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Original article

Safety and clinical activity of atacicept in the long-term extension of the phase 2b ADDRESS II study in systemic lupus erythematosus

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Abstract

Objectives. Atacicept reduced SLE disease activity in the phase 2b ADDRESS II study, particularly in patients with high disease activity (HDA; SLEDAI-2K $\geq$10) at screening. We assessed long-term safety and efficacy of atacicept in the long-term extension (LTE) of ADDRESS II.

Methods. In the 24-week, randomized, double-blind, placebo-controlled ADDRESS II study, patients received weekly atacicept (75 or 150 mg) or placebo. Atacicept was continued at the same dose in atacicept-treated patients in the LTE; placebo-treated patients switched to atacicept 150 mg. Long-term safety was the primary endpoint. Secondary endpoints included SLE responder index (SRI)-4 and SRI-6 response rates and flares.

Results. In total, 253 patients entered the ADDRESS II LTE; 88 received atacicept 150 mg, 82 atacicept 75 mg and 83 placebo/atacicept 150 mg. Median active treatment duration in the LTE was 83.8 weeks. Frequencies of treatment-emergent adverse events (TEAEs) were similar across groups (90.4–93.2%), and 12.5%, 14.6% and 21.7% of patients in the atacicept 150 mg, atacicept 75 mg and placebo/atacicept 150 mg groups reported serious TEAEs during the treatment period. The proportions of patients with TEAEs leading to discontinuation were 5.7%, 4.9% and 10.8%, respectively. SRI-4 and SRI-6 response rates were maintained with atacicept in the modified intent-to-treat and HDA populations and those on continuous 150 mg had a reduced risk of first severe flare and longer time to first severe flare *vs* those who initially received placebo.

Conclusion. Long-term treatment with atacicept 150 mg in SLE patients had an acceptable safety profile, with durable efficacy.

Trial registration. ClinicalTrials.gov, http://clinicaltrials.gov, NCT02070978.

Key words: systemic lupus erythematosus, atacicept, TACI, APRIL/BLyS inhibitor, long-term extension study

Rheumatology key messages

- In this long-term extension study, SLE patients received atacicept for a median of 83.8 weeks.
- No new safety signals were observed, and risk-mitigation measures to limit infection risk were effective.
- Efficacy was sustained over the study, particularly for patients with high disease activity at screening.

Introduction

SLE is a heterogeneous, multisystem autoimmune disease characterized by sporadic and unpredictable disease flares [1, 2]. Standard treatments include CSs, immunosuppressive drugs and antimalarials [3]. Disease control with the available treatments is often inadequate, resulting in progressive organ damage and impaired quality of life [4, 5].

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The activation and differentiation of B cells to autoantibody-producing plasma cells plays a central role in SLE pathogenesis. These processes are mediated by the cytokines B lymphocyte stimulator (BLyS) and a proliferation-inducing ligand (APRIL), which signal through overlapping and distinct receptors. Both cytokines bind to transmembrane activating factor and cyclophilin ligand interactor (TACI) [6]. In patients with SLE, elevated serum levels of BLyS and APRIL correlate with disease activity [7, 8], organ damage [9] and autoantibody production [9–12].

Atacicept is a recombinant human TACI-immunoglobulin fusion protein that binds to BLyS and APRIL, inhibiting interactions with their receptors. Atacicept reduced SLE disease activity in two large phase 2 studies [13, 14]. In the phase 2/3 APRIL-SLE study, atacicept 150 mg showed a beneficial effect over placebo in patients with active SLE although this treatment arm was terminated following two fatal infections [14]. In the phase 2b ADDRESS II study in patients with active, autoantibody-positive SLE, a risk mitigation strategy was put in place to ensure appropriate immunizations prior to entry and sites were educated to monitor immunoglobulins and signs/symptoms of infection. There was a trend towards improved SLE responder index (SRI)-4 response rate at week 24 (primary endpoint) with atacicept 75 and 150 mg *vs* placebo. In a subpopulation of patients with high disease activity (HDA; SLEDAI-2K $\geq$10) at screening, 24-week SRI-4 and SRI-6 response rates were significantly improved with atacicept 150 mg *vs* placebo [13]. The risk of severe flares, measured by the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI flare index (SFI) and the BILAG 2004 index, was significantly reduced with atacicept *vs* placebo in the overall study population and HDA subpopulation. Atacicept demonstrated acceptable safety in the ADDRESS II study [13].

In an exploratory *post hoc* analysis of ADDRESS II that assessed potential treat-to-target (T2T) endpoints in the HDA subpopulation, atacicept 150 mg improved low disease activity (LDA), Lupus Low Disease Activity State (LLDAS) and remission compared with placebo at week 24 [15].

Here, we present the safety and efficacy of atacicept for up to 144 weeks for SLE patients who completed the ADDRESS II study and entered the long-term extension (LTE) study.

Methods

Study design

The ADDRESS II core study was a multicentre, randomized, double-blind, placebo-controlled, parallel-arm, phase 2b study of atacicept in patients with active, autoantibody-positive SLE (NCT01972568) as described previously [13]. Patients receiving standard therapy were randomized (1:1:1) to weekly, subcutaneous injections of atacicept (75 or 150 mg) or placebo for 24 weeks. Patients were stratified by SLEDAI-2K score at screening, and a subpopulation with HDA (SLEDAI-2K $\geq$10) was defined *post hoc* for exploratory analysis.

Patients who completed ADDRESS II, who did not meet any of the discontinuation criteria based on safety and compliance, were eligible for the LTE study (NCT02070978). Exclusion criteria included severe or progressive neurological symptoms of SLE and major and/or clinically significant infections. Patients treated with atacicept during the core study continued at the same dose and placebo-treated patients were switched to weekly atacicept 150 mg (placebo/atacicept 150 mg) with blinding maintained (Fig. 1).

