SUPPLEMENTARY APPENDIX

Supplementary methods: Serum TCZ and anti-TCZ antibody measurements

Serum samples for measurement of TCZ concentrations were obtained at baseline and at weeks 2, 4, 12, 16, 24, 36, 52, 76 and 104 and at study withdrawal. Samples were obtained before dose on dosing days. TCZ concentrations were determined using a validated enzyme-linked immunosorbent assay (ELISA) method (QPS, Zeist, Netherlands), with a lower limit of quantification of 100 mg/mL.

Anti-TCZ antibodies were measured in serum samples obtained at baseline, week 52 and study withdrawal. All samples underwent a screening assay; if findings were positive, a confirmation assay was performed (bridging ELISA; QPS). If findings of both the screening and the confirmation assays were positive, a neutralising assay was performed to determine the presence of anti-TCZ antibodies (inhibition ELISA; QPS). The lower limit of quantification for anti-TCZ antibodies was 211 ng·Eq/mL.

Supplementary Table S1 Methotrexate dose at weeks 52 and 104 (ITT population)

	Placebo + MTX n=287	**4 mg/kg TCZ + MTX n=288**	**8 mg/kg TCZ + MTX n=290**
Week 52, mean (SD)	17.3 (4.53) n=221	16.9 (5.71) n=216	15.4 (5.29) n=213
Week 104, mean (SD)	16.2 (6.18) n=86	15.5 (4.92) n=82	14.4 (5.10) n=99

MTX, methotrexate; SD, standard deviation; TCZ, tocilizumab.

Supplementary Table S2 Baseline demographics and disease characteristics in escape patients (ITT population, escape patients)

	Placebo + MTX pre-escape n=142	**4 mg/kg TCZ + MTX pre-escape n=95**
Female, n (%)	116 (82)	81 (85)
Age, years	49.9 (12.42)	50.6 (12.58)
Duration of RA, years	0.5 (0.50)	0.5 (0.52)
Receiving corticosteroids, n (%)	51 (36)	33 (35)
RF positive, n (%)	128 (90)	86 (91)
Anti-CCP antibody positive, n (%)	123 (87)	77 (82)
DAS28-ESR	6.7 (0.96)	6.9 (1.06)
TJC (68 joints)	29.8 (17.2)	31.2 (15.7)
SJC (66 joints)	17.5 (11.7)	17.3 (11.9)
ESR (mm/h)	53.2 (28.7)	62.1 (35.1)
CRP (mg/dl)	2.4 (2.7)	2.4 (2.8)
HAQ-DI	1.5 (0.6)	1.7 (0.7)
Previous number of DMARDs	0.2 (0.4)	0.2 (0.5)
vdH mTSS	7.04 (21.06)	8.31 (17.26)

Data are mean (SD) unless stated otherwise.

CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, Disease Activity Score based on 28 joints; DMARDs, disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire–Disability Index; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SJC,

swollen joint count; TCZ, tocilizumab; TJC, tender joint count; vdH mTSS, van der Heijde–modified total Sharp score.

Supplementary Table S3 Radiographic endpoints in escape patients

	Placebo + MTX **Post-escape** **n=142**	**4 mg/kg TCZ + MTX** **Post-escape** **n=95**
Change from baseline in vdH mTSS[a]		
Week 52	1.49 (3.952)	0.68 (2.703)
Week 104	1.57 (4.557)	0.56 (2.627)
APR for vdH mTSS[a]		
Baseline to week 52	1.43 (3.811)	0.65 (2.555)
Weeks 52 to 104	0.10 (1.156)	0.01 (0.692)

Based on observed data (no imputation for missing data) with post-withdrawal data included.

Data are mean (SD).

[a]Based on original baseline.

APR, annualised progression rate; MTX, methotrexate; TCZ, tocilizumab; vdH mTSS, van der Heijde–modified total Sharp score.

Supplementary Table S4 Efficacy at week 104 according to achievement of DAS28-ESR LDA at week 52

	Achieved DAS28-ESR LDA at week 52							
Week 104 response	**Yes**				**No**			
	Placebo + MTX n=86	**4 mg/kg TCZ + MTX n=137**	**8 mg/kg TCZ + MTX n=168**	**8 mg/kg TCZ + placebo n=147**	**Placebo + MTX n=201**	**4 mg/kg TCZ + MTX n=151**	**8 mg/kg TCZ + MTX n=122**	**8 mg/kg TCZ + placebo n=145**
ACR20, n (%)	71 (82.6)	112 (81.8)	144 (85.7)	126 (85.7)	2 (1.0)	2 (1.3)	45 (36.9)	54 (37.2)
ACR50, n (%)	62 (72.1)	103 (75.2)	134 (79.8)	116 (78.9)	1 (0.5)	2 (1.3)	33 (27.0)	39 (26.9)
ACR70, n (%)	50 (58.1)	90 (65.7)	116 (69.0)	89 (60.5)	0 (0.0)	1 (0.7)	19 (15.6)	26 (17.9)
DAS28-ESR remission, n (%)	46 (53.5)	79 (57.7)	121 (72.0)	102 (69.4)	0 (0.0)	2 (1.3)	17 (13.9)	25 (17.2)
Change from baseline in vDH mTSS, mean (SD)	0.7 (1.92) n=85	0.4 (1.50) n=135	-0.01 (1.10) n=165	0.2 (1.70) n=145	2.5 (7.39) n=181	2.5 (16.53) n=131	0.5 (3.01) n=107	1.1 (6.7) n=130

