ORIGINAL ARTICLE

Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis

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ABSTRACT

BACKGROUND

In adults with active lupus nephritis, the efficacy and safety of intravenous belimumab as compared with placebo, when added to standard therapy (mycophenolate mofetil or cyclophosphamide–azathioprine), are unknown.

METHODS

In a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, 104-week trial conducted at 107 sites in 21 countries, we assigned adults with biopsy-proven, active lupus nephritis in a 1:1 ratio to receive intravenous belimumab (at a dose of 10 mg per kilogram of body weight) or matching placebo, in addition to standard therapy. The primary end point at week 104 was a primary efficacy renal response (a ratio of urinary protein to creatinine of ≤0.7, an estimated glomerular filtration rate [eGFR] that was no worse than 20% below the value before the renal flare (pre-flare value) or ≥60 ml per minute per 1.73 m^2 of body-surface area, and no use of rescue therapy), and the major secondary end point was a complete renal response (a ratio of urinary protein to creatinine of <0.5, an eGFR that was no worse than 10% below the pre-flare value or ≥90 ml per minute per 1.73 m^2, and no use of rescue therapy). The time to a renal-related event or death was assessed.

RESULTS

A total of 448 patients underwent randomization (224 to the belimumab group and 224 to the placebo group). At week 104, significantly more patients in the belimumab group than in the placebo group had a primary efficacy renal response (43% vs. 32%; odds ratio, 1.6; 95% confidence interval [CI], 1.0 to 2.3; P=0.03) and a complete renal response (30% vs. 20%; odds ratio, 1.7; 95% CI, 1.1 to 2.7; P=0.02). The risk of a renal-related event or death was lower among patients who received belimumab than among those who received placebo (hazard ratio, 0.51; 95% CI, 0.34 to 0.77; P=0.001). The safety profile of belimumab was consistent with that in previous trials.

CONCLUSIONS

In this trial involving patients with active lupus nephritis, more patients who received belimumab plus standard therapy had a primary efficacy renal response than those who received standard therapy alone. (Funded by GlaxoSmithKline; BLISS-LN ClinicalTrials.gov number, NCT01639339.)

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N Engl J Med 2020;383:1117-28.
DOI: 10.1056/NEJMoa2001180

Systemic lupus erythematosus (SLE), a chronic autoimmune disease characterized by loss of immune tolerance, leads to multisystem inflammation and organ injury.[1-4] Lupus nephritis, which occurs in 25 to 60% of patients with SLE, is the most common severe manifestation of SLE and a major cause of illness and death.[5] The percentage of patients who have a renal response despite aggressive treatment remains unacceptably low, and in 10 to 30% of patients with lupus nephritis, this condition progresses to end-stage kidney disease.[4-6] This risk has remained unchanged during the past three decades.[7]

Belimumab, a recombinant human IgG-1λ monoclonal antibody that inhibits B-cell activating factor, is approved for patients with active autoantibody-positive SLE who are 5 years of age or older.[8] The Food and Drug Administration approved belimumab after the results of two pivotal phase 3 clinical trials (Belimumab in Subjects with Systemic Lupus Erythematosus [BLISS]-52 and BLISS-76) of intravenous belimumab involving patients with SLE were reported.[9,10] However, because patients with acute, severe lupus nephritis were excluded from those trials, data on the efficacy and safety of belimumab in patients with active lupus nephritis are lacking. Post hoc analyses involving patients in BLISS-52 and BLISS-76 who had proteinuria at baseline showed decreased proteinuria and a lower incidence of renal flares in patients who received belimumab.[11] Those observations led us to conduct the current trial, Belimumab International Study in Lupus Nephritis (BLISS-LN), to evaluate the efficacy and safety of belimumab plus standard therapy (mycophenolate mofetil or cyclophosphamide–azathioprine) in patients with active lupus nephritis.

METHODS

TRIAL DESIGN AND OVERSIGHT

This phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, 104-week trial was performed in accordance with the principles of the Declaration of Helsinki. The trial was conducted at 107 sites in 21 countries; all the trial sites received approval from ethics committees or institutional review boards, and written informed consent was obtained from all the patients. This trial was reported in accordance with the Consolidated Standards of Reporting Trials guidelines.[12,13]

The sponsor (GlaxoSmithKline) — which contributed to the design of the trial, the collection, analysis, and interpretation of the data, and the decision to submit the manuscript for publication — supported the authors in the development of the manuscript. All the authors, including those employed by the sponsor, approved the content of the submitted manuscript. Medical writing support was funded by the sponsor. All the authors vouch for the accuracy and completeness of the data and the reporting of adverse events and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org.

ENTRY CRITERIA

Enrolled patients were at least 18 years of age and had autoantibody-positive SLE (antinuclear antibody titers ≥1:80, anti–double-stranded DNA antibodies, or both) that fulfilled the 1982 American College of Rheumatology classification criteria for SLE, which were updated in 1997. At screening, the patients had a ratio of urinary protein to creatinine of 1 or more and biopsy-proven lupus nephritis of International Society of Nephrology and Renal Pathology Society class III (focal lupus nephritis) or IV (diffuse lupus nephritis) with or without coexisting class V (membranous lupus nephritis), or pure class V lupus nephritis within 6 months before, or during, screening. Only patients with biopsy specimens showing active lesions or active and chronic lesions were enrolled. Induction therapy was initiated within 60 days before randomization. Exclusion criteria included dialysis within 1 year; an estimated glomerular filtration rate (eGFR) of less than 30 ml per minute per 1.73 m^2 of body-surface area; previous failures of both cyclophosphamide and mycophenolate mofetil induction; receipt of cyclophosphamide induction therapy within 3 months before the trial; and receipt of B-cell–targeted therapy (including belimumab) within 1 year before randomization.

