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We performed a *post hoc* analysis of the Belimumab International Study in Lupus Nephritis (BLISS-LN), a Phase 3, multinational, double-blind, 104-week trial, in which 448 patients with lupus nephritis were randomized to receive intravenous belimumab 10 mg/kg or placebo with standard therapy (cyclophosphamide/azathioprine or mycophenolate mofetil). Add-on belimumab was found to be most effective in improving the primary efficacy kidney response and complete kidney response in patients with proliferative lupus nephritis and a baseline urine protein/creatinine ratio under 3 g/g. However, there was no observed improvement in the kidney response with belimumab treatment in patients with lupus nephritis and sub-epithelial deposits or with a baseline protein/creatinine ratio of 3 g/g or more. Belimumab significantly reduced the risk of kidney-related events or death and lupus nephritis flare in the overall population. Belimumab reduced the risk of a sustained 30% or 40% decline in estimated glomerular filtration rate (eGFR) versus standard treatment alone and attenuated the annual rate of eGFR decline in patients who remained on-study. Thus, our data suggest that the addition of belimumab to standard therapy could attenuate the risk of lupus nephritis flare and eGFR decline in a broad spectrum of patients with lupus nephritis.

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Lupus nephritis (LN) is one of the most severe organ manifestations of systemic lupus erythematosus.[1] Cyclophosphamide (CYC), azathioprine (AZA), and mycophenolate mofetil (MMF) are routinely used as standard therapies (STs) alongside glucocorticoids for the treatment of LN,[1,2] but kidney response rates remain low.[3] Up to 25% of patients who achieve remission have a flare within 3 to 4 years,[4,5] and up to 30% of patients progress to end-stage kidney disease (ESKD) and require kidney replacement therapy within 10 to 15 years of diagnosis.[6,7]

Belimumab is a recombinant human IgG1λ monoclonal antibody that inhibits B-lymphocyte stimulator (BLyS) and is approved for patients 5 years or older with active autoantibody-positive systemic lupus erythematosus.[8] To address unmet needs in patients with LN, the Belimumab International Study in Lupus Nephritis (BLISS-LN) was conducted to determine whether the addition of belimumab to standard immunosuppressive regimens improved kidney outcomes compared with ST plus placebo. The results of BLISS-LN were recently reported[9] and supported belimumab approval for the treatment of adults with active LN in the United States and the European Union.[8]

BLISS-LN was the first successful phase 3 randomized controlled trial in patients with LN to show superior kidney outcomes and a similar safety profile after the addition of a novel biologic drug to ST. The design of the trial had many unique features, including an ST regimen chosen by each site's principal investigator; a very strict glucocorticoid tapering

and maintenance schedule; 2-year duration; unique end point criteria for the assessment of kidney response; and evaluation of kidney-related events associated with long-term progression to kidney failure.[9]

In addition to BLISS-LN, other novel therapies are being evaluated for LN treatment. Despite these latest positive advances, the question remains how effective the emerging therapies will be in different subpopulations of patients with LN and in preserving long-term kidney function. Given the considerable number of patients who progress to ESKD,[7,10] this is a particularly important concern. To investigate this question for belimumab, secondary and exploratory analyses of BLISS-LN were performed, focusing on primary and secondary efficacy end points in different subgroups and on other kidney outcomes directly relevant to long-term kidney health and survival. The results of these analyses are reported here.

METHODS

Study design, setting, and population

BLISS-LN (GlaxoSmithKline Study 114054; ClinicalTrials.gov identifier NCT01639339) was a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, 104-week trial designed to assess the efficacy and safety of belimumab plus ST (CYC/AZA or MMF) in adult patients with active LN. Full methods have been published.[9]

The study was conducted between July 2012 and July 2019 and randomized 448 patients from 107 sites in 21 countries. Eligible patients were 18 years or older with autoantibody-positive systemic lupus erythematosus as per updated American College of Rheumatology classification criteria.[11] In addition, patients had a urine protein/creatinine ratio (uPCR) of ≥1 and biopsy-confirmed International Society of Nephrology and the Renal Pathology Society 2003–defined[12] class III or IV LN with or without coexisting class V LN or pure class V LN within 6 months before or during screening. Only patients with biopsy specimens showing active lesions or active and chronic lesions were enrolled. Key exclusion criteria were dialysis or B cell–targeted therapy (including belimumab) within the preceding year, receipt of CYC induction therapy within 3 months before the start of the trial, previous failures of both MMF and CYC induction therapy, and an estimated glomerular filtration rate (eGFR) of <30 ml/min per 1.73 m^2 of body surface area.

