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ORIGINAL RESEARCH

Immunogenicity of Sarilumab Monotherapy in Patients with Rheumatoid Arthritis Who Were Inadequate Responders or Intolerant to Disease-Modifying Antirheumatic Drugs

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ABSTRACT

Introduction: This open-label study evaluated the immunogenicity, safety, and efficacy of sarilumab monotherapy in patients with active, moderate-to-severe rheumatoid arthritis (RA) and inadequate response or intolerance to prior conventional synthetic disease-modifying antirheumatic drugs.

Methods: Adults with RA (n = 132) were randomized to receive subcutaneous sarilumab (150 [n = 65] or 200 mg [n = 67]) every 2 weeks (q2w) for 24 weeks. Endpoints included incidence of antidrug antibodies (ADAs) at week 24, safety, and efficacy.

Results: Persistent ADAs occurred in eight patients (12.3%) receiving sarilumab 150 mg q2w, seven of whom (10.8%) had neutralizing antibodies (NAbs), and in four patients (6.1%) receiving sarilumab 200 mg q2w, two of whom (3.0%) had NAbs; all exhibited low antibody titers. Infections and neutropenia were the most common adverse events (AEs). There were three serious AEs, no reports of anaphylaxis, and few hypersensitivity reactions (e.g., rash) with no notable differences in hypersensitivity reactions in ADA-positive patients relative to ADA-negative patients. Changes in absolute neutrophil count, alanine aminotransferase level, and platelet count were consistent with interleukin-6 signaling blockade and in agreement with previous observations. At week 24, overall American College of Rheumatology 20%/50%/70% improvement criteria responses were 73.8%/53.8%/29.2%, respectively, with sarilumab 150 mg q2w and 71.6%/50.7%/29.9% with sarilumab 200 mg q2w. No patients with an ADA-positive response showed loss of efficacy.

Conclusions: ADA titers were low and persistent ADAs and NAbs occurred relatively infrequently in both sarilumab dose groups. ADA did not meaningfully impact the safety or efficacy of either dose of sarilumab over 24 weeks.

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PLAIN LANGUAGE SUMMARY

Rheumatoid arthritis is a disease in which cells from the body's immune system attack cells in the joints by mistake. This makes the joints stiff, swollen, and tender. The drug sarilumab, which targets these immune cells, improves symptoms and physical functioning in patients with rheumatoid arthritis. Sarilumab is a type of protein called a monoclonal antibody and may be neutralized by the immune system. When this happens, the drug can work less well, and side effects may occur. There is some evidence that monoclonal antibody drugs are more likely to be attacked when they are given on their own than when they are given in combination with other rheumatoid arthritis drugs. Our study looked at the level of immune attack on sarilumab when it was given on its own, and whether this affected how well sarilumab worked, and whether it produced unwanted side effects. We studied 132 patients with rheumatoid arthritis who received sarilumab given as an injection under the skin every 2 weeks for 24 weeks. Blood tests showed that approximately one in five patients developed some level of immune activity against sarilumab at least once, and approximately one in ten patients showed immune activity against sarilumab more than once. However, importantly, the immune activity against sarilumab did not affect how well sarilumab worked and did not result in more or worse unwanted side effects.

INTRODUCTION

Current guidelines from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) recommend the use of biologic disease-modifying antirheumatic drugs (bDMARDs) in patients with rheumatoid arthritis (RA) and insufficient response to methotrexate (MTX) or other conventional synthetic DMARDs (csDMARDs) [1, 2]. bDMARDs provide significant clinical benefit to patients with RA when used in combination with csDMARDs [3, 4]. However, some patients either are intolerant or have contraindications to csDMARDs that preclude their use. Thus, biologic monotherapy has become an important consideration for patients with active RA [5, 6].

Some data suggest that the incidence of antidrug antibodies (ADAs) with biologic treatment may be greater with monotherapy administration relative to use with concomitant csDMARDs [7–10]. Correlation of ADAs with clinical outcomes is necessary to assess the clinical impact of ADA formation on both safety and efficacy, as not all ADAs may be expected to have clinical consequences. For example, the development of antibodies with neutralizing activity (NAbs), high titers, and/or persistent responses may lead to loss of clinical efficacy or increase the risk of adverse reactions, such as hypersensitivity reactions [11–13]. Low-titer, transient, and non-neutralizing ADAs, in contrast, are unlikely to impact clinical outcomes.

