Haemoglobin changes and disease activity in Japanese patients with rheumatoid arthritis treated with sarilumab

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Abstract

Objective

Anaemia is a frequent extra-articular manifestation in rheumatoid arthritis (RA); haemoglobin level changes are associated with changes in disease activity. This post-hoc analysis assessed potential relationships between haemoglobin and disease activity in Japanese patients with RA, enrolled in the KAKEHASI study (NCT02293902).

Methods

In this study, adult patients with moderate-to-severe active RA, who had an inadequate response to methotrexate, were randomised to subcutaneous sarilumab 150 mg every 2 weeks (q2w) or 200 mg q2w or placebo for 24 weeks. Post-hoc analyses were conducted on changes in haemoglobin and proportion of anaemic patients, using a mixed-effects model for repeated measures assuming an unstructured covariance. Relationships between haemoglobin and efficacy measures were explored.

Results

At baseline, nearly half of patients had anaemia, defined by World Health Organization criteria (haemoglobin <12 g/dL, female; or <13 g/dL, male). At Week 24, the least squares mean change in haemoglobin levels was greater in sarilumab groups than for placebo (150 mg: 1.23 g/dL, 200 mg: 1.19 g/dL, placebo: 0.17 g/dL; p=0.0002 for both doses vs. placebo). By Week 24, the proportion of patients with anaemia was 17.8%, 22.9%, and 30.1% for sarilumab 150 mg, 200 mg, and placebo, respectively.

Conclusion

In Japanese patients with RA, both doses of sarilumab were associated with greater improvement in haemoglobin levels and reduction in proportion of patients with anaemia, compared with placebo. Sarilumab may be a suitable treatment for patients with RA and anaemia.

Key words

rheumatoid arthritis, sarilumab, anaemia, haemoglobin, Japan

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with high morbidity and characterised by persistent joint inflammation, which leads to destruction and deformation of bone and cartilage (1). The global prevalence of RA is estimated as 0.46%, and that in Japan as 0.75% (2, 3). The pathophysiology of RA is complex and histopathological and immunopathological studies suggest that the inflammation and associated damage to articular cartilage and underlying bone involves antigen presentation, activation of T-cells, and an autoimmune response to produce inflammatory mediators (4). Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumour-necrosis factor α (TNF-α) play an important role in pathogenesis of RA, contributing to chronic inflammation (5).

In addition to progressive joint damage, RA is associated with an extra-articular manifestation anaemia, which affects 30–70% of patients and contributes to reduced quality of life (6, 7). Older patients in particular are likely to have more comorbidities and lower haemoglobin levels than younger patients (8). Multiple mechanisms are involved in the pathogenesis of anaemia in RA, including impaired erythropoiesis, iron homeostasis, and a blunted erythropoietin response (9).

Several studies, including the MEASURE trial have shown that IL-6 contributes to the development of anaemia in patients with RA by modulating iron metabolism and suppressing bone marrow erythropoiesis (10, 11). It has also been reported that IL-6 induces hepcidin, a critical regulator of iron metabolism in anaemia (12, 13). The change in haemoglobin levels may correlate with either clinical response to treatment or reduction of inflammatory markers (10). As IL-6 and other cytokines are involved in the pathogenesis of anaemia in RA, biologic therapies, such as IL-6 inhibitors and TNF-α inhibitors, could potentially increase haemoglobin levels after treatment (10).

Sarilumab is a human immunoglobulin (IgG1) antibody that selectively binds membrane-bound and soluble IL-6 receptor-α, thus inhibiting IL-6-mediated signal transduction (14). It is approved in the United States, Europe, and Japan for treatment in patients with moderate-to-severe active RA as monotherapy and in combination with csDMARDs in patients with an inadequate response or intolerance to one or more csDMARDs (15-17).

In a multicentre, phase III, 24-week MONARCH (NCT02332590) study, sarilumab monotherapy was associated with a greater reduction in the proportion of RA patients who had anaemia, from baseline to Week 24, than adalimumab (14.1% *vs.* 8.8%). The increase in haemoglobin levels was greater in the sarilumab group than in the adalimumab group (least squares mean [LSM] change from baseline to Week 24; sarilumab 0.591 g/dL and adalimumab 0.075 g/dL) (18).

The aim of this *post-hoc* analysis was to assess potential relationships between haemoglobin, disease activity, and physical function in Japanese patients with RA, enrolled in the KAKEHASI study (NCT02293902) (19).

Materials and methods

Study design and patient population

The methodology, safety and efficacy results of the 52-week, phase III, multicentre, parallel-group, KAKEHESI study have been published previously (19). Briefly, adult patients (aged 20–75 years) with moderate-to-severe active RA (defined as ≥8 of 68 tender joints and ≥6 of 66 swollen joints, and high-sensitivity C-reactive protein [hs-CRP] ≥0.6 mg/dL), and who had an inadequate response to methotrexate (MTX), were eligible for inclusion.

Patients were randomised (2:2:1:1) to one of the four following regimens with MTX as background therapy: sarilumab 150 mg; sarilumab 200 mg; placebo, switching to sarilumab 150 mg at Week 24; or placebo, switching to sarilumab 200 mg at Week 24, administered subcutaneously every 2 weeks (q2w). Patients with an inadequate response by Week 16, defined as <20% improvement from baseline on 2 consecutive visits (at least 4 weeks apart) in tender or swollen joint counts were eligible for rescue with sarilumab 200 mg q2w. Patients were analysed according to

Table I. Patient demographics, disease characteristics by anaemia (i.e. Low Hb) WHO criteria* at baseline - Randomised population

	Placebo + MTX (n=82)		Sarilumab 150 mg + MTX (n=81)		Sarilumab + MTX 200 mg (n=80)		Total (n=243)		*p*-value¥
	Low Hb (n=40)	Normal Hb (n=42)	Low Hb (n=36)	Normal Hb (n=45)	Low Hb (n=43)	Normal Hb (n=37)	Low Hb (n=119)	Normal Hb (n=124)	
Demographics									
Age (years), mean (SD)	52.15 (11.87)	54.57 (11.12)	57.64 (8.90)	54.82 (9.80)	55.09 (10.71)	55.49 (11.46)	54.87 (10.76)	54.94 (10.68)	0.9644
Age <65 years, n (%)	33 (82.5)	33 (78.6)	28 (77.8)	38 (84.4)	33 (76.7)	25 (67.6)	94 (79.0)	96 (77.4)	0.8767
Female, n (%)	33 (82.5)	32 (76.2)	27 (75.0)	36 (80.0)	35 (81.4)	26 (70.3)	95 (79.8)	94 (75.8)	0.5373
Weight (kg), mean (SD)	52.56 (10.66)	60.35 (12.44)	55.18 (11.80)	57.77 (12.93)	57.59 (11.29)	55.66 (10.43)	55.17 (11.35)	58.02 (12.12)	0.0598
Disease activity, mean (SD)									
CRP (mg/L)	28.62 (24.57)	16.42 (15.71)	24.26 (17.52)	21.84 (21.69)	30.17 (22.58)	14.82 (14.21)	27.86 (21.86)	17.91 (17.86)	0.0001
DAS28-CRP	5.52 (0.91)	5.35 (0.91)	5.84 (0.99)	5.49 (0.93)	5.63 (0.91)	5.11 (0.90)	5.66 (0.94)	5.33 (0.92)	0.0067
HAQ-DI score (0–3)	1.21 (0.66)	0.99 (0.63)	1.26 (0.69)	1.18 (0.65)	1.25 (0.66)	0.95 (0.62)	1.24 (0.66)	1.04 (0.64)	0.0218
CDAI	33.00 (9.95)	33.28 (10.86)	38.24 (12.86)	33.98 (12.19)	34.56 (12.21)	31.05 (11.41)	35.15 (11.81)	32.87 (11.49)	0.1283
Haematological parameters, mean (SD)									
RBC (10^{12}/L)	3.89 (0.36)	4.35 (0.33)	3.80 (0.37)	4.30 (0.27)	3.92 (0.34)	4.31 (0.32)	3.87 (0.36)	4.32 (0.31)	**<0.0001**
Haematocrit (%)	0.35 (0.03)	0.41 (0.03)	0.35 (0.03)	0.40 (0.03)	0.35 (0.02)	0.41 (0.03)	0.35 (0.03)	0.41 (0.03)	**<0.0001**
MCV (fL)	91.23 (7.38)	93.99 (5.01)	91.91 (6.54)	93.72 (5.21)	89.85 (6.75)	94.91 (4.72)	90.93 (6.90)	94.17 (4.98)	**<0.0001**
MCH (pg)	29.05 (2.93)	30.55 (1.93)	29.18 (2.77)	30.47 (1.53)	28.50 (3.00)	30.96 (1.81)	28.89 (2.90)	30.64 (1.75)	**<0.0001**
MCHC (g/dL)	31.80 (1.04)	32.50 (1.08)	31.70 (1.17)	32.53 (1.01)	31.66 (1.33)	32.61 (0.74)	31.72 (1.18)	32.55 (0.95)	**<0.0001**
Albumin (g/L)	39.18 (2.52)	41.60 (2.29)	39.25 (2.79)	41.13 (3.04)	38.86 (3.39)	41.38 (3.10)	39.08 (2.92)	41.36 (2.81)	**<0.0001**

