Efficacy and safety of monotherapy with sirukumab compared to adalimumab monotherapy in biologic-naïve patients with active rheumatoid arthritis (SIRROUND-H): a randomised, double-blind, parallel-group, multinational, 52-week, phase 3 study

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ABSTRACT

Objective: This randomised, double-blind, parallel-group, phase 3 study compared monotherapy with sirukumab, an anti–interleukin-6 cytokine monoclonal antibody, to adalimumab monotherapy in patients with rheumatoid arthritis (RA).

Methods: Biologic-naïve patients with active RA who were inadequate responders or were intolerant to, or inappropriate for, methotrexate were randomised to subcutaneous sirukumab 100 mg every 2 weeks (q2w; n=187), sirukumab 50 mg every 4 weeks (q4w; n=186), or adalimumab 40 mg q2w (n=186). Primary endpoints at week 24 were change from baseline in Disease Activity Score in 28 joints (DAS28) using erythrocyte sedimentation rate (ESR) and proportion of patients achieving an American College of Rheumatology (ACR) 50 response; these endpoints were tested in sequential order. This study is registered at EudraCT (number: 2013-001417-32) and ClinicalTrials.gov (number: NCT02019472).

Results: Significantly greater improvements from baseline in mean (standard deviation) DAS28 (ESR) were observed at week 24 with sirukumab 100 mg q2w (–2.96 [1.580]) versus adalimumab 40 mg q2w (–2.19 [1.437]; p<0.001). Sirukumab 50 mg q4w also showed significantly greater improvement from baseline at week 24 in DAS28 (ESR) (–2.58 [1.524]) compared with adalimumab (p=0.013). The ACR50 response rates with the 100-mg (35.3%) and 50-mg (26.9%) doses of sirukumab were comparable to that with adalimumab (31.7%) at week 24. The safety profile of sirukumab was consistent with that observed with anti–interleukin-6 receptor antibodies. A dose-related effect on the incidence of injection-site reactions was observed with sirukumab.

Conclusion: Sirukumab monotherapy showed greater improvements in DAS28 (ESR), but similar ACR50 response rates, versus adalimumab monotherapy.

Keywords: rheumatoid arthritis, sirukumab, IL-6, adalimumab, monotherapy

INTRODUCTION

Currently, in the treatment of established rheumatoid arthritis (RA), a combination of biologic disease-modifying antirheumatic drugs (bDMARDs) with methotrexate (MTX) is superior to bDMARD monotherapy.[1, 2] However, a number of patients discontinue MTX, most commonly due to side effects.[3] For example, in a study of 157 patients with RA who were currently or had previously used MTX, 29.3% of patients discontinued MTX therapy, most often due to gastrointestinal or hepatic side effects.[3] For patients who cannot use conventional synthetic DMARDs (csDMARDs), monotherapy with IL-6 pathway or JAK inhibitors may have advantages compared to monotherapy with other bDMARDs.[2, 4]

Elevated IL-6 levels are present in synovial tissue of patients with RA and correlate with disease activity.[5-7] Sirukumab is a fully human monoclonal antibody that binds to IL-6 with high affinity and specificity, preventing IL-6 from binding to membrane and soluble forms of IL-6R.[8] The 2 dose regimens chosen for the phase 3 pivotal studies, sirukumab 50 mg every 4 weeks (q4w) and 100 mg every 2 weeks (q2w) significantly improved signs and symptoms of disease among patients with active RA refractory to csDMARDs and refractory to ≥1 anti-tumor necrosis factor (TNF) drug or intolerant to ≥2 anti-TNF drugs.[9, 10] The majority of patients in these trials received sirukumab in combination with csDMARDs.[9, 10]

The primary objective of this phase 3 study (SIRROUND-H) was to demonstrate superior efficacy of sirukumab monotherapy compared to adalimumab monotherapy (the most commonly used bDMARD for the treatment of RA[11]) over 52 weeks in patients with active RA who had an inadequate response to MTX or were intolerant to or inappropriate for MTX.

METHODS

This phase 3, randomised, double-blind, parallel-group, active comparator study evaluated the superiority (in terms of efficacy) of subcutaneous (SC) sirukumab monotherapy compared with adalimumab monotherapy, along with safety, physical function, pharmacokinetic properties, and immunogenicity, in biologic-naïve patients with active RA (**Supplementary Figure 1**).

Patients/study population

Eligible patients were ≥18 years of age with active RA (≥8 of 68 tender joints and ≥6 of 66 swollen joints at screening/baseline, and CRP levels of ≥10 mg/L or erythrocyte sedimentation rate [ESR] of ≥28 mm/hr at screening) and were considered inadequate responders to MTX (after ≥12 weeks of MTX [dose of ≥15 mg/week]) or intolerant to or inappropriate for treatment with MTX for safety reasons (including MTX-naïve patients).

Study design

This 68-week study included a 52-week treatment period and 16-week safety follow-up period. The study protocol and amendments were reviewed by an Independent Ethics Committee or Institutional Review Board. This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements, and patients provided written informed consent.

Patients were randomised at 102 centres in the United States of America, Europe, Latin America and South Africa from April 2014 to May 2015. Eligible patients were randomised 1:1:1 to sirukumab SC 100 mg q2w, sirukumab SC 50 mg q4w, or adalimumab 40 mg SC q2w. Details of randomization and masking are provided in the **Supplementary Methods and**

Results. Patients with <20% improvement from baseline in both swollen joint counts (SJC)/tender joint counts (TJC) at week 16 qualified for early escape (EE): patients receiving adalimumab 40 mg q2w changed to weekly dosing, patients receiving sirukumab 50 mg q4w changed to 100 mg q2w, and patients on sirukumab 100 mg q2w remained on their randomised dose. Patients receiving sirukumab who met EE criteria received weekly placebo injections in between to maintain blinding.

