Supplementary material

METHODS

Study population

Patients were also excluded if they had active angiitis or a history of cancer (in last 5 years). Other exclusion criteria included pregnancy or lactation, administration of biologic disease-modifying antirheumatic drugs (DMARDs) other than methotrexate (MTX) within 4 weeks before day 1, or current symptoms of severe, progressive or uncontrolled renal, hepatic, haematological, gastrointestinal, pulmonary, cardiac, neurological or cerebral disease.

Randomisation

At enrolment, each patient was assigned a unique sequential number via a central randomisation system and was enrolled into a centralised database. After screening, each eligible patient was assigned a unique randomisation number via the central randomisation system in the order of qualification for treatment.

Concomitant medications

Patients were permitted to continue with a low dose of concomitant oral corticosteroids (equivalent to <10 mg/day prednisone) and concomitant non-steroidal anti-inflammatory drugs (NSAIDs) at the study initiation dose. Intra-articular/-muscular or intravenous corticosteroid injections were permitted up to twice (two joints every 6 months). However, these injections were prohibited 4 weeks before efficacy evaluation at weeks 16, 24 and 52. In addition, intra-articular injection of corticosteroids was prohibited in joints that were to be evaluated using the van der Heijde-modified total Sharp score (vdH-mTSS). When patients received an intra-articular corticosteroid, the treated joint was counted as an active tender/swollen

joint. After evaluation at week 24, the dosage of oral corticosteroids and NSAIDs could be changed, and inclusion of an additional non-biologic DMARD was permitted.

Radiographic assessment

Tertiary efficacy endpoints included the changes from baseline in vdH-mTSS at week 52 and erosion and joint-space narrowing scores at weeks 24 and 52.

Safety assessment

Adverse events (AEs) were defined as any new medical occurrence or worsening of a pre-existing medical condition that did not necessarily have a causal relationship with the treatment as determined by a physician. Serious adverse events (SAEs) were defined as any untoward medical occurrence that resulted in death, life-threatening, persistent or significant disability/incapacity, that required inpatient hospitalisation or caused prolongation of existing hospitalisation, or that was a congenital anomaly/birth defect or an important medical event. AEs were classified using the Medical Dictionary for Regulatory Activities version 19.1. Vital sign changes and laboratory test abnormalities or changes were recorded. AEs and SAEs are presented as exposure-adjusted incidence rate per 100 person-years of exposure.

Statistical analyses

The definition of the population for safety analysis was the same as the intent-to-treat population. American College of Rheumatology 20 (ACR20) responses were determined using non-responder imputation for missing values or after discontinuation. Patients who received rescue abatacept treatment or discontinued were considered as non-responders. Missing or post-rescue radiographic data at weeks 24 and 52 were imputed by linear extrapolation for any patient with one

baseline assessment and at least one post-baseline assessment before rescue abatacept therapy. The two sensitivity analyses were performed to investigate the robustness of the linear extrapolation method, with the use of multiple imputation instead of linear extrapolation or the use of observed change from baseline in vdH-mTSS at week 24. The radiographic non-progressor rates with three cut-off levels, which were defined as the proportion of patients meeting the change from baseline in vdH-mTSS at week 24 (day 169) ≤1.9 (smallest detectable change),[1] ≤0 and ≤0.5, were estimated. The cumulative probability plots of change from baseline vdH-mTSS at week 24 were generated. The responses for the other binary response variables, such as ACR50, ACR70, Disease Activity Score 28 (C-reactive protein) (DAS28 [CRP]), Simplified Disease Activity Index and Clinical Disease Activity Index remission, were determined using the same non-responder imputation for missing values or after discontinuation as ACR20. A longitudinal repeated measures model was used to assess the change from baseline in DAS28 (CRP). The frequency of safety AEs and laboratory marked abnormalities were descriptively summarised. Subgroup analyses for ACR20 at week 16 and the radiographic non-progressor rates at week 24 were performed by age, gender and baseline values for duration of rheumatoid arthritis, DAS28 (CRP), mTSS, rheumatoid factor (RF) status and MTX weekly dose.