The LTE was designed for a treatment period of up to 7 years, followed by a 24-week safety follow-up after study completion or discontinuation. Due to a shortage of study medication the study was terminated prematurely, and patients had a shorter treatment duration than planned. Safety and key efficacy data were collected up to 144 weeks, including a 24-week safety follow-up. Timepoints are described relative to the ADDRESS II core study baseline, i.e. week 24 of the LTE study is referred to as week 48, including the 24-week core study.

The ADDRESS II study and LTE were conducted according to the Declaration of Helsinki, the International Conference on Harmonization Guidance on Good Clinical Practice and applicable regulatory requirements. The study was approved by Cedars-Sinai Medical Center Institutional Review Board. The study was also conducted at a further 80 sites; all received local ethics board approval. All patients provided written informed consent.

Assessment of endpoints in the ADDRESS II LTE study

Safety and efficacy endpoints

The primary objective was to assess the long-term safety and tolerability of atacicept in patients with SLE, based on the number of patients with at least one serious adverse event (SAE) during the treatment period and the number of patients who discontinued treatment due to adverse events (AEs; see Supplementary Methods, available at *Rheumatology* online for further details).

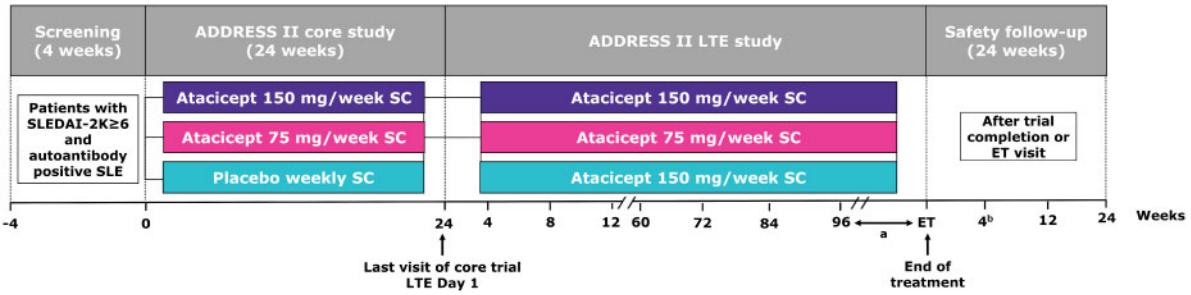
Evaluation of the effect of atacicept on SLE disease activity over time was a secondary objective, assessed using SRI-4 [16] and SRI-6 response rates and the incidence of and time to SFI and BILAG flares [17].

Pharmacodynamic endpoints included serum levels of immunoglobulins (IgG, IgA, IgM), antibodies to dsDNA (anti-dsDNA) in patients positive for anti-dsDNA at screening ($\geq$15 IU/ml) and complement proteins (C3, C4) in patients with low complement (C3 $<$ 0.9 g/l; C4 $<$ 0.1 g/l) at screening. Antibody titres to tetanus toxoid and diphtheria toxoid were also evaluated.

*Potential treat-to-target endpoints (*post hoc *exploratory analysis)*

Potential T2T endpoints were evaluated *post hoc* and included LLDAS [18], remission [19] and LDA [13], as

Fig. 1 Study design



CS dose was adjustable during screening, up to week 4 of the core study and during the LTE study. CS dose reductions were allowed during weeks 5–16 of the core study but no changes were allowed during weeks 17–24 of the core study. [a]Study visits were every 16 weeks after week 96. [b]Required only for those who discontinued the trial prematurely. ET: early termination; LTE: long-term extension; SC: subcutaneous.

defined in the Supplementary Methods, available at *Rheumatology* online.

See Supplementary Methods, available at *Rheumatology* online for statistical analyses.

Results

Study population and baseline characteristics

Of 306 patients enrolled, 262 completed 24 weeks of treatment in the ADDRESS II core study and 253 (HDA subpopulation, $n = 132$) entered the LTE: 88 continued treatment with atacicept 150 mg (HDA, $n = 45$), 82 with 75 mg (HDA, $n = 45$) and 83 placebo-treated patients switched to atacicept 150 mg (HDA, $n = 42$). Most patients enrolled in the LTE completed at least 48 weeks of treatment (89.3%, $n = 226$); 43.9% ($n = 111$) completed at least 96 weeks of treatment. The median duration of active treatment was 96.2, 96.1 and 72.1 weeks for the atacicept 150 mg, 75 mg and placebo/atacicept 150 mg groups, respectively.

During the LTE, 209 (82.6%) patients discontinued treatment, predominately due to a shortage of study medication that resulted in early study termination by the sponsor ($n = 153$, 60.5%). Other reasons for discontinuation included AEs ($n = 15$, 5.9%) and patient withdrawal ($n = 12$, 4.7%). Two patients were lost to follow-up and two died during the study; both deaths were unrelated to the study medication. Treatment discontinuation rates were similar in the modified intent-to-treat (mITT) population and HDA subpopulation (Supplementary Fig. S1A and B, available at *Rheumatology* online).

Baseline demographics and disease characteristics of LTE patients (in the mITT population and HDA subpopulation) were generally balanced across treatment groups (Table 1). Most mITT patients were female (91.3%), white (70.0%) and Hispanic or Latino (51.8%). The mean age was 39 (S.D. 11.8) years. The mean duration of SLE disease in the mITT population (6.4–6.9 years) and the proportion of patients with severe BILAG were balanced across groups. Mean SLEDAI-2K score was 10 in all groups.

Safety

For the primary endpoint, the proportion of patients with treatment-emergent SAEs during the treatment period was 12.5% with atacicept 150 mg, 14.6% with atacicept 75 mg and 21.7% with placebo/atacicept 150 mg (Table 2). Infections and infestations were the most frequently reported SAEs, with a higher frequency (8.4%) in the placebo/atacicept 150 mg group compared with atacicept 150 mg (3.4%) and 75 mg (7.3%; see Supplementary Results, available at *Rheumatology* online). Serious treatment-emergent adverse events (TEAEs) deemed to be related to the study treatment were similar between groups (Table 2).

