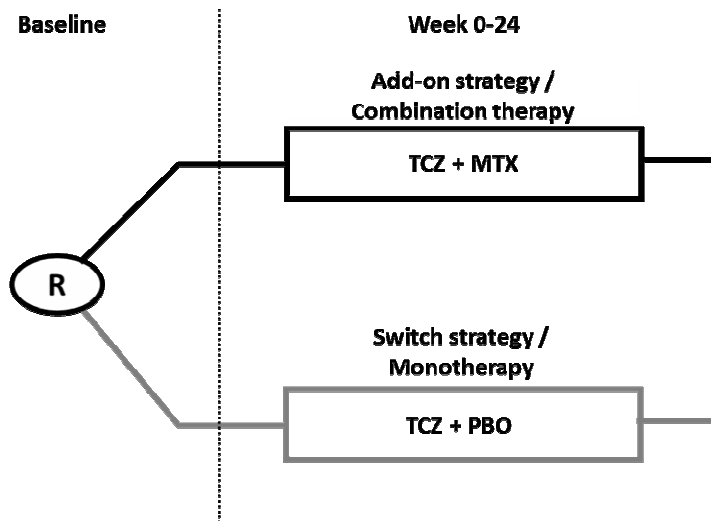


Study Design

ACT-RAY study design (through week 24)



Inclusion Criteria

To be eligible for this trial, patients must meet all of the following criteria:

1. Male or non-pregnant, non-nursing female
2. ≥ 18 years of age
3. Body weight ≤ 150 kg
4. Patients currently experiencing active moderate to severe RA (DAS28 > 4.4) according to the revised 1987 ACR criteria for the diagnosis of RA at baseline. At screening the DAS28 must be equal or greater than 4.0 (DAS28 ≥ 4.0).
5. Radiographic evidence of at least one joint with definite erosion attributable to RA as determined by the central reading site. Any joint of the hands, feet or wrists can be considered with the exception of distal interphalangeal joints of the hands
6. Patients currently receiving MTX (oral or parenteral) for at least 12 weeks and who have received MTX at a stable dose of at least 15 mg/week for at least 6 weeks prior to treatment (day 1), with the following exception: 10 mg instead of 15 mg is acceptable in patients with a body weight < 50 kg, low grade toxicity to MTX (such as nausea), or calculated glomerular filtration rate (or creatinine clearance) < 60 mL/min. Patients with a history of parenteral (subcutaneous or intramuscular) MTX prior to baseline are eligible. However, prior to treatment (day 1) these patients must have been on a stable dose of oral MTX of at least 15 mg/week for at least 6 weeks.

7. If patients are receiving an oral corticosteroid, the dose must have been ≤ 10 mg/day prednisone (or equivalent) and stable for at least 25 out of 28 days prior to treatment (day 1)
8. Patients receiving treatment on an outpatient basis
9. Patients able and willing to give written informed consent and comply with the requirements of the study protocol

Exclusion Criteria

Patients with any of the following criteria will not be eligible to participate in the study:

Disease

1. Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 6 months following randomization
2. Rheumatic autoimmune disease other than RA, including systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), scleroderma, polymyositis, or significant systemic involvement secondary to RA (e.g. vasculitis, pulmonary fibrosis or Felty's syndrome). Patients with interstitial pulmonary fibrosis and still able to tolerate MTX therapy are permitted. Sjögren's Syndrome with RA is permitted
3. Functional class IV as defined by the ACR Classification of Functional Status in RA (largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care)
4. Prior history of or current inflammatory joint disease other than RA (e.g. gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease)

Drug-specific

5. Treatment with traditional DMARDs other than MTX within 1 month (for leflunomide 3 months) prior to baseline
6. Treatment with any investigational agent within 4 weeks (or 5 half-lives of investigational agent, whichever is longer) before screening
7. Previous treatment with TCZ.
8. Previous treatment with any biologic drug that is used in the treatment of RA
9. Any previous treatment with alkylating agents, such as cyclophosphamide or chlorambucil, or with total lymphoid irradiation
10. Treatment with IV gamma globulin, plasmapheresis or ProSORBA® column within 6 months before baseline
11. Intraarticular or parenteral corticosteroids within 6 weeks prior to baseline

