change from baseline in the HAQ DI at week 12 ($P = 0.9407$) (Supplementary Table 5, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39944/abstract).

Concomitant corticosteroid treatment. Approximately 60% of patients were receiving concomitant corticosteroids at dosages of ≤10 mg/day at baseline. ACR20 response rates at week 24 and LSM change from baseline in the HAQ DI at week 12 in sarilumab-treated patients were superior to those in placebo-treated patients, regardless of concomitant corticosteroid use (see Supplementary Table 6, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39944/abstract). When treatment-by-subgroup interaction testing was performed for ACR20 response rates and LSM change from baseline in the HAQ DI scores according to subgroups of patients with and those without baseline corticosteroid treatment, no statistically significant treatment-by-subgroup interaction was observed (P for interaction = 0.2768 for ACR20, and P for interaction = 0.8845 for HAQ DI).

Secondary efficacy end points. Clinical benefit of sarilumab was demonstrated for most secondary end points (Table 2). More patients receiving sarilumab achieved an ACR50 response at week 24 compared with those receiving placebo (37.0% for sarilumab 150 mg and 40.8% for sarilumab 200 mg versus 18.2% for placebo; $P < 0.0001$ versus placebo for both doses). The rate of ACR70 responses at week 24 was also greater with sarilumab 150 mg every 2 weeks (19.9%; $P = 0.0002$) and sarilumab 200 mg every 2 weeks (16.3%; $P = 0.0056$) relative to placebo (7.2%) (Figure 2A). Individual ACR core components were improved in the sarilumab groups at both 12 weeks (data not shown) and 24 weeks (Table 2).

Improvement from baseline in the DAS28-CRP at week 24 was significantly greater in patients receiving either dose of sarilumab compared with patients receiving placebo. More patients in the sarilumab groups had DAS28-CRP scores of <2.6 (24.9% and 28.8% for 150 mg and 200 mg, respectively, versus 7.2% for placebo [$P < 0.0001$ versus placebo for both doses]) and ≤3.2 at week 24 (32.6% and 40.2% for sarilumab 150 mg and 200 mg, respectively, versus 13.8% for placebo [nominal $P < 0.0001$ versus placebo for both doses]) (Table 2).

Safety. Total exposure (patient-years of treatment) to double-blind treatment was slightly longer for both sarilumab groups than for the placebo group; differences in total exposure resulted from more early terminations in the placebo group relative to the sarilumab groups (Table 3).

Investigator-reported AEs. A higher incidence of treatment-emergent AEs was reported with sarilumab compared with placebo. Infections were the most frequently reported treatment-emergent AE across all treatment groups (Table 3). There were 3 cases of nondisseminated herpes zoster infection (n = 1 in the placebo group; n = 2 in the sarilumab 200 mg group) but no cases of tuberculosis or systemic disseminated opportunistic infection. Discontinuations due to treatment-emergent AEs were more common in the sarilumab groups and were generally attributable to infections, neutropenia, and increased transaminase levels. One patient in the placebo group died due to a motor vehicle accident.

Serious AEs were reported in 6 patients (3.3%), 6 patients (3.3%), and 10 patients (5.4%) in the placebo, sarilumab 150 mg, and sarilumab 200 mg groups, respectively. Infections were the most frequently reported SAE across treatment groups and occurred in 5 patients (n = 1 in the sarilumab 150 mg group, n = 2 in the sarilumab 200 mg group, and n = 2 in the placebo group). SAEs occurred most frequently in the sarilumab 200 mg group and included decreased neutrophil counts, elevated transaminase levels, and cardiovascular disorders. Serious cardiovascular events occurred in 3 patients in the sarilumab 200 mg group: 1 patient developed noninfectious

Table 3. Summary of treatment-emergent AEs in the safety population and most frequent treatment-emergent AEs according to system organ class*

