Long-term safety and efficacy of abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: a 7-year extended study

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Abstract

Objective

To assess the safety and efficacy of intravenous (IV) abatacept plus methotrexate (MTX) over 7 years, the longest observational period to date, in patients with established rheumatoid arthritis (RA) and an inadequate response to MTX.

Methods

Patients randomised to IV abatacept (10 or 2 mg/kg) or placebo, plus MTX, during the 1-year double-blind (DB) period of a Phase 2b study could enter the long-term extension (LTE) and receive IV abatacept 10 mg/kg monthly. Safety was assessed in patients who received ≥1 dose of abatacept; efficacy was assessed in patients originally randomised to 10 mg/kg abatacept (as-observed data).

Results

A total of 219 patients entered the LTE; 114 (52.1%) completed 7 years of treatment with abatacept plus MTX. Cumulative (DB + LTE) incidence rates of serious adverse events, serious infections, malignancies, and autoimmune events were 17.6, 3.2, 1.8, and 1.2/100 patient-years, respectively. Safety was consistent between the DB (n=220) and cumulative (n=287) periods. Improvements in American College of Rheumatology responses, disease activity, and normalisation of physical function and health-related quality of life were maintained over time. Approximately 80% of patients who achieved low disease activity or normalised modified Health Assessment Questionnaire scores at Year 1, and who remained in the study, sustained these responses in each subsequent year.

Conclusion

IV abatacept in combination with MTX demonstrated consistent safety and sustained efficacy over 7 years in MTX inadequate responders with established RA. Furthermore, some patients demonstrated a normalisation of physical function and health-related quality of life that was sustained over time.

Key words

abatacept, rheumatoid arthritis, long-term effects, treatment efficacy, safety.

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Introduction

The chronic nature of rheumatoid arthritis (RA) results in patients receiving biologic treatment for long periods of time. Therefore, it is important to assess the long-term outcomes of treatment with biologic therapies, to ensure that they are safe, tolerable and continue to offer clinical benefit. Low disease activity and remission are now more achievable goals in the treatment of RA. Adapting treatment to target these endpoints can result in significant benefits for patients, for example by reducing structural damage and promoting normalisation of physical function (1-4). It is also important to ensure that patients adhere to therapy over time to attain optimal treatment benefits. Retention rates achieved in clinical trials, especially in long-term extension (LTE) studies, can provide an indication of whether patients are likely to continue treatment. These data should also be confirmed by real-world observations, such as registry data and daily practice cohort follow-ups (5-8).

Consistent safety and sustained efficacy of the selective co-stimulation modulator, abatacept, which acts via the CD80/CD86:CD28 co-stimulatory signal required for full T-cell activation (9), has been demonstrated for up to 5 years in patients with RA and an inadequate response to methotrexate (MTX) (10-12). In a Phase 2b trial, significantly more patients achieved an American College of Rheumatology (ACR) 20 response with intravenous (IV) abatacept (~10 mg/kg) *versus* placebo at Month 6, and improvements in physical function and health-related quality of life (HRQoL) were significantly greater with abatacept compared with placebo at Month 6 (13). Clinical benefits observed during the 1-year double-blind (DB) period of this trial (14) were sustained through 4 years of open-label treatment, supported by a retention rate of ~60% for patients who entered the LTE (12). Here, we present the safety and efficacy of IV abatacept plus MTX treatment over 7 years from this Phase 2b trial in patients with established RA and an inadequate response to MTX, representing the longest assessment of IV abatacept-treated patients with RA reported to date. In accordance with the European League Against Rheumatism (EULAR) and ACR guidelines, which emphasise the importance of the sustainability of response (15), we evaluate the persistence of low disease activity and remission over 7 years of treatment. For the first time, we also examine the proportion of patients in this trial showing sustained improvements ("normalisation") in physical function and quality of life over time.

Methods

Study design and patients

The study design, conduct, and patient population (ClinicalTrials.gov identifier NCT00162266) have been reported previously (12, 14). All eligible patients entering the DB period were randomly assigned (1:1:1) to receive a 30-minute IV infusion of abatacept (10 or 2 mg/kg), or placebo, plus MTX, on Days 1, 15, and 30, and every 4 weeks thereafter (14). Patients completing the DB period were eligible to enter the open-label LTE, during which they received fixed-dose IV abatacept (~10 mg/kg according to weight range), plus MTX, every 4 weeks. All patients continued to receive MTX during the LTE; adjustments in MTX and corticosteroid dose, ≤30 mg/week and 10 mg/day (prednisone equivalent), respectively, were permitted at the investigators' discretion. During the LTE, patients were allowed any one of the following disease-modifying anti-rheumatic drugs (DMARDs) at the investigators' discretion: hydroxychloroquine, sulfasalazine, or leflunomide. Patients treated for *Mycobacterium tuberculosis* in the 3 years before study initiation were excluded.

Safety assessments

Safety was evaluated monthly, on scheduled abatacept infusion days. Assessments included all reported adverse events (AEs), serious AEs (SAEs), discontinuations due to AEs, deaths, clinically significant changes in vital signs, and physical examination and clinical laboratory test abnormalities. All AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA; version 11.1). Patients were monitored for acute in-

fusional reactions (reactions occurring within 1 hour of infusion start). Autoimmune events and acute-infusional AEs were prespecified based on a list of MedDRA-preferred terms.

Efficacy assessments

Efficacy assessments were performed quarterly during the LTE. Treatment response was evaluated as the proportions of patients experiencing a 20, 50, or 70% improvement in ACR criteria (ACR20, -50, or -70, respectively) (16). Disease activity was evaluated using the Disease Activity Score 28 (DAS28), based on C-reactive protein (CRP). Low Disease Activity State (LDAS) and remission were defined as DAS28 (CRP) ≤3.2 and <2.6, respectively (17). Physical function was evaluated by the modified Health Assessment Questionnaire (mHAQ) (18); scores ≤0.5 were defined as representing normalised physical function (19).

