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Original article

Efficacy and safety of epratuzumab in patients with moderate/severe flaring systemic lupus erythematosus: results from two randomized, double-blind, placebo-controlled, multicentre studies (ALLEVIATE) and follow-up

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Abstract

Objective. To evaluate epratuzumab treatment in patients with moderately-to-severely active SLE in two international, randomized, controlled trials (ALLEVIATE-1 and -2) and an open-label extension study (SL0006).

Methods. Ninety ALLEVIATE patients (43% BILAG A, median BILAG score 12.0) received standard of care plus 10 total doses of placebo ($n = 37$) or 360 mg/m^2 ($n = 42$) or 720 mg/m^2 ($n = 11$) epratuzumab, administered across 12-week cycles for up to 48 weeks, with BILAG assessments every 4 weeks. Patients were followed for $\geqslant$6 months and their data combined for analysis. The primary endpoint was BILAG response at week 12 (all BILAG A scores reduced to B/C/D and B scores to C/D, no new A and $<$2 new B scores). Twenty-nine patients continued in SL0006, receiving 12-week cycles of 360 mg/m^2 epratuzumab; this interim analysis was performed at median 120 weeks (range 13–184) of exposure.

Results. Both ALLEVIATE trials were discontinued prematurely because of interruption in drug supply. Exploratory pooled analyses found that responses at week 12 were 15/34 (44.1%) and 2/10 (20.0%) for epratuzumab 360 and 720 mg/m^2, respectively, *vs* 9/30 (30.0%) for placebo. Total BILAG scores were lower in both epratuzumab arms *vs* placebo at week 48 and at all but two time points. The incidence of adverse events was similar between groups. In SL0006, median total BILAG score was 8.0 ($n = 29$) at study entry and 7.0 ($n = 19$) at week 100, with no additional safety signals.

Conclusion. This initial efficacy and safety profile of epratuzumab supports its continued development for SLE treatment.

Key words: epratuzumab, CD22, ALLEVIATE, lupus, SLE, BILAG, clinical trial, monoclonal antibody.

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Introduction

SLE is a relapsing, remitting, heterogeneous autoimmune disease involving multiple organ systems [1, 2]. Current SLE regimens incorporate NSAIDs, corticosteroids, antimalarials and immunosuppressive agents, which have the potential for multiple and serious adverse effects [3]. The development of new treatments has been hampered by the complexity of SLE and the heterogeneity of the patient population [4–8].

B cells are considered to have a central role in the pathogenesis of SLE [9–12] and may either promote or inhibit the autoimmune response [13]. Biological agents have been designed to eliminate B cells, either through direct killing (anti-CD20 antibodies such as rituximab) or inhibition of survival (anti-BLyS/BAFF agents such as belimumab) [13–15]. Despite positive results in small, open-label studies, the primary endpoints were not met in two phase III trials of rituximab [16, 17]. Belimumab significantly improved SLE disease activity and severe flares and has been approved for SLE treatment in the USA and Europe [18, 19].

CD22 is a 135-kDa transmembrane sialoglycoprotein expressed on most mature B-cell lineages and a known regulator of B-cell activation and migration [20, 21]. Epratuzumab, the first potential SLE treatment to target CD22, is a humanized monoclonal antibody containing the complementarity-determining regions of the murine monoclonal antibody mLL2 (formerly EPB-2) grafted onto a human IgG1 genetic backbone [22].

Initial evidence of the clinical effect of epratuzumab in SLE patients comes from a small, open-label study. There were few significant adverse events (AEs) and no evidence of immunogenicity [23]. Two similar, international, multicentre randomized controlled trials (RCTs) [ALLEVIATE-1 (SL0003; NCT00111306) and ALLEVIATE-2 (SL0004; NCT00383214)] were initiated in larger numbers of patients with BILAG A and BILAG B disease activity, respectively [24, 25], but were prematurely discontinued owing to interruption of drug supply. Available data were pooled and subjected to exploratory analysis. In addition, patients at US sites who had participated in either ALLEVIATE trial were considered for inclusion in an open-label, ongoing, long-term study (SL0006; NCT00383513). This article reports efficacy and safety results from the ALLEVIATE studies and SL0006. A separate manuscript has been submitted summarizing the results of health-related quality of life and corticosteroid use Strand *et al.* submitted for publication.

Patients and methods

The ALLEVIATE and SL0006 trials were conducted in accordance with the International Conference on Harmonization E6 Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Informed consents, reviewed and approved by independent ethics committees or institutional review boards from all sites, were signed by all patients.

ALLEVIATE RCTs

Patients

Patients were aged $\geqslant$18 years, with ANA titre $\geqslant$1:40 (measured by enzyme immunoassay with indirect fluorescent antibody confirmation for pattern) and $\geqslant$4 of the ACR revised classification criteria [26].