Study evaluations

All analyses were prespecified in the statistical analysis plan. The two primary efficacy endpoints were change from baseline in DAS28 (ESR) at week 24 and proportion of patients with an ACR50 response at week 24 (see details of hierarchical statistical testing in Statistical Analyses section). Major secondary efficacy endpoints included the proportion of patients with DAS28 (ESR) remission and the proportion with an ACR20 response at week 24. Additional efficacy endpoints included ACR70 response, clinical disease activity index (CDAI), the Health Assessment Questionnaire-Disability Index (HAQ-DI), the 36-item Short Form Health Survey (SF-36), the Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue questionnaire (**Supplementary Methods and Results**). Efficacy endpoints were assessed through week 52. Safety was monitored throughout the 68-week study, and included evaluations of treatment-emergent adverse events (TEAEs) and clinical laboratory tests. Serum sirukumab or adalimumab concentrations and immunogenicity to sirukumab or adalimumab were assessed (**Supplementary Methods and Results**).

Statistical methods

Based on the results of a phase 4, active-controlled study of tocilizumab monotherapy (the ADACTA study [12]) and assuming a treatment difference of 0.6 to 0.8 for the change from baseline in DAS28 at week 24 (SD of 1.6 to 1.8) and an ACR50 response rate at Week 24 of 45% to 50% with sirukumab versus 30% with adalimumab, a sample size of 170 patients per treatment arm was needed to achieve a power of ≥81% for the primary endpoints to detect a treatment difference between sirukumab and adalimumab using an α of 0.05 (2-sided). The primary hypotheses to be tested in this study, in sequential order, were: 1) sirukumab 100 mg q2w demonstrates superior efficacy versus adalimumab 40 mg q2w in change from baseline in DAS28 (ESR) at week 24, and 2) sirukumab 100 mg q2w demonstrates superior efficacy versus adalimumab 40 mg q2w in the proportion of patients with an ACR50 response at week 24. The change from baseline in DAS28 (ESR) was tested using an analysis of covariance model, controlling for treatment group, reason for MTX failure, and baseline value; missing values were imputed using baseline observation carried forwards methodology. ACR50 response was tested using a Cochran-Mantel-Haenszel test stratified by reason for MTX failure; missing values, EE, or treatment failures (see **Supplementary Methods and Results** for definition) were imputed as non-responders. As prespecified, if the first (DAS28 [ESR] endpoint) comparison of sirukumab 100 mg q2w to adalimumab 40 mg q4w was statistically significant at a 2-sided α-level of 0.05, the study was considered positive. Differences in the change from baseline in DAS28 (ESR) at week 24 and proportion of patients with an ACR50 response at week 24 were evaluated between the sirukumab 50 mg q4w and adalimumab 40 mg q2w groups as major secondary analyses using similar methodology to that used for sirukumab 100 mg q2w. **Supplementary Figure 2** outlines testing procedures for primary and secondary hypotheses and how they differed for

global and USA-specific regulatory requirements. Statistical methods are detailed in the **Supplementary Methods and Results**.

RESULTS

Study population

Of 776 patients screened, 559 were randomised (**Figure 1)**. Demographic and baseline disease characteristics were well balanced across treatment groups (**Table 1**). Among randomised patients, 57.1% (n=319) and 42.9% (n=240) failed MTX for efficacy and safety/tolerability reasons, respectively (**Supplementary Table 1**). Overall, 97.9% (547/559) of patients had prior MTX use (**Supplementary Table 1)**. Treatment compliance was >95% and >93% across all groups through weeks 24 and 52, respectively. Through week 52, 131 patients discontinued study drug, most often due to AEs (**Figure 1; Supplementary Table 2**).

Efficacy

For the first primary endpoint, the improvement from baseline in DAS28 (ESR) was significantly greater at week 24 for sirukumab 100 mg compared with adalimumab ($p<0.001$; **Table 2**). For the second primary endpoint, the difference in ACR50 responses at week 24 between patients receiving sirukumab 100 mg and those receiving adalimumab was not statistically significant ($p=0.464$; **Table 2**). Following the prespecified testing procedure, the change from baseline in DAS28 (ESR) at week 24 was significantly greater for sirukumab 50 mg compared with adalimumab ($p=0.013$; **Table 2**). The difference in ACR50 responses at week 24 between patients receiving sirukumab 50 mg and those receiving adalimumab was not statistically

significant (p=0.306; **Table 2**). Based on the testing hierarchy, no further hypothesis testing was performed. Results from sensitivity analyses to explore the impact of handling missing data on the primary endpoints were similar to the primary analysis (data not shown). For both doses of sirukumab and adalimumab, decreases (improvements) from baseline in DAS28 (ESR) were observed from as early as week 2 through week 52 (**Figure 2A**). Across all 3 treatment groups, a clinically relevant proportion of patients achieved an ACR50 response through week 52 (**Figure 2B**). At week 52, improvements from baseline in DAS28 (ESR) and the proportion of patients achieving ACR50 response were comparable to those at week 24 (**Supplementary Table 3**). Improvements from baseline at week 24 in individual ACR components were similar for adalimumab and sirukumab 100 mg, and slightly lower for sirukumab 50 mg for some parameters (**Supplementary Table 4**).

Major secondary endpoints and other efficacy endpoint analyses showed similar clinically meaningful improvements for both sirukumab groups and the adalimumab group and are summarised in **Table 2** for week 24 and **Supplementary Table 3** for week 52. Changes from baseline in the SJC, TJC, patient's global assessment of disease activity, and ESR at Week 24 are also summarized in **Table 2**. DAS28 (ESR) remission rates were numerically higher across all treatment groups at week 52 compared with week 24; a numerically higher remission rate was observed in the sirukumab ~~100 mg and 50 mg~~ groups compared to the adalimumab group at weeks 24 and 52. ACR20 response rates at week 24 were similar across groups and remained generally comparable at week 52, while ACR70 response rates increased slightly from week 24 to week 52 across all groups. For the primary efficacy endpoints and major secondary endpoints, there was a trend for numerically greater improvements in patients randomized to sirukumab who had failed MTX for safety reasons compared with those that failed for efficacy reasons;

however, this finding was not consistent for both doses of sirukumab across multiple endpoints and timepoints (**Supplementary Table 5)**.