Patients were free to withdraw from treatment at any time during the study. Of note, even if treatment was discontinued prematurely, patients were encouraged to remain in the study and continue with assessments up to week 104.

Randomization and interventions

Patients were randomized (1:1) to receive belimumab 10 mg/kg i.v. or placebo as an add-on to ST, stratified by induction regimen and race. Treatment was administered on days 1 (baseline), 15, and 29 and every 28 days thereafter to week 100, with final assessments at week 104. Within 60 days before randomization, patients initiated standard induction therapy of CYC followed by maintenance with AZA, or induction and maintenance with MMF, according to the choice of the investigator. High-dose glucocorticoids were administered as part of the induction regimen but had to be tapered to ≤10 mg/d by week 24. Short-term low-dose rescue treatment was allowed until week 76 for reasons other than LN, and no increase in glucocorticoid dose was permitted between week 76 and week 104.

Outcomes and study subgroups

The primary end point of BLISS-LN was the primary efficacy renal response (PERR) at week 104. Key secondary end points included complete renal response (CRR) at week 104, PERR at week 52, and time to kidney-related event or death.

The secondary and *post hoc* analyses reported here investigated PERR, CRR, and time to kidney-related event or death in study subgroups, along with the following outcomes predictive of long-term kidney health and survival: time to first LN flare, time to a confirmed 30% or 40% decline in eGFR, sustained 30% and 40% decline in eGFR, and eGFR slope—which were performed in the overall study population and subgroups.

Study subgroups included LN histologic class (class III or IV, class III + V or IV + V, and pure class V), ST regimen (CYC/AZA or MMF), and baseline proteinuria level defined by nephrotic range proteinuria threshold (uPCR of ≥3 g/g or <3 g/g).

End point measurements

Proteinuria was measured using uPCR, and eGFR was measured using the Modification of Diet in Renal Disease formula.[13] Patients who achieved PERR had a uPCR of ≤0.7 g/g with an eGFR no less than 20% below the preflare value or ≥60 ml/min per 1.73 m^2 of body surface area and did not receive rescue therapy resulting in treatment failure. Patients who achieved CRR had a uPCR of <0.5 g/g with an eGFR no less than 10% below the preflare value or ≥90 ml/min per 1.73 m^2 of body surface area and did not receive rescue therapy resulting in treatment failure.

Time to kidney-related event or death was defined as the time from baseline to occurrence of one of the following: ESKD, doubling of serum creatinine, increased proteinuria and/or impaired kidney function, kidney disease–related treatment failure, or death for any cause.

LN flares were assessed from week 24, by when all the patients had completed induction therapy and tapered glucocorticoids to ≤10 mg/d. *LN flares* were defined as (i) impaired kidney function (i.e., reproducible eGFR decrease of >20% from week 24) accompanied by proteinuria (uPCR of >1 g/g) and/or cellular casts (red blood cells, white blood cells in the absence of infection, or both), (ii) increase in proteinuria compared with week 24, or (iii) treatment failure due to kidney disease–related intake of prohibited medications. *Increase in proteinuria* was defined as an increase in uPCR of >1 if week 24 uPCR was <0.2 g/g, uPCR of >2.0 g/g if week 24 uPCR was 0.2 to 1 g/g, or as a doubling of uPCR if week 24 uPCR was >1 g/g. A subgroup analysis of LN flares in patients who achieved PERR at week 24 and patients with week 24 uPCR ≤ 0.5 g/g was also performed. The analysis included only patients who were on treatment at week 24.

Time to confirmed eGFR decline of 30% and 40% were measured from day 1 and analyzed using either only on-treatment data or all data. The first analysis included all eGFR measurements obtained while patients received treatment ("on treatment"), in which data from patients who discontinued belimumab or placebo or withdrew from the study were censored from the earliest treatment discontinuation or study withdrawal time point. The second analysis included all eGFR measurements obtained while patients remained enrolled in the study (on study), even if they prematurely discontinued belimumab or placebo, with study withdrawal leading to censoring from that time point.