Sarilumab is a human immunoglobulin G1 monoclonal antibody (mAb) that binds specifically to both soluble and membrane-bound interleukin-6 receptors (IL-6Rs) and has been shown to inhibit IL-6-mediated signaling through these receptors. Sarilumab is approved in the United States and Canada for the treatment of moderate-to-severe RA with or without background csDMARDs [14, 15]. Sarilumab 200 mg every 2 weeks (q2w) as monotherapy (MONARCH; NCT02332590) demonstrated superiority to adalimumab monotherapy in reduction of disease activity and improvement in signs and symptoms and physical function in patients with active RA [16]. In the MONARCH monotherapy study (which completed after the study presented here), ADA titers for sarilumab at 200 mg subcutaneous (SC) q2w were low and did not have meaningful clinical consequences. Sarilumab was generally well tolerated, with the most common treatment-emergent adverse events (TEAEs) including infections, neutropenia, injection-site reactions, and increased

transaminases [16–18]. Here we report the findings of the only study to date that has evaluated the immunogenicity of sarilumab monotherapy at both 150 and 200 mg q2w doses as the primary study objective (including the impact of immunogenicity on safety, pharmacokinetics and efficacy as secondary/other objectives) in patients with moderate-to-severe RA.

METHODS

Study Design

The ONE study was a phase 3, 24-week, open-label, multicenter, randomized, parallel-group trial. Study duration was 34 weeks, consisting of up to 4 weeks of screening, 24 weeks of treatment, and 6 weeks of post-treatment follow-up. Randomization was performed centrally, with patients allocated 1:1 to receive SC sarilumab 150 or 200 mg q2w monotherapy. Patients were stratified by region and prior bDMARD use. A placebo group was not included, as the primary objective of the study was to evaluate immunogenicity. Safety and efficacy parameters were the secondary and exploratory endpoints, respectively.

The protocol was approved by Compass IRB, 85206 Mesa, Arizona, USA, and by appropriate local ethics committees/institutional review boards as listed in Supplementary Table 1. All patients provided written informed consent before study participation. 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.

Patient Population

Patients in the ONE study were $\geq$ 18 years of age and fulfilled the ACR/EULAR 2010 classification criteria for RA. Patients were included if they had active disease [defined as swollen joint count $\geq$ 4 of 66 joints assessed, tender joint count $\geq$ 4 of 68 joints assessed and high-sensitivity C-reactive protein (CRP) $\geq$ 4 mg/l at screening] and (per investigator judgment) had an incomplete response or intolerance to continuous treatment with one or a combination of csDMARDs, including MTX, sulfasalazine, leflunomide, or hydroxychloroquine, for $\geq$ 12 weeks.

Key exclusion criteria included: prior treatment with an anti-IL-6 agent, IL-6R antagonist or Janus kinase inhibitor; history of nonresponse to a bDMARD; uncontrolled concomitant diseases; or severe, active, systemic RA. Patients were excluded if treated with tumor necrosis factor (TNF) inhibitors or the non-TNF inhibitors anakinra and abatacept within 28–42 days of randomization, or rituximab within 6 months of randomization. Patients using prednisone > 10 mg/day or equivalent, parenteral or intra-articular glucocorticoids, nonsteroidal anti-inflammatory drugs, or cyclooxygenase-2 inhibitors within 28 days of randomization were also excluded.

Study Treatment

Patients received sarilumab 150 or 200 mg q2w for 24 weeks. SC injections of sarilumab were self-administered or administered by a caregiver into the abdomen, thigh, or upper arm.

Assessments

Blood samples for immunogenicity and pharmacokinetic assessments were collected at baseline and before sarilumab administration at weeks 2, 4, 12, and 24. Samples were assessed for concentrations of functional sarilumab in serum using a validated enzyme-linked immunosorbent assay. Detectable concentrations of functional sarilumab were defined as > 0.313 mg/l (> the lower limit of quantification of the assay). The presence and titers of ADAs and NAbs to sarilumab were assessed using a validated, titer-based, bridging immunoassay. Biotinylated sarilumab and ruthenium-labeled sarilumab were the bridge components, and a mouse anti-sarilumab mAb was the positive control. Immune complexes were captured on streptavidin-coated plates and bridging was detected by electrochemiluminescence on application of a voltage. The following definitions were used for classification:

- Treatment-emergent ADA responses were defined as ≥ 1 post-dose ADA-positive sample in a patient who was ADA negative at baseline.
- Persistent ADA responses were defined as treatment-emergent ADAs detected at ≥ 2 consecutive sampling time points during the TEAE period, where the first and last ADA-positive samples were separated by a period ≥ 16 weeks or if the last measured sample was positive.
- Transient ADA responses were defined as treatment-emergent ADAs that were not detected over a period of ≥ 16 weeks and were not positive in the last measured sample.
- Treatment-boosted ADA responses were defined as a ≥ fourfold increase in titer compared with baseline titer in patients who were ADA positive at baseline.
- Pre-existing ADA responses were defined as positive responses at baseline that did not increase ≥ fourfold in titer in any post-dose samples.
- Antibody titers < 1000 were defined as a low titer.

