SUPPLEMENTARY INFORMATION

Supplementary methods

Study endpoints

Secondary and exploratory endpoints included: other remission rates (Simplified Disease Activity Index [SDAI; ≤3.3], Clinical Disease Activity Index [CDAI; ≤2.8] and Boolean remission [28-joint tender joint count ≤1 and 28-joint swollen joint count ≤1 and patient global assessment of disease activity [0–10 cm] ≤1 and high-sensitivity CRP ≤1 mg/dL]), American College of Rheumatology (ACR) responses and Major Clinical Response (ACR 70 response for 6 months at any time period) in each arm.

Statistical analysis of secondary and exploratory endpoints

Endpoints of Disease Activity Score (DAS)-defined remission, SDAI remission, CDAI remission, Boolean remission, ACR 20/50/70 response and Major Clinical Response over time were summarised using descriptive statistics (with 95% confidence intervals at each time point). Missing remission data not due to premature discontinuation and not at Day 1 of the treatment period or at Day 169 of the withdrawal period were imputed as a remission if the missing value occurred between two observed remissions. Missing ACR response data not due to premature discontinuation and not at Day 1 of the treatment period or at Day 169 of the withdrawal period were imputed as an ACR response if the missing value occurred between two observed ACR responses.

Post hoc analyses

For each treatment arm, a *post hoc* analysis was performed of mean baseline characteristics for patients who achieved DAS-defined remission at only Month 12 and at both Months 12 and 18, and of the proportions of patients who achieved DAS-defined remission

based on these characteristics. An analysis of the overall treatment effect in mean change from baseline in DAS28 (CRP) (including data up to Month 12 of the treatment period) was performed for each treatment arm. Overall treatment effect and treatment differences between the three arms were obtained using a longitudinal repeated measures model including fixed categorical effects of treatment, months and prior corticosteroid use as well as the continuous fixed covariate of baseline value. An unstructured covariance matrix was used to represent the correlation of the repeated measures within each subject.

Table S1. **Inclusion and Exclusion Criteria.**

Inclusion Criteria	Exclusion Criteria
• Willing to participate in the study and provided signed informed consent • Active clinical synovitis of ≥2 joints (including ≥1 small joint and not including distal interphalangeal joints), for ≥8 weeks at screening • Onset of persistent symptoms ≤2 years prior to screening • DAS28 (CRP) ≥3.2 at screening • Anti−CCP-2 positive • MTX naïve or MTX ≤10 mg/kg for ≤4 weeks and no dose for 1 month prior to screening • Biologic naïve • Chloroquin, hydroxychloroquine and sulfasalazine stopped for ≥28 days (if received) • Stable dose oral corticosteroids (≤10 mg prednisone equivalent for ≥4 weeks) or intramuscular, intravenous or intra-articular corticosteroids ≥4 weeks prior to randomisation (if received) • Age ≥18 years • Men and women of childbearing potential using an acceptable method of contraception to avoid pregnancy for up to 10 weeks (14 weeks in European Union) after last dose of study medication • Women with negative serum or urine pregnancy test within 48 hours prior to the start of investigational product • Women must not be breastfeeding • Investigators should follow the manufacturer's recommendations for MTX • Able to receive an MRI	• Met the diagnostic criteria for another rheumatic disease • Impaired, incapacitated or incapable of completing study-related assessments • Current symptoms of severe, progressive or uncontrolled renal, hepatic, hematological, gastrointestinal, pulmonary, cardiac, neurological or cerebral disease • Concomitant medical conditions that, in the opinion of the investigator, might place the patient at unacceptable risk for participation in this study • Women with a breast cancer screening study that is suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations • History of cancer within the last 5 years (other than non-melanoma skin cell cancers cured by local resection). Existing non-melanoma skin cell cancers must be removed prior to dosing. Patients with carcinoma *in situ*, treated with definitive surgical intervention prior to study entry, were allowed • Clinically significant drug or alcohol abuse • Any serious acute bacterial infection (unless treated and completely resolved with antibiotics) • Severe chronic or recurrent bacterial infections • Risk for TB: current clinical, radiographic or laboratory evidence of TB; history of active TB ≤3 years ago; history of active TB >3 years ago unless documentation to support appropriate duration and type of prior anti-TB treatment; latent TB that was not successfully treated (unless active TB infection ruled out and

