## Supplementary data

Additional methodology

### Biomarker analysis

All biomarker serum concentrations, except C-reactive protein (CRP), were analysed retrospectively using a validated proprietary enzyme-linked immunosorbent assay (ELISA) at Bioclinica Lab (Lyon, France). CRP was assessed at Covance Laboratories (Indianapolis, IN, USA, Geneva, Switzerland or Singapore) using the Siemens high-sensitivity CRP nephelometry assay. The intra-assay precision was <3%, inter-assay precision was <5.4%, and the reference range for healthy controls was ≤2.87 mg/L. Serum levels of chemokine (C-X-C motif) ligand 13 and soluble intercellular adhesion molecule-1 were assessed using an ELISA (Quantikine® ELISA kit, R&D Systems, Minneapolis, MN, USA), with inter-assay coefficient of variation (CV) <8% and intra-assay CV <15%. Serum procollagen type 1 *N*-terminal propeptide (P1NP) was measured using the Roche Modular S P1NP assay, with intra- and inter-assay CVs <7%. Serum amyloid A was measured using an ELISA (Anogen) with intra- and inter-assay CVs <7%. Ferritin was measured using the Roche Modular Serum Ferritin assay, with intra- and inter-assay CVs <3%. Total iron-binding capacity was measured using a Kone 20 analyser, Konelab (Total Iron-Binding Capacity [RANDOX]) with intra- and inter-assay CVs <5.5% and <4.7%, respectively. Serum levels of iron were measured using a Kone 20 analyser, Konelab (Iron [Thermo Scientific]) with intra- and inter-assay CVs <7.8% and <6%, respectively. Hepcidin levels were measured using an ELISA (Human Hepcidin 25 (bioactive) HS ELISA [DRG]) with intra- and inter-assay CVs <9.6% and <8.1%, respectively. Biomarker levels below the lower limit of quantification (LLOQ) were replaced by LLOQ/2 in all analyses, and those above upper limit of quantification (ULOQ) by ULOQ.

## Supplementary tables and figures

**Table S1** Individual serum biomarker assessment schedule

**Table S2** Efficacy and PROs at week 24 in the biomarker and ITT populations

**Table S3** Baseline biomarker serum concentrations in the biomarker population

**Table S4** Absolute change from baseline in biomarker concentrations through week 24

**Table S5** Percentage of patients with CRP ≤10 mg/L and ≤3 mg/L at weeks 12 and 24 (ITT population)

**Table S6** Percentage of patients with anaemia at weeks 2 and 24 (ITT population)

**Table S7** Treatment-by-tertile biomarker interactions for efficacy endpoints at week 24 analysed by baseline biomarker in tertiles

**Table S8** Treatment-by-tertile biomarker interactions for PROs at week 24 analysed by baseline biomarker in tertiles

**Fig. S1** Correlation matrix for baseline biomarkers and haematology parameters

**Fig. S2** Median percentage changes from baseline in (A) CXCL13 and (B) sICAM-1 through week 24

**Fig. S3** Median percentage changes from baseline in biomarkers of anaemia of chronic disease 2 weeks post treatment

**Fig. S4** ACR50 responses at week 24 and corresponding ORs with differential combinations of CXCL13 and sICAM-1

**Table S1** Individual serum biomarker assessment schedule

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Function** | **Biomarker** | **Baseline** | **Week 2** | **Week 4** | **Week 8** | **Week 12** | **Week 16** | **Week 20** | **Week 24** |
| Acute-phase response | SAA | X |  |  |  | X |  |  | X |
| CRP | X |  | X | X | X | X | X | X |
| Atherothrombosis | Lp(a) | X |  |  |  | X |  |  | X |
| Synovial inflammation | MMP-3 | X |  |  |  |  |  |  | X |
| Bone remodelling | Total RANKL | X | X |  |  |  |  |  | X |
| P1NP | X |  |  |  |  |  |  | X |
| OPG | X | X |  |  |  |  |  | X |
| Osteocalcin | X |  |  |  |  |  |  | X |
| Marker reflecting synovial lymphoid cell infiltrate  Marker reflecting synovial myeloid cell infiltrate | CXCL13 | X | X |  |  |  |  |  | X |
| sICAM-1 | X | X |  |  |  |  |  | X |
| Anaemia of chronic disease | Iron | X | X |  |  |  |  |  |  |
| Ferritin | X | X |  |  |  |  |  |  |
| TIBC | X | X |  |  |  |  |  |  |
| Hepcidin | X | X |  |  |  |  |  |  |