Similar decreases (improvements) in CDAI (a disease activity index that includes clinical parameters and no acute phase reactants) and HAQ-DI scores from baseline were observed with sirukumab (both doses) and adalimumab treatment at weeks 24 and 52 (**Supplementary Table 6).** Approximately 50% to 60% of the patients in each treatment group achieved clinically meaningful improvements from baseline (≥5-point increase) in SF-36 physical component summary and mental component summary scores at weeks 24 and 52 (**Supplementary Table 6**). High proportions of patients (≥60%) achieved clinically meaningful improvements from baseline (≥4-point increase) in FACIT-Fatigue score across all groups (**Supplementary Table 6**).

Safety

All reported safety assessments are for the entire 68-week study, unless otherwise specified. Overall incidences of TEAEs for patients randomised to adalimumab, sirukumab 50 mg, and sirukumab 100 mg were 69.9% (130/186), 74.7% (139/186), and 71.7% (134/187), respectively (**Table 3**). The most frequently reported (>5%) individual TEAEs for sirukumab and adalimumab are summarized in **Table 3**. TEAEs leading to treatment discontinuation and serious TEAEs occurred in more patients with sirukumab 50-mg compared with sirukumab 100-mg or adalimumab treatment (**Table 3**); detailed listings of these TEAEs are provided in **Supplementary Tables 7 and 8**.

The percentage of patients with injection-site reactions was approximately two-fold greater with sirukumab 100 mg compared with sirukumab 50 mg q4w and adalimumab; none

was considered serious (**Table 3**). One patient each in the sirukumab 100-mg group (injection-site swelling) and adalimumab group (injection-site induration) discontinued treatment due to injection-site reactions. Rates of hypersensitivity reactions were low for all groups; no cases of anaphylaxis occurred (**Table 3**).

The rate of infections was similar with sirukumab compared to adalimumab, with nasopharyngitis, upper respiratory tract infections, and bronchitis being the most frequently reported (**Table 3**). Among patients receiving adalimumab, sirukumab 50 mg, and sirukumab 100 mg, rates of serious infections were 2.2% (4/186), 7.5% (14/186), and 2.7% (5/187), respectively. Two cases of reactivated pulmonary tuberculosis, one case of opportunistic infection, three major adverse cardiovascular events, six malignancies, seven pregnancies, two gastrointestinal perforations, and four deaths were reported. Details of these events are summarized in the **Supplementary Methods and Results**. ~~were reported (one each in the sirukumab 50-mg and adalimumab groups). One opportunistic infection (ophthalmic herpes zoster) was reported in a patient treated with sirukumab 50 mg. Three patients experienced major adverse cardiovascular events (strokes; two with sirukumab 100 mg and one with sirukumab 50 mg). Six malignancies were reported: one basal cell carcinoma (sirukumab 100-mg group); one endometrial adenocarcinoma (sirukumab 100-mg group); one low-grade glioma (sirukumab 50-mg group); one clear cell renal cell carcinoma (sirukumab 50-mg group); one stage IV adenocarcinoma (lung primary with metastases; sirukumab 50-mg group); and one pancreatic adenocarcinoma (adalimumab group). Seven pregnancies were reported (1 in adalimumab group, 4 in sirukumab 50-mg group, and 2 in sirukumab 100-mg group). Of the five pregnancies through week 52, one patient receiving sirukumab 100 mg experienced an SAE of pre-eclampsia, resulting in hospitalisation. All five pregnancies resulted in the birth of healthy babies. Two~~

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~~gastrointestinal perforations (one with each sirukumab dose) were reported. Four deaths (three in the sirukumab 50-mg group [one each related to pneumonia, progressive respiratory and cardiovascular failure, and metastatic adenocarcinoma] and one in the sirukumab 100-mg group [related to asystolic-type circulatory arrest]) were reported. Details of these deaths are summarized in the **Supplementary Methods and Results**.~~

Laboratory abnormalities of interest (associated with IL-6 inhibition) were more common with both sirukumab doses compared with adalimumab through week 52. All treatments were associated with liver enzyme increases; lipid level elevations and neutrophil count reductions were more frequently associated with sirukumab treatment (**Table 4**). Additional details about laboratory abnormalities are included in the **Supplementary Methods and Results**.

Immunogenicity

The incidence of antibodies to sirukumab through week 68 was low (sirukumab 100 mg, 4.9% [9/183]; sirukumab 50 mg, 3.8% [7/182]), while the incidence of antibodies to adalimumab was 91.9% (171/186). The presence of antibodies to sirukumab or adalimumab did not appear to markedly reduce response rates. More detailed pharmacokinetic and immunogenicity results are summarized in the **Supplementary Methods and Results**.

DISCUSSION

Some patients are unable to use csDMARDs, possibly due to tolerability issues.[3] For these patients, there may be advantages to using monotherapy with agents targeting the IL-6 pathway or JAK inhibitors.[2, 4] Thus, the efficacy of sirukumab monotherapy was compared

with that of adalimumab monotherapy, the most commonly used bDMARD for the treatment of RA.[11] For the first primary endpoint in this study, monotherapy with sirukumab 100 mg was superior to monotherapy with adalimumab 40 mg in biologic-naïve patients with active RA in terms of improvements in DAS28 (ESR) from baseline to week 24. However, for the second primary endpoint, ACR50 response rates were comparable for sirukumab 100 mg and adalimumab. It should be noted, however, that the proportion of patients achieving ACR50 responses in the adalimumab group in this study (31.7%) was slightly higher than that reported for adalimumab monotherapy in other RA studies (22.1% to 29.7%).[12-17] Similar results were observed for sirukumab 50 mg. Sirukumab's direct and greater effect on acute phase reactants (ESR and CRP) compared with adalimumab, coupled with the finding that sirukumab and adalimumab produced comparable improvements in the CDAI measure, may account for the superiority of sirukumab on the DAS28 (ESR) endpoint, but non-superiority on the ACR 50 response endpoint in this study. The acute phase reactant component is weighted more heavily in the DAS28 (ESR) formula than in the ACR 50 criteria, and not at all in the CDAI.[18-20] Both sirukumab and adalimumab showed early efficacy, with improvements in RA signs and symptoms as early as week 2. Overall, improvements in measures of signs and symptoms, physical function, and patient-reported outcomes were generally similar across the sirukumab and adalimumab groups.