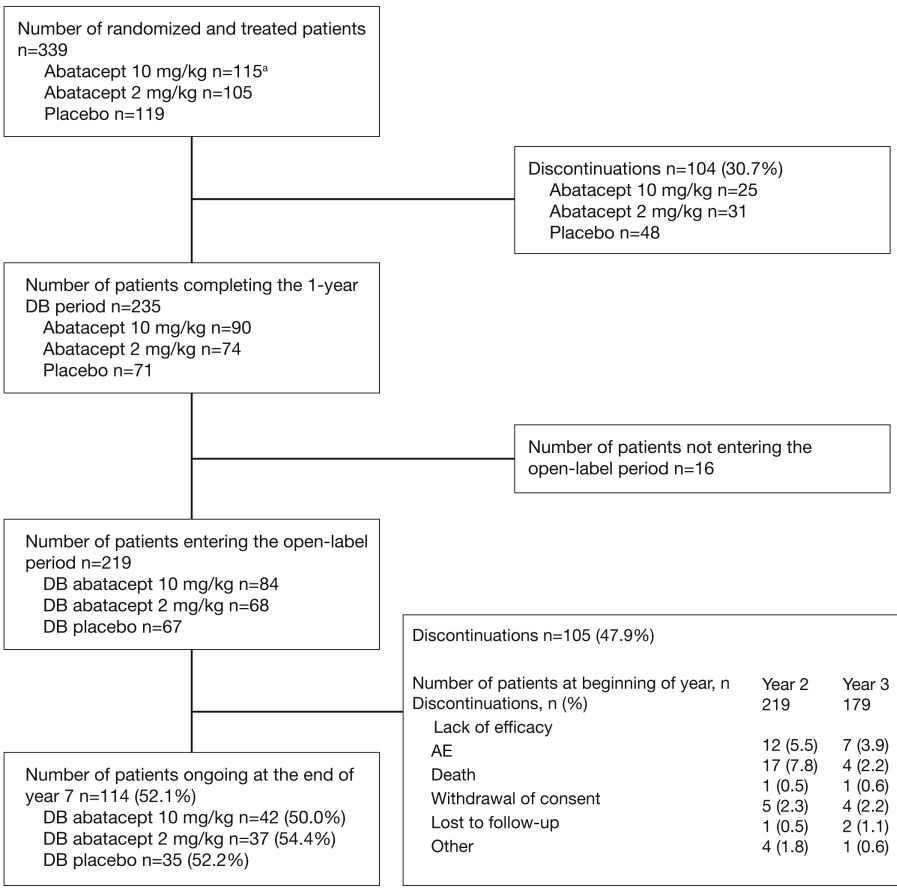
The Short Form-36 (SF-36) was used to measure HRQoL (20). The SF-36 includes eight domains that are used to derive Physical Component Summary (PCS) and Mental Component Summary (MCS) scores (20). Normalised PCS or MCS scores were defined as scores ≥50 (21).

The proportion of patients who achieved multiple efficacy outcomes was also analysed, including patients with both DAS28 (CRP)-defined remission and normalised mHAQ, and patients who were ACR50 responders and achieved each of the following: DAS28 (CRP) remission, and normalised mHAQ, PCS, and MCS.

Statistical analysis

Baseline demographic data, clinical characteristics, and concomitant medications are described for patients who entered the LTE and received ≥1 dose of abatacept. The safety population included patients who received ≥1 dose of abatacept in the DB period (10 or 2 mg/kg) or LTE (10 mg/kg). For the original placebo group, only AEs that occurred while receiving active therapy during the LTE are reported. Events that occurred ≤60 days after the last infusion are included. Data are summarised as frequencies and incidence rates (IRs), and are presented for the DB and cumulative (DB plus LTE) periods. IRs were calculated as the number of patients with the event of interest, divided by the total exposure during the specified treatment period, multiplied by 100 (events/100 patient-years of exposure). A patient's contribution to the exposure in the IR of each AE ended at the time of its first occurrence.

Patients randomised to IV abatacept 10 mg/kg in the DB period who received ≥1 infusion of abatacept during the LTE, and who had data available at the visit of interest (as-observed), were included in the efficacy analyses. ACR responses were calculated over time, with 95% confidence intervals (CIs). All other analyses were performed *post hoc*. The percentages of patients who achieved outcomes (DAS28 [CRP]-defined LDAS, remission, normalised mHAQ) at Year 1 and sustained the outcome at each yearly visit were evalu-



Number of patients at beginning of year, n Discontinuations, n (%)	Year 2 219	Year 3 179	Year 4 160	Year 5 148	Year 6 137	Year 7 122	Total
Lack of efficacy	12 (5.5)	7 (3.9)	2 (1.3)	1 (0.7)	2 (1.5)	0	24 (11.0)
AE	17 (7.8)	4 (2.2)	5 (3.1)	5 (3.4)	9 (6.6)	2 (1.6)	42 (19.2)
Death	1 (0.5)	1 (0.6)	0	0	0	2 (1.6)	4 (1.8)
Withdrawal of consent	5 (2.3)	4 (2.2)	4 (2.5)	1 (0.7)	2 (1.5)	3 (2.5)	19 (8.7)
Lost to follow-up	1 (0.5)	2 (1.1)	0	0	0	0	3 (1.4)
Other	4 (1.8)	1 (0.6)	1 (0.6)	4 (2.7)	2 (1.5)	1 (0.8)	13 (5.9)

Fig. 1. Patient disposition.
Data are for all patients, according to original DB treatment group; all patients received open-label IV abatacept 10 mg/kg plus MTX in the long-term extension. [a]For patients originally randomised to IV abatacept 10 mg/kg (n=115), 6/115 (5.2%), 4/84 (4.8%), 1/71 (1.4%), 2/64 (3.1%), 2/59 (3.4%), 3/53 (5.7%), and 0/47 (0%) patients discontinued because of AEs at Year 1, 2, 3, 4, 5, 6, and 7, respectively. AE: adverse event; DB: double-blind; IV: intravenous; MTX: methotrexate.

ated. Mean mHAQ scores are presented over time with standard error. The proportion of patients who achieved PCS or MCS normalisation at each year of the study was calculated.

For the analyses of multiple efficacy outcomes, patients had to have data available for both outcomes at both visits of interest (as-observed population) for evaluation.

Results

Patient disposition

Of 219 patients who entered the LTE (84, 68, and 67 patients originally randomised to the abatacept 10 and 2 mg/kg and placebo groups, respectively), 114 (52.1%) were still receiving IV abatacept at the end of Year 7 (Fig. 1). Reasons for discontinuation during the LTE are presented in Figure 1. For patients who were originally randomised to abatacept 10 mg/kg and entered the LTE, 42 (50.0%) were ongoing at Year 7.

Patient demographics and baseline characteristics

Demographics and baseline characteristics for patients entering the LTE were comparable with the DB period, as reported previously (12-14). Clinical characteristics, including duration of RA, were similar between treatment groups (Table I). Patients had a high degree of disease activity based on the mean number of tender and swollen joints.