	treatment for latent TB with isoniazid for ≥4 weeks prior to dosing of study drug and negative chest radiograph at enrolment) • *Herpes zoster* resolved <2 months prior to enrolment • Evidence of active or latent bacterial or viral infections at time of potential enrolment • Hepatitis B surface antigen positivity • Hepatitis C antibody positivity and RIBA positivity or PCR positivity • Haemoglobin <8.5 g/dL • White blood cells <3000/mm^3 • Platelets <100,000/mm^3 • Serum creatinine, ALT or AST >2 times upper limit of normal • Any other laboratory test result that, in the opinion of the study investigator, might place the patient at unacceptable risk for participation in the study • Prior exposure to abatacept • Exposure to any investigational drug within 4 weeks or 5 half-lives, whichever is longer • Currently receiving (or in the last 3 months) azathioprine, gold, leflunomide, immunoadsorption columns, mycophenylate mofetil, cyclosporine, other calcineurin inhibitors or D-penicillamine • Intramuscular, intravenous or intra-articular corticosteroids ≤4 weeks prior to randomisation • Sexually active fertile men not using effective birth control if partners are women of childbearing potential • Prisoners or patients who are involuntarily incarcerated • Compulsorily detained for treatment of either a psychiatric or physical illness • Illiterate

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CCP = cyclic citrullinated peptide, CRP = C-reactive protein, DAS = Disease Activity Score, MRI = magnetic resonance imaging, MTX = methotrexate, PCR = polymerase chain reaction, RIBA =

recombinant immunoblot assay, TB = tuberculosis

Table S2. **Proportion of Patients with Response on Health Assessment Questionnaire-Disability Index (HAQ-DI) at Months 12 and 18.***

	HAQ-DI Response (≥0.3)	
	Month 12	**Month 18**
Abatacept plus MTX	78 (65.5) (57.0, 74.1)	26 (21.8) (14.4, 29.3)
Abatacept monotherapy	61 (52.6) (43.5, 61.7)	19 (16.4) (9.6, 23.1)
MTX	51 (44.0) (34.9, 53.0)	12 (10.3) (4.8, 15.9)