For certain endpoints that are generally harder to achieve (DAS28 remission, ACR50), a numerically greater treatment response was observed for sirukumab 100 mg compared with sirukumab 50 mg, suggesting a possible dose-response relationship for sirukumab monotherapy, although the study was not designed to compare the two doses. In contrast, no efficacy-related

dose response was identified when sirukumab was administered in combination with csDMARDs.[9, 10]

In the ADACTA and MONARCH studies, both of which were direct comparative studies versus adalimumab, tocilizumab and sarilumab demonstrated significant improvements compared with adalimumab in CDAI and other measures, including ACR response and various patient reported outcomes, when administered as monotherapy in patients with RA who were intolerant or inadequate responders to MTX.[12, 17] In this study, improvements from baseline in signs and symptoms and patient-reported outcomes were generally comparable between sirukumab and adalimumab groups. There is no clear evidence-based mechanistic or scientific reason why ~~that~~ the 2 anti–IL-6R antibody monotherapy regimens would be ~~ere~~ more efficacious than adalimumab, while sirukumab, which inhibits IL-6, and adalimumab were comparable in efficacy in the SIRROUND-H trial~~, is unclear~~. In addition to the targeted mechanism of action, the studies differed in study design (eg, 52-week double-blind treatment period in this study vs 24 weeks in ADACTA and MONARCH), the geographic distribution of the study population (eg, >60% of patients were from Eastern Europe in this study, higher than ADACTA and MONARCH), as well as blinding and analysis methods.[12, 17] The response rate in the adalimumab comparator groups varied across the 3 studies.[12, 17] .

The strengths of the study were that it was the only large study of sirukumab in bio-naïve patients, and was a randomized, blinded, controlled monotherapy trial of 52 weeks duration with an active comparator, which evaluated 2 doses of the investigational agent. The limitations were that adalimumab monotherapy control treatment yielded responses that were higher than in other adalimumab studies [12-17], rendering indirect comparisons to other studies challenging. A direct comparative study of sirukumab against an anti–IL-6R antibody would be of interest but,

at the time of study design, such a trial was not feasible for reasons of uncertain effect size, blinding, and compound availability. Due to the effects of sirukumab on acute phase reactants, the use of DAS28 (ESR) as one of the 2 primary objectives may also have presented challenges for comparing efficacy between sirukumab and adalimumab, as discussed above. Methotrexate carryover effects may also have been present and differed between treatment groups; a MTX washout period of more than 2 weeks and/or balancing treatment groups based on this variable could have been useful.

The safety profile of sirukumab was generally consistent with the known safety profile of anti−IL-6R antibody treatment and previous sirukumab RA studies.[9, 12, 17, 21, 22] In this study, the rate of serious infections was numerically higher with sirukumab 50 mg than with adalimumab or sirukumab 100 mg. Two sirukumab-treated patients had gastrointestinal perforations, while none occurred with adalimumab. Four sirukumab-treated patients died, while no deaths were reported in the adalimumab group. All deaths occurred after week 24, lacked dose-dependence, and the causes of death were diverse and typical of RA patients. In the 24-week ADACTA and MONARCH studies, of the 2 deaths and 1 death reported, respectively, none occurred in the adalimumab groups.[12, 17] Through week 68, no dose response was observed in AE or SAE rates, except for injection-site reactions. Laboratory abnormalities commonly observed with sirukumab were liver transaminase increases, lipid level elevations, and neutrophil count reductions. The safety and tolerability of adalimumab in this study were consistent with published data of adalimumab monotherapy in RA.[12, 13, 15, 23, 24] When determining which biologic DMARD monotherapy to use, individual patient comorbidities and risk profiles in relation to anti-TNF or IL-6 pathway inhibitor class effects should be taken into account.

The immunogenicity rate was low for sirukumab monotherapy (4.4%) through week 68, similar to that observed for sirukumab combined with csDMARD treatment in other studies.[9, 10] The immunogenicity rate for adalimumab monotherapy through week 68 was high (91.9%) in this study, which could be related to the use of a validated, sensitive immunoassay and to administration of adalimumab as monotherapy. In this study, the presence of antibodies to either sirukumab or adalimumab did not appear to be associated with a reduction in efficacy. However, previous studies have shown that rates of anti-adalimumab antibodies are higher when adalimumab is used as monotherapy and appear to be associated with loss of response after prolonged treatment.[25-27]

In conclusion, treatment with sirukumab monotherapy demonstrated rapid and sustained improvement in signs and symptoms of RA, comparable to those achieved with adalimumab monotherapy, in a population of biologic-naïve patients with an inadequate response or intolerance to/inappropriateness for MTX. Unfortunately, because health authorities requested additional clinical data, which would have significantly delayed access to sirukumab in parts of the world, the sponsor company made the strategic decision to prioritize other therapies in development and to terminate the sirukumab RA program.

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Contributors

PCT contributed to the design of the study and analysis and interpretation of the data. MS contributed to the analysis and interpretation of the data. QW contributed to the design and conduct of the study, recruitment and treatment of patients, and collection, analysis, and interpretation of the data. YJ contributed to the analysis and interpretation of the data. YZ contributed to the design of the study and the analysis and interpretation of the data. RK contributed to the design of the study and the analysis and interpretation of the data. SD contributed to the analysis and interpretation of the data. RR contributed to the design of the study and the analysis and interpretation of the data. BH contributed to the design and conduct of the study and the analysis and interpretation of the data. PPT contributed to the design of the study and the analysis and interpretation of the data. All authors contributed to drafting the work

or revising it critically for important intellectual content, provided final approval of the version published, and agreed to be accountable for all aspects of the work.