	Placebo plus csDMARD(s) (n = 181)	Sarilumab 150 mg every 2 weeks plus csDMARD(s) (n = 181)	Sarilumab 200 mg every 2 weeks plus csDMARD(s) (n = 184)
Patient-years of exposure	65.0	69.8	72.5
AEs	90 (49.7)	119 (65.7)	120 (65.2)
Serious AEs	6 (3.3)	6 (3.3)	10 (5.4)
AEs leading to treatment discontinuation	8 (4.4)	14 (7.7)	17 (9.2)
AEs leading to death	1 (0.6)	0	0
AEs according to system organ class			
Infections and infestations	48 (26.5)	40 (22.1)	56 (30.4)
Urinary tract infection	12 (6.6)	6 (3.3)	13 (7.1)
Nasopharyngitis	9 (5.0)	11 (6.1)	7 (3.8)
Pharyngitis	3 (1.7)	2 (1.1)	6 (3.3)
Upper respiratory tract infection	6 (3.3)	4 (2.2)	6 (3.3)
Blood and lymphatic disorders	9 (5.0)	25 (13.8)	29 (15.8)
Neutropenia	2 (1.1)	23 (12.7)	23 (12.5)
Thrombocytopenia	0	0	5 (2.7)
Leukopenia	0	2 (1.1)	3 (1.6)
Anemia	5 (2.8)	0	1 (0.5)
Laboratory investigations	8 (4.4)	19 (10.5)	30 (16.3)
ALT level increased	2 (1.1)	5 (2.8)	10 (5.4)
AST level increased	0	2 (1.1)	6 (3.3)
Transaminase levels increased†	0	2 (1.1)	3 (1.6)
Lipid levels			
Total cholesterol increase from <240 to ≥240 mg/dl	22/158 (13.9)	58/152 (38.2)	59/161 (36.6)
LDL cholesterol increase from <160 to ≥160 mg/dl	15/165 (9.1)	48/169 (28.4)	42/171 (24.6)
HDL cholesterol increase from <60 to ≥60 mg/dl	32/108 (29.6)	42/106 (39.6)	38/105 (36.2)

* Values are the number/number assessed (%). AEs = adverse events; csDMARD(s) = conventional synthetic disease-modifying antirheumatic drug(s); LDL = low-density lipoprotein; HDL = high-density lipoprotein.
† Patients with increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, as reported by the investigator.

endocarditis of the mitral valve, 1 patient with a prior episode of syncope developed an atrioventricular block, and 1 patient had venous thrombosis that improved with traditional management. Similar numbers of serious infections occurred in patients receiving concomitant corticosteroids (n = 3; 2 in the placebo group and 1 in the sarilumab 200 mg group) and in those not receiving concomitant corticosteroids (n = 2; 1 in the sarilumab 150 mg group and 1 in the sarilumab 200 mg group).

There were no cases of gastrointestinal perforation, lupus-like syndrome, or demyelinating disorders. Hypersensitivity reactions (based on a standardized Medical Dictionary for Regulatory Activities query) occurred in 10 patients (5.5%) receiving sarilumab 150 mg and 11 patients (6.0%) receiving sarilumab 200 mg, versus 7 (3.9%) of those receiving placebo; none of the hypersensitivity reactions were serious, and no cases of anaphylaxis were reported.

Injection-site reactions occurred in 7.2% and 8.2% of patients receiving sarilumab 150 mg and 200 mg, respectively, versus 1.1% of those receiving placebo. These events were generally mild to moderate in intensity, with no patients discontinuing treatment because of an injection-site reaction. Malignancy was diagnosed in 3 patients: 1 in the placebo group (ureter carcinoma), 1 in the sarilumab 150 mg group (renal cell carcinoma), and 1 in the sarilumab 200 mg group (skin carcinoma).

