Supplementary material

INCLUSION CRITERIA

For inclusion in the double-blind (DB) phase, patients were ≥18 years of age and were of self-identified black race with a diagnosis of systemic lupus erythematosus (SLE) classified according to American College of Rheumatology criteria. Patients were required to have a Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score ≥8 at screening as well as autoantibodies (anti-nuclear antibody titer ≥1:80 by HEP-2 immunofluorescence assay and/or positive enzyme immunoassay (EIA) and/or anti–double-stranded deoxyribonucleic acid (anti-dsDNA; ≥30 IU/mL by EIA with a reference range of ≤29.99 IU/mL) at two independent time points within the screening period. They were also on standard SLE therapy for ≥30 days prior to Day 0, consisting of any of the following (alone or in combination): prednisone or equivalent (0–40 mg/day when used in combination with other SLE treatment or 7.5–40 mg/day when used alone); one immunosuppressive or immunomodulatory therapy (methotrexate, azathioprine, leflunomide, mycophenolate, calcineurin inhibitors, sirolimus, oral cyclophosphamide, 6-mercaptopurine, mizoribine, or thalidomide); antimalarials; non-steroidal anti-inflammatory drugs. For inclusion in the optional open-label extension (OLE) phase, patients must have completed Week 52 of the DB phase. Standard therapy could be adjusted during the OLE phase as clinically appropriate.
EXCLUSION CRITERIA

Key exclusion criteria included previous treatment with belimumab, severe lupus kidney disease (defined by proteinuria >6 g/24 h or equivalent using spot urine protein/creatinine ratio, or serum creatinine >2.5 mg/dL) or active nephritis requiring acute therapy not permitted by the protocol ≤90 days prior to Day 0, central nervous system lupus requiring therapeutic intervention within 60 days prior to Day 0, history of a major organ transplant, clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to SLE that could confound the results of the study or put the patient at undue risk, and new SLE medications other than corticosteroids added within 60 days prior to Day 0. Other notable exclusion criteria included receipt of any B-cell–targeted therapy at any time and receipt of specific treatments (eg, abatacept, anti-tumor necrosis factor, intravenous [IV] cyclophosphamide, interleukin-1 receptor antagonist, IV immunoglobulin, high-dose corticosteroids [>100 mg/day prednisone or equivalent], plasmapheresis, live vaccine) within protocol-defined timeframes prior to Day 0.

RANDOMIZATION AND TREATMENT

Belimumab and placebo was supplied in open-label vials. The randomization sequence was generated by Human Genome Sciences using an SAS program (SAS Institute Inc., Cary, NC, USA) and restrictions included a block size of 3. The interactive web response system used for randomization was operated by The Almac Group, Northern Ireland. The unblinded site pharmacist or designee reconstituted and diluted the study agent, was responsible for receiving and dispensing study agent and was independent of all other study activities. Except for a limited number of safety oversight personnel, all other study site personnel, the patient, the sponsor, and the contract research organization remained
blinded to the study agent received and to certain biomarkers and pharmacodynamic laboratory results. Separate monitors were responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study. An Independent Data Monitoring Committee reviewed unblinded safety data for this study on an ongoing basis until the data were locked and analyzed up to Week 52.

**COMPLEMENT DEFINITION**

Complement level was determined by fixed-time nephelometry, where low was defined as below the lower limit of normal (LLN): <90 mg/dL for C3 and <10 mg/dL for C4; other was defined as the LLN or above.

**SRI-S2K RESPONSE DEFINITION**

≥4-point reduction from baseline in the modified SELENA-SLEDAI score using S2K scoring for proteinuria (SS-S2K); AND no worsening, where worsening was defined as an increase of ≥0.30 points from baseline in Physician’s Global Disease Assessment; AND no new British Isles Lupus Assessment Group (BILAG) A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment.

**RENAL FLARE DEFINITION**

DB phase: increased proteinuria (a reproducible increase in 24-h urine protein levels [as measured by urine protein/creatinine (g/g) ratio] to: >1 if the baseline value was <0.2; OR >2 if the baseline value was between 0.2 and 1; OR more than twice the value at baseline if the baseline value was >1) and impaired renal function (a reproducible decrease in glomerular filtration rate of >20%, accompanied by proteinuria [≥1], and/or cellular [red
blood cell and white blood cell] casts). Urine protein in g/24-h will be approximated by the urine protein: creatine ratio in mg/mg.