CRP: C-reactive protein; CXCL13: chemokine (C-X-C motif) ligand 13; Lp(a): lipoprotein (a); MMP-3: matrix metalloproteinase-3; OPG: osteoprotegerin; P1NP: procollagen type 1 *N*-terminal propeptide; RANKL: receptor activator of nuclear factor-κB ligand; SAA: serum amyloid A; sICAM-1: soluble intercellular adhesion molecule-1; TIBC: total iron-binding capacity.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table S2** Efficacy and PROs at week 24 in the biomarker and ITT populations | | | | |
|  | **ITT population** | | **Biomarker population** | |
|  | **Adalimumab  40 mg q2w (*n* = 185)** | **Sarilumab  200 mg q2w (*n* = 184)** | **Adalimumab  40 mg q2w (*n* = 154)** | **Sarilumab  200 mg q2w (*n* = 153)** |
| **Efficacy results at week 24a** | | | | |
| ACR20 responders, % | 58.4 | 71.7 | 59.1 | 73.9 |
| ACR50 responders, % | 29.7 | 45.7 | 29.2 | 49.7 |
| ACR70 responders, % | 11.9 | 23.4 | 12.3 | 25.5 |
| ΔDAS28-ESR | –2.2 (1.4) | –3.4 (1.4) | –2.3 (1.3) | –3.4 (1.3) |
| DAS28-ESR <2.6, % | 7.0 | 26.6 | 8.4 | 27.5 |
| DAS28-ESR <3.2, % | 14.1 | 42.9 | 15.6 | 43.8 |
| ΔDAS28-CRP | –2.1 (1.2) | –2.9 (1.3) | –2.1 (1.3) | –3.0 (1.2) |
| DAS28-CRP <2.6, % | 13.5 | 34.2 | 13.0 | 34.6 |
| DAS28-CRP <3.2, % | 24.3 | 51.6 | 24.0 | 52.3 |
| ΔTJC | –16.4 (12.0) | –19.0 (13.3) | –16.6 (12.3) | –19.4 (12.5) |
| ΔSJC | –12.2 (9.1) | –14.3 (9.6) | –12.1 (8.9) | –14.6 (9.8) |
| ΔCDAI | –25.5 (12.9) | –29.7 (12.7) | –25.9 (13.3) | –30.2 (12.0) |
| CDAI ≤2.8, % | 2.7 | 7.1 | 3.2 | 7.2 |
| CDAI ≤10, % | 24.9 | 41.8 | 24.7 | 43.1 |
| ΔPhysician global  VAS (0–100 mm) | –37.3 (22.5) | –45.3 (21.4) | –37.6 (22.8) | –45.7 (20.5) |
| **PROs at week 24a** | | | | |
| ΔHAQ-DI | –0.4 (0.6) | –0.6 (0.7) | –0.4 (0.6) | –0.7 (0.7) |
| ΔFACIT-Fatigue  (0–52) | 8.2 (10.4) | 10.4 (10.2) | 8.4 (10.3) | 11.3 (10.0) |
| ΔPatient global  VAS (0–100 mm) | –25.0 (25.2) | –33.5 (26.2) | –25.5 (24.9) | –33.8 (26.3) |
| ΔPain VAS  (0–100 mm) | –27.9 (24.7) | –36.4 (26.9) | –28.0 (24.4) | –36.9 (27.0) |
| ΔSF-36 PCS | 5.5 (7.1) | 8.6 (7.7) | 5.3 (7.1) | 9.0 (7.6) |
| ΔSF-36 MCS | 7.0 (11.3) | 8.2 (10.8) | 6.9 (11.0) | 8.5 (11.3) |
| ΔMorning stiffness VAS  (0–100 mm) | –27.0 (27.4) | –36.1 (27.9) | –26.7 (27.8) | –36.7 (27.3) |
| ΔRAID (0–10) | –2.1 (2.4) | –3.2 (2.4) | –2.1 (2.4) | –3.3 (2.4) |