The proportion of patients with TEAEs leading to treatment discontinuation was 5.7%, 4.9% and 10.8% in the atacicept 150 mg, 75 mg and placebo/atacicept 150 mg groups. Study drug-related TEAEs leading to discontinuation were reported by 4.5%, 2.4% and 4.8% of patients, respectively. Safety findings in the HDA subpopulation were similar (Table 2).

The proportion of patients who reported one or more TEAE was similar across treatment groups; 93.2%, 91.5% and 90.4% of patients in the atacicept 150 mg, 75 mg and placebo/atacicept 150 mg groups, respectively (Table 2). Treatment-related TEAEs were reported in a higher proportion of patients treated with atacicept 150 mg (73.9%) compared with atacicept 75 mg (56.1%) and placebo/atacicept 150 mg (59.0%).

Six patients developed severe hypogammaglobulinaemia (IgG <3 g/l) after 36 weeks of treatment (atacicept 150 mg, $n = 4$; atacicept 75 mg, $n = 1$; placebo/atacicept 150 mg, $n = 1$), three of whom were in the HDA subpopulation (atacicept 150 mg, $n = 2$; atacicept 75 mg, $n = 1$). Four of these patients were on concomitant MMF. Serum IgG levels improved spontaneously to above 3 g/l in five of these patients without study treatment interruption or intervention (e.g. intravenous immunoglobulin). The cases of severe hypogammaglobulinaemia were not associated with serious or severe infections.

There were two deaths in the atacicept 150 mg group; one following abdominal pain and vomiting with

TABLE 1 Baseline demographics and disease characteristics of patients enrolled in the LTE of the ADDRESS II study (mITT population and HDA subpopulation)

	mITT			HDA		
	Placebo/atacicept 150 mg (*n* = 83)	Atacicept 75 mg (*n* = 82)	Atacicept 150 mg (*n* = 88)	Placebo/atacicept 150 mg (*n* = 42)	Atacicept 75 mg (*n* = 45)	Atacicept 150 mg *n* = 45
Female, *n* (%)	74 (89.2)	75 (91.5)	82 (93.2)	37 (88.1)	41 (91.1)	43 (95.6)
Race, *n* (%)						
White	64 (77.1)	58 (70.7)	55 (62.5)	32 (76.2)	29 (64.4)	26 (57.8)
Asian	7 (8.4)	13 (15.9)	13 (14.8)	3 (7.1)	9 (20.0)	7 (15.6)
Black/African American	3 (3.6)	3 (3.7)	7 (8.0)	1 (2.4)	1 (2.2)	4 (8.9)
Other[a]	9 (10.8)	8 (9.8)	13 (14.8)	6 (14.3)	6 (13.3)	8 (17.7)
Hispanic or Latino ethnicity, *n* (%)	48 (57.8)	43 (52.4)	40 (45.5)	25 (59.5)	25 (55.6)	21 (46.7)
Age, mean (S.D.) years	41 (13.0)	37 (10.7)	38 (11.5)	40 (13.9)	34 (10.1)	37 (10.3)
Patients with ACR criteria and ≥4 ACR classification criteria for SLE met, *n* (%)	83 (100)	82 (100)	88 (100)	42 (100)	45 (100)	45 (100)
Disease duration, mean (S.D.) years	6.9 (8.1)	6.6 (6.8)	6.4 (6.2)	6.9 (8.2)	6.9 (7.4)	5.4 (5.2)
Disease activity						
SLEDAI-2K, mean (S.D.)	10 (2.9)	10 (3.4)	10 (3.0)	12 (2.5)	12 (3.0)	12 (2.4)
Severe BILAG (A), *n* (%)	20 (24.1)	20 (24.4)	20 (22.7)	11 (26.2)	13 (28.9)	11 (24.4)
Moderate BILAG (2B), *n* (%)	31 (37.3)	28 (34.1)	42 (47.7)	20 (47.6)	21 (46.7)	26 (57.8)
Laboratory assessments, *n* (%)						
ANA titre ≥1:80	80 (96.4)	79 (96.3)	82 (93.2)	40 (95.5)	43 (95.6)	42 (93.3)
Anti-dsDNA titre ≥15 IU/ml	38 (45.8)	43 (52.4)	41 (46.6)	30 (71.4)	33 (73.3)	28 (62.2)
ANA titre ≥1:80 and/or anti-dsDNA titre ≥15 IU/ml	83 (100)	81 (98.8)	88 (100)	42 (100)	45 (100)	45 (100)
C3 < 0.9 g/l LLN	27 (32.5)	31 (37.8)	27 (30.7)	20 (47.6)	24 (53.3)	18 (40.0)
C4 < 0.1 g/l LLN	15 (18.1)	13 (15.9)	17 (19.3)	13 (31.0)	11 (24.4)	13 (28.9)
Medication use, *n* (%)						
Prednisone-equivalent CS use						
Mean (S.D.) dose, mg/day	10.0 (7.7)	10.0 (8.4)	10.0 (7.6)	11.6 (8.0)	10.8 (7.3)	11.5 (8.8)
>7.5 mg/day	46 (55.4)	45 (54.9)	50 (56.8)	27 (64.3)	28 (62.2)	26 (57.8)
Antimalarial agents	63 (75.9)	62 (75.6)	67 (76.1)	31 (73.8)	36 (80.0)	34 (75.6)
Immunosuppressive agents						
AZA	17 (20.5)	16 (19.5)	18 (20.5)	9 (21.4)	9 (20.0)	6 (13.3)
MTX	13 (15.7)	8 (9.8)	10 (11.4)	6 (14.3)	6 (13.3)	6 (13.3)
Ciclosporin	0	1 (1.2)	1 (1.1)	0	0	0
LEF	0	0	1 (1.1)	0	0	0
MMS/MPF	11 (13.3)	13 (15.9)	12 (13.6)	5 (11.9)	7 (15.6)	6 (13.3)

[a]Other includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and other. HDA: high disease activity; LLN: lower limit of normal; mITT: modified intent-to-treat; MMS/MPF: mycophenolate sodium.

haematemesis, and one due to a cerebrovascular accident (stroke). Both deaths were considered unrelated to treatment.

