Effects of Sarilumab on Patient-Reported Impact of Rheumatoid Arthritis Using the Rheumatoid Arthritis Impact of Disease Scale

Laure Gossec, Vibeke Strand, Clare Proudfoot, Chieh-I Chen, Sophie Guillonneau, Toshio Kimura, Hubert van Hoogstraten, Erin Mangan, and Matthew Reaney

L. Gossec, MD, PhD, Sorbonne Université and Rheumatology Department, Hôpital Pitié Salpêtrière; V. Strand, MD, Stanford University; Clare Proudfoot, PhD, Novartis (formerly of Sanofi); Chieh-I Chen, MPH, Regeneron Pharmaceuticals, Inc.; Sophie Guillonneau, MSc, Sanofi; Toshio Kimura, MSc, Regeneron Pharmaceuticals, Inc.; Hubert van Hoogstraten, MD/PhD, Sanofi; Erin Mangan, PhD, Regeneron Pharmaceuticals, Inc.; Matthew Reaney, MSc, Sanofi.

[1]*Sorbonne Université, Institut Pierre Louis d'Epidémiologie et de Santé Publique (UMRS 1136), GRC-UPMC 08 (EEMOIS), Paris, France;* [2]*Rheumatology Department, Hôpital Pitié Salpêtrière, AP-HP, Paris, France*; [3]Stanford University, Palo Alto, CA, USA; [4]Formerly of Sanofi, Guildford, UK; [5]Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA; [6]Sanofi, Paris, France; [7]Sanofi, Bridgewater, NJ, USA; [8]Sanofi, Guildford, UK

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Address correspondence to Matthew Reaney, Sanofi, One Onslow Street, Guildford, Surrey, GU1 4YS, UK. Tel: 44 (0) 1483 55 4077; Fax: 44 (0) 1483 535 432; E-mail: matthew.reaney@sanofi.com

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ABSTRACT

Objective. The impact of rheumatoid arthritis (RA) symptoms on patients' lives is significant. This study evaluated the effect of sarilumab on patient-perceived impact of RA using the 7-domain RA Impact of Disease (RAID) scale.

Methods. Two phase III, randomized, controlled trials of sarilumab in patients with active, long-standing RA were analyzed: sarilumab 150 mg and 200 mg twice-weekly plus conventional synthetic disease-modifying antirheumatic drugs (+csDMARDs) versus placebo+csDMARDs [TARGET (NCT01709578)]; sarilumab 200 mg versus adalimumab 40 mg monotherapy (MONARCH [NCT02332590]). Least squares mean (LSM) differences in RAID total score (range 0–10), and 7 key RA symptoms, including pain and fatigue (baseline to weeks 12 and 24), were compared. 'Responders' by RAID total score were defined by improvements from baseline ≥Minimal Clinically Important Difference (MCID), and ≥Patient Acceptable Symptom State (PASS) at end point.

Results. Sarilumab 150 mg and 200 mg+csDMARDs were nominally superior ($p<0.05$) versus placebo+csDMARDs and 200 mg versus adalimumab 40 mg in LSM differences for RAID total score at weeks 12 (–0.93 and –1.13; –0.49, respectively) and 24 (–0.75 and –1.01; –0.78), and all impacts of RA (except functional impairment in MONARCH week 12). Effects were greater in physical domains (e.g., pain) than mental domains (e.g., emotional well-being). More patients receiving sarilumab versus placebo or adalimumab reported improvements ≥MCID and PASS in total RAID scores at both assessments.

Conclusion. Based on the RAID, sarilumab+csDMARDs or as monotherapy reduced the impact of RA on patients' lives to a greater extent than placebo+csDMARDs or adalimumab monotherapy.

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Patients with rheumatoid arthritis (RA) experience a variety of signs and symptoms, and report significant physical and psychological impacts of living with this condition[1, 2, 3]. Quantifying key clinical symptoms and impacts of RA from the patient perspective, in addition to evaluating clinical markers, is therefore vital for comprehensively understanding the disease and evaluate its treatment, in line with current international consensuses and guidelines[4, 5, 6, 7].