Laboratory findings. Changes in laboratory values in sarilumab-treated patients included reductions in the absolute neutrophil count and platelet count, and elevations in transaminase and plasma lipid levels (Table 3; see also Supplementary Table 7, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39944/abstract). Reductions in the absolute neutrophil count that occurred most frequently were reductions from baseline to levels that were between

the lower limit of normal (LLN) and $\geq 1.0 \times 10^9$/liter: for sarilumab 150 mg, 24.9%; for sarilumab 200 mg, 29.5%; for placebo, 3.3%. Reductions in the absolute neutrophil count to $<1.0 \times 10^9$/liter were observed in 7.7% of patients in the sarilumab 150 mg group, 9.8% in the sarilumab 200 mg group, and 0.6% in the placebo group (Supplementary Table 7). Decreases in the absolute neutrophil count were generally self-limited and returned toward baseline. Few patients discontinued treatment because of absolute neutrophil count decreases (2.8%, 1.6%, and 0.6% in the sarilumab 150 mg group, the sarilumab 200 mg group, and the placebo group, respectively). Patients with an absolute neutrophil count below the LLN, including those with an absolute neutrophil count of $<1.0 \times 10^9$/liter, did not have a higher incidence of infection compared with those with a normal absolute neutrophil count.

Increases in the alanine aminotransferase (ALT) level of >3 times the upper limit of normal occurred in 2.2%, 4.3%, and 1.1% of patients receiving sarilumab 150 mg, sarilumab 200 mg, or placebo, respectively (Supplementary Table 7). These events were generally asymptomatic and resolved during continued treatment or after dose delays, with 1 patient (sarilumab 150 mg) discontinuing treatment.

Total cholesterol levels of ≥239 mg/dl were observed in 46.1%, 44.5%, and 24.3% of patients in the sarilumab 150 mg group, sarilumab 200 mg group, and placebo group, respectively. The mean changes from baseline in the high-density lipoprotein:low-density lipoprotein ratios at week 24 were −0.04 and −0.05 in the sarilumab 150 mg and 200 mg groups, respectively, compared with 0.03 in the placebo group. Initiation of lipid-modifying therapies (mainly statins) occurred in 7 patients (3.9%) in the sarilumab 150 mg group and 8 patients (4.3%) in the sarilumab 200 mg group during the study; no patients receiving placebo began treatment with statins.

Decreases in the platelet count occurred in 6 patients, all of whom received sarilumab 200 mg (Supplementary Table 7). Decreases in platelet counts from 1.0 to $\geq 0.5 \times 10^9$/liter were observed in 5 patients (2.7%), whereas decreases of $<0.5 \times 10^9$/liter were observed in 1 patient.

Persistent anti-sarilumab antibody positivity was observed in 6.1%, 4.9%, and 1.1% of patients in the sarilumab 150 mg group, the sarilumab 200 mg group, and the placebo group, respectively. No notable differences were observed with regard to loss of or lack of efficacy or hypersensitivity reactions, including systemic and local, between anti-sarilumab antibody−positive and anti-sarilumab antibody−negative patients.

Improvements in the hemoglobin, CRP, and albumin levels were more frequent in patients receiving sarilumab versus placebo. The mean hemoglobin levels after 24 weeks of treatment were 135.1 gm/liter and 134.3 gm/liter in patients receiving sarilumab 150 mg and 200 mg every 2 weeks, respectively, whereas the mean hemoglobin level in patients receiving placebo was 127.6 gm/liter. Also, fewer anemia-associated AEs occurred in the sarilumab groups: for sarilumab 150 mg, n = 0; for sarilumab 200 mg, n = 1 (0.5%); for placebo, n = 5 (2.8%) (Table 3). Greater reductions in the hsCRP level were observed with both doses of sarilumab compared with placebo (Table 2). Serum albumin concentrations at week 24 in patients receiving sarilumab 150 mg and those receiving 200 mg were 41.0 gm/liter and 41.4 gm/liter, respectively, versus 38.8 gm/liter in patients receiving placebo.