Concomitant medications

Patients received MTX throughout the 7-year cumulative study period (DB plus LTE periods). A small number of patients (14/219 [6.4%]) received an additional non-biologic DMARD during the cumulative period: 7 (8.3%), 4 (5.9%), and 3 (4.5%) patients in the abatacept 10 mg/kg, abatacept 2 mg/kg, and placebo groups, respectively. Among those randomised to IV abatacept 10 mg/kg, one patient (1.2%) each year received additional non-biologic DMARDS, with the exception of Year 2 (0) and Year 4 (2 patients). At baseline, 50/84 (59.5%) patients randomised to IV abatacept 10 mg/kg were receiving steroids (mean [standard deviation; SD] oral dose was 6.2 [2.6] mg/day). At Years 1, 2, 3, 4, 5, 6, and 7, respectively, a total of 56/84 (66.7%), 49/73 (67.1%), 48/66 (72.7%), 46/60 (76.7%), 41/54 (75.9%), 37/48 (77.1%), and 34/43 (79.1%) patients originally randomised to the 10-mg/kg group had received steroids at some point during treatment.

Table I. Baseline demographics and clinical characteristics for patients who entered the long-term extension.

Characteristic	Abatacept 10 mg/kg (n=84)	Abatacept 2 mg/kg (n=68)	Placebo (n=67)
Age, years	55.6 (12.6)	54.3 (11.5)	53.6 (11.9)
Weight, kg	78.1 (18.1)	78.3 (23.0)	82.2 (19.5)
Female, %	74	62	67
White, %	87	85	88
Duration of rheumatoid arthritis, years	9.9 (10.1)[a]	8.5 (7.8)	8.2 (8.4)[b]
Tender joint count	30.4 (11.4)	26.2 (10.3)	29.2 (11.4)
Swollen joint count	21.2 (7.6)	18.6 (7.8)	22.2 (8.5)
Pain score, 100 mm VAS	60.8 (21.3)[a]	65.2 (21.1)[c]	64.5 (18.6)
Physical function score, HAQ-DI	1.0 (0.6)	1.1 (0.6)	0.9 (0.6)
Patient global assessment of disease, 100 mm VAS	60.0 (21.2)[a]	59.2 (24.6)	61.2 (19.7)
Physician global assessment of disease, 100 mm VAS	61.3 (15.3)[d]	59.6 (17.9)	61.0 (16.0)
C-reactive protein, mg/dL	2.8 (2.2)	3.2 (2.4)	2.7 (2.2)
Rheumatoid factor positive, %	89	84	81

[a]n=83; [b]n=66; [c]n=67; [d]n=82.
HAQ-DI: Health Assessment Questionnaire–Disability Index; VAS: visual analogue scale.
Values are mean (standard deviation), unless indicated otherwise.

Table II. Summary of safety during the double-blind and cumulative study periods.

Incidence rate per 100 patient-years (95% confidence interval)	Double-blind period[a] (IV abatacept, 10- and 2-mg/kg groups, Year 1, n=220)	Cumulative period[b] (All treatment groups combined, baseline to Year 7, n=287)
Adverse events[c]	489.73 (425.46, 561.03)	366.91 (325.40, 412.24)
Serious adverse events	20.04 (14.03, 27.74)	17.59 (14.80, 20.76)
Infections	94.15 (78.06, 112.58)	76.42 (66.84, 86.99)
Serious infections	2.10 (0.57, 5.38)	3.23 (2.25, 4.49)
Malignancies	2.11 (0.57, 5.40)	1.78 (1.09, 2.75)
Autoimmune events	0.53 (0.01, 2.93)	1.15 (0.61, 1.97)

[a]All patients who received at least one dose of study medication (IV abatacept 10 or 2 mg/kg, plus MTX) during the double-blind period.
[b]All patients who were originally randomised to IV abatacept (10 or 2 mg/kg), plus MTX, and received one dose, plus all patients who were originally randomised to placebo and entered the long-term extension (and subsequently received one dose of IV abatacept, plus MTX). Data includes events occurring up to 60 days after last infusion.
[c]Bacterial arthritis, pneumonia, tendon rupture, depression, and psoriasis resulted in discontinuation by two patients each; the remaining AEs resulted in discontinuation by no more than one patient.
IV: intravenous; MTX: methotrexate.

Safety

Mean (SD) exposure to IV abatacept during the cumulative period was 49.1 (35.04) months, with a total exposure of 1174.7 patient-years. Table II presents the safety summary through 7 years of treatment. There was no increase in the IRs of safety events between the DB and cumulative periods. During the LTE, 42 patients discontinued because of an AE; 29 of these patients discontinued due to an SAE.

The IR of AEs in the 7-year cumulative period was 366.91 events/100 patient-years (Table II). The AEs reported most commonly during this period (excluding worsening of RA) were nasopharyngitis (31.4%), back pain (26.8%), headache (24.7%), upper respiratory tract infection (24.7%), diarrhoea (21.3%), bronchitis (21.3%), and hypertension (20.2%). The IR of SAEs during the 7-year cumulative period was 17.59 events/100 patient-years (Table II). The most common SAEs were pneumonia (n=7; 2.4%), chest

pain (n=7; 2.4%), arthralgia (n=6; 2.1%), osteoarthritis (n=6; 2.1%), basal cell carcinoma (n=6; 2.1%), and cholelithiasis (n=5; 1.7%).
Eight deaths were reported during the 7-year cumulative period (two during the DB period and six during the LTE); all were considered unrelated or unlikely to be related to the study drug by the investigators.

Infection
Infections and serious infections were reported in 229/287 (79.8%) and 35/287 (12.2%) patients, respectively, during the 7-year cumulative period; respective IRs were 76.42 events/100 patient-years and 3.23 events/100 patient-years (Table II). The serious infections reported most frequently (≥1% of patients) in the cumulative period were pneumonia (n=7), abscess (n=3), and diverticulitis (n=3). There were no reports of opportunistic infections or tuberculosis.

Malignancy
Twenty-four malignant neoplasms were reported in 20/287 (7.0%) patients in the cumulative period; the cumulative IR of malignancies was 1.78 events/100 patient-years (Table II). Cases of malignancy included 12 non-melanoma skin cancers, 11 solid organ malignancies, and one haematologic malignancy (Supplementary Table I). All patients with malignant neoplasms related to the lungs were smokers or had a history of smoking.

Autoimmune events
A total of 15 autoimmune events were reported in 13/287 (4.5%) patients (Supplementary Table II), with an IR per 100 patient-years of 1.15 during the cumulative period (Table II); the most common event was psoriasis (n=7). All events were mild or moderate, with the exception of one case of severe multiple sclerosis, which led to discontinuation, and two cases of psoriasis that were considered severe and very severe in one patient each. In both cases of psoriasis, patients had either a pre-existing condition or a family history of psoriasis, and were subsequently discontinued from the study.

