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EXTENDED REPORT

Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period

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ABSTRACT

Objectives To evaluate clinical remission with subcutaneous abatacept plus methotrexate (MTX) and abatacept monotherapy at 12 months in patients with early rheumatoid arthritis (RA), and maintenance of remission following the rapid withdrawal of all RA treatment.

Methods In the *A*ssessing *V*ery *E*arly *R*heumatoid arthritis *T*reatment phase 3b trial, patients with early active RA were randomised to double-blind, weekly, subcutaneous abatacept 125 mg plus MTX, abatacept 125 mg monotherapy, or MTX for 12 months. Patients with low disease activity (Disease Activity Score (DAS)28 (C reactive protein (CRP)) <3.2) at month 12 entered a 12-month period of withdrawal of all RA therapy. The coprimary endpoints were the proportion of patients with DAS28 (CRP) <2.6 at month 12 and both months 12 and 18, for abatacept plus MTX versus MTX.

Results Patients had <2 years of RA symptoms, DAS28 (CRP) ≥3.2, anticitrullinated peptide-2 antibody positivity and 95.2% were rheumatoid factor positive. For abatacept plus MTX versus MTX, DAS28 (CRP) <2.6 was achieved in 60.9% versus 45.2% (p=0.010) at 12 months, and following treatment withdrawal, in 14.8% versus 7.8% (p=0.045) at both 12 and 18 months. DAS28 (CRP) <2.6 was achieved for abatacept monotherapy in 42.5% (month 12) and 12.4% (both months 12 and 18). Both abatacept arms had a safety profile comparable with MTX alone.

Conclusions Abatacept plus MTX demonstrated robust efficacy compared with MTX alone in early RA, with a good safety profile. The achievement of sustained remission following withdrawal of all RA therapy suggests an effect of abatacept's mechanism on autoimmune processes.

Trial registration number NCT01142726.

INTRODUCTION

Rheumatoid arthritis (RA) is a progressive disease characterised by chronic joint inflammation and subsequent structural damage.[1] There may be a 'window of opportunity' in early RA to alter the course of the disease if tightly controlled, which diminishes once the inflammatory processes are more established.[2] If so, this could aid decisions on the use of a combination of biological disease-modifying antirheumatic drugs (DMARD) and conventional synthetic (cs)DMARDs versus step-up therapy in early RA.[3] Once RA is well controlled, the ability to sustain remission following the withdrawal of immunomodulatory medications would be an indication of disease modification.

Abatacept, a fusion protein of cytotoxic T lymphocyte-associated antigen-4 and immunoglobulin G1, selectively modulates the CD80/CD86:CD28 costimulatory signal required for full T-cell activation.[4] Due to a greater impact on naive T cells, there is a rationale for the use of abatacept in early RA; the unique upstream mechanism of abatacept impacts downstream inflammatory mediators and autoantibodies, and may allow removal of drug therapy. In the *A*batacept study to *G*auge *R*emission and joint damage progression in methotrexate naïve patients with *E*arly *E*rosive rheumatoid arthritis (AGREE), after all patients had completed 2 years of abatacept treatment, 50 patients had a dose reduction from 10 mg/kg to 5 mg/kg without change in efficacy.[5] In patients with undifferentiated and early RA in the *A*batacept study to *D*etermine the effectiveness in preventing the development of rheumatoid arthritis in patients with *U*ndifferentiated inflammatory arthritis and to evaluate *S*afety and *T*olerability (ADJUST), abatacept was withdrawn following 6 months of monotherapy, and maintained inhibition of joint damage progression for 6 months after withdrawal.[6] Similarly, in a study of patients with type 1 diabetes, the treatment effect observed with abatacept was maintained for a year following drug withdrawal.[7]

In this phase 3b trial, we evaluated the efficacy and safety of subcutaneous (SC) abatacept plus methotrexate (MTX), and abatacept monotherapy versus MTX in inducing clinical remission after 12 months in patients with early RA, and their ability to sustain drug-free remission at 18 months. Whereas a few studies have examined the strategy of achieving disease control followed by various de-escalation approaches reducing either steroids,

MTX or biologicals,[8–17] this is the first study to investigate the possibility of achieving absolute drug-free remission after removing all RA therapies.

METHODS

Study design

*A*ssessing *V*ery *E*arly *R*heumatoid arthritis *T*reatment (AVERT) was a phase 3b, randomised, active-controlled trial of 24 months, with a 12-month, double-blind treatment period (see online figure S1 in the supplementary appendix).

The study population included adults (≥18 years old) with active clinical synovitis of ≥2 joints for ≥8 weeks, persistent symptoms for ≤2 years, Disease Activity Score (DAS)28 (C reactive protein (CRP)) ≥3.2 and anticitrullinated peptide (CCP)-2 antibody positivity (see online table S1 in the supplementary appendix). Patients were MTX naive or received MTX (≤10 mg/week) for ≤4 weeks with no MTX for 1 month prior to enrolment. Patients receiving oral corticosteroids were required to be on a stable dose (≤10 mg/day for ≥4 weeks) at initiation and to maintain that dose until month 12.

In the 12-month treatment period, patients were randomised (1:1:1) to abatacept plus MTX, abatacept monotherapy or MTX, stratified by corticosteroid use at baseline (yes/no) using a Centralised Randomisation System. SC abatacept was administered at 125 mg/week. MTX was initiated at 7.5 mg/week and titrated to 15–20 mg/week within 6–8 weeks (≤10 mg/week permitted in patients with intolerance). All patients received concomitant folic acid therapy.

Patients with DAS28 (CRP) <3.2 at month 12 could enter the 12-month withdrawal period, during which all treatment was stopped; abatacept immediately and MTX and steroids tapered over 1 month. Patients with DAS28 (CRP) ≥3.2 discontinued the study.

After month 15, patients in the withdrawal period who experienced a flare of RA defined as two of the following: doubling of tender and swollen joint counts relative to month 12, increase in DAS28 (CRP) ≥1.2 from month 12, or investigator's judgement of RA flare, were eligible to enter a re-exposure period with open-label SC abatacept 125 mg plus MTX.

All patients underwent contrast MRI of the wrist and hand of the major affected upper limb at baseline and at 6, 12, 18 and 24 months.

The study (NCT01142726) was conducted in accordance with Good Clinical Practice.[18–20] Bristol-Myers Squibb (the sponsor) provided the study drug, designed the study, conducted the study in collaboration with the principal investigators, collected the data, monitored the conduct of the study and performed statistical analyses.

Outcome measures

For the purpose of this study, DAS-defined remission was DAS28 (CRP) <2.6. Co-primary endpoints were: the proportion of randomised and treated patients in DAS-defined remission at (A) month 12 and (B) months 12 and 18 for abatacept plus MTX versus MTX.