*WHO criteria, haemoglobin <12 g/dL (female) or 13 g/dL (male).
¥Nominal *p*-values were obtained using t-test for equality of variance; if latter assumption was not met, Satterthwaite's p-value was provided.
CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28-CRP: Disease Activity Score-28 for rheumatoid arthritis with CRP; Hb: haemoglobin; HAQ-DI: Health Assessment Questionnaire-Disability Index; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; MCV: mean corpuscular volume; MTX: methotrexate; RBC: red blood cell count; SD: standard deviation; WHO: World Health Organization.

the haemoglobin levels at each visit (with or without anaemia; as defined by World Health Organisation [WHO] criteria (haemoglobin <12 g/dL, female; or <13 g/dL, male) (15, 20). Baseline haematological data were collected for all patients, such as haemoglobin levels, mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), mean corpuscular volume (MCV), red blood cell (RBC) count, and albumin levels.

The protocol was approved by independent ethics committees/institutional review boards, and all patients provided written informed consent prior to the conduct of any study-related procedures. The study was conducted in compliance with applicable laws and regulations, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki.

Endpoints

The endpoints for this *post-hoc* analysis included: (1) proportion of patients with anaemia at each visit, (2) LSM change from baseline in the haemoglobin level at each visit, and (3) LSM change from baseline in Disease Activity Score 28-joint count-CRP (DAS28-CRP), CRP, Clinical Disease Activity Index (CDAI), and pain visual analogue scale (VAS). These endpoints were evaluated in patients with and without anaemia status at baseline.

The relationship between haemoglobin levels and clinical and laboratory markers of disease activity, including CRP, DAS28-CRP, CDAI, and pain VAS were explored using Spearman rank correlation coefficient at Week 24.

Statistical analysis

The primary analysis population was the modified intent-to-treat (mITT) population, defined as randomised patients who received at least one dose of study drug and had an evaluable primary endpoint, post-baseline. Safety population included randomised population who received at least one dose. Continuous data were summarised using the number of available data, mean, standard deviation, median, minimum, and maximum for each treatment group. Binary exploratory efficacy variables (proportion of patients with anaemia) were analysed up to Week 24 by the two-sided Cochran-Mantel-Haenszel test stratified by prior biologic use and weight (<55 kg, ≥55 kg) at screening to assess treatment differences in the endpoints.

The continuous exploratory efficacy variables were analysed, up to Week 24, with a mixed model repeated measures (MMRM) approach. The model, including treatment, prior biologic use, weight (<55 kg, ≥55 kg) at screening, visit, and treatment-by-visit interaction as fixed effects and baseline as a covariate, was used to test the difference between each active treatment group vs. placebo in the change from baseline. Descriptive statistics, including number of subjects, mean, standard error, and LSM, were provided at each visit. In addition, difference in LSM, and the corresponding 95% confidence interval (CI) were provided along with the *p*-values. Missing data were not imputed. A logistic regression model with terms of treatment, prior biological use, prior biological use-by-treatment interaction, and weight (<55 kg, ≥55 kg) at screening was conducted to evaluate the interaction between change in haemoglobin and efficacy of sarilumab.

Results

Baseline demographics and patient characteristics

Of the 243 randomised patients in the KAKEHESI study, nearly half of patients had anaemia at baseline (119/243, 49.0%). The proportions of patients with baseline anaemia in the placebo (40/82, 49.8%), sarilumab 150

Table II. Correlation of haemoglobin level with clinical and laboratory markers relating to disease activity.

Parameters	Week 16 Sarilumab			Week 24 Sarilumab		
	Placebo + MTX (n=81)	150 mg + MTX (n=81)	200 mg + MTX (n=80)	Placebo + MTX (n=81)	150 mg + MTX (n=81)	200 mg + MTX (n=80)
CDAI						
n	75	77	73	30	67	62
Correlation coefficient	–0.19	–0.05	–0.14	–0.03	–0.03	–0.13
p-value	0.1035	0.6512	0.2336	0.8865	0.8166	0.3168
HAQ-DI						
n	75	77	73	30	67	62
Correlation coefficient	–0.35	–0.35	–0.11	–0.03	–0.16	–0.12
p-value	0.0022	0.0015	0.3478	0.8584	0.2109	0.3586
DAS28-CRP						
n	74	77	73	30	67	62
Correlation coefficient	–0.25	–0.03	–0.23	0.07	–0.12	–0.18
p-value	0.0280	0.8137	0.0494	0.7100	0.3152	0.1654
CRP						
n	74	77	73	30	67	62
Correlation coefficient	–0.11	–0.27	–0.43	–0.05	–0.17	–0.34
p-value	0.3505	0.0168	0.0001	0.7948	0.1649	0.0059
Pain VAS						
n	75	77	73	30	67	62
Correlation coefficient	–0.28	–0.24	–0.17	–0.02	–0.04	–0.18
p-value	0.0143	0.0336	0.1453	0.9200	0.7235	0.1635
Patient Global VAS						
n	75	77	73	30	67	62
Correlation coefficient	–0.28	–0.12	–0.15	–0.12	–0.10	–0.13
p-value	0.0157	0.3197	0.2125	0.5246	0.4108	0.3026

CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28-CRP: Disease Activity Score-28 for rheumatoid arthritis with CRP; HAQ-DI: Health Assessment Questionnaire-Disability Index; MTX: methotrexate; VAS: visual analogue scale.

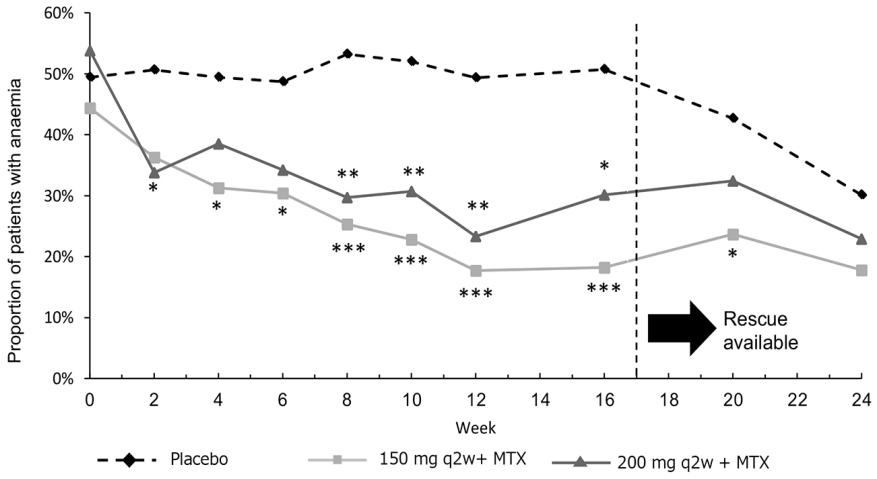

Fig. 1. Proportion of patients with anaemia, by week – Safety population
*nominal $p<0.05$, **nominal $p<0.01$, ***nominal $p<0.001$ *vs*. placebo; CMH test stratified by prior biologic use (Yes, No) and weight at screening (<55 kg, ≥55 kg).
CMH: Cochran-Mantel-Haenszel; MTX: methotrexate; q2w, every 2 weeks.

mg (36/81, 44.4%), sarilumab 200 mg (43/80, 53.8%), and sarilumab pooled (79/161, 49.1%) groups were comparable (Table I). The baseline demographics were generally well-balanced between patients with anaemia and without anaemia at baseline, across all treatment groups was 54.9 (10.8) and 54.9 (10.7) years, respectively (Table I). At baseline, patients with anaemia were predominantly females (79.8% *vs*. 75.8%) and had lower body weight (55.2 *vs*. 58.0 kg), compared with patients with normal haemoglobin (Table I).