Patients in ALLEVIATE-1 had BILAG A disease activity in $\geqslant$1 body/organ system, excluding renal or central neurological systems [24, 25]. Patients in ALLEVIATE-2 had BILAG B activity in $\geqslant$2 body/organ systems [24, 25] and had received oral corticosteroids (prednisone 5–20 mg/day or equivalent) at stable levels for $\geqslant$4 weeks before study entry. Patients on immunosuppressives or antimalarials had to have been receiving them for $\geqslant$8 or $\geqslant$12 weeks, respectively, with stable dose regimens for $\geqslant$4 weeks before study entry.

Patients were excluded for pregnancy, previous B-cell-targeted therapy, prior malignancy, active infection, allergy to murine or human antibodies, receipt of experimental therapy or any therapy with human or murine antibodies within 3 months, thrombosis, spontaneous or induced abortion, stillbirth or live birth within 4 weeks, or antiphospholipid antibodies plus a history of thromboembolic events. For ALLEVIATE-2, patients were also excluded if they had any BILAG A score.

Study design and treatment

The ALLEVIATE trials were international, multicentre, 48-week RCTs with almost identical designs with regard to visit intervals, treatment cycle dosing schedules and scheduled assessments. ALLEVIATE-1 was conducted at 16 sites in six countries (Belgium, Hungary, The Netherlands, Spain, UK and USA) and ALLEVIATE-2 at 28 sites in six countries (Belgium, Italy, The Netherlands, Spain, UK and USA). Patients in ALLEVIATE-1 were randomized to either individualized standard of care (SOC) plus repeated administrations of 360 or 720 mg/m^2 epratuzumab or individualized SOC plus placebo (1:1:1). Patients in ALLEVIATE-2 were randomized to SOC plus repeated administrations of epratuzumab 360 mg/m^2 or individualized SOC plus placebo (1:1). In both studies, epratuzumab or placebo was administered intravenously in 12-week cycles for up to 48 weeks (four infusions, at weeks 0, 1, 2 and 3, for cycle 1; two infusions, at weeks 0 and 1, for subsequent cycles), totalling 10 doses.

At study entry, patients began a protocol-prescribed corticosteroid regimen, but continued antimalarials or other baseline immunosuppressants unchanged. ALLEVIATE-1 patients received a flare regimen of oral or IV corticosteroids (1 g methylprednisolone, 150 mg dexamethasone or equivalent) administered three times in $<$1 week, followed by oral corticosteroids. Oral corticosteroid dose was selected on an individual patient basis (0.5–0.8 mg/kg/day prednisone or equivalent, not exceeding 60 mg/day). In ALLEVIATE-2, patients increased their oral corticosteroid dosage by 10 mg/day prednisone (or equivalent), maintained for at least 4 weeks. The tapering goal in ALLEVIATE-1 was 7.5–10 mg/day prednisone

(or equivalent) by weeks 20 and 24; the goal in ALLEVIATE-2 was 5–7.5 mg/day prednisone (or equivalent) at the same time points.

Recruitment started in Spring 2005. Dosing and enrolment in both trials were prematurely discontinued on 1 September 2006, owing to interruption of drug supply. Patients were followed for $\geqslant$6 months, and data from both RCTs were combined for analysis.

Efficacy endpoints

BILAG disease activity was measured every 4 weeks and centrally graded by an independent, blinded reviewer [24, 25]. The original primary efficacy endpoint in both studies was week 24 three-category patient response. However, because few patients had been treated for 24 weeks at discontinuation and the original endpoint was unlikely to be met within 12 weeks, this endpoint was revised within the statistical analysis plan before unblinding. The revised primary endpoint was BILAG response with no treatment failure at week 12. BILAG response was defined as follows: all BILAG A scores at entry reduced to B or lower or both BILAG B scores at entry reduced to C or lower, with no new BILAG A and $<$2 new BILAG B scores in other body/organ systems. Treatment failure was defined as new or increased use of oral corticosteroids or other immunosuppressants above baseline.

Secondary efficacy endpoints included the following: BILAG responses at weeks 24 and 36; time to initial BILAG response; total BILAG score at weeks 12, 24 and 48 (BILAG A = 9, BILAG B = 3, BILAG C = 1, BILAG D/E = 0) [27] and time to first sustained BILAG response (over $\geqslant$2 consecutive visits).

Safety and laboratory endpoints

AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 8.0. Their severity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0, where possible. The following safety endpoints were evaluated: incidence of AEs, including infusion-related AEs and serious AEs (SAEs); incidence of infections; immunogenicity by human anti-human antibody (HAHA), specifically anti-epratuzumab antibody titres; and vital sign measurements. Serum biochemistry, haematological parameters and urinalysis results were also evaluated. Serum immunoglobulins (IgA, IgG and IgM) and circulating B- and T-cell levels were measured at screening, at weeks 4 and 12 following each infusion and at early termination.

Statistical analyses

The base population for all analyses was the intention to treat (ITT) (all randomized patients) population. Values for individual time points for members of that population were calculated using an observed case (including only subjects with a non-missing value) analysis. All analyses used a two-sided hypothesis test at the overall 5% level of significance but were exploratory and not adjusted for multiple testing. Hence, *P* values and other statistical tests are of limited validity and should be interpreted cautiously.