Secondary endpoints included: DAS-defined remission at (A) month 12 and (B) months 12 and 18 for abatacept monotherapy versus MTX; Health Assessment Questionnaire-Disability Index (HAQ-DI) response (≥0.3 points reduction from baseline); osteitis, synovitis and erosion score by MRI; safety and tolerability. Additional assessments are given in the online supplementary information.

Statistical analyses

A sample size of 116 patients per arm yielded 90% power to detect an expected difference of 22% for the first co-primary endpoint. This power estimate assumed that 60% of patients in the abatacept plus MTX arm and 38% of patients in the MTX arm would achieve DAS-defined remission (DAS28 (CRP) <2.6) at month 12. Conditional on achieving the first co-primary endpoint, a sample size of 116 patients per arm yielded 98% power to detect an expected difference of 22% for the second co-primary endpoint. This power estimate assumed that 30% of patients in the abatacept plus MTX arm and 8% of patients in the MTX arm would achieve DAS-defined remission (DAS28 (CRP) <2.6) at both months 12 and 18.

Co-primary endpoints were tested in hierarchical fashion. ORs (with 95% CIs) were calculated for abatacept plus MTX versus MTX using logistic regression adjusted for treatment group, corticosteroid use at baseline (yes/no) and baseline DAS28 (CRP); patients with missing baseline DAS28 (CRP) were not included. All patients who discontinued prior to completing the treatment or withdrawal period were imputed as non-responders for the month 12 or 18 analyses. Patients who entered the re-exposure period during the withdrawal period, prior to month 18, were imputed as non-responders at month 18.

Adjusted mean MRI change from baseline and SE was calculated for all arms using a longitudinal repeated measures model. Safety assessments were based on the intent-to-treat population (patients who received ≥1 dose of study medication). Analysis of other secondary endpoints is described in the online supplementary information.

Details on posthoc analyses of baseline characteristics of patients who achieved DAS-defined remission, the proportions of patients who achieved DAS-defined remission based on these characteristics, and overall treatment effect on mean change from baseline in DAS28 (CRP) are provided in the online supplementary materials.

RESULTS

Results up to the 18-month co-primary endpoint are presented.

Demographics and baseline characteristics

A total of 511 patients were enrolled, and 351 patients at 72 worldwide sites were randomly assigned to treatment (abatacept plus MTX, n=119; abatacept monotherapy, n=116; MTX, n=116) (see online figure S2 in the supplementary appendix). Patients had early RA (mean symptom duration 0.56 years) with highly inflammatory disease (mean tender joint count 13.6, swollen joint count 11.1 and CRP 17.5 mg/L), severe disease activity (mean DAS28 (CRP) 5.4 and HAQ-DI 1.4) and poor prognostic factors (95.2% rheumatoid factor and anti-CCP-2 double positive) (table 1). The numbers of patients entering the withdrawal period were 84/119 (70.6%), 66/116 (56.9%) and 73/116 (62.9%) in the abatacept plus MTX, abatacept monotherapy and MTX arms, respectively (see online figure S2 in the supplementary appendix).

Signs and symptoms

Abatacept plus MTX versus MTX during treatment period

Abatacept plus MTX achieved statistically significantly higher rates of DAS-defined remission versus MTX at month 12 (70/115 (60.9%) patients vs 52/115 (45.2%) patients; OR (95% CI) 2.01 (1.18 to 3.43); p=0.010). Numerically higher DAS-defined remission rates were observed in the abatacept plus

Table 1 Demographics and baseline characteristics

Characteristic	Abatacept plus MTX (n=119)	Abatacept monotherapy (n=116)	MTX (n=116)	Total (N=351)
Age—year (median)	46.4±13.2 (45.0)	45.4±11.9 (45.0)	49.1±12.4 (49.0)	47.0±12.6 (47.0)
Weight—kg (median)	73.0±17.7 (68.7)	72.1±16.8 (69.5)	74.1±17.1 (71.5)	73.1±17.2 (69.9)
Female sex—number (%)	95 (79.8)	89 (76.7)	89 (76.7)	273 (77.8)
White race—number (%)	100 (84.0)	95 (81.9)	102 (87.9)	297 (84.6)
Geographic region—number (%)				
North America	17 (14.3)	21 (18.1)	15 (12.9)	53 (15.1)
South America	26 (21.8)	24 (20.7)	25 (21.6)	75 (21.4)
Europe	47 (39.5)	42 (36.2)	48 (41.4)	137 (39.0)
ROW	29 (24.4)	29 (25.0)	28 (24.1)	86 (24.5)
RA symptom duration—year	0.58±0.50	0.59±0.52	0.50±0.49	0.56±0.50
RA symptom duration <3 months—number (%)	36 (30.3)	36 (31.0)	48 (41.4)	120 (34.2)
RF positive—number (%)	113 (95.0)	111 (95.7)	110 (94.8)	334 (95.2)
Tender joint count (28 joints)	14.0±7.7	14.0±7.6	12.8±7.8	13.6±7.7
Swollen joint count (28 joints)	11.2±6.9	11.4±7.66	10.7±7.0	11.1±7.1
CRP—mg/L	18.1±28.4	16.9±23.9	17.3±22.4	17.5±25.0
Patient global assessment (0–100 mm VAS)	62.7±21.0	57.3±22.4	58.2±19.7	59.4±21.1
Physician global assessment (0–100 mm VAS)	58.4±19.1	58.7±20.6	58.6±20.3	58.6±20.0
DAS28 (CRP)	5.5±1.3	5.5±1.1	5.3±1.3	5.4±1.2
HAQ-DI	1.5±0.68	1.4±0.66	1.4±0.65	1.4±0.66
Pain (0–100 mm VAS)	62.4±20.8	61.3±21.6	59.5±18.3	61.1±20.3
Physical function (0–100, Short Form-36 subscale)	38.5±25.9	41.6±25.6	39.1±24.5	39.7±25.3

Plus-minus values are means±SD.
CRP, C reactive protein; DAS, Disease Activity Score; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; ROW, rest of the world; VAS, visual analogue scale.

MTX group versus MTX from day 57, which were maintained over time for the rest of the treatment period (figure 1A). A posthoc analysis of the overall treatment effect over the 12 months of the treatment period in change from baseline in DAS28 (CRP) demonstrated an estimated treatment difference (95% CI) of –0.52 (–0.74 to –0.30) for abatacept plus MTX versus MTX.

The proportion of patients achieving other remission endpoints (including Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and Boolean remission), American College of Rheumatology (ACR) responses and major clinical response (MCR) were numerically greater for abatacept plus MTX versus MTX over time (figure 1 and see online figure S3 in the supplementary appendix); HAQ-DI response rates at month 12 were 65.5% versus 44.0%, respectively (see online table S2 in the supplementary appendix).