12. Immunization with a live/attenuated vaccine within 4 weeks prior to baseline

Laboratory analyses (at screening)

13. Serum creatinine > 142 $\mu\text{mol/L}$ (1.6 mg/dL) in female patients and > 168 $\mu\text{mol/L}$ (1.9 mg/dL) in male patients and no active renal disease
14. ALT (SGPT) or AST (SGOT) > 1.5 x ULN
15. Platelet count < $100 \times 10^9/\text{L}$ (100,000/ mm^3)
16. Hemoglobin < 85 g/L (8.5 g/dL; 5.3 mmol/L)
17. WBC count < $1.0 \times 10^9/\text{L}$ (1000/ mm^3), absolute neutrophil count < $1.0 \times 10^9/\text{L}$ (1000/ mm^3). Patients enrolled prior to amendment based on a lower ANC threshold may continue to stay in the study, if deemed appropriate by the investigator.
18. Absolute lymphocyte count < $0.5 \times 10^9/\text{L}$ (500/ mm^3)
19. Positive HBsAg or HCV antibody
20. Total bilirubin > ULN
21. Triglycerides > 10 mmol/L (> 900 mg/dL) at screening (non-fasting or fasting)

General medical

22. Pregnant women or nursing (breastfeeding) mothers
23. Females of child-bearing potential who are not using reliable means of contraception (such as physical barrier [patient and partner], contraceptive pill or patch, spermicide and barrier, or intrauterine device)
24. History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies
25. CXR evidence of any clinically significant abnormality
26. Evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus) or GI disease
27. In patients with a history of diverticulitis or diverticulosis requiring antibiotic treatment, the treating physician needs to consider the benefit-risk ratio
28. A history of chronic ulcerative lower GI disease such as Crohn's disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose to perforations
29. Uncontrolled disease states, such as asthma, psoriasis, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids

30. Current liver disease as determined by investigator. Patients with prior history of ALT (SGPT) elevation are not excluded
31. Known active current or history of recurrent bacterial, viral, fungal, mycobacterial, or other infections (including but not limited to tuberculosis (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 hospitalization or treatment with IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening (does not apply to the treatment of latent TB)
32. History of, or currently active, primary or secondary immunodeficiency
33. Evidence of active malignant disease, malignancies active or diagnosed within the previous 5 years (including hematological malignancies and solid tumors, except nonmelanoma skin cancer that has been excised and cured)
34. Active TB requiring treatment within the previous 3 years. Patients treated for tuberculosis with no recurrence in 3 years are permitted.
Latent TB: Patients with latent tuberculosis are not eligible, unless having started treatment with standard antimycobacterial therapy before initiating TCZ and have a negative CXR for active TB at screening. Therefore patients should be screened for latent TB, prior to biologics use, as per local guidelines or clinical practice in the country of study conduct. The assessment of the presence or absence of latent TB will take place during the screening period. However, if local practice or guidelines allow to refer to test results that were obtained prior to the screening period as part of routine clinical practice, this is allowed.
35. HIV positive patient
36. History of alcohol, drug, or chemical abuse within the 6 months prior to screening
37. Neuropathies or other painful conditions that might interfere with pain evaluation
38. Patients with lack of peripheral venous access

Supplemental Methods:

The study Steering Committee made assumptions concerning the expected DAS28-ESR remission rates at week 24 using the phase II dose-finding study CHARISMA as a guide. With a relatively small sample size CHARISMA indicated that TCZ + MTX combination therapy might be superior to TCZ monotherapy at week 16 (DAS28 remission achieved by 34% of combination therapy and 17% of monotherapy patients). The assumption of a 12.5% difference in the ACT-RAY study at week 24 (determined from an anticipated 42.5% remission rate in TCZ + MTX patients and a 30% remission rate in TCZ + PBO) was developed by the Steering Committee through discussions taking design differences as well as preliminary data from studies in slightly different populations into account. The steering committee considered the demonstration of a significant difference between the two treatment strategies with an estimated difference of 12.5% as valuable information for clinical practice, but also noted that different clinicians might find other differences clinically meaningful. The steering committee included, Maxime Dougados, Tom Huizinga, Paul Peter Tak (initially), Georg Schett, Emilio Martin Mola, and Philip Conaghan.