TRIAL PROCEDURES

Patients were randomly assigned in a 1:1 ratio with the use of an interactive Web-response system at day 1 (the baseline visit) to receive intravenous belimumab (at a dose of 10 mg per kilogram of body weight) or matching placebo. Randomization was stratified according to induction regimen (cyclophosphamide or mycophenolate mofetil) and race group (Black or non-Black). The trial agents were prepared by

pharmacists who were aware of the trial-group assignments. Patients and staff were unaware of the trial-group assignments, although independent monitors were aware of these assignments.

In addition to standard therapy, patients received intravenous belimumab or placebo on days 1 (baseline), 15, and 29 and every 28 days thereafter to week 100, with final assessments at week 104. Standard induction therapy, chosen by the investigators and initiated within 60 days before day 1, consisted of intravenous cyclophosphamide (500 mg every 2 weeks [±3 days] for 6 infusions) or mycophenolate mofetil (target dose, 3 g per day). In patients receiving cyclophosphamide–azathioprine, maintenance therapy (target dose, 2 mg per kilogram per day; ≤200 mg per day) until trial end was initiated 2 weeks after the last dose of cyclophosphamide. For mycophenolate mofetil induction, maintenance therapy consisted of mycophenolate mofetil at a dose of 1 to 3 g per day until the end of the trial, although after 6 months, the dose could be reduced to 1 g per day. At the investigator's discretion, high-dose glucocorticoids (1 to 3 intravenous pulses of methylprednisolone [500 to 1000 mg each]) could be administered during induction, followed by oral prednisone (0.5 to 1.0 mg per kilogram per day; total daily dose, ≤60 mg). Treatment regimens were based on those in the Euro-Lupus Nephritis Trial and the Aspreva Lupus Management Study.[14-17] Receipt of angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) as well as hydroxychloroquine was recommended in the trial protocol.

EFFICACY END POINTS

The original primary end point, the original ordinal renal response (complete, partial, or no response) at week 104, was determined according to the ratio of urinary protein to creatinine, urinary sediment, and the calculated glomerular filtration rate (see the Supplementary Appendix, available at NEJM.org). To harmonize with accumulating evidence on predictors of long-term kidney outcomes, the primary end point was changed to the primary efficacy renal response at week 104, a dichotomous end point that does not include the partial renal response, an outcome of uncertain long-term clinical value. The primary efficacy renal response is defined as a ratio of urinary protein to creatinine of 0.7 or less, an eGFR that was no worse than 20% below the pre-flare value or at least 60 ml per minute per 1.73 m^2, and no use of rescue therapy for treatment failure.

The major secondary end points were a complete renal response at week 104 (a ratio of urinary protein to creatinine of <0.5, an eGFR that was no worse than 10% below the pre-flare value or ≥90 ml per minute per 1.73 m^2, and no rescue therapy), the primary efficacy renal response at week 52, the time to a renal-related event or death, and an ordinal renal response without urinary sediment at week 104. Complete definitions of the primary and major secondary end points are provided in the Supplementary Appendix. Other efficacy measures were a primary efficacy renal response and complete renal response over time, the time to a sustained primary efficacy renal response and complete renal response through week 104, and changes in levels of urinary protein and biomarkers and in the eGFR (see the Supplementary Appendix and the protocol).

DEFINITIONS OF TREATMENT FAILURE

Patients were required to taper glucocorticoids to 10 mg or less per day by week 24 and to not exceed this dose through week 104, except for protocol-allowed short-term rescue treatment between weeks 24 and 76 for reasons other than lupus nephritis. No glucocorticoid rescue treatments were allowed between weeks 76 and 104. Patients were considered to have treatment failure if they violated the glucocorticoid rules or received additional immunosuppressive agents (except topical agents) beyond the induction and maintenance regimens; initiated the use of ACE inhibitors, ARBs, or antimalarial drugs after week 24; or if the standard therapy (cyclophosphamide–azathioprine or mycophenolate mofetil) exceeded permitted doses.

SAFETY ASSESSMENTS

Safety assessments included adverse events, serious adverse events, and adverse events of special interest (cancer; infusion, anaphylactic, or hypersensitivity reactions; infections of special interest; and depression, suicide, or self-injury); death; and immunogenicity. An independent data and safety monitoring committee provided an ongoing review of safety data.

STATISTICAL ANALYSIS

We calculated that a sample of 448 patients would provide the trial with 80% power to detect

a 13.6-percentage-point between-group difference and a minimum detectable difference of 9.7 percentage points in the primary end point (the primary efficacy renal response at week 104). We assumed that 40% of the patients in the placebo group would have a response.

Efficacy end points were analyzed in the modified intention-to-treat population, which included all the patients who underwent randomization and received at least one dose of belimumab or placebo. Two patients from sites with compliance issues were excluded from the modified intention-to-treat population. Safety end points were analyzed in all the patients who underwent randomization and received at least one dose of belimumab or placebo. End points were analyzed with the use of a step-down sequential testing procedure in a prespecified hierarchy to control overall type I error. The end points of a primary efficacy renal response and complete renal response were analyzed with logistic regression. The time to a renal-related event or death was analyzed with the use of a Cox proportional-hazards regression. Ordinal renal response without urinary sediment was analyzed with a rank analysis of covariance. Statistical models controlled for induction regimen, race or ethnic group, baseline ratio of urinary protein to creatinine, and baseline eGFR.