The patient perspective can be feasibly and systematically collected through administration of patient-reported outcomes (PRO). Using well-defined and reliable PROs, in addition to physician-reported and laboratory data, is essential for drawing comprehensive conclusions regarding RA treatment outcomes. The RA Impact of Disease (RAID) scale is an internationally validated, composite PRO measure specifically designed for use in RA[8, 9, 10, 11, 12]. RAID evaluates seven domains, each containing a single item, including 2 key symptoms (severity of pain and fatigue), and 5 primary impacts (coping, emotional and physical well-being, functional impairment and sleep). It also provides additional information for assessment of RA, such as coping and emotional well-being, compared with traditionally evaluated PROs of patient global assessment of disease activity, pain and physical functioning[8, 13, 14, 15].

Sarilumab is a recently approved human monoclonal antibody directed against both soluble and membrane-bound interleukin-6 receptor α (anti-IL-6Rα). The RAID scale was administered to patients in 2 phase III randomized controlled trials (RCTs) of sarilumab: TARGET [NCT01709578][16] and MONARCH [NCT02332590][17]. Change from baseline in RAID score was a secondary end-point in both the TARGET and MONARCH RCTs.

TARGET compared the efficacy and safety of subcutaneous (SC) sarilumab 150 mg and 200 mg every 2 weeks (q2w) versus placebo plus conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) in patients with moderate-to-severely active RA intolerant of or with inadequate response to ≥1 tumor necrosis factor inhibitors (TNF-IR)[16]. The co-primary end points in TARGET were the proportion of patients achieving American College of Rheumatology ≥20% (ACR20) responses[7] at week 24, and change from baseline in physical function assessed by the Health Assessment Questionnaire-Disability Index (HAQ-DI)[18] at week 12.

MONARCH compared the efficacy and safety of sarilumab SC 200 mg q2w monotherapy versus adalimumab SC 40 mg q2w monotherapy in patients with active RA who discontinued treatment with MTX[17]. The primary efficacy end point in MONARCH was change from baseline in the 28-joint Disease Activity Score using erythrocyte sedimentation rate (ESR) (DAS28-ESR) at week 24. In both RCTs, sarilumab showed superiority over placebo or adalimumab reducing signs and symptoms of RA and improving physical function and its safety profile was consistent with IL-6R blockade[16].

The RAID is recognized by researchers, patients, and organizations such as EULAR[19] and OMERACT[20] as a promising instrument since it was developed with patient input and addresses all the key issues for patients with RA. However, as a relatively new scale, RAID has so far only been applied in few clinical trials[15, 21] other than TARGET[16] and MONARCH[17], with the publications for these trials only describing high-level data on the RAID. Thus, the present paper is interesting because it contributes to further validating the RAID score.

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The objective of the present analysis was, thus, to assess the effects of sarilumab treatment in combination with csDMARD or monotherapy on patient-reported impact of RA by the RAID scale.

PATIENTS AND METHODS

Data were collected from 2 phase III RCTs of sarilumab, TARGET and MONARCH; details of which have been published previously[16, 17]. Both trials enrolled adult patients fulfilling the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria for RA[22]. In TARGET, TNF-IR patients with moderate-to-severely active RA were included if disease duration was ≥6 months. Patients with uncontrolled concomitant diseases, significant extra-articular manifestations of RA, functional class IV RA, other inflammatory diseases, current/recurrent infections or receiving prednisone were excluded.

In MONARCH, moderate-to severely active RA patients with ACR class I–III functional status[23] were enrolled if they had disease duration ≥3 months, and no prior use of bDMARDs. Eligible patients were randomized to sarilumab SC 200 mg plus placebo q2w or adalimumab SC 40 mg plus placebo q2w for 24 weeks. After 16 weeks, patients without ≥20% improvement in tender and swollen joint counts in the sarilumab group were switched to once-weekly adalimumab or matching placebo[17].

RAID scale. The RAID scale consists of 7 single-item domains, each rated by patients on an 11-point numeric rating scale from 0 (best) to 10 (worst)[8]. There are 2 symptom domains, pain and fatigue, and 5 impact domains, consisting of functional impairment, emotional well-being, physical well-being, quality of sleep, and ability to cope. The domains can be reported separately[14] and as a total score, which is a continuous variable ranging from 0 (best) to 10 (worst); lower scores are indicative of less impact of disease. In the total RAID score, each domain is given a specific weight reflecting its importance to patients (e.g., more given to pain, fatigue and functional impairment). Weights were obtained from international studies and are as

follows: pain 0.21, functional disability 0.16, fatigue 0.15, and sleep problems, emotional well-being, physical well-being and coping all 0.12[8, 10]. The RAID scale has been psychometrically validated at an international level[8, 10, 12, 24].