Sustained 30% and 40% decline in eGFR was defined as a 30% and 40% decrease in eGFR from baseline before withdrawal and confirmed by the last 2 eGFR values in the study.

The annual rate of eGFR decline was evaluated as a chronic slope from week 24 to account for acute effects of the LN flare and induction therapy on kidney function early in the study.[14] Like the time to confirmed eGFR decline, this analysis was performed using both the on-treatment and on-study data, but similar to the LN flare analysis, it included only patients who remained on treatment at week 24.

Statistical analysis

Efficacy end points were analyzed using the modified intention-to-treat population that included 223 patients in each treatment group. Two patients in the total randomized population ($n = 448$) were excluded from the modified intention-to-treat population because of compliance issues at the research site.

In general, statistical models controlled for race (Black African ancestry vs. non-Black African ancestry), induction regimen (CYC vs. MMF), baseline uPCR, and baseline eGFR. In the derivation of PERR and CRR, treatment (belimumab or placebo) discontinuation, study withdrawal, or treatment failure were imputed as "no response." In the derivation of the time to kidney-related event or death, data were censored after discontinuation of treatment, study withdrawal, or treatment failure unrelated to a kidney event.

PERR and CRR were analyzed using logistic regression models (analyses for the baseline proteinuria subgroups were *post hoc*). Time to renal-related event or death was analyzed using a Cox proportional hazards regression model (subgroup analyses were *post hoc* except for the analysis according to induction regimen, which was prespecified in the study protocol).

The *post hoc* end point of time to first LN flare from week 24 was analyzed using a Cox proportional hazards model adjusted for induction regimen, race, week 24 uPCR, and week 24 eGFR.

The annual rate of eGFR decline from week 24 (*post hoc* analysis) was estimated from a linear mixed model consisting of treatment group (belimumab vs. placebo), analysis visit (study week), and their interaction as well as random intercept and slope at the patient level. The covariance structure for the random intercept and slope was unstructured and heterogeneous for treatment groups.

The *post hoc* end points of time to 30% and 40% decline in eGFR from baseline were analyzed with Cox proportional hazards models adjusted for induction regimen, race, baseline uPCR, and baseline eGFR. Sustained 30% and 40% decline in eGFR (*post hoc* analysis) were analyzed using logistic regression models with the following covariates: treatment group, induction regimen, race, baseline uPCR, and baseline eGFR.

Analyses other than PERR, CRR, and time to death or renal-related event as specified above were *post hoc* and results should only be regarded as descriptive in nature. Additionally, the study was not powered to investigate subgroups and therefore any analyses by subgroup should be regarded as descriptive.

RESULTS

Study population

The baseline characteristics of the BLISS-LN modified intention-to-treat population were reported previously[9] and are summarized in Table 1. More than half of the patients (258 [57.8%]) had class III or IV LN, 116 (26.0%) had

Table 1 | Baseline characteristics (mITT population)

Characteristic	Placebo ($n = 223$)	Belimumab 10 mg/kg i.v. ($n = 223$)	Total ($N = 446$)
Female	196 (87.9)	197 (88.3)	393 (88.1)
Age, yr	33.1 ± 10.6	33.7 ± 10.7	33.4 ± 10.7
Race[a]			
Asian	109 (48.9)	114 (51.1)	223 (50.0)
White	75 (33.6)	73 (32.7)	148 (33.2)
Black African ancestry	31 (13.9)	30 (13.5)	61 (13.7)
American Indian or Alaska Native	6 (2.7)	4 (1.8)	10 (2.2)
Multiple	2 (0.9)	2 (0.9)	4 (0.9)
SLE disease duration,[b] yr	3.3 (0.2–8.0)	3.3 (0.3–8.1)	3.3 (0.2–8.1)
LN disease duration,[b] yr	0.2 (0.1–3.4)	0.2 (0.1–3.3)	0.2 (0.1–3.3)
Induction regimen			
CYC	59 (26.5)	59 (26.5)	118 (26.5)
MMF	164 (73.5)	164 (73.5)	328 (73.5)
Kidney biopsy class			
III or IV	132 (59.2)	126 (56.5)	258 (57.8)
III and V or IV and V	55 (24.7)	61 (27.4)	116 (26.0)
V	36 (16.1)	36 (16.1)	72 (16.1)
uPCR at screening, g/g	4.3 (3.9)	3.8 (2.6)	4.1 (3.3)
≥3	117 (52.5)	119 (53.4)	236 (52.9)
uPCR at baseline, g/g	3.5 (3.6)	3.2 (2.7)	3.4 (3.2)
≥3	92 (41.3)	91 (40.8)	183 (41.0)
eGFR at baseline, ml/min per 1.73 m^2	101.0 (42.7)	100.0 (37.7)	100.5 (40.2)
≥60	182 (81.6)	190 (85.2)	372 (83.4)
≥90	133 (59.6)	131 (58.7)	264 (59.2)

CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; mITT, modified intention-to-treat; MMF, mycophenolate mofetil; SLE, systemic lupus erythematosus; uPCR, urine protein/creatinine ratio.
[a]Patients were counted in only 1 category.
[b]*Duration* was defined as (date of the first dose – diagnosis date + 1)/365.25 yr.
Data are expressed as mean ± SD, median (interquartile range), or *n* (%).

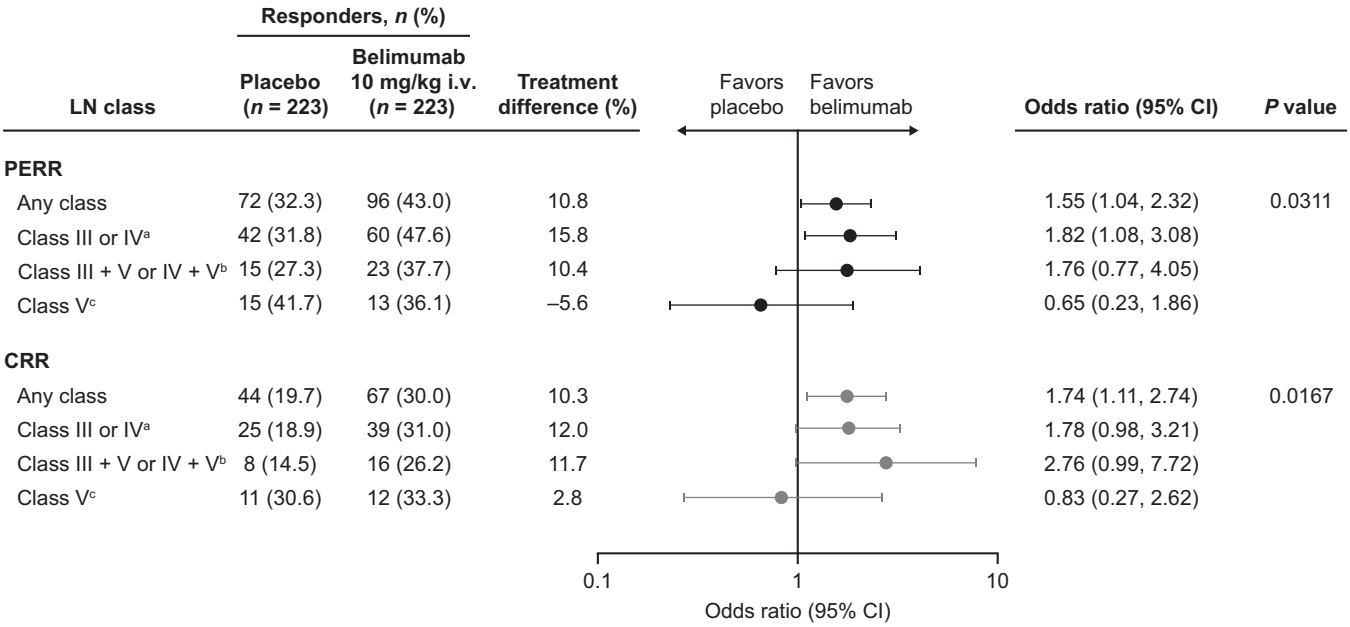


Figure 1 | Primary efficacy renal response (PERR) and complete renal response (CRR) at week 104 by lupus nephritis (LN) class (modified intention-to-treat population). [a]Placebo, $n = 132$; belimumab, $n = 126$. [b]Placebo, $n = 55$; belimumab, $n = 61$. [c]Placebo, $n = 36$; belimumab, $n = 36$. CI, confidence interval.