*Values are no. (%) (95% CI).
CI = confidence interval, MTX = methotrexate

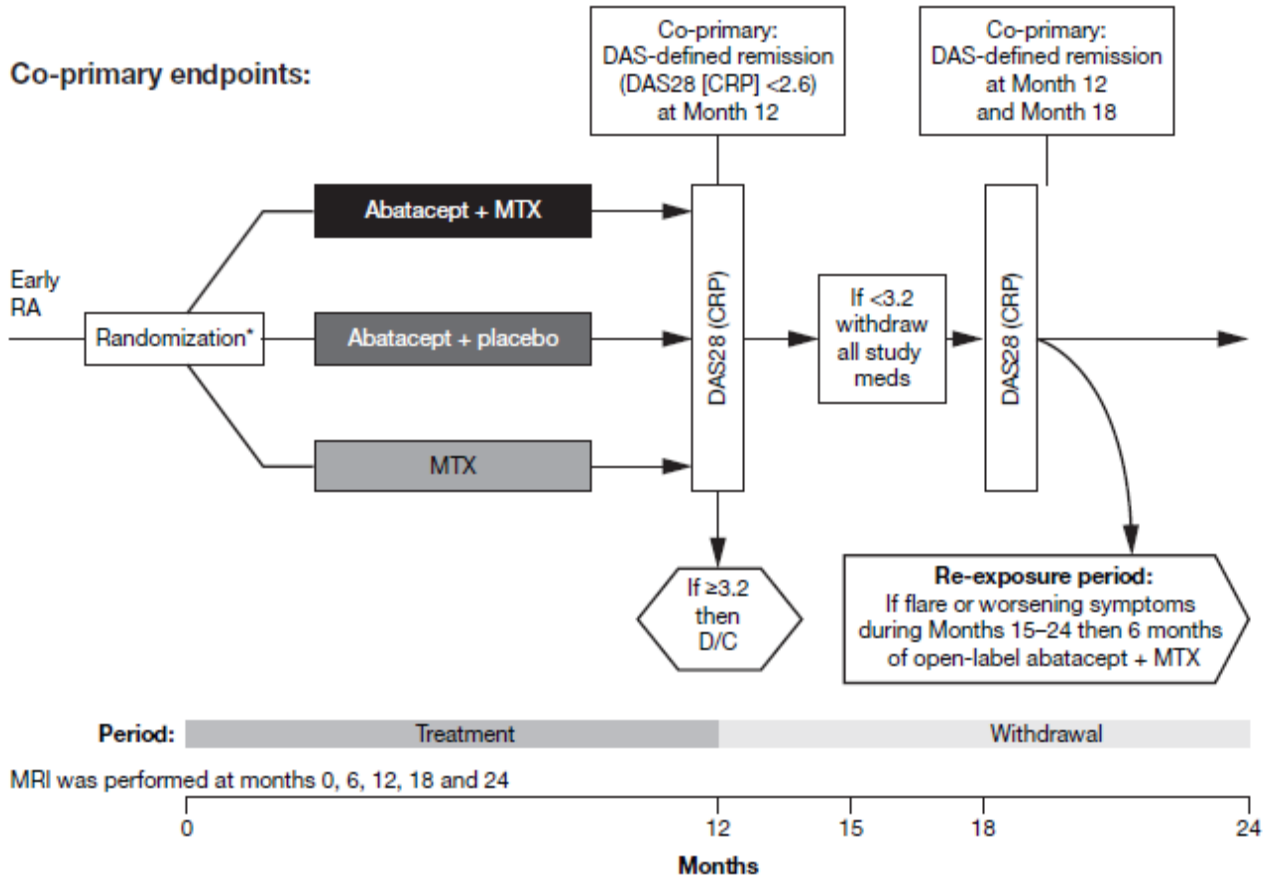
Table S3. **Baseline Characteristics of Patients With or Without Drug-Free DAS-Defined Remission (DAS28 [CRP] <2.6) at Month 18 Following Attainment of Remission at Month 12 (*Post Hoc* Analyses).**

	DAS-Defined Remission					
Parameter (Mean)	**Abatacept Plus MTX**		**Abatacept Monotherapy**		**MTX**	
	At Month 12 but not Month 18 (N=55)	**At both Months 12 and 18 (N=18)**	**At Month 12 but not Month 18 (N=36)**	**At both Months 12 and 18 (N=14)**	**At Month 12 but not Month 18 (N=44)**	**At both Months 12 and 18 (N=9)**
Symptom duration at baseline – year	0.6	0.4	0.7	0.5	0.4	0.4
Tender joint count (28 joints) at baseline	14.5	9.1	15.6	8.3	12.8	13.4
Swollen joint count (28 joints) at baseline	12.0	6.7	14.1	6.4	10.6	9.2
Pain (0–100 mm VAS)	62.8	51.9	59.5	50.5	59.8	50.7
HAQ-DI	1.5	1.1	1.4	1.0	1.3	1.5
CRP at baseline – mg/dL	16.8	11.2	13.9	7.2	13.5	24.9
DAS28 (CRP)	5.7	4.5	5.7	4.3	5.2	5.4

MRI synovitis	6.0	4.4	5.6	4.2	5.8	5.2
MRI osteitis	5.1	2.5	4.6	4.0	3.7	2.7
MRI erosion	6.2	5.0	5.7	3.4	6.3	4.7

CRP = C-reactive protein, DAS = Disease Activity Score, HAQ-DI = Health Assessment Questionnaire-Disability Index, MRI = magnetic resonance imaging, MTX = methotrexate, VAS = visual analog scale