The null hypothesis for the primary efficacy analysis was that the proportion of responders would be equal among patients receiving 360 mg/m^2 epratuzumab, 720 mg/m^2 epratuzumab or placebo. The analysis used a Cochran–Mantel–Haenszel test, stratified by ethnicity (Caucasian *vs* non-Caucasian), baseline immunosuppressive medications (used *vs* not used) and corticosteroid flare regimen (oral *vs* i.v. *vs* none). The originally planned sample sizes were not achieved—36 *vs* 510 (7%) for ALLEVIATE-1; 54 *vs* 300 (18%) for ALLEVIATE-2—and although the patient groups were combined, the combined analysis remains underpowered to detect differences. Statistical analyses were also carried out for some secondary endpoints. Differences in total BILAG score between treatment groups were assessed using analysis of covariance with effects for treatment group, ethnicity, baseline immunosuppressant use, corticosteroid flare regimen and baseline total BILAG score.

SL0006 open-label extension study

All ALLEVIATE patients at US sites were eligible for enrolment in SL0006, if in the investigator's judgment, the patient had benefited from randomized treatment, and there were no safety concerns that precluded receiving epratuzumab. The primary objective was to assess the long-term safety and efficacy of epratuzumab 360 mg/m^2. All patients were assigned to receive this dose in 12-week maintenance cycles (two infusions, on weeks 0 and 1 of each cycle). Because of interruption of drug supply, there was a median delay of 165 days (range 1–400) between completion of the ALLEVIATE studies and entry into SL0006. Safety and efficacy assessments in SL0006 were similar to those in the ALLEVIATE RCTs, performed every 4 weeks. An interim analysis was conducted to obtain preliminary long-term safety and efficacy data. The cutoff for these analyses was 31 December 2009, representing a median 120 weeks (range 13–184) of exposure.

