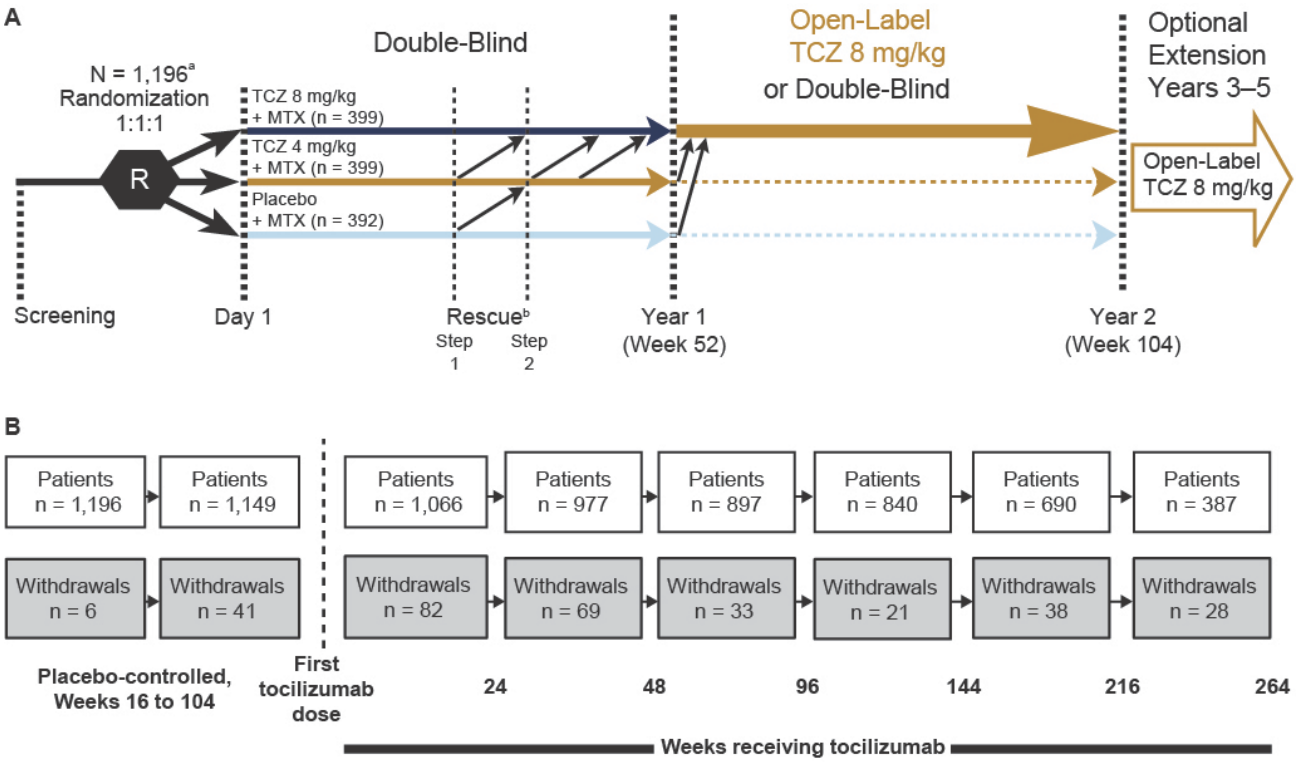
Supplementary material

Immunogenicity methods

Immunogenicity was assessed throughout the study by screening patients in the tocilizumab group for anti-tocilizumab antibodies throughout the study. Post-baseline tallies of positive results on screening and confirmation assays included only patients who seroconverted from negative at baseline to positive after baseline on the respective assays.



Supplementary Fig. S1. (**A**) Study design and (**B**) patient disposition. Study duration was 264 weeks, including the placebo-controlled portion (in this period, patients received either placebo or tocilizumab [4 mg/kg or 8 mg/kg]). Given that some patients were randomly assigned to placebo for this first portion of the study, not all patients received the total 264 weeks of tocilizumab treatment. Patients who were randomly assigned to placebo received between 16 and 104 weeks of placebo treatment before moving on to receive their first tocilizumab dose. (A) [a]Six patients (one in the placebo + MTX arm, two in the tocilizumab 4 mg/kg + MTX arm and three in the tocilizumab 8 mg/kg + MTX arm) did not receive study medication. [b]Patients could receive rescue at any point between week 16 and the end of year 1. MTX: methotrexate; TCZ: tocilizumab.

