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Efficacy and Safety of Epratuzumab in Moderately to Severely Active Systemic Lupus Erythematosus

Results From Two Phase III Randomized, Double-Blind, Placebo-Controlled Trials

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Objective. **Epratuzumab, a monoclonal antibody that targets CD22, modulates B cell signaling without substantial reductions in the number of B cells. The aim of this study was to report the results of 2 phase III multicenter randomized, double-blind, placebo-controlled trials, the EMBODY 1 and EMBODY 2 trials, assessing the efficacy and safety of epratuzumab in patients with moderately to severely active systemic lupus erythematosus (SLE).**

Methods. **Patients met ≥4 of the American College of Rheumatology revised classification criteria for SLE, were positive for antinuclear antibodies and/or anti–double-stranded DNA antibodies, had an SLE Disease Activity Index 2000 (SLEDAI-2K) score of ≥6 (increased disease activity), had British Isles Lupus Assessment Group 2004 index (BILAG-2004) scores of grade A (severe disease activity) in ≥1 body system or**

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grade B (moderate disease activity) in ≥2 body systems (in the mucocutaneous, musculoskeletal, or cardiorespiratory domains), and were receiving standard therapy, including mandatory treatment with corticosteroids (5–60 mg/day). BILAG-2004 grade A scores in the renal and central nervous system domains were excluded. Patients were randomized 1:1:1 to receive either placebo, epratuzumab 600 mg every week, or epratuzumab 1,200 mg every other week, with infusions delivered for the first 4 weeks of each 12-week dosing cycle, for 4 cycles. Patients across all 3 treatment groups also continued with their standard therapy. The primary end point was the response rate at week 48 according to the BILAG-based Combined Lupus Assessment (BICLA) definition, requiring improvement in the BILAG-2004 score, no worsening in the BILAG-2004 score, SLEDAI-2K score, or physician's global assessment of disease activity, and no disallowed changes in concomitant medications. Patients who discontinued the study medication were classified as nonresponders.

Results. **In the EMBODY 1 and EMBODY 2 trials of epratuzumab, 793 patients and 791 patients, respectively, were randomized, 786 (99.1%) and 788 (99.6%), respectively, received study medication, and 528 (66.6%) and 533 (67.4%), respectively, completed the study. There was no statistically significant difference in the primary end point between the groups, with the week 48 BICLA response rates being similar between the epratuzumab groups and the placebo group (response rates ranging from 33.5% to 39.8%). No new safety signals were identified.**

Conclusion. **In patients with moderate or severely active SLE, treatment with epratuzumab + standard therapy did not result in improvements in response rates over that observed in the placebo + standard therapy group.**

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease (1) that most frequently affects the musculoskeletal, mucocutaneous, hematologic, and renal systems (2). The disease commonly follows a relapsing–remitting pattern, with flares of high disease activity followed by temporary reductions in symptoms. Therapeutic options are limited. Corticosteroids, often at high doses, form the cornerstone of treatment. Their long-term use at high doses (e.g., use of oral prednisone at a dosage of 0.5–1.0 mg/kg/day) is associated with significant complications, which may have a substantial impact on a patient's health and quality of life (3,4). Immunosuppressants and antimalarial drugs are frequently included in the patient's regimen, with the aim of reducing disease activity and limiting the long-term organ damage arising either from the disease itself or from corticosteroid use.

Recent advances in the understanding of SLE pathogenesis and the central role of B cells in the pathologic processes of the disease have led to the advent of biologic therapies for the management of lupus. One such therapy is epratuzumab, a humanized monoclonal antibody of the IgG1 class that targets CD22 on B cells, perturbing the B cell receptor signaling complex and resulting in the modulation of B cell activity without substantial reductions in the number of peripheral B cells (5,6).

Epratuzumab has been evaluated as a therapy for SLE in 12 sponsored clinical studies. In the 2 phase II/III double-blind, placebo-controlled ALLEVIATE studies (addressing the efficacy and safety of epratuzumab in patients with moderate/severe flaring SLE), the doses of epratuzumab used were based on body surface area, and clinical outcomes were measured using the British Isles Lupus Assessment Group (BILAG) improvement response. Patients receiving a dose of 360 mg/m^2 had improvements in the clinical signs and symptoms of SLE (7) as well as improvements in quality of life measures and reductions in their corticosteroid dose (8). In the phase IIb EMBLEM study (addressing the safety and efficacy of epratuzumab in patients with serologically positive active SLE), fixed doses of epratuzumab were investigated. This double-blind, placebo-controlled, dose-ranging and dose regimen–ranging study utilized a composite response index, the BILAG-based Combined Lupus Assessment (BICLA), which emphasizes improvement based on changes in the BILAG index, a measure of disease activity. The study comprised 1 dosing cycle, with the study drug administered over 4 weeks, and the primary end point was assessed at week 12. A positive treatment effect, compared to placebo, was seen in patients receiving epratuzumab at a cumulative dose of 2,400 mg. This dose was therefore carried forward into the phase III studies, using the 2 different dosing regimens studied in the phase IIb study (5,7,9).

In the present report, we present the results of the 2 phase III multicenter, randomized, placebo-controlled, double-blind EMBODY 1 and EMBODY 2 trials, which aimed to demonstrate the efficacy and safety of epratuzumab in the treatment of patients with moderately to severely active SLE.

PATIENTS AND METHODS

Patients. *Inclusion criteria.* Eligible patients were age ≥18 years and had a diagnosis of moderately to severely active SLE that fulfilled ≥4 of the 11 American College of Rheumatology (ACR) revised criteria for SLE (10) (if patients were

positive for a neurologic disorder, the diagnosis had to meet ≥5 of 11 ACR criteria). All patients had, at a minimum, disease activity in the musculoskeletal, mucocutaneous, or cardiorespiratory body systems, as defined by the 2004 version of the BILAG index (BILAG-2004) (11). Patients were required to have a BILAG-2004 grade A (severe disease activity) in ≥1 of these body systems or a BILAG-2004 grade B (moderate disease activity) in ≥2 of these body systems. In addition, all patients had to have an SLE Disease Activity Index 2000 (SLEDAI-2K) score of ≥6 (indicating increased disease activity) (12), and to be positive, at screening, for antinuclear antibodies (ANAs; titer ≥1:80) and/or anti–double-stranded DNA (anti-dsDNA) antibodies (defined as a positive result from either a multiplex immunoassay or the Farr assay).

Patients must have been receiving corticosteroids at a stable dosage of 5–60 mg/day (prednisone or equivalent) for at least 5 days (±1 day) prior to baseline. Antimalarials (hydroxychloroquine, chloroquine, or quinacrine) and immunosuppressants (azathioprine, mycophenolate mofetil, leflunomide, or methotrexate) were not mandatory but were permitted, whereas other immunosuppressants were excluded. Patients treated with these agents must have received them at a stable dose for at least 28 days (±1 day) prior to baseline.