Abatacept monotherapy versus MTX during treatment period

Abatacept monotherapy resulted in a similar proportion of patients achieving DAS-defined remission at month 12 compared with MTX (48/113 (42.5%) vs 52/115 (45.2%)). However, over time, DAS-defined remission rates were numerically higher for abatacept monotherapy (figure 1A) at most other time points. In fact, as determined by posthoc analysis, the overall estimated treatment difference (95% CI) between abatacept monotherapy versus MTX in change from baseline in DAS28 (CRP) was –0.26 (–0.11 to –0.48). Additionally, abatacept monotherapy demonstrated numerically higher rates of CDAI, SDAI, Boolean remission and ACR 20/50/70 and MCR rates versus MTX over time (figure 1 and see online figure S3 in the supplementary appendix) and HAQ-DI (see online table S2 in the supplementary appendix).

Abatacept plus MTX and abatacept monotherapy versus MTX during withdrawal period

Abatacept plus MTX achieved statistically significantly higher rates of DAS-defined remission versus MTX at both months 12 and 18 (17/115 (14.8%) patients vs 9/115 (7.8%) patients; OR (95% CI) 2.51 (1.02 to 6.18); p=0.045). The proportion of patients achieving DAS-defined remission at both months 12 and 18 was 14/113 (12.4%) versus 9/115 (7.8%) for abatacept monotherapy and MTX groups, respectively (analysis included only patients with DAS28 (CRP) available at baseline).

Of the patients who entered the withdrawal period, 73, 50 and 53 patients in each treatment group were in DAS-defined remission at month 12. Of these, 18/73 (24.7%), 14/50 (28%) and 9/53 (17.0%) remained in DAS-defined remission at month 18 (figure 2).

A posthoc analysis indicated that in both abatacept treatment arms the proportions of patients with sustained DAS-defined remission following treatment withdrawal were numerically higher in patients who had lower baseline DAS28 (CRP), lower HAQ-DI and shorter symptom duration; this was not the case in the MTX arm (table 2). The same baseline factors were associated with DAS-defined remission at months 12 and 18 versus DAS-defined remission at month 12 only, also in the abatacept arm (see online table S3 in the supplementary appendix). Patients receiving abatacept also had more time with DAS28 (CRP) <2.6 than patients receiving MTX during the treatment period (10.2 vs 8.1 months for abatacept plus MTX; 8.9 vs 6.6 months for abatacept monotherapy; 5.8 vs 5.7 months for MTX).

Effect on structural damage

Radiographic changes measured by MRI in each of the treatment groups were consistent with clinical efficacy

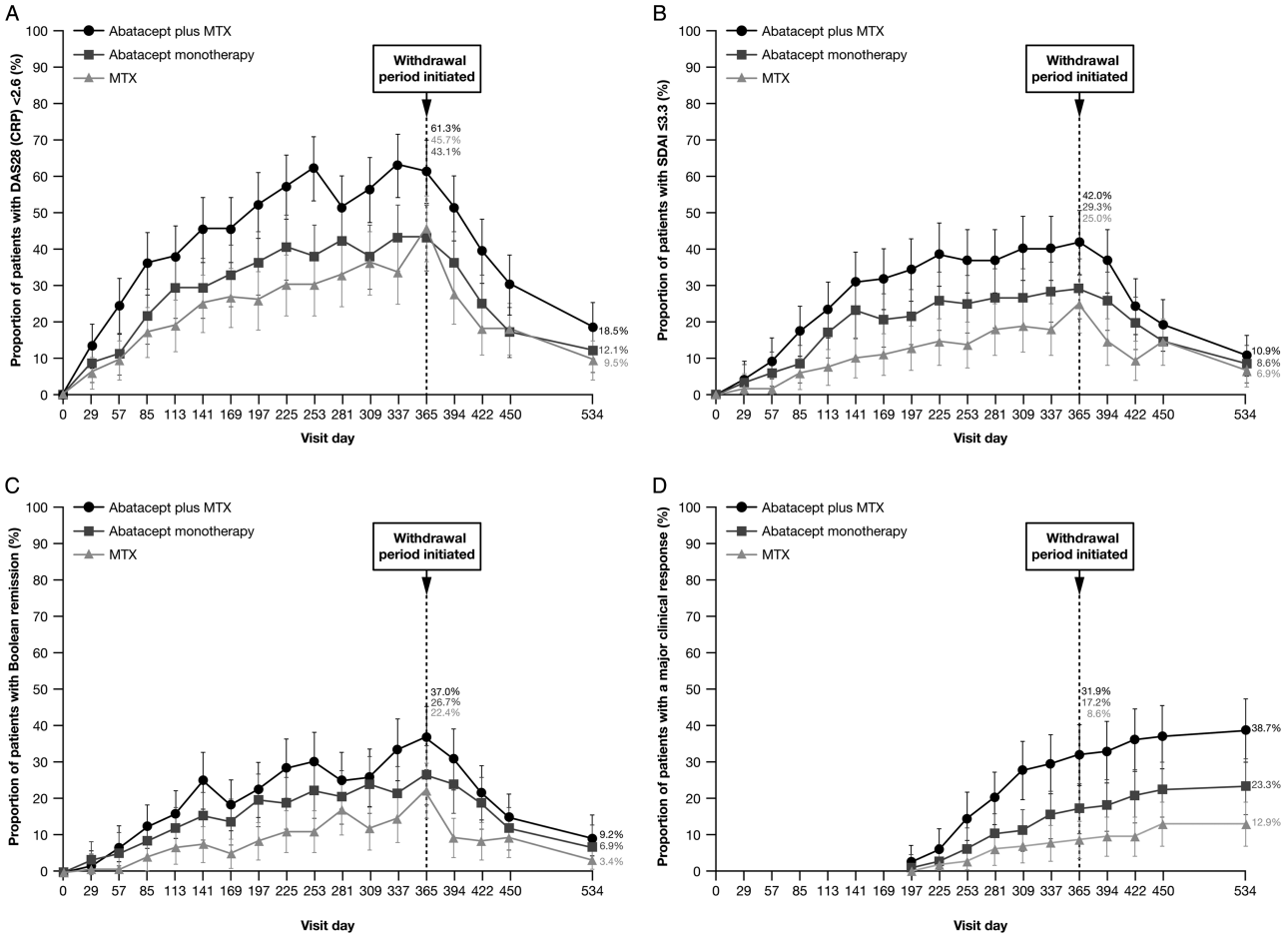

Figure 1 Efficacy outcomes over time. (A) proportion of patients with DAS-defined remission (DAS28 (CRP) <2.6); (B) proportion of patients with SDAI remission (≤3.3); (C) proportion of patients with Boolean remission (tender joint count ≤1, swollen joint count ≤1, patient global assessment of disease activity ≤1 (0–10 scale), high-sensitivity CRP ≤1 mg/dL); (D) major clinical response (ACR 70 response for a minimum of six consecutive months at any time period prior to the time point). Error bars represent 95% CIs. 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; CRP, C reactive protein; DAS, Disease Activity Score; MTX, methotrexate; SDAI, Simplified Disease Activity Index.

outcomes. Abatacept plus MTX and abatacept monotherapy resulted in numerically greater decreases from baseline in synovitis and osteitis scores, and abatacept plus MTX resulted in less progression of erosion score than MTX at 12 months (see online figure S4 in the supplementary appendix).