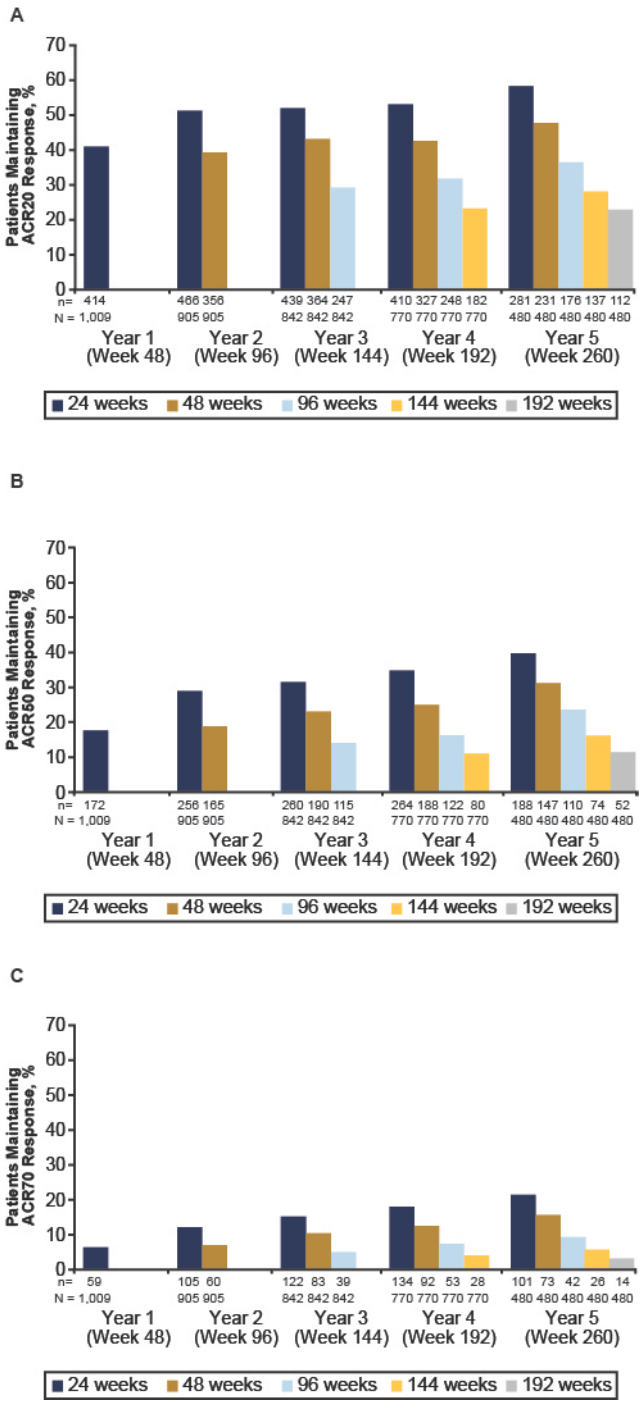
Supplementary Table S1. Baseline demographics and clinical characteristics (tocilizumab population)

	All tocilizumab N = 1,149
Patient demographics	
Female, %	83
Age, years	51.9 (12.2)
RA duration, years, mean (range)	9.6 (0.6-48.8)
MTX dose, mg/wk	15.1 (7.1)
No. previous DMARDs/aTNF agents[a]	2.0 (1.4)
Patients using concomitant steroids, %	68
RF positivity, %	82
Disease activity	
DAS28 ESR	6.3 (1.2)
SJC (66 joint count)	16.3 (10.6)
TJC (68 joint count)	27.3 (15.9)
HAQ-DI	1.5 (0.7)
CRP, mg/dl	2.2 (2.5)

aTNF: anti–tumour necrosis factor-α; CRP: C-reactive protein; DAS28: Disease Activity Score at 28 joints; DMARD: disease-modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire–Disability Index; MTX: methotrexate; RA: rheumatoid arthritis; RF: rheumatoid factor; SJC:, swollen joint count; TJC: tender joint count.