ACR, American College of Rheumatology; DAS28-ESR, Disease Activity Score based on 28 joints and the erythrocyte sedimentation rate; LDA, low disease activity; MTX, methotrexate; SD, standard deviation; TCZ, tocilizumab; vDH mTSS, van der Heijde–modified total Sharp score

Supplementary Table S5 Causes of death

Patient, gender, age	Treatment group at randomisation	Study day of death	Cause of death (relevant medical history)
Male, 64	Placebo+MTX	157	Pneumonia [influenza type A] (ILD and diagnosed with DM during the study)
Female, 64	Placebo+MTX	363	Sepsis (extra-peritoneal subcutaneous abscess in right subchondral region reported on day 293)
Female, 51	4 mg/kg TCZ MTX	67	Subarachnoid haemorrhage (previously unknown aneurysm was the secondary cause of death)
Female, 83	4 mg/kg TCZ+MTX	96	Pneumonia (malnutrition reported as underlying cause of death; history of dyspepsia and hypertension)
Male, 83	4 mg/kg TCZ MTX	115	Lung infection (history of hypertension, mitral valve prolapse, ulcer of unspecified cite)
Male, 82	4 mg/kg TCZ MTX	349	Arteriosclerosis [cardiac arrest] (history of hypertension and CAD)
Female, 74	4 mg/kg TCZ+MTX	526	Duodenal ulcer haemorrhage (patient had experienced ischaemic stroke with signs of haemorrhage in the vertebrobasilar basin on day 486)
Female, 41	8 mg/kg TCZ+MTX	84	Hypoglycaemic coma (history of IDDM with complications
Male, 60	8 mg/kg TCZ+MTX	102	Tension pneumothorax following a tracheostomy to treat an SAE of pneumonia (previous COPD, DM, cardiac disorder and hypertension)
Male, 53	8 mg/kg TCZ+MTX	627	ILD (with previous history of ILD)
Female, 56	8 mg/kg TCZ+MTX	644	Endometrial cancer
Male, 70	8 mg/kg	49	Malignant lung neoplasm (history of COPD,

	TCZ+placebo		smoking and abnormalities on screening chest x-ray not noted until after baseline visit; patient was discontinued from treatment)
Female, 69	8 mg/kg TCZ+placebo	470	Metastatic neoplasm (primary malignancy not determined)
Male, 69	8 mg/kg TCZ+placebo	733	Congestive heart failure (history of hypertension dyslipidaemia, peripheral oedema, atrial fibrillation, CVA and DM)

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVA, cardiovascular accident; DM, diabetes mellitus; ILD, interstitial lung disease; SAE, serious adverse event.

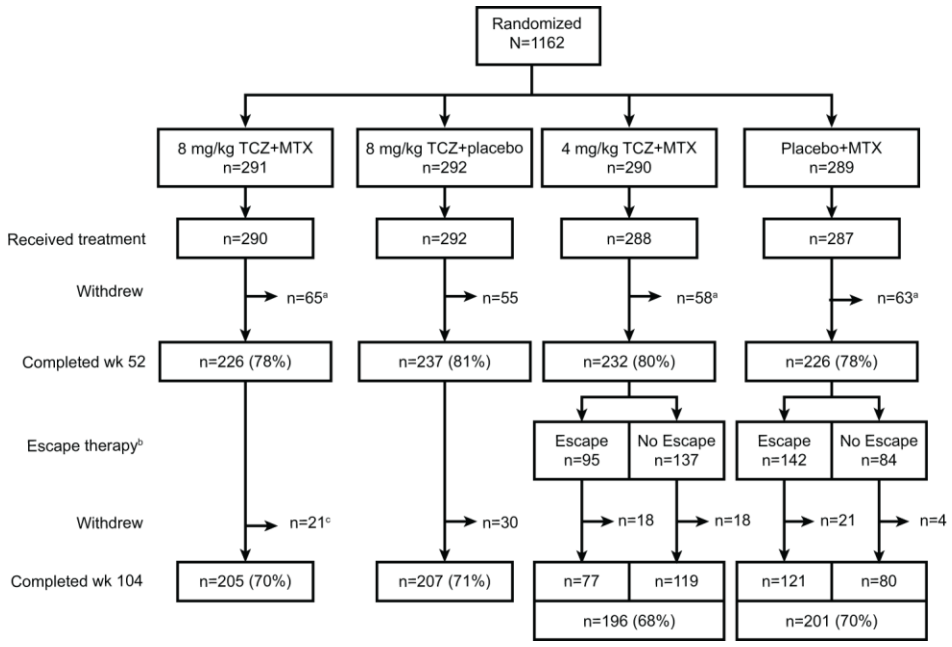
Supplementary Table S6 Safety in escape patients