Exclusion criteria. Patients with severe lupus nephritis or severe neuropsychiatric SLE at screening were excluded. Thus, BILAG-2004 grade A scores in these body systems (renal and neuropsychiatric domains) were not permitted (with the exception of patients achieving a BILAG-2004 neuropsychiatric grade A because of the presence of mononeuritis [single or multiple] and/or polyneuropathy, provided that this was not new or worsening at screening). Serum creatinine levels of >2.5 mg/dl, a clinically significant increase in the serum creatinine level within 4 weeks prior to screening, or proteinuria levels of >3.5 gm/day were also exclusion criteria.

Other exclusions included patients with known antiphospholipid syndrome, those who were pregnant or breastfeeding, those who had a profoundly immunosuppressed state, and those with significant hematologic abnormalities, active infections, a history of chronic infections, or a history of malignancies or thromboembolic events. Significant hematologic abnormalities (any laboratory finding of a hemoglobin level <8.0 gm/dl, a white blood cell count <2,000/mm^3, an absolute neutrophil count <1,500/mm^3, or a platelet count <30,000/mm^3) were not allowed. Furthermore, patients were excluded if they had received oral anticoagulants within 12 weeks prior to screening, cyclophosphamide within 6 months prior to screening, or calcineurin inhibitors within 4 weeks prior to screening. Previous use of biologic therapies was allowed, subject to an appropriate protocol-defined washout period before screening.

Study design. The EMBODY 1 and EMBODY 2 trials were identical phase III, multicenter, randomized, double-blind, placebo-controlled studies, with the only difference being the sites at which the studies took place (both studies included sites in North America, Latin America, Western Europe, Eastern Europe, and the Middle East and India; EMBODY 1 additionally included the Pacific region [Australia] and the Far East [Republic of Korea and Taiwan]; EMBODY 2 additionally included South Africa). All patients provided their written informed consent, and the studies received approval from the local institutional review boards/independent ethics committees.

The primary end point was the responder rate at week 48, according to the BICLA composite end point (13), which requires improvement from baseline in the BILAG-2004 score, with no worsening in the BILAG-2004 score, SLEDAI-2K score, or physician's global assessment of disease activity, and no disallowed changes in concomitant medications (discussed in more detail below).

The studies consisted of a 2-week screening period, followed by a 48-week double-blind treatment period, and a 4-week safety follow-up (13 weeks for patients discontinuing treatment prior to week 48). The sample size was selected to provide 90% power to detect a 15% higher response, based on the primary end point, in epratuzumab-treated patients compared to placebo-treated patients (5,7).

In each study, 780 patients were planned for randomization, and patients were randomized 1:1:1 through an interactive voice and web response system to 1 of 3 treatment arms: placebo, epratuzumab 600 mg every week, or epratuzumab 1,200 mg every other week. Infusions were delivered over a 4-week dosing period at the beginning of each 12-week treatment cycle, i.e., 600-mg infusions of epratuzumab given at weeks 0, 1, 2, and 3, or 1,200-mg infusions of epratuzumab given at weeks 0 and 2 (with infusions of placebo at weeks 1 and 3, to maintain blinding), or infusions of placebo at weeks 0, 1, 2, and 3 (Figure 1). This dosing pattern was repeated every 12 weeks for 4 cycles, with a final assessment at week 48. Assessments were performed at baseline, and then at weeks 4, 8, and 12 of each cycle. Patients who either remained in the study to completion at week 48 or withdrew at week 16 or later, due to lack of efficacy, were allowed to enroll in the open-label extension study (NCT01408576). The study drug was given in conjunction with the patients' existing standard therapy (all concomitant medications are described below).

All patients must have been approved for randomization by an external central reviewer to determine whether adequate disease activity was present. Randomization was stratified by geographic region (Eastern Europe, Western Europe, Middle East and India, Far East, North America, Latin America, and the Pacific) and by disease severity at baseline. Disease severity was determined using the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) (14), categorized as follows: 1) an SDI score of 0 and a BILAG-2004 grade A in <2 body systems, 2) an SDI score of >0 or a BILAG-2004 grade A in ≥2 body systems, or 3) an SDI score of >0 and a BILAG-2004 grade A in ≥2 body systems.

Concomitant medications. At baseline, all patients must have been receiving oral corticosteroids at a dosage of 5–60 mg/day (prednisone or equivalent). Between weeks 0 and 8, temporary increases in the dose of corticosteroids up to a maximum of 25% above baseline levels were permitted at the discretion of the investigator. Patients were classified as nonresponders if their corticosteroid dose remained above the baseline level after week 8. From week 4, tapering of oral corticosteroids was encouraged, at a rate of 5 mg every 2 weeks to a target dose of ≤7.5 mg/day. Corticosteroid dose changes were to be avoided within 4 weeks of the week 24 and week 48 assessments.

Patients receiving immunosuppressants and/or antimalarial agents had to continue their stable baseline dose throughout the study, unless there was suspected toxicity.

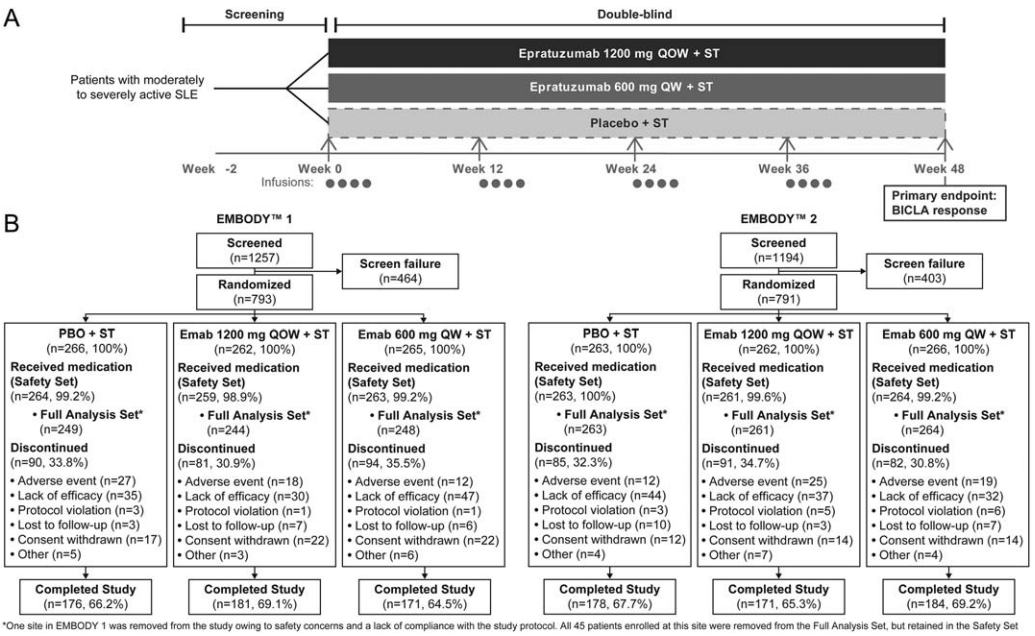


Figure 1. A, Design of the EMBODY studies on efficacy and safety of epratuzumab monoclonal antibody (Emab) treatment in patients with moderately to severely active systemic lupus erythematosus (SLE). **B,** Disposition of patients in the EMBODY 1 and EMBODY 2 trials. * = One site in EMBODY 1 was removed from the study owing to safety concerns and a lack of compliance with the study protocol; all 45 patients enrolled at this site were removed from the full analysis set, but retained in the safety set. QOW = every other week; ST = standard therapy; QW = every week; BICLA = British Isles Lupus Assessment Group–based Combined Lupus Assessment; PBO = placebo.