To assess the potential impact of persistent ADAs on drug concentration, serum concentrations of functional sarilumab for individual patients were plotted over time. In order to provide a meaningful assessment, patients with persistent ADAs were only included in the analysis if they continued in the study until at least week 4.

Patients were monitored for TEAEs, serious AEs (SAEs), treatment discontinuations due to TEAEs, deaths, and clinically significant changes in laboratory tests, including hematology, liver function, plasma lipids, and clinical chemistry profiles. Adverse events (AEs) were reported as described at the Medical Dictionary for Regulatory Activities (version 18.0) preferred-term level.

Exploratory efficacy endpoints [incidence of ACR 20%/50%/70% improvement criteria (ACR20/50/70) response, incidence of 28-joint disease activity score by CRP (DAS28-CRP) < 2.6 at week 24] were assessed as previously described [17, 18]. Patients were automatically categorized as non-responders for all time points beyond the time point they discontinued study treatment (non-responder imputation). Lack and loss of efficacy were also assessed. Lack of efficacy was defined as permanent treatment discontinuation due to lack of efficacy, as determined by the investigator. Loss of efficacy was defined as permanent discontinuation due to a loss of efficacy in patients who had previously achieved an ACR50 or EULAR good response (defined as an improvement of DAS28-CRP > 1.2 units and an overall DAS28-CRP ≤ 3.2, consistent with other studies) [19].

Statistical Analysis

The number of patients included in the study was based on practical considerations and with the aim of a large enough study of adequate duration to provide the data necessary to reliably assess the safety profile of sarilumab monotherapy. The expected ADA positivity (including transient ADAs) was 15–20% based on data from MOBILITY, a study that demonstrated the efficacy and safety of sarilumab in combination with MTX in a population with an inadequate response to MTX [18]. In the current study, a sample size of 120 patients (60 patients per dose group) was chosen to adequately measure a ≥ 50% increase in ADA incidence compared with the historical rate for combination therapy and to allow for a 20% dropout rate.

The randomized population included patients who provided informed consent and were allocated to receive treatment, irrespective of whether treatment was received (n = 132). The safety population consisted of the randomized patients who received the study drug (n = 132). Randomized patients who received ≥ 1 dose of sarilumab and had ≥ 1 post dose evaluable ADA sample were included in the immunogenicity population (n = 131).

No formal statistical comparisons were performed between treatment groups. Patient characteristics and immunogenicity results were presented using descriptive statistics.

RESULTS

Study Population

Of the 201 patients who were screened, 132 were randomized to receive sarilumab 150 mg q2w ($n = 65$) or sarilumab 200 mg q2w ($n = 67$) as monotherapy. Baseline demographics and disease characteristics were similar between treatment groups (Table 1). Mean patient age was 52.4 years, and 80.3% were female. Mean RA duration was 10.5 years. All patients had prior exposure to csDMARDs and 28.8% of patients had prior exposure to bDMARDs. The most commonly used prior csDMARDs were MTX (97.7%), sulfasalazine (34.1%), leflunomide (28.8%), and hydroxychloroquine (28.0%); the most commonly used prior bDMARDs were etanercept (12.1%) and adalimumab (7.6%).

Most patients (87.9%; $n = 116$) completed the study: 89.2% ($n = 58$) in the sarilumab 150 mg q2w group and 86.6% ($n = 58$) in the sarilumab 200 mg q2w group. The most common reason for treatment discontinuation was AEs (7.7% [$n = 5$] with sarilumab 150 mg q2w and 10.4% [$n = 7$] with sarilumab 200 mg q2w, including two patients who discontinued due to pre-treatment AEs; supplementary figure).

Safety by Dose Group and ADA Status

No clinically meaningful differences between the sarilumab 150 and 200 mg q2w groups were observed in incidence of TEAEs (63.1 vs. 68.7%, respectively) or treatment discontinuation due to TEAEs (7.7 vs. 7.5%; Table 2). Infections and neutropenia were the most frequently reported TEAEs. Infections occurred in 27.7% and 32.8% of patients in the sarilumab 150 and 200 mg q2w groups, respectively. No serious infections were reported in the trial. Neutropenia occurred in 12.3% and 17.9% of patients in the sarilumab 150 and 200 mg q2w groups, respectively (Table 2). The incidence of infections was not increased in patients with decreased absolute neutrophil count (ANC). Treatment discontinuations due to TEAEs were generally attributable to infections, neutropenia, injection-site erythema, musculoskeletal disorders [one patient with osteoarthritis and two with RA (all in the 150 mg q2w group)], and increased transaminases. There were three SAEs in the study: one in the sarilumab 150 mg q2w group and two in the sarilumab 200 mg q2w group (Table 2). SAEs included worsening of osteoarthritis, a laceration (finger cut requiring hospitalization due to swelling), and a grade IV neutropenia. There were no cases of gastrointestinal perforation. Squamous cell carcinoma of the skin occurred in one patient (1.5%) receiving sarilumab 200 mg q2w; no malignancies were reported in patients receiving sarilumab 150 mg q2w. No deaths occurred during the study.