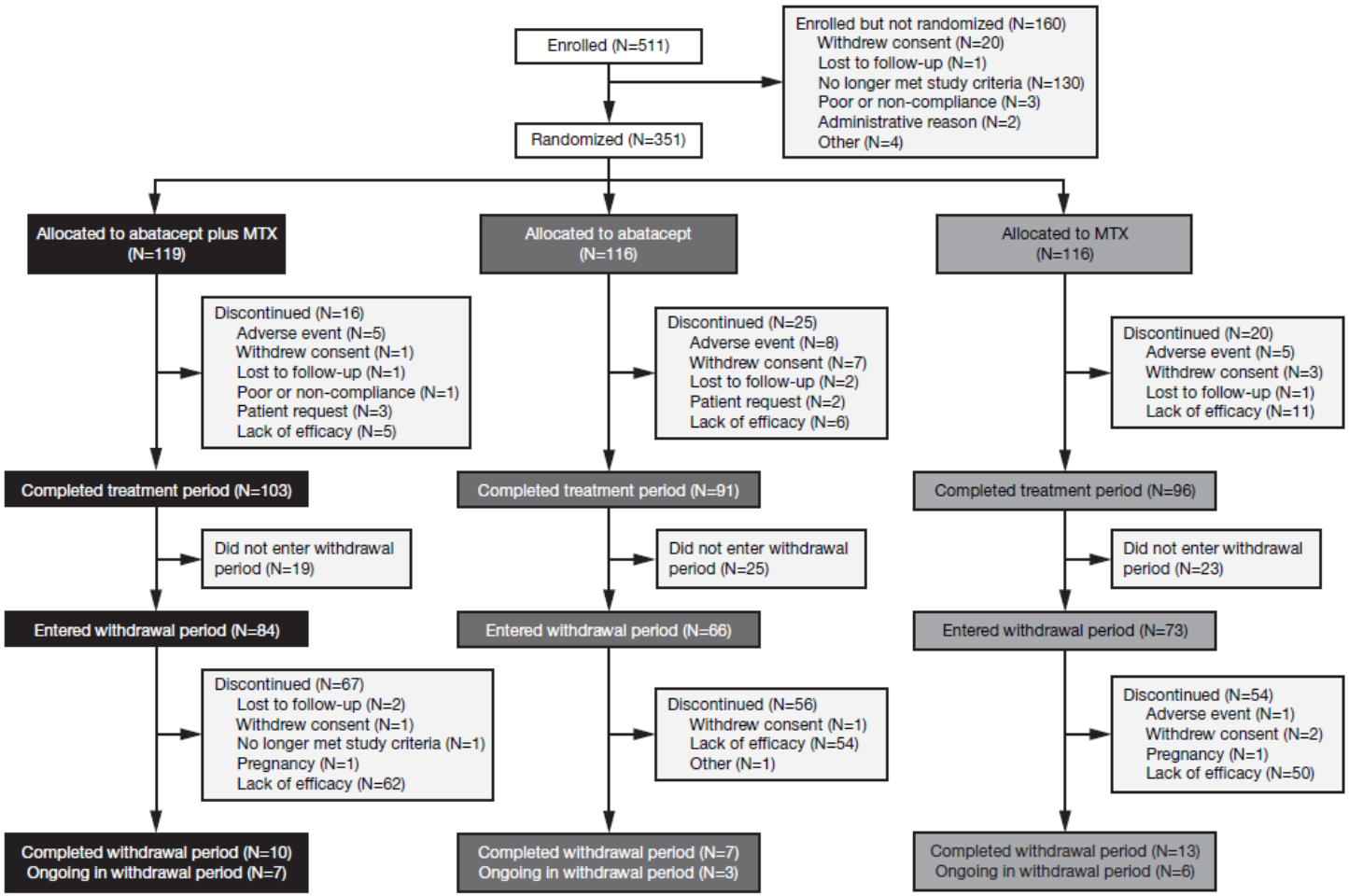
Figure S1. **Study Design.**



*Randomisation stratified by corticosteroid use at baseline.

CRP = C-reactive protein, D/C = discontinuation, DAS = Disease Activity Score, MRI = magnetic resonance imaging, MTX = methotrexate, RA = rheumatoid arthritis.