Results

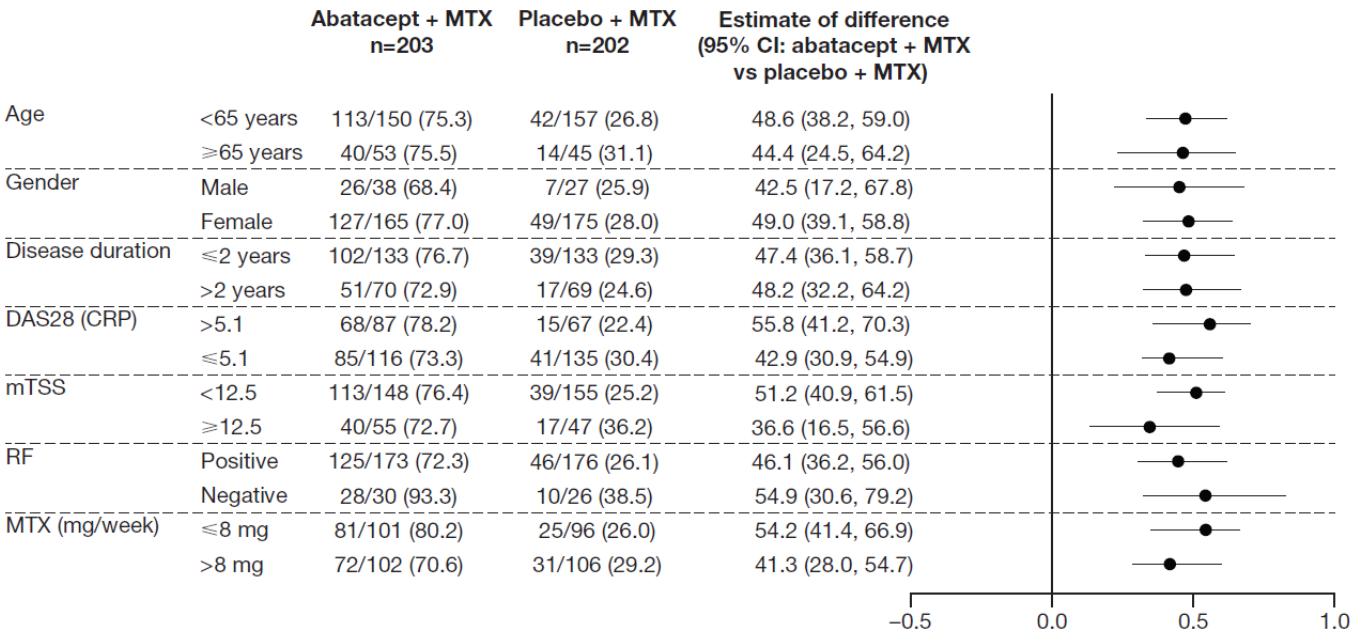
Subgroup analysis

The subgroup factors that showed >10% in estimated difference between their comparators were baseline DAS28 (CRP), mTSS and MTX weekly dose. In the abatacept plus MTX group, differences >10% between the subgroup factors were seen in RF status (positive: 72.3%, negative: 93.2%) and MTX weekly dose at

baseline (≤8.0 mg: 80.2%, >8 mg: 70.6%); while in the placebo plus MTX group, differences were seen in mTSS at baseline (<12.5: 25.2%, ≥12.5: 36.2%) and RF status (positive: 26.1%, negative: 38.5%). Subgroup analyses for non-progression in change of mTSS at the cut-off level of ≤0 at week 24 are shown in supplementary figure S1B. Higher non-progressor rates were observed in the abatacept plus MTX group in all subgroups except RF negative. The subgroup factors that showed >10% in estimated difference between their subgroup comparators were disease duration and RF positivity. In RF-positive patients, the non-progressor rates were 64.9% (111/171 patients) in the abatacept plus MTX group and 50.9% (88/173 patients) in the placebo plus MTX group (estimate of difference: 14.0, 95% confidence interval [CI]: 3.1, 25.0). In RF-negative patients, the rates were 73.3% (20/30 patients) in the abatacept plus MTX group and 76.9% (20/26 patients) in the placebo plus MTX group (estimate of difference: −3.6, 95% CI: −29.8, 22.6). In the abatacept plus MTX group, differences >10% between the subgroup factors were seen in disease duration (≤2 years: 61.8%, >2 years: 74.3%), baseline DAS28 (CRP) (≤5.1: 74.8%, >5.1: 54.7%), baseline mTSS (<12.5: 71.2%, ≥12.5: 52.7%) and RF positivity (positive: 64.9%, negative: 73.3%). In the placebo plus MTX group, such differences were seen in baseline DAS28 (CRP) (≤5.1: 60.2%, >5.1: 42.4%), baseline mTSS (<12.5: 60.1%, ≥12.5: 34.8%) and RF positivity (positive: 50.9%, negative: 76.9%).

Figure S1 Subgroup analyses (A) for ACR20 response rate at week 16 and (B) for non-progression in change of mTSS at the cut-off level of ≤0 at week 24 by age, gender, duration of RA at baseline, DAS28 (CRP) at baseline, mTSS at baseline, baseline RF status, and baseline MTX weekly dose at the cut-off levels indicated in the figure. Data are proportion of patients (%) unless otherwise specified. ACR20, American College of Rheumatology 20; CI, confidence interval; CRP, C-reactive protein; DAS28, Disease Activity Score 28; mTSS, modified Total Sharp Score; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor.