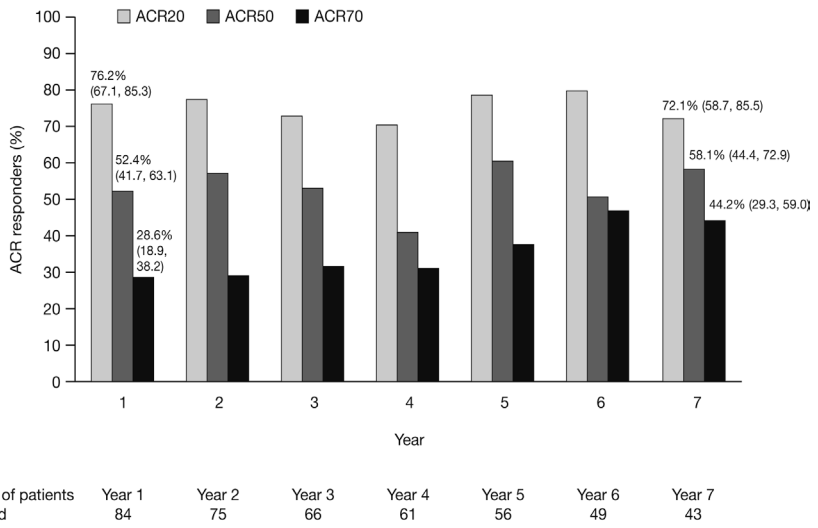


Fig. 2. ACR20, -50, and -70 response rates. Data are for all patients originally randomised to IV abatacept 10 mg/kg plus MTX, who entered the long-term extension, with data available at the visit of interest (as-observed population), and are presented with 95% confidence intervals within parentheses. ACR: American College of Rheumatology; IV: intravenous; MTX: methotrexate.

Efficacy
– Clinical efficacy
In patients originally randomised to IV abatacept 10 mg/kg who entered the LTE, ACR20, -50, and -70 response rates achieved at the end of the DB period were maintained at Year 7 (Fig. 2).

– Disease activity
The proportions of patients achieving DAS28 (CRP)-defined LDAS and remission at the end of the DB period were sustained throughout the LTE in patients originally randomised to the IV abatacept 10-mg/kg group (Fig. 3). At Year 7 (n=33), 69.7% (95% CI: 54.0, 85.4) and 51.5% (95% CI: 34.5, 68.6) of patients achieved DAS28 (CRP)-defined LDAS and remission, respectively, *vs*. 48.2% (95% CI: 37.4, 58.9) and 25.3% (95% CI: 15.9, 34.7) at Year 1 (n=83; Fig. 3A). Sustainability of LDAS and remission from Year 1 to each subsequent year are summarised in Fig. 3B. Of patients who achieved LDAS or remission at Year 1 and remained on treatment at Year 7 (and had available data at both time points), 77.8 and 60.0% were in LDAS and remission, respectively, at Year 7 (Fig. 3B).

– Physical function and HRQoL
At baseline, LTE-treated patients originally randomised to IV abatacept 10 mg/kg (n=84) had a mean (SD) mHAQ score of 1.0 (0.55). Reductions in mean mHAQ scores were observed by Month 6, and the mean score remained <0.6 at all subsequent time points (Fig. 4A). At Year 1 (n=84) and Year 7 (n=38), 64.3% (95% CI: 54.0, 74.5) and 60.5% (45.0, 76.1) of patients, respectively, achieved a normalised mHAQ score (≤0.5). Fig. 4B presents the sustainability of this score from Year 1 to each yearly time point through Year 7. Of the patients who achieved a normalised mHAQ at Year 1, 81.5% maintained this level of function at Year 7 (Fig. 4B).
For patients originally randomised to abatacept 10 mg/kg, mean (SD) PCS and MCS scores, respectively, were 40.6 (11.0) and 52.3 (9.9) at Year 1 (n=84), improved from 30.9 (8.1) and 46.3 (12.1) at baseline. Mean (SD) scores were maintained at Year 7 for patients who remained on treatment: 42.0 (13.4) and 49.2 (11.4) for PCS and MCS, respectively (n=38). Over the LTE, the proportions of patients achieving normalised PCS or MCS scores (≥50) were maintained (Fig. 4C).

– Multiple measures of efficacy
For patients with data available at each time point, the proportion who achieved multiple efficacy outcomes at the same time was evaluated to determine the effect of treatment on multiple disease aspects. The proportions of patients who