In the analyses of the primary efficacy renal response, complete renal response, and ordinal renal response, patients who discontinued belimumab or placebo, had treatment failure, or withdrew from the trial were considered to not have had a response. In the Cox proportional-hazards model, discontinuation of belimumab or placebo, treatment failure that was not related to a kidney event, or withdrawal from the trial before a renal-related event or death occurred were bases for censoring of patient data. Safety data were analyzed while the patients were receiving belimumab or placebo.

RESULTS

TRIAL POPULATION

From July 2012 through July 2017, a total of 797 patients underwent screening, and 448 patients underwent randomization (224 in the belimumab group and 224 in the placebo group); the modified intention-to-treat population included 223 patients in each group. Randomization was stratified according to induction regimen (59 patients in each group had received cyclophosphamide, and 164 patients in each group had received mycophenolate mofetil) and race (31 patients in the belimumab group and 32 patients in the placebo group were Black, and 192 patients in the belimumab group and 191 patients in the placebo group were not Black). A total of 146 of 223 patients (65%) in the belimumab group and 132 of 223 patients (59%) in the placebo group received a trial agent through week 100 (Fig. S1 in the Supplementary Appendix).

Baseline characteristics were balanced between the two groups (Table 1). The mean (±SD) age was 33.4±10.6 years, and the median duration of lupus nephritis was 0.2 years (interquartile range, 0.1 to 3.3). A total of 58% of the cohort (258 of 446 patients) had kidney-biopsy specimens classified according to International Society of Nephrology and Renal Pathology Society criteria as class III or IV lupus nephritis, whereas 116 patients (26%) had class III or IV coexisting with class V, and 72 patients (16%) had pure class V.

PRIMARY AND MAJOR SECONDARY EFFICACY END POINTS

The results with respect to the primary and major secondary end points are provided in Table 2. At week 104, significantly more patients in the belimumab group than in the placebo group had a primary efficacy renal response (96 of 223 patients [43%] vs. 72 of 223 patients [32%]; odds ratio, 1.6; 95% confidence interval [CI], 1.0 to 2.3; P=0.03). Components of the primary efficacy renal response at week 104, including a decrease in the ratio of urinary protein to creatinine to 0.7 or less and no treatment failure, occurred more often in recipients of belimumab than in recipients of placebo (Table S1). More patients in the belimumab group than in the placebo group had a primary efficacy renal response at an earlier time point (week 52) (104 of 223 patients [47%] vs. 79 of 223 patients [35%]; odds ratio, 1.6; 95% CI, 1.1 to 2.4; P=0.02). Starting at week 24, at each visit, more patients receiving belimumab had a primary efficacy renal response than those receiving placebo (Fig. 1A). The chance of having a primary efficacy renal response that was sustained through week 104 was higher with belimumab than with placebo (hazard ratio, 1.46; 95% CI, 1.07 to 1.98) (Fig. 1B). The results of the analysis incorporating the original primary end point are provided in Table S2.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients in the Modified Intention-to-Treat Population.*

Characteristic	Belimumab (N=223)	Placebo (N=223)	Total (N=446)
Female sex — no. (%)	197 (88)	196 (88)	393 (88)
Age — yr	33.7±10.7	33.1±10.6	33.4±10.7
Race or ethnic group — no. (%)†			
Asian	114 (51)	109 (49)	223 (50)
White	73 (33)	75 (34)	148 (33)
Black	30 (13)	31 (14)	61 (14)
American Indian or Alaska Native	4 (2)	6 (3)	10 (2)
Multiple races or ethnic groups	2 (1)	2 (1)	4 (1)
Geographic region — no. (%)			
Asia	106 (48)	105 (47)	211 (47)
Europe	41 (18)	45 (20)	86 (19)
United States or Canada	38 (17)	38 (17)	76 (17)
Americas, excluding United States and Canada	38 (17)	35 (16)	73 (16)
Median time from initial diagnosis of SLE to randomization (IQR) — yr‡	3.3 (0.3–8.1)	3.3 (0.2–8.0)	3.3 (0.2–8.1)
Median time from initial diagnosis of lupus nephritis to randomization (IQR) — yr‡	0.2 (0.1–3.3)	0.2 (0.1–3.4)	0.2 (0.1–3.3)
Kidney-biopsy lupus nephritis class — no. (%)§			
III or IV	126 (56)	132 (59)	258 (58)
III and V or IV and V	61 (27)	55 (25)	116 (26)
V	36 (16)	36 (16)	72 (16)
Ratio of urinary protein to creatinine	3.2±2.7	3.5±3.6	3.4±3.2
Ratio of urinary protein to creatinine ≥3 — no. of patients (%)	91 (41)	92 (41)	183 (41)
Estimated GFR — ml per minute per 1.73 m^2	100.0±37.7	101.0±42.7	100.5±40.2
Estimated GFR category — no. (%)			
≥60 ml per minute per 1.73 m^2	190 (85)	182 (82)	372 (83)
≥90 ml per minute per 1.73 m^2	131 (59)	133 (60)	264 (59)
SLEDAI-2K score¶	12.5±5.3	12.2±4.8	12.3±5.0
Biomarkers			
Antinuclear antibodies — no. (%)	194 (87)	197 (88)	391 (88)
Anti–double-stranded DNA antibodies — no. (%)	173 (78)	169 (76)	342 (77)
Anti-C1q antibodies — no./total no. (%)	181/223 (81)	172/221 (78)	353/223 (79)
Anti-Sm antibodies — no./total no. (%)	73/223 (33)	72/219 (33)	145/223 (33)
Complement C3 <90 mg/dl — no. (%)	134 (60)	133 (60)	267 (60)
Complement C4 <10 mg/dl — no. (%)	65 (29)	58 (26)	123 (28)
Previous treatment — no. (%)			
Any antimalarial drug	166 (74)	154 (69)	320 (72)
ACE inhibitor or ARB	147 (66)	150 (67)	297 (67)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, GFR glomerular filtration rate, IQR interquartile range, and SLE systemic lupus erythematosus.