Safety

During the treatment period, adverse events (AE) occurred in 101/119 (84.9%), 93/116 (80.2%) and 96/116 (82.8%) patients treated with abatacept plus MTX, abatacept monotherapy and MTX, respectively (table 3). Serious AEs occurred in 8/119 (6.7%), 14/116 (12.1%) and 9/116 (7.8%) patients; there were 2/119 (1.7%), 5/116 (4.3%) and 3/116 (2.6%) discontinuations due to serious AEs; and serious infections occurred in 1/119 (0.8%), 4/116 (3.4%) and 0 patients, respectively. There were no deaths during the treatment period. During the withdrawal period, two patients died in the MTX arm (uterine neoplasm, renal failure).

DISCUSSION

AVERT is the first study to demonstrate that remission can be maintained after rapid withdrawal of all therapy (including csDMARDs, biological DMARDS and corticosteroids) in patients with early RA receiving abatacept plus MTX. Patients treated with abatacept plus MTX achieved significantly higher rates of DAS-defined remission than MTX on-treatment, and a small but significantly higher number of patients achieved sustained, absolute, drug-free, DAS-defined remission following withdrawal of all RA treatment. These results support the hypothesis that early treatment with a T-cell immunomodulator that can impact naive T-cell activation can induce drug-free remission in some patients.[21]

The results from this study are consistent with those of previous studies of abatacept in early RA, including ADJUST and AGREE.[6 22] In AVERT, patients had highly active disease and poor prognostic markers; 95% of patients were anti-CCP-2-positive and rheumatoid factor-positive, a combination associated with enhanced probability of joint damage and disease progression.[23 24] Abatacept plus MTX achieved robust efficacy versus MTX, as demonstrated by multiple measures of remission and HAQ-DI, and consistent structural benefits. While joint counts can be subjective and month-by-month variability was evident, the MRI results provide an objective measure of comparative efficacy in support of the clinical endpoints. Additionally, the safety

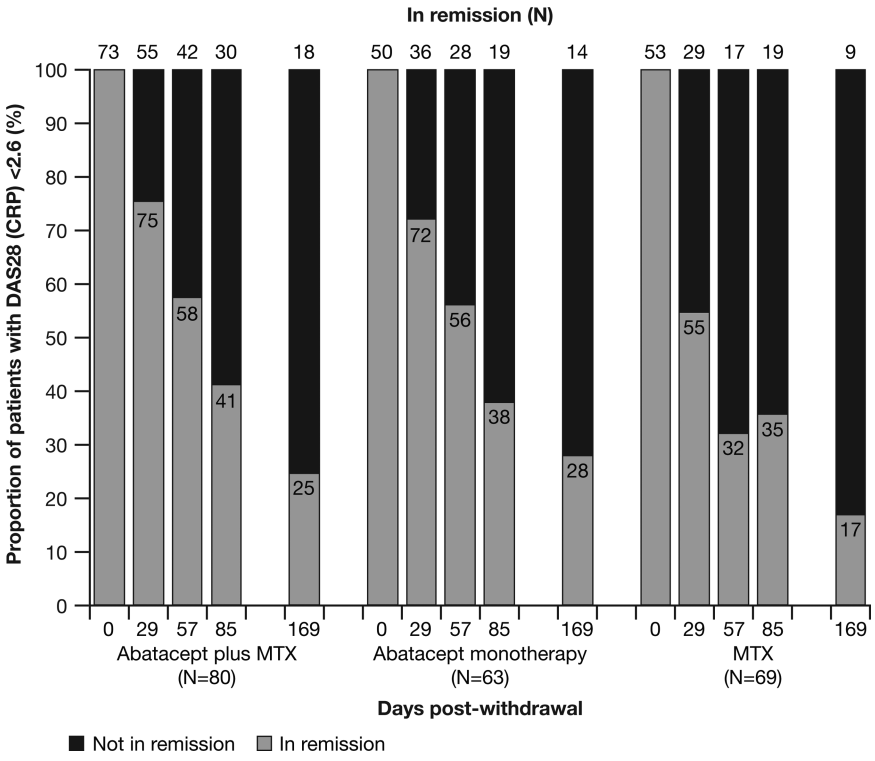

Figure 2 Proportion of patients in Disease Activity Score (DAS)-defined remission (DAS28 (C reactive protein, CRP) <2.6) during the withdrawal period. The numbers within the bars are percentages. Missing remission data not due to premature discontinuation and not at day 1 of the treatment period or at day 169 of the withdrawal period were imputed as a remission if the missing value occurred between two observed remissions. MTX, methotrexate.

profile observed in this study is consistent with the known safety profile of abatacept,[25] with low rates of serious AEs and serious infections, which is relevant for early treatment with biologicals.

AVERT provides a large dataset assessing abatacept monotherapy, which is of interest because many patients cannot tolerate MTX; approximately 30% of patients receive biologicals as monotherapy.[26] AVERT showed that a similar number of patients receiving abatacept monotherapy achieved DAS-defined remission versus MTX at month 12. However, the numerically greater benefit on osteitis and synovitis measured by MRI, and the posthoc analysis estimating average efficacy over the 12-month treatment period, are suggestive that abatacept monotherapy may have a greater efficacy benefit compared with MTX. This remains to be confirmed in a prospective, randomised, controlled study.

Following withdrawal of all therapy, a small but significant number of patients sustained drug-free remission following prior treatment with abatacept plus MTX compared with MTX alone. The data indicate that, with abatacept plus MTX treatment, one in four patients was able to maintain drug-free remission through 6 months. This effect is not a consequence of the half-life of abatacept (14.3 days), as assessments were performed up to 6 months after the withdrawal of all treatment (>5 half-lives).[27] Moreover, the posthoc analyses of the patients who sustained drug-free remission suggest that patients with shorter symptom duration and lower disease activity at baseline, or longer, sustained, DAS-defined remission prior to treatment withdrawal, were more likely to maintain drug-free remission. These associations were observed specifically in both abatacept arms, suggesting that a biological effect was responsible. Low baseline HAQ-DI, low baseline disease activity, and shorter disease duration are predictors of remission with antitumour necrosis factor agents.[28–32] These data, therefore, generate a hypothesis that patients with early RA, with a very short symptom duration and milder disease activity who are possibly presenting within the 'window of opportunity', may be able to achieve sustained and complete drug-free remission following treatment with abatacept.