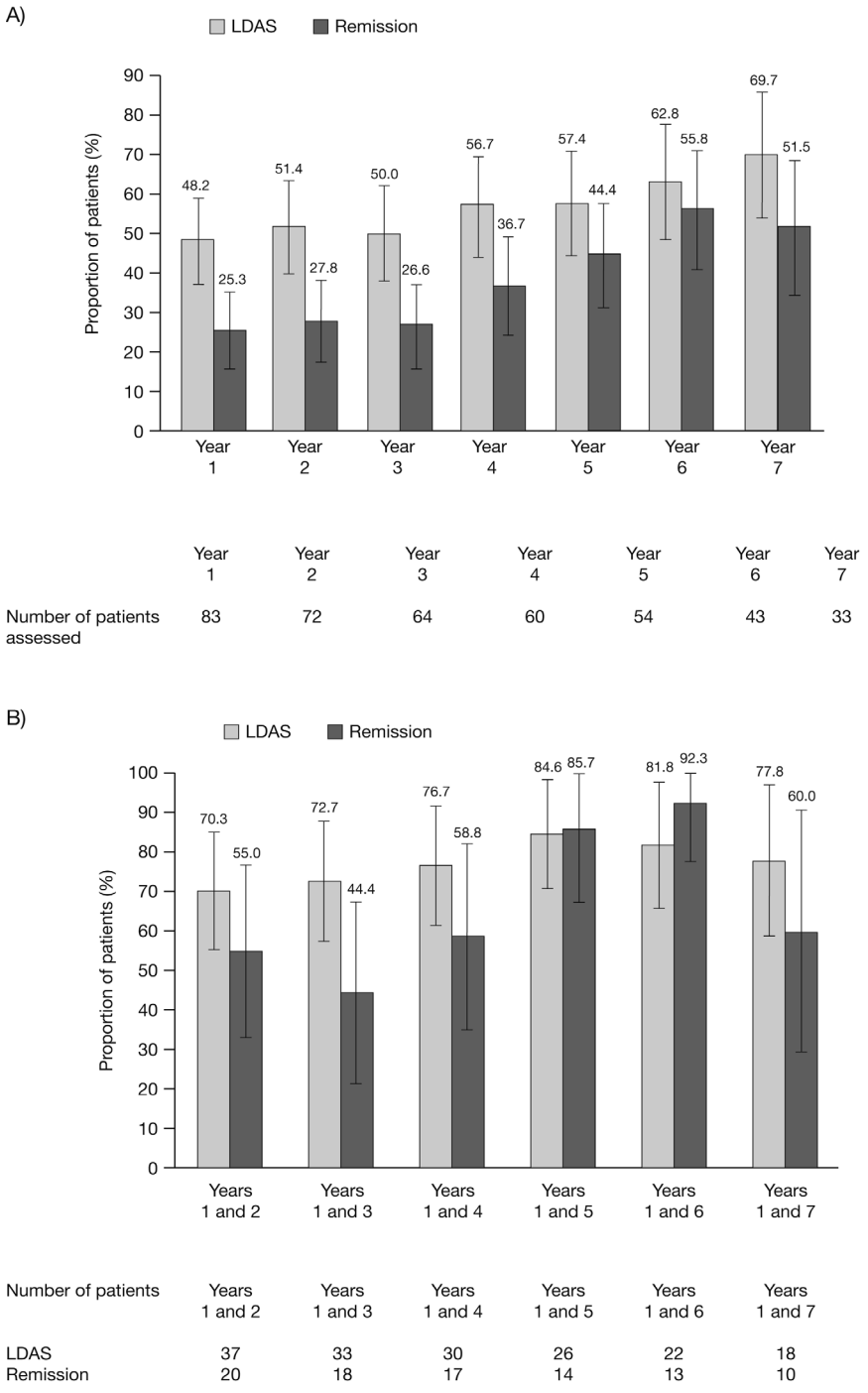


Fig. 3. Proportions of patients in DAS28 (CRP)-defined LDAS or remission (**A**) over the 7-year treatment period and (**B**) those who were in LDAS or remission at Year 1 who sustained their status over time. Data are for all patients originally randomised to IV abatacept 10 mg/kg plus MTX who entered the long-term extension, with data available at the visit of interest (as-observed population). Error bars represent 95% confidence intervals. LDAS and remission were defined as DAS28 (CRP) ≤3.2 and <2.6, respectively. DAS28 (CRP): Disease Activity Score 28 (based on C-reactive protein); IV: intravenous; LDAS: Low Disease Activity State; MTX: methotrexate.

were originally randomised to abatacept 10 mg/kg and who achieved both DAS28 (CRP)-defined remission and a normalised mHAQ score are shown in Fig. 5A. For patients who achieved an ACR50 response at each yearly time point, the proportions of patients who also achieved remission, normalised mHAQ, or normalised PCS and MCS are shown in Fig. 5B (as-observed population).

Discussion

Reducing the signs and symptoms of RA and maintaining improvements over time are fundamental goals for biologic treatment. Consistent safety and tolerability are essential to ensure that patients remain on and adhere to treatment, thereby optimising the potential to sustain a response. The data reported here for this long-term Phase 2b study in patients with established RA and an inadequate response to MTX demonstrate the consistent safety and sustained efficacy benefits observed with IV abatacept plus MTX treatment over 7 years, the longest observational period of patients on IV abatacept to date. Furthermore, we demonstrate that patients treated with abatacept plus MTX can achieve normalised levels of physical function (Fig. 4B) and quality of life (Fig. 4C) that are maintained through 7 years of treatment.

Over 7 years (1174.7 patient-years of exposure), IV abatacept plus MTX was well tolerated and associated with consistent safety. No unexpected safety events were detected with long-term abatacept exposure relative to DB treatment. IRs of AEs, SAEs, infections, and serious infections reported during the 7-year cumulative period were comparable to, or lower than, those observed during the 1-year DB period, and were at the lower end of the range reported with anti-tumour necrosis factor agents (22-25). These observations are consistent with those reported in integrated analyses of data across the abatacept clinical trial programme, including >4000 patients with 12,132 patient-years of exposure and up to 8 years of IV abatacept treatment (26), and 1879 patients with 3086 patient-years of exposure and up to 4.5 years of treatment with subcutaneous abatacept (27).

Compared with the general population, patients with RA have an elevated risk of malignancy – specifically lung cancer and lymphoma – even before the effect of treatment with biologic therapies is considered (28, 29). Integrated analyses using standardised IRs have demonstrated that the risk of malignancy observed with IV abatacept is within the range expected for patients with RA treated with non-biologic DMARDs