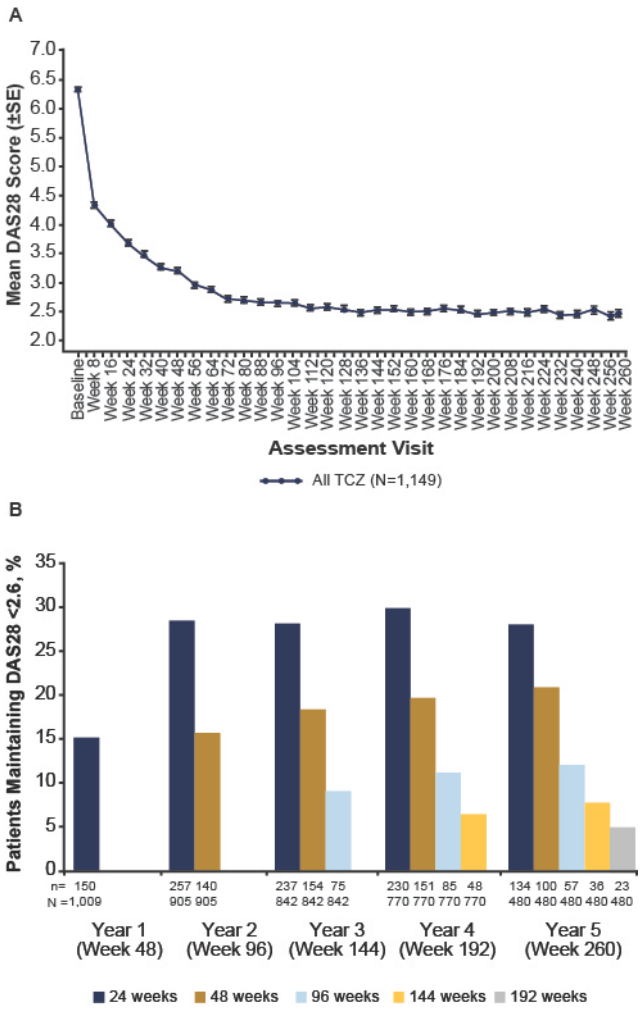
Values are mean (SD) unless otherwise indicated.

[a]This did not include MTX, to which patients showed inadequate response at screening.

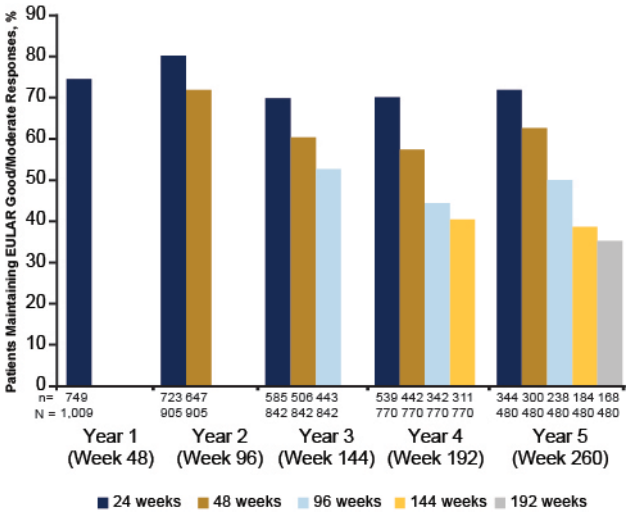


Supplementary Fig. S2. Rates of (**A**) ACR20, (**B**) ACR50 and (**C**) ACR70 response maintenance by visit (tocilizumab population). The maintenance group was defined as patients who continually met criteria for ACR20/50/70 from the first achievement of response. Bars represent the proportions of patients who maintained ACR response for 24, 48, 96 144 and 192 weeks at each time point in the

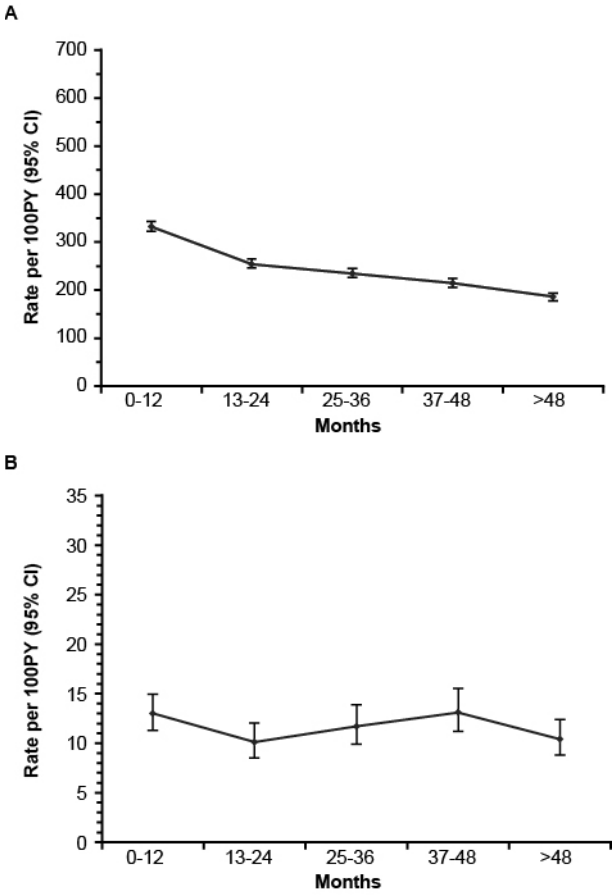
5-year study (week 48, week 96, week 144, week 192, week 260). There was no imputation for missing data. ACR: American College of Rheumatology.