aMean (standard deviation) unless otherwise stated. Δ: absolute change from baseline; ACR20/50/70: American College of Rheumatology 20/50/70% improvement criteria; CDAI: Clinical Disease Activity Index; DAS28-CRP: Disease Activity Score (28 joints) using C-reactive protein; DAS28-ESR: Disease Activity Score (28 joints) using erythrocyte sedimentation rate; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire-Disability Index; ITT: intent-to-treat; MCS: mental component summary; PCS: physical component summary; PRO: patient-reported outcome; q2w: every 2 weeks; RAID: rheumatoid arthritis impact of disease; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale.

**Table S3** Baseline biomarker serum concentrations in the biomarker population

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Biomarker** | **Adalimumab  40 mg q2w  (*n* = 154)** | **Sarilumab 200 mg q2w (*n* = 153)** | **Low tertile** | **Medium tertile** | **High tertile** | **Reference rangea** |
| SAA, ng/L | 22 806.0  (5817.2, 115 200.0) | 16 089.0  (4997.5, 85 918.0) | 3734.7  (2192.7, 5346.4) | 18549.5  (11 832.0, 30 082.0) | 174 900.0 (105 200.0, 256 000.0) | 1000.0–9249.3 |
| CRP, mg/L | 9.4 (3.8, 33.5) | 7.8 (2.8, 24.7) | 1.9 (1.0, 3.4) | 8.5 (6.9, 13.1) | 37.6 (27.9, 65.1) | ≤2.9 |
| Lp(a), mg/L | 235.5 (111.0, 559.0) | 179.0 (78.0, 402.0)\* | 48.5  (17.5, 100.0) | 192.0  (157.0, 236.0) | 689.5  (450.0, 1116.0) | 19.0–1028.0 |
| MMP-3, ng/mL | 44.0 (25.2, 80.9) | 40.8 (19.3, 74.4) | 16.0 (10.3, 20.8) | 42.8 (35.5, 54.1) | 99.9 (77.0, 154.3) | 6.0–15.8 |
| Total RANKL, pmol/L | 484.5 (254.7, 1423.1) | 547.6 (268.5, 1361.3) | 200.1  (136.7, 258.5) | 515.0  (424.3, 674.0) | 2252.8  (1417.6, 3657.6) | 35.1–639.7 |
| P1NP, ng/mL | 45.9 (34.9, 63.9) | 44.7 (30.3, 59.9) | 27.6 (21.4, 32.9) | 45.6 (41.6, 50.1) | 73.2 (63.0, 87.6) | 47.9–204.1 |
| OPG, pmol/L | 5.9 (5.0, 8.0) | 6.0 (4.7, 7.5) | 4.3 (3.9, 5.0) | 5.9 (5.6, 6.5) | 8.8 (7.7, 10.5) | 3.6–7.9 |
| OC, ng/mL | 19.0 (13.8, 26.0) | 18.0 (13.9, 25.8) | 12.0 (9.6, 13.8) | 18.6 (16.8, 21.1) | 28.9 (26.0, 35.6) | 13.9–30.6 |
| CXCL13, pg/mL | 120.1 (72.4, 184.7) | 112.8 (70.8, 180.8) | 61.8 (52.4, 72.0) | 116.4 (98.2, 130.6) | 236.8 (180.8, 323.9) | 37.8–153.6 |
| sICAM-1, ng/mL | 258.6 (212.1, 324.8) | 257.3 (212.7, 304.0) | 199.3 (179.7, 212.1) | 257.7 (239.7, 272.3) | 339.4 (313.7, 380.0) | 186.0–331.0 |
| Iron μmol/L | 10.5 (7.0, 14.9) | 11.3 (7.2, 16.0) | 6.1 (4.2, 7.0) | 10.9 (9.8, 12.2) | 17.2 (15.5, 20.3) | 10.8–28.9 |
| Ferritin, ng/mL | 80.0 (41.1, 174.0) | 74.9 (35.1, 130.6) | 24.9 (13.9, 35.5) | 76.7 (60.5, 93.5) | 204.3 (154.9, 283.4) | 18.6–148.3 |
| TIBC, μg/dL | 321.5 (293.5, 350.5) | 324.0 (303.0, 361.0) | 286.0 (267.0, 297.0) | 322.0 (313.0, 332.0) | 373.0 (357.0, 397.0) | 247.2–363.0 |
| Hepcidin, ng/mL | 24.8 (9.7, 48.9) | 20.9 (9.2, 39.3) | 6.0 (3.7, 9.3) | 23.0 (17.0, 28.9) | 62.4 (43.9, 77.0) | 0.6–46.4 |