Remission following withdrawal or tapering of RA therapy is an important goal in early RA. The unique study design of AVERT included the rapid withdrawal of all RA treatment, including abatacept, MTX and corticosteroids. Previous studies have examined a variety of treatment withdrawal paradigms with a number of biological agents, but have not assessed the rapid withdrawal of all RA treatment.[8–17] Most antitumour necrosis factor withdrawal studies maintained MTX or maintained the biological at half dose. While in many withdrawal studies DAS28 remission was assessed at 6 months after biological withdrawal,[8 9 11 12 14 15] in AVERT, assessment of drug-free remission was made by comparing the proportion of patients in DAS-defined remission at both 12 and 18 months. The approach of withdrawing or tapering biological therapy after achievement of remission may reflect a treatment benefit for patients and physicians that could be justifiable given the economic burden of treating patients with early RA. This is especially true if patients who are likely to maintain remission on MTX alone, following biological withdrawal, can be identified prospectively.

The DAS-defined remission cut-off of <2.6, although corresponding to the American Rheumatology Association definition of clinical remission in RA,[33] has now been replaced with other measures of remission,[34] such as SDAI and Boolean remission, which are also reported here. The cut-off is based on erythrocyte sedimentation rate (ESR), and a CRP cut-off has yet to be defined.[33] In AVERT, CRP was interchanged with ESR to reduce the variability of the acute phase reactant and aid standardisation across study centres. Data were obtained from patients with early RA with active disease and poor prognostic factors, which limit their generalisability to the overall RA population. The withdrawal analyses were limited by the small number of patients who remained in the withdrawal period. The gradual

Table 2 Proportion of patients with DAS-defined remission (DAS28 (CRP) <2.6) at both months 12 and 18 by baseline characteristic subgroup (posthoc analyses)

Baseline characteristic	Abatacept plus MTX (n=119)	Abatacept monotherapy (n=116)	MTX (n=116)
DAS28 (CRP)			
Missing—number/N (%)	1/4 (25.0)	0/3 (0)	0/1 (0)
≤Median (5.4)—number/N (%)	14/56 (25.0)	12/56 (21.4)	6/60 (10.0)
>Median (5.4)—number/N (%)	3/59 (5.1)	2/57 (3.5)	3/55 (5.5)
HAQ-DI, number (%)			
Missing—number/N (%)	3/6 (50.0)	1/3 (33.3)	0/11 (0)
≤Median (1.375)—number/N (%)	12/58 (20.7)	10/59 (16.9)	4/56 (7.1)
>Median (1.375)—number/N (%)	3/55 (5.5)	3/54 (5.6)	5/49 (10.2)
Symptom duration			
≤Median (0.37 years)—number/N (%)	12/58 (20.7)	7/50 (14.0)	5/69 (7.2)
>Median (0.37 years)—number/N (%)	6/61 (9.8)	7/66 (10.6)	4/47 (8.5)
≤6 months—number/N (%)	14/70 (20.0)	11/71 (15.5)	7/77 (9.1)
>6 months—number/N (%)	4/49 (8.2)	3/45 (6.7)	2/39 (5.1)
Pain (100 mm VAS)			
Missing—number/N (%)	3/6 (50.0)	1/3 (33.3)	0/11 (0.0)
≤Median (62)—number/N (%)	11/48 (22.9)	8/58 (13.8)	7/60 (11.7)
>Median (62)—number/N (%)	4/65 (6.2)	5/55 (9.1)	2/45 (4.4)
Erosion			
Missing—number/N (%)	1/15 (6.7)	0/14 (0)	2/13 (15.4)
≤Median (4.5)—number/N (%)	7/50 (14.0)	10/58 (17.2)	4/53 (7.5)
>Median (4.5)—number/N (%)	10/54 (18.5)	4/44 (9.1)	3/50 (6.0)
≤Q1 (1.5)—number/N (%)	4/23 (17.4)	5/28 (17.9)	2/30 (6.7)
>Q1 (1.5)–Q2 (4.5)—number/N (%)	3/27 (11.1)	5/30 (16.7)	2/23 (8.7)
>Q2 (4.5)–Q3 (8.5)—number/N (%)	8/25 (32.0)	3/23 (13.0)	2/23 (8.7)
>Q3 (8.5)—number/N (%)	2/29 (6.9)	1/21 (4.8)	1/27 (3.7)
Osteitis			
Missing—number/N (%)	1/15 (6.7)	0/14 (0)	2/13 (15.4)
≤Median (0.5)—number/N (%)	8/54 (14.8)	10/47 (21.3)	4/54 (7.4)
>Median (0.5)—number/N (%)	9/50 (18.0)	4/55 (7.3)	3/49 (6.1)
≤Q1 (0)—number/N (%)	6/41 (14.6)	9/43 (20.9)	4/49 (8.2)
>Q1 (0)–Q2 (0.5)—number/N (%)	2/13 (15.4)	1/4 (25.0)	0/5 (0)
>Q2 (0.5)–Q3 (5)—number/N (%)	7/25 (28.0)	2/27 (7.4)	2/26 (7.7)
>Q3 (5)—number/N (%)	2/25 (8.0)	2/28 (7.1)	1/23 (4.3)
Synovitis			
Missing—number/N (%)	1/15 (6.7)	0/14 (0)	2/13 (15.4)
≤Median (4.5)—number/N (%)	12/57 (21.1)	9/52 (17.3)	4/47 (8.5)
>Median (4.5)—number/N (%)	5/47 (10.6)	5/50 (10.0)	3/56 (5.4)
≤Q1 (2)—number/N (%)	5/30 (16.7)	4/24 (16.7)	3/24 (12.5)
>Q1 (2)–Q2 (4.5)—number/N (%)	7/27 (25.9)	5/28 (17.9)	1/23 (4.3)
>Q2 (4.5)–Q3 (8.5)—number/N (%)	3/23 (13.0)	4/33 (12.1)	1/30 (3.3)
>Q3 (8.5)—number/N (%)	2/24 (8.3)	1/17 (5.9)	2/26 (7.7)

CRP, C reactive protein; DAS, Disease Activity Score; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; Q, quartile; VAS, visual analogue scale.

tapering of RA medication may result in higher remission rates than the rapid withdrawal of all RA therapy applied in AVERT and will be assessed in other trials.

In conclusion, AVERT establishes the benefit of abatacept treatment in combination with MTX in an early RA population, and suggests that, in early RA, drug-free remission may be possible following treatment with abatacept. The novel achievement of sustained remission following withdrawal of all RA therapy in a small but significant number of patients is suggestive of an underlying effect of abatacept's mechanism on autoimmune processes. A withdrawal treatment strategy is a highly desirable goal for patients and physicians in the long-term treatment of RA, and further investigations with abatacept are warranted. Treat-to-remission is now a well-accepted goal of RA therapy.