DISCUSSION

In this phase III study of patients with RA who had an inadequate response to anti-TNF therapy, both doses of sarilumab combined with background conventional synthetic DMARD(s) provided statistically significant amelioration of the signs and symptoms of RA and improved physical function compared with placebo. A significantly greater proportion of sarilumab-treated patients, in addition to achieving ACR20 responses, achieved ACR50 and ACR70 responses. ACR20, ACR50, and ACR70 responder rates of 61%, 41%, and 16% observed with sarilumab 200 mg in this population with an inadequate response to anti-TNF agents are consistent with those in patients who had an inadequate response to MTX in the MOBILITY trial (20) and in trials of other biologic DMARDs in patients with an inadequate response to anti-TNF treatment (3). Improved ACR20 response rates were observed as early as 8 weeks after treatment initiation and were sustained throughout the 24-week study.

Treatment with either dose of sarilumab also resulted in statistically significant and clinically relevant improvements in physical function compared with placebo at week 12. The improvement in physical function observed in TARGET patients was consistent with that observed in the MOBILITY study, which assessed the effects of sarilumab in patients with an inadequate response to MTX (LSM change from baseline in the HAQ DI at week 16 −0.53 for sarilumab 150 mg and −0.55 for sarilumab 200 mg, versus −0.29 for placebo; $P < 0.0001$ versus placebo for both doses) (20) and with those observed in studies of other biologic agents in the population of patients with an inadequate response to anti-TNF agents (28,29). The HAQ DI was evaluated at week 12 (landmark analysis) to reduce the amount of missing data, because patients

demonstrating an inadequate response were eligible for rescue treatment at this time. However, the onset of treatment benefit was rapid; HAQ DI improvements were observed by week 4 of treatment and persisted throughout the 24-week study. The improvement in physical function at week 12 was clinically meaningful; a greater proportion of sarilumab-treated patients had HAQ DI improvements of $\geq$0.22 and $\geq$0.30 units (nominal $P < 0.05$) compared with placebo.

In addition to increased ACR20 responses and improvements in the HAQ DI, both sarilumab doses demonstrated clinical benefit in multiple secondary efficacy end points such as a DAS28-CRP of $<$2.6 and a DAS28-CRP of $\leq$3.2 (30). The observation that sarilumab results in improvement in the ACR core set components, including the TJC, SJC, physician's assessment of global status, and patient's assessment of pain, indicates that it provides consistent and clinically meaningful benefit, independent of pharmacodynamic effects on the acute-phase reactant CRP.

Sarilumab was generally well tolerated in the TARGET study. AEs and laboratory abnormalities were consistent with IL-6 blockade and observations from the MOBILITY study (20,31–33). The incidence of treatment discontinuation due to AEs, SAEs, and laboratory abnormalities was greater with sarilumab compared with placebo. Infection was the most frequent treatment-emergent AE in the sarilumab groups, but most events were mild or moderate in severity.

Changes in clinical laboratory findings in the sarilumab groups included reductions in the absolute neutrophil count and elevations in lipid and transaminase levels. A decreased absolute neutrophil count was observed more frequently with sarilumab than placebo. However, the incidence of serious infections was similar in the placebo and sarilumab groups, with no clear relationship with absolute neutrophil count reductions. Increases in the lipid levels in the sarilumab groups occurred early in the treatment period but stabilized by week 12, with few patients starting statin treatment and no cases of pancreatitis. Increases in the transaminase level were frequently reported with sarilumab, although previous studies showed that alterations in the ALT and aspartate aminotransferase levels may result in part from interactions with concomitantly administered conventional synthetic DMARDs such as MTX (34,35). These changes in laboratory values are consistent with IL-6 blockade, with reductions in the absolute neutrophil count and increases in the levels of transaminases and lipids being commonly reported with IL-6R antagonists and anti–IL-6 agents (15,17,32,33,35).

At baseline, patients in TARGET had elevated CRP levels and reduced albumin, hemoglobin, and cholesterol levels, consistent with the characteristics observed in patients with moderate-to-severe disease (36,37). Treatment with sarilumab resulted in favorable changes in these parameters, which may be attributable to blockade of IL-6 signaling and subsequent attenuation of the inflammatory response (38).