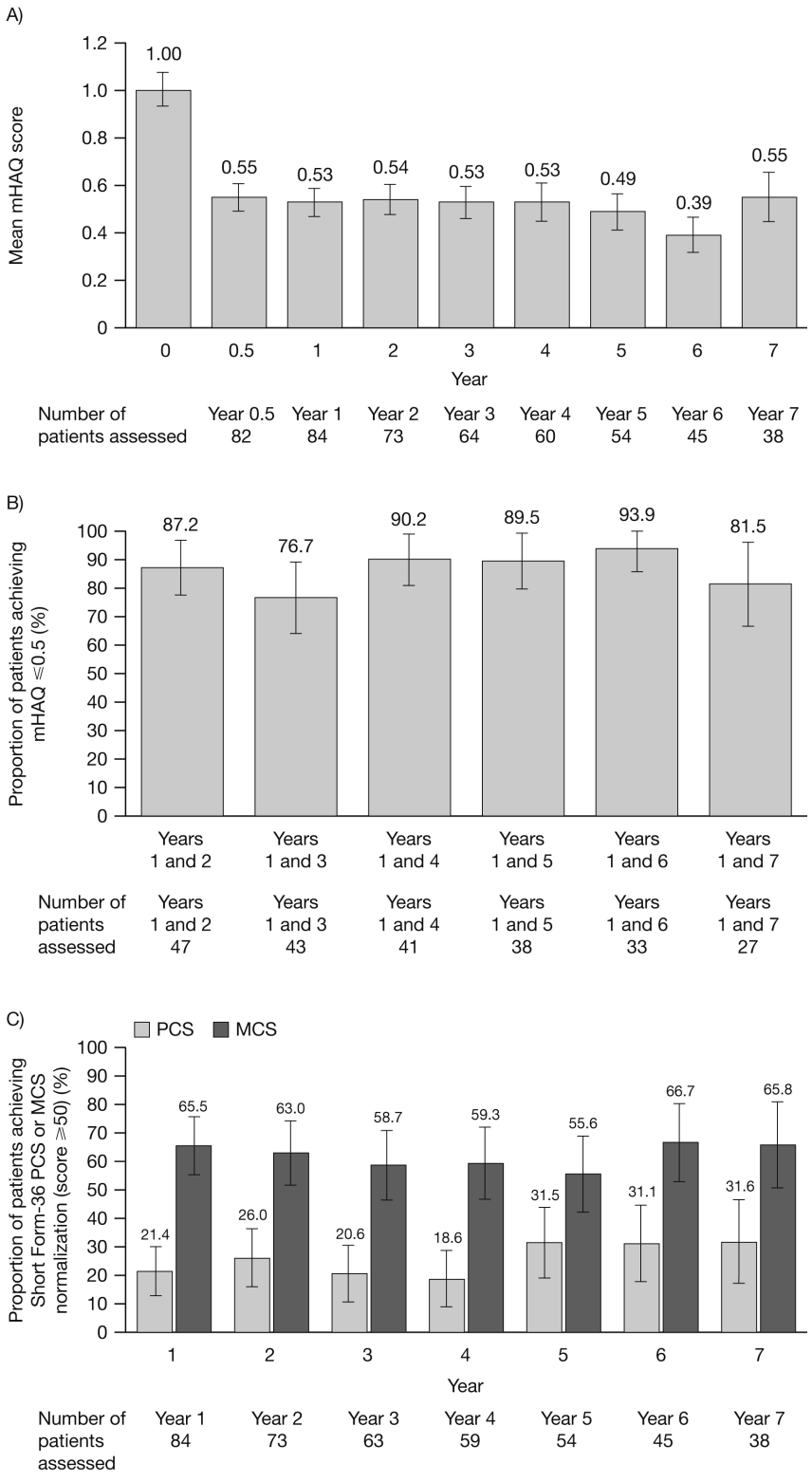


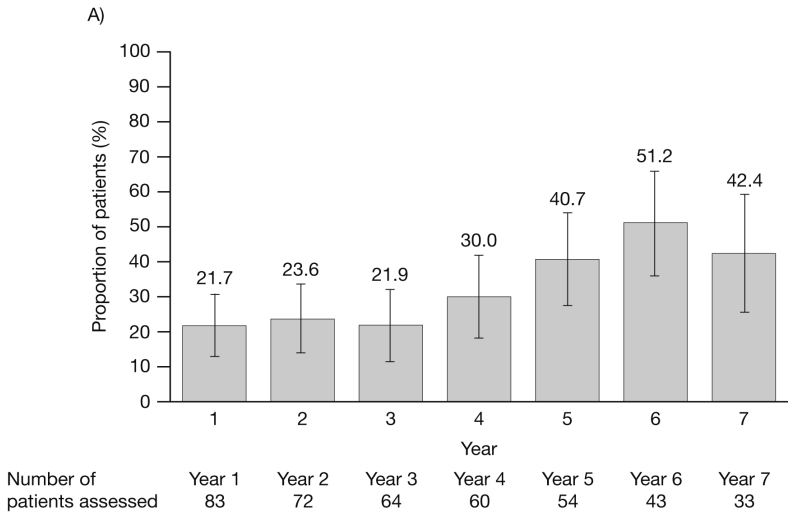
Fig. 4. Physical function and health-related quality of life. (**A**) Mean (standard error) mHAQ scores over time; (**B**) proportions (95% confidence intervals) of patients achieving an mHAQ score of ≤0.5 at Year 1 who sustained their response over time; (**C**) proportions of patients achieving SF-36 PCS or MCS normalisation over time (score ≥50). Data are for all patients originally randomised to IV abatacept 10 mg/kg plus MTX who entered the long-term extension, with data available at the visit of interest (as-observed population). IV: intravenous; MCS: Mental Component Summary; mHAQ: modified Health Assessment Questionnaire; MTX: methotrexate; PCS: Physical Component Summary; SF-36: Short Form-36.

(30). The IRs of malignancies over the cumulative 7-year period of this study did not increase with continued treatment *versus* the DB period, and were consistent with previously reported IRs for IV abatacept-treated patients with RA (11, 31-34).

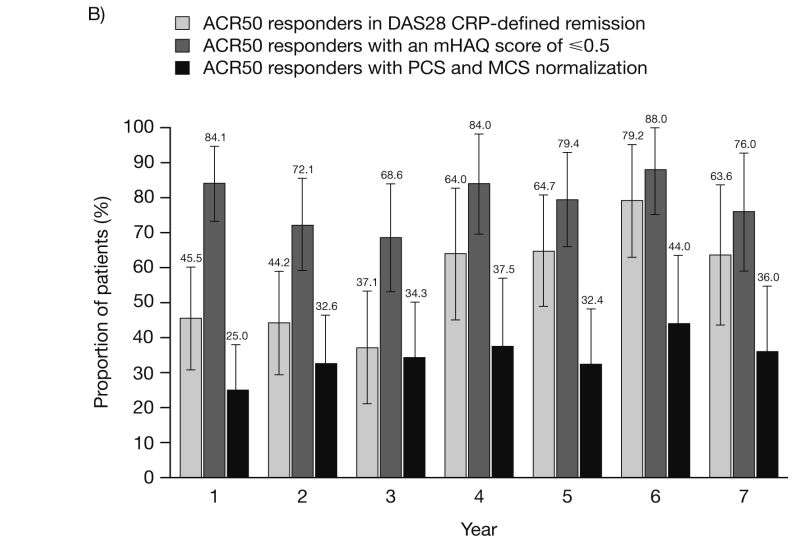
There is potential for an increased risk of autoimmune events with biologic therapies (35). In this current study, the IR of autoimmune events was not increased in the cumulative period compared with the DB period, and is consistent with previously reported IRs in other trials of IV abatacept in established disease (11, 31-34).

Given the observation that some biologic therapies may be associated with an increased risk of opportunistic infections in patients with RA (36), it is clinically important that no opportunistic infections or cases of tuberculosis were reported with IV abatacept during the 7-year cumulative period of this trial. These findings are in keeping with those from a Cochrane review of biologic therapies, which demonstrated no statistical differences between abatacept and control in the number of SAEs, AEs, serious infections, or withdrawals due to AEs (37). The Cochrane analysis reported a significantly lower risk of SAEs with abatacept compared with most other biologics, and a significantly lower risk of serious infections with abatacept *versus* infliximab and tocilizumab.