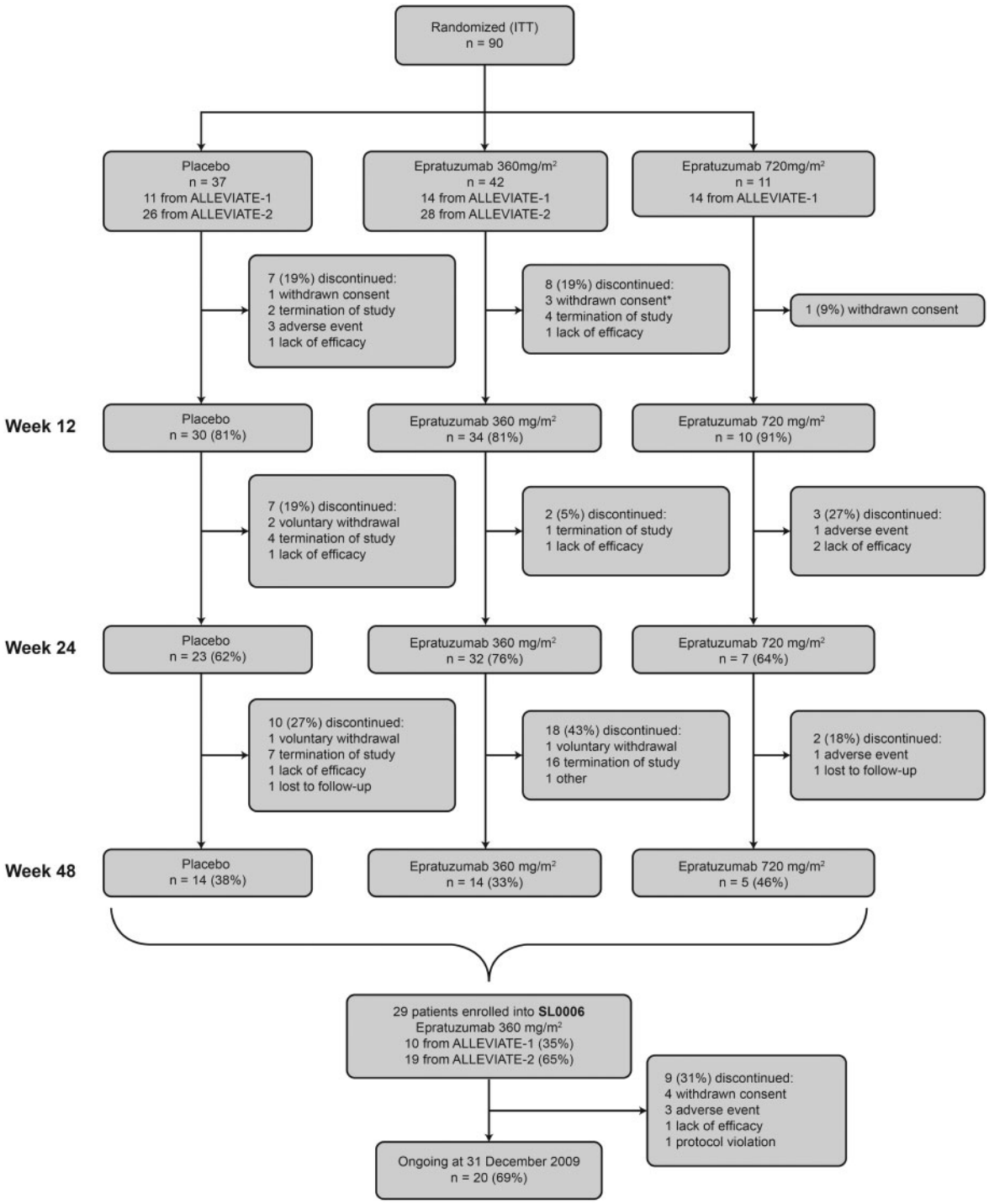
Results

ALLEVIATE RCTs

Patient characteristics

Ninety patients were randomized in the ALLEVIATE RCTs: 36 in ALLEVIATE-1 and 54 in ALLEVIATE-2 (Fig. 1). Baseline demographics are shown in Tables 1 and 2. Patients had high disease activity overall and as anticipated, given the differing entry criteria for ALLEVIATE-1 and ALLEVIATE-2, patients receiving epratuzumab 720 mg/m^2 had higher disease activity than those receiving epratuzumab 360 mg/m^2. Although most baseline demographics were largely comparable between treatment groups, some differences were observed between the 720 mg/m^2 group *vs* the placebo and epratuzumab 360 mg/m^2 groups, such as the nature of body systems affected (fewer patients in the 720 mg/m^2 group had mucocutaneous system involvement) and distribution of ethnic groups (more patients in the 720 mg/m^2 group were of African descent). In addition, median (range)

Fig. 1 Patient disposition (ITT population) through ALLEVIATE and SL0006.



Patients who continued to week 12 received a total of 4 infusions (1 treatment cycle); patients who continued to week 24 received a total of 8 infusions (2 treatment cycles) and patients who continued to week 48 received a total of 12 infusions (3 treatment cycles). *Two patients were randomized but did not receive epratuzumab.

Table 1 Patient demographics at baseline in the ALLEVIATE studies and at study entry into SL0006

	Pooled data from ALLEVIATE-1 and ALLEVIATE-2			SL0006
	Placebo ($n = 37$)	Epratuzumab 360 mg/m^2 ($n = 42$)	Epratuzumab 720 mg/m^2 ($n = 11$)	Epratuzumab 360 mg/m^2 ($n = 29$)
Age (years), median (range)	38.0 (18–58)	39.0 (20–59)	38.0 (21–52)	39.0 (22–61)
Gender				
Male	3 (8.1)	1 (2.4)	1 (9.1)	3 (10.3)
Female	34 (91.9)	41 (97.6)	10 (90.9)	26 (89.7)
Ethnicity				
Caucasian	25 (67.6)	27 (64.3)	7 (63.6)	23 (79.3)
Black	8 (21.6)	7 (16.7)	3 (27.3)	3 (10.3)
Asian	1 (2.7)	4 (9.5)	1 (9.1)	2 (6.9)
Other	3 (8.1)	4 (9.5)	0 (0.0)	1 (3.4)
Median total BILAG score[a] (range)	12.0 (7–26)	12.0 (6–26)	15.0 (10–34)	11.0 (8–21)
Median total SLEDAI score (range)	12.0 (4–32)	10.0 (0–18)	8.0 (4–14)	N/A
No. of patients with $\geqslant 1$ BILAG A	13 (35)	15 (35.7)	11 (100)	10 (34.5)
Use of immunosuppressive(s)	24 (64.9)	28 (66.7)	5 (45.5)	29 (100)
Prednisone equivalent dose (mg/day)				
$\leqslant 7.5$	0	2 (4.8)	0	17 (58.6)
>7.5–15	3 (8.1)	1 (2.4)	2 (18.2)	9 (31.0)
>15–25	21 (56.8)	21 (50.0)	1 (9.1)	2 (6.9)
>25	13 (35.1)	18 (42.9)	8 (72.7)	1 (3.5)

Data as *n* (%) unless specified otherwise. N/A: not measured. [a]The total BILAG score is calculated as the sum of eight organs/systems where categories A–E are converted into numerical scores (A = 9, B = 3, C = 1, D = 0, E = 0) [27].

Table 2 Number (%) of patients with BILAG A or B scores for each body system at baseline in the ALLEVIATE studies and at study entry into SL0006