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Competing Interests

PCT has served as a consultant to AbbVie, Biogen, Bristol-Myers Squibb, Eli Lilly, Galapagos, GlaxoSmithKline, Janssen, Novartis, Pfizer, Roche, Sandoz, and UCB Pharma and has received research grant funding from Celgene, GlaxoSmithKline, Janssen, and UCB Pharma. MS has served as a consultant to AbbVie, Bristol-Myers Squibb, Johnson & Johnson, Eli Lilly, and UCB Pharma and as a speaker for AbbVie and Bristol-Myers Squibb. QW, YZ, and BH are employees and shareholders of Janssen Research and Development, LLC. YJ is a contractor of Janssen Research & Development, LLC. RK, SD, RR, and PPT are employees and shareholders of GlaxoSmithKline.

Patient Consent

All patients provided written informed consent.

Ethics Approval

The study protocol and amendments were reviewed by an Independent Ethics Committee or Institutional Review Board. This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements.

Provenance and Peer Review

Not commissioned; externally peer reviewed.

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FIGURE LEGENDS

Figure 1. Patient distribution and disposition through Week 52.

q2w, every 2 weeks; q4w, every 4 weeks; EE, early escape.

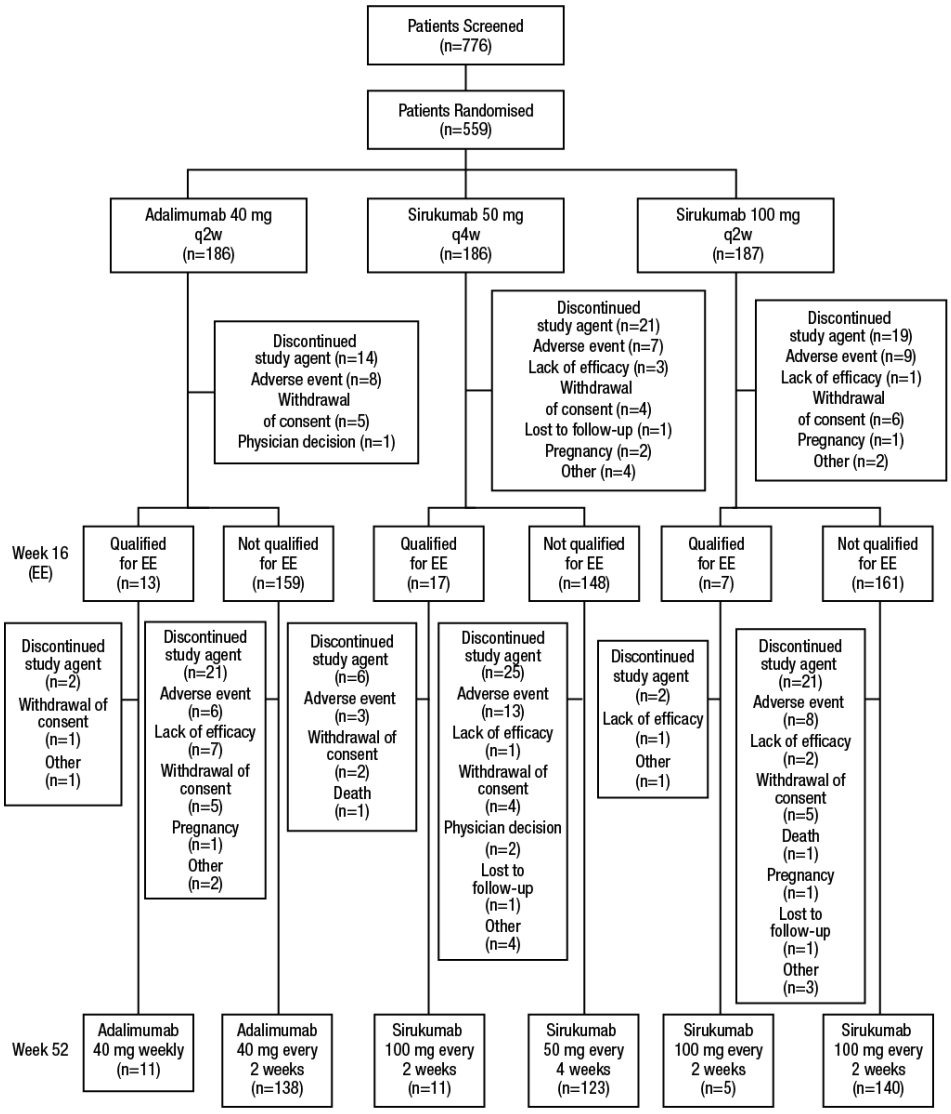
Figure 2. Primary endpoints: A) Change from baseline in DAS28 (ESR)[a] and B) proportion of patients achieving an ACR50 response by visit through week 52.[b~~a~~]

DAS28 (ESR), Disease Activity Score in 28 joints, using erythrocyte sedimentation rate; SE, standard error; q2w, every 2 weeks; q4w, every 4 weeks; ACR, American College of Rheumatology.

[a]Observed values; patients with missing baseline values were excluded from analysis.

[b]Imputed values.

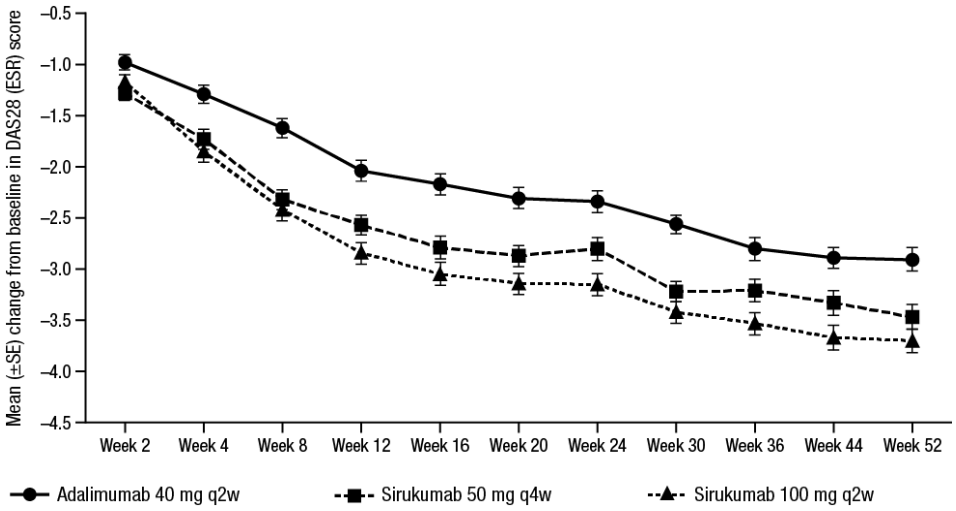
Figure 1. Patient distribution and disposition through Week 52.



