**Supplementary data**

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| **Supplementary Table 1.** Key inclusion/exclusion criteria for ASCERTAIN and Study 1309 |
| **ASCERTAIN** |
| Inclusion criteria |
| * ACR/EULAR diagnosis of RA disease duration ≥3 months
* ACR class I–III functional status based on the 1991 revised criteria
* Moderately-to-severely active RA, defined as ≥4 of 68 tender joints and ≥4 of 66 swollen joints, and hs-CRP ≥4 mg/L at screening
* Inadequate response to ≥1 TNFi, after being treated for ≥3 consecutive months, any time before randomization or patients intolerant of ≥1 TNFi, resulting in discontinuation
* Continuous treatment with 1 or a combination of csDMARDs (except for simultaneous use of LEF and MTX) for ≥12 consecutive weeks before screening and on a stable dose(s) for ≥6 consecutive weeks before screening: MTX, 10–25 mg/week orally or by parenteral route (or per local labelling requirements if the dose range differs); LEF, 10–20 mg orally daily; SSZ, 1000–3000 mg orally daily; HCQ, 200–400 mg orally daily
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| Exclusion criteria |
| * Patients <18 years of age
* Use of parenteral corticosteroids or intra-articular corticosteroids within 4 weeks prior to screening
* Use of oral corticosteroids at a dose higher than prednisone 10 mg or equivalent per day, or a change in dosage within 4 weeks of screening
* History of, or current, autoimmune or inflammatory systemic or localized joint disease(s) other than RA, or a history of juvenile idiopathic arthritis or arthritis onset before age 16
* Severe systemic RA
* Participation in any clinical research study that evaluated an investigational drug or therapy within 5 half-lives or 60 days of the screening visit, whichever is longer
* Pregnant or breastfeeding women
* Prior treatment with anti-IL-6 or anti-IL-6R therapies, including but not limited to tocilizumab or sarilumab or a Janus kinase inhibitor (e.g. tofacitinib)
* Patients who received any live, attenuated vaccine within 3 months prior to randomization (baseline) visit
* Patients with a positive HIV test at the screening visit or who previously had a positive test, or who are suspected to be positive for HIV
* Patients with a history of recurrent herpes zoster or active herpes zoster
* Patients with any of the following laboratory abnormalities at the screening visit (identified by the central laboratory): haemoglobin <8.5 g/dL, white blood cells <3000/mm3, neutrophils <2000/mm3, platelet count <150 000 cells/mm3, AST or ALT >1.5 × ULN, bilirubin (total) > ULN, unless documented Gilbert’s disease diagnosed by genetic testing
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| **Study 1309** |
| Inclusion criteria |
| * Patients with ≥3 months of RA as defined by the 2010 revised ACR criteria at screening
* ACR class I–III functional status, based on the 1991 revised criteria
* Continuous treatment with MTX 10–25 mg/week, oral or parenteral, for ≥12 consecutive weeks before screening and on a stable dose for ≥8 consecutive weeks before screening
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| Exclusion criteria |
| * Patients <18 years of age or the minimum legal age in the location of the investigative site, whichever is higher
* Prior treatment with any biologic anti-IL-6 or IL-6R antagonists
* Use of parenteral corticosteroids or intra-articular corticosteroids within 4 weeks of screening
* Use of oral corticosteroids at a dose higher than prednisone 10 mg or equivalent per day, or a change in dosage within 4 weeks prior to randomization
* History of, or current, autoimmune or inflammatory systemic or localized joint

diseases other than RA or a history of juvenile idiopathic arthritis or arthritis onset before age 16* Severe systemic RA
* History of any disease or treatment that might affect ANC (e.g. bone marrow fibrosis, cyclic idiopathic neutropenia)
* Participation in any clinical research study that evaluated an investigational drug or therapy within 5 half-lives or 60 days of the screening visit, whichever is longer
* Pregnant or breastfeeding women
* Patients who received bacillus Calmette-Guérin vaccination within 12 months of screening
* Treatment with oral DMARDs (other than MTX) before screening visit as follows: penicillamine, SSZ, HCQ, gold, cyclosporin, mycophenolate or tacrolimus within 4 weeks; azathioprine or cyclophosphamide within 12 weeks; LEF within 12 weeks or within 4 weeks after 11 days of cholestyramine washout; Janus kinase inhibitors (e.g. tofacitinib) within 28 days
* Treatment with bDMARDs before screening visit: etanercept or anakinra within 4 weeks infliximab, golimumab, adalimumab, certolizumab pegol or abatacept within 6 weeks, rituximab within 6 months or until total lymphocyte count and CD19-positive lymphocyte counts are normalized, whichever is longer
* Patients who received any live, attenuated vaccine within 3 months prior to of randomization (baseline)
* Patients with a positive test at the screening visit, or who previously had a positive test, or who are suspected to be positive for HIV
* Patients with a history of recurrent herpes zoster or active herpes zoster
* Patients with any of the following laboratory abnormalities at the screening or known at baseline: haemoglobin <8.5 g/dL; white blood cells <3000/mm3; neutrophils <2000/mm3; platelet count <150 000 cells/mm3; AST or ALT >1.5 × ULN; bilirubin (total) > ULN, unless documented Gilbert’s disease diagnosed by genetic testing
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| ALT: alanine aminotransferase; ANC: absolute neutrophil count; AST: aspartate aminotransferase; bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic DMARD; hs-CRP: high-sensitivity C-reactive protein; IL-6R: IL-6 receptor; TNFi: tumour necrosis factor inhibitor; ULN: upper limit of normal. |