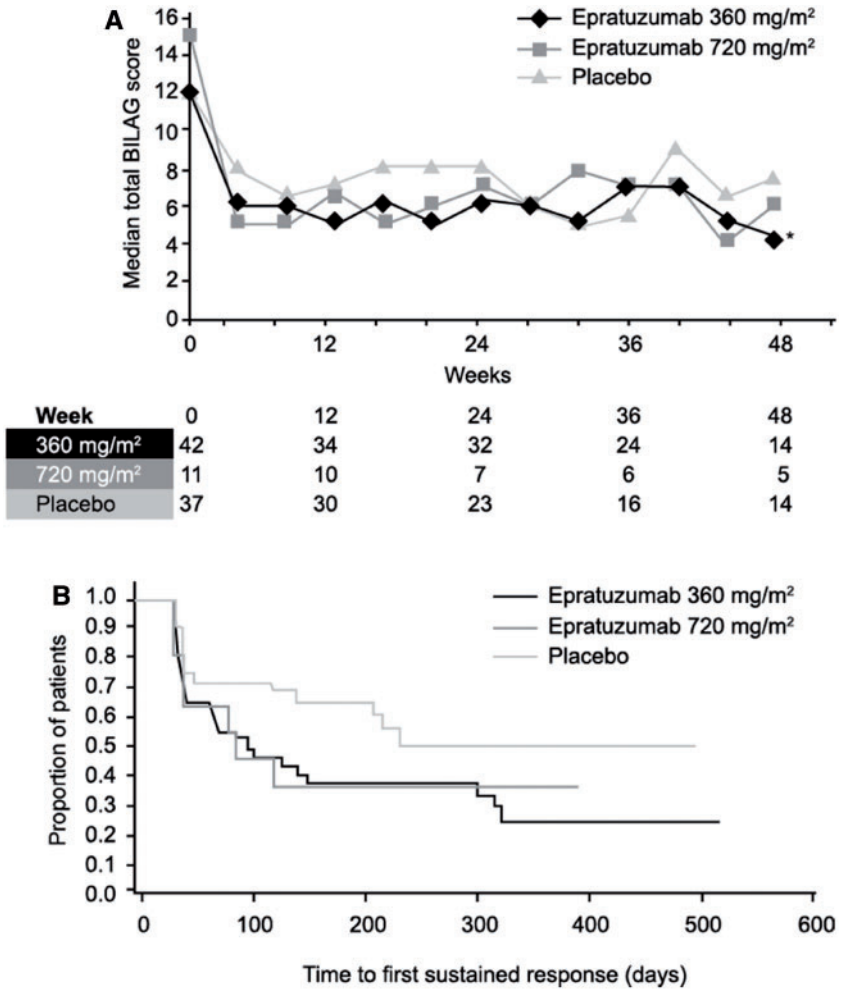
	Pooled data from ALLEVIATE-1 and ALLEVIATE-2						SL0006	
	Placebo ($n = 37$)		Epratuzumab 360 mg/m^2 ($n = 42$)		Epratuzumab 720 mg/m^2 ($n = 11$)		Epratuzumab 360 mg/m^2 ($n = 29$)	
Body system	A	B	A	B	A	B	A	B
General	0 (0)	11 (30)	1 (2)	16 (38)	1 (9)	3 (27)	0 (0)	14 (48)
Mucocutaneous	5 (14)	26 (70)	10 (24)	26 (62)	3 (27)	3 (27)	5 (17)	19 (66)
Neurological	0 (0)	1 (3)	0 (0)	2 (5)	1 (9)	0 (0)	1 (3)	3 (10)
Musculoskeletal	5 (14)	24 (65)	4 (10)	29 (69)	6 (55)	3 (27)	2 (7)	23 (79)
CV and respiratory	1 (8)	6 (16)	2 (5)	3 (7)	1 (9)	1 (9)	2 (7)	2 (7)
Vasculitis	2 (5)	7 (19)	0 (0)	5 (12)	1 (9)	1 (9)	0 (0)	4 (14)
Renal	1 (3)	5 (14)	0 (0)	4 (10)	0 (0)	1 (9)	0 (0)	1 (3)
Haematological	1 (3)	3 (8)	0 (0)	7 (17)	0 (0)	1 (9)	0 (0)	1 (3)

baseline steroid use was higher in the epratuzumab 720 mg/m^2 group [46.0 (10.0–80.0) mg/day] than in the placebo and epratuzumab 360 mg/m^2 groups [20.0 (15.0–60.0) mg/day and 25.0 (10.0–60.0) mg/day, respectively]. Patients who had received one cycle of therapy between weeks 0 and 3 (four infusions) were evaluated at week 12 ($n = 74$). Similarly, 33 patients who received three cycles of therapy were evaluated at week 48 (Fig. 1). Placebo groups from both studies were combined for analysis.

Efficacy

Beginning at week 4 and continuing through week 48, total BILAG scores in the epratuzumab treatment arms remained numerically lower than placebo at all but two time points (Fig. 2A). The median time to initial BILAG response was shorter in both epratuzumab arms [median 57.0 (95% CI 38.0, 93.0) days in the 360 mg/m^2 arm and 39.0 (35.0–84.0) days in the 720 mg/m^2 arm] than in the placebo arm [median 93.0 (40.0–120.0) days], but did not achieve significance [hazard ratio (HR) 1.19 and 1.21,

FIG. 2 Total BILAG scores and time to first sustained BILAG response in the ALLEVIATE studies.