Patients changing their dose or starting a new immunosuppressant or antimalarial were considered nonresponders.

Study variables. The primary efficacy variable was the improvement response at week 48 based on the BICLA definition (13), which required all of the following criteria: improvement in the BILAG-2004 score (improvement in all BILAG-2004 grade A scores at study entry to grades B, C, or D at follow-up; improvement in all BILAG-2004 grade B scores at study entry to grades C or D at follow-up); no worsening in the BILAG-2004 score (no new BILAG-2004 grade A scores; no more than 1 new BILAG-2004 grade B score); no worsening (no increase) in the SLEDAI-2K total score, as compared to that at study entry; no worsening (<10-mm increase on a 100-mm visual analog scale) in the physician's global assessment of disease activity, as compared to that at study entry; and no disallowed changes in concomitant medications. The BILAG-2004 body system scores and SLEDAI-2K data were verified by a central review and adjudication committee to ensure consistent application of the assessments.

Secondary efficacy variables were the BICLA response rates at weeks 12, 24, and 36, and the change from baseline in daily corticosteroid doses at weeks 24 and 48.

Exploratory efficacy variables included each component of the BICLA composite end point, the BICLA response at time points other than those included in the primary and secondary end points, and changes from baseline in the BILAG-2004 total score (scores were converted from grades A, B, C, D, and E to scores of 12, 8, 1, 0, and 0, respectively) (15), changes from baseline in the SLEDAI-2K total score, changes from baseline in the patient's and physician's global assessments of disease activity (on 100-mm visual analog scales), and the average change from baseline in corticosteroid dose (calculated as the time-weighted area under the curve minus baseline, for baseline to week 48).

Analyses of patient-reported outcome measures included the proportions of patients who achieved a minimal clinically important difference (MCID) from baseline in the 36-item Short Form (SF-36) Health Survey physical and mental component summary scores (defined as a ≥2.5-point improvement) (16), mean changes from baseline in each of the LupusQoL health-related quality of life domains (17), mean changes from baseline in the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale (18), and the proportions of patients achieving an MCID (≥4-point increase) in the FACIT-F scale.

Time to a new flare was also determined, with a new flare defined as the development of a BILAG-2004 grade A in ≥1 body system from a previous grade of B, C, D, or E at baseline, or the development of a concurrent BILAG-2004 grade B in ≥2 body systems from a grade of C, D, or E at baseline (systems flaring at baseline were not included). Flares were based only on items that were new and were confirmed by the central review and adjudication committee.

Pharmacodynamic and immunologic variables included levels of CD19+ B cells, CD3+ T cells, CD19+CD22+ B cells, immunoglobulins, autoantibodies (anti-dsDNA), extractable nuclear antigen antibodies, and complement C3 and C4 proteins.

Statistical analysis. Efficacy variables were analyzed using the full analysis set, consisting of randomized patients who received at least one partial dose of study medication. One of the EMBODY 1 study sites was found, by an audit, to have failed to conduct the study in line with applicable regulations, International Conference on Harmonisation/

Good Clinical Practice Guidelines, and the study protocol, and consequently all 45 patients enrolled at that site were excluded from the full analysis set and the efficacy analyses. These patients were retained in the safety set, to provide complete safety data.

For determination of the primary end point, BICLA response rates were calculated using logistic regression, with patients who discontinued prior to week 48 or did not have a week 48 assessment being classified as nonresponders. In those cases in which single components of the BICLA (BILAG-2004 scores, SLEDAI-2K scores, or physician's global assessment of disease activity) were missing, the value was imputed from the previous visit value. Patients with disallowed changes in concomitant medications were classified as nonresponders from that time point forward.

In the primary analysis, *P* values for pairwise comparisons between each active treatment group and the placebo group were generated using a logistic regression model, including factors for pooled geographic region and disease severity at baseline. The Hochberg method was used to adjust for the comparison of the 2 doses of epratuzumab to placebo. The response rate based on the primary variable was also analyzed in an exploratory manner for subgroups of patients, including those defined by geographic region, body mass index, baseline disease severity, lupus-associated laboratory parameters, and concomitant medication use at baseline. Subgroup analyses were not adjusted for multiplicity. Odds ratios and corresponding 95% confidence intervals were calculated for each epratuzumab treatment group compared to placebo, using logistic regression models that included factors for treatment, pooled region, and baseline disease status, as well as for the subgroup being analyzed and the treatment-by-subgroup interaction.

Five key secondary efficacy variables were tested for statistical significance according to a hierarchical testing procedure, with Hochberg adjustment for multiplicity within each step of the procedure. BICLA response rates at weeks 36, 24, and 12 were calculated and analyzed using the same methods as those used for response rates at week 48. The key secondary end points for the corticosteroid dose were ordered categorical end points (patients were categorized according to their change in daily corticosteroid dose, defined as a >50% decrease, 0–50% decrease, no change, or an increase in dose or missing data), analyzed using nonparametric rank analysis of covariance, with missing values imputed as the worst possible outcome. All other secondary and exploratory efficacy variables were summarized using descriptive statistics, with missing data imputed using last observation carried forward for continuous variables or nonresponder imputation for dichotomous variables.

The SLE Responder Index (SRI) at week 48, which was originally categorized as a ≥4-point (SRI-4), ≥6-point (SRI-6), or ≥8-point (SRI-8) reduction in score on the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLEDAI (SELENA-SLEDAI) (19), were analyzed post hoc, with modifications from the original SRI end point definition to include the variables used in the EMBODY studies, i.e., improvement in the SLEDAI-2K scores, BILAG-2004 scores, and the physician's global assessment of disease activity (instead of the SRI-4 calculated from the SELENA-SLEDAI, the classic BILAG index, and the physician's global assessment of disease activity). To be considered a responder in our SRI analyses, patients must have achieved all of the following: improvement in the SLEDAI-2K score of at least 4, 6, or 8 points (SRI-4, SRI-6, and SRI-8, respectively) from study entry; no worsening in the BILAG-2004 total score (no new BILAG-2004 grade A scores, no more than 1 new BILAG-2004 grade B score); no worsening (<10-mm increase on a 100-mm visual analog scale) in the physician's global assessment of disease activity, compared to that at study entry; and no disallowed changes in concomitant medications at any time point from baseline. Missing data were imputed using modified nonresponder imputation, as was used for the primary end point.