Efficacy

SRI-4 and SRI-6 response rates

SRI-4 and SRI-6 response rates recorded at week 24 of the core study [13] were maintained in all treatment groups during the LTE study and slightly increased at week 48 (Supplementary Fig. S2A and B, available at *Rheumatology* online). At week 72, SRI-4 responses were observed in 58.0% [odds ratio (OR) *vs* placebo/atacicept 150 mg, 1.2; 95% CI: 0.7, 2.2; $P = 0.516$] and 56.1% (OR, 1.1; 95% CI: 0.6, 2.1; $P = 0.691$) of patients treated with atacicept 150 mg and75 mg, respectively, and in 53.0% of patients who switched from placebo to atacicept 150 mg in the LTE. Corresponding SRI-6 response rates were 43.2% (OR, 1.5; 95% CI: 0.8, 2.8; $P = 0.206$), 40.2% (OR, 1.3; 95% CI: 0.7, 2.5; $P = 0.387$) and 33.7%.

As previously reported, SRI-4 and SRI-6 response rates at week 24 in the HDA subpopulation were higher in the atacicept 75 and 150 mg groups compared with

TABLE 2 Overview of TEAEs reported during the ADDRESS II core study and the LTE study (mITT population and HDA subpopulation)

	mITT			HDA		
	Placebo/atacicept 150 mg (n = 83)	Atacicept 75 mg (n = 82)	Atacicept 150 mg (n = 88)	Placebo/atacicept 150 mg (n = 42)	Atacicept 75 mg (n = 45)	Atacicept 150 mg (n = 45)
Any TEAE[a]	75 (90.4)	75 (91.5)	82 (93.2)	38 (90.5)	41 (91.1)	41 (91.1)
Any TEAE during treatment period[b]	72 (86.7)	75 (91.5)	82 (93.2)	36 (85.7)	41 (91.1)	41 (91.1)
Any study drug-related TEAE	49 (59.0)	46 (56.1)	65 (73.9)	23 (54.8)	20 (44.4)	30 (66.7)
Any SAE	21 (25.3)	15 (18.3)	13 (14.8)	14 (33.3)	10 (22.2)	3 (6.7)
Any SAE during treatment period[c]	18 (21.7)	12 (14.6)	11 (12.5)	11 (26.2)	7 (15.6)	2 (4.4)
Any study drug-related serious TEAE[d]	5 (6.0)	4 (4.9)	4 (4.5)	2 (4.8)	3 (6.7)	0
Any TEAE leading to treatment discontinuation	9 (10.8)	4 (4.9)	5 (5.7)	5 (11.9)	1 (2.2)	2 (4.4)
Any study drug-related TEAE leading to treatment discontinuation	4 (4.8)	2 (2.4)	4 (4.5)	2 (4.8)	0	2 (4.4)
Any TEAE leading to study withdrawal	7 (8.4)	4 (4.9)	3 (3.4)	4 (9.5)	2 (4.4)	0
Any severe TEAE	14 (16.9)	10 (12.2)	10 (11.4)	9 (21.4)	7 (15.6)	2 (4.4)
Any TEAE with fatal outcome	0	0	2 (2.3)	0	0	0

Data are number of patients (%). [a]TEAEs are defined as events with an onset date on or after first dose of study treatment in the ADDRESS II core study or after the first dose date of the LTE. These include AEs ongoing at the time of study entry into the LTE study and TEAEs in the safety follow-up period. [b]TEAEs during the treatment period are defined as occurring between dates of the first and last dose + 7 days. [c]Related TEAEs are events considered to be related to study treatment or where the relationship is missing or unknown. HDA: high disease activity; mITT: modified intent-to-treat; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

placebo [13]. In the continuous atacicept groups, week 72 SRI-4 response rates for HDA patients were 64.4% with 150 mg (OR, 1.1; 95% CI: 0.5, 2.7; $P = 0.806$) and 62.2% with 75 mg (OR, 1.0; 95% CI: 0.4, 2.4; $P = 0.976$) (Fig. 2A), and week 72 SRI-6 response rates were 62.2% (OR, 2.0; 95% CI: 0.9, 4.7; $P = 0.114$) and 53.3% (OR, 1.4; 95% CI: 0.6, 3.2; $P = 0.451$) (Fig. 2B). Among HDA patients in the placebo/atacicept 150 mg group, SRI-4 response rates increased from 52.4% at week 24 to 61.9% at week 72, and SRI-6 response rates increased from 35.7% to 45.2%.