Approximately three-fourths of the patients in TARGET had been treated unsuccessfully with 1 prior anti-TNF agent; therefore, comparison of response rates according to the number of prior anti-TNF agents is limited. Additionally, the benefit of sarilumab in patients with an inadequate response to biologic therapies with mechanisms distinct from that of TNF blockade was not evaluated in TARGET and remains a topic for further investigation. Radiographic progression was also not assessed in this study. However, 1 study has shown that treatment with a mechanistically distinct agent reduces progression of joint damage in patients with an inadequate response to anti-TNF treatment (39). In addition, evaluation of biomarkers associated with radiographic progression may also prove helpful for effective RA treatment (40).

The TARGET study was not powered to evaluate statistical differences between the 2 sarilumab groups. However, the results indicate a trend toward numerically greater responses with the sarilumab 200 mg every 2 weeks dosage compared with the sarilumab 150 mg every 2 weeks dosage for several end points, including the proportion of patients achieving ACR20 and ACR50 responses, the incidence of patients with changes in the HAQ DI of $\geq$0.22 and $\geq$0.30 units of improvement, and the proportion of patients achieving DAS28-CRP scores of $<$2.6 and $\leq$3.2. A comparable trend was observed in the 52-week MOBILITY study, in which sarilumab at a dosage of 200 mg every 2 weeks led to greater improvements in all co-primary end points, including reduced radiographic progression compared with sarilumab 150 mg every 2 weeks (20). The overall incidence of AEs was similar between the 150 mg and 200 mg groups. There was a numerically higher incidence of SAEs with sarilumab 200 mg compared with sarilumab 150 mg, with no particular event contributing to the difference.

The TARGET population of patients with an inadequate response to anti-TNF treatment consisted of patients from Central and South America, Europe, and Asia. Although the baseline characteristics were similar among treatment groups, higher response rates in the placebo and sarilumab groups were observed in region 2. However, differences between the sarilumab and placebo groups were maintained despite the differential responses in this region; hence, sarilumab was shown to be efficacious irrespective of geographic region.

In conclusion, sarilumab at dosages of 150 mg every 2 weeks and 200 mg every 2 weeks plus conventional synthetic DMARD(s) demonstrated clinical efficacy and improvement in physical function compared with placebo plus conventional synthetic DMARD(s) in patients with active, moderate-to-severe RA who had an inadequate response or intolerance to anti-TNF agents. AEs and changes in laboratory values were consistent with IL-6 signaling blockade and observations from the MOBILITY study. These data indicate that sarilumab is effective and generally well tolerated in patients in whom prior treatment with anti-TNF agents failed.

AUTHOR CONTRIBUTIONS

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

Study conception and design. Fleischmann, van Adelsberg, Lin, Graham, van Hoogstraten.

Acquisition of data. Fleischmann, Lin, da Rocha Castelar-Pinheiro, Brzezicki, Hrycaj, Bauer, Burmester.

Analysis and interpretation of data. Fleischmann, van Adelsberg, Lin, da Rocha Castelar-Pinheiro, Brzezicki, Hrycaj, Graham, van Hoogstraten, Bauer, Burmester.

ROLE OF THE STUDY SPONSOR

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APPENDIX A: ETHICS COMMITTEES AND INSTITUTIONAL REVIEW BOARDS THAT APPROVED THE STUDY