† Race or ethnic group was reported by the patients. Patients were counted in only one category.

‡ Duration refers to the length of time (in years) the disease had been present at the time of screening. The duration was calculated as the screening date minus the diagnosis date plus 1, divided by 365.25.

§ Lupus nephritis kidney-biopsy classes (according to the International Society of Nephrology and Renal Pathology Society classification) range from I to VI. These classes are defined according to the morphologic changes in the glomeruli. Class III denotes focal lupus nephritis, class IV diffuse lupus nephritis, and class V membranous lupus nephritis.

¶ Disease activity was assessed with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), a 24-item weighted score of lupus activity that ranges from 0 to 105, with higher scores indicating greater disease activity. The proteinuria descriptor was modified with the use of the SLEDAI-2000 (SLEDAI-2K) version that captures new as well as persistent proteinuria of more than 0.5 g per 24 hours.

Table 2. Primary and Major Secondary Efficacy End Points in the Modified Intention-to-Treat Population.

End Point	Belimumab (N=223)	Placebo (N=223)	Difference	Odds Ratio or Hazard Ratio (95% CI)*	P Value
	number (percent)		*percentage points*		
Primary end point: primary efficacy renal response at wk 104†	96 (43)	72 (32)	11	1.6 (1.0 to 2.3)	0.03
Major secondary end points					
Complete renal response at wk 104‡	67 (30)	44 (20)	10	1.7 (1.1 to 2.7)	0.02
Primary efficacy renal response at wk 52§	104 (47)	79 (35)	11	1.6 (1.1 to 2.4)	0.02
Time to renal-related event or death¶	NA	NA	NA	0.5 (0.3 to 0.8)	0.001
Ordinal renal response without urinary sediment at wk 104‖					
Complete renal response	67 (30)	44 (20)	10	NA	0.01
Partial renal response**	39 (18)	38 (17)	<1	NA	
No response	117 (52)	141 (63)	−11	NA	

* Odds ratios are provided for the primary end point and the first two major secondary end points. The hazard ratio is provided for the time to a renal-related event or death. Odds ratios with 95% confidence intervals and P values were calculated with the use of a logistic-regression model for the comparison between belimumab and placebo, with covariates of trial group, induction regimen (cyclophosphamide vs. mycophenolate mofetil), race(Black vs. non-Black), baseline ratio of urinary protein to creatinine, and baseline estimated GFR (eGFR). Withdrawal from the trial, treatment failure, and discontinuation of belimumab or placebo were imputed as a nonresponse. NA denotes not applicable.

† The primary efficacy renal response at week 104 (week 100, confirmed at week 104) is defined as a ratio of urinary protein to creatinine of 0.7 or less and an eGFR that is no worse than 20% below the pre-flare value or at least 60 ml per minute per 1.73 m^2 and no rescue therapy for treatment failure.

‡ The complete renal response at week 104 (week 100, confirmed at week 104) is defined as a ratio of urinary protein to creatinine of less than 0.5, an eGFR that is no worse than 10% below the pre-flare value or at least 90 ml per minute per 1.73 m^2, and no rescue therapy.

§ The primary efficacy renal response at week 52 was the response at week 48, confirmed at week 52.

¶ For this end point, events were defined as the first event that occurred among the following: death; progression to end-stage kidney disease; doubling of the serum creatinine level from the baseline level; increased proteinuria, impaired kidney function, or both; or kidney-related treatment failure. Data on patients who discontinued belimumab or placebo, withdrew from the trial, or were lost to follow-up were censored on the date of the event. Data on patients who completed the 104-week treatment period were censored at the week 104 visit. The time to event in days was defined as the event date minus the treatment start date plus 1. A Cox proportional-hazards model for the comparison between belimumab and placebo was used, with adjustment for induction regimen, race, baseline ratio of urinary protein to creatinine, and baseline eGFR.

‖ The P value was from a rank analysis-of-covariance model comparing belimumab with placebo, with covariates for trial group, induction regimen (cyclophosphamide vs. mycophenolate mofetil), race (Black vs. non-Black), baseline ratio of urinary protein to creatinine, and baseline eGFR. Withdrawal from the trial, treatment failure, and discontinuation of belimumab or placebo were imputed as a nonresponse.

** This end point is defined as an eGFR that is no worse than 10% below the baseline value or within normal range and at least a 50% decrease in the ratio of urinary protein to creatinine with one of the following: a ratio of urinary protein to creatinine of less than 1.0 if the baseline ratio was 3.0 or less, or a ratio of urinary protein to creatinine of less than 3.0 if the baseline ratio was greater 3.0; no treatment failure; and not a complete renal response.