Injection-site reactions occurred in 9.2% ($n = 6$) and 3.0% ($n = 2$) of patients with sarilumab 150 and 200 mg q2w, respectively. Two patients with injection-site reactions (one from each sarilumab group) discontinued treatment.

Sarilumab monotherapy resulted in reductions in ANC and platelet count, and in elevations in transaminases (Table 2). Reduction in ANC of ≤ 1.0 giga/l (grade III and IV) was reported in 4.6% and 7.5% of patients receiving sarilumab 150 and 200 mg q2w, respectively (Table 2). Patients with an ANC below the lower limit of normal did not have a higher incidence of infection compared with patients who had a normal ANC. No patients in either sarilumab group had decreases in platelet count to < 100 giga/l or increases in alanine aminotransferase level $> 5 \times$ upper limit of normal.

TEAEs and laboratory abnormalities by ADA status are shown in Supplementary Table 3. Data should be interpreted with caution due to the small number of patients who were ADA-positive and the particularly small number of patients in whom persistent ADAs were detected; however, there was no evidence of an increased incidence of TEAEs or laboratory abnormalities based on ADA status. Safety assessments by ADA status also focused on hypersensitivity reactions (including delayed and acute hypersensitivity reactions, local injection-site reactions and systemic reactions). No cases of anaphylaxis were reported. There were no notable differences in hypersensitivity reactions based on ADA status. The hypersensitivity reactions occurred in three ADA-

Table 1 Summary of patient demographics and baseline disease characteristics

No. of patients (%)[a]	Sarilumab		
	150 mg q2w (*n* = 65)	200 mg q2w (*n* = 67)	Total (*n* = 132)
Female	49 (75.4)	57 (85.1)	106 (80.3)
Age, years, mean (SD)	51.1 (12.7)	53.6 (14.1)	52.4 (13.4)
Race			
White	65 (100)	64 (95.5)	129 (97.7)
Black	0	1 (1.5)	1 (0.8)
Asian	0	1 (1.5)	1 (0.8)
Other	0	1 (1.5)	1 (0.8)
Regions			
Region 1: Czech Republic, Hungary, USA	34 (52.3)	36 (53.7)	70 (53.0)
Region 2: Argentina, Chile	3 (4.6)	5 (7.5)	8 (6.1)
Region 3: Estonia, Poland, Russia	28 (43.1)	26 (38.8)	54 (40.9)
Medications			
Prior bDMARDs	20 (30.8)	18 (26.9)	38 (28.8)
Prior csDMARDs	65 (100)	67 (100)	132 (100)
Duration of RA, years, mean (SD)	9.7 (8.8)	11.2 (9.2)	10.5 (9.0)
Rheumatoid factor positive	49 (75.4)	52 (78.8)[b]	101 (77.1)[c]
Anti-CCP autoantibody positive	49 (77.8)[d]	53 (80.3)[d]	102 (79.1)[e]
DAS28-CRP, mean (SD)	5.8 (1.0)	6.1 (1.0)	5.9 (1.0)
Tender joint count (68 assessed), mean (SD)	24.8 (14.9)	25.6 (12.3)	25.2 (13.6)
Swollen joint count (66 assessed), mean (SD)	17.6 (10.2)	16.5 (8.5)	17.0 (9.4)
HAQ-DI score, mean (SD)	1.4 (0.7)	1.7 (0.7)	1.6 (0.7)
CRP, mg/l, mean (SD)	22.5 (21.8)	25.8 (31.5)	24.1 (27.1)
Positive ADA response at baseline	1 (1.5)	2 (3.0)[b]	3 (2.3)[c]

ADA antidrug antibody, *bDMARD* biologic disease-modifying antirheumatic drug, *CCP* cyclic citrullinated peptide, *CRP* C-reactive protein, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *DAS28-CRP* 28-joint disease activity score by C-reactive protein, *HAQ-DI* Health Assessment Questionnaire–Disability Index, *q2w* every 2 weeks, *RA* rheumatoid arthritis, *SD* standard deviation

[a] Values are provided as number and percentage of patients unless otherwise indicated