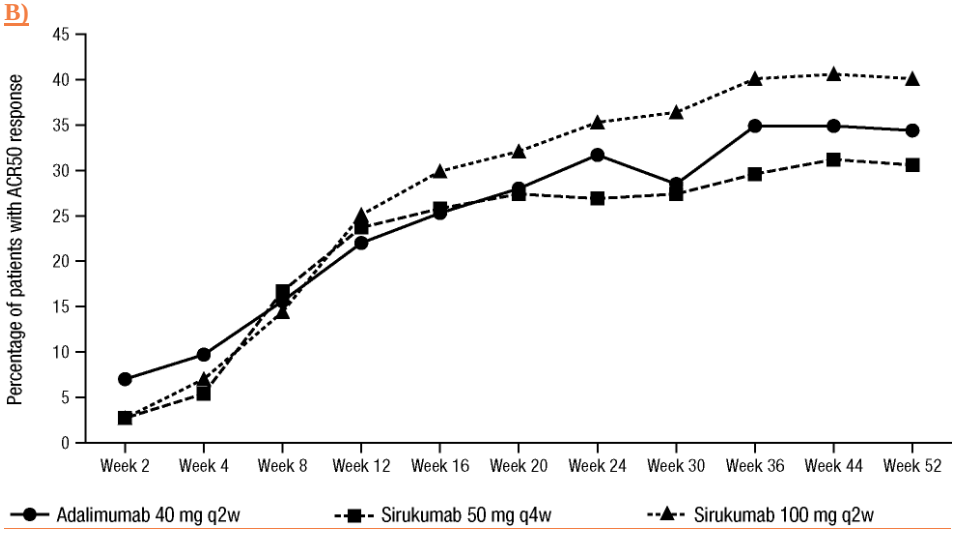
q2w, every 2 weeks; q4w, every 4 weeks; EE, early escape.

Figure 2. Primary endpoints: A) c~~C~~hange from baseline in DAS28 (ESR)[a] and B) proportion of patients achieving an ACR50 response by visit through week 52.[b,c~~a~~]

A)



B)



DAS28 (ESR), Disease Activity Score in 28 joints, using erythrocyte sedimentation rate; SE, standard error; q2w, every 2 weeks; q4w, every 4 weeks; ACR, American College of Rheumatology.

[a]Observed values; patients with missing baseline values were excluded from analysis.

[b]Imputed values.

[c]Data for these Figures 2A and 2B are included in Supplemental Tables 9 and 10, respectively

Table 1. Baseline and demographic characteristics

	Adalimumab	Sirukumab	
	40 mg q2w (n=186)	50 mg q4w (n=186)	100 mg q2w (n=187)
Sex, n (%)			
Female	156 (83.9)	157 (84.4)	154 (82.4)
Male	30 (16.1)	29 (15.6)	33 (17.6)
Age (years)			
Mean (SD)	52.6 (12.15)	52.5 (12.46)	49.8 (12.31)
Median, (IQR)	54.5 (46-60)	54.5 (46-60)	49.9 (40-59)
Race, n (%)			
White	173 (93.0)	166 (89.2)	174 (93.0)
Asian	1 (0.5)	2 (1.1)	5 (2.7)
Black or African American	2 (1.1)	5 (2.7)	3 (1.6)
Unknown	1 (0.5)	1 (0.5)	1 (0.5)
Other	9 (4.8)	12 (6.5)	4 (2.1)
Region, n (%)			
Europe	138 (74.2)	132 (71.0)	142 (75.9)
North America	25 (13.4)	32 (17.2)	31 (16.6)
Latin America	15 (8.1)	13 (7.0)	7 (3.7)
South Africa	8 (4.3)	9 (4.8)	7 (3.7)
BMI (kg/m^2), mean (SD)	27.86 (5.63)	27.77 (5.99)	27.60 (6.53)
Duration of RA, median (IQR)	4.00 (1.4-8.4)	4.24 (1.6-9.5)	4.60 (2.1-9.0)
Number of swollen joints, mean (SD)	18.5 (10.06)	19.8 (11.91)	20.0 (11.93)
0-66	12.7 (5.65)	13.3 (6.47)	13.5 (6.01)
0-28			
Number of tender joints, mean (SD)			
0-68	30.8 (14.36)	32.4 (15.83)	32.6 (14.93)
0-28	17.8 (6.37)	17.8 (7.22)	18.3 (6.57)
Patient's assessment of pain (VAS; 0-10)			
n	186	185	185
Mean (SD)	6.78 (1.96)	6.82 (1.89)	6.55 (2.09)

	Adalimumab	Sirukumab	
	40 mg q2w (n=186)	50 mg q4w (n=186)	100 mg q2w (n=187)
Patient's global assessment of disease activity (VAS; 0-10)			
n	186	185	185
Mean (SD)	6.85 (2.04)	6.80 (1.94)	6.70 (2.05)
Physician's global assessment of disease activity (VAS; 0-10), mean (SD)	6.79 (1.55)	6.78 (1.51)	6.83 (1.59)
HAQ-DI score, range: 0-3			
n	186	185	185
Mean (SD)	1.70 (0.63)	1.75 (0.55)	1.62 (0.61)
CRP (mg/dL), mean (SD)	2.07 (3.06)	2.11 (2.60)	1.79 (2.26)
ESR (mm/h), mean (SD)	48.6 (23.17)	49.5 (23.50)	46.8 (21.91)
DAS28 (ESR)			
n	186	185	185
Mean (SD)	6.89 (0.85)	6.90 (0.88)	6.91 (0.86)
DAS28 (CRP)			
n	185	185	185
Mean (SD)	6.05 (0.96)	6.12 (0.96)	6.08 (0.97)
CDAI			
n	186	185	185
Mean (SD)	44.09 (12.17)	44.62 (13.39)	45.39 (12.84)
Anti-CCP positive, n (%)	142 (76.8)	138 (74.6)	141 (76.2)
RF positive, n (%)	130 (70.3)	140 (75.3)	134 (71.7)
SF-36			
PCS, mean (SD)	31.60 (6.92)	31.76 (5.97)	32.48 (6.77)
MCS, mean (SD)	41.08 (10.79)	40.86 (10.68)	40.93 (10.34)
FACIT-Fatigue, mean (SD)	26.8 (10.65)	25.7 (10.15)	25.0 (10.25)