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Table 3 Summary of safety in the treatment period*

	Abatacept plus MTX (n=119)	Abatacept monotherapy (n=116)	MTX (n=116)
Deaths	0	0	0†
Adverse events	101 (84.9)	93 (80.2)	96 (82.8)
Serious adverse events	8 (6.7)	14 (12.1)	9 (7.8)
Discontinuations due to serious adverse events	2 (1.7)	5 (4.3)	3 (2.6)
Serious infections	1 (0.8)	4 (3.4)	0
Pneumonia	1 (0.8)	1 (0.9)	0
Limb abscess	0	1 (0.9)	0
Herpes zoster	0	1 (0.9)	0
Viral infection	0	1 (0.9)	0
Malignancies	1 (0.8)	2 (1.7)	1 (0.9)
Basal cell carcinoma	1 (0.8)	0	0
Bowen's disease	0	1 (0.9)	0
Pulmonary carcinoid tumour	0	1 (0.9)	0
Invasive ductal breast carcinoma	0	0	1 (0.9)

Includes data up to 56 days after the last dose of study medication.
*All values are number (%).
†Two patients in the MTX arm died during the withdrawal period (uterine neoplasm, renal failure).
MTX, methotrexate.

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Contributors PE, GRB, VPB, BGC, DEF and TWJH were involved in the conception and design of the study, acquisition of data, analysis and interpretation of data; drafting of manuscript and revising it critically for important intellectual content; final approval of the version to be published. EB and DAW were involved in the conception and design of the study, analysis and interpretation of data; drafting of manuscript and revising it critically for important intellectual content; final approval of the version to be published. CSK was involved in the acquisition, analysis and interpretation of data; drafting of manuscript and revising it critically for important intellectual content; final approval of the version to be published.

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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

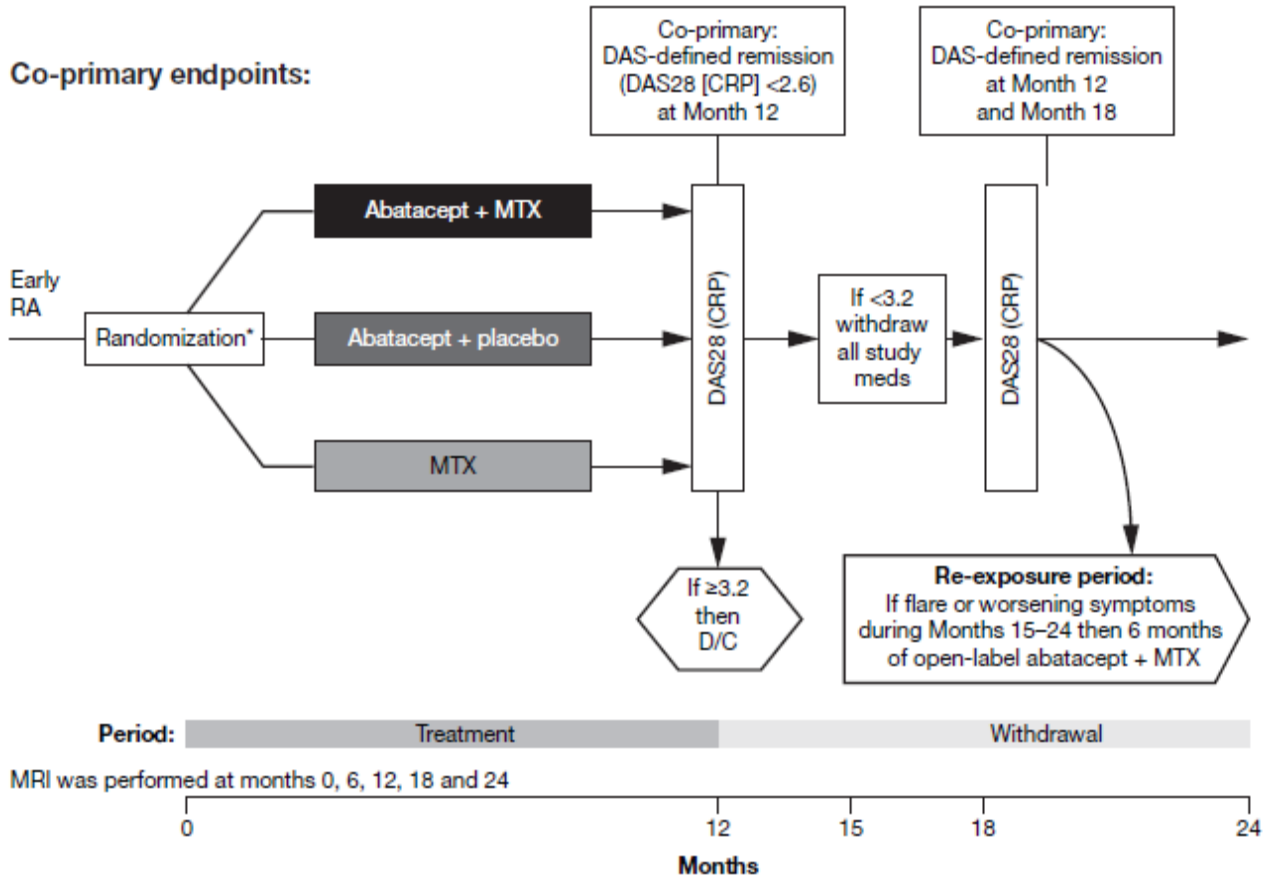
Table S3. **Baseline Characteristics of Patients With or Without Drug-Free DAS-Defined Remission (DAS28 [CRP] <2.6) at Month 18 Following Attainment of Remission at Month 12 (*Post Hoc* Analyses).**