***Statistical analyses*.** Least squares mean (LSM) differences from baseline in total RAID and domain scores were analyzed with a mixed model for repeated measures, including treatment, region, visit, and treatment-by-visit interaction (and number of prior TNFi in TARGET) as fixed effects and baseline as a covariate.

Post-hoc analyses were conducted to identify 'responders' in the total RAID score. Three 'responder' definitions were used. Two were based on an established Minimal Clinically Important Difference (MCID) from baseline. This was previously defined by different techniques using data from 108 patients receiving TNFi treatment for active RA, who were evaluated at screening and baseline, then after 4 and 12 weeks of treatment[11]. The reliability of the overall RAID score, and various possible improvement thresholds proposed in the rheumatology scientific literature (e.g., improvements of at least 1, 2 or 3 points in total RAID score (total range 0–10 points), and relative changes ≥20%, 30% and 50% from baseline)[24, 25] were evaluated. The reliability of the RAID score between screening and baseline was found to be high: intra-class coefficients of correlation 0.85 (95% CI 0.79–0.90), with smallest detectable differences and smallest detectable changes of 1.8 and 1.3, respectively. The 2 optimal MCID thresholds were identified as a 3-point reduction in total RAID score from baseline, or a relative improvement of 50% in total RAID score. A patient was defined as a responder if they reported improvements from baseline ≥MCID. A third responder definition was based on a Patient Acceptable Symptom State (PASS), defined as a score ≤3[11]. Patients who discontinued therapy

or required rescue medication prior to achieving responder end points were classified as nonresponders[26, 27, 28, 29].

In TARGET, RAID was positioned after the break in the hierarchy used to control for multiple testing and, therefore, statistical significance cannot be claimed; other analyses were conducted *post hoc*. In MONARCH, RAID was not included in the hierarchy. Therefore, to aid interpretation, statistical comparisons between treatment groups (to test for nominal significance) were supplemented by between-group effect size analyses (standardized mean differences) using Cohen's *d* Rule for Change Interpretation: important: $d \leq -0.8$; moderate: $-0.8 < d \leq -0.5$; and small: $-0.5 < d \leq -0.2$[30].

RAID scores were separately evaluated in each trial at baseline, week 12 and week 24. For missing data at the item level, an imputation using the mean of the 6 other items was used.

Ethics approval. The analyses carried out in this study were conducted on data from two previously published randomized controlled trials of sarilumab, TARGET (NCT01709578) and MONARCH (NCT02332590)[16, 17]. The protocols for both of these studies were approved by the appropriate ethics committees/institutional review boards, and each patient provided written informed consent before participation in the studies. The studies were conducted in compliance with institutional review board regulations, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki[16, 17].

RESULTS

***Analysis population*.** Overall, 546 patients from TARGET and 369 from MONARCH were included in the analysis (Table 1). Between-group baseline demographics were generally comparable within each study; however, in MONARCH, disease duration was longer in the sarilumab group versus the adalimumab group [mean years, standard deviation (SD) 8.1 (8.1) versus 6.6 (7.8), respectively]. Between studies, mean disease duration in MONARCH was shorter than in TARGET (mean 7.3 vs mean 12.1 years). Baseline RAID scores were generally comparable across all groups within the individual RCTs, ranging from a mean (SD) of 6.5 (2.0) to 6.8 (1.8) in TARGET[31] and 6.4 (2.0) to 6.7 (1.7) in MONARCH[17] (Table 1). All other demographics, including age, sex and race, were relatively comparable among the patients in the 2 studies.

Changes in RAID score from baseline. Total score: LSM differences in RAID total scores were greater with sarilumab versus placebo in TARGET at weeks 12 (–0.93 and –1.13, respectively, for sarilumab 150 mg and 200 mg versus placebo; nominal $p < 0.0001$) and 24 (–0.75 and –1.01, respectively, for sarilumab 150 mg and 200 mg vs placebo; nominal $p < 0.01$). LSM differences in RAID total score were also greater with sarilumab versus adalimumab in MONARCH at weeks 12 (–0.49 for sarilumab 200 mg vs adalimumab; nominal $p < 0.05$) and 24 (–0.78 for sarilumab 200 mg vs adalimumab; nominal $p < 0.001$) (**Figure 1**). Between-group effect sizes for RAID total scores (**Figure 2**) met thresholds for small to moderate levels of importance by Cohen's *d* Rule for Change Interpretation in both sarilumab dose groups versus placebo at weeks 12 and 24 (TARGET), and in the sarilumab 200 mg group versus adalimumab at week 24 (MONARCH)[30].