BMI, body mass index; RA, rheumatoid arthritis; VAS, visual analog scale; HAQ-DI, Health Assessment Questionnaire-Disability Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DAS28 (ESR), Disease Activity Score in 28 joints, using erythrocyte sedimentation rate; DAS28 (CRP) Disease Activity Score in 28 joints, using C-reactive protein; CDAI, clinical disease activity index; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; SF-36, Short Form-36; PCS, physical component score; MCS, mental component score; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue.

Table 2. Primary, major secondary, and other ~~ACR~~ endpoints at week 24

	Adalimumab	Sirukumab	
	40 mg q2w	**50 mg q4w**	**100 mg q2w**
Change from baseline in DAS28 (ESR) at Week 24			
All evaluable patients	186	185	185
n	–2.19 (1.437)	–2.58 (1.524)	–2.96 (1.580)
Mean (SD)		0.013	<0.001
P value[a]			
Proportion of patients achieving ACR50 at Week 24			
All evaluable patients			
n	186	186	187
Patients in response, n (%)	59 (31.7)	50 (26.9)	66 (35.3)
P value[a]		0.306	0.464
Proportion of patients achieving DAS28 (ESR) remission at Week 24			
All evaluable patients			
n	186	186	187
Patients in remission, n (%)	14 (7.5)	24 (12.9)	38 (20.3)
Proportion of patients achieving ACR20 at Week 24			
All evaluable patients			
n	186	186	187
Patients in response, n (%)	105 (56.5)	100 (53.8)	110 (58.8)
Proportion of patients achieving ACR70 at Week 24			
All evaluable patients			
n	186	186	187
Patients in response, n (%)	24 (12.9)	22 (11.8)	29 (15.5)
Proportion of patients achieving SDAI-based ACR/EULAR remission at Week 24			
All evaluable patients			
n	186	186	187
Patients in response, n (%)	12 (6.5)	14 (7.5)	15 (8.0)

	Adalimumab	Sirukumab	
	40 mg q2w	50 mg q4w	100 mg q2w
Proportion of patients achieving Boolean-based ACR/EULAR remission at Week 24			
All evaluable patients			
n	186	186	187
Patients in response, n (%)	7 (3.8)	7 (3.8)	7 (3.7)
SJC (0-66) at Week 24			
All evaluable patients			
n	174	172	176
Mean (SD) % change from baseline	−69.2 (35.45)	−62.0 (39.40)	−68.9 (54.95)
TJC (0-68) at Week 24			
All evaluable patients			
n	174	172	176
Mean (SD) % change from baseline	−61.4 (36.02)	−54.0 (35.87)	−59.0 (38.01)
Patient's global assessment of disease activity (VAS; 0-10) at week 24			
All evaluable patients			
n	174	172	176
Mean (SD) % change from baseline	−36.06 (44.17)	−32.08 (60.57)	−36.05 (54.06)
ESR (mm/hr) at week 24			
All evaluable patients			
n	175	173	176
Mean (SD) change from baseline	−13.7 (26.86)	−34.1 (28.56)	−34.7 (22.65)

DAS28 (ESR), Disease Activity Score in 28 joints, using erythrocyte sedimentation rate; ACR, American College of Rheumatology; SDAI, simplified disease activity index; EULAR, European League Against Rheumatism; SJC, swollen joint count; SD, standard deviation; TJC, tender joint count; VAS, visual analog scale; ESR, erythrocyte sedimentation rate.

Data presented are based on imputed values.

[a]*P* value compared with adalimumab 40 mg q2w.

Table 3. Overall summary of safety through week 68

Adverse event[a] outcome, n (%)	Adalimumab 40 mg q2w (n=186)	Sirukumab 50 mg q4w (n = 186)	Sirukumab 100 mg q2w (n = 187)
Patients with ≥1 TEAE, n (%)	130 (69.9)	139 (74.7)	134 (71.7)
TEAEs (≥5% of patients in any sirukumab group)			
Injection-site erythema	13 (7.0)	17 (9.1)	33 (17.6)
Increased ALT	12 (6.5)	21 (11.3)	24 (12.8)
Rheumatoid arthritis	18 (9.7)	20 (10.8)	16 (8.6)
Increased AST	11 (5.9)	13 (7.0)	20 (10.7)
Neutropenia	4 (2.2)	17 (9.1)	11 (5.9)
Headache	11 (5.9)	11 (5.9)	13 (7.0)
Injection-site pruritus	8 (4.3)	6 (3.2)	17 (9.1)
Hypertension	10 (5.4)	12 (6.5)	8 (4.3)
Nasopharyngitis	16 (8.6)	10 (5.4)	9 (4.8)
Upper respiratory tract infection	10 (5.4)	10 (5.4)	9 (4.8)
Bronchitis	4 (2.2)	10 (5.4)	8 (4.3)
Injection site swelling	4 (2.2)	4 (2.2)	11 (5.9)
Patients with ≥1 serious TEAE, n (%)	16 (8.6)	29 (15.6)	22 (11.8)
Patients with ≥1 TEAE that caused study agent discontinuation, n (%)	15 (8.1)	25 (13.4)	20 (10.7)