(**A**) Median total BILAG scores at each time point in the ALLEVIATE studies for patients receiving epratuzumab 360 mg/m^2, epratuzumab 720 mg/m^2 or placebo. Numbers shown below graph are number of patients evaluable at each time point (overall treatment effect $P = 0.028$). (**B**) Time to first sustained BILAG response (ITT population; 360 mg/m^2 $P = 0.021$ *vs* placebo, 720 mg/m^2 $P = 0.704$ *vs* placebo). *$P = 0.024$ for 360 mg/m^2 epratuzumab *vs* placebo at week 48.

respectively]. The median time to first sustained BILAG response was 93.0 days (HR 2.18; 95% CI 1.12, 4.24; $P = 0.021$ *vs* placebo) for patients receiving epratuzumab 360 mg/m^2 and 84.0 days (HR 1.21; 95% CI 0.46, 3.16; $P = 0.704$ *vs* placebo) for patients receiving epratuzumab 720 mg/m^2 (Fig. 2B).

Among the 74 patients receiving 12 weeks of treatment, the percentage of responders was higher in the epratuzumab 360 mg/m^2 arm (44.1%, 15/34) than in the 720 mg/m^2 (20.0%, 2/10) or placebo (30.0%, 9/30) arms, although these differences were not statistically significant ($P = 0.177$). Among patients from ALLEVIATE-1, week 12 BILAG response was 63.6% (7/11) in the 360 mg/m^2 arm, 20.0% (2/10) in the 720 mg/m^2 arm and 30.0% (3/10) in the placebo arm. Among patients from ALLEVIATE-2, week 12 BILAG response was 34.8% (8/23) in the 360 mg/m^2 arm and 30.0% (6/20) in the placebo arm.

A total of 62 and 46 patients reached weeks 24 and 36, respectively. At week 24, the percentage of responders was also higher with epratuzumab 360 mg/m^2 (34.4%, 11/32) than 720 mg/m^2 (28.6%, 2/7) or placebo (17.4%, 4/23; $P = 0.165$ and $P = 0.375$, respectively). At week 36, there was no treatment advantage for the epratuzumab 360 mg/m^2 treatment group over placebo.

At week 48, median (range) total numerical BILAG scores in patients treated with 360 mg/m^2 ($n = 14$) and 720 mg/m^2 ($n = 5$) epratuzumab were reduced from 12 (6–26) and 15 (10–34), respectively, at baseline to 4 (2–14) and 6 (1–15). Placebo-treated patients on individualized SOC background ($n = 14$) had reductions from 12 (7–26) at baseline to 7.5 (3–16), yielding a treatment advantage for epratuzumab 360 mg/m^2 over placebo of 3.9 points (least-squares mean change, 95% CI 0.6, 7.2; $P = 0.024$). The change from baseline in total BILAG score

for all patients receiving epratuzumab *vs* placebo at week 48 was also significant ($P = 0.028$).

Median (range) corticosteroid dose was lower at week 24 than at baseline in all three arms: 9.64 (0–137.4) mg/day in the placebo arm, 10.55 (0–24.6) mg/day in the 360 mg/m^2 arm and 13.51 (4.3–49.0) mg/day in the 720 mg/m^2 arm. Detailed analysis of corticosteroid use during the ALLEVIATE studies has been presented as an abstract and is discussed in a separate article Strand *et al.* submitted for publication [28].

Adverse events

The safety population included 88 treated patients (two randomized patients were not treated owing to withdrawn consent or clinical hold) of whom 51 received either 360 mg/m^2 ($n = 40$) or 720 mg/m^2 ($n = 11$) epratuzumab. Median (range) epratuzumab exposure was 2920 (1413–7191) mg and 4341 (2103–7360) mg for the 360 and 720 mg/m^2 arms, respectively. The incidences of AEs, SAEs and infusion-related AEs were similar in the epratuzumab and placebo groups (Table 3). Assessment of vital signs (pulse rate, blood pressure, respiratory rate, temperature and body weight) did not reveal clinical concerns. All infusion events were mild or moderate by NCI CTCAE grading (Version 3.0) and the overall incidence was similar between epratuzumab and placebo groups.

One patient who received 720 mg/m^2 epratuzumab died of a cerebral haemorrhage 16 weeks after the last dose of study medication. This patient had a prior history of seizure disorder resulting from an occipital infarction and had been hospitalized after completion of this study as a result of acute respiratory distress due to a pneumococcal

Table 3 Number (%) of patients with AEs in the ALLEVIATE safety population (all patients who received study medication) and SL0006