Data presented as median (Q1, Q3) at baseline. aReference range for CRP is based on population of healthy men and women (reference range provided by Covance); for all other biomarkers, reference range is based on healthy post-menopausal women (5th–95th percentile; reference ranges provided by Bioclinica). \*Nominal Wilcoxon test *p* value <5%. CRP: C-reactive protein; CXCL13: chemokine (C-X-C motif) ligand 13; Lp(a): lipoprotein (a); MMP‑3: matrix metalloproteinase-3; OC: osteocalcin; OPG: osteoprotegerin; P1NP: procollagen type 1 *N*-terminal propeptide; Q: quartile; q2w: every 2 weeks; RANKL: receptor activator of nuclear factor-κB ligand; SAA: serum amyloid A; sICAM-1: soluble intercellular adhesion molecule-1; TIBC: total iron-binding capacity.

**Table S4** Absolute change from baseline in biomarker concentrations through week 24

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Median absolute change from baseline (Q1, Q3)** | | **Week 2** | **Week 12** | **Week 24** |
| SAA, ng/mL | Adalimumab 40 mg q2w | — | –2442.7  (–22330.7, 1930.9) | –476.4  (–19654.3, 3342.1) |
| Sarilumab  200 mg q2w | — | –9066.5  (–80132.7, –1902.8) | –9604.7  (–79255.8, –1398.0) |
| CRP, mg/L | Adalimumab 40 mg q2w | — | –1.3  (–13.7, 1.3) | –1.3  (–13.7, 3.5) |
| Sarilumab  200 mg q2w | — | –6.8  (–22.9, –1.6) | –6.6  (–22.8, –1.3) |
| Lp(a), mg/L | Adalimumab 40 mg q2w | — | –2.0  (–54.0, 28.0) | –4.5  (–40.0, 28.0) |
| Sarilumab  200 mg q2w | — | –59.0  (–134.0, –13.0) | –60.3  (–157.0, –21.0) |
| MMP-3, ng/mL | Adalimumab 40 mg q2w | — | — | –5.6  (–23.6, 6.3) |
| Sarilumab  200 mg q2w | — | — | –6.8  (–33.1, 1.4) |
| Total RANKL, pmol/L | Adalimumab 40 mg q2w | 15.9  (–7.2, 129.1) | — | 31.5  (–93.5, 223.2) |
| Sarilumab  200 mg q2w | –10.5  (–69.5, 31.0) | — | –76.8  (–438.5, 20.4) |
| P1NP, ng/mL | Adalimumab 40 mg q2w | — | — | 2.0  (–5.5, 13.5) |
| Sarilumab  200 mg q2w | — | — | 8.6  (–0.8, 18.7) |
| OPG, pmol/L | Adalimumab 40 mg q2w | –0.2 (–0.7, 0.3) | — | 0.2  (–0.6, 0.9) |
| Sarilumab  200 mg q2w | 0.1  (–0.5, 0.7) | — | 0.1  (–0.7, 0.7) |
| OC, ng/mL | Adalimumab 40 mg q2w | — | — | 0.9  (–1.7, 5.1) |
| Sarilumab  200 mg q2w | — | — | 2.4  (–1.4, 5.7) |
| CXCL13, pg/mL | Adalimumab 40 mg q2w | –45.4  (–81.7, –22.9) | — | –30.5  (–65.7, –1.5) |
| Sarilumab  200 mg q2w | –12.8  (–41.0, 5.6) | — | –35.7  (–80.5, –4.5) |
| sICAM-1 | Adalimumab 40 mg q2w | –23.2  (–37.8, –9.3) | — | –10.8  (–41.7, 14.4) |
| Sarilumab  200 mg q2w | –0.7  (–15.6, 12.8) | — | –11.0  (–36.7, 1.9) |
| Iron, µmol/L | Adalimumab 40 mg q2w | 1.4  (–0.6, 4.5) | — | — |
| Sarilumab  200 mg q2w | 3.7  (0.5, 8.3) | — | — |
| Ferritin, ng/mL | Adalimumab 40 mg q2w | –8.5  (–31.7, 0.5) | — | — |
| Sarilumab  200 mg q2w | –7.7  (–26.4, 0.1) | — | — |
| TIBC, µg/dL | Adalimumab 40 mg q2w | 9.0  (–2.0, 22.0) | — | — |
| Sarilumab  200 mg q2w | 20.0  (5.0, 35.0) | — | — |
| Hepcidin, ng/mL | Adalimumab 40 mg q2w | –5.8  (–19.1, –0.1) | — | — |
| Sarilumab  200 mg q2w | –3.3  (–16.3, 0.4) | — | — |