Lower blood count values (RBC, haematocrit, MCV, MCH, MCHC) and serum albumin levels ($p<0.0001$; for all) were reported in patients with anaemia at baseline, than those without anaemia. Patients with anaemia at baseline reported higher DAS28-CRP ($p=0.0067$), HAQ-DI ($p=0.0218$), and CRP ($p=0.0001$) values than those with normal haemoglobin. No significant difference in CDAI scores was reported between the 2 groups ($p=0.1283$).

Effect of sarilumab treatment on change in proportion of patients with anaemia, by week

A greater reduction in the proportion of patients with anaemia was observed for the sarilumab group than for the placebo group (Fig. 1). Data after 16 Weeks at which patients may transition to rescue therapy (sarilumab 200 mg), include data from each group of patients who were rescued. In the sarilumab group, there was a reduction in the proportion of patients with anaemia starting at Week 2 and anaemia was resolved by 24 weeks in more than half of patients treated with sarilumab. The proportion of patients classified as having anaemia at Week 16, *i.e*. prior to the availability of rescue medication, was 50.7% (38/75), 18.2% (14/77), and 30.1% (22/73) in the placebo, sarilumab 150 mg, and sarilumab 200 mg groups compared with 49.4% (40/81), 44.4% (36/81), and 53.8% (43/80) at baseline, respectively (Fig. 1). At Week 20, 32 patients in the placebo arm were anaemic, of whom 43.8% (14/32) received rescue therapy with 200 mg sarilumab. Few patients in the sarilumab groups received rescue therapy after Week 16. By Week 20, 1 and 3 patients in the sarilumab 150 mg and 200 mg groups, respectively, were classified as anaemic and receiving rescue therapy. At Week 24 there was a reduction in the proportion of patients with anaemia

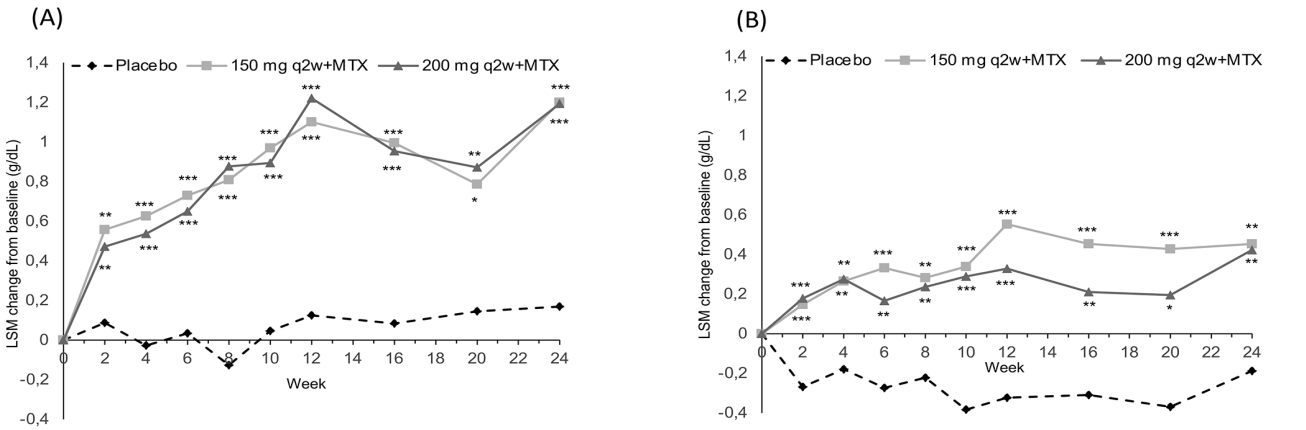

Fig. 2. Least squares mean change from baseline in haemoglobin levels in patients with anaemia (**A**) and without anaemia (**B**) at baseline - Safety population. *nominal $p<0.05$, **nominal $p<0.01$, ***nominal $p<0.001$ *vs.* placebo[a].
[a]Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biologic use (Yes, No), weight at screening (<55 kg, ≥55 kg), visit, and treatment-by-visit interaction.
LSM: least squares mean; MMRM: mixed model repeated measures; MTX: methotrexate; q2w: every 2 weeks.

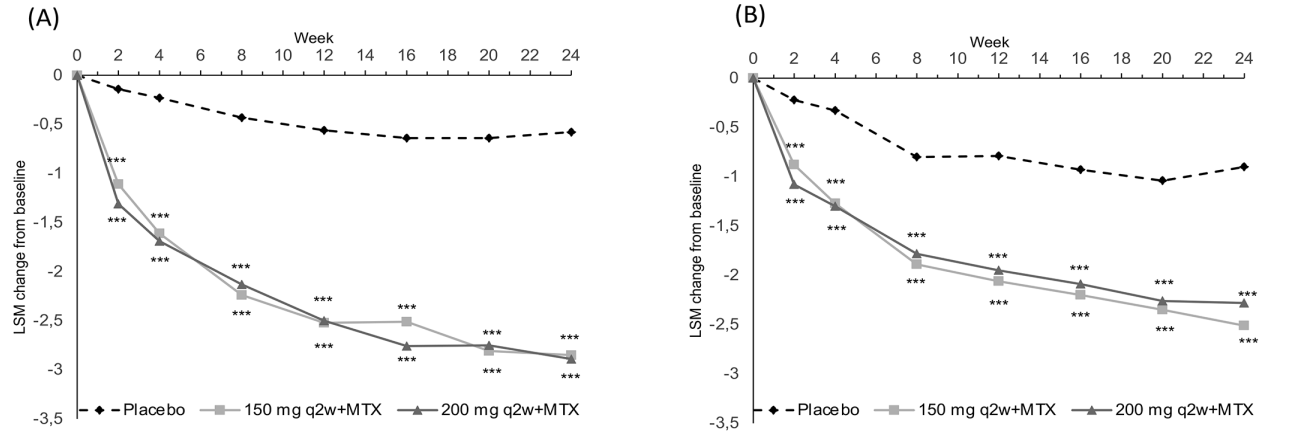

Fig. 3. Least squares mean change from baseline in DAS28-CRP in patients with anaemia (**A**) and without anaemia (**B**) at baseline - mITT population. *nominal $p<0.05$, **nominal $p<0.01$, ***nominal $p<0.001$ *vs.* placebo[a].
[a]Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biologic use (Yes, No), weight at screening (<55 kg, ≥55 kg), visit, and treatment-by-visit interaction.
DAS28-CRP: Disease Activity Score-28 for rheumatoid arthritis with C-reactive protein; LSM: least squares mean; mITT: modified intent-to-treat; MMRM: mixed model repeated measures; MTX: methotrexate; q2w: every 2 weeks.