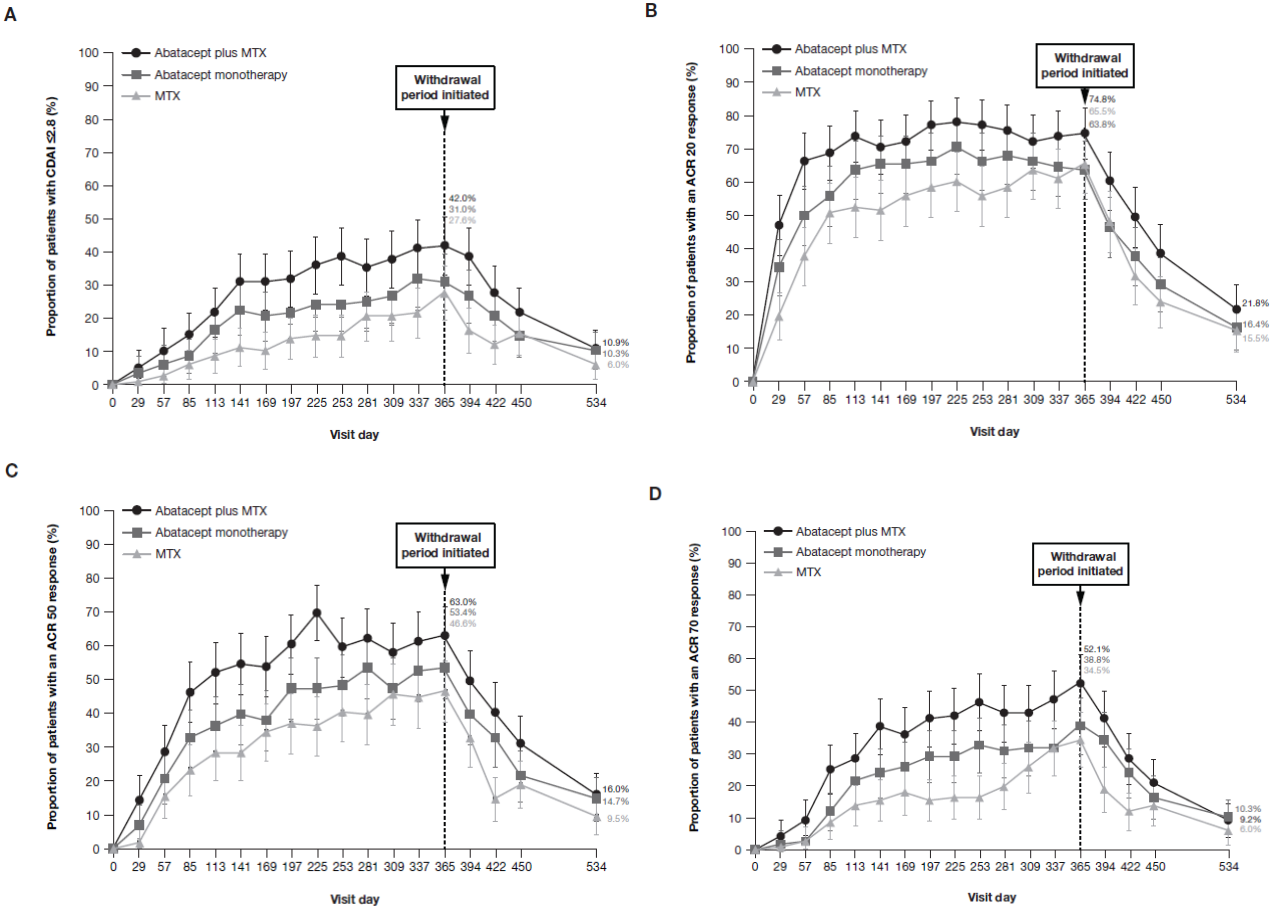
Figure S2. **Patient Disposition Flow Chart.**



MTX = methotrexate. Patients were ongoing in the withdrawal period as of November 12, 2013.

Figure S3. **Efficacy Outcomes Over Time.**

Panel A: proportion of patients with Clinical Disease Activity Index remission (≤2.8); Panel B: American College of Rheumatology (ACR) 20; Panel C: ACR 50; Panel D: ACR 70; Panel E: ACR 90.