A



B

		Abatacept + MTX n=203	Placebo + MTX n=202	Estimate of difference (95% CI: abatacept + MTX vs placebo + MTX)
Age	<65 years	99/149 (66.4)	82/154 (53.2)	13.2 (1.6, 24.8)
	⩾65 years	34/52 (65.4)	26/45 (57.8)	7.6 (–13.8, 29.1)
Gender	Male	28/37 (75.7)	15/25 (60.0)	15.7 (–11.3, 42.7)
	Female	105/164 (64.0)	93/174 (53.4)	10.6 (–0.5, 21.6)
Disease duration	⩽2 years	81/131 (61.8)	71/132 (53.8)	8.0 (–4.6, 20.7)
	>2 years	52/70 (74.3)	37/67 (55.2)	19.1 (1.9, 36.2)
DAS28 (CRP)	>5.1	47/86 (54.7)	28/66 (42.4)	12.2 (–5.0, 29.5)
	⩽5.1	86/115 (74.8)	80/133 (60.2)	14.6 (2.3, 26.9)
mTSS	<12.5	104/146 (71.2)	92/153 (60.1)	11.1 (–0.2, 22.5)
	⩾12.5	29/55 (52.7)	16/46 (34.8)	17.9 (–3.1, 39.0)
RF	Positive	111/171 (64.9)	88/173 (50.9)	14.0 (3.1, 25.0)
	Negative	22/30 (73.3)	20/26 (76.9)	–3.6 (–29.8, 22.6)
MTX (mg/week)	⩽8 mg	68/101 (67.3)	50/94 (53.2)	14.1 (–0.5, 28.8)
	>8 mg	65/100 (65.0)	58/105 (55.2)	9.8 (–4.6, 24.1)

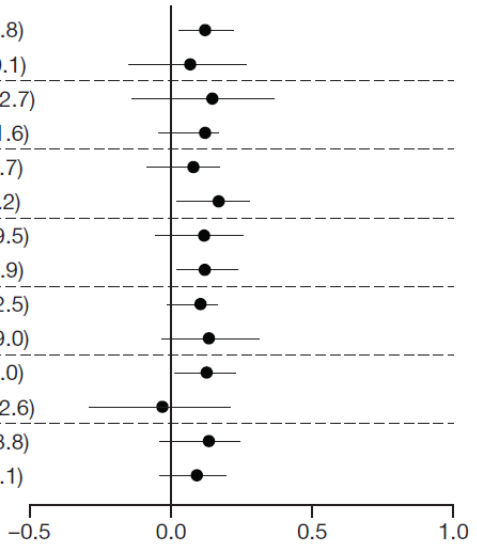


Table S1 Proportion of radiographic non-progressors at weeks 24 and 52

Category	Abatacept + MTX (n=203)	Placebo + MTX (n=202)	Estimate of difference (95% CI: abatacept + MTX vs placebo + MTX)
Week 24			
ΔTSS ≤SDC (=1.9)*	177/201 (88.1) (83.6, 92.5)	150/199 (75.4) (69.4, 81.4)	12.7 (4.7, 20.7)
ΔTSS ≤0.5	154/201 (76.6) (70.8, 82.5)	123/199 (61.8) (55.1, 68.6)	14.8 (5.4, 24.2)
ΔTSS ≤0	133/201 (66.2) (59.6, 72.7)	108/199 (54.3) (47.3, 61.2)	11.9 (1.9, 21.9)
Week 52			
ΔTSS ≤SDC (=1.9)*	168/201 (83.6) (78.5, 88.7)	136/199 (68.3) (61.9. 74.8)	15.2 (6.5, 24.0)
ΔTSS ≤0.5	143/201 (71.1)	112/199 (56.3)	14.9 (5.0, 24.7)

	(64.9, 77.4)	(49.4, 63.2)	
ΔTSS ≤0	121/201 (60.2)	102/199 (51.3)	8.9 (−1.3, 19.1)
	(53.4, 67.0)	(44.3, 58.2)	

Data are number of patients n/m (%) (95% CI) unless otherwise specified.

Missing TSS (including data treated as missing due to the use of rescue therapy) were imputed with linear extrapolation.

*SDC=SD/sqrt (2)*1.96/sqrt (2).

CI, confidence interval; MTX, methotrexate; SD, standard deviation; SDC, smallest detectable change; TSS, total Sharp score.

REFERENCE

1 Bruynesteyn K, Boers M, Kostense P, et al. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. *Ann Rheum Dis* 2005;64:179-82.