Sample size in the overall biomarker population: adalimumab 40 mg q2w: *n* = 154, sarilumab 200 mg q2w: *n* = 153. CRP: C-reactive protein; CXCL13: chemokine (C-X-C motif) ligand 13; Lp(a): lipoprotein (a); MMP‑3: matrix metalloproteinase-3; OC: osteocalcin; OPG: osteoprotegerin; P1NP: procollagen type 1 *N*-terminal propeptide; Q: quartile; q2w: every 2 weeks; RANKL: receptor activator of nuclear factor-κB ligand; SAA: serum amyloid A; sICAM-1: soluble intercellular adhesion molecule-1; TIBC: total iron-binding capacity.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table S5** Percentage of patients with CRP ≤10 mg/L and ≤3 mg/L at weeks 12 and 24 (overall safety population) | | | | |
|  | **Week 12** | | **Week 24** | |
|  | **Adalimumab  40 mg q2w (*n* = 185)** | **Sarilumab  200 mg q2w (*n* = 184)** | **Adalimumab  40 mg q2w (*n* = 154)** | **Sarilumab  200 mg q2w (*n* = 153)** |
| CRP ≤3 mg/L, n (%) | 64 (38.1) | 148 (89.2) | 53 (34.0) | 149 (90.9) |
| CRP ≤10 mg/L, n (%) | 110 (65.5) | 156 (94.0) | 100 (64.1) | 157 (95.7) |

CRP: C-reactive protein; q2w: every 2 weeks

|  |  |  |
| --- | --- | --- |
| **Table S6** Percentage of patients with anaemia at weeks 2 and 24 (overall safety population) | | |
|  | **Adalimumab  40 mg q2w (*n* = 185)** | **Sarilumab  200 mg q2w (*n* = 184)** |
| Baseline | 25.4% | 24.5% |
| Week 2 | 21.1% | 19.6% |
| Week 24 | 16.2% | 10.9% |

Anaemia defined by World Health Organization criteria (haemoglobin <12 g/dL [women]/<13 g/dL [men]). q2w: every 2 weeks

**Table S7** Treatment-by-tertile biomarker interactions for efficacy endpoints at week 24 analysed by baseline biomarker in tertiles