OLE phase: the requirement for a reproducible increase in 24-h urine protein levels was relaxed to allow 1 increase if the next measurement was >1 month later.

PRIMARY AND KEY SECONDARY ENDPOINT TESTING PROCEDURE

A step-down sequential testing procedure was used to limit the overall type 1 error rate. Endpoints were evaluated for statistical significance based on a prespecified sequence for interpretation: i) SRI-S2K response rates at Week 52; ii) SRI-SS response rates at Week 52; iii) time to first severe SFI flare using the SELENA-SLEDAI without the proteinuria adjustment; and iv) proportion of patients with average prednisone dose that had decreased by ≥25% from baseline to ≤7.5 mg/day during Weeks 40 up to 52. Endpoints were tested in the sequence above (2-sided, alpha=0.05); if at any point in the sequence statistical significance was not met, subsequent endpoints in the sequence were deemed not statistically significant.

SECONDARY ENDPOINT RESULTS: SLE RESPONDER INDEX–SELENA-SLEDAI (SRI-SS) RESPONSE

During the DB phase, the percentage of SRI-SS responders at Week 52 was numerically greater for the belimumab group (146/298, 49.0%) than the placebo group (62/149, 41.6%) (OR 1.42; 95% CI: 0.94, 2.15; p=0.0937). The SRI-SS response rate over time is included in Supplementary Figure S1B. During the OLE phase, the percentages of SRI-SS responders at Week 24 from the start of belimumab were 73.1% (continuous-belimumab group 152/208) and 19.4% (placebo-to-belimumab group 13/67)
Supplementary Figure S1. SRI-S2K (A) and SRI-SS (B) response rates over time up to Week 52 in the double-blind phase (mITT)

Error bars represent SE.

mITT = modified intention-to-treat; SE = standard error; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index; SLE =
systemic lupus erythematosus; SRI-S2K = SLE Responder Index using the SELENA-SLEDAI with modified scoring for proteinuria; SRI-SS, SLE Responder Index–SELENA-SLEDAI.
**Supplementary Figure S2.** Time to the start of the Week 52 SRI-S2K response in the double-blind phase (mITT)

The gray reference line represents the 25th percentile.

mITT = modified intention-to-treat; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index; SLE = systemic lupus erythematosus; SRI-S2K = SLE Responder Index using the SELENA-SLEDAI with modified scoring for proteinuria.
Supplementary Figure S3. SS-S2K change from baseline over time up to Week 52 in the double-blind phase (mITT)

Error bars represent SE.

mITT = modified intention-to-treat; SE = standard error; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index; SLE = systemic lupus erythematosus; SS-S2K = modified SELENA-SLEDAI score for proteinuria.
Supplementary Figure S4. Proteinuria percentage change from baseline by visit among patients with baseline proteinuria >0.5 g/24 h in the double-blind phase (mITT)

Error bars represent quartiles.

mITT = modified intention-to-treat.
**Supplementary Figure S5.** Odds ratio of the primary endpoints for the pivotal Phase 3 studies compared with the current study stratified by baseline SELENA-SLEDAI score (A) and complement levels (B)

EMBRACE uses SRI-S2K scoring. Low C3/C4 is defined as less than the LLN: <90 mg/dL for C3 and <10 mg/dL for C4 and other was defined as LLN or above.

C = complement component; CI, confidence interval; LLN = lower limit of normal; OR, odds ratio; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index; SLE = systemic lupus erythematosus; SRI-S2K = SLE Responder Index using the SELENA-SLEDAI with modified scoring for proteinuria.
**Supplementary Table S1.** Summary of SELENA-SLEDAI organ involvement at baseline in the double-blind phase (mITT)

| n (%)                  | Belimumab 10 mg/kg | Placebo, (n=149) |
|------------------------|--------------------|-------------------|
|                        | IV, (n=299)        |                   |
| Mucocutaneous          | 274 (91.6)         | 139 (93.3)        |
| Musculoskeletal        | 235 (78.6)         | 115 (77.2)        |
| Immunologic            | 197 (65.9)         | 106 (71.1)        |
| Renal                  | 39 (13.0)          | 23 (15.4)         |
| Hematologic            | 39 (13.0)          | 19 (12.8)         |
| Cardiovascular and respiratory | 23 (7.7) | 12 (8.1)         |
| Vascular               | 18 (6.0)           | 9 (6.0)           |
| CNS                    | 0                  | 1 (0.7)           |