The safety and tolerability findings of this study were accompanied by sustained clinical and functional benefits. Improvements in the signs and symptoms of RA, disease activity, and physical function achieved with initial therapy were maintained throughout the LTE in patients remaining on treatment. Sustainability of treatment outcomes, in particular low disease activity, is important to demonstrate over time, as highlighted by EULAR and ACR guidelines (15). Here, we also evaluated the sustainability of normalised physical function, as this represents a tangible, real-life benefit to the patient. We assessed the proportion of patients initially achieving DAS28 (CRP)-defined LDAS and remission, and normalised mHAQ at Year 1, who sustained these



Number of patients assessed	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
	83	72	64	60	54	43	33



Number of patients assessed	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
DAS28 CRP-defined remission	44	43	35	25	34	24	22
mHAQ score of ⩽0.5	44	43	35	25	34	25	25
PCS and MCS normalization	44	43	35	24	34	25	25

Fig. 5. Multiple measures of efficacy. (**A**) Proportions of patients achieving both DAS28 (CRP)-defined remission and normalised mHAQ over time; (**B**) proportions of ACR50 responders achieving DAS28 (CRP)-defined remission, normalised mHAQ, or normalised Short Form-36 PCS and MCS over time. Data are for all patients originally randomised to IV abatacept 10 mg/kg who entered the long-term extension, with data for each outcome available at the visit of interest (as-observed population). Remission was defined as DAS28 (CRP) <2.6. Normalised mHAQ was defined as scores of ≤0.5; normalised PCS and MCS were defined as scores ≥50. ACR: American College of Rheumatology; DAS: Disease Activity Score; IV: intravenous; mHAQ: modified Health Assessment Questionnaire; MCS: Mental Component Summary; PCS: Physical Component Summary.

outcomes at each subsequent study-year. Of the IV abatacept-treated patients in LDAS or remission at Year 1, a large percentage who remained on treatment sustained their response when assessed at each follow-up year. Similarly, reductions in functional disability, as measured by the mHAQ, were maintained throughout the LTE, as was the proportion of patients sustaining a low level of physical disability (as indicated by a normalised mHAQ score of ≤0.5) from Year 1 to each subsequent study-year. To determine whether clinical improvements translated into benefits for the patient, HRQoL was evaluated. PCS and MCS scores are particularly relevant as they encompass domains for pain, physical function, energy – fatigue, and social functioning – key concerns for patients with RA (38, 39). In the present study, improvements seen in PCS and MCS during the DB period were maintained with continued treatment. Additionally, a proportion of this DMARD-refractory population with established disease achieved, and maintained, scores considered to be in the range of 'normal'.

Multiple measures of efficacy were examined to evaluate more broadly the impact of treatment on multiple aspects of disease, in addition to assessing clinical, functional, and HRQoL outcomes individually. At Year 7, >40% of all patients achieved remission together with normalised mHAQ. Similarly, among ACR50 responders, a considerable proportion also achieved remission, normalised mHAQ, or PCS and MCS normalisation when assessed at yearly intervals. It has been suggested that some measures of clinical efficacy, such as tender and swollen joint counts, are poorly correlated to improvements in HRQoL (40, 41). These data, which evaluated the response to treatment from different endpoints, suggest that the clinical efficacy benefits seen with abatacept plus MTX are accompanied by improvements in function and HRQoL that are meaningful to patients. The consistent safety and sustained efficacy observed in this study were supported by high patient retention rates. Indeed, >50% of patients who entered the LTE were still continuing treatment at the end of Year 7, with only 11% discontinuing due to lack of efficacy.

All patients received MTX throughout the study, and the proportion of patients receiving steroids over 7 years remained relatively stable, and few patients received additional non-biologic DMARDs (14 over the cumulative period), suggesting that the combination of IV abatacept plus MTX continues to provide benefits over time.

These findings should be interpreted within the context of this clinical trial. Randomised patients had well-established and severe disease, which may be atypical of daily clinical practice.

Although the DB period of this trial was randomised and controlled, the LTE period was open-label, which can be subject to bias. As-observed data were used in these analyses to evaluate the efficacy over time of patients who remain on long-term treatment. This type of analysis, however, is vulnerable to the discontinuation of patients responding less well to treatment. However, an analysis of efficacy based on the intent-to-treat population would not be appropriate given the objective, the length of the study, and the fact that patients discontinued for any number of reasons. Approximately 50% of patients discontinued treatment during this LTE (Fig. 1). As such, patient numbers decreased over this 7-year analysis, and efficacy results should be interpreted within this context.

In summary, these data demonstrate the ability of IV abatacept, in combination with MTX, to deliver significant clinical efficacy benefits that are maintained over the long term, coupled with consistent safety and tolerability, in patients with established RA and an inadequate response to MTX. Importantly, some patients also experienced normalisation of physical function and HRQoL that persisted over time. These findings support the use of abatacept in patients with RA and an inadequate response to MTX, to obtain early, effective, and sustained clinical and functional outcomes.