[b] $n = 66$

[c] $n = 131$

[d] $n = 63$ for sarilumab 150 mg; $n = 66$ for sarilumab 200 mg

[e] $n = 129$

Table 2 Overview of TEAEs and laboratory abnormalities

No. of patients (%)	Sarilumab	
	150 mg q2w (*n* = 65)	200 mg q2w (*n* = 67)
TEAEs	41 (63.1)	46 (68.7)
SAEs	1 (1.5)	2 (3.0)
TEAEs leading to treatment discontinuation	5 (7.7)	5 (7.5)
TEAEs leading to death	0	0
Most frequent TEAEs (≥ 5% in at least 1 treatment group)		
Infections and infestations	18 (27.7)	22 (32.8)
Upper respiratory tract infection	3 (4.6)	4 (6.0)
Urinary tract infection	2 (3.1)	4 (6.0)
Blood and lymphatic system disorders	8 (12.3)	13 (19.4)
Neutropenia	8 (12.3)	12 (17.9)
Vascular disorders	0	4 (6.0)
Hypertension	0	4 (6.0)
Administration-site conditions	8 (12.3)	4 (6.0)
Injection-site erythema	5 (7.7)	2 (3.0)
Laboratory abnormalities		
Absolute neutrophil count		
≥ 1.0 to 1.5 giga/l	10 (15.4)	6 (9.0)
≥ 0.5 to 1.0 giga/l	3 (4.6)	4 (6.0)
< 0.5 giga/l	0	1 (1.5)
Alanine aminotransferase		
> ULN to 3 × ULN	15 (23.1)	23 (34.8)[a]
> 3 to 5 × ULN	0	1 (1.5)[a]
> 5 × ULN	0	0
Aspartate aminotransferase		
> ULN to 3 × ULN	6 (9.3)	14 (21.2)[a]
> 3 to 5 × ULN	0	1 (1.5)[a]
> 5 × ULN	0	0
Total cholesterol		
< 200 mg/dl	10 (15.4)	11 (16.7)[a]
200 to < 240 mg/dl	28 (43.1)	16 (24.2)[a]
≥ 240 mg/dl	27 (41.5)	39 (59.1)[a]
Platelet count		
≥ 50 to 100 giga/l	0	0
< 50 giga/l	0	0

q2w every 2 weeks, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event, *ULN* upper limit of normal

[a] *n* = 66

negative patients (2.9%) and one ADA-positive patient (3.6%). The events in the ADA-negative patients were rash (two patients) and pruritic rash (one patient). The patient who was ADA-positive and had a hypersensitivity reaction experienced an erythematous, pruritic generalized rash, assessed as mild in intensity, which resolved; this patient continued to receive sarilumab. The ADA-positive response in this patient was non-neutralizing and the event was not concurrent with the rash, occurring > 50 days after the rash had resolved.

Immunogenicity and Pharmacokinetics

During the TEAE period, treatment-emergent ADA incidence was 24.6% (12.3% persistent and 12.3% transient) in the sarilumab 150 mg q2w group (*n* = 16/65) and 18.2% (6.1% persistent and 12.1% transient) in the sarilumab 200 mg q2w group (*n* = 12/66; Table 3); none of the

Table 3 Incidence of ADA-positive assay responses during TEAE period

Anti-sarilumab antibody, *n* (%)	Sarilumab	
	150 mg q2w (*n* = 65)	200 mg q2w (*n* = 66)
ADA-negative patients	49 (75.4)	54 (81.8)
Pre-existing ADA	1 (1.5)	2 (3.0)
Treatment-emergent ADA	16 (24.6)	12 (18.2)
Median peak titer (min–max)	30 (30–240)	30 (30–120)
Transient positive response	8 (12.3)	8 (12.1)
Persistent positive response	8 (12.3)	4 (6.1)
Neutralizing	7 (10.8)	2 (3.0)
Non-neutralizing	1 (1.5)	2 (3.0)

ADA antidrug antibody, *q2w* every 2 weeks, *TEAE* treatment-emergent adverse event

ADA responses were treatment boosted. Antibody titers were low in both dose groups, with a median ADA titer of 30 (lowest titer for the assay). Seven patients (10.8%) in the sarilumab 150 mg q2w group and two patients (3.0%) in the sarilumab 200 mg q2w group had ADAs that were both persistent and had neutralizing activity. None of the patients with transient positive responses had NAbs.

As expected, mean trough concentrations of functional sarilumab in serum increased in a greater than dose-proportional manner (2.34-fold at week 24) from 150 mg q2w to 200 mg q2w doses and accumulated approximately fourfold over time after q2w SC administration of sarilumab. Mean (standard deviation) sarilumab concentrations at steady state (week 12) in ADA-negative and ADA-positive patients were 5.36 (6.25 [*n* = 41]) and 2.10 (2.76 [*n* = 13]) at 150 mg q2w and 15.62 (13.95 [*n* = 45]) and 9.39 (9.26 [*n* = 10]) at 200 mg q2w, respectively. Transient ADAs were not associated with a meaningful difference in sarilumab concentration compared with patients without an ADA response (data not shown). Mean sarilumab levels were lower in patients with persistent ADAs compared with patients without an ADA response. Figure 1 shows individual sarilumab exposure in patients with persistent ADAs by dose, with/without NAbs, and by sarilumab concentration (always detectable/non-detectable).