The ethics committees/institutional review boards that approved this study (Trial ID: EFC10832) are as follows: CIEMNOA (Comité independiente de Ética del Noroeste Argentino, Tucumán; Comité de ética en Investigación Clínica (CEIC), Buenos Aires; Comité de ética Independiente del Instituto de Investigaciones Clínicas Zárate, Buenos Aires; Comité de Ética en Investigación DIM Clínica Privada, Buenos Aires; Comité de Ética CAICI CIAP, Santa Fe; Comité de Ética San Isidro, Buenos Aires; Comité de Ética San Isidro, Buenos Aires; Comité de Ética en Investigación, Buenos Aires; Comité de Ética Framingham, Buenos Aires; Comité de Ética en Investigación–Fundación Sanatorio Guëmes, Buenos Aires; Comité Institucional de Ética de Investigación en Salud, Córdoba; Bellberry Limited Human Research Ethics Committee, Eastwood; Ethikkommission der Medizinische Universität Graz, Graz; Comité de Ética em Pesquisa em Seres Humanos do Hospital de clínicas da Universidade Federal do Paraná, Curitiba; Comissão Nacional de Ética em Pesquisa–CONEP, Brasilia; Comité de Ética em Pesquisa em Seres Humanos de Hospital Pedro Ernesto – UERJ, Rio de Janeiro; Comité de Ética em Pesquisa do Hospital Alberto Rassi–HGG, Goiânia; Comité de Ética em Pesquisa do Hospital Universitário da Universidade Federal de Juiz de For a, Juiz de Fora; Comité de Ética em Pesquisa em Seres Humanos - Hospital Pró-Cardiaco/RJ, Rio de Janeiro; University Health Network Research Ethics Board, Toronto; Institutional Review Board Services, Aurora; Comite Ético Científico Servicio de Salud Araucania Sur, Temuco; Institutional Review Board of CGMF, Taipei; Kaohsiung Veterans General Hospital Institutional Review Board, Kaohsiung; Institutional Review Board of CSMUH, Taichung; Comité de Ética de la Investigación - Riesgo De Fractura S.A., Bogotá; Comite de etica en investigaciones del Oriente, Bucaramanga; Comité de Ética en Investigación Servimed E.U., Bucaramanga; Comité de Ética Clínica Fundación Instituto de Reumatología Fernando Chalem, Bogotá; Comité de Etica de la Investigación de CEMDE, Medellin; Eticka komise Uherskohradistske nemocnice, a.s., Uherske Hradiste; Eticka komise IKEM a TN Thomayerova nemocnice, Prague; Eticka komise Revmatologickeho ustavu, Prague; Comité de Bioética (COBI), Quito; Ethikkomission der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen; National Ethics Committee (NEC), Athens; Comité de Ética Independiente ZUGUEME, Guatemala; Comite Independiente de Etica Latin Ethics, Guatemala; Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottsag, Budapest; Helsinki Committee Bnai Zion Medical Center, Haifa; Sheba Medical Center Helsinki Committee, Tel Hashomer, Ramat Gan; Rabin Medical Center Helsinki Committee, Petah Tikva; Comitato Etico Area Vasta Centro, Firenze; Comitato Etico dell'azienda Ospedaliera Universitaria S. Martino di Genova, Genova; Comitato Etico AOU Pol. Vittorio Emanuele, Catania; Comitato Etico Regione Liguria Sezione 2 c/o IRCCS dell'Azienda Ospedaliera Universitaria san Martino - IST, Genova; Comitato Etico Aziendale dell'Azienda Ospedaliero