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References

1. SMOLEN JS: Treat-to-target: rationale and strategies. *Clin Exp Rheumatol* 2012; 30: S2-S6.
2. YAZICI Y: Treat-to-target: measures. *Clin Exp Rheumatol* 2012; 30: S7-S9.
3. BYKERK VP, KEYSTONE EC, KURIYA B, LARCHE M, THORNE JC, HARAOUI B: Achieving remission in clinical practice: lessons from clinical trial data. *Clin Exp Rheumatol* 2013; 31: 621-32.
4. TURCHETTI G, SMOLEN JS, KAVANAUGH A, BRAUN J, PINCUS T, BOMBARDIERI S: Treat-to-target in rheumatoid arthritis: clinical and pharmacoeconomic considerations. Introduction. *Clin Exp Rheumatol* 2012; 30: S1.
5. GOTTENBERG JE, RAVAUD P, BARDIN T *et al*.: Prospective follow-up of RA patients (1200 patient/years) treated with abatacept in real life: results from the ORA registry. *Ann Rheum Dis* 2011; 70 (Suppl. 3): 466.
6. KRISTENSEN LE, SAXNE T, NILSSON JA, GEBOREK P: Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. *Arthritis Res Ther* 2006; 8: R174.
7. SCHIFF M, PONCET C, LE BARS M: Efficacy and safety of abatacept therapy for rheumatoid arthritis in routine clinical practice. *Int J Clin Rheumatol* 2010; 5: 581-91.
8. VERSCHUEREN P, ESSELENS G, WESTHOVENS R: Daily practice effectiveness of a step-down treatment in comparison with a tight step-up for early rheumatoid arthritis. *Rheumatology* (Oxford) 2008; 47: 59-64.
9. YAMADA A, SALAMA A, SAYEGH M: The role of novel T cell costimulatory pathways in autoimmunity and transplantation. *J Am Soc Nephrol* 2002; 13: 559-75.
10. KREMER JM, GENANT HK, MORELAND LW *et al*.: Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006; 144: 865-76.
11. KREMER JM, RUSSELL AS, EMERY P *et al*.: Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. *Ann Rheum Dis* 2011; 70: 1826-30.
12. WESTHOVENS R, KREMER JM, MORELAND LW *et al*.: Safety and efficacy of the selective costimulation modulator abatacept in patients with rheumatoid arthritis receiving background methotrexate: a 5-year extended phase IIB study. *J Rheumatol* 2009; 36: 736-42.
13. KREMER JM, WESTHOVENS R, LEON M *et al*.: Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. *N Engl J Med* 2003; 349: 1907-15.
14. KREMER JM, DOUGADOS M, EMERY P *et al*.: Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase IIb, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 2263-71.
15. ALETAHA D, LANDEWÉ R, KARONITSCH T *et al*.: Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. *Ann Rheum Dis* 2008; 67: 1360-4.
16. FELSON DT, ANDERSON JJ, LANGE ML, WELLS G, LAVALLEY MP: Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent? *Arthritis Rheum* 1998; 41: 1564-70.
17. FRANSEN J, VAN RIEL PL: The Disease Activity Score and the EULAR response criteria. *Rheum Dis Clin North Am* 2009; 35: 745-57.
18. PINCUS T, SUMMEY JA, SORACI SA, JR., WALLSTON KA, HUMMON NP: Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983; 26: 1346-53.
19. FELSON DT, SMOLEN JS, WELLS G *et al*.: American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011; 70: 404-13.
20. WARE JE, JR., SHERBOURNE CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; 30: 473-83.
21. KOSINSKI M, ZHAO SZ, DEDHIYA S, OSTERHAUS JT, WARE JE, JR.: Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 1478-87.
22. KLARESKOG L, GAUBITZ M, RODRIGUEZ-VALVERDE V, MALAISE M, DOUGADOS M, WAJDULA J: A long-term, open-label trial of the safety and efficacy of etanercept (Enbrel) in patients with rheumatoid arthritis not treated with other disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2006; 65: 1578-84.
23. KREMER JM, WEINBLATT ME, BANKHURST AD *et al*.: Etanercept added to background methotrexate therapy in patients with rheumatoid arthritis: continued observations. *Arthritis Rheum* 2003; 48: 1493-9.
24. SCHIFF M, KEISERMAN M, CODDING C *et al*.: Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* 2008; 67: 1096-103.
25. SCHIFF MH, BURMESTER GR, KENT JD *et al*.: Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. *Ann Rheum Dis* 2006; 65: 889-94.
26. WEINBLATT ME, MORELAND LW, WESTHOVENS R *et al*.: Safety of abatacept administered intravenously in treatment of rheumatoid arthritis: integrated analyses of up to 8 years of treatment from the abatacept clinical trial program. *J Rheumatol* 2013; 40: 787-97.
27. ALTEN R, KAINE J, KEYSTONE EC *et al*.: Safety profile of subcutaneous abatacept focusing on clinically relevant events in patients with rheumatoid arthritis (RA) and up to 4.5 years of exposure. *Arthritis Rheum* 2011; 63 (10 Suppl.): S150.
28. KHURANA R, WOLF R, BERNEY S, CALDITO G, HAYAT S, BERNEY SM: Risk of development of lung cancer is increased in patients with rheumatoid arthritis: a large case control study in US veterans. *J Rheumatol* 2008; 35: 1704-8.
29. SMITTEN AL, SIMON TA, HOCHBERG MC, SUISSA S: A meta-analysis of the incidence of malignancy in adult patients with rheumatoid

arthritis. *Arthritis Res Ther* 2008; 10: R45.
30. SIMON TA, SMITTEN AL, FRANKLIN J *et al*.: Malignancies in the rheumatoid arthritis abatacept clinical development programme: an epidemiological assessment. *Ann Rheum Dis* 2009; 68: 1819-26.
31. GENOVESE MC, SCHIFF M, LUGGEN M *et al*.: Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. *Ann Rheum Dis* 2008; 67: 547-54.
32. GENOVESE MC, SCHIFF M, LUGGEN M *et al*.: Longterm safety and efficacy of abatacept through 5 years of treatment in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor inhibitor therapy. *J Rheumatol* 2012; 39: 1546-54.
33. KREMER J, RUSSELL A, EMERY P *et al*.: Abatacept demonstrates consistent safety and sustained improvements in efficacy through 5 years of treatment in biologic-naïve patients with RA. *Ann Rheum Dis* 2009; 68 (Suppl. 3): 444.
34. SCHIFF M, PRITCHARD C, HUFFSTUTTER JE *et al*.: Safety and efficacy of abatacept (ABA) in patients with rheumatoid arthritis (RA) and an inadequate response to anti-tumour necrosis factor (TNF) therapy through 2 years of the ARRIVE trial. *Ann Rheum Dis* 2010; 69 (Suppl. 3): 540.
35. RAMOS-CASALS M, BRITO-ZERON P, MUNOZ S *et al*.: Autoimmune diseases induced by TNF-targeted therapies: analysis of 233 cases. *Medicine* (Baltimore) 2007; 86: 242-51.
36. FISHER MC, GREENBERG JD: Assessing infection risk with biologic agents in RA: methodological challenges. *Nat Rev Rheumatol* 2009; 5: 288-91.
37. SINGH JA, WELLS GA, CHRISTENSEN R *et al*.: Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011; CD008794.
38. SANDERSON T, MORRIS M, CALNAN M, RICHARDS P, HEWLETT S: What outcomes from pharmacologic treatments are important to people with rheumatoid arthritis? Creating the basis of a patient core set. *Arthritis Care Res* (Hoboken) 2010; 62: 640-6.
39. SANDERSON T, MORRIS M, CALNAN M, RICHARDS P, HEWLETT S: Patient perspective of measuring treatment efficacy: the rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. *Arthritis Care Res* (Hoboken) 2010; 62: 647-56.
40. EICHLER HG, MAVROS P, GELING O, HUNSCHE E, KONG S: Association between health-related quality of life and clinical efficacy endpoints in rheumatoid arthritis patients after four weeks treatment with anti-inflammatory agents. *Int J Clin Pharmacol Ther* 2005; 43: 209-16.
41. TUTTLEMAN M, PILLEMER SR, TILLEY BC *et al*.: A cross sectional assessment of health status instruments in patients with rheumatoid arthritis participating in a clinical trial. Minocycline in Rheumatoid Arthritis Trial Group. *J Rheumatol* 1997; 24: 1910-5.