To assess the potential impact of persistent ADAs on drug concentration, individual spaghetti plots of sarilumab concentration over time are provided in Fig. 1; three of the 12 patients with persistent ADAs were not included as they discontinued prior to week 4 after receiving only one or two doses of study drug [two in the 150 mg q2w group (due to worsening RA and lack of efficacy) and one in the 200 mg q2w group (due to increased transaminases in a patient with a history of the same)] and insufficient data were available for a meaningful assessment. Of the remaining nine patients with persistent antibodies, six received sarilumab 150 mg q2w and three received sarilumab 200 mg q2w. Of the six patients treated with sarilumab 150 mg q2w, five had NAbs; two of these five patients with persistent ADAs and NAbs maintained detectable sarilumab concentrations throughout the dosing period. The patient with persistent ADAs without NAbs also maintained detectable sarilumab concentrations. In the 200 mg q2w group, all three patients (two with and one without NAbs) assessed for a relationship between pharmacokinetics and persistent ADAs maintained detectable sarilumab drug concentrations. In both dose groups, for the patients who had detectable sarilumab concentrations, the drug concentrations were within the ranges observed in ADA-negative patients.

Efficacy by Dose Group and ADA Status

Efficacy was examined as an exploratory endpoint in the ONE study to determine the clinical significance of the development of ADAs. Both sarilumab doses led to a reduction in RA signs and symptoms. The proportions of patients achieving ACR20 (150 mg, 73.8%; 200 mg, 71.6%), ACR50 (150 mg, 53.8%; 200 mg, 50.7%), and ACR70 responses (150 mg, 29.2%; 200 mg, 29.9%; Fig. 2) were similar in the two dose groups and also similar to those

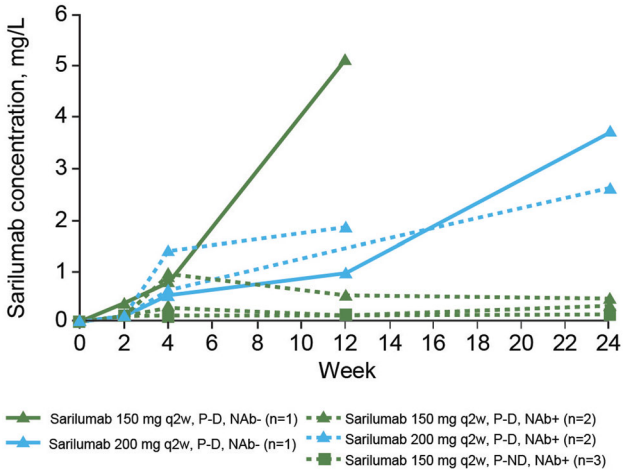

Fig. 1 Detectable (≥ 0.313 mg/l) and non-detectable (< 0.313 mg/l) sarilumab concentrations in patients with persistent ADA-positive response. All six patients shown in the 150 mg q2w group received all doses of study drug. Among the three patients shown in the 200 mg q2w group, two received all doses and one missed a dose on day 140 (before visit 11). Three patients (two in the 150 mg q2w group and one in the 200 mg q2w group) discontinued the study before week 4 after receiving only one or two doses of drug and insufficient data were available to include in the analysis. Note: no patients were classified as non-detectable in the sarilumab 200 mg q2w group. Non-detectable concentrations below the lower limit of quantification (0.313 mg/l) were set to zero. *ADA* antidrug antibody, *NAb* neutralizing antibody, *P-D* persistent ADA positivity with detectable sarilumab concentrations, *P-ND* persistent ADA positivity with non-detectable sarilumab concentrations, *q2w* every 2 weeks

observed in other studies of sarilumab [16–18]. DAS28-CRP < 2.6 was achieved by 43.1% of patients in the sarilumab 150 mg q2w group and 40.3% of patients in the sarilumab 200 mg q2w group.

Development of ADAs had no impact on the efficacy of sarilumab monotherapy (Table 4). One ADA-positive and one ADA-negative patient (both treated with sarilumab 150 mg q2w) showed a lack of efficacy and permanently discontinued therapy. The ADA-positive patient did not exhibit neutralizing or persistent ADAs. No patients exhibited a loss of efficacy after achieving an ACR50 or EULAR good response.