Domain scores: Changes from baseline in individual domain scores were significantly greater with sarilumab versus placebo for differences between groups (all nominal $p < 0.05$ except sleep domain; see **Figure 3**). In MONARCH, sarilumab treatment demonstrated greater improvement compared with adalimumab at week 12 only in the functional impairment domain, and in all domains by week 24. Moderate benefits were reported in the pain domain at week 12 (effect sizes of 0.54 and 0.58 for sarilumab 150 mg and 200 mg, respectively, vs placebo) and week 24 in TARGET (effect sizes of 0.54 and 0.68 for sarilumab 150 mg and 200 mg, respectively, vs placebo) (all nominal $p < 0.05$). In addition, most other domains (other than sleep) met thresholds for small importance at week 24 in both studies[30].

Responder analyses, MCID ≥3: In TARGET, greater proportions of patients in the sarilumab 150 mg and 200 mg groups versus placebo were responders defined by an MCID ≥3 (nominal $p \leq 0.0001$ at week 12 for both doses; nominal $p \leq 0.01$ and nominal $p \leq 0.0001$ for sarilumab 150 mg and 200 mg, respectively, at week 24) (Figure 4A). In MONARCH, a greater proportion of the sarilumab 200 mg group versus adalimumab were responders (nominal $p \leq 0.01$ at both weeks 12 and 24) (Figure 4A).

MCID ≥50%: There were greater proportions of responders in both dose groups of sarilumab in TARGET than placebo (nominal $p \leq 0.001$ at week 12); nominal $p \leq 0.01$ and nominal $p \leq 0.001$ for sarilumab 150 mg and 200 mg, respectively, at week 24). In MONARCH greater improvement with sarilumab 200 mg versus adalimumab was reported at week 24 (nominal $p \leq 0.05$) (Figure 4B).

PASS: Absolute total RAID scores ≤3 were reported by both sarilumab dose groups versus placebo in TARGET at weeks 12 (sarilumab 150 mg, nominal

p ≤ 0.01; sarilumab 200 mg, nominal p ≤ 0.001) and 24 (sarilumab 200 mg, nominal p ≤ 0.05; sarilumab 200 mg, nominal p ≤ 0.001). In MONARCH at week 24, a greater proportion of patients receiving sarilumab 200 mg than adalimumab were defined as responders (nominal p ≤ 0.01), and in (Figure 4C).

DISCUSSION

The benefits of sarilumab treatment as combination therapy with csDMARDs or as monotherapy across a range of PROs have been previously reported in MTX-IR and TNF-IR populations, including patient global assessment of disease activity, pain, physical function, fatigue, and general health status. Based on the patient-reported RAID scale collected in the TARGET and MONARCH RCTs, data indicate that sarilumab SC 150 mg or 200 mg q2w as combination therapy with a csDMARD or as 200 mg monotherapy reduced the impacts of RA on patients' lives to a greater extent than placebo+csDMARD or adalimumab SC 40 mg q2w or once weekly monotherapy. Mean baseline scores ranged from 6.4 to 6.8, indicating a high impact of disease in these trial populations. In both the TARGET and MONARCH RCTs, the benefits of sarilumab treatment on symptoms and impact of disease were clinically meaningful assessed by two definitions of MCID and by PASS, with differential effects compared with placebo or adalimumab across the majority of RAID domains (with exception of sleep for sarilumab vs placebo in the TARGET study), with marked improvements in RAID total scores and domains of pain and functional impairment across all sarilumab treatment groups.

The relatively new RAID scale has so far only been applied in 1 other clinical trial[15], a smaller, open-label, single-arm study of etanercept 50 mg/wk. In this study 56% of 120 patients with active RA reported total RAID scores ≤3.0 at week 12, indicating reduced disease impact from baseline[15]. In comparison, patients in TARGET and MONARCH had longer disease duration and higher baseline RAID scores than in the etanercept study[15, 16, 17].

In these 2 larger RCTs, 35% sarilumab-treated patients in TARGET at week 12 and 36% at week 24 reported RAID scores ≤3, in MONARCH it was 41% at week 24.