CNS = central nervous system; IV = intravenous; mITT = modified intention-to-treat; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index; SLE = systemic lupus erythematosus.
**Supplementary Table S2.** Summary of biomarker percentage change from baseline (mITT)

|                          | Double-blind phase (Week 52) | Open-label extension phase (Week 24) |
|--------------------------|-----------------------------|-------------------------------------|
|                          | Belimumab 10 mg/kg IV (n=299) | Placebo (n=149) | Continuous belimumab 10 mg/kg IV (n=225) | Placebo to belimumab 10 mg/kg IV (n=109) |
| n                        | 228                         | 111                        | 198                         | 95                                           |
| Mean (SE) IgG % change from baseline | -13.0 (1.16) | -0.6 (1.64) | -13.6 (1.25) | -10.17 (1.33) |
| Treatment difference      | -12.4                       |                           |                             |                                              |
| 95% CI                   | (-16.1, -8.6)               |                           |                             |                                              |
| p-value^a                | <0.0001                      |                           |                             |                                              |
| n                        | 138                         | 70                        | 118                         | 55                                           |
| Median (IQR) anti-dsDNA % change among patients | -42.14 (-67.31, -3.39) | -10.67 (-45.45, 35.36) | -41.3 (-67.4, -7.1) | -31.5 (-48.5, -9.7) |
positive at baseline
(≥30 IU/mL)

| p-value<sup>b</sup> | 0.0004 |
|---------------------|--------|
| n (C3 and C4)       | 227    | 112    | 198    | 94     |

Mean (SE) C3 levels
% change from baseline

| Treatment difference | 7.2 |
|----------------------|-----|
| 95% CI               | (1.8, 12.6) |
| p-value<sup>c</sup>  | 0.0087 |

Mean (SE) C4 levels
% change from baseline

| Treatment difference | 20.9 |
|----------------------|------|
| 95% CI               | (11.5, 30.2) |
| p-value<sup>c</sup>  | <0.0001 |

<sup>a</sup>All DB statistics are from an analysis of covariance (ANCOVA) model comparing belimumab and placebo with covariates for treatment group, baseline immunoglobulin value, baseline
SS-S2K score (≤9 vs ≥10), baseline complement levels (≥1 low C3/C4 vs other) and region (USA/Canada vs rest of world). \(^b\)Wilcoxon Rank Sum test with continuity correction. \(^c\)All DB statistics are from an ANCOVA model comparing belimumab and placebo with covariates for treatment group, baseline complement value, baseline SS-S2K score (≤9 vs ≥10) and region (USA/Canada vs rest of world).

C = complement; CI = confidence interval; IgG = immunoglobulin G; IQR = interquartile range; SE = standard error.
**Supplementary Table S3.** Summary of treatment-emergent AEs (safety population)

|                      | Double-blind phase | Open-label extension phase |
|----------------------|--------------------|-----------------------------|
|                      | Belimumab 10 mg/kg IV (n=331) | Placebo, 10 mg/kg IV (n=165) | Continuous belimumab 10 mg/kg IV (n=242) | Placebo to belimumab 10 mg/kg IV (n=117) |
| n (%)                | 277 (83.7)         | 144 (87.3)                  | 152 (62.8)                                 | 78 (66.7)                               |