class III + V or class IV + V LN, and 72 (16.1%) had pure class V LN. The majority of patients (82.5%, $n = 368$) initiated induction therapy within 4 weeks of randomization, with more than half (57.6%, $n = 257$) starting it within 2 weeks of day 1. More patients received induction therapy with MMF than with CYC (328 [73.5%] vs. 118 [26.5%], respectively). The mean baseline uPCR was 3.38 g/g in patients with class III or IV LN, 3.42 g/g in patients with

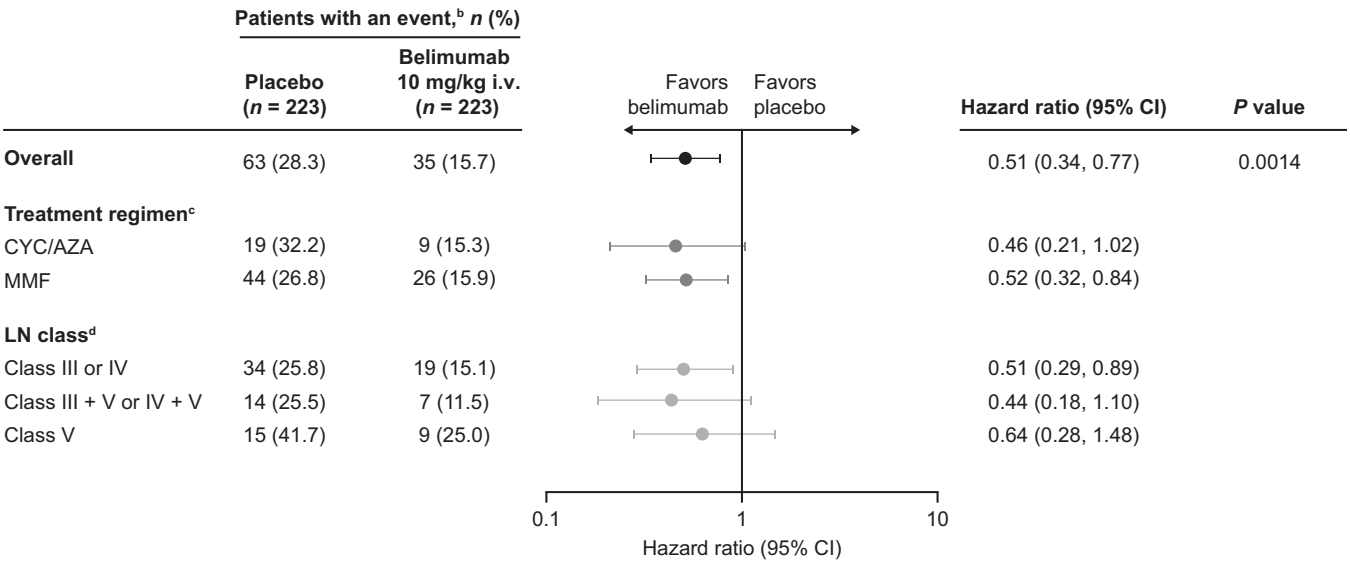
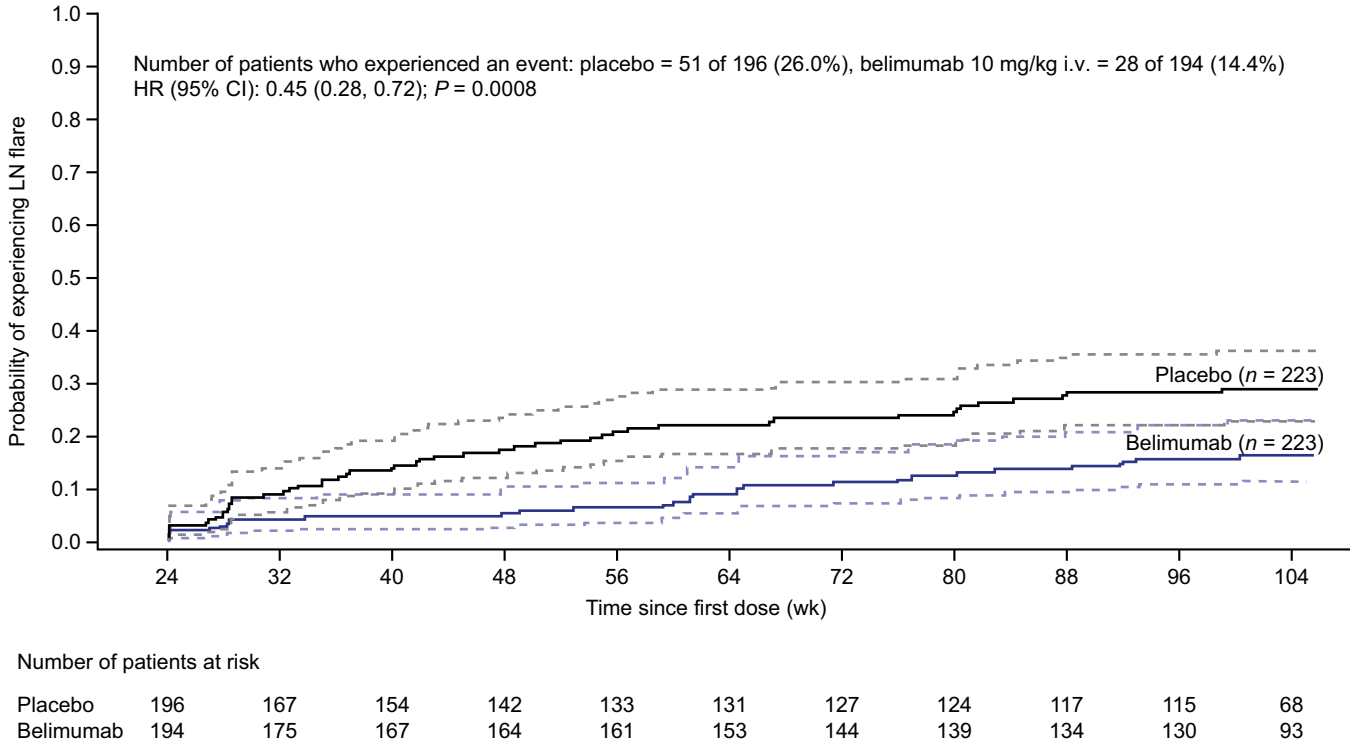