Newer PROs such as the RAID scale are demonstrating the additional importance of evaluating multidimensional patient outcomes, with content and construct validity, responsiveness, and precision. It is now widely recognized that PROs should reflect what is important for patients, and that they should be developed with patient input[32, 33]. As RAID was developed by a EULAR international task force of both clinicians and patients to provide a single instrument that integrates all relevant patient domains, with relevance in different disease states, countries and cultures, it is designed to better quantify the experience of living with RA. Several studies have shown that the domains assessed in RAID are applicable and important for patients[8, 10, 12, 25, 34]. The advantage of sarilumab treatment over adalimumab and placebo improving RAID domains in these trials offers important information for physicians to consider in the context of shared treatment decision-making[35].

Pain, fatigue, sleep disturbance and ability to cope are all symptoms that are of importance to patients with RA, but not all (e.g., sleep and ability to cope) are routinely assessed in RA RCTs, or even in clinical practice[36]. RAID is unique in that it not only assesses patient-reported symptoms such as pain, but also fatigue, sleep disturbance and coping. Fatigue, frequently reported in RA can severely impact all aspects of health-related quality of life, with a multifactorial origin, not just inflammation but personal factors and psychological distress as well[37].

In this analysis, some differences in responses to treatment were noted: sleep

and coping were less responsive than other domains, suggesting these may be less amenable to short-term treatment effects of DMARDs and biologics than, for example, pain. It appears that sleep and coping in particular, are less accessible to biologic treatment than other patient-reported domains of impact. This raises the question whether these aspects of HRQoL are less directly linked to the inflammatory process, than for example pain.[14] This is consistent with findings from other RCTs of DMARD with other mechanisms of action where sleep responsiveness in particular has been reported as less than other PROs[14, 38].

Our finding must be considered in light of some study limitations. While the RAID data were included in the statistical hierarchy in MONARCH and TARGET, results were after the break in the hierarchy; therefore, p-values were not controlled for multiplicity, and are nominal. Hence, we applied multiple approaches to assess the clinical relevance of the observed results, including Cohen's *d*, responder analysis using 2 different MCID definitions and PASS. All of the approaches consistently indicated clinically meaningful improvements across the RAID domains. A further exploration of the relationships of the endpoints with RAID, and any added value of RAID within the context of a clinical trial, is warranted for a separate study. Nonetheless, despite the relative novelty of the RAID scale, a range of tests support interpretation of the present results. In addition, as adalimumab is usually used as combination therapy, the added value of the current paper should not be seen as a comparison with adalimumab only, but also as further validating a recent outcome measure, the RAID.

While the extreme burden on RA patients caused by their joint damage is widely recognized[39, 40, 41] other manifestations of this systemic disease including

multiple comorbidities and psychosocial outcomes continue to be revealed.[42, 43] Hence, in addition to the clinical markers of disease activity which are unequivocally necessary for informing RA treatment decisions, assessing improvement on PROs including HRQoL reveals the ultimate benefit of treatment in reducing patient burden.[39, 40, 44] The objective of the RAID scale is to provide a comprehensive assessment of the effects of treatment on patient burden, and from their perspective.

As a relatively new measure, RAID has yet to be widely applied in either RA RCTs or clinical practice settings. Although its use is increasing, its further inclusion in large prospective studies will provide more evidence of the scale's sensitivity[8], assessment of acceptable levels of missing data and MCID/PASS definitions, and data from clinical practice settings in diverse patient populations will indicate its generalizability.

In conclusion, the present analyses indicate that RAID efficiently evaluated the benefits of sarilumab treatment on patient-reported impact of RA in both TARGET and MONARCH RCTs.

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Figure 1. Mean change in total Rheumatoid Arthritis Impact of Disease scores from baseline in TARGET (+ csDMARD) and MONARCH (monotherapy).

*Nominal p ≤ 0.05; **Nominal p ≤ 0.01; ***Nominal p ≤ 0.001; ****Nominal p ≤ 0.0001 all versus placebo (TARGET) or adalimumab (MONARCH).

csDMARD: conventional synthetic disease-modifying antirheumatic drug; qw: once weekly; q2w: every 2 weeks; SC: subcutaneous; SD: standard deviation.

Figure 2. Between-group effect sizes on Rheumatoid Arthritis Impact of Disease total score – sarilumab 150 mg or 200 mg versus placebo (TARGET: + csDMARD) or adalimumab (MONARCH: monotherapy).