DISCUSSION

Previous studies in patients receiving bDMARDs have demonstrated ADA incidences of up to 60% [20, 21], although considerable variability in ADA rates is often reported for any drug. Dramatic differences in reported immunogenicity can often be attributed to the design and robustness of the assays used to assess ADAs. Assays for ADA assessment, particularly those established before 2004 when new recommendations for the development and validation of immunogenicity assays were first published, may not exhibit the same level of drug tolerance and sensitivity. Work has continued towards enhancing validation of immunogenicity assays, which has resulted in recommended improvements for various assay parameters. In addition, factors such as sampling frequency, detection method, dosing frequency, concomitant medications, and comorbidities can also contribute to variability in the detection of immunogenicity [20, 22]. Similarly, the impact of ADAs is variable but tends to be most clinically relevant in the presence of high ADA titers and neutralizing activity [22, 23]. For these reasons, direct comparison of ADA incidence across clinical programs is not appropriate and can be misleading.

The effects of ADAs and NAbs on efficacy (particularly loss of efficacy) and safety are clinically more relevant parameters than overall antibody incidence rates. Within the sarilumab

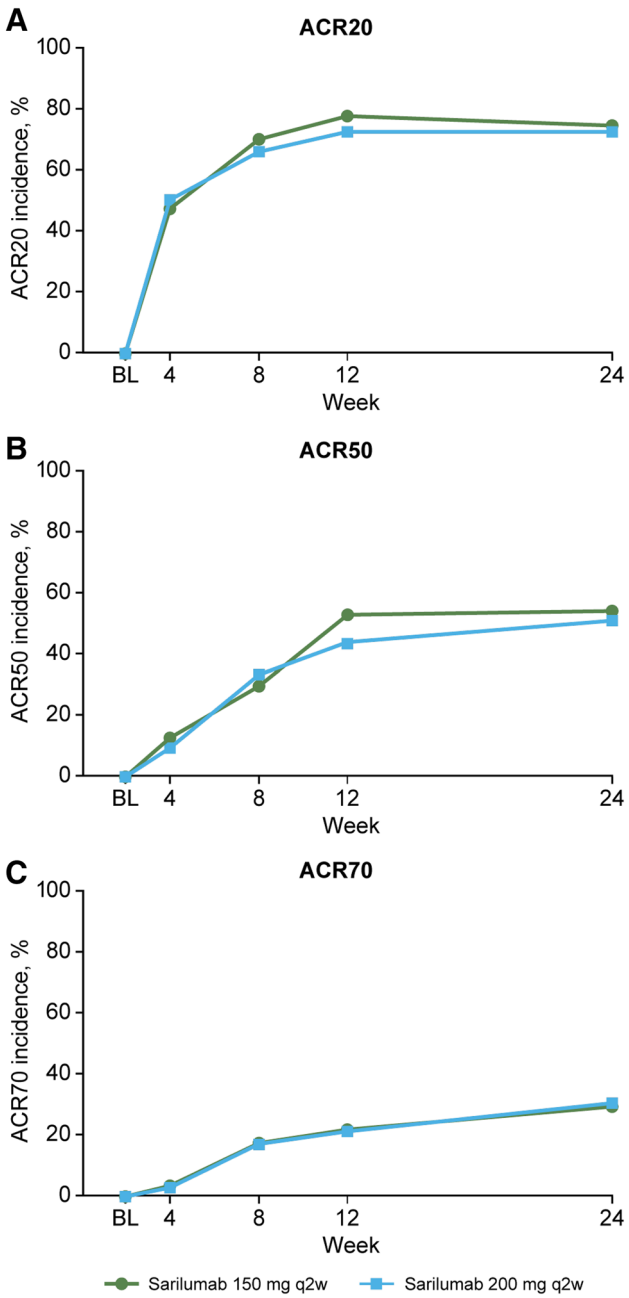

Fig. 2 Proportions of patients achieving ACR20, ACR50, and ACR70 responses over time. *ACR20/50/70* American College of Rheumatology 20%/50%/70% improvement criteria, *BL* baseline, *q2w* every 2 weeks

program, immunogenicity has been consistently evaluated using highly sensitive assays based on recent industry and agency guidelines [22, 23], including the recommended drug tolerance and false-positive rates for the assays.

The magnitude and nature (persistent vs. transient, neutralizing vs. non-neutralizing) of the ADA response are of primary importance. Transient ADAs usually resolve without consequence, whereas the presence of high-titer, persistent, and/or neutralizing ADAs may be associated with poor clinical and safety outcomes [13, 22, 23]. High ADA titers may clear the drug from the circulation and be associated with hypersensitivity reactions [22, 23]. NAbs may not only promote drug clearance but also

Table 4 Patients with lack or loss of efficacy by ADA status

No. of patients (%)	ADA negative (n = 103)	ADA positive (n = 28)
Lack of efficacy	1 (1.0)	1 (3.6)
Permanent treatment discontinuation due to lack of efficacy	1 (1.0)	1 (3.6)
Loss of efficacy	0	0

ADA antidrug antibody

attenuate the clinical response by directly binding to the domains critical for efficacy [12, 22, 24].