Low disease activity and remission

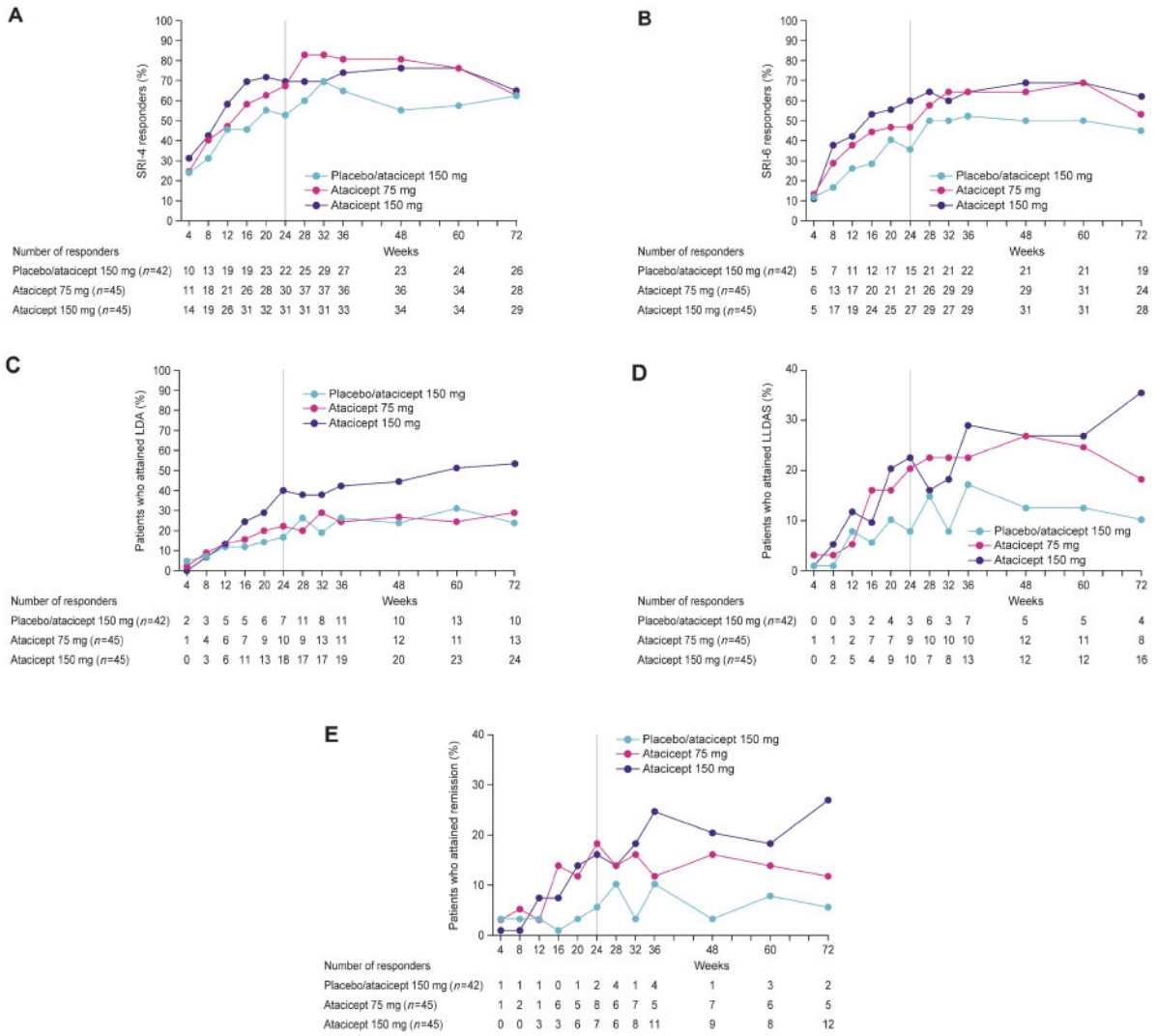
More patients in the continuous atacicept groups, particularly atacicept 150 mg, attained LDA, LLDAS and remission at week 72 compared with the placebo/atacicept 150 mg group (Supplementary Fig. S2C and E, available at *Rheumatology* online). The proportion of patients attaining LDA was 47.7% with atacicept 150 mg (OR, 1.9; 95% CI: 1.0, 3.5; $P = 0.044$), 35.4% with 75 mg (OR, 1.1; 95% CI: 0.6, 2.2; $P = 0.701$) and 32.5% with placebo/atacicept 150 mg; the corresponding proportions for LLDAS were 30.7% (OR, 1.9; 95% CI: 0.9, 3.8; $P = 0.088$), 22% (OR, 1.2; 95% CI: 0.6, 2.5; $P = 0.671$) and 19.3%; and for remission were 26.1% (OR, 3.3; 95% CI: 1.4, 7.9; $P = 0.007$), 15.9% (OR, 1.8; 95% CI: 0.7, 4.5; $P = 0.235$) and 9.6%.

In the HDA subpopulation, LDA, LLDAS and remission at week 72 was attained by more patients in the continuous atacicept groups, particularly atacicept150 mg, than in the placebo/atacicept 150 mg group (Fig. 2C–E): LDA attainment was 53.3% with atacicept 150 mg (OR, 3.7; 95% CI: 1.5, 9.2; $P = 0.006$), 28.9% with atacicept 75 mg (OR, 1.3; 95% CI: 0.5, 3.4; $P = 0.592$) and 23.8% with placebo/atacicept 150 mg. LLDAS was reached by 35.6% (OR, 5.2; 95% CI: 1.6, 17.4; $P = 0.007$), 17.8% (OR, 2.1; 95% CI: 0.6, 7.4; $P = 0.271$) and 9.5%, respectively, and remission by 26.7% (OR, 7.3; 95% CI: 1.5, 34.8; $P = 0.013$), 11.1% (OR, 2.5; 95% CI: 0.5, 13.7; $P = 0.290$) and 4.8%, respectively.

Severe flares

Fewer patients in the atacicept 150 mg group (6.8%) experienced at least one new severe SFI flare compared with the atacicept 75 mg (14.6%) and placebo/atacicept 150 mg groups (15.7%). Time to first severe SFI flare was longer in the atacicept 150 mg group than in the placebo/atacicept 150 mg group [hazard ratio (HR), 0.36; 95% CI: 0.14, 0.97; $P = 0.035$] (Supplementary Fig. S3A, available at *Rheumatology* online).

Fig. 2 Effect of atacicept on clinical response of patients with high disease activity



SRI-4 response (**A**), SRI-6 response (**B**), LDA (**C**), LLDAS (**D**), and remission (**E**) in the HDA subpopulation up to week 96. The grey line indicates the switch from placebo to atacicept 150 mg at Week 24. HDA: high disease activity; LDA: low disease activity; LLDAS: lupus low disease activity state; SRI: SLE responder index.