	ALLEVIATE population[a]			SL0006[b]
	Placebo ($n = 37$)	Epratuzumab 360 mg/m^2 ($n = 40$)[c]	Epratuzumab 720 mg/m^2 ($n = 11$)	Epratuzumab 360 mg/m^2 ($n = 29$)
All AEs	34 (92)	36 (90)	11 (100)	29 (100)
Infusion-related AEs	7 (19)	7 (18)	2 (18)	6 (21)
Serious AEs	11 (30)	10 (25)	4 (36)	10 (35)
Infections ($\geqslant 1$)	26 (70)	28 (70)	7 (64)	26 (90)
Serious infections[d]	8 (22)	5 (12)	4 (36)	3 (10)
AEs leading to discontinuation	3 (8)	0 (0)	3 (27)	3 (10)
Deaths	0 (0)	0 (0)	1 (9)	0 (0)
AEs $\geqslant 10$ incidence				
Conjunctivitis	2 (5)	1 (3)	2 (18)	3 (10)
Upper respiratory tract infection	13 (35)	8 (20)	3 (27)	13 (45)
Urinary tract infection	6 (16)	6 (15)	2 (18)	8 (28)
Diarrhoea	9 (24)	7 (18)	3 (27)	8 (28)
Headache	6 (16)	6 (15)	6 (55)	6 (21)
Migraine	1 (3)	1 (3)	2 (18)	4 (14)
Nasopharyngitis	4 (11)	4 (10)	0 (0)	10 (34)
Arthralgia	4 (11)	9 (23)	3 (27)	1 (3)
Nausea	5 (14)	5 (13)	3 (27)	7 (24)
Bronchitis	2 (5)	4 (10)	0 (0)	7 (24)
Dizziness	4 (11)	4 (10)	0 (0)	3 (10)
Pyrexia	3 (8)	5 (13)	2 (18)	3 (10)
Sinusitis	0 (0)	5 (13)	1 (9)	9 (31)
Abdominal pain	3 (8)	4 (10)	2 (18)	9 (31)
Oral candidiasis	2 (5)	6 (15)	1 (9)	2 (7)
Peripheral oedema	2 (5)	4 (10)	2 (18)	2 (7)
SLE[e]	2 (5)	4 (10)	0 (0)	4 (14)
Pharyngo-laryngeal pain	2 (5)	4 (10)	1 (9)	3 (10)
Chest pain	1 (3)	5 (13)	1 (9)	3 (10)
Cough	0 (0)	4 (10)	2 (18)	3 (10)
Blurred vision	0 (0)	4 (10)	0 (0)	0 (0)

[a]Duration of exposure in ALLEVIATE-1 and ALLEVIATE-2 varied between patients. [b]Incidence of events was not corrected for duration of exposure in SL0006. [c]Safety analyses exclude 2 of the 42 patients assigned to this treatment arm who did not receive any epratuzumab. [d]Serious infection: life-threatening, required hospitalization or prolongation of existing hospitalization. [e]AEs that could potentially reflect symptoms of active SLE disease that were experienced by 5 or more patients in the active treatment groups were arthralgia, myalgia, SLE, pyrexia (if not related to infusion), rash (if not related to infusion), joint effusion and headache. Although these were experienced by a slightly higher percentage of patients in the 360 mg/m^2 treatment group, the relatively low number of patients experiencing these events makes it difficult to draw conclusions.

infection of the larynx. The day after this infection resolved, the patient experienced acute hypertension and headache and died 2 h after onset of symptoms.

Of 51 patients receiving epratuzumab, all serum samples were negative for HAHA except for two patients who developed low-level titres (maximum, 690 ng/ml) of uncertain significance with no clinical sequelae nor changes in laboratory safety parameters.

Haematological and immunological parameters

At week 12, median B-cell levels were lower than at baseline by 31% and 52% in the 360 and 720 mg/m^2 groups, respectively, compared with 9.1% in the placebo arm. Median B-cell levels continued to be lower in the treatment arms than in the placebo arm through to week 48 (supplementary Fig. 1a, available at *Rheumatology* Online). Statistical testing was not carried out on these data. T-cell levels remained stable in all treatment groups (supplementary Fig. 1b, available at *Rheumatology* Online). The median percentage changes from baseline in IgG and IgA levels were similar across treatment groups in ALLEVIATE-1 and -2 (supplementary Fig. 2, available at *Rheumatology* Online).

SL0006 open-label extension study

A total of 29 patients were enrolled in SL0006 (10 from ALLEVIATE-1 and 19 from ALLEVIATE-2). All received epratuzumab 360 mg/m^2 (Fig. 1). At the cutoff for the efficacy and safety analyses, the median (range) treatment duration was 120 weeks (13–184, $n = 29$). Median (range) total BILAG score was 8.0 (3–21, $n = 29$) at study entry and 7.0 (3–11, $n = 19$) at week 100. One patient discontinued because of lack of efficacy. Changes in BILAG disease activity for individual body systems during SL0006 are shown in Table 4; most instances of BILAG A/B at SL0006 visit 1 improved to BILAG C/D during the study.

All patients reported at least one AE, with 10 patients (35%) experiencing at least one SAE and 3 (10%) discontinuing because of AEs (Table 3). After adjusting for duration of exposure, the highest rates of AE were for nasopharyngitis, sinusitis, upper respiratory tract infection and urinary tract infection. Infusion-related AEs were reported in 6 (21%) patients in SL0006, corresponding to an infusion-related AE rate of 10.8 per 100 years of exposure. Serious infections were reported in 3 (10%) patients and included pneumonia, pyelonephritis and urinary tract infection.

B-cell and T-cell levels remained stable over the 2 years of data from SL0006 included for this evaluation (supplementary Fig. 3, available at *Rheumatology* Online). No statistical testing was performed on these results. Immunoglobulin responses followed a similar pattern to the two ALLEVIATE trials (supplementary Fig. 4, available at *Rheumatology* Online). All laboratory parameters continue to be monitored in the study follow-up.