Supplemental Figure:

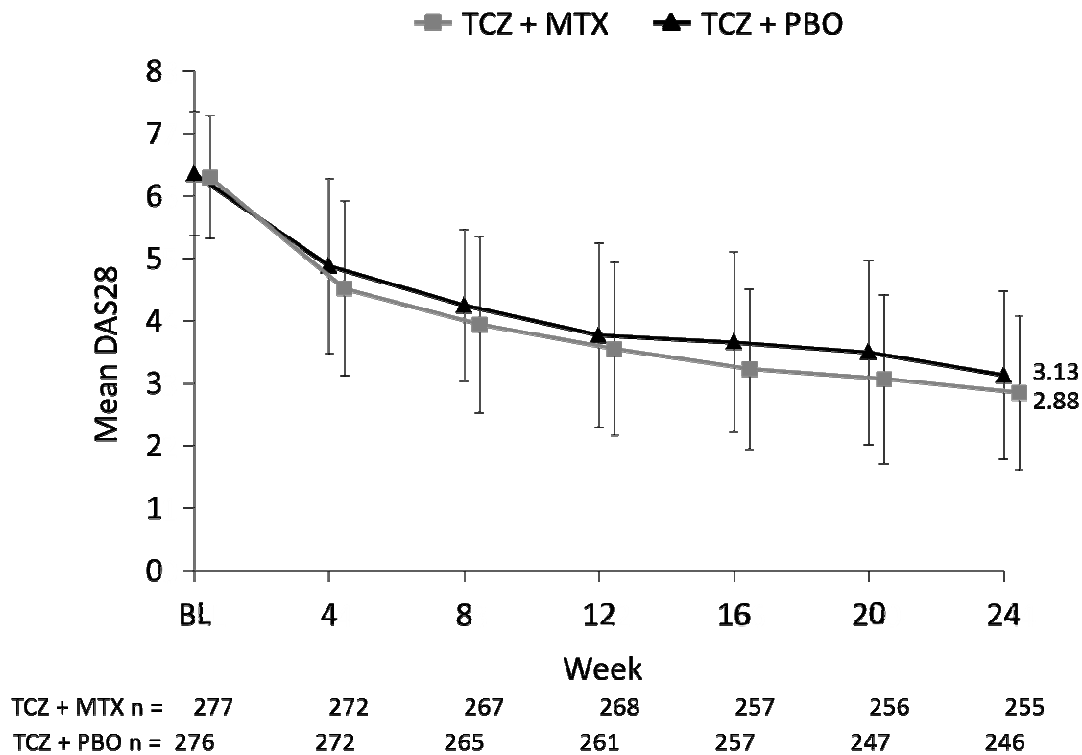


Figure S1. Mean DAS28 scores and standard deviation over time (ITT population). The TCZ + MTX series is shifted slightly to the right relative to TCZ + PBO for better readability. DAS28, disease activity score based on 28 joints. ITT, intention-to-treat.

Supplemental Table:**Table S1** HAQ-DI <0.5 and clinical remission (DAS28 <2.6) at Week 24

Patients	TCZ+MTX (N=277)	TCZ+PBO (N=276)
HAQ-DI <0.5, % (n)	29.2% (81)	25.0% (69)
DAS28 <2.6, % (n)	40.4% (112)	34.8% (96)
HAQ-DI <0.5 and DAS28 <2.6, % (n)	17.7% (49)	17.4% (48)

DAS28, Disease Activity Score based on 28 joints; HAQ-DI, health assessment questionnaire – disability index; MTX, methotrexate; PBO, placebo; TCZ, tocilizumab.