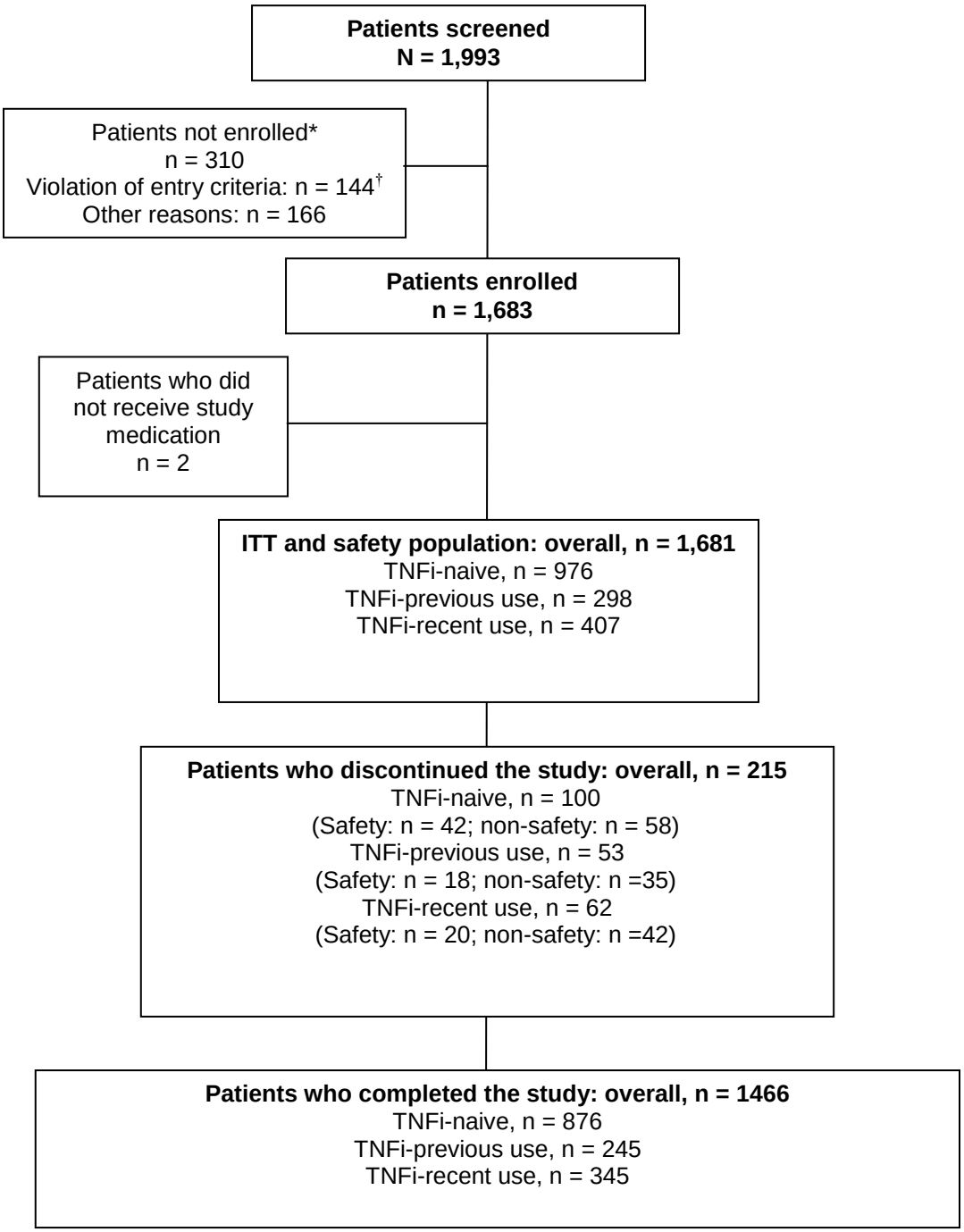
SUPPLEMENTARY MATERIAL

Supplementary Table S1 Mean (SD) improvements [% decrease] from baseline to week 24 in ACR core set parameters