Safety and immunologic variables were analyzed using the safety set. These variables were summarized with descriptive statistics.

RESULTS

Disposition of the patients and baseline characteristics. In the EMBODY 1 trial, 1,257 patients were screened, and 793 were randomized. In the EMBODY 2 trial, 1,194 patients were screened, and 791 were randomized. The majority of patients failed screening because they were deemed ineligible on the basis of the inclusion and exclusion criteria (367 of 464 screen failures in the EMBODY 1 trial, and 315 of 403 screen failures in the EMBODY 2 trial). Other reasons for exclusion included occurrence of adverse events, loss to follow-up, and withdrawal of consent during the screening period.

Overall, 265 patients (33.4%) in EMBODY 1 and 258 (32.6%) in EMBODY 2 discontinued from the studies, most commonly due to lack of efficacy (112 patients in EMBODY 1, and 113 patients in EMBODY 2). One study site in the EMBODY 1 trial was removed due to protocol violations, and all 45 patients randomized at that site were removed from the full analysis set. Despite this, discontinuations were balanced across the treatment groups and across the studies (range of discontinuations across groups 30.9–35.5% in EMBODY 1, and 30.8–34.7% in EMBODY 2) (Figure 1).

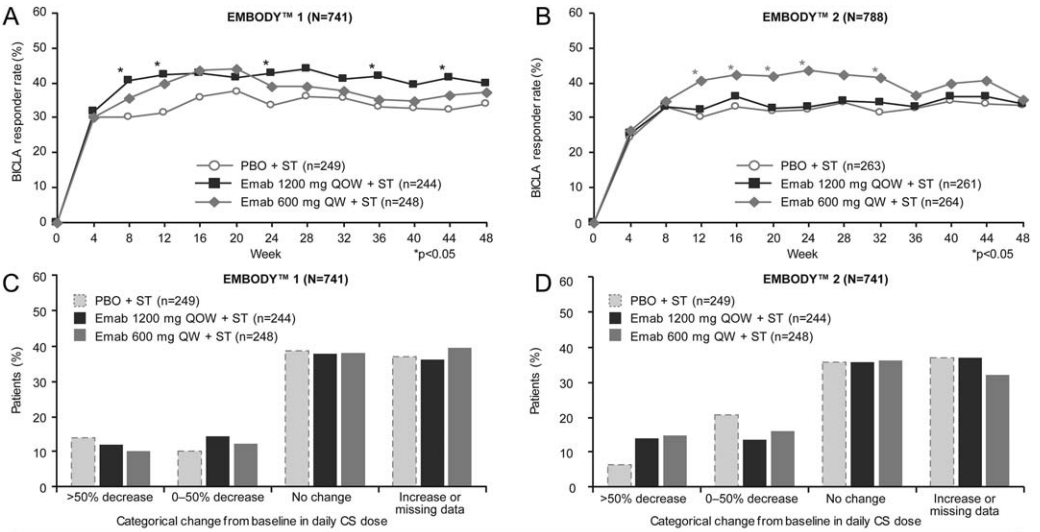
Patient characteristics at baseline were also balanced between the 2 studies (Table 1). More than 90% of patients were female, and the mean age was 42.1 years in EMBODY 1 and 41.0 years in EMBODY 2. Time since diagnosis ranged from 0 years to 43 years, with a median of 6.3 years in EMBODY 1 and 5.1 years in EMBODY 2. The mean ± SD daily corticosteroid dosage was 11.2 ± 8.8 mg/day in EMBODY 1 and 13.0 ± 9.6 mg/day in EMBODY 2, with 45.1% of patients in EMBODY 1 and 36.0% of patients in EMBODY 2 receiving a dosage of ≤7.5 mg/day. The proportion of patients receiving antimalarials at baseline was slightly lower in EMBODY 2 than in EMBODY 1 (72.5% of patients in EMBODY 1 versus 63.6% of patients in EMBODY 2).

Table 1. Patient demographics and disease characteristics at baseline in the EMBODY 1 and EMBODY 2 trials*

	EMBODY 1			EMBODY 2		
	Placebo + standard therapy (n = 249)	Emab (1,200 mg QOW) + standard therapy (n = 244)	Emab (600 mg QW) + standard therapy (n = 248)	Placebo + standard therapy (n = 263)	Emab (1,200 mg QOW) + standard therapy (n = 261)	Emab (600 mg QW) + standard therapy (n = 264)
Age, mean ± SD years	41.2 ± 12.8	42.2 ± 11.7	42.2 ± 11.4	41.1 ± 11.8	40.8 ± 11.5	41.2 ± 12.7
Female	237 (95.2)	228 (93.4)	226 (91.1)	245 (93.2)	247 (94.6)	245 (92.8)
Race						
Asian	26 (10.4)	22 (9.0)	18 (7.3)	7 (2.7)	7 (2.7)	12 (4.5)
Black/African American	26 (10.4)	32 (13.1)	33 (13.3)	25 (9.5)	29 (11.1)	34 (12.9)
White	187 (75.1)	178 (73.0)	188 (75.8)	204 (77.6)	198 (75.9)	193 (73.1)
Hispanic/Latino	50 (20.1)	52 (21.3)	44 (17.7)	56 (21.3)	50 (19.2)	50 (18.9)
Years since diagnosis, median (range)	5.8 (0–36)	7.3 (0–34)	6.1 (0–43)	5.7 (0–37)	5.0 (0–29)	4.8 (0–42)
Physician-reported measure						
SLEDAI-2K total score, mean ± SD	10.7 ± 4.1	9.9 ± 3.7	10.2 ± 3.6	10.1 ± 3.6	10.1 ± 3.8	10.2 ± 3.6
PhGA, mean ± SD	55.5 ± 12.9	55.7 ± 14.3	56.5 ± 14.9	56.2 ± 14.4	57.2 ± 14.0	57.3 ± 15.6
Patients with ≥1 BILAG-2004 grade A	139 (55.8)	142 (58.2)	147 (59.3)	157 (59.7)	148 (56.7)	161 (61.0)
BILAG-2004 total score, mean ± SD†	20.0 ± 5.5	19.8 ± 5.9	19.6 ± 5.6	21.0 ± 6.7	21.3 ± 6.6	21.0 ± 6.7
Patient-reported measure						
PtGA, mean ± SD	58.3 ± 19.2	58.5 ± 19.1	58.1 ± 20.2	58.6 ± 19.6	60.2 ± 19.0	59.1 ± 18.9
SF-36, mean ± SD						
PCS score	35.0 ± 9.2	34.2 ± 10.1	34.2 ± 8.0	34.6 ± 9.7	34.9 ± 8.8	35.2 ± 9.5
MCS score	38.3 ± 11.8	38.0 ± 11.3	37.8 ± 13.4	37.9 ± 12.0	37.9 ± 12.6	38.0 ± 11.9
FACIT-F score, mean ± SD	24.4 ± 12.0	24.1 ± 11.7	23.6 ± 10.7	24.3 ± 11.5	24.1 ± 11.4	25.3 ± 11.4
Concomitant medication						
Immunosuppressant	116 (46.6)	123 (50.4)	112 (45.2)	121 (46.0)	113 (43.3)	129 (48.9)
Azathioprine	53 (21.3)	52 (21.3)	41 (16.5)	48 (18.3)	51 (19.5)	56 (21.2)
Leflunomide	1 (0.4)	3 (1.2)	7 (2.8)	3 (1.1)	6 (2.3)	6 (2.3)
Methotrexate	41 (16.5)	49 (20.1)	41 (16.5)	40 (15.2)	39 (14.9)	45 (17.0)
Mycophenolate	22 (8.8)	29 (11.4)	30 (12.1)	38 (14.4)	32 (12.3)	34 (12.9)
Antimalarial	175 (70.3)	181 (74.2)	181 (73.0)	162 (61.6)	160 (61.3)	179 (67.8)
Corticosteroid	248 (99.6)	241 (98.8)	247 (99.6)	256 (97.3)	257 (98.5)	263 (99.6)
0–≤7.5 mg/day	120 (48.2)	112 (45.9)	102 (41.1)	97 (36.9)	88 (33.7)	99 (37.5)
7.5–≤20 mg/day	117 (47.0)	105 (43.0)	131 (52.8)	137 (52.1)	142 (54.4)	135 (51.1)
>20 mg/day	11 (4.4)	24 (9.8)	14 (5.6)	22 (8.4)	27 (10.3)	29 (11.0)
Laboratory parameter						
ANAs >1:80	216 (86.7)	212 (86.9)	218 (87.9)	231 (87.8)	232 (88.9)	233 (88.3)
Anti-dsDNA positive	133 (53.4)	126 (51.6)	131 (52.8)	143 (54.4)	126 (48.3)	134 (50.8)
Low complement levels	115 (46.2)	104 (42.6)	110 (44.4)	125 (47.5)	122 (46.7)	134 (50.8)