Cohen's *d* Rule for Change Interpretation: important: $d \leq -0.8$; moderate: $-0.8 < d \leq -0.5$; and small: $-0.5 < d \leq -0.2$ (25).

*Nominal p ≤ 0.05; **Nominal p ≤ 0.01; ***Nominal p ≤ 0.001; ****Nominal p ≤ 0.0001 all versus placebo (TARGET) or adalimumab (MONARCH) for the difference between the groups in the least squares mean change from baseline.

csDMARD: conventional synthetic disease-modifying antirheumatic drug; qw: once weekly; q2w: every 2 weeks; SC: subcutaneous.

Figure 3. Between-group effect sizes on Rheumatoid Arthritis Impact of Disease domain scores in TARGET - sarilumab 150 mg +csDMARD or 200 mg +csDMARD versus placebo and in MONARCH – monotherapy with sarilumab 200 mg versus adalimumab 40 mg: A) week 12, B) week 24.

Cohen's *d* Rule for Change Interpretation: important: $d \leq -0.8$; moderate: $-0.8 < d \leq -0.5$; and small: $-0.5 < d \leq -0.2$ (25).

*Nominal p ≤ 0.05; **Nominal p ≤ 0.01; ***Nominal p ≤ 0.001; all versus placebo for the difference between the groups in the least squares mean change from baseline.

csDMARD: conventional synthetic disease-modifying antirheumatic drug.

Figure 4. Proportion of patients in TARGET (+ csDMARD) and MONARCH (monotherapy) who: (A and B) reported improvements in RAID scores ≥MCID; (C) reached a Patient Acceptable Symptom State of 3 or lower.

Nominal p ≤ 0.05; **Nominal p ≤ 0.01; ***Nominal p ≤ 0.001; ****Nominal p ≤ 0.0001 all versus placebo (TARGET) or adalimumab (MONARCH).

csDMARD: conventional synthetic disease-modifying antirheumatic drug; MCID: Minimal Clinically Important Differences; qw: once weekly; q2w: every 2 weeks; RAID: Rheumatoid Arthritis Impact of Disease; SC: subcutaneous.

Table 1. Patient demographics and disease characteristics.

	TARGET study[17]			MONARCH study[16]	
	Placebo + csDMARD (n = 181)	**Sarilumab SC 150 mg q2w + csDMARD (n = 181)**	**Sarilumab SC 200 mg q2w + csDMARD (n = 184)**	**Adalimumab SC 40 mg q2w/qw (n = 185)**	**Sarilumab SC 200 mg q2w (n = 184)**
Age, years, mean ± SD	51.9 ± 12.4	54.0 ± 11.7	52.9 ± 12.9	53.6 ± 11.9	50.9 ± 12.6
Female, n (%)	154 (85.1)	142 (78.5)	151 (82.1)	150 (81.1)	157 (85.3)
Caucasian, n (%)	124 (68.5)	134 (74.0)	130 (70.7)	164 (88.6)	171 (92.9)
Duration of RA, years, mean ± SD	12.0 ± 10.0	11.6 ± 8.6	12.7 ± 9.6	6.6 ± 7.8	8.1 ± 8.1
Background[a] or prior[b] csDMARDs					
Methotrexate	158 (87.3)	154 (85.1)	156 (84.8)	185 (100%)	184 (100%)
Leflunomide	17 (9.4)	17 (9.4)	18 (9.8)	45 (24.3)	42 (22.8)
Sulfasalazine	5 (2.8)	12 (6.6)	15 (8.2)	44 (23.8)	59 (32.1)
Hydroxychloroquine	10 (5.5)	14 (7.7)	13 (7.1)	43 (23.2)	41 (22.3)
Baseline DAS28-CRP, mean ± SD	6.2 ± 0.9	6.1 ± 0.9	6.3 ± 1.0	6.0 ± 0.9	6.0 ± 0.9
Baseline RAID scores, mean ± SD					
Total score	6.6 ± 2.0	6.5 ± 2.0	6.8 ± 1.8	6.4 ± 2.0	6.7 ± 1.7
Pain	7.3 ± 1.9	7.2 ± 2.0	7.5 ± 1.8	6.9 ± 2.1	7.2 ± 1.9
Functional impairment	7.0 ± 2.1	6.9 ± 2.0	7.2 ± 1.9	6.7 ± 2.2	6.9 ± 2.1