**AEs by system organ class**

| Category                                         | Double-blind phase | Open-label extension phase |
|--------------------------------------------------|--------------------|-----------------------------|
| Infections and infestations                      | 196 (59.2)         | 99 (60.0)                   | 85 (35.1)                                 | 38 (32.5)                               |
| Gastrointestinal disorders                       | 105 (31.7)         | 43 (26.1)                   | 28 (11.6)                                 | 14 (12.0)                               |
| Musculoskeletal and connective tissue disorders   | 82 (24.8)          | 49 (29.7)                   | 31 (12.8)                                 | 17 (14.5)                               |
| Nervous system disorders                         | 71 (21.5)          | 34 (20.6)                   | 25 (10.3)                                 | 12 (10.3)                               |
| Respiratory, thoracic and mediastinal disorders   | 48 (14.5)          | 29 (17.6)                   | 16 (6.6)                                  | 9 (7.7)                                 |
| General disorders and administration site conditions | 47 (14.2) | 28 (17.0)                   | 17 (7.0)                                  | 10 (8.5)                                |
| Psychiatric disorders                            | 47 (14.2)          | 26 (15.8)                   | 8 (3.3)                                   | 6 (5.1)                                 |
| Disorder Category                                | Double-blind phase | Open-label extension phase |
|------------------------------------------------|--------------------|----------------------------|
|                                               | Belimumab (n=331)  | Placebo, (n=165)           |
|                                               | 10 mg/kg IV        | Continuous belimumab       |
|                                               |                    | 10 mg/kg IV (n=242)        |
|                                               |                    | Placebo to belimumab       |
|                                               |                    | 10 mg/kg IV (n=117)        |
| Skin and subcutaneous tissue disorders        | 48 (14.5)          | 23 (13.9)                  |
|                                               | 16 (6.6)           | 7 (6.0)                    |
| Injury, poisoning and procedural complications | 36 (10.9)          | 18 (10.9)                  |
|                                               | 15 (6.2)           | 8 (6.8)                    |
| Metabolism and nutrition disorders            | 34 (10.3)          | 17 (10.3)                  |
|                                               | 8 (3.3)            | 4 (3.4)                    |
| Investigations                                | 31 (9.4)           | 18 (10.9)                  |
|                                               | 7 (2.9)            | 2 (1.7)                    |
| Renal and urinary disorders                   | 29 (8.8)           | 17 (10.3)                  |
|                                               | 3 (1.2)            | 2 (1.7)                    |
| Blood and lymphatic system disorders          | 30 (9.1)           | 12 (7.3)                   |
|                                               | 10 (4.1)           | 4 (3.4)                    |
| Vascular disorders                            | 31 (9.4)           | 9 (5.5)                    |
|                                               | 9 (3.7)            | 4 (3.4)                    |
| Reproductive system and breast disorders       | 22 (6.6)           | 10 (6.1)                   |
|                                               | 5 (2.1)            | 1 (0.9)                    |