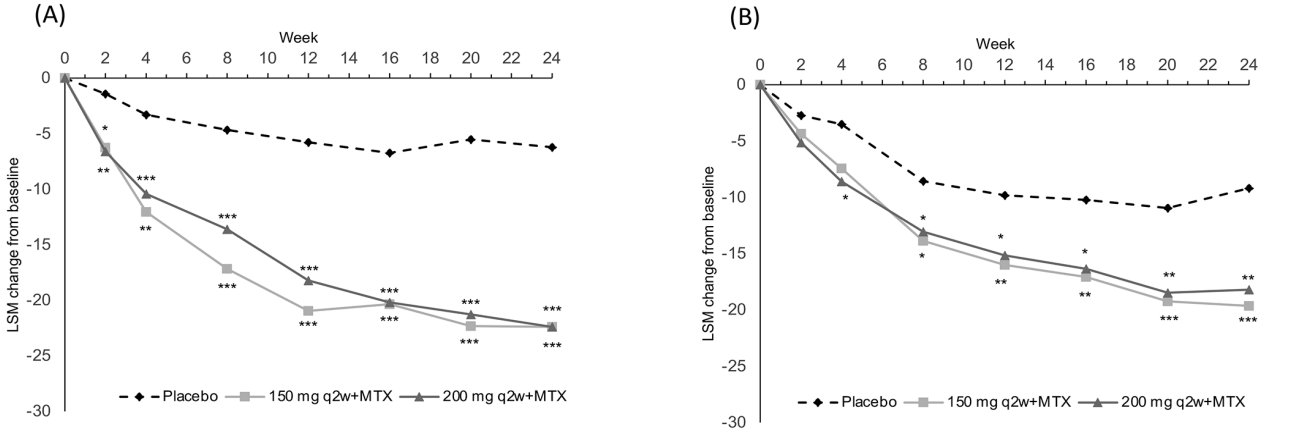

Fig. 4. Least squares mean change from baseline in CDAI scores in patients with anaemia (A) and without anaemia (B) at baseline - mITT population. *nominal $p<0.05$, **nominal $p<0.01$, ***nominal $p<0.001$ *vs.* placebo[a].
[a]Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biologic use (Yes, No), weight at screening (<55 kg, ≥55 kg), visit, and treatment-by-visit interaction.
CDAI: Clinical Disease Activity Index; LSM: least squares mean; mITT: modified intent-to-treat; MMRM: mixed model repeated measures; MTX: methotrexate; q2w: every 2 weeks.

across all groups; 30.1% (22/73) in placebo, 17.8% (13/73) in sarilumab 150 mg, and 22.9% (16/70) in sarilumab 200 mg groups. Similar trends in use of rescue medication at Week 20 were also observed at Week 24.

Effect of sarilumab on haemoglobin levels

Sarilumab-treated patients had a greater improvement in haemoglobin levels than the placebo group at Week 2, and these improvements were maintained at Week 24 (Fig. 2). A similar improvement in haemoglobin levels at Week 24 was reported for both sarilumab groups. At Week 16 the change in haemoglobin levels was greater in the sarilumab groups than in the placebo: sarilumab 150 mg *versus* placebo (0.995 *vs*. 0.083 g/dL; LSM difference: 0.912 g/dL; $p<0.0001$) and sarilumab 200 mg *versus* placebo (0.953 *vs*. 0.083 g/dL; LSM difference: 0.870 g/dL; $p<0.0001$). This change was sustained at Week 24; sarilumab 150 mg *versus* placebo (1.200 *vs*. 0.169 g/dL; LSM difference: 1.314 g/dL; $p=0.0002$) and sarilumab 200 mg *versus* placebo (1.193 *vs*. 0.169 g/dL; difference: 1.239 g/dL; $p=0.0002$) (Fig. 2A) (see Supplementary Table S1 for absolute values). Even in patients without anaemia at baseline, the changes in haemoglobin level was greater in sarilumab groups, compared with placebo group at both Weeks 16 and 24; Week 16: sarilumab 150 mg *versus* placebo: 0.454 *versus* -0.309 g/dL; difference: 0.7627 g/dL; $p<0.0001$ and sarilumab 200 mg *versus* placebo: 0.210 *versus* -0.309 g/dL; difference: 0.517 g/dL; $p=0.0042$); Week 24, the change in haemoglobin levels were: sarilumab 150 mg *versus* placebo: 0.453 *versus* -0.187 g/dL; difference: 0.640 g/dL; $p=0.0041$ and sarilumab 200 mg *versus* placebo: 0.423 *versus* -0.187 g/dL; difference: 0.609 g/dL; $p=0.0093$ (Fig. 2B). No clear differences were apparent in the LSM changes of haemoglobin between the treatment groups at any timepoint (Suppl. Table S2). However, for patients with anaemia at baseline, LSM haemoglobin notably increased from Week 8 to 16 for sarilumab 150 mg *versus* placebo (11.89 *vs*. 11.14 g/dL, $p=0.0041$) and 200 mg (11.98 *vs*. 11.14, $p=0.001$) treatment groups (Suppl. Table SI). In patients without anaemia at baseline, from Week 2 onwards LSM haemoglobin in the sarilumab 200 mg group was higher than in placebo (13.47 g/dL *vs*. 12.88, $p=0.0024$) and from Week 10 onwards for the sarilumab 150 mg (13.38 *vs*. 12.78 g/dL, $p=0.0041$) (Suppl. Table S1).

Effect of sarilumab treatment on RA disease activity: DAS28-CRP and CDAI score

In patients with anaemia at baseline, compared with placebo, treatment with sarilumab showed greater improvement in DAS28-CRP scores at Week 2 and these continued to decline to Week 24 (Fig. 3A). At Week 16, the LSM change from baseline in DAS28-CRP score was greater in the sarilumab groups than in the placebo group (sarilumab 150 mg *vs*. placebo: -2.51 *vs*. -0.64; difference: -1.878; $p<0.0001$ and sarilumab 200 mg *vs*. placebo: -2.76 *vs*. -0.64; difference: -2.121; $p<0.0001$) (Fig. 3A). In patients without anaemia at baseline (Fig. 3B), the improvement in DAS28-CRP at Week 16 was lower than in patients with anaemia at baseline (for patients without anaemia at baseline, LSM change in sarilumab 150 mg, sarilumab 200 mg and placebo was -2.20, -2.09, and -0.93, respectively [($p<0.0001$ for both doses *vs*. placebo]) (Fig. 3B). In patients with anaemia at baseline, LSM changes from baseline in DAS28-CRP scores at Week 24 were consistent for sarilumab 150 mg and sarilumab 200 mg *vs*. placebo; -2.85, -2.89, and -0.58, respectively; difference, -2.271 (for 150 mg) and -2.302 (for 200 mg); $p<0.0001$ (for both doses *vs*. placebo) (Fig. 3A). At Week 24, the LSM change from baseline in DAS28-CRP scores was -2.51, -2.28, and -0.90, respectively, ($p<0.0001$ for both doses *vs*. placebo) for patients without anaemia at baseline (Fig. 3B). However, the absolute LSM DAS28-CRP scores were initially higher in patients with anaemia at baseline than in those without anaemia (5.45 *vs*. 5.26, placebo; 5.81 *vs*. 5.47, sarilumab 150 mg; 5.62 *vs*. 5.07, sarilumab 200 mg; Supplementary Table S1).

Results for CDAI were similar to those for DAS28-CRP. Sarilumab demonstrated greater efficacy compared with placebo in CDAI scores throughout the study duration. Changes in CDAI scores were more prominent in patients with anaemia at baseline *versus* patients without anaemia.

At Week 16, in patients with anaemia at baseline, the LSM change in CDAI scores was greater for both doses of sarilumab compared with placebo (sarilumab 150 mg: -20.34, sarilumab 200 mg: -20.19 and placebo: -6.74; $p<0.0001$ for both doses *vs*. placebo) (Fig. 4). At Week 24, sarilumab treated patients with anaemia at baseline had lower mean CDAI compared with patients receiving placebo (for 150 mg: -22.39 *vs*. -6.21; difference: -16.187 and for 200 mg: -22.40 *vs*. -6.21; difference: -16.188; $p<0.0001$ for both doses *vs*. placebo) (Fig. 4, Suppl. Table S1).

In patients without anaemia at baseline, the LSM change in CDAI scores at Week 16 was greater for both dos-s of sarilumab compared with placebo (sarilumab 150 mg: -17.06, sarilumab 200 mg: -16.34 and placebo: -10.23; $p=0.0068$ for 150 mg and $p=0.023$ for 200 mg *vs*. placebo). At Week 24, these changes were -19.64 in sarilumab 150 mg, -18.21 in sarilumab 200 mg and -9.18 in placebo groups ($p=0.0001$ for 150 mg and $p=0.0014$ for 200 mg *vs*. placebo) (Fig. 4); refer to Supplementary Table S1 for LSM values.

Effect of sarilumab treatment on inflammatory marker, CRP

Changes of CRP from baseline were similar between the 2 treatment groups over most time points. In patients with anaemia at baseline a reduction in LSM CRP level was observed from Week 2 onwards with both sarilumab treatment groups *versus* placebo and was sustained throughout the treatment period (Fig. 5A). In patients without anaemia at baseline, improvements *versus* placebo were found for sarilumab 200 mg from Week 2 and for sarilumab 150 mg from Week 4 (Fig. 5B).