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Efficacy endpoint at week 24** | **Biomarker at baseline** | | | | | | | | | | | | | |
|  | SAA | | CRP | | MMP-3 | | OPG | | OC | | CXCL13 | | Hepcidin | |
| M/L | H/L | M/L | H/L | M/L | H/L | M/L | H/L | M/L | H/L | M/L | H/L | M/L | H/L |
| ACR20 | NS | **0.015** | NS | **0.039** | NS | **0.013** | NS | NS | **0.031** | NS | NS | **0.003** | NS | **0.021** |
| ACR50 | NS | **0.004** | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| ACR70 | NS | **0.008** | NS | NS | NS | NS | **0.032** | NS | NS | NS | NS | NS | NS | NS |
| DAS28-ESR <2.6 | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| DAS28-ESR <3.2 | **0.004** | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| DAS28-CRP <2.6 | NS | **0.041** | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS |
| DAS28-CRP <3.2 | NS | **0.044** | NS | **0.049** | NS | **0.014** | NS | NS | NS | NS | NS | NS | NS | NS |

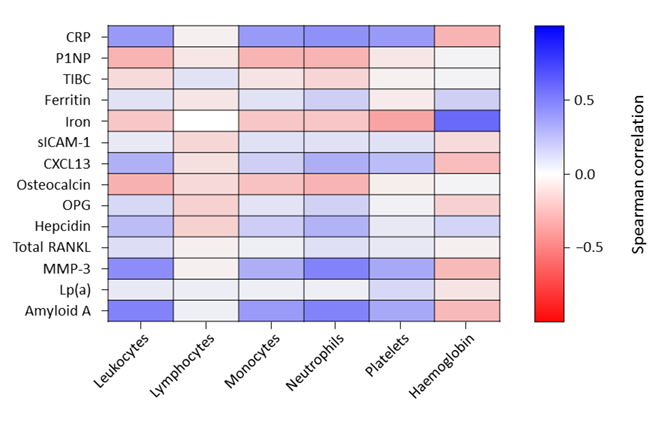
M/L: Nominal treatment-by-biomarker interaction *p*-value for Medium vs. Low tertile; H/L: Nominal treatment-by-biomarker interaction *p* value for High vs. Low tertile. ACR20/50/70: American College of Rheumatology 20/50/70% responses; CRP: C-reactive protein; CXCL13: chemokine (C-X-C motif) ligand 13; DAS28 CRP: Disease Activity Score (28 joints) C-reactive protein; DAS28-ESR: Disease Activity Score (28 joints) erythrocyte sedimentation rate; MMP-3: matrix metalloproteinase 3; NS: not significant at 5%; OC: osteocalcin; OPG: osteoprotegerin; SAA: serum amyloid A.