	TNFi-naive (n = 976)	**TNFi-previous use (n = 298)**	**TNFi-recent use (n = 407)**
DAS28 change	3.52 (1.37) [59.9]	3.44 (1.44) [55.5]	3.17 (1.58) [53.2]
SJC, 66 joints	8.2 (10.5) [67.8]	8.5 (11.9) [61.2]	7.7 (12.1) [57.5]
TJC, 68 joints	14.6 (15.1) [66.7]	13.6 (15.8) [55.5]	13.2 (16.3) [55.5]
PGA VAS, mm	35.9 (25.3) [59.1]	37.9 (25.7) [55.7]	32.9 (26.0) [52.3]
PhGA VAS, mm	38.8 (21.5) [67.7]	40.7 (21.2) [64.7]	38.8 (23.7) [65.2]
Pain VAS, mm	32.3 (25.7) [58.4]	34.5 (26.9) [54.7]	29.9 (25.8) [50.9]
CRP, mg/dl	1.5 (2.3) [88.2]	2.3 (3.1) [95.8]	1.9 (2.9) [86.4]
ESR, mm/h	29.4 (23.0) [78.2]	36.9 (27.1) [86.0]	31.0 (26.8) [76.5]
HAQ-DI	0.59 (0.59) [42.8]	0.60 (0.61) [35.3]	0.50 (0.54) [31.3

ACR, American College of Rheumatology; CRP, C-reactive protein; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; PGA, patient global assessment; PhGA, physician global assessment; SJC, swollen joint count; TJC, tender joint count; TNFi, tumour necrosis factor inhibitor; TNFi-naive, patients who had never received TNFi therapy; TNFi-previous use, patients who had discontinued TNFi therapy for >2 months before baseline (washout period); TNFi-recent use, patients who had discontinued TNFi therapy for ≤2 months before baseline (no washout period); VAS, visual analogue scale.

Supplementary Figure S1 Summary of patient disposition. AE, adverse event; DMARD, disease-modifying anti-rheumatic drug; ITT, intent-to-treat; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor; TNFi-naive, patients who had never received TNFi therapy; TNFi-previous use, patients who had discontinued TNFi therapy for >2 months before baseline (washout period); TNFi-recent use, patients who had discontinued TNFi therapy for ≤2 months before baseline (no washout period).



*Patients not enrolled: mean age 54.8 years, RA duration 9.3 years, tender joint count 20.2, swollen joint count 11.3

†Most common criteria leading to exclusion (each contributing to >5% of exclusions):

- CXR evidence of any clinically significant abnormality (9%)
- Patients should be screened for latent tuberculosis (TB), before biologics use, in accordance with local guidelines or Good Clinical Practice in each country. If screening results are positive, patients with latent TB should be treated with standard anti-mycobacterial therapy (at least 4 weeks) before initiation of TCZ and should have a negative CXR for active TB at screening. (8%)
- Active TB requiring treatment within the previous 3 years (7%)
- Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to TB and atypical mycobacterial disease, clinically significant abnormalities on CXR as determined by the investigator, hepatitis B and C and herpes zoster, but excluding fungal infections of nail beds), or any major episode of infection requiring hospitalisation or treatment with IV antibiotics within 4 weeks of screening, or oral antibiotics within 2 weeks before screening (7%)

Supplementary Information

Methods

Inclusion Criteria

1. Male or non-pregnant, non-nursing female ≥18 years of age
2. Diagnosis of moderate to severe active RA (DAS28 ≥3.2) of ≥6-months' duration
3. Undergoing treatment on an outpatient basis
4. ≥1 non-biologic DMARDs at a stable dose for a period ≥8 weeks before treatment (day 1)
5. Inadequate clinical response to a stable dose of non-biologic DMARD or anti-TNF therapy
6. If receiving an oral corticosteroid, the dose must have been stable for at least 25 of 28 days before treatment (day 1)
7. Able and willing to give written informed consent and to comply with the requirements of the study protocol

Exclusion Criteria

1. Major surgery (including joint surgery) within 8 weeks before screening or planned major surgery within 6 months after enrollment
2. Diseases
    a. Rheumatic autoimmune disease other than rheumatoid arthritis (RA), including systemic lupus erythematosus, mixed connective tissue disease, scleroderma, polymyositis or significant systemic involvement secondary to RA (e.g. vasculitis, pulmonary fibrosis or Felty's syndrome)
    b. Interstitial pulmonary fibrosis but able to tolerate methotrexate (MTX) therapy; and Sjögren's syndrome with RA

c. Functional class IV as defined by the American College of Rheumatology (ACR) Classification of Functional Status in RA

d. Past history of or current inflammatory joint disease other than RA (e.g. gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease)