At Week 16, the LSM change in CRP levels from baseline in patients with anaemia was higher in the sarilumab 150 mg (-2.19) and sarilumab 200 mg

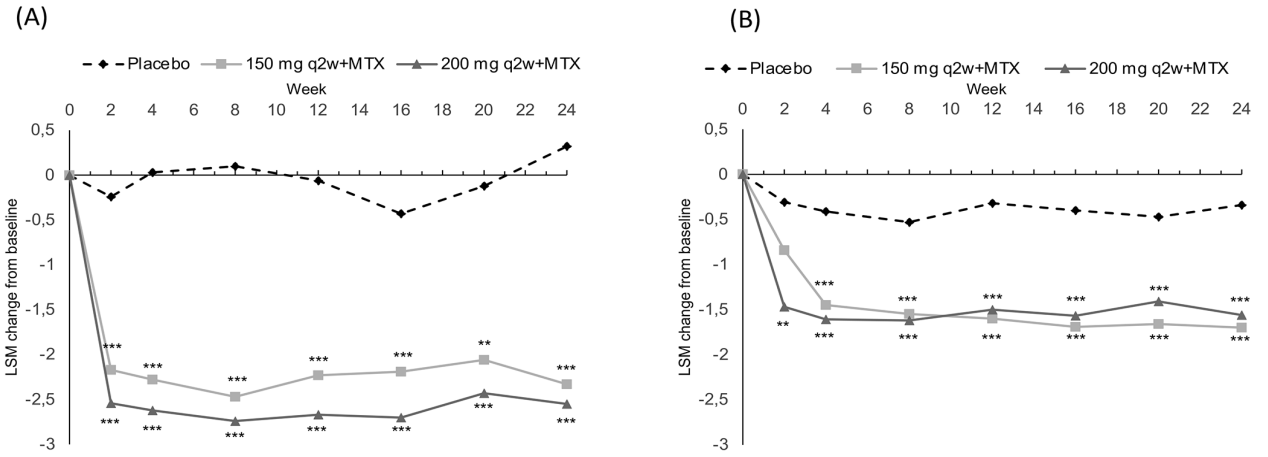

Fig. 5. Least squares mean change from baseline in CRP levels in patients with anaemia (**A**) and without anaemia (**B**) at baseline - mITT population. *nominal $p<0.05$, **nominal $p<0.01$, ***nominal $p<0.001$ *vs*. placebo[a].
[a]Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biologic use (Yes, No), weight at screening (<55 kg, ≥55 kg), visit, and treatment-by-visit interaction.
CRP: C-reactive protein; LSM: least squares mean; mITT: modified intent-to-treat; MMRM: mixed model repeated measures; MTX: methotrexate; q2w: every 2 weeks.

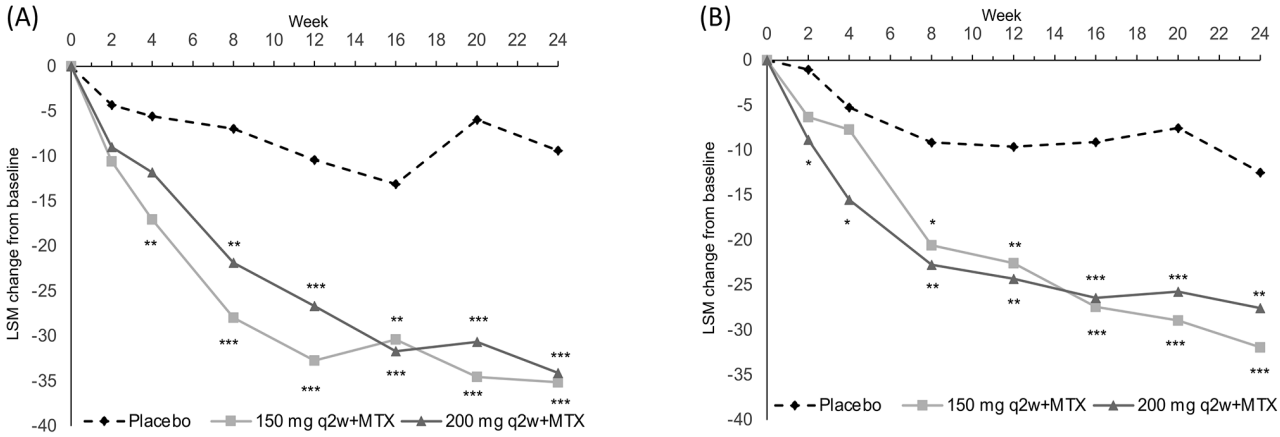

Fig. 6. Least squares mean change from baseline in pain-VAS score in patients with anaemia (**A**) and without anaemia (**B**) at baseline - mITT population. *nominal $p<0.05$, **nominal $p<0.01$, ***nominal $p<0.001$ *vs*. placebo[a].
[a]Type III sum of squares MMRM with PROC MIXED assuming an unstructured covariance structure: model = baseline, treatment, prior biologic use (Yes, No), weight at screening (<55 kg, ≥55 kg), visit, and treatment-by-visit interaction.
LSM: least squares mean; mITT: modified intent-to-treat; MMRM: mixed model repeated measures; MTX: methotrexate; q2w: every 2 weeks; VAS: visual analogue scale.

groups (-2.70), compared with placebo (-0.43). The differences between groups were -1.765 for sarilumab 150 mg *versus* placebo and -2.277 for sarilumab 200 mg *versus* placebo ($p<0.0001$ for both doses *vs*. placebo). Similar changes in CRP levels were reported at Week 24 in sarilumab 150 mg, sarilumab 200 mg and placebo: -2.33, -2.55, and 0.32, respectively ($p<0.0001$ for both doses *vs*. placebo) (Fig. 5, Suppl. Table S1).

In patients without anaemia at baseline, the LSM change in CRP levels at Week 16 was greater for both doses of sarilumab compared with placebo (sarilumab 150 mg: -1.69, sarilumab 200 mg: -1.57 and placebo: -0.40*;* $p<0.0001$ for both doses *vs*. placebo). At Week 24, these changes were -1.70 in sarilumab 150 mg, -1.56 in sarilumab 200 mg and -0.34 in placebo groups ($p<0.0001$ for both doses *vs*. placebo) (Fig. 5, Suppl. Table S1).

Effect of sarilumab treatment on pain

There were no notable differences between the LSM changes of pain-VAS from baseline between the 2 treatment groups (Suppl. Table S2). Patients with anaemia at baseline receiving sarilumab 150 mg and 200 mg had improvements over placebo from Week 8. This improvement was maintained through Week 24 (LSM change -35.13, -34.09, and -9.36, respectively; $p<0.0001$ for each dose *vs*. placebo) (Fig. 6A); see Supplementary Table S1 for absolute values.

As for other parameters, the improvement in pain-VAS scores was more evident in patients with anaemia at baseline, compared with those without anaemia. In patients without anaemia at baseline, LSM pain VAS scores were similar between treatment groups but became notably different compared with placebo from Week 4 and Week 12 for sarilumab 200 mg and 150 mg,

Table III. Number (%) of patients with TEAE(s) >3% at Week 52 subgroup by WHO defined anaemia criteria at baseline according to MedDRA system organ class and preferred terms.