	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

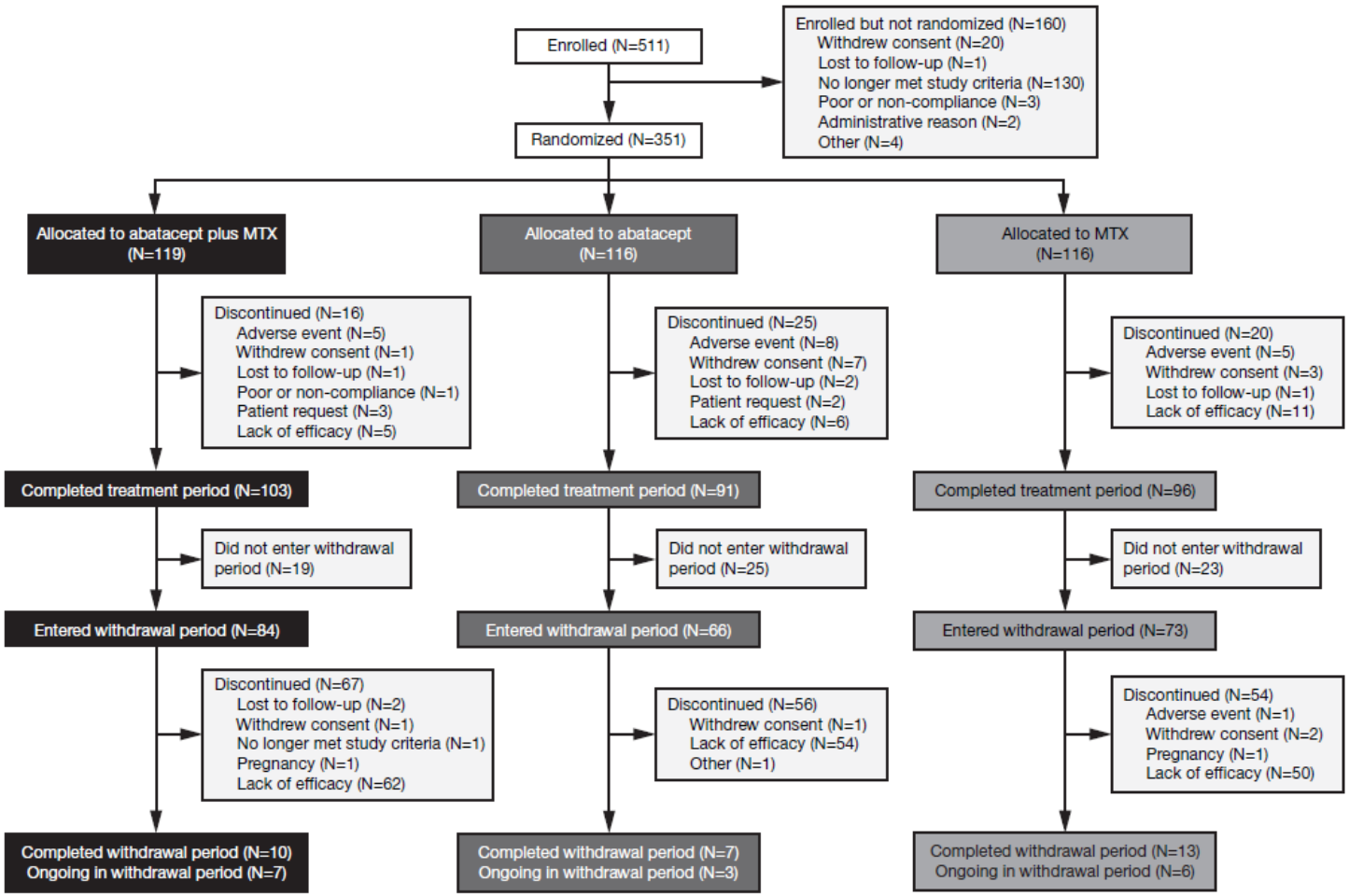
Figure S1. **Study Design.**



*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.

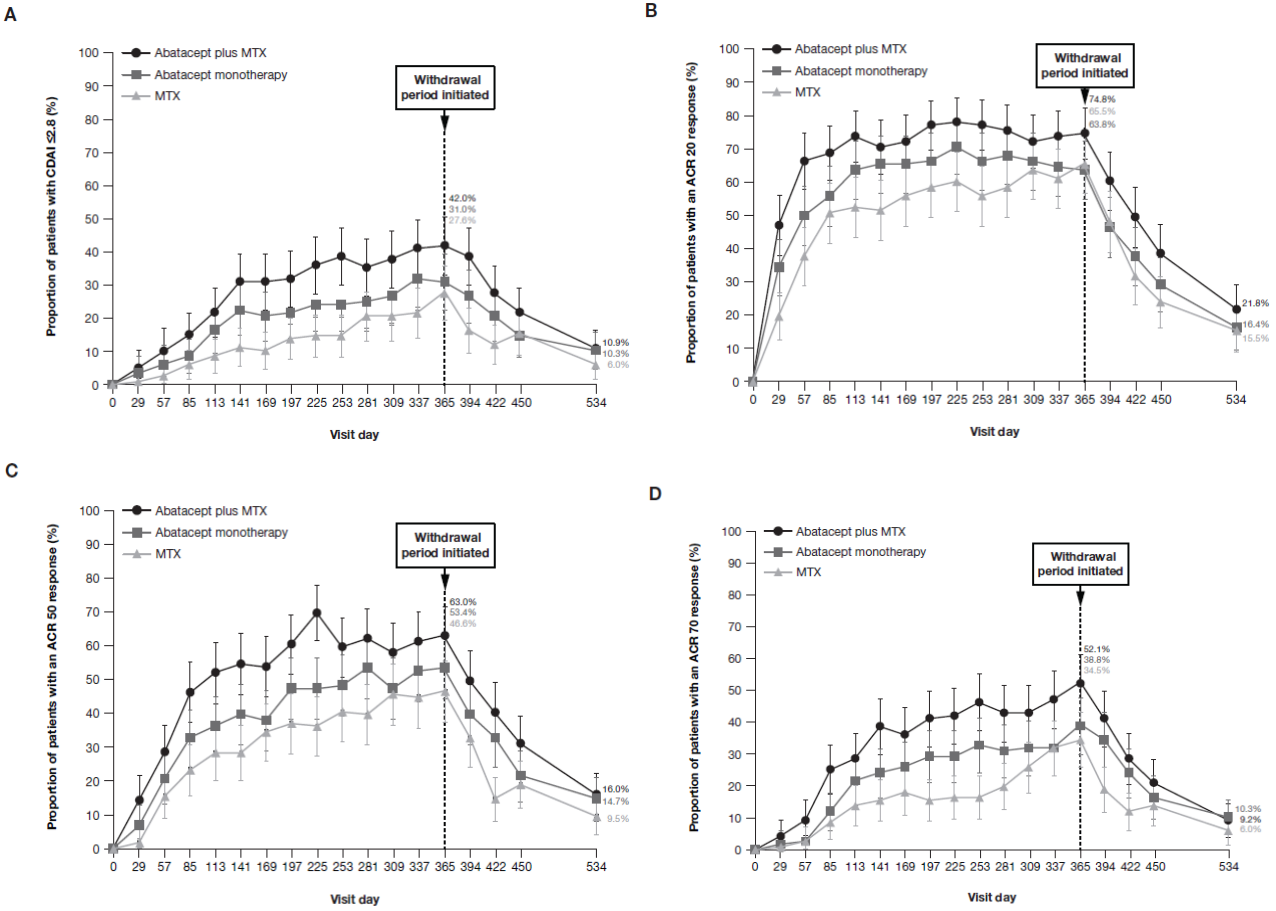
Figure S2. **Patient Disposition Flow Chart.**