* Except where indicated otherwise, values are the number (%) of patients. Emab = epratuzumab monoclonal antibody; QOW = every other week; QW = every week; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; PhGA = physician's global assessment of disease activity (on 0–100-mm visual analog scale); PtGA = patient's global assessment of disease activity (on 0–100-mm visual analog scale); SF-36 = 36-item Short Form; PCS = physical component summary; MCS = mental component summary; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; ANAs = antinuclear antibodies; anti-dsDNA = anti–double-stranded DNA.

† The British Isles Lupus Assessment Group 2004 index (BILAG-2004) was calculated as follows: A = 12, B = 8, C = 1, D = 0, and E = 0.



E

	EMBODY™ 1 (N=741)			EMBODY™ 2 (N=788)		
	PBO + ST	Emab 1200 mg QOW + ST	Emab 600 mg QW + ST	PBO + ST	Emab 1200 mg QOW + ST	Emab 600 mg QW + ST
Average change from baseline in daily CS dose, mg/day, mean (SD)	-0.5 (5.7)	-0.7 (8.6)	-0.5 (6.8)	-1.3 (5.9)	-1.3 (7.8)	-1.4 (5.3)

Figure 2. BICLA responder rates by treatment group in the EMBODY 1 trial **(A)** and EMBODY 2 trial **(B)**, and week 48 change from baseline in daily corticosteroid (CS) dose in EMBODY 1 **(C)** and EMBODY 2 **(D)**, as well as average change from baseline **(E)**. See Figure 1 for other definitions.

At baseline, 428 patients (57.8%) in EMBODY 1 and 466 patients (59.1%) in EMBODY 2 had a BILAG-2004 grade A in ≥1 body system, while 371 patients (50.1%) in EMBODY 1 and 411 patients (52.2%) in EMBODY 2 had a BILAG-2004 grade B in ≥2 body systems. Most patients had moderate-to-severe disease activity in the musculoskeletal and mucocutaneous body systems: for the musculoskeletal system, BILAG-2004 grades A or B were present in 92.2% of EMBODY 1 patients and 93.5% of EMBODY 2 patients; for the mucocutaneous system, BILAG-2004 grades A or B were present in 80.3% of EMBODY 1 patients and 83.0% of EMBODY 2 patients. Other patient characteristics were also similar across treatment groups (Table 1).

Efficacy. The primary end point was not met in either study. At week 48, improvements in disease activity, as measured by the BICLA response rates, occurred in similar proportions of patients across treatment groups; no significant differences were seen in the proportion of responders between patients receiving placebo + standard therapy and those receiving either dose of epratuzumab + standard therapy (Figures 2A and B). In the EMBODY 1 study, BICLA response rates were 34.1% in the placebo + standard therapy group, 39.8% in the epratuzumab 1,200 mg every other week + standard therapy group ($P = 0.175$ versus placebo), and 37.5% in the epratuzumab 600 mg every week + standard therapy group ($P = 0.442$ versus placebo). In the EMBODY 2 study, BICLA response rates were 33.5% in the placebo + standard therapy group, 34.1% in the epratuzumab 1,200 mg every other week + standard therapy group ($P = 0.899$ versus placebo), and 35.2% in the epratuzumab 600 mg every week + standard therapy group ($P = 0.716$ versus placebo).

In the EMBODY 1 trial, 87 patients who received placebo (34.9%) and 160 patients who received epratuzumab (32.5%) did not achieve a treatment response at week 48, which was attributed to early withdrawal or missing data. Moreover, 54 patients in the placebo group (21.7%) and 134 patients in the epratuzumab groups (27.2%) were classified as nonresponders as a result of disallowed changes in concomitant medications (predominantly, disallowed increases in the dose of corticosteroids; patients may have had more than one reason for a nonresponse). In the EMBODY 2 trial, 84 patients who received placebo (31.9%) and 166 patients who received epratuzumab (31.6%) had missing data or withdrew early from the study. Moreover, 60 patients in the placebo group (22.7%) and 119 patients in the epratuzumab groups (22.7%) had prohibited medication changes (again, primarily increases in the dose of corticosteroids, with more than one reason for a nonresponse being possible).