	Placebo + MTX (n=81)		Sarilumab 150 mg (n=81)		Sarilumab 200 mg (n=80)		Total (n=242)	
Primary System Organ Class Preferred Term	Low Hb (n=40)	Normal Hb (n=41)	Low Hb (n=36)	Normal Hb (n=45)	Low Hb (n=43)	Normal Hb (n=37)	Low Hb (n=119)	Normal Hb (n=123)
Any class	30 (75.0)	28 (68.3)	33 (91.7)	43 (95.6)	36 (83.7)	35 (94.6)	99 (83.2)	106 (86.2)
Infections and infestations	16 (40.0)	19 (46.3)	20 (55.6)	35 (77.8)	22 (51.2)	20 (54.1)	58 (48.7)	74 (60.2)
Nasopharyngitis	11 (27.5)	9 (22.0)	9 (25.0)	18 (40.0)	12 (27.9)	11 (29.7)	32 (26.9)	38 (30.9)
Upper respiratory tract infection	2 (5.0)	2 (4.9)	2 (5.6)	6 (13.3)	3 (7.0)	4 (10.8)	7 (5.9)	12 (9.8)
Gastroenteritis	0	1 (2.4)	2 (5.6)	0	3 (7.0)	3 (8.1)	5 (4.2)	4 (3.3)
Cystitis	0	1 (2.4)	1 (2.8)	4 (8.9)	1 (2.3)	0	2 (1.7)	5 (4.1)
Pharyngitis	1 (2.5)	1 (2.4)	2 (5.6)	2 (4.4)	1 (2.3)	1 (2.7)	4 (3.4)	4 (3.3)
Bronchitis	0	2 (4.9)	1 (2.8)	3 (6.7)	0	1 (2.7)	1 (0.8)	6 (4.9)
Cellulitis	0	0	2 (5.6)	1 (2.2)	1 (2.3)	0	3 (2.5)	1 (0.8)
Herpes zoster	1 (2.5)	0	1 (2.8)	2 (4.4)	1 (2.3)	0	3 (2.5)	2 (1.6)
Periodontitis	1 (2.5)	0	1 (2.8)	3 (6.7)	0	0	2 (1.7)	3 (2.4)
Conjunctivitis	0	0	0	3 (6.7)	0	0	0	3 (2.4)
Influenza	0	2 (4.9)	0	1 (2.2)	2 (4.7)	0	2 (1.7)	3 (2.4)
Oral herpes	2 (5.0)	2 (4.9)	0	0	2 (4.7)	0	4 (3.4)	2 (1.6)
Pyelonephritis	0	1 (2.4)	0	2 (4.4)	0	0	0	3 (2.4)
Tinea pedis	0	2 (4.9)	1 (2.8)	1 (2.2)	0	0	1 (0.8)	3 (2.4)
Blood and lymphatic system disorders	4 (10.0)	1 (2.4)	6 (16.7)	9 (20.0)	10 (23.3)	3 (8.1)	20 (16.8)	13 (10.6)
Neutropenia	2 (5.0)	1 (2.4)	4 (11.1)	6 (13.3)	7 (16.3)	2 (5.4)	13 (10.9)	9 (7.3)
Thrombocytopenia	0	0	1 (2.8)	2 (4.4)	2 (4.7)	1 (2.7)	3 (2.5)	3 (2.4)
Iron deficiency anaemia	0	0	1 (2.8)	0	2 (4.7)	0	3 (2.5)	0
Leukopenia	2 (5.0)	0	0	2 (4.4)	1 (2.3)	0	3 (2.5)	2 (1.6)
Metabolism and nutrition disorders	2 (5.0)	1 (2.4)	2 (5.6)	2 (4.4)	1 (2.3)	2 (5.4)	5 (4.2)	5 (4.1)
Hyperlipidaemia	0	0	0	0	0	2 (5.4)	0	2 (1.6)
Psychiatric disorders	2 (5.0)	0	0	3 (6.7)	1 (2.3)	2 (5.4)	3 (2.5)	5 (4.1)
Insomnia	1 (2.5)	0	0	2 (4.4)	1 (2.3)	2 (5.4)	2 (1.7)	4 (3.3)
Nervous system disorders	5 (12.5)	2 (4.9)	1 (2.8)	5 (11.1)	4 (9.3)	5 (13.5)	10 (8.4)	12 (9.8)
Headache	2 (5.0)	1 (2.4)	1 (2.8)	0	1 (2.3)	2 (5.4)	4 (3.4)	3 (2.4)
Dizziness	2 (5.0)	1 (2.4)	0	0	1 (2.3)	2 (5.4)	3 (2.5)	3 (2.4)
Sciatica	0	0	0	2 (4.4)	1 (2.3)	0	1 (0.8)	2 (1.6)
Vascular disorders	1 (2.5)	0	1 (2.8)	4 (8.9)	3 (7.0)	2 (5.4)	5 (4.2)	6 (4.9)
Hypertension	0	0	1 (2.8)	3 (6.7)	3 (7.0)	2 (5.4)	4 (3.4)	5 (4.1)
Gastrointestinal disorders	11 (27.5)	6 (14.6)	9 (25.0)	10 (22.2)	14 (32.6)	11 (29.7)	34 (28.6)	27 (22.0)
Stomatitis	3 (7.5)	2 (4.9)	3 (8.3)	3 (6.7)	4 (9.3)	4 (10.8)	10 (8.4)	9 (7.3)
Abdominal pain upper	1 (2.5)	0	0	1 (2.2)	4 (9.3)	0	5 (4.2)	1 (0.8)
Dental caries	1 (2.5)	2 (4.9)	1 (2.8)	1 (2.2)	3 (7.0)	0	5 (4.2)	3 (2.4)
Diarrhoea	1 (2.5)	1 (2.4)	0	2 (4.4)	0	2 (5.4)	1 (0.8)	5 (4.1)
Nausea	1 (2.5)	0	0	0	2 (4.7)	2 (5.4)	3 (2.5)	2 (1.6)
Gastroesophageal reflux disease	0	1 (2.4)	0	0	2 (4.7)	1 (2.7)	2 (1.7)	2 (1.6)
Hepatobiliary disorders	4 (10.0)	3 (7.3)	3 (8.3)	8 (17.8)	7 (16.3)	3 (8.1)	14 (11.8)	14 (11.4)
Hepatic function abnormal	2 (5.0)	2 (4.9)	2 (5.6)	6 (13.3)	5 (11.6)	2 (5.4)	9 (7.6)	10 (8.1)
Hepatic steatosis	1 (2.5)	1 (2.4)	0	0	2 (4.7)	0	3 (2.5)	1 (0.8)
Skin and subcutaneous tissue disorders	4 (10.0)	5 (12.2)	10 (27.8)	15 (33.3)	10 (23.3)	9 (24.3)	24 (20.2)	29 (23.6)
Eczema	2 (5.0)	0	5 (13.9)	2 (4.4)	3 (7.0)	1 (2.7)	10 (8.4)	3 (2.4)
Rash	0	0	0	4 (8.9)	2 (4.7)	2 (5.4)	2 (1.7)	6 (4.9)
Dermatitis contact	1 (2.5)	2 (4.9)	0	1 (2.2)	0	3 (8.1)	1 (0.8)	6 (4.9)
Ingrowing nail	0	2 (4.9)	1 (2.8)	1 (2.2)	0	0	1 (0.8)	3 (2.4)
Rash pruritic	0	0	0	0	0	2 (5.4)	0	2 (1.6)
Musculoskeletal and connective tissue disorders	6 (15.0)	5 (12.2)	3 (8.3)	7 (15.6)	4 (9.3)	5 (13.5)	13 (10.9)	17 13.8)
Rheumatoid arthritis	3 (7.5)	1 (2.4)	1 (2.8)	1 (2.2)	1 (2.3)	3 (8.1)	5 (4.2)	5 (4.1)
Myalgia	0	0	0	2 (4.4)	0	0	0	2 (1.6)
General disorders and administration site conditions	3 (7.5)	1 (2.4)	6 (16.7)	10 (22.2)	9 (20.9)	6 (16.2)	18 (15.1)	17 (13.8)
Injection site erythema	1 (2.5)	0	3 (8.3)	5 (11.1)	4 (9.3)	3 (8.1)	8 (6.7)	8 (6.5)
Injection site pruritus	1 (2.5)	0	2 (5.6)	3 (6.7)	2 (4.7)	2 (5.4)	5 (4.2)	5 (4.1)
Fatigue	1 (2.5)	0	1 (2.8)	1 (2.2)	2 (4.7)	0	4 (3.4)	1 (0.8)
Injection site rash	0	0	3 (8.3)	0	0	0	3 (2.5)	0
Injection site swelling	0	0	0	2 (4.4)	0	0	0	2 (1.6)
Investigations	6 (15.0)	3 (7.3)	5 (13.9)	9 (20.0)	9 (20.9)	5 (13.5)	20 (16.8)	17 (13.8)
Alanine aminotransferase increased	3 (7.5)	3 (7.3)	1 (2.8)	6 (13.3)	3 (7.0)	1 (2.7)	7 (5.9)	10 (8.1)
White blood cell count decreased	0	0	1 (2.8)	3 (6.7)	1 (2.3)	1 (2.7)	2 (1.7)	4 (3.3)
Aspartate aminotransferase increased	1 (2.5)	0	0	4 (8.9)	0	0	1 (0.8)	4 (3.3)
Neutrophil count decreased	1 (2.5)	0	2 (5.6)	0	0	0	3 (2.5)	0
Injury, poisoning and procedural complications	3 (7.5)	4 (9.8)	7 (19.4)	9 (20.0)	2 (4.7)	5 (13.5)	12 (10.1)	18 (14.6)
Skin abrasion	0	0	2 (5.6)	2 (4.4)	0	0	2 (1.7)	2 (1.6)
Contusion	1 (2.5)	0	0	2 (4.4)	0	1 (2.7)	1 (0.8)	3 (2.4)
Fjll	0	0	0	3 (6.7)	0	0	0	3 (2.4)