Fewer patients in the atacicept 75 mg group (11.0%) experienced at least one new BILAG A flare compared with the atacicept 150 mg (13.6%) and placebo/150 mg groups (15.7%). There was a trend toward a longer time to first severe BILAG A flare with atacicept 75 mg *vs* placebo/atacicept 150 mg (HR, 0.53; 95% CI: 0.22, 1.30; $P = 0.158$; Supplementary Fig. S3B, available at *Rheumatology* online).

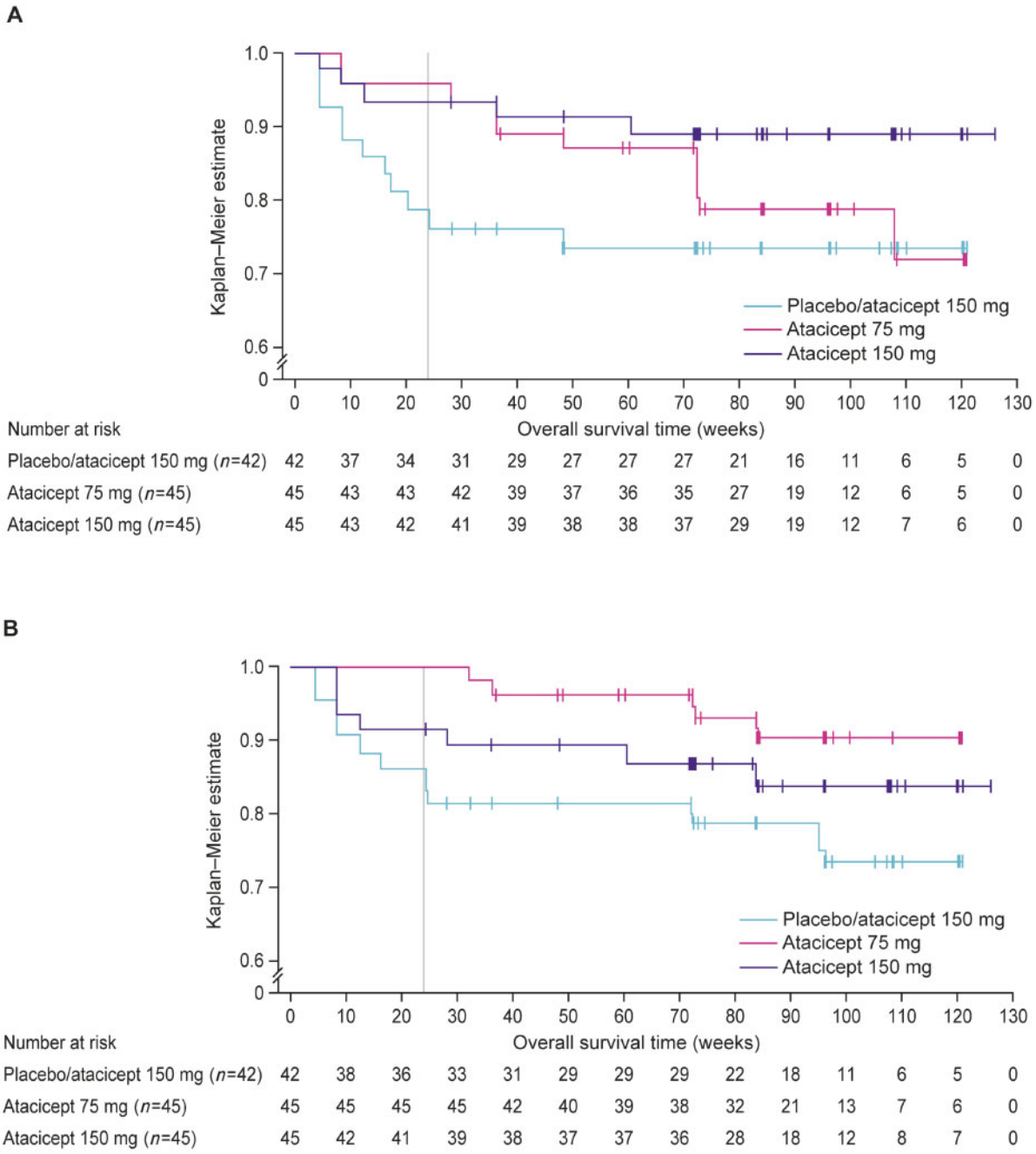
In the HDA subpopulation, fewer patients in the atacicept 150 mg group (11.1%) experienced at least one new severe SFI flare compared with the atacicept 75 mg (22.2%) and placebo/atacicept 150 mg (26.2%) groups. Time to first severe SFI flare was longer for HDA patients the atacicept 150 mg group than for the placebo/atacicept 150 mg group (HR, 0.347; 95% CI: 0.12, 1.02; $P = 0.045$; Fig. 3A).

Also, fewer HDA patients in the atacicept 150 mg (15.6%) and 75 mg groups (8.9%) experienced at least one new BILAG A flare compared with placebo/atacicept 150 mg group (23.8%). Time to first new severe BILAG A was longer with atacicept 75 mg *vs* placebo/atacicept 150 mg (HR, 0.33; 95% CI: 0.10, 1.04; $P = 0.047$). There was a trend toward a longer time to first severe BILAG A flare with atacicept 150 mg *vs* placebo/atacicept 150 mg (HR, 0.60; 95% CI: 0.22, 1.59; $P = 0.297$; Fig. 3B).

Biomarkers

Biomarker levels from baseline (core study day 1) through week 96 for the mITT population are shown in Fig. 4. At week 48, serum IgG levels decreased from baseline by a median of 36% with atacicept 150 mg,

Fig. 3 Kaplan–Meier analysis of time to first severe flare with atacicept in patients with high disease activity



Time from baseline (core study day 1) to first severe SFI flare (**A**) and to first severe BILAG A flare (**B**) in the HDA subpopulation. The grey line indicates the switch from placebo to atacicept 150 mg at week 24. HDA: high disease activity; SFI: SLEDAI flare index.