Fatigue	6.6 ± 2.5	6.6 ± 2.5	6.9 ± 2.3	6.4 ± 2.4	6.7 ± 2.1
Sleep difficulties	6.4 ± 2.9	5.8 ± 2.9	6.1 ± 2.8	5.9 ± 2.8	6.1 ± 2.7
Physical well-being	6.8 ± 2.1	6.5 ± 2.2	6.8 ± 2.2	6.5 ± 2.3	6.9 ± 2.0
Emotional well-being	5.9 ± 2.7	6.0 ± 2.6	6.1 ± 2.5	6.0 ± 2.6	6.4 ± 2.4
Coping	5.7 ± 2.6	5.8 ± 2.5	6.2 ± 2.5	5.8 ± 2.6	6.1 ± 2.3

[a]Background csDMARDSs used in TARGET; concomitant use of 2 or 3 csDMARDs was reported by 6.4% and 0.7% of patients, respectively.

[b]Prior csDMARDs other than methotrexate used in MONARCH: named csDMARDs were included if used in >5% of the population.

DAS28-CRP: 28-joint Disease Activity Score using C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; qw: once weekly; q2w: every 2 weeks; RA: rheumatoid arthritis; SC: subcutaneous; SD: standard deviation

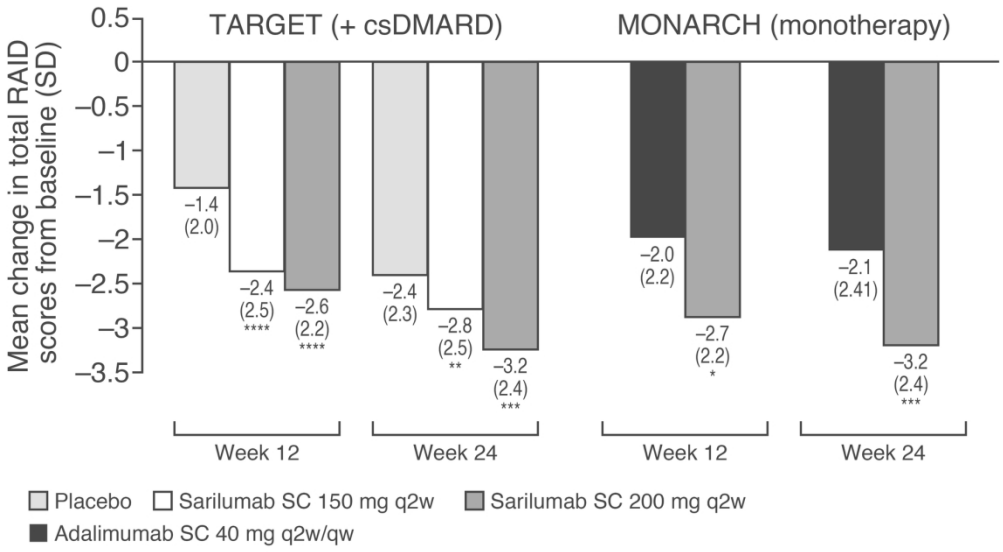

Figure 1

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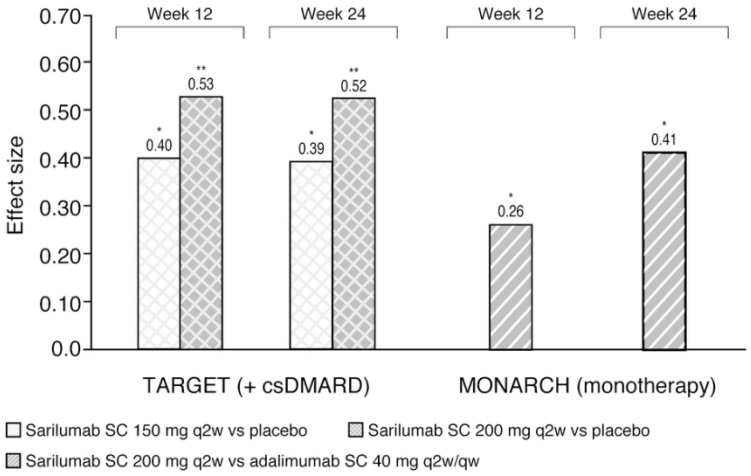