**Table S8** Treatment-by-tertile biomarker interactions for PROs at week 24 analysed by baseline biomarker in tertiles

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Change from baseline in PROs at Week 24** | **Biomarker at baseline** | | | | | | | | | | | | | | | | | |
|  | **SAA** | | **CRP** | | **MMP-3** | | **OC** | | **CXCL13** | | **Hepcidin** | | **s-ICAM1** | | **Iron** | | **Ferritin** | |
| M/L | H/L | M/L | H/L | M/L | H/L | M/L | H/L | M/L | H/L | M/L | H/L | M/L | H/L | M/L | H/L | M/L | H/L |
| Patient global VAS | NS | **0.011** | **0.002** | **0.040** | NS | **0.010** | NS | NS | NS | NS | NS | **0.009** | NS | NS | NS | NS | NS | NS |
| HAQ-DI | **0.035** | **<0.001** | NS | **0.005** | NS | **<0.001** | NS | NS | **0.032** | **0.004** | NS | NS | NS | NS | NS | **0.032** | NS | NS |
| Pain VAS | NS | **0.002** | **0.021** | **0.029** | **0.047** | **0.002** | NS | NS | NS | NS | **0.010** | **0.002** | NS | NS | NS | NS | NS | NS |
| SF-36 – PCS score | NS | **<0.001** | **0.009** | **0.016** | NS | **0.026** | NS | NS | NS | **0.031** | NS | NS | NS | NS | NS | NS | NS | NS |
| SF-36 – MCS score | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | **0.030** | **0.023** | NS | NS | NS | NS | NS | **0.050** |
| SF-36 – PF domain | NS | **0.003** | NS | NS | NS | **0.036** | NS | NS | NS | **0.003** | NS | NS | NS | NS | NS | NS | NS | NS |
| SF-36 – BP domain | NS | NS | NS | NS | NS | NS | **0.037** | NS | NS | NS | **0.002** | **0.016** | NS | NS | NS | NS | NS | NS |
| SF-36 – VT domain | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | **0.043** | **0.005** | NS | NS | NS | NS | NS | NS |
| SF-36 – RE domain | NS | NS | **0.049** | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | **0.030** | NS | NS | NS | NS |
| SF-36 –MH domain | NS | NS | NS | NS | NS | NS | NS | NS | NS | NS | **0.004** | **0.004** | NS | NS | NS | NS | **0.047** | NS |
| Morning stiffness VAS | NS | **0.004** | **0.002** | **0.017** | NS | **<0.001** | NS | NS | NS | NS | **0.029** | **<0.001** | NS | NS | NS | NS | NS | NS |
| RAID score | NS | **0.017** | **0.045** | NS | NS | **0.020** | NS | NS | NS | NS | NS | **0.009** | **0.032** | NS | NS | NS | NS | NS |

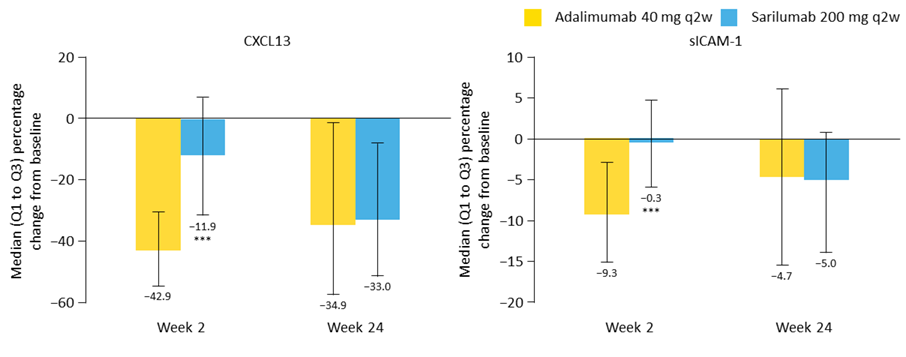
M/L: Nominal treatment-by-biomarker interaction *p* value for Medium vs. Low tertile; H/L: Nominal treatment-by-biomarker interaction *p* value for High vs.Low tertile. BP: bodily pain; CRP: C-reactive protein; CXCL13: chemokine (C-X-C motif) ligand 13; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ-DI: Health Assessment Questionnaire-Disability Index; Lp(a): lipoprotein (a); MCS: mental component summary; MH: mental health; MMP-3: matrix metalloproteinase-3; NS: not significant at 5%; OC: osteocalcin; OPG: osteoprotegerin; P1NP: procollagen type 1 *N*-terminal propeptide; PCS: physical component summary; PF: physical functioning; RAID: rheumatoid arthritis impact of disease; RANKL: receptor activator of nuclear factor-κB ligand; RE: role-emotional; SAA: serum amyloid A; SF-36: Medical Outcomes Study Short-Form (36-item) Health Survey; sICAM-1: soluble intercellular adhesion molecule-1; TIBC: total iron-binding capacity; VAS: visual analogue scale; VT: vitality.