MedDRA: Medical Dictionary for Regulatory Activities; Hb: haemoglobin; MTX, methotrexate; TEAE: treatment emergent adverse event; WHO: World Health Organization.

respectively (Suppl. Table S1). At Week 16, in patients without anaemia at baseline, the LSM change in sarilumab 150 mg, sarilumab 200 mg and placebo was -27.44, -26.42, and -9.08, respectively (for 150 mg, $p<0.0001$ *vs*. placebo; for 200 mg, $p=0.0005$ *vs*. placebo) and at Week 24 was -31.92, -27.56, and -12.46, respectively (for 150 mg, $p=0.0002$ *vs*. placebo; for 200 mg, $p=0.0059$ *vs*. placebo) (Fig. 6); refer to Supplementary Table S1 for LSM values.

Interaction between haemoglobin change in sarilumab efficacy

In this *post-hoc* analysis, except some associations between CRP and haemoglobin change for the sarilumab 200 mg group, there were no meaningful correlations with LSM changes from baseline in haemoglobin and LSM changes from baseline in disease activity measures at Week 16 and Week 24 in the treatment groups (Suppl. Table S3). A subgroup analysis of patients by baseline anaemia status found that in patients with anaemia at baseline, change in haemoglobin from baseline was associated with CRP levels for sarilumab 200 mg (corelation coefficient: -0.35, $p=0.0483$ at Week 24) (Suppl. Table S3). However, no such correlation was present in patients without anaemia at baseline.

Safety

In the placebo group, all treatment emergent adverse events (TEAEs), of all types, were reported in 75.0% (30/40) and 68.3% (28/41) of patients with and without anaemia at baseline, respectively (Table III). The incidence of TEAEs was higher in the active treatment groups, but there were no notable differences between patients with and without anaemia, respectively, at 91.7% (33/36) and 95.6% (43/45) for the sarilumab 150 mg group and 83.7% (36/43) and 94.6% (35/37) for the sarilumab 200 mg group.

Serious adverse events in the active treatment arms (data not shown) occurred for 11.4% (9/79) and 17.1% (14/82) of patients with and without anaemia at baseline compared with 7.5% (3/40) and 9.8% (4/41) in the placebo group. There were no serious adverse events that affected more than one patient.

Discussion

In this *post-hoc* analysis of the KAKEHASI study, both doses of sarilumab showed beneficial effects on haemoglobin levels and disease activity compared with placebo in Japanese patients with active RA and anaemia at baseline. Nearly half of the patients had anaemia at baseline, which was higher than the proportion of patients with anaemia in a phase III, multicentre, MOBILITY study (with 52 weeks of treatment, 4 weeks of screening and 6 weeks of follow-up) in patients with moderate-to-severe RA (49% *vs*. 35%, respectively) (21, 22).

An improvement in haemoglobin level was demonstrated by both doses of sarilumab in this *post-hoc* analysis, among patients with RA from Week 2 and was consistent up to Week 24. Notably, for patients without anaemia at baseline, differences in LSM haemoglobin from placebo were found earlier for the sarilumab 200 mg than for the sarilumab 150 mg group (Week 2 *vs*. Week 10). However, among patients with anaemia at baseline, significant to notable differences in LSM haemoglobin from placebo were observed at Week 8 for both treatment groups.

Approximately 10% of the patients in the treatment groups were considered to have inadequate response (*i.e*. <20% improvement from baseline on 2 consecutive visits at least 4 weeks apart) in tender or swollen joint counts) compared with approximately a quarter of patients in the placebo group. Patients with anaemia at baseline had a greater increase in haemoglobin levels over time, than those without anaemia. These results are in line with those from the MONARCH study, wherein treatment with sarilumab resulted in a larger increase in haemoglobin levels, compared with adalimumab at Weeks 12 and 24 ($p<0.001$, for both) (18).

Changes in DAS28-CRP scores were also greater among patients with anaemia at baseline, although this reflected an improvement of the absolute values to be similar to those of patients without anaemia. Notably, LSM changes in CRP and VAS-pain scores among patients without anaemia at baseline tended to become apparent earlier for patients receiving sarilumab 200 mg than those receiving 150 mg sarilumab. However, improvements in RA disease activity observed in patients with and without anaemia receiving both doses of sarilumab were clinically meaningful and included improvements at Weeks 16 and 24 in DAS28-CRP, CRP and CDAI, and pain-VAS. This was consistent with the results from a *post-hoc* analysis of the MONARCH study (18, 21). In the KAKEHASI study, changes in haemoglobin levels had no correlation with changes in disease activities in patients receiving sarilumab treatment, these results were consistent with findings from the global MONARCH study (18). In the current study, among patients with anaemia at baseline, an improvement in haemoglobin was associated with decreases in CRP levels. However, no such correlation was present in patients without anaemia at baseline.

Improvement of anaemia after biologic therapies, such as tocilizumab or TNFα inhibitors, has been reported in previous studies of patients with RA (10, 23, 24). In a cohort of 147 patients with RA enrolled in the Kyoto University Hospital, Japan, the increase in haemoglobin levels was greater in the tocilizumab group than the non-tocilizumab groups (1.1 g/dL in the TCZ group *vs*. 0.3 g/dL in the non-TCZ group, $p=0.009$) (10). Furthermore, in that study increased haemoglobin levels were associated with improvements in CDAI scores and CRP levels ($p=0.01$ and <0.001, respectively) (10). These results suggest the central role of IL-6 in patients with RA and anaemia. Similarly, in another study, patients with RA were treated with tocilizumab or TNF inhibitors for 16 weeks (6); wherein, anaemia at baseline was present in 66% of patients. Significant improvements in anaemia and disease activity, and reductions in serum hepcidin-25 levels ($p<0.01$) were observed within 2 weeks in both groups, and these effects were more pronounced in the tocilizumab group than in the TNF-α inhibitors group. These results further emphasise that IL-6 inhibitors could better improve

haematologic parameters, serum iron, and ferritin levels in patients with RA as compared with the effect of TNF-α inhibitors (6). In another *post-hoc* analysis of the MEASURE study, increase in haemoglobin levels and early reduction in CRP were observed in association with tocilizumab treatment in patients with RA (n=70) (11). Haemoglobin levels increased by Week 4 and increased further to Week 12, reaching a plateau by Week 24 (11). These results are similar to our *post-hoc* analysis where an increase in haemoglobin levels was reported from Week 2 and maintained up to Week 24.

The results of the current *post-hoc* analysis are consistent with a previous small study (18 patients with RA who were receiving adalimumab 40 mg fortnightly), which improved with adalimumab at Week 12 (p=0.013) and this was sustained until Week 24 (25).

In the *post-hoc* analysis of the MONARCH study, reductions in hepcidin and ferritin were observed at Week 2 with both sarilumab and adalimumab (26). The increase in iron and total iron binding capacity from baseline to Week 2 correlated with an increase in haemoglobin at Weeks 2–24 in the sarilumab group compared with the adalimumab group (p<0.01 *vs*. adalimumab) (26). Thus, sarilumab may be exerting direct effects on iron metabolism, possibly via decreasing hepcidin levels, as supported by the lack of correlation between haemoglobin levels and disease activity (27).