AEs by preferred terma
| Condition                     | Double-blind phase | Open-label extension |
|------------------------------|--------------------|----------------------|
|                              | Belimumab 10 mg/kg IV (n=331) | Placebo, n=165 |
|                              | Continuous belimumab 10 mg/kg IV (n=242) | Placebo to belimumab 10 mg/kg IV (n=117) |
| Upper respiratory tract infection | 49 (14.8)           | 14 (8.5)             | 20 (8.3)           | 4 (3.4)           |
| Urinary tract infection      | 43 (13.0)           | 21 (12.7)            | 13 (5.4)           | 7 (6.0)           |
| Headache                     | 39 (11.8)           | 18 (10.9)            | 9 (3.7)            | 3 (2.6)           |
| Influenza                    | 28 (8.5)            | 17 (10.3)            | 16 (6.6)           | 7 (6.0)           |
| Diarrhea                     | 32 (9.7)            | 9 (5.5)              | 4 (1.7)            | 4 (3.4)           |
| Sinusitis                    | 26 (7.9)            | 9 (5.5)              | 6 (2.5)            | 2 (1.7)           |
| Nausea                       | 18 (5.4)            | 15 (9.1)             | 2 (0.8)            | 1 (0.9)           |
| Insomnia                     | 19 (5.7)            | 10 (6.1)             | 0                  | 1 (0.9)           |
| Back pain                    | 16 (4.8)            | 10 (6.1)             | 3 (1.2)            | 7 (6.0)           |
| Vomiting                     | 19 (5.7)            | 7 (4.2)              | 1 (0.4)            | 0                 |
| Cough                        | 18 (5.4)            | 7 (4.2)              | 5 (2.1)            | 3 (2.6)           |
|                      | Double-blind phase | Open-label extension phase |
|----------------------|--------------------|---------------------------|
|                      | Belimumab 10 mg/kg IV \(n=331\) | Placebo, 10 mg/kg IV \(n=165\) | Continuous belimumab 10 mg/kg IV \(n=242\) | Placebo to belimumab 10 mg/kg IV \(n=117\) |
| Depression           | 15 (4.5)           | 9 (5.5)                   | 2 (0.8)                      | 2 (1.7)                |
| Hypertension         | 18 (5.4)           | 4 (2.4)                   | 7 (2.9)                      | 3 (2.6)                |
| SAEs\(^b\)           | 36 (10.9)          | 31 (18.8)                 | 13 (5.4)                     | 6 (5.1)                |
| Infections and infestations | 11 (3.3)   | 13 (7.9)                  | 4 (1.7)                      | 0                    |
| Musculoskeletal and connective tissue disorders | 9 (2.7)     | 7 (4.2)                   | 2 (0.8)                      | 1 (0.9)                |
| Renal and urinary disorders | 7 (2.1)  | 3 (1.8)                   | 0                            | 0                    |
| Respiratory, thoracic and mediastinal disorders | 7 (2.1)    | 3 (1.8)                   | 2 (0.8)                      | 0                    |
| Cardiac disorders    | 3 (0.9)            | 4 (2.4)                   | 0                            | 2 (1.7)                |
| Gastrointestinal disorders | 5 (1.5)  | 2 (1.2)                   | 0                            | 0                    |
| General disorders and administration site conditions | 3 (0.9)    | 4 (2.4)                   | 1 (0.4)                      | 0                    |
| Disorder                                | Double-blind phase | Open-label extension |
|----------------------------------------|--------------------|----------------------|
|                                        | Belimumab 10 mg/kg IV (n=331) | Placebo, n=165 |
|                                        | Continuous belimumab 10 mg/kg IV (n=242) | Placebo to belimumab 10 mg/kg IV (n=117) |
| Nervous system disorders               | 3 (0.9)            | 2 (1.2)             |
|                                        | 3 (1.2)            | 2 (1.7)             |
| Vascular disorders                     | 3 (0.9)            | 2 (1.2)             |
|                                        | 1 (0.4)            | 0                   |
| Metabolism and nutrition disorders     | 2 (0.6)            | 2 (1.2)             |
|                                        | 0                  | 0                   |
| Psychiatric disorders                  | 1 (0.3)            | 2 (1.2)             |
|                                        | 0                  | 0                   |
| AEs resulting in treatment discontinuation | 22 (6.6)         | 12 (7.3)            |
|                                        | 0                  | 1 (0.9)             |

AESIs

| All malignancies excluding NMSC        | 1 (0.3)            | 0                  |
| All malignancies including NMSC        | 1 (0.3)            | 0                  |
|                          | Double-blind phase | Open-label extension phase |
|--------------------------|---------------------|-----------------------------|
|                          | Belimumab           | Placebo, Continuous          |
|                          | 10 mg/kg IV (n=331) | belimumab 10 mg/kg IV (n=242)|
|                          | Placebo,           | Placebo to belimumab 10 mg/kg IV (n=117) |
| Post-infusion systemic   | reactions          |                             |
|                          | 21 (6.3)           | 8 (4.8)                     | 2 (0.8) | 3 (2.6) |
| All infections of special interest<sup>c</sup> | 19 (5.7) | 13 (7.9) | 7 (2.9) | 2 (1.7) |
| All opportunistic infections | 2 (0.6) | 2 (1.2) | 1 (0.4) | 0 |
| Active tuberculosis      | 0                  | 1 (0.6)                     | 0       | 0       |
| All herpes zoster        | 7 (2.1)            | 4 (2.4)                     | 2 (0.8) | 2 (1.7) |
| Sepsis                   | 1 (0.3)            | 2 (1.2)                     | 1 (0.4) | 0       |
| Any depression/suicide/self-injury<sup>c</sup> | 26 (7.9) | 17 (10.3) | 8 (3.3) | 5 (4.3) |
| Deaths                   | 2 (0.6)            | 0                           | 0       | 0       |

<sup>a</sup>Occurring in ≥5% of patients in any treatment group.  
<sup>b</sup>Occurring in ≥1% of patients in any treatment group.  
<sup>c</sup>Per custom MedDRA query (version 21.0 in DB phase; version 21.1 in OLE phase).
AE = adverse event; AESI = adverse event of special interest; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; NMSC = non-melanoma skin cancer; SAE = serious adverse event.