30% with 75 mg and 30% with placebo/atacicept 150 mg (Fig. 4A).

At week 24, 13 patients in the atacicept 150 mg group, 7 in the atacicept 75 mg group and zero in the placebo/atacicept 150 mg group had IgG levels <6 g/l. At week 48, the respective number of patients with IgG <6 g/l was 18, 10 and 9. Two patients with IgG <6 g/l developed serious or severe infections within 6 months of IgG <6 g/l occurrence (atacicept 75 mg, $n=1$; placebo/atacicept 150 mg, $n=1$), and one patient in the atacicept 150 mg group developed two serious or severe infections within 8 months of IgG <6 g/l occurrence.

Qualitatively similar results were observed for serum levels of IgA (Fig. 4B) and IgM (Fig. 4C). At week 48, median percentage decreases from baseline were ~51–

60% for IgA and 65–72% for IgM, and these were maintained throughout the treatment period.

Following discontinuation of atacicept treatment, by the end of the 24-week safety follow up-period, serum IgG, IgA and IgM levels had increased and reached a level ~50% of the maximal reduction observed from baseline (core study day 1).

In placebo-treated patients who had positive anti-dsDNA antibodies at screening, anti-dsDNA antibody levels increased during the 24 weeks of the core study [13]. Levels then decreased following the switch to atacicept 150 mg in the LTE, reaching levels similar to those seen in the continuous atacicept 75 mg group at week 48 but remaining higher than those in the continuous atacicept 150 mg group (Fig. 4D).

Among mITT patients with low serum complement levels at screening (C3 < 0.9 g/l; C4 < 0.1 g/l), there was an increase in C3 and C4 from baseline in the placebo/atacicept 150 mg group at week 48 (after 24 weeks of atacicept treatment). This was similar to that observed in the continuous atacicept 75 mg and 150 mg groups from baseline to week 24 (Fig. 4E and F).

Titres of antibodies to tetanus toxoid and diphtheria vaccinations remained protective following atacicept treatment from day 1 to week 72. Median changes in titre for tetanus toxoid antibodies were 0% with atacicept 75 mg and 150 mg and −3.5% with placebo/atacicept 150 mg. Median titre changes for diphtheria toxoid antibodies from day 1 to week 72 were −3.8% in the atacicept 150 mg group and 0% in the other groups.

Discussion

The ADDRESS II LTE study assessed long-term safety and efficacy of atacicept at weekly doses of 75 and 150 mg in patients with active SLE. No new safety signals were observed and the proportion of patients with SAEs, including infections and infestations, was consistent with those reported in the core study [13]. There were no deaths in the core study. Two deaths in the continuous atacicept 150 mg group during the LTE were both considered unrelated to treatment. A greater proportion of patients in the placebo arm of the core study reported serious TEAEs [13], which likely contributed to the higher incidence of serious TEAEs in the placebo/atacicept 150 mg group than the continuous atacicept groups.

Very few patients developed severe hypogammaglobulinaemia (IgG <3 g/l) during the LTE and none of these events were associated with serious or severe infections. The risk-mitigation measures implemented for ADDRESS II [13] and the LTE study seemed effective in optimizing patient safety.

Memory B cells and long-lived antibody-producing plasma cells are key to successful vaccination [19]. The observed decrease in Ig levels over time associated with atacicept's mechanism of action raises concerns over the maintenance of vaccination-derived immunity in atacicept-treated patients. However, long-term exposure to atacicept did not impact the status of tetanus toxoid or diphtheria antibody titres, and both remained protective to week 72. A systematic literature review reported that immunosuppressive therapies, such as MMF, prednisolone, and rituximab, have a negative effect on anti-pneumococcal immunization in patients with SLE, while belimumab, an inhibitor of BLyS, had no significant impact [20].

Response rates observed with atacicept 75 and 150 mg in the core study [13] were maintained over 72 weeks in both the mITT population and HDA subpopulation. Potential T2T endpoints (LDA, LLDAS, remission), which are more stringent outcome measures, appeared to improve over time in patients receiving atacicept 150 mg, with attainment rates higher at week 72 than week 24 [15] in both the mITT population and HDA subpopulation. Patients were more likely to attain LDA, LLDAS and remission with continuous atacicept 150 mg than with atacicept 75 mg or placebo/atacicept 150 mg.

Prospective studies have shown that LLDAS and remission are associated with protection from damage accrual [18, 21]. Higher attainment of these states with atacicept treatment could therefore result in such protection; however, damage accrual has to be analysed in a study with longer treatment duration. The higher attainment of these endpoints in patients who were not exposed to six months of placebo prior to atacicept suggests that earlier intervention is associated with improved response rates, supporting a T2T approach.