**Fig. S1** Correlation matrix for baseline biomarkers and haematology parameters



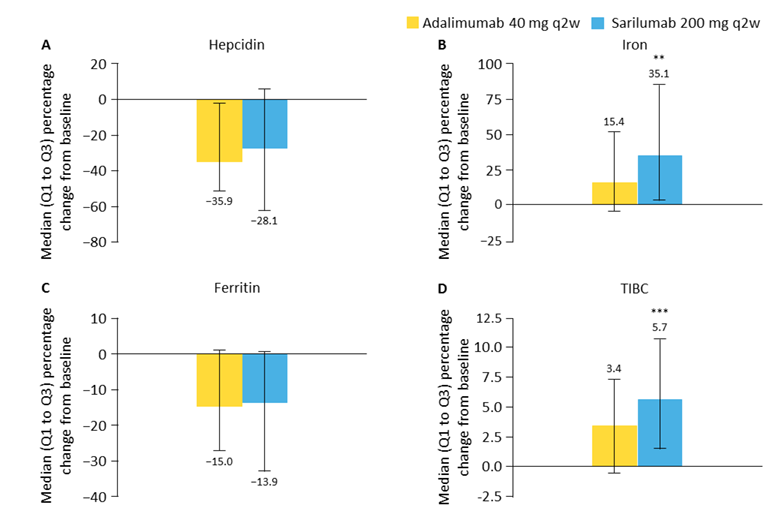
CRP: C-reactive protein; CXCL13: chemokine (C-X-C motif) ligand 13; Lp(a): lipoprotein (a); MMP-3: matrix metalloproteinase-3; OPG: osteoprotegerin; P1NP: procollagen type 1 *N*-terminal propeptide; RANKL: receptor activator of nuclear factor-κB ligand; sICAM-1: soluble intercellular adhesion molecule-1; TIBC: total iron-binding capacity

**Fig. S2** Median percentage changes from baseline in (A) CXCL13 and (B) sICAM-1 through week 24

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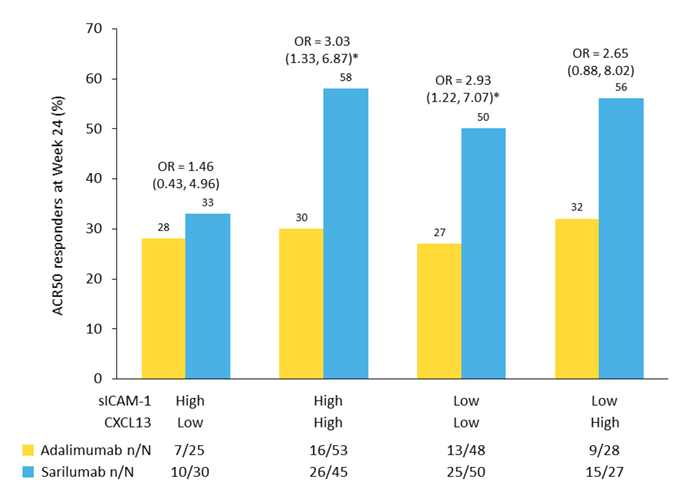
\*\*\*Adjusted *p* < 0.0001 vs. adalimumab (Benjamini–Hochberg procedure). CXCL13: chemokine (C-X-C motif) ligand 13; Q: quartile; q2w: every 2 weeks; sICAM-1: soluble intercellular adhesion molecule-1

**Fig. S3** Median percentage changes from baseline in biomarkers of anaemia of chronic disease 2 weeks post-treatment

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Median percentage changes from baseline in (A) hepcidin, (B) iron, (C) ferritin, and (D) TIBC at week 2 post-treatment. \*\*\*Adjusted *p* < 0.0001 vs. adalimumab (Benjamini–Hochberg procedure). \*\*Adjusted *p* < 0.01 vs. adalimumab (Benjamini–Hochberg procedure). Q: quartile; q2w: every 2 weeks; TIBC: total iron-binding capacity

**Fig. S4** ACR50 responses at week 24 and corresponding ORs with differential combinations of CXCL13 and sICAM-1

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\*Nominal *p* < 0.05. ORs presented with 95% CIs. ACR50: American College of Rheumatology 50% improvement criteria; CI: confidence interval; CXCL13: chemokine (C-X-C motif) ligand 13; OR: odds ratio; q2w: every 2 weeks; sICAM-1: soluble intercellular adhesion molecule-1.