Figure 2

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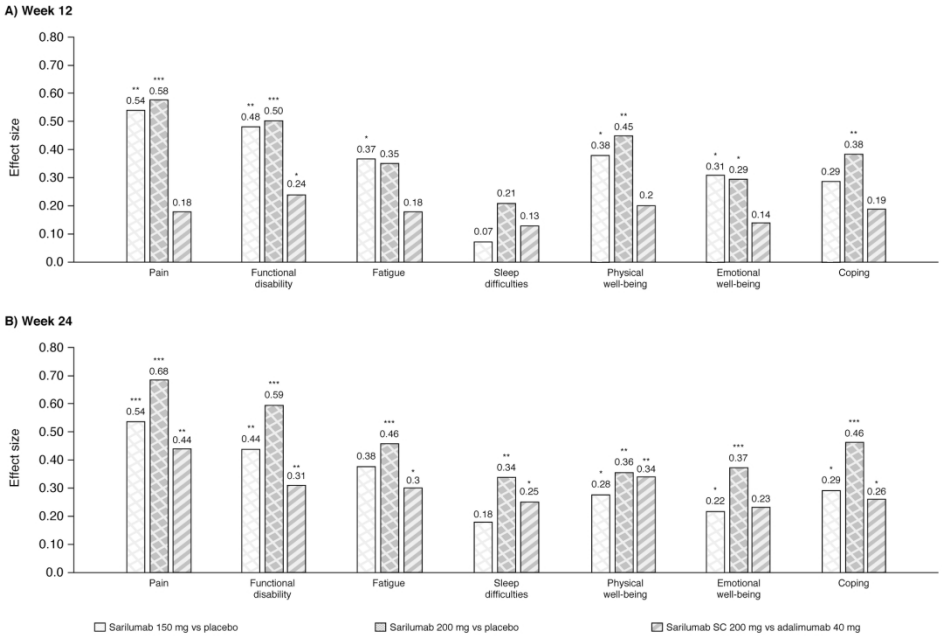

Figure 3

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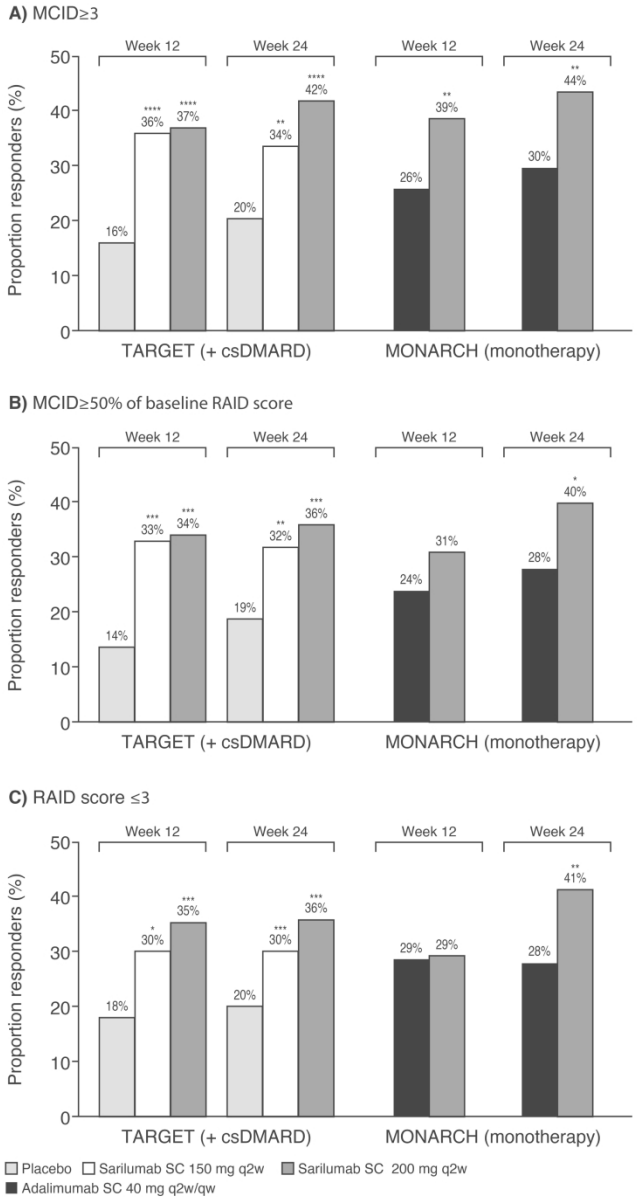

Figure 4

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