Rapid improvements from baseline were initially seen in both the placebo group and the epratuzumab dosing groups in both studies. At several time points,

Table 2. Efficacy outcomes at week 48*

	EMBODY 1			EMBODY 2		
	Placebo + standard therapy (n = 249)	Emab (1,200 mg QOW) + standard therapy (n = 244)	Emab (600 mg QW) + standard therapy (n = 248)	Placebo + standard therapy (n = 263)	Emab (1,200 mg QOW) + standard therapy (n = 261)	Emab (600 mg QW) + standard therapy (n = 264)
Clinical outcomes						
BICLA response rate	85 (34.1)	97 (39.8)	93 (37.5)	88 (33.5)	89 (34.1)	93 (35.2)
BILAG-2004 index						
Improvement and no worsening	103 (41.4)	126 (51.6)	120 (48.4)	115 (43.7)	104 (39.8)	110 (41.7)
Average CFB in total score, LS mean ± SD	−8.6 ± 6.3	−9.8 ± 6.5	−9.1 ± 6.4	−8.1 ± 6.7	−9.1 ± 7.6	−9.6 ± 6.6
SLEDAI-2K score						
Average CFB in total score, LS mean ± SD	−3.6 ± 4.8	−3.8 ± 4.2	−3.6 ± 4.5	−3.3 ± 4.2	−3.5 ± 4.6	−3.9 ± 4.3
No worsening	228 (91.6)	221 (90.6)	228 (91.9)	234 (89.0)	230 (88.1)	242 (91.7)
PhGA						
Average CFB, LS mean ± SD mm	−23.8 ± 22.2	−25.6 ± 22.4	−21.9 ± 24.2	−22.3 ± 23.9	−23.7 ± 22.6	−26.0 ± 23.2
No worsening	228 (1.6)	229 (93.9)	223 (90.3)	228 (87.0)	236 (91.1)	247 (94.3)
Concomitant medication use, no disallowed changes	195 (78.3)	175 (71.7)	183 (73.8)	203 (77.2)	198 (75.9)	208 (78.8)
SRI-4 response rate	89 (35.7)	93 (38.1)	83 (33.5)	85 (32.3)	91 (34.9)	96 (36.4)
Patient-reported outcomes						
PtGA, average CFB, LS mean ± SD mm	−15.5 ± 27.1	−17.1 ± 28.1	−15.7 ± 28.1	−13.7 ± 28.0	−16.8 ± 27.6	−17.5 ± 29.3
SF-36 score						
MCID in PCS	119 (48.6)	129 (54.0)	125 (50.4)	117 (45.0)	125 (48.8)	134 (51.7)
MCID in MCS	116 (47.3)	116 (48.5)	102 (41.1)	121 (46.5)	115 (44.9)	106 (40.9)
Stabilization/lack of deterioration	53 (21.6)	70 (29.3)	65 (26.2)	63 (24.2)	62 (24.2)	67 (25.9)
FACIT-F score						
LS mean ± SD	4.0 ± 10.1	4.2 ± 9.9	3.8 ± 10.4	2.6 ± 9.3	2.6 ± 10.1	2.6 ± 10.0
MCID	110 (44.5)	110 (45.8)	105 (43.0)	110 (42.6)	113 (44.1)	116 (44.8)

* Except where indicated otherwise, values are the number (%) of patients. BICLA = British Isles Lupus Assessment Group–based Combined Lupus Assessment; CFB = change from baseline; LS = least squares; SRI-4 = Systemic Lupus Erythematosus Disease Activity Index Responder Index 4-point improvement; MCID = minimal clinically important difference (see Table 1 for other definitions).

Table 3. Immunologic outcomes at week 48*

	EMBODY 1			EMBODY 2		
	Placebo + standard therapy (n = 249)	Emab (1,200 mg QOW) + standard therapy (n = 244)	Emab (600 mg QW) + standard therapy (n = 248)	Placebo + standard therapy (n = 263)	Emab (1,200 mg QOW) + standard therapy (n = 261)	Emab (600 mg QW) + standard therapy (n = 264)
CD19+ B cells, % CFB, median (range) cells/μl	−9.7 (−93, 783) (n = 175)	−31.5 (−100, 1,800) (n = 179)	−36.5 (−94, 24,500) (n = 169)	−10.2 (−100, 1,367) (n = 178)	−32.7 (−97, 24,500) (n = 173)	−37.7 (−96, 646) (n = 184)
CD3+ T cells, % CFB, median (range) cells/μl	−3.0 (−85, 1,106) (n = 175)	5.3 (−78, 974) (n = 180)	−3.2 (−65, 359) (n = 169)	0.9 (−83, 856) (n = 178)	3.8 (−80, 301) (n = 173)	−3.2 (−85, 1,364) (n = 184)
% of CD22+ WBCs, CFB, mean ± SD†	−1.4 ± 2.7 (n = 2)	−60.8 ± 36.4 (n = 2)	–	2.7 ± 6.2 (n = 10)	−56.6 ± 31.7 (n = 16)	−61.8 ± 24.6 (n = 18)
IgA, % CFB, median (range) gm/liter	3.0 (−42.7, 113.2) (n = 175)	6.5 (−39.5, 64.4) (n = 178)	4.1 (−79.8, 536.0) (n = 168)	3.6 (−56.2, 59.5) (n = 175)	7.9 (−61.1, 858.3) (n = 172)	4.3 (−79.2, 119.2) (n = 183)
IgG, % CFB, median (range) gm/liter	0.9 (−88.7, 143.5) (n = 175)	0.8 (−53.5, 94.1) (n = 178)	2.3 (−48.8, 128.1) (n = 168)	2.2 (−51.9, 79.6) (n = 175)	3.6 (−42.5, 857.6) (n = 172)	1.6 (−77.2, 65.2) (n = 183)
IgM, % CFB, median (range) gm/liter,	0.8 (−53.0, 98.2) (n = 174)	−18.7 (−65.4, 142.7) (n = 178)	−22.0 (−85.4, 185.7) (n = 168)	0 (−75.8, 200.0) (n = 175)	−17.7 (−83.8, 712.5) (n = 172)	−20.0 (−70.0, 53.3) (n = 183)
Reduction in anti-dsDNA, no. (%)‡	11 (6.4) (n = 47)	12 (6.7) (n = 47)	7 (4.2) (n = 38)	17 (9.7) (n = 44)	14 (8.2) (n = 45)	11 (6.0) (n = 39)
ANA shift from positive to negative, no. (%)§	8 (4.9) (n = 162)	3 (1.7) (n = 173)	5 (3.1) (n = 163)	7 (4.1) (n = 169)	12 (7.4) (n = 162)	8 (4.5) (n = 176)
C3 normalization, no. (%)¶	11 (22.4) (n = 49)	11 (24.4) (n = 45)	8 (20.5) (n = 39)	12 (21.4) (n = 56)	12 (24.5) (n = 49)	11 (20.8) (n = 53)
C4 normalization, no. (%)¶	14 (21.9) (n = 64)	12 (21.8) (n = 55)	6 (12.5) (n = 48)	5 (7.7) (n = 65)	15 (22.4) (n = 67)	15 (18.8) (n = 80)

* CFB = change from baseline; WBCs = white blood cells (see Table 1 for other definitions).
† CD19+CD22+ cells, as a percentage of CD19+ cells, were measured in a subset of patients.
‡ Reduction in anti-dsDNA is defined as reverting to negative in only patients testing positive via standard assay at baseline.
§ Positive ANA values are defined as those above the lower limit of quantification, and negative values are those below the lower limit of quantification. Only patients testing positive at baseline are shown.
¶ Only patients with low baseline levels are shown.

including weeks 12, 24, and 36, a trend toward improvement in epratuzumab-treated patients over placebo was seen, with nominally significant differences between the placebo + standard therapy group and the epratuzumab + standard therapy treatment groups (i.e., $P < 0.05$ versus placebo, without adjustment for multiple comparisons). However, results were not consistent between the 2 studies, with the patients receiving epratuzumab 1,200 mg every other week + standard therapy showing a generally greater response in the EMBODY 1 trial, and those receiving epratuzumab 600 mg every week + standard therapy showing a greater response in the EMBODY 2 trial. Analyses of the primary efficacy variable in predefined subgroups of subjects defined by geographic region, ethnicity, immunologic parameters, and concomitant medication usage at baseline yielded results similar to those observed in the overall population. Higher levels of treatment efficacy were not observed in any of these subgroups (see Supplementary Figures 1 and 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39856/abstract).