Significantly more patients who received belimumab than those who received placebo had a complete renal response at week 104 (67 of 223 patients [30%] vs. 44 of 223 patients [20%]; odds ratio, 1.7; 95% CI, 1.1 to 2.7; P=0.02). More patients receiving belimumab than those receiving placebo had components of a complete renal response at week 104, including a decrease in the ratio of urinary protein to creatinine to less than 0.5 and no treatment failure. From week 12 onward, more patients receiving belimumab than those receiving placebo had a complete renal response (Fig. 1C). The chance of a complete renal response that was sustained through week 104 was higher with belimumab than with placebo (hazard ratio, 1.58; 95% CI, 1.08 to 2.31) (Fig. 1D). The results of unadjusted sensitivity analyses for a primary efficacy renal response and a complete renal response at week 104 were consistent with the results of the primary analyses.

The group of patients who received belimumab had a significantly lower risk of a renal-related event or death during the trial than the group of patients who received placebo (hazard ratio, 0.51; 95% CI, 0.34 to 0.77; P=0.001) (Fig. 2A). These results were primarily because of increased proteinuria, impaired kidney function, or both (in 17 patients in the belimumab

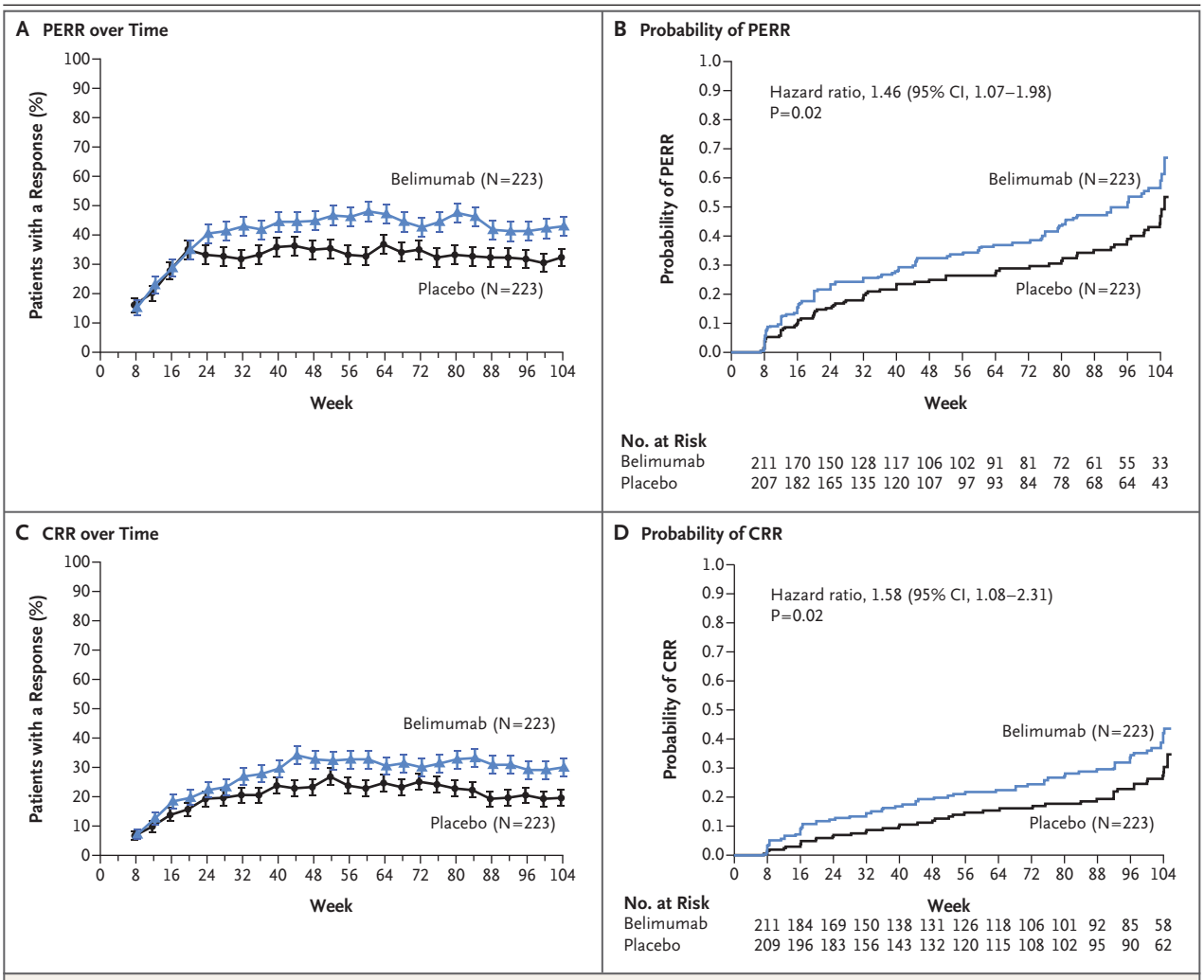


Figure 1. Renal Responses over Time in the Modified Intention-to-Treat Population.