There are some limitations to the study findings. First, this was a *post-hoc* analysis conducted in Japanese patients, well-defined according to inclusion and exclusion criteria of the study; therefore, additional analyses are required to further understand the effect of sarilumab treatment on haematological changes in a wider population of patients with RA. Second, due to the lack of data on markers of iron status (serum iron, ferritin, and transferrin), hepcidin or erythropoietin, the mechanism of anaemia could not be assessed in this study population. Third, the KAKEHASI was a 52-week study; however, this *post-hoc* analysis focused on the results up to Week 24 as the treatment period with comparison to placebo at 24 weeks; hence, further exploration of more frequent and/or later timepoints may provide a more complete picture of haematological changes following treatment with sarilumab.

Conclusion

In Japanese patients with RA, treatment with 150 mg or 200 mg of sarilumab q2w was associated with a greater improvement in haemoglobin levels and reduction in the proportion of patients with anaemia, compared with placebo. Sarilumab also improved disease activity in patients with anaemia to a similar level to that of patients without anaemia. The results of this study suggest that sarilumab may be a suitable treatment choice for patients with RA, especially those with anaemia, which may be more common in Japanese than in non-Japanese patients (21, 22). However, further studies are needed to confirm these findings.

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References

1. CROTTI C, BIGGIOGGERO M, BECCIOLINI A, FAVALLI EG: Sarilumab: patient-reported outcomes in rheumatoid arthritis. *Patient Relat Outcome Meas* 2018; 9: 275-84. https://doi.org/10.2147/PROM.S147286
2. ALMUTIRI K, NOSSENT J, PREEN D, KEEN H, INDERJEETH C: The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. *Rheumatol Int* 2021; 41: 863-77. https://doi.org/10.1007/s00296-020-04731-0
3. KOJIMA M, NAKAYAMA T, TSUTANI K *et al*.: Epidemiological characteristics of rheumatoid arthritis in Japan: Prevalence estimates using a nationwide population-based questionnaire survey. *Mod Rheumatol* 2020; 30: 941-7. https://doi.org/10.1080/14397595.2019.1682776
4. YAP H-Y, TEE SZ-Y, WONG MM-T, CHOW S-K, PEH S-C, TEOW S-Y: Pathogenic role of immune cells in rheumatoid arthritis: Implications in clinical treatment and biomarker development. *Cells* 2018; 7: 161. https://doi.org/10.3390/cells7100161
5. PELECHAS E, VOULGARI PV, DROSOS AA: Clinical evaluation of the safety, efficacy and tolerability of sarilumab in the treatment of moderate to severe rheumatoid arthritis. *Ther Clin Risk Manag* 2019; 15: 1073-9. https://doi.org/10.2147/TCRM.S167452
6. SONG S-N, IWAHASHI M, TOMOSUGI N *et al*.: Comparative evaluation of the effects of treatment with tocilizumab and TNF-α inhibitors on serum hepcidin, anemia response and disease activity in rheumatoid arthritis patients. *Arthritis Res Ther* 2013; 15: R141. https://doi.org/10.1186/ar4323
7. PEREIRA ICP, SOUSA NCF, PEREIRA DMS *et al*.: Treatment with either leflunomide or adalimumab reduces anaemia in patients with rheumatoid arthritis. *An Acad Bras Cienc* 2018; 90: 2161-6. https://doi.org/10.1590/0001-3765201820170091
8. SPECKER C, ARINGER M, BURMESTER GR *et al*.: The safety and effectiveness of tocilizumab in elderly patients with rheumatoid arthritis and in patients with comorbidities associated with age. *Clin Exp Rheumatol* 2022; 40(9); 1657-65. https://doi.org/10.55563/clinexprheumatol/f7ff6q
9. WEISS G, GOODNOUGH LT: Anemia of chronic disease. *N Engl J Med* 2005; 352: 1011-23. https://doi.org/10.1056/NEJMra041809
10. HASHIMOTO M, FUJII T, HAMAGUCHI M *et al*.: Increase of hemoglobin levels by anti-IL-6 receptor antibody (tocilizumab) in rheumatoid arthritis. *PLoS One* 2014; 9: e98202. https://doi.org/10.1371/journal.pone.0098202
11. ISAACS JD, HARARI O, KOBOLD U, LEE JS, BERNASCONI C: Effect of tocilizumab on haematological markers implicates interleukin-6 signalling in the anaemia of rheumatoid arthritis. *Arthritis Res Ther* 2013; 15: R204. https://doi.org/10.1186/ar4397
12. RAJ DSC: Role of interleukin-6 in the anemia of chronic disease. *Semin Arthritis Rheumatol* 2009; 38: 382-8. https://doi.org/10.1016/j.semarthrit.2008.01.006
13. GANZ T: Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood* 2003; 102: 783-8. https://doi.org/10.1182/blood-2003-03-0672
14. GENOVESE MC, VAN DER HEIJDE D, LIN Y *et al*.: Long-term safety and efficacy of sarilumab plus methotrexate on disease activity, physical function and radiographic progression: 5 years of sarilumab plus methotrexate treatment. *RMD Open* 2019; 5: e000887. http://dx.doi.org/10.1136/rmdopen-2018-000887
15. LAMB YN, DEEKS ED: Sarilumab: a review in moderate to severe rheumatoid arthritis. *Drugs* 2018; 78: 929-40. https://doi.org/10.1007/s40265-018-0929-z
16. FDA. Kevzara (sarilumab) Prescribing Information [August 3, 2021]. Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2017/761037s000lbl.pdf
17. EMA. Summary of Product Characteristics. [Available from: www.ema.europa.eu/docs/en_GB/document_library/EPAR_ProductInformation/human/004254/WC500230068.pdf
18. BURMESTER GR, HAGINO O, THANGAVELU K *et al*.: Unique changes in hemoglobin with

sarilumab versus adalimumab are independent of better disease control in patients with rheumatoid arthritis. 2018 ACR/ARHP Annual Meeting, October 19-24, 2018 in Chicago, IL, USA, 2018.

19. TANAKA Y, WADA K, TAKAHASHI Y *et al*.: Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a randomized, placebo-controlled phase III trial in Japan. *Arthritis Res Ther* 2019; 21: 79. https://doi.org/10.1186/s13075-019-1856-4
20. DEMAEYER E, ADIELS-TEGMAN M: The prevalence of anaemia in the world. *World Health Stat Q* 1985; 38: 302-16.
21. GENOVESE MC, FLEISCHMANN R, KIVITZ AJ *et al*.: Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study. *Arthritis Rheumatol* 2015; 67: 1424-37. https://doi.org/10.1002/art.39093
22. BURMESTER G, MORELLO J, HAGINO O, PRAESTGAARD A, FIORE S, GENOVESE M: Association between low hemoglobin and radiographic progression over 52 weeks in patients with rheumatoid arthritis: Results from a phase 3 trial of sarilumab. *Ann Rheum Dis* 2020; 79: 983.
23. PAPADAKI H, KRITIKOS H, VALATAS V, BOUMPAS DT ELIOPOULOS GD: Anemia of chronic disease in rheumatoid arthritis is associated with increased apoptosis of bone marrow erythroid cells: improvement following anti-tumor necrosis factor-alpha antibody therapy. *Blood* 2002; 100: 474-82. https://doi.org/10.1182/blood-2002-01-0136
24. DOYLE M, RAHMAN M, FREDERICK B *et al*.: Effects of subcutaneous and intravenous golimumab on inflammatory biomarkers in patients with rheumatoid arthritis: Results of a phase 1, randomized, open-label trial. *Rheumatology* (Oxford) 2013; 52: 1214-19. https://doi.org/10.1093/rheumatology/kes381
25. SAKTHISWARY R, SYAHARUL SALIYANA S, MOHD SHAHRIR M, SHAHRIL N, HUSSEIN H: Beyond the joints in rheumatoid arthritis: effects of adalimumab on hematologic and lipid indices. *EXCLI J* 2012; 11: 142-9.
26. GABAY C, BURMESTER GR, STRAND V *et al*.: Sarilumab and adalimumab differential effects on bone remodelling and cardiovascular risk biomarkers, and predictions of treatment outcomes. *Arthritis Res Ther* 2020; 22: 70. https://doi.org/10.1186/s13075-020-02163-6
27. MASSON C: Rheumatoid anemia. *Joint Bone Spine* 2011; 78: 131-7. https://doi.org/10.1016/j.jbspin.2010.05.017