Various sensitivity analyses were performed to assess the robustness of the study results, focusing on study protocol adherence, handling of missing data, and misstratification. The results of these sensitivity analyses were generally consistent with the primary study results, as was an analysis including only those patients completing the studies to week 48. Similarly, a post hoc analysis using an adjusted BICLA definition of response, in which the BILAG-2004 scores, SLEDAI-2K scores, and physician's global assessment of disease activity components were retained but the rules regarding disallowed changes in concomitant medications were omitted, did not show any major difference in response rates between the treatment groups.

Other key secondary end points also showed no differences between the treatment groups. At weeks 48 and 24, similar proportions of patients in each treatment group achieved reductions in the daily corticosteroid dose (Figures 2C and D). At week 48, ~40% of patients, irrespective of treatment group, had no change in their corticosteroid dose relative to baseline (range across groups 37.7–38.6% in EMBODY 1, and 35.6–36.7% in EMBODY 2). Correspondingly, although the average reductions in daily corticosteroid dose were greater in EMBODY 2 than in EMBODY 1, within each study, the average dose reductions from baseline that patients were able to achieve were similar across the treatment groups (Figure 2E).

Improvements were seen across a multitude of exploratory end points, including improvements in the BILAG-2004 scores, SLEDAI-2K scores, and physician's and patient's global assessments of disease activity (see Supplementary Figures 3 and 4, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39856/abstract), as well as improvements in patient-reported outcomes such as the SF-36 and FACIT-F scores (Table 2), and the LupusQoL scores (see Supplementary Figure 5, http://onlinelibrary.wiley.com/doi/10.1002/art.39856/abstract). However, in all cases, improvements were comparable between the placebo group and the epratuzumab-treated groups (Table 2 and Supplementary Figures 3, 4, and 5).

New flares in disease activity (i.e., lower BILAG-2004 scores at baseline developing to a new BILAG-2004 grade A in ≥1 body system or a concurrent new BILAG-2004 grade B in ≥2 body systems at follow-up, among items recorded as new) occurred at a similar rate across the treatment groups, both among all patients irrespective of the treatment response and among those patients who had previously achieved an improvement in their BILAG-2004 score.

A post hoc analysis using the modified SRI response criteria consistently failed to detect any differences in response between the placebo group and the epratuzumab treatment groups, at either the SRI-4, SRI-6, or SRI-8 levels of improvement in SLEDAI scores.

Immunologic response. Consistent with the findings of previous studies (5), a median reduction of 30–40% in peripheral B cell levels was seen in epratuzumab-treated patients, but not in placebo-treated patients (Table 3). These changes occurred rapidly, with reductions in peripheral B cell levels of ~20% in the first 4 weeks of treatment, followed by a gradual decline in B cell numbers up to week 48. Levels of T cells, IgA, and IgG were stable throughout the studies, with only minor fluctuations from baseline and no consistent trends. Levels of IgM decreased by ~20% from baseline in epratuzumab-treated patients in both studies (Table 3).

Safety. In both studies, the incidence of adverse events was comparable between the placebo and epratuzumab treatment groups (Table 4). Treatment-emergent adverse events occurred in 79.9–88.0% of patients across all treatment groups, the most common being upper respiratory tract infections, urinary tract infections, headache, and nausea. Serious adverse events occurred in 17.0–18.9% of patients (Table 4). The only serious adverse event that occurred in ≥2% of patients was worsening of SLE, reported in 1.1–2.7% of patients across the treatment groups.

Table 4. Safety data*

	EMBODY 1			EMBODY 2		
	Placebo + standard therapy (n = 263)	Emab (1,200 mg QOW) + standard therapy (n = 259)	Emab (600 mg QW) + standard therapy (n = 264)	Placebo + standard therapy (n = 263)	Emab (1,200 mg QOW) + standard therapy (n = 261)	Emab (600 mg QW) + standard therapy (n = 264)
Exposure duration, mean ± SD days	295.4 ± 87.9	302.6 ± 82.6	296.8 ± 83.4	297.6 ± 83.9	295.9 ± 85.1	306.0 ± 77.0
Total exposure, patient-years	212.7	214.6	214.6	214.3	211.5	221.2
Any TEAEs, no. (%)†	222 (84.4)	228 (88.0)	211 (79.9)	225 (85.6)	220 (84.3)	230 (7.1)
Blood and lymphatic system disorders	17 (6.5)	19 (7.3)	18 (6.8)	36 (13.7)	24 (9.2)	31 (11.7)
Gastrointestinal disorders	73 (27.8)	87 (33.6)	90 (34.1)	79 (30.0)	81 (31.0)	78 (29.5)
Nausea	23 (8.7)	30 (11.6)	39 (14.8)	36 (13.7)	32 (12.3)	25 (9.5)
General disorders and administration site conditions	48 (18.3)	51 (19.7)	53 (20.1)	71 (27.0)	49 (18.8)	50 (18.9)
Infections and infestations	157 (59.7)	151 (58.3)	148 (56.1)	158 (60.1)	135 (51.7)	160 (60.6)
Upper respiratory tract infection	30 (11.4)	32 (12.4)	32 (12.1)	37 (14.1)	38 (14.6)	37 (14.0)
Urinary tract infection	30 (11.4)	25 (9.7)	30 (11.4)	46 (17.5)	37 (14.2)	38 (14.4)
Herpes zoster	5 (1.9)	10 (3.9)	6 (2.3)	8 (3.0)	3 (1.1)	8 (3.0)
Pulmonary tuberculosis	0	0	0	0	0	1 (0.4)
Injury, poisoning, and procedural complications	32 (12.2)	28 (10.8)	36 (13.6)	42 (16.0)	33 (12.6)	38 (14.4)
Investigations	28 (10.6)	39 (15.1)	34 (12.9)	26 (9.9)	29 (11.1)	33 (12.5)
Metabolism and nutrition disorders	19 (7.2)	19 (7.3)	25 (9.5)	18 (6.8)	24 (9.2)	27 (10.2)
Musculoskeletal and connective tissue disorders	67 (25.5)	90 (34.7)	62 (23.5)	75 (28.5)	77 (29.5)	65 (24.6)
Nervous system disorders	58 (22.1)	75 (29.0)	72 (27.3)	77 (29.3)	64 (24.5)	72 (27.3)
Headache	29 (11.0)	34 (13.1)	38 (14.4)	45 (17.1)	29 (11.1)	34 (12.9)
Psychiatric disorders	34 (12.9)	32 (12.4)	36 (13.6)	32 (12.2)	31 (11.9)	38 (14.4)
Renal and urinary disorders	21 (8.0)	22 (8.5)	15 (5.7)	27 (10.3)	13 (5.0)	16 (6.1)
Respiratory, thoracic, and mediastinal disorders	42 (16.0)	46 (17.8)	42 (15.9)	54 (20.5)	44 (16.9)	55 (20.8)
Skin and subcutaneous tissue disorders	47 (17.9)	44 (17.0)	44 (16.7)	51 (19.4)	47 (18.0)	41 (15.5)
Vascular disorders	23 (8.7)	33 (12.7)	24 (9.1)	25 (9.5)	27 (10.3)	37 (14.0)
Serious TEAEs	48 (18.3)	44 (17.0)	45 (17.0)	45 (17.1)	45 (17.2)	50 (18.9)
Worsening of SLE	3 (1.1)	5 (1.9)	3 (1.1)	7 (2.7)	6 (2.3)	6 (2.3)
Drug-related TEAEs	71 (27.0)	77 (29.7)	64 (24.2)	84 (31.9)	97 (37.2)	87 (33.0)
Deaths	1 (0.4)	2 (0.8)	2 (0.8)	3 (1.1)	1 (0.4)	0