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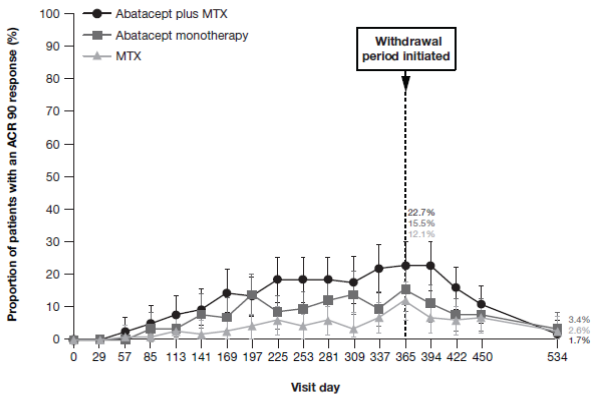
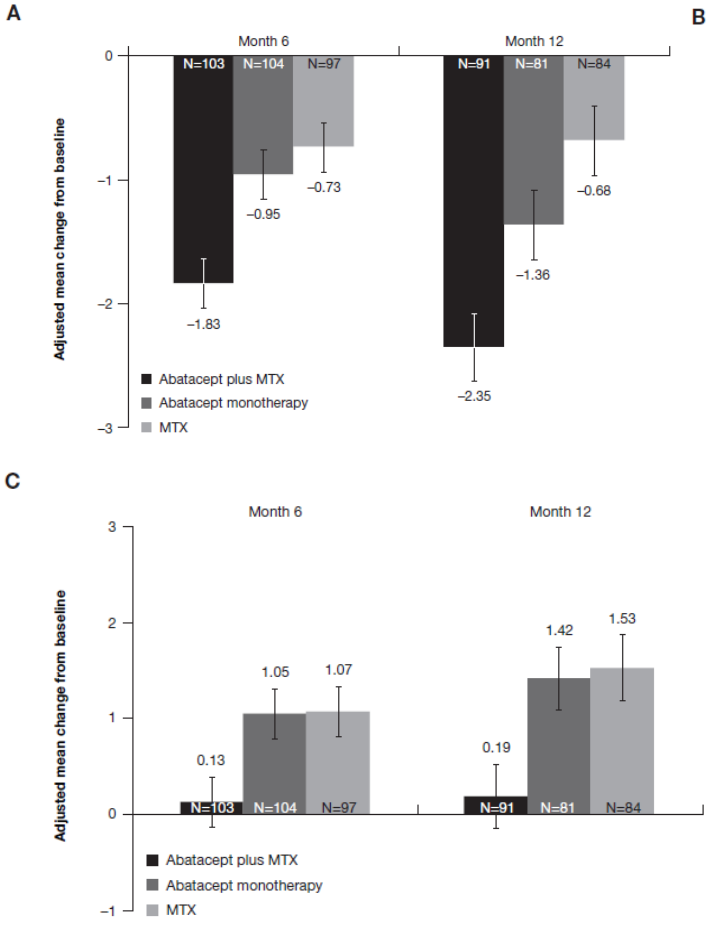
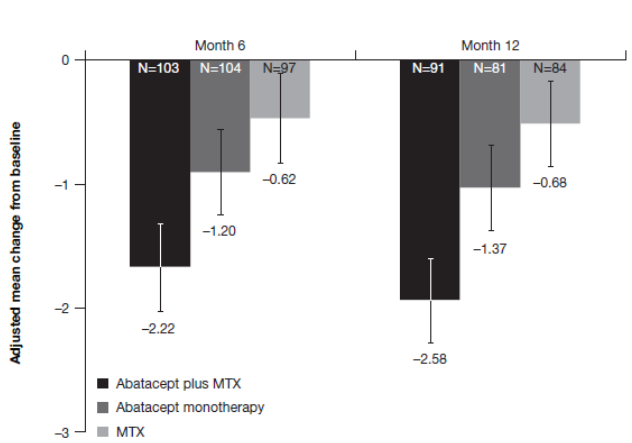


Error bars represent 95% confidence intervals. Missing remission data not due to premature discontinuation and not at Day 1 of the treatment period or at Day 169 of the withdrawal period were imputed as a remission if the missing value occurred between two observed remissions. Missing ACR response data not due to premature discontinuation and not at Day 1 of the treatment period or at Day 169 of the withdrawal period were imputed as an ACR response if the missing value occurred between two observed ACR responses. ACR = American College of Rheumatology, CDAI = Clinical Disease Activity Index, MTX = methotrexate.

Figure S4. **Progression on Magnetic Resonance Imaging.** Adjusted mean change from baseline in total synovitis score (Panel A), total osteitis score (Panel B) and total erosion score (Panel C).





Error bars represent standard error. MTX = methotrexate.