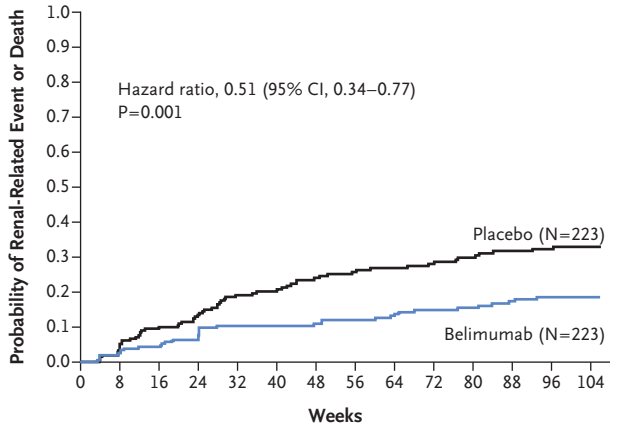
Panel A shows the primary efficacy renal responses (PERRs) over time. Panel B shows the probability of a PERR that was sustained through week 104. Patients who discontinued belimumab or placebo, had treatment failure, or withdrew from the trial were counted as not having had a response. Panel C shows the complete renal response (CRR) over time. Panel D shows the probability of a CRR that was sustained through week 104 (discontinuation of belimumab or placebo, treatment failure, or withdrawal from the trial were counted as a nonresponse). Data on patients who did not have a PERR or a CRR at week 104 were censored at the last available visit up through week 104. Data on patients who discontinued belimumab or placebo, had treatment failure, withdrew from the trial, were lost to follow-up, or died were censored. The time to event in days was calculated as the event date minus the treatment start date plus 1. I bars indicate standard errors. CI denotes confidence interval.

group and 39 patients in the placebo group) or kidney-related treatment failure (in 16 and 20 patients, respectively) (Fig. 2B).

SUBGROUP ANALYSES

The primary efficacy renal response and complete renal response at week 104 according to stratification-factor subgroups (induction regimen and race) were investigated (Fig. S2). In both the mycophenolate mofetil and cyclophosphamide–azathioprine subgroups, more patients who received belimumab had a primary efficacy renal response than patients in the placebo group (odds ratio in the mycophenolate mofetil subgroup, 1.6; 95% CI, 1.0 to 2.5; odds ratio in the cyclophosphamide–azathioprine subgroup, 1.5; 95% CI, 0.7 to 3.5), with the overall response driven by the results in the larger mycophenolate mofetil subgroup. In the mycophenolate mofetil subgroup, the percentage of patients with a complete renal response was higher in the belimumab group than in the placebo group; however,

A



No. at Risk

Placebo	203	185	175	154	147	137	129	126	120	116	112	110	78
Belimumab	209	192	186	167	162	159	157	151	142	139	133	130	102

B

Event	Belimumab (N=223)	Placebo (N=223)
	no.	
Any event	35	63
Death from any cause	1	2
Progression to ESKD	0	1
Doubling of creatinine level from baseline	1	1
Increased proteinuria, impaired kidney function, or both	17	39
Treatment failure related to kidney event	16	20

Figure 2. Time to a Renal-Related Event or Death in the Modified Intention-to-Treat Population.

Panel A shows the time to a renal-related event or death. The figure is truncated at week 106. A renal-related event was defined as any of the following: end-stage kidney disease (ESKD); doubling of the serum creatinine level from the baseline level; increased proteinuria (a reproducible increase in the ratio of urinary protein to creatinine to >1.0 if the baseline value was <0.2, to >2.0 if the baseline value was 0.2 to 1.0, or to more than twice the value at baseline if the baseline value was >1.0) or impaired kidney function (a reproducible decrease in the glomerular filtration rate of >20%, accompanied by proteinuria [>1.0 g], cellular [red-cell, white-cell, or both] casts, or both); or kidney disease–related treatment failure. Panel B shows event details (data on patients who discontinued belimumab or placebo, had treatment failure not related to kidney disease, or withdrew from the trial were censored). Events listed are the first event or events for each patient with an event; therefore, events of lower severity were more common. Screening proteinuria values were used for eligibility assessment and differed from the baseline values obtained up to 35 days later. Treatment failure related to a kidney event was determined by adjudication of treatment failure.

in the cyclophosphamide–azathioprine subgroup, the percentages of patients with a response were equivalent in the belimumab and placebo groups.

Although few Black patients participated in the trial (31 of 223 patients in the belimumab group and 32 of 223 patients in the placebo group), Black patients who received belimumab appeared to be more likely to have a primary efficacy renal response and a complete renal response at week 104 than those who received placebo. However, in both groups, the percentage of Black patients who had a response was lower than the percentage of patients in the overall population who had a response.

OTHER EFFICACY END POINTS

A post hoc analysis showed that among patients who completed 104 weeks of the trial intervention, more patients who received belimumab (88 of 131 [67%]) had decreases in the ratio of urinary protein to creatinine (from ≥0.5 to <0.5) at week 104 than those who received placebo (70 of 124 [56%]) (Fig. S3). The mean observed eGFR values initially increased from baseline in both trial groups; however, from week 52, eGFR values declined in the placebo group, whereas the eGFR remained stable through week 104 in the belimumab group (Fig. S4).

BIOMARKER END POINTS

Patients who received belimumab had greater reductions in double-stranded DNA and C1q autoantibodies and greater increases in complement C3 and C4 levels and more conversions to normal levels than patients who received placebo (Table S3 and Fig. S5). After normalization of autoantibody concentrations according to IgG serum concentrations to correct for proteinuria-related effects, the ratios of anti–double-stranded DNA to IgG at week 104 decreased by 58% in the belimumab group and by 20% in the placebo group; similar decreases in normalized concentrations were observed for anti-C1q ratios (Fig. S6).