Supplementary Fig. S3. (**A**) Mean DAS28-ESR score and (**B**) maintenance of DAS28 ESR <2.6 over time (tocilizumab population). (**A**) Last observation carried forward was used for tender and swollen joints; no imputation was used for ESR and Patient's Global Assessment of Disease Activity Visual Analog Scale. (**B**) The maintenance group was defined as patients who continually met criteria for DAS28 <2.6 from the first achievement of response. Bars represent the proportion of patients who maintained DAS28 <2.6 for 24, 48, 96, 144 and 192 weeks at each time point in the 5-year study (week 48, week 96, week 144, week 192, week 260). There was no imputation for missing data. DAS28: Disease Activity Score at 28 joints; ESR: erythrocyte sedimentation rate; TCZ: tocilizumab.



Supplementary Fig. S4. Maintenance of EULAR good/moderate response (tocilizumab population). The maintenance group was defined as patients who continually met criteria for good/moderate EULAR response from the first achievement of response. Bars represent the proportion of patients who maintained good/moderate EULAR response for 24, 48, 96, 144 and 192 weeks at each time point in the 5-year study (week 48, week 96, week 144, week 192, week 260). There was no imputation for missing data. EULAR: European League Against Rheumatism.



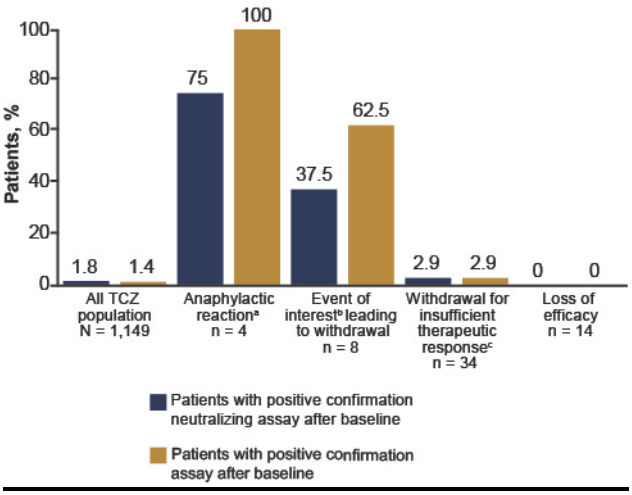
Supplementary Fig. S5. Reduction and maintenance of (**A**) AE and (**B**) SAE rates per 100 PY by 12-month periods (tocilizumab population). PY refers to duration in study, calculated from first active drug intake to last safety assessment available + 1. Month is equivalent to 28 days. Multiple occurrences of the same AE in a patient are counted as individual events. AE: adverse event; CI: confidence interval; PY: patient-years; SAE: serious adverse event.

Supplementary Table S2. Patient deaths (tocilizumab population)

Cause of Death	Patients, n	Day of Death[a]
Acute hepatic failure	1	1,374
Acute interstitial pneumonitis	1	1,869
Bronchopneumonia	1	275
Cardiomyopathy	1	757
Cerebrovascular accident	1	1,796
Enteritis	1	1,214
Gastroenteritis	1	324
Gastro-oesophageal cancer	1	262
Haemorrhagic infarct of lung	1	1,017
Metastatic lung adenocarcinoma	1	861
Metastatic malignant melanoma	1	858
Necrotizing pancreatitis	1	1,299
Neuroendocrine carcinoma	1	1,896
Periprosthetic femoral fracture	1	1,040
Pulmonary embolism	2	74
		822
Sepsis	1	284
Septic shock	2	690
		1,239
Splenic rupture	1	1,661

Staphylococcal sepsis	1	592
Subarachnoid haemorrhage	1	280

[a]Day of death was calculated relative to the first active dose of tocilizumab.



Supplementary Fig. S6. Summary of events in patients with a positive anti-tocilizumab assay result. Patients positive after baseline were those who had no positivity at baseline for the same assay. [a]Anaphylactic reactions included preferred terms anaphylactic reaction, anaphylactic shock, anaphylactic transfusion reaction, anaphylactoid reaction, anaphylactoid shock, shock, type I hypersensitivity, circulatory collapse, first use syndrome, and Kounis syndrome. [b]Events of interest were any AEs during or within 24 hours of infusion or injection that led to withdrawal, including anaphylactic reactions, and only in the SOC skin and subcutaneous tissue disorders, general disorders and administration site conditions, nervous system disorders, immune system disorders, and cardiac disorders. [c]Loss of efficacy patients were in the tocilizumab population. They withdrew because of insufficient therapeutic response and experienced ACR50 or DAS28 EULAR good response before withdrawal. ACR: American College of Rheumatology; AEs: adverse events; DAS28: Disease Activity Score at 28 joints; EULAR: European League Against Rheumatism; SOC: system organ class; TCZ: tocilizumab.