**Supplementary Table 2.** Geographical distribution of patients in ASCERTAIN

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| Geographical region, n (%) | **Tocilizumab q4w i.v. + csDMARDs** **(n=102)a**  | **Sarilumab150 mg q2w s.c. + csDMARDs** **(n=49)** | **Sarilumab 200 mg q2w s.c. + csDMARDs** **(n=51)** |
| Belgium, Czech Republic, Finland, Hungary, Israel, Italy, Netherlands, Norway, Spain, Sweden, UK, USA | 41 (40) | 21 (43) | 20 (39) |
| Argentina, Brazil, Mexico | 25 (25) | 11 (22) | 13 (26) |
| Estonia, Poland, Romania, Russia | 36 (35) | 17 (35) | 18 (35) |

aTocilizumab q4w i.v. starting at 4 mg/kg could be increased to 8 mg/kg based on clinical response as assessed by investigator

**Supplementary Table 3.** Concomitant csDMARDs

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|  | **ASCERTAIN** | **Study 1309** |
| **Patients, n (%)** | **Tocilizumab q4w i.v. + csDMARDs (n=102)a**  | **Sarilumab 150 mg q2w s.c. + csDMARDs (n=49)** | **Sarilumab 200 mg q2w s.c. + csDMARDs (n=51)** | **Tocilizumab 4 mg/kg i.v. + MTX (n=25)** | **Tocilizumab 8 mg/kg i.v. + MTX (n=24)** | **Sarilumab 150 mg s.c. + MTX (n=26)** | **Sarilumab 200 mg s.c. + MTX (n=26)** |
| **csDMARDsb** | 102 (100) | 49 (100) | 51 (100) | 25 (100) | 24 (100) | 26 (100) | 26 (100) |
|  MTX | 88 (86) | 37 (76) | 41 (80) | 25 (100) | 24 (100) | 26 (100) | 26 (100) |
|  Leflunomide | 7 (7) | 10 (20) | 5 (10) | – | – | – | – |
|  Sulfasalazine | 8 (8) | 4 (8) | 5 (10) | – | – | – | – |
|  Hydroxychloroquine | 10 (10) | 2 (4) | 5 (10) | – | – | – | – |
| csDMARD, conventional synthetic disease-modifying antirheumatic drug; MTX, methotrexate; RAS, renin–angiotensin systemaTocilizumab q4w i.v. starting at 4 mg/kg could be increased to 8 mg/kg based on clinical response as assessed by investigator. bPatients could take >1 csDMARD in ASCERTAIN; all patients had to take MTX in Study 1309 |

**Supplementary Table 4.** Treatment-emergent adverse events reported in >1 patient in any treatment group in Study 1309.

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| **Number of patients, n (%)****Preferred term** |  | **Tocilizumab 4 mg/kg i.v. + MTX (n=25)** | **Tocilizumab 8 mg/kg i.v. + MTX (n=24)** | **Sarilumab 150 mg s.c. + MTX (n=26)** | **Sarilumab 200 mg s.c. + MTX (n=26)** |
| Neutropenia |  | 3 (12.0) | 6 (25.0) | 4 (15.4) | 7 (26.9) |
|  Upper respiratory tract infection |  | 1 (4.0) | 2 (8.3) | 0 | 0 |
| Headache |  | 3 (12.0) | 0 | 0 | 0 |
| Thrombocytopenia |  | 0 | 0 | 2 (7.7) | 0 |
| Rheumatoid arthritis |  | 0 | 0 | 2 (7.7) | 0 |

**Supplementary Figure 1.** CONSORT diagram for tocilizumab dose adjustments during ASCERTAIN.

csDMARD: conventional synthetic disease-modifying antirheumatic drug; q4w: every 4 weeks. aSubset of patients included in further laboratory analyses of absolute neutrophil count, alanine aminotransferase and low-density lipoprotein cholesterol.