Adverse event[a] outcome, n (%)	Adalimumab 40 mg q2w (n=186)	Sirukumab 50 mg q4w (n = 186)	Sirukumab 100 mg q2w (n = 187)
Patients with ≥1 infection, n (%)	58 (31.2)	63 (33.9)	59 (31.6)
Infections reported in ≥2% of patients in any group			
Nasopharyngitis	14 (7.5)	9 (4.8)	9 (4.8)
Upper respiratory tract infection	10 (5.4)	9 (4.8)	9 (4.8)
Bronchitis	4 (2.2)	9 (4.8)	8 (4.3)
Pharyngitis	3 (1.6)	3 (1.6)	6 (3.2)
Urinary tract infection	6 (3.2)	6 (3.2)	3 (1.6)
Influenza	2 (1.1)	5 (2.7)	2 (1.1)
Sinusitis	2 (1.1)	4 (2.2)	3 (1.6)
Pneumonia	1 (0.5)	4 (2.2)	2 (1.1)
Cellulitis	0	4 (2.2)	1 (0.5)
Cystitis	1 (0.5)	1 (0.5)	4 (2.1)
Respiratory tract infection, viral	2 (1.1)	1 (0.5)	4 (2.1)
Oral herpes	4 (2.2)	1 (0.5)	3 (1.6)
Respiratory tract infection	3 (1.6)	0	4 (2.1)
Patients with ≥1 serious infection, n (%)	4 (2.2)	14 (7.5)	5 (2.7)
Patients with ≥1 injection-site reaction,[b] n (%)	16 (8.6)	20 (10.8)	43 (23.0)
Patients with ≥1 MACE,[c] n (%)	0	1 (0.5)	2 (1.1)
Patients with ≥1 hypersensitivity/ serum sickness AE, n (%)	2 (1.1)	2 (1.1)	4 (2.1)
Patients with ≥1 malignancy, n (%)	1 (0.5)	3 (1.6)	2 (1.1)
Patients with ≥1 GI perforation, n (%)	0	1 (0.5)	1 (0.5)

Adverse event[a] outcome, n (%)	Adalimumab 40 mg q2w (n=186)	Sirukumab 50 mg q4w (n = 186)	Sirukumab 100 mg q2w (n = 187)
Patients who died on study,[d] n (%)	0	3 (1.6)	1 (0.5)

q2w, every 2 weeks; q1w, weekly; TEAE, treatment-emergent adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MACE, major adverse cardiovascular event; AE, adverse event; GI, gastrointestinal; SAE, serious adverse event.

[a]AEs were reported for the group to which the patient was initially randomized.

[b]All patients were observed by a blinded staff member for symptoms of injection-site reactions for ≥30 minutes after study drug administration through Week 16; injection-site reactions included erythema, pain, pruritus, and/or swelling.

[c]The 3 MACE that occurred in this study were all adjudicated as strokes (1 in the sirukumab 50 mg q4w group and 2 in the 100 mg q2w group).

[d]There were four deaths reported in the study through Week 68 (three in the sirukumab 50-mg q4w group and one in the sirukumab 100-mg q2w group), all of which occurred after Week 24. In the 50-mg q4w group, one patient experienced an SAE of respiratory failure of severe intensity and subsequently died due to pneumonia (events considered not related to study agent); one patient had an SAE of metastatic adenocarcinoma with involvement of the brain, lungs, skeletal system, and thoraco-lumbar lymph nodes and died as a result (considered not related to study agent); and one patient experienced an SAE of erysipelas of severe intensity and died as a result of progressive respiratory and cardiovascular failure (SAE considered possibly related to study agent). In the sirukumab 100 mg q2w group, one patient experienced an SAE of haemorrhagic stroke and died as a result of circulatory arrest (events considered not related to study agent).

Table 4. Number of patients with NCI-CTCAE toxicity grades 3 and 4 postbaseline laboratory abnormalities through week 68[a]

NCI-CTCAE Toxicity Grades 3 and 4 Abnormalities, n (%)	Adalimumab 40 mg q2w (n=186)	Sirukumab 50 mg q4w (n = 186)	Sirukumab 100 mg q2w (n = 187)
ALT (increased)			
N	186	186	187
Grade 3 (>5-20 × ULN)	3 (1.6)	1 (0.5)	5 (2.7)
Grade 4 (>20 × ULN)	0	0	1 (0.5)
AST (increased)			
N	186	186	187
Grade 3 (>5-20 × ULN)	1 (0.5)	0	0
Grade 4 (>20 × ULN)	0	0	1 (0.5)
Cholesterol (increased)			
N	186	182	183
Grade 3 (>10.36-12.95 mmol/L)	1 (0.5)	7 (3.8)	4 (2.2)
Grade 4 (>12.95 mmol/L)	0	1 (0.5)	0
Triglycerides (increased)			
N	185	182	182
Grade 3 (>5.65-11.30 mmol/L)	2 (1.1)	6 (3.3)	7 (3.8)
Grade 4 (>11.30 mmol/L)	1 (0.5)	2 (1.1)	1 (0.5)

NCI-CTCAE Toxicity Grades 3 and 4 Abnormalities, n (%)	Adalimumab 40 mg q2w (n=186)	Sirukumab 50 mg q4w (n = 186)	Sirukumab 100 mg q2w (n = 187)
Neutrophils (decreased)			
N	186	186	187
Grade 3 (<1-0.5 × 10^9/L)	1 (0.5)	6 (3.2)	7 (3.7)
Grade 4 (<0.5 × 10^9/L)	0	0	1 (0.5)
Platelets (decreased)			
N	186	186	187
Grade 3 (<50-25 × 10^9/L)	0	0	0
Grade 4 (<25 × 10^9/L)	0	1 (0.5)	0
Haemoglobin (decreased)			
N	186	186	187
Grade 3 (<80 g/L)	3 (1.6)	0	0
Grade 4 (N/A)[b]	0	0	0

NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; q2w, every 2 weeks; q1w, weekly; ALT, alanine aminotransferase; ULN, upper limit of normal; AST, aspartate aminotransferase; N/A, not applicable.

[a]Laboratory abnormalities were reported for the group to which the patient was initially randomized.

[b]Life-threatening consequences; urgent intervention indicated.