	Placebo+MTX		4 mg/kg TCZ+MTX	
	Pre-escape n=142	**Post-escape n=142**	**Pre-escape n=95**	**Post-escape n=95**
Exposure, PY	142.43	137.80	95.50	92.65
AEs, rate/100 PY [95% CI] (n, events)				
Overall AEs	411.4 [378.8, 446.1] (586)	294.6 [266.7, 324.7] (406)	442.9 [401.7, 487.2] (423)	310.9 [276.0, 348.9] (288)
Overall SAEs	7.0 [3.4, 12.9] (10)	10.9 [6.1, 18.0] (15)	8.4 [3.6, 16.5] (8)	9.7 [4.4, 18.4] (9)
Serious infections	1.4 [0.2, 5.1] (2)	3.6 [1.2,8.5] (5)	3.1 [0.6,9.2] (3)	3.2 [0.7,9.5] (3)
Clinical laboratory abnormalities, n (%)				
Neutropenia				
Grade –3 <1.0-0.5 × 10^9/L	0 (0.0)	6 (4.2)	2 (2.1)	1 (1.1)
Grade –4 <0.5 × 10^9/L	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia (based on platelet count)				
Grade –3 <50-25 × 10^9/L	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade –4 <25 × 10^9/L	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT elevations				
Grade 1 >ULN-2.5× ULN	58 (40.8)	77 (54.2)	38 (40.4)	44 (46.3)
Grade 2 >2.5-5× ULN	10 (7.0)	20 (14.1)	14 (14.9)	9 (9.5)

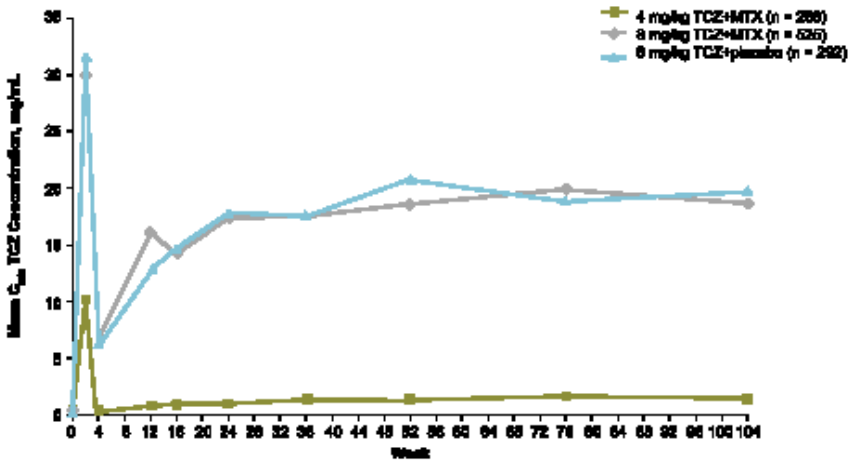
Grade 3 >5.0-20× ULN	1 (0.7)	2 (1.4)	0 (0.0)	2 (2.1)
Grade 4 >20× ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST elevations				
Grade 1 >ULN-2.5× ULN	47 (33.3)	68 (47.9)	38 (40.0)	40 (42.1)
Grade 2 >2.5-5× ULN	2 (1.4)	6 (4.2)	1 (1.1)	4 (4.2)
Grade 3 >5.0-20× ULN	1 (0.7)	0 (0.0)	0 (0.0)	2 (2.1)
Grade 4 >20× ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; MTX, methotrexate; PY, patient-years; SAEs, serious adverse events; TCZ, tocilizumab; ULN, upper limit of normal.

Supplementary Figure S1 Patient disposition. Percentages are based on the number of randomly assigned patients. [a]Includes patients who did not receive study treatment (one 8 mg/kg TCZ+MTX, two 4 mg/kg TCZ+MTX, two placebo+MTX). [b]Patients in the 4 mg/kg TCZ+MTX and placebo+MTX treatment groups switched to 8 mg/kg TCZ+MTX at week 52 if DAS28-ESR >3.2. [c]Includes a patient reported to have completed the study, though the exit data indicate that the patient withdrew during weeks 64–72. The reason for withdrawal is unknown. DAS28, Disease Activity Score based on 28 joints; ESR, erythrocyte sedimentation rate; MTX, methotrexate; TCZ, tocilizumab.



Supplementary Figure S2 Mean C_{min} TCZ serum concentration over time (PK-evaluable population). Assessments made on escape therapy are included under the treatment group in which they occurred. Patients receiving escape therapy were re-baselined at the time of escape. N values are the overall number of patients in each treatment group, but the number of evaluable patients at each time point was variable. C_{min}, pre-dose concentration (minimum or trough) concentration; MTX, methotrexate; PK, pharmacokinetics; TCZ, tocilizumab.


4 mg/kg TCZ+MTX (n = 286)
8 mg/kg TCZ+MTX (n = 526)
8 mg/kg TCZ+placebo (n = 292)
Week