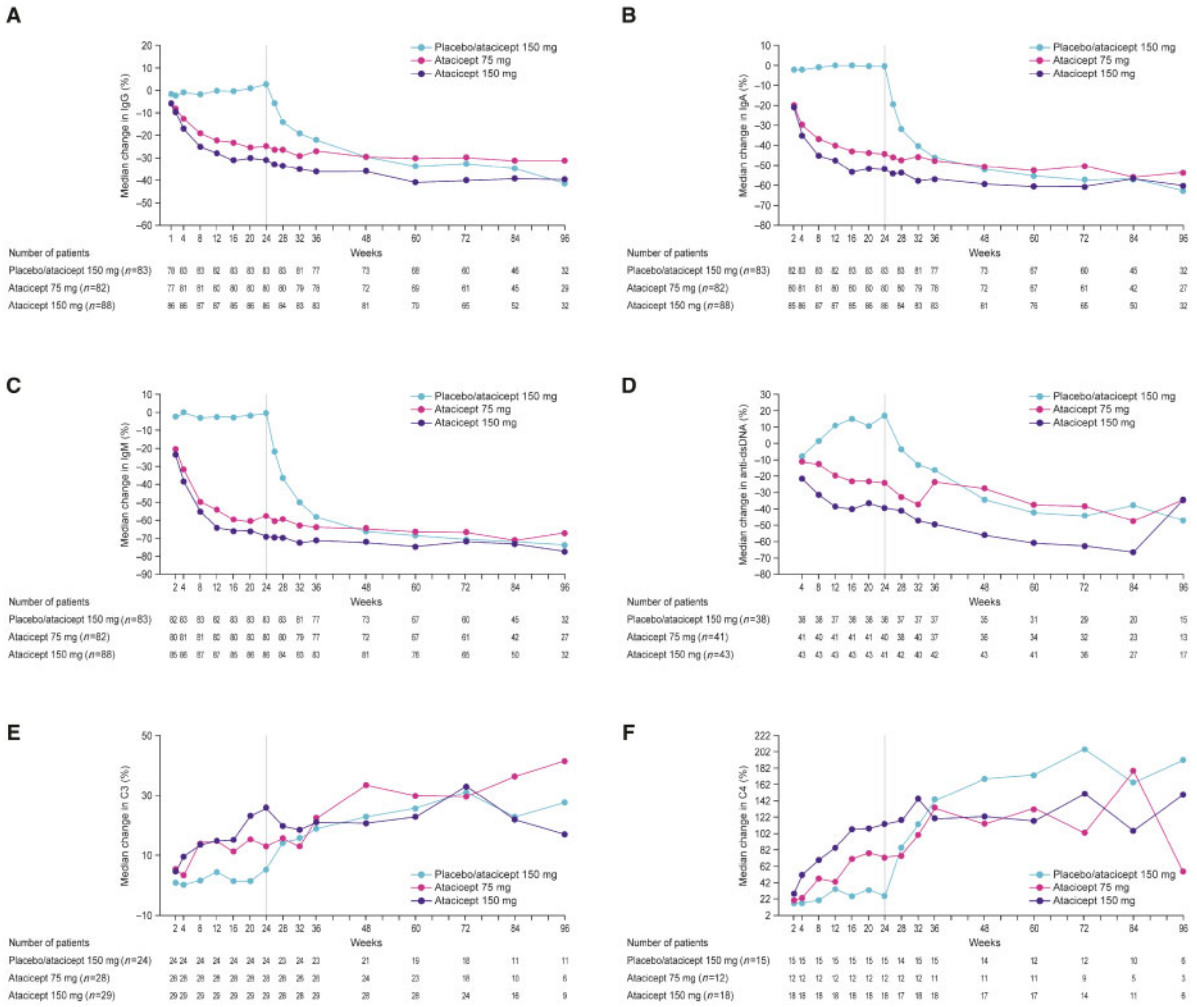
Reduction in the incidence of severe flares and longer time to first severe flare (measured by either SFI or new BILAG A) were observed with atacicept compared with placebo in the ADDRESS II core study [13]. This was maintained in the LTE study in both the mITT population and HDA subpopulation, reaching statistical significance in patients who received continuous atacicept compared with patients in the placebo/atacicept group. Few patients in the placebo/atacicept 150 mg group experienced new severe flares following the switch to active treatment.

The switch from placebo to atacicept 150 mg in the LTE study improved outcomes over time for all efficacy endpoints in both the mITT population and HDA subpopulation. However, these patients did not reach the same degree of improvement as patients who received continuous atacicept 150 mg. This may be in part due to the delay in receiving active treatment.

Changes observed in serum IgG, IgA, IgM, C3, C4 and anti-dsDNA levels following the switch from placebo to atacicept 150 mg were comparable to the changes observed for the atacicept 75 mg and 150 mg groups from baseline to week 24.

Limitations of this study include: (i) the lack of a placebo control in the LTE period; (ii) the small number of patients remaining on treatment after week 72, which precluded meaningful comparisons at later timepoints; (iii) multiple endpoints were evaluated without adjustment for multiple testing; and (iv) the study was terminated early due to a shortage of study medication—this was unrelated to the efficacy or safety results of this study.

FIG. 4 Effect of atacicept on serum biomarkers over time



Median percentage change from baseline in serum IgG (**A**), IgA (**B**), IgM (**C**), anti-dsDNA in patients with positive anti-dsDNA antibodies (≥15 IU/ml) at baseline (**D**), C3 in patients with C3 <0.9 g/l at baseline (**E**) and C4 in patients with C4 <0.1 g/l at baseline (**F**) in the mITT population up to week 96. The grey line indicates the switch from placebo to atacicept 150 mg at week 24. C3: complement 3; C4: complement 4.

In conclusion, in this ADDRESS II LTE study atacicept demonstrated an acceptable safety profile at both doses and sustained efficacy over the study period, particularly among patients with HDA at baseline. The simple and reasonable risk mitigation strategy used in this study, whereby patients received appropriate vaccinations prior to treatment and immunoglobulin levels were monitored [13], provides a sensible clinical approach for all patients with SLE receiving immunomodulatory therapy. These results strongly support further clinical development of atacicept in SLE.

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Data availability statement

The data underlying this article will be shared on reasonable request to the study sponsor.

Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck KGaA, Darmstadt, Germany's Data Sharing Policy. All requests should be submitted in writing to Merck KGaA, Darmstadt, Germany's data sharing portal. When Merck KGaA, Darmstadt, Germany, has a co-research, co-development, or co-marketing or co-promotion agreement, or when the product has been out licensed, the responsibility for disclosure might be dependent on the agreement between parties. Under these circumstances, Merck KGaA, Darmstadt, Germany, will endeavour to gain agreement to share data in response to requests.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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