Discussion

The original primary endpoint for the ALLEVIATE studies could not be evaluated as intended. However, despite being underpowered, some of the exploratory analyses performed here provide support for the hypothesis that treatment of SLE with 360 mg/m^2 epratuzumab plus SOC and corticosteroids may be effective at reducing SLE disease activity. In addition, epratuzumab plus SOC showed a safety profile similar to placebo plus SOC.

Based on BILAG and SLEDAI scores at baseline, this patient population had high initial disease activity compared with other recent SLE trials [18, 19]. In addition, patients receiving epratuzumab 720 mg/m^2 were small in number, $n = 11$, as well as having higher disease activity with more corticosteroid and antimalarial therapies than the other groups. This may partly explain why, despite higher response rates with 360 mg/m^2 epratuzumab, overall treatment response (both epratuzumab dosing groups combined) at weeks 12 and 24 were not statistically significantly different from the placebo group. Evidence of treatment effect based on total BILAG scores did not achieve statistical significance except at week 48.

Table 4 Changes in BILAG disease activity system scores during SL0006

	Baseline C/D/E scores		Baseline A/B scores	
	n	A/B grade during study[a]	*n*	C/D grade during study
General	21	7 (33.3%)	8	8 (100.0%)
Mucocutaneous	12	9 (75.0%)	17	15 (88.2%)
Neurological	27	8 (29.6%)	2	2 (100.0%)
Musculoskeletal	15	10 (66.7%)	14	14 (100.0%)
CV and respiratory	27	8 (29.6%)	2	2 (100.0%)
Vasculitis	28	2 (7.1%)	1	1 (100.0%)
Renal	27	9 (33.3%)	2	2 (100.0%)
Haematological	27	5 (18.5%)	2	1 (50.0%)

This table shows patients with BILAG C/D/E at baseline that worsened to A/B and patients with BILAG A/B at baseline that improved to C/D. [a]Only two BILAG As occurred during the study, one in the general category and the other in the neurological category.

These results are consistent with the first clinical trial of epratuzumab in SLE, a small, single-centre, single-arm, open-label study in which epratuzumab was administered at 360 mg/m^2 every other week for a total of four doses, and a statistically significant improvement in total BILAG scores was observed up to 32 weeks after study initiation [23]. Differences in clinical responses between the two epratuzumab dose groups are consistent with the pattern seen in EMBLEM (NCT00624351), a phase IIB study of epratuzumab with five active arms, initiated in 2008. In that study, responses at week 12 were greater in patients receiving total epratuzumab doses of 2400 mg than in those receiving total doses of 1200 and 1800 mg, and greater than in those receiving 3600 mg [29].

Analyses of safety endpoints did not identify any additional signals compared with the anticipated risks in an SLE population, and there were no apparent dose-related toxicities. The larger proportion of patients in the placebo group experiencing upper respiratory tract infections (35% *vs* 22%) may reflect higher corticosteroid dosing in this group compared with the epratuzumab treatment groups and merits further investigation. The incidence of AEs leading to discontinuation of study medication was similar across treatment groups: three patients each in the placebo and 720 mg/m^2 epratuzumab arms. No patient in the 360 mg/m^2 epratuzumab arm discontinued for safety reasons. In addition, no new or unexpected AEs were observed while total numerical BILAG scores were maintained during approximately 2 years of continued exposure in SL0006. HRQOL changes and corticosteroid use during the ALLEVIATE studies are described in a separate report (Strand *et al.* submitted for publication).

The limitations of our conclusions must be acknowledged. The analyses were designed before unblinding but are based on data pooled from two interrupted RCTs with differences in disease activity between treatment groups and in which the original planned sample sizes were not achieved. Even the pooled analysis was underpowered to detect clinically relevant differences between treatment groups and may also be subject to survivorship bias at later time points. The follow-up data in SL0006 also are complicated by the variable treatment duration and the delay between ALLEVIATE and SL0006 due to interruption of study drug supply.

Finally, while the mechanism of action of epratuzumab is not yet fully defined, treatment leads to selective modulation of B-cell activation and induces changes in B-cell migration [23, 30, 31]. These changes in migration are consistent with the observation that CD27$^-$ B cells are preferentially reduced in the peripheral blood during epratuzumab treatment [31]. In the ALLEVIATE RCTs, median B-cell counts were partially reduced from baseline (about 50% reduction) in both active treatment groups, while T-cell levels remained stable. This suggests that epratuzumab may have a complex immunomodulatory effect on B-cell activity.

These exploratory analyses of the efficacy and safety profile of epratuzumab over a substantial follow-up period support its continued development for the treatment of patients with moderately-to-severely active SLE. RCTs are currently underway to confirm the efficacy of epratuzumab in this patient population.

Rheumatology key messages

- This exploratory pooled analysis provided evidence of epratuzumab treatment effect in SLE patients.
- The safety profile of epratuzumab plus SOC in patients with SLE was similar to placebo plus SOC.
- This initial efficacy and safety profile of epratuzumab supports its continued development for SLE treatment.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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