SAFETY END POINTS

The safety profile for belimumab plus standard therapy was similar to that of standard therapy alone (Table 3). Anti-belimumab antibodies were not detected. A total of 11 patients died during the trial (6 in the belimumab group and 5 in the placebo group). Infection-associated deaths were balanced between the two groups (3 patients in each group), and no deaths were directly attributed to lupus nephritis by the investigators.

Table 3. Adverse Events, Adverse Events of Special Interest, and Suicidality in the Safety Population.*

Event	Belimumab (N=224)	Placebo (N=224)
	no. of patients (%)	
All adverse events†	214 (96)	211 (94)
All treatment-related adverse events†	123 (55)	119 (53)
Upper respiratory tract infection	26 (12)	24 (11)
Urinary tract infection	15 (7)	13 (6)
Herpes zoster	13 (6)	10 (4)
Bronchitis	11 (5)	10 (4)
Nasopharyngitis	8 (4)	8 (4)
Headache	9 (4)	5 (2)
Nausea	8 (4)	5 (2)
Rash	6 (3)	5 (2)
All serious adverse events†	58 (26)	67 (30)
All treatment-related serious adverse events†	23 (10)	25 (11)
Most common treatment-related serious adverse events, according to system organ class, occurring in ≥1% of patients in either group		
Infections and infestations	15 (7)	18 (8)
Respiratory, thoracic, and mediastinal disorders	5 (2)	1 (<1)
Blood and lymphatic system disorders	3 (1)	2 (1)
Nervous system disorders	0	3 (1)
Most common treatment-related serious adverse events occurring in ≥1% of patients in either group		
Pneumonia	3 (1)	4 (2)
Herpes zoster	3 (1)	2 (1)
Adverse events resulting in discontinuation of trial drug	29 (13)	29 (13)
Adverse events of special interest‡		
Cancer		
Excluding nonmelanoma skin cancer§	2 (1)	0
Including nonmelanoma skin cancer§	3 (1)	0
Postinfusion reactions¶	26 (12)	29 (13)
All infections of special interest, including opportunistic infections, herpes zoster, tuberculosis, and sepsis	30 (13)	34 (15)
Serious infections	9 (4)	7 (3)
Depression, suicide, or self-injury	11 (5)	16 (7)
C-SSRS suicidal ideation or behavior during trial intervention	7 (3)	12 (5)
Death	6 (3)	5 (2)
Fatal serious adverse events that began during trial intervention	4 (2)	3 (1)
Fatal serious adverse events that did not begin during trial intervention	2 (1)	2 (1)

* Only adverse events that occurred during the intervention period (from the first infusion to the first missed infusion or the last infusion, whichever was later, plus 28 days) are listed. Patients were counted once in each row and column for any adverse event that met the criterion. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 22.0.

† This category includes all patients who had at least one event. Relatedness of the intervention to the event was determined by the site investigators.

‡ These events were determined according to a custom MedDRA query.

§ This category includes tumors of unspecified cancer that were adjudicated as cancer.

¶ These events were determined according to a custom MedDRA query or sponsor adjudication.

DISCUSSION

Despite aggressive treatment, approximately 60% of patients with lupus nephritis do not have complete remission, and these patients have poor long-term outcomes.[18-21] Furthermore, 27 to 66% of patients with lupus nephritis that is in remission have subsequent flares.[22] Thus, safer therapies that reduce kidney inflammation, prevent flares, and preserve kidney function are needed.

Heightened production of B-cell activating factor within the kidney and increased levels of serum B-cell activating factor in patients with lupus nephritis have been observed.[23-27] Therefore, neutralizing B-cell activating factor, with the subsequent down-regulation of B-cell function, decreases in autoantibody production, and inhibition of tertiary lymphoid structure formation in the kidney is a compelling therapeutic approach to lupus nephritis. In the current trial, significantly more patients had a primary end-point event with standard therapy plus belimumab than with standard therapy alone. In addition, significantly more patients who received belimumab had favorable responses with respect to major secondary end points. The effects of belimumab on serologic tests in patients with lupus nephritis were consistent with those in previous studies.[28]

Our definition of the primary end point (the primary efficacy renal response) was based on observations that a decrease in the urinary protein level to less than 0.5 to 0.8 g per day is the best predictor of long-term preservation of renal function in patients with kidney disease, whereas a decrease in the eGFR to less than 60 ml per minute per 1.73 m^2 is an independent predictor of a poor prognosis.[19,20,29] Urinary sediment was not included in the outcome measures, given its negligible contribution to and possible confounding of the evaluation of renal response.[19]

Our trial has several unique features that align with principles of management of lupus nephritis. The 2-year, double-blind treatment period permitted evaluation of both early responses and treatment durability. Nearly all previous induction studies involving patients with lupus nephritis had 6- or 12-month primary end points and used entry criteria as well as outcome metrics that differ from ours; thus, we cannot compare our 2-year outcomes with those of such studies.[30] In addition, most studies involving patients with lupus nephritis have excluded those who were receiving cyclophosphamide. Furthermore, the end points of the current trial had additional rigorous response requirements, including a sustained reduction in the dose of glucocorticoids and confirmation of a primary efficacy renal response and complete renal response across two consecutive visits.