Figure 2 | Time to kidney-related event or death by standard therapy regimen and lupus nephritis (LN) class[a] (modified intention-to-treat population). [a]Subgroup analyses were *post hoc*, except for the analysis for time to kidney-related event or death by induction regimen, which were prespecified in the study protocol. [b]*Events* were defined as the first incidence of the following: death, progression to end-stage kidney disease, doubling of serum creatinine from baseline, kidney worsening, or kidney-related treatment failure. Patients who discontinued study treatment, withdrew from the study, have treatment failure unrelated to a kidney event, or were lost to follow-up were censored on the date of the event. Patients who completed the study were censored at week 104. [c]Cyclophosphamide (CYC)/azathioprine (AZA), placebo, $n = 59$; belimumab, $n = 59$; mycophenolate mofetil (MMF), placebo, $n = 164$; belimumab, $n = 164$. [d]Class III or IV, placebo, $n = 132$; belimumab, $n = 126$; class III + V or IV + V, placebo, $n = 55$; belimumab, $n = 61$; class V, placebo, $n = 36$; belimumab, $n = 36$. CI, confidence interval.



Number of patients at risk

Placebo	196	167	154	142	133	131	127	124	117	115	68
Belimumab	194	175	167	164	161	153	144	139	134	130	93

Figure 3 | Time to first lupus nephritis (LN) flare from week 24 (modified intention-to-treat population). Analyses were *post hoc*. Dashed lines show 95% confidence intervals (CIs). Patients who discontinued study treatment, withdrew from the study, are lost to follow-up, or have treatment failure not related to kidney disease were censored on the date of the event. Patients who completed the study were censored at week 104. HR, hazard ratio.

class III + V or class IV + V LN, and 3.22 g/g in patients with pure class V LN. A total of 183 (41.0%) patients had a uPCR of ≥3 g/g at baseline. The mean eGFR was 100.5 ± 40.2 ml/min per 1.73 m^2.