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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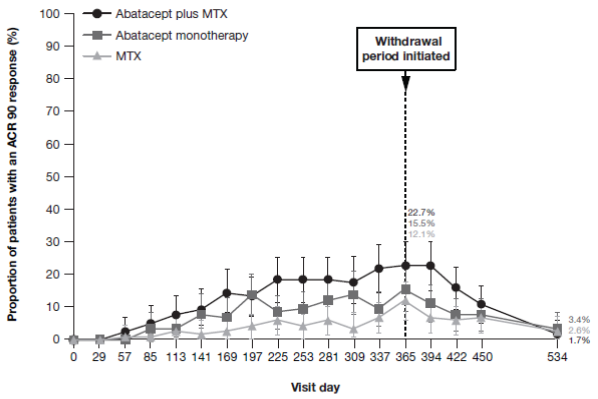
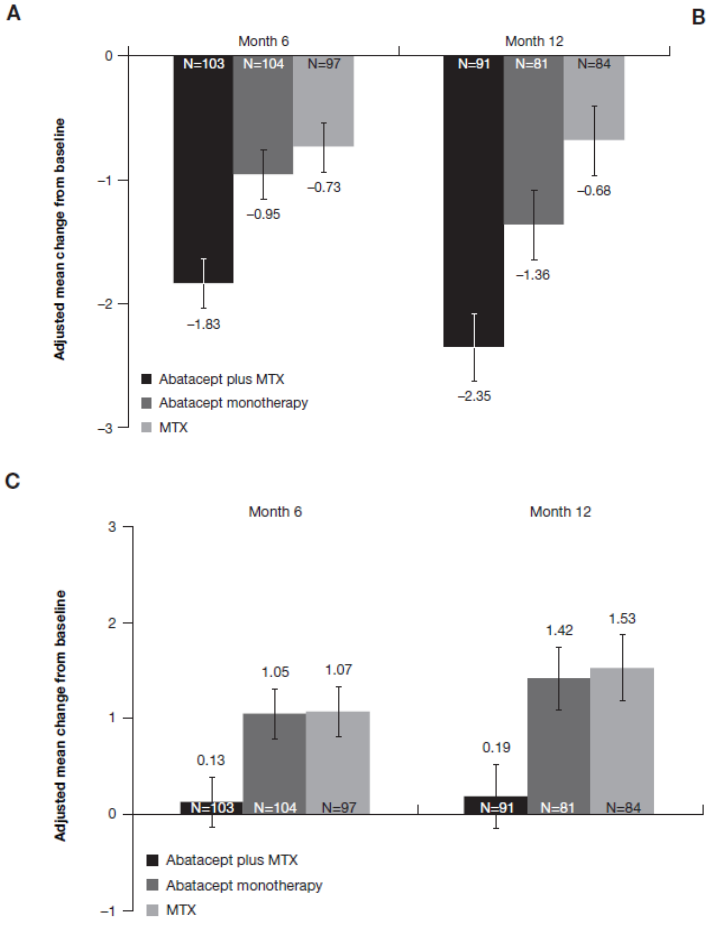
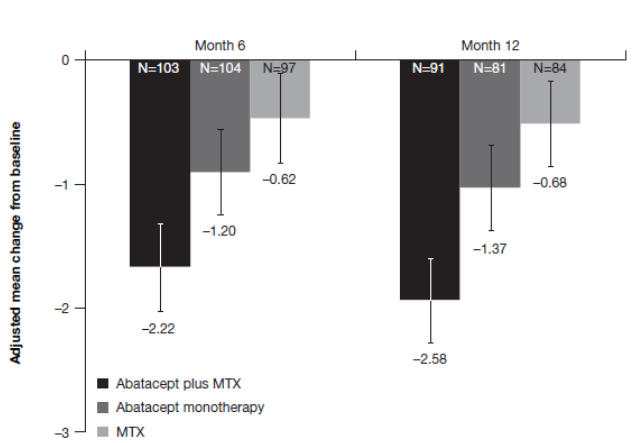


Error bars represent 95% confidence intervals. Missing remission data not due to premature discontinuation and not at Day 1 of the treatment period or at Day 169 of the withdrawal period were imputed as a remission if the missing value occurred between two observed remissions. Missing ACR response data 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.

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Abatacept slows development of early-stage RA

Abatacept and methotrexate may work better at slowing the development of early-stage rheumatoid arthritis than methotrexate alone.

INTRODUCTION

Rheumatoid arthritis (RA) is a disease that causes inflamed (swollen) joints. The inflammation may eventually damage the cartilage and bone. Many doctors believe that there is a narrow 'window of opportunity' to stop the progress of the disease when it has just started. It's much harder to treat the disease when you have had it for a while and the joints have been damaged.

Doctors prescribe disease-modifying anti-rheumatic drugs (DMARDs) to slow the development of RA and its effects on the joints. There are two types: conventional DMARDs and biological DMARDs. Biological DMARDs are a newer type of drug.

This research compared the effects of a conventional DMARD, methotrexate, with a newer biological drug, abatacept, on their ability to slow down the development of RA in people whose disease is still at an early stage.

WHAT DID THE RESEARCHERS HOPE TO FIND?

The study was paid for by Bristol-Myers Squibb, the maker of abatacept. The researchers wanted to find out whether abatacept – either alone or combined with methotrexate – worked better than methotrexate at improving people's signs and symptoms of RA. In particular, they wanted to compare how many people went into remission while they were taking the medicines – and how many people continued to be in remission six months after they stopped taking them. ('Remission' means that a person has few, if any, signs or symptoms of the disease.)

WHO WAS STUDIED?

The 351 people who took part in the study were adults (18 years and older) with early RA. None of the participants had reported having signs or symptoms of the disease for more than two years.

The people were selected from a number of centres in North and South America and Europe.

HOW WAS THE STUDY CONDUCTED?

The researchers randomly split the people into three groups. The first group was given abatacept and methotrexate (119 people). The second group was given abatacept on its own (116 people). And the third group was given methotrexate on its own (116 people).

After a year of treatment, the researchers looked at the people's 'disease activity score' – a standard measure of how bad someone's RA is. If people had a low score at this point, they stopped taking their RA medicines. The researchers then monitored them to see if their RA symptoms came back.

WHAT DOES THE NEW STUDY SAY?

The study found that taking abatacept and methotrexate together worked better than taking methotrexate alone. After a year of treatment, around 60 in every 100 people taking both drugs were in remission. This compared with about 45 in every 100 people taking methotrexate alone.

Abatacept alone and methotrexate alone were about as effective as each other. The study did not find any real differences in side effects between the two drugs. About 80 in 100 people in either group had side effects of some kind. These were not usually serious.

Six months after people stopped taking their RA medicines, nearly 15 in 100 of those who had taken abatacept plus methotrexate were still in remission. This compared with about 8 in 100 of those in the methotrexate group.

HOW RELIABLE ARE THE FINDINGS?

This was a type of study called a randomised controlled trial or RCT. This is the best way for testing how well treatments work.

However, these findings show only what happened to the people six months after they stopped taking their treatments. So we do not know whether their RA continued to be in remission after that point.

WHAT DOES THIS MEAN FOR ME?

Different countries may have different criteria for use of abatacept. In general, abatacept is only recommended after failing conventional treatment, at least methotrexate . This study supports the use of abatacept in combination with methotrexate, but also indicates that stopping therapy even when you are in remission is associated with a rather high risk of relapse. If you want to know more about this treatment, you can talk to your rheumatologist or rheumatology nurse specialist.

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From: Emery P, Burmester GR, Bykerk VP, *et al*. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. *Ann Rheum Dis* 2015;**74**:19–26. doi: 10.1136/annrheumdis-2014-2061066LaySummary