Although the proteinuria component of the complete renal response in this trial is identical to the outcome requirements of most studies involving patients with lupus nephritis, the requirement of an eGFR response in our trial (no worse than 10% below the pre-flare value or ≥90 ml per minute per 1.73 m^2) is more stringent than that in other studies involving patients with lupus nephritis.[31] In patients with low baseline serum creatinine levels, small absolute increases result in relatively large percentage changes; such patients may thus be at risk for inappropriate classification as not having a response.[32] That phenomenon, coupled with glucocorticoid-tapering requirements and end-point confirmations, may, in part, be responsible for the seemingly low incidence of a complete renal response at 2 years (30% in the belimumab group and 20% in the placebo group).

We evaluated the efficacy of belimumab according to stratification-factor subgroups (induction regimen and race). Given global variations in preferred induction regimens, the trial design allowed a choice between the cyclophosphamide–azathioprine and mycophenolate mofetil regimens, which were used in the Euro-Lupus Nephritis Trial and the Aspreva Lupus Management Study[14-17] and are included in current treatment guidelines.[33,34] In the mycophenolate mofetil subgroup, more patients had a primary efficacy renal response and complete renal response at week 104 with belimumab than with placebo. In the smaller cyclophosphamide–azathioprine subgroup, more patients in the belimumab group than in the placebo group had a primary efficacy renal response at week 104, although no between-group difference was observed for the end point of complete renal response at week 104. Some notable disparities in baseline characteristics between the mycophenolate mofetil group and the cyclophosphamide–azathioprine group, such as a higher level of urinary protein, lower eGFR, lower complement concentrations, longer disease duration, and greater exposure to previous treatment for lupus nephritis suggest that more patients who received cyclophospha-

mide–azathioprine, especially those who received belimumab, had resistant lupus nephritis that might have been related to greater accrual of kidney damage.[35-37]

Black patients with lupus nephritis are more likely to have a worse prognosis than those in other racial groups.[35,38,39] The primary efficacy renal response and complete renal response at week 104 in the Black patients enrolled in the modified intention-to-treat population (61 of 446 patients [14%]) were consistent with those in the overall trial population.

Our trial has limitations owing to the low enrollment of Black patients and patients receiving cyclophosphamide–azathioprine. Only two induction and maintenance regimens were permitted as background therapy, although additional therapies for lupus nephritis, such as calcineurin inhibitors, are currently used in practice. In addition, patient-reported outcomes were not included.

The current international trial involving 448 patients showed that belimumab plus standard therapies for lupus nephritis enhanced renal responses; furthermore, the risk of a renal-related event during the trial was almost 50% lower among patients who received belimumab than among those who received standard therapy alone. Up to 3 g of mycophenolate mofetil or cyclophosphamide–azathioprine was combined with belimumab in our trial, and we did not observe adverse events that differed from those in previous trials involving patients with SLE who received belimumab[9,10] or other trials involving patients with lupus nephritis.[15-17,40,41]

Supported by GlaxoSmithKline.

Dr. Furie reports receiving advisory board fees and travel support from GlaxoSmithKline, AbbVie, AstraZeneca (MedImmune), Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, EMD Serono, Equillium, Galápagos, Genentech, Glenmark Pharmaceuticals, Novartis, Reistone Biopharma, Sanofi, Takeda, and Union Chimique Belge and consulting fees from Alexion, Aurinia Pharmaceuticals, Daiichi Sankyo, Janssen Pharmaceutica, Kezar Life Sciences, and MorphoSys; Dr. Rovin, receiving advisory fees from Aurinia Pharmaceuticals, Callidatis Therapeutics, ChemoCentryx, Retrophin, Novartis, Omeros, MorphoSys, EMD Serono, Bristol Myers Squibb, Janssen Pharmaceutica, AstraZeneca, and GlaxoSmithKline; Dr. Malvar, receiving advisory board fees from GlaxoSmithKline; Dr. Teng, receiving grant support and consulting fees from GlaxoSmithKline and consulting fees from Aurinia Pharmaceuticals and Novartis; Dr. Contreras, receiving advisory board fees from GlaxoSmithKline and Aurinia Pharmaceuticals and fees for serving on an independent data and safety monitoring board from Roche and EMD Serono; Dr. Amoura, receiving grant support and advisory board fees from GlaxoSmithKline and AstraZeneca and grant support from Amgen and Roche; Dr. Yu, receiving grant support from Baxter Healthcare, Wanbang Biopharmaceuticals, Kyowa Kirin, AstraZeneca, and GlaxoSmithKline; Dr. Santiago, receiving fees for serving as principal investigator for clinical trials for Aurinia Pharmaceuticals, Roche, Novartis, GlaxoSmithKline, Bristol Myers Squibb, and Pfizer; Dr. Saxena, receiving advisory board fees from GlaxoSmithKline; Drs. Green and Ji, being employed by and owning shares and stock options in GlaxoSmithKline; Ms. Kleoudis, being previously employed by and owning shares and stock options in GlaxoSmithKline and being previously employed by Parexel; and Ms. Burriss, Ms. Barnett, and Dr. Roth, being employed by and owning shares and stock options in GlaxoSmithKline. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families and all the investigators and site personnel for participating in this trial; Maddalena Bolognesi and Giorgio Cattoretti (Universitá di Milano–Bicocca,Monza, Italy), Franco Ferrario (San Gerardo Hospital, Monza, Italy), Terry Cook (Imperial College London, London), Ingeborg Bajema and Jan Bruijn (Leiden University Medical Center, Leiden, the Netherlands), and Laure-Helene Noel (Necker Hospital, Paris) for evaluating the renal-biopsy specimens; and Sam Halliwell(Fishawack Indicia) for medical writing support with an earlier version of the manuscript.

APPENDIX

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