3. Treatment with

   a. Any investigational agent or with anakinra, calcineurin inhibitors (e.g. tacrolimus or cyclosporine), mycophenolate mofetil or mycophenolic acid sodium within 4 weeks (or 5 half-lives of investigational agent, whichever is longer) before screening; previous treatment with any cell-depleting therapies, including investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19 and anti-CD20)

   b. Leflunomide in combination with MTX

   c. IV gamma globulin, plasmapheresis or Prosorba® column within 6 months before baseline

   d. Intra-articular or parenteral corticosteroids within 6 weeks before baseline

4. Immunisation with a live/attenuated vaccine within 4 weeks before baseline

5. Previous treatment with

   a. Abatacept

   b. Tocilizumab (an exception to this criterion may be granted for single-dose exposure on application to the sponsor on a case-by-case basis)

   c. Alkylating agents, such as cyclophosphamide and chlorambucil, or with total lymphoid irradiation

6. Laboratory values

a. Serum creatinine >142 μmol/L (1.6 mg/dl) in female patients and >168 μmol/L (1.9 mg/dl) in male patients and no active renal disease
b. Alanine aminotransferase (ALT [SGPT]) or aspartate aminotransferase (AST [SGOT]) >1.5 the upper limited of normal (ULN). (If initial sample showed ALT [SGPT] or AST [SGOT] >1.5 ULN, a second sample was to be taken and tested during the screening period)
c. Platelet count $<100 \times 10^9$/L (100,000/mm^3)
d. Haemoglobin <85 g/L (8.5 g/dl; 5.3 mmol/L)
e. White blood cell count $<1.0 \times 10^9$/L (1,000/mm^3), absolute neutrophil count $<1 \times 10^9$/L (1000/mm^3)
f. Absolute lymphocyte count $<0.5 \times 10^9$/L (500/mm^3)
g. Positive hepatitis B surface antigen or hepatitis C antibody
h. Total bilirubin >ULN (if initial sample showed bilirubin >ULN, a second sample was to be taken and tested during the screening period)
i. Triglycerides >10 mmol/L (>900 mg/dl) at screening (non-fasted)

7. Pregnant women or nursing (breastfeeding) mothers; or females of child-bearing potential who were not using reliable means of contraception, such as physical barrier (patient and partner), contraceptive pill or patch, spermicide and barrier or intrauterine device
8. History of severe allergic or anaphylactic reactions to human, humanised or murine monoclonal antibodies
9. Concomitant disorders
    a. Chest X-ray evidence of any clinically significant abnormality
    b. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic,

endocrine (including uncontrolled diabetes mellitus) or gastrointestinal (GI) disease

c. Uncontrolled disease states, such as asthma, psoriasis and inflammatory bowel disease in which flares are commonly treated with oral or parenteral corticosteroids
d. Current liver disease as determined by the principal investigator. Patients with past history of ALT (SGPT) elevation were not to be excluded
e. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections (including but not limited to tuberculosis and atypical mycobacterial disease, clinically significant abnormalities on chest x-ray as determined by the principal investigator, hepatitis B and C, and herpes zoster, but excluding fungal infections of nail beds), or any major episode of infection requiring hospitalisation or treatment with IV antibiotics within 4 weeks of screening, or oral antibiotics within 2 weeks before screening (does not apply to treatment of latent TB)
f. History of or currently active primary or secondary immunodeficiency
g. Evidence of active malignant disease, malignancies diagnosed within the previous 5 years (including hematological malignancies and solid tumours, except non-melanoma skin cancer that had been excised and cured), or breast cancer diagnosed within the previous 5 years
h. Active TB requiring treatment within the previous 3 years
    i. Patients were to be screened for latent TB, before biologics use, in accordance with local guidelines or Good Clinical Practice in their country. Patients with latent TB were to be treated with standard anti-

mycobacterial therapy (at least 4 weeks) before initiation of TCZ and to have negative CXR for active TB at screening.

i. Human immunodeficiency virus (HIV)–positive patient

10. History of alcohol, drug or chemical abuse within the 6 months before screening
11. Neuropathies or other painful conditions that might interfere with pain evaluation
12. Patients with lack of peripheral venous access
13. Body weight >150 kg

Sample Size

The following considerations justify the sample size of approximately 1,500 patients from the clinical point of view. We assume that at least 1,200 patients (i.e. 80% of the recruited patients) will conclude the study, providing a sample of patients with full exposure to the study drug from which the following can be expected:

- Assuming that a specific event (such an AE, treatment discontinuation, or transaminase elevation) occurs in 5% of patients in the study, the 95% CI around that incidence will extend from 3.8% to 6.2%. If the event occurs in 10% of patients, the CI will extend from 8.3% to 11.7%
- A TCZ-associated AE occurring in 1/1,000 patients would have a 70% chance to occur at least once in the patient population, and an event occurring in 1/522 patients would have a 90% chance to be detected

Results

Patient-Reported Outcomes

Health Assessment Questionnaire-Disability Index (HAQ-DI) clinical remission (HAQ-DI <0.5) was achieved by 31.5% of patients at week 24, at which time TNFi-recent patients had

a numerically smaller improvement (–0.50 ± 0.54; 31.3% decrease) than did TNFi-previous (–0.60 ± 0.61; 35.3% decrease) and TNFi-naive (–0.59 ± 0.59; 42.8% decrease) patients. The same was true at earlier visits (supplementary table 1). At week 4, 47.7% of patients experienced improvement in HAQ-DI ≥minimum clinically important difference (MCID; –0.22) from baseline, which increased to 72.7% at week 24.

SF-36 physical (PCS) and mental (MCS) component summary scores and all domain scores increased over time, with improvement ≥MCID for PCS (10 points) and each of the eight domains (5 points). At week 4, 19.1% and 25.9% of patients experienced improvement ≥MCID from baseline in PCS and MCS, respectively; at week 24, percentages increased to 44.9% and 39.6%, respectively. Bodily pain, vitality and mental health domain scores and MCS were restored to scores seen in the general population according to US normative data. FACIT-fatigue score improved by 10.76 (SD ±10.93) points from baseline to week 24; half the improvement was noted by week 4 (change from baseline, 5.01). At week 4, 49.0% of patients experienced improvement ≥MCID (4 points) from baseline, which increased to 69.5% at week 24.

Supplementary Information Table S1 Changes in laboratory parameters according to category of previous TNFi therapy

	TNFi-naive (n = 976)	**TNFi-previous use (n = 298)**	**TNFi-recent use (n = 407)**
ALT: % (n) patients with plasma level 1–3× ULN at any time post-BL after normal at BL	34.6 (338)	24.5 (73)	28.3 (115)
ALT: % (n) patients with plasma level >3× ULN at any time post-BL after normal at BL	2.4 (23)	3.0 (9)	0.7 (3)
AST: % (n) patients with plasma level 1–3× ULN at any time post-BL after normal at BL	24.6 (240)	16.4 (49)	15.2 (62)
AST: % (n) patients with plasma level >3× ULN at any time post-BL after normal at BL	0.6 (6)	0.7 (2)	0.5 (2)
Neutrophils: % (n) patients with absolute count $<1.0 \times 10^9$/L	2.9 (28)	2.3 (7)	4.2 (17)
Haemoglobin: mean (SD) change from baseline to week 24 (g/dl)	0.83 (1.10)	1.04 (1.23)	0.83 (1.26)
Total cholesterol: mean (SD) change from baseline to week 24 (mmol/L)	0.52 (0.93)	0.63 (0.90)	0.49 (0.93)
LDL cholesterol: mean (SD) change from baseline to week 24 (mmol/L)	0.28 (0.81)	0.37 (0.75)	0.26 (0.81)
HDL cholesterol: mean (SD) change from baseline to week 24 (mmol/L)	0.16 (0.28)	0.18 (0.32)	0.15 (0.28)
Triglycerides: mean (SD) change from baseline to week 24 (mmol/L)	0.17 (0.69)	0.22 (0.76)	0.18 (0.74)
Total cholesterol/HDL ratio: mean (SD) change from baseline to week 24	0.013 (0.792)	0.048 (0.760)	-0.009 (0.838)

ALT, alanine aminotransferase; BL, baseline; DMARD, disease-modifying anti-rheumatic drug; LDL, low-density lipoprotein; TNFi-naive, patients who had never received TNFi therapy; TNFi-previous use, patients who had discontinued TNFi therapy for >2 months before baseline (washout period); TNFi-recent use, patients who had discontinued TNFi therapy for ≤2 months before baseline (no washout period); TCZ, tocilizumab; ULN, upper limit of normal.