* Except where indicated otherwise, values are the number (%) of patients. SLE = systemic lupus erythematosus (see Table 1 for other definitions).
† Comprises treatment-emergent adverse events (TEAEs) occurring in ≥10% of patients in any treatment group, or those considered of special interest.

There were 5 deaths in the EMBODY 1 trial and 4 deaths in the EMBODY 2 trial (4 occurring in the placebo + standard therapy group and 5 occurring in the epratuzumab treatment groups). Deaths in the patients who received placebo were attributable to pneumonia (Australia), lupus myocarditis (India), SLE (Ukraine), and pneumothorax (Hungary). Deaths in the epratuzumab-treated patients were attributable to sepsis (2 patients [1 in the US, 1 in Brazil]), pulmonary embolism (Bulgaria), acute renal failure and septic shock (Taiwan), and pneumonia and pulmonary alveolar hemorrhage (Brazil).

DISCUSSION

In both of these phase III trials, the observed immunologic effects of epratuzumab treatment were as expected for this agent, based on previous observations (5). Treatment of patients with moderately to severely active SLE with epratuzumab led to reductions in the levels of CD22, with the number of B cells in the peripheral blood decreasing by ~30–40% and IgM levels decreasing by 20%. However, treatment with epratuzumab in conjunction with standard therapy did not result in improved efficacy outcomes at week 48 as compared to treatment with placebo in conjunction with standard therapy; neither of these phase III studies achieved statistically significant differences in the primary end point. Across a multiplicity of end points, including clinical parameters, corticosteroid use, and patient-reported outcomes, no increased benefit from the addition of epratuzumab treatment to standard care was detected. The planned and exploratory analyses suggested that this was not a failure of the BICLA composite end point or the study design, but rather a failure of the study drug and/or the regimens tested.

The treatment differences observed in these studies were far lower than those seen in the phase IIb EMBLEM study, in which 21% of patients who received placebo and 40–45% of patients who received 1,200 mg epratuzumab every other week or 600 mg epratuzumab every week achieved a response at week 12 (compared to response rates in the present study of 34% of patients who received placebo and 34–40% of patients who received epratuzumab). Several factors can be hypothesized to have influenced the analysis of the primary end point at week 48 in the EMBODY studies.

First, the rate of discontinuation was higher and earlier than expected across all treatment groups, mainly due to a perceived lack of efficacy as assessed by the investigator and a desire to enter the open-label extension study. Approximately one-third of patients discontinued the study prior to week 48, and therefore were classified as nonresponders. Discontinuations from the studies were generally low from week 0 to week 16, but increased at weeks 20 and 24, which were the first visits at which patients were allowed to enroll in the open-label study. Some separation of improvement with epratuzumab as compared to placebo was visible in both studies at time points prior to week 48 (although it should be noted that differences were not consistent between the studies). However, sensitivity analyses conducted using alternate methods of imputation for missing data were consistent with those of the primary analysis, and did not detect any significant differences in BICLA response rates between the placebo group and the epratuzumab treatment groups at week 48.

Second, evident in nearly all of the end points examined were the high placebo response rates in these trials. This in itself may be informative, suggesting that with ongoing monitoring and regular attention from their care teams, patients are likely to experience greater improvements in their disease activity than would otherwise be the case. This phenomenon has been described previously in the TICORA study (Tight Control for Rheumatoid Arthritis), in which a program of intensive outpatient management resulted in improvements in disease when compared to routine care (20). Although further studies are needed to formally explore this notion, the data herein suggest that the same may be true in other chronic diseases such as SLE. Although the doses of corticosteroids used initially were not as high as some previous trials, it is notable that ~40% of patients did not reduce their dosage of corticosteroids during the EMBODY trials, and another 40% increased their dosage or had missing data.

The kinetics of response to epratuzumab are likely to be complex, and its mechanism of action is not fully understood, but based on the phase IIb EMBLEM trial data, the doses chosen were expected to be efficacious (5,6). It is possible that the doses or dosing regimens adopted in these trials were not optimal. In the phase IIb EMBLEM trial, it was noted that the dose-response followed a bell-shaped curve, with the highest dose of medication eliciting a smaller clinical response than more moderate doses (5). The data presented herein do not formally exclude the possibility of a subgroup of responders, but none of the analyses conducted were able to identify this subset, although mean B cell numbers and IgM levels were reduced in epratuzumab-treated patients.

Clinical trials of biologic agents in SLE have generally been met with failure. To date, only one agent, belimumab, which inhibits the activity of soluble B

lymphocyte stimulator, is licensed for use in active and autoantibody-positive SLE in the US and Europe (21), having met its primary end points in 2 phase III trials (22,23). Even in these trials, there was a higher than expected placebo response, and one of the trials only just marginally showed a significant difference in favor of belimumab (22,23). The failure of the EMBODY studies, as well as studies of other agents that have suffered similar fates (24–28), highlights the tremendous challenges of drug development research in SLE.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Clowse had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Clowse, Wallace, Furie, Petri, Pike, Leszczyński, Neuwelt, Hobbs, Keiserman, Duca, Kalunian, Stach, Beaudot, Kilgallen, Gordon.

Analysis and interpretation of data. Clowse, Wallace, Furie, Petri, Pike, Leszczyński, Neuwelt, Hobbs, Keiserman, Duca, Kalunian, Galateanu, Bongardt, Stach, Beaudot, Kilgallen.

ROLE OF THE STUDY SPONSOR

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ADDITIONAL DISCLOSURE

Author Pike is an employee of MedPharm Consulting.

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APPENDIX A: THE EMBODY TRIAL INVESTIGATOR GROUPS

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