Consistent with other programs assessing immunogenicity with monotherapy, including tocilizumab, adalimumab, and infliximab, the rates of ADA formation with sarilumab monotherapy in ONE were higher than those observed previously with combination therapy; the incidence of ADAs with sarilumab was slightly higher with monotherapy for 150 mg q2w than the rates reported in MOBILITY and TARGET (Supplementary Table 2) [16–18]. It is important to note, however, that the incidence of ADAs is dependent on the duration of exposure; MOBILITY was a 52-week study compared with the 24-week ONE, MONARCH, and TARGET studies. Persistent ADA responses observed in the larger MONARCH monotherapy study (n = 369) comparing sarilumab monotherapy at 200 mg q2w with adalimumab monotherapy at 40 mg q2w were similar to rates seen in the studies of sarilumab in combination with another csDMARD (MOBILITY, TARGET).

As evidence of the lack of clinical consequence of ADAs in ONE, safety (including hypersensitivity) and efficacy of sarilumab in this trial were consistent with results observed in the controlled clinical trials (monotherapy: MONARCH [n = 369]; combination therapy: MOBILITY [n = 1197] and TARGET [n = 546]) [17, 18]. Although the development of persistent ADAs and NAbs was associated with lower circulating sarilumab levels, no correlation was observed between ADA development and either AEs or loss of efficacy in patients who had previously achieved ACR50 or EULAR good response (improvement of DAS28-CRP > 1.2 units and an overall DAS28-CRP ≤ 3.2). The ONE study was not designed to evaluate efficacy (and lack or loss of efficacy) in terms of the Clinical Disease Activity Index, and it would have been interesting to understand whether using this composite index (which does not incorporate an acute-phase response) showed consistent results with those reported. We also appreciate that MONARCH is a 24-week study and longer study periods may be required to confirm our findings regarding loss of efficacy longer term. Of note, MOBILITY (a 52-week study) also found the presence of ADA was not associated with hypersensitivity reactions or discontinuations due to lack of efficacy [18]. In addition, development of a positive ADA response is continuing to be evaluated in open-label follow-up studies.

Fully human mAb therapeutics are less likely to generate an immune response than animal-derived antibodies or humanized antibodies [25]. However, even a fully human mAb has unique sequences in the idiotypic antigen-binding domain or post-translational modifications that might be recognized by the immune system of the patient [25, 26]. Also, fully human mAbs that bind to targets on the cell surface, particularly on cells involved in the immune system, may undergo antigen internalization and presentation by target cells resulting in an immune response and the generation of anti-drug antibodies [25].

It is common for lower drug levels to lead to increased detection of ADAs in the ADA assay and for ADAs to interfere with the drug measurement. Thus, although patients receiving sarilumab 150 mg q2w who exhibited persistent antibodies with NAbs were most likely not to have detectable concentrations of sarilumab in the drug assay, sarilumab may still have been present in the circulation. Consequently, the best way to assess the potential impact of ADAs is to examine results from individual patients. Based on this analysis, the data from the sarilumab program indicate that the development of ADAs with monotherapy does not lead to increased risk of loss of efficacy,

hypersensitivity, or anaphylaxis for those patients who are ADA-assay positive. A limitation of this study, however, is its uncontrolled open-label design and smaller sample size compared with MONARCH, where sarilumab 200 mg q2w was compared with adalimumab 40 mg q2w in a blinded fashion. It is also important to acknowledge that the study collected limited information on the reason for discontinuation of the DMARD before inclusion in ONE (simply that investigators considered the patients to have had an incomplete response with, or been intolerant to, continuous treatment with one or more csDMARDs) and therefore patient selection bias cannot be excluded completely.

CONCLUSIONS

In conclusion, results from this study demonstrate that the emergence of ADAs to sarilumab administered as monotherapy in patients with RA did not alter the safety or efficacy of sarilumab 150 or 200 mg q2w. Furthermore, sarilumab monotherapy led to reduction in the signs and symptoms of RA, measured by incidence of ACR20/50/70 responses and DAS28-CRP < 2.6, with responses comparable to those observed when sarilumab was administered with concomitant MTX or other csDMARDs. These results support the use of sarilumab as monotherapy in patients with RA who cannot tolerate concomitant csDMARDs or in whom concomitant csDMARDs are contraindicated. As it has been estimated previously that approximately one-third of patients with RA receive biologics as a monotherapy, the availability of a drug that is effective as monotherapy for those patients who cannot, or will not, use MTX is of value and will contribute to fulfilling an unmet medical need in RA [5, 27, 28].

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Compliance with Ethics Guidelines. The protocol was approved by Compass IRB, 85206 Mesa, Arizona, USA, and by appropriate local

ethics committees/institutional review boards as listed in Supplementary Table 1. All patients provided written informed consent before study participation. 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.

Data Availability. Qualified researchers may request access to patient level data and related study documents including clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.clinicalstudydatarequest.com.

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