Universitaria Santa Maria della Misericordia di Udine, Udine; Comitato Etico Locale per la Sperimentazione Clinica dell'A.O. Luigi Sacco, Milano; Severance Hospital, Seoul; Chungnam National University Hospital Institutional Review Board, Daejeon; Lithuanian Bioethics Committee, Vilnius; Comité Independiente de Ética e Investigación del Centro de Estudios de Investigación Básica y Clínica, S.C., Guadalajara; Comité de Ética de la Facultad de Medicina de la UANL y Hospital Universitario "Dr. José Eleuterio González," Monterrey; Comité Bioético para la Investigación Clínica, Mexico; Comite de Bioética Unidad de Investigación en Enfermedades Crónico-Degenativas, SC, Guadalajara; Comité de Etica en Investigación, Monterrey; Comite de Etica e Investigacion del Hospital y Clinica OCA, S.A. de C.V., Monterrey; Comité de Ética en Investigación Christus Muguerza del Parque, Chihuahua; Comité de Ética, Investigación y Bioseguridad Hospital Bernardette, S.C., Guadalajara; Central Health and Disability Ethics Committee, Wellington; Comité Institucional de Etica en Investigación de la Asociacion Benefica Prisma, Lima; Comité de Etica del Hospital Nacional Edgardo Rebagliati Martins, Lima; Comité Institucional de Etica en Investigacion de la Universidad de San Martin de Porres-Clinica CadaMujer (CEIE-USMP-CCC), Lima; Comité de Etica en Investigacion - Hospital Nacional Guillermo Almenara Irigoyen - ESSALUD, Lima; Komisja Bioetycznea przy Okregowej Izbie Lekarskie, Bialystok; Comissão de Ética para a Investigação Clínica (CEIC) Parque da Saúde de Lisboa, Lisboa; Comisia Nationala de Bioetica a Medicamentului si Sos Stefan Cel Mare Nr 19-21, Bucuresti; Federal State Budget Inst "Scientific-Research Ins, Moscow; EC MoH of Russian Federation, Moscow; State Institution St Petersburg Research Inst of Urgent Care named for I. I. Dzhanelidze, St Petersburg; State budgetary medical inst Samara Reg. Clinical, Samara; State budgetary med inst of Moscow, City Clinical, Moscow; LLC City Neurology Center "Sibneyromed," Novosibirsk; Kosice Self-Governing Region Ethics Committee, Kosice; Comite Etico de Investigacion Clinica de la Corporació Sanitària Parc Taulí Fundació Parc Taulí, Barcelona; Edirne Klinik Arastirmalar Etik Kurulu Trakya Universitesi Balkan Yerleskesi Tip Fakultesi Temel, Edirne; Ethics Committee within the Public Institution: Zaporizhia Regional Clinical Hospital under Zaporizhia Regional Council, Zaporizhia; EC Vinnytsia M.I. Pyrohov Regional Clinical Hospital, Vinnytsia; EC within the Public Healthcare Institution: Kharkiv City Clinical Hospital #8, Kharkiv; EC Kyiv Pechersk Dist Central District Outpatient Clinic, Kyiv; EC SI: National Research Centre "M.D. Strazhesko Institute of Cardiology" under NAMS of Ukraine, Kyiv; Compass Independent Review Board, LLC, Mesa; North Mississippi Health Services Institutional Review Board, Tupelo; Human Subjects Committee of the University of Kansas, Kansas City; Stanford University Institutional Review Board Administrative Panel on Human Subjects Research, Palo Alto; University of California, San Diego Human Research Protections Program, La Jolla; Ochsner Clinic Foundation Institutional Review Board, New Orleans; Comité Institucional de Ética de la Investigación en Salud del Niño y del Adulto - Polo Hospitalario, Córdoba; Human Research Ethics Committee (TQEH/LMH/MH) DX: 465 101 The Queen Elizabeth Hospital, Woodville South; Mount Sinai Hospital, Toronto; Health Research Ethics Authority, St John's; Institutional Review Board of Taipei VGH, Taipei; REC of Buddhist Dalin Tzu Chi General Hospital, Chiayi County; REC of NTUH, Taipei; Comite de Ética en Investigación de la Clínica del Country, Bogotá; Joint CUHK-NTEC CREC, Hong Kong; Institutional Review Board of University of Hong Kong, Hong Kong; NTW Cluster Clinical & Research Ethics Committee, Hong Kong; Hadassah Medical Organization Helsinki Committee, Jerusalem; Comitato Etico per la Sperimentazione clinica dei medicinal dell'A.O.U Pisana, Pisa; Kyungpook National University Hospital Institutional Review Board, Daegu; Pusan National University Hospital Institutional Review Board 179 Gudeok-Ro, Seo-Gu, Busan; Chonbuk National University Hospital Institutional Review Board, Jeollabuk-do; Institutional Review Board of Hanyang University Seoul Hospital, Seoul; Institutional Review Board of Daegu Catholic University Medical Center, Daegu; Ethics Committee Faculty Hospital F.D. Roosevelta, Banská Bystrica; NYU Institutional Review Board, New York; Western Institutional Review Board, Olympia.