Of the 446 patients in the modified intention-to-treat population, 278 (62.3%) completed the investigational treatment through to the scheduled last dose at week 100 (146 [65.5%] and 132 [59.2%] patients randomized to belimumab

	Patients with an LN flare,[b] *n* (%)				
	Placebo (*n* = 223)	Belimumab 10 mg/kg i.v. (*n* = 223)	Favors belimumab / Favors placebo	Hazard ratio (95% CI)	*P* value
Overall[c]	51 (26.0)	28 (14.4)		0.45 (0.28, 0.72)	0.0008
Treatment regimen[d]					
CYC/AZA	18 (35.3)	7 (14.3)		0.30 (0.12, 0.75)	
MMF	33 (22.8)	21 (14.5)		0.55 (0.32, 0.96)	
LN class[e]					
Class III or IV	27 (23.3)	16 (14.3)		0.51 (0.27, 0.95)	
Class III + V or IV + V	13 (27.1)	7 (13.5)		0.43 (0.17, 1.13)	
Class V	11 (34.4)	5 (16.7)		0.40 (0.14, 1.15)	

Figure 4 | Time to first lupus nephritis (LN) flare from week 24 by standard therapy regimen and LN class[a] (modified intention-to-treat population). [a]Analyses were *post hoc*. [b]Patients who discontinued the study treatment, withdrew from the study, are lost to follow-up, or have treatment failure not related to kidney disease were censored on the date of the event. Kidney-related treatment failure is considered an event. Patients who completed the study were censored at week 104. [c]Placebo, *n* = 196; belimumab, *n* = 194. [d]Cyclophosphamide (CYC)/azathioprine (AZA), placebo, *n* = 51; belimumab, *n* = 49; mycophenolate mofetil (MMF), placebo, *n* = 145; belimumab, *n* = 145. [e]Class III or IV, placebo, *n* = 116; belimumab, *n* = 112; class III + V or IV + V, placebo, *n* = 48; belimumab, *n* = 52; class V, placebo, *n* = 32; belimumab, *n* = 30. CI, confidence interval.

Table 2 | eGFR slope from week 24 to week 104[a] (mITT population)

Variable	On treatment[b]		On study[c]	
	Placebo (n = 223)	Belimumab 10 mg/kg i.v. (n = 223)	Placebo (n = 223)	Belimumab 10 mg/kg i.v. (n = 223)
Patients with ≥1 eGFR value from week 24, n	198	196	198	196
Patients with eGFR value at week 104, n	128	140	163	173
eGFR (SE) at week 24[d]	106.6 (2.49)	109.4 (2.36)	106.8 (2.55)	109.5 (2.39)
eGFR slope (SE), ml/min per 1.73 m^2 per yr[d]	−3.18 (1.10)	−0.99 (0.77)	−5.72 (1.46)	−2.12 (0.97)
eGFR slope difference vs. placebo (SE)[d]		2.19 (1.34)		3.61 (1.76)
95% CI[d]		−0.45 to 4.84		0.15 to 7.06
P value[d]		0.1041		0.0407

CI, confidence interval; eGFR, estimated glomerular filtration rate; mITT, modified intention-to-treat; SE, standard error.
[a]Analyses were *post hoc*.
[b]Data from after treatment discontinuation were excluded.
[c]Includes all available data for patients on treatment at week 24.
[d]Statistics are from a linear mixed model consisting of treatment group (belimumab vs. placebo), analysis visit (weeks), and their interaction as well as random intercept and slope at the patient level. The covariance structure for the random intercept and slope is unstructured and heterogeneous for treatment groups.

and placebo, respectively) (Supplementary Figure S1). Including patients who discontinued treatment prematurely, 355 patients (79.6%) completed the study (186 [83.4%] and 169 [75.8%] in the belimumab and placebo groups, respectively; Supplementary Figure S1).

Effect of belimumab on kidney response by LN histologic class

The results of PERR and CRR at week 104 in the overall study population and in subgroups by ST regimens have been published.[9] Because BLISS-LN enrolled patients with proliferative and membranous forms of LN, including pure class V LN, a subgroup analysis was performed to evaluate whether response to therapy differed by histologic LN class. These data suggest that the overall increase in PERR and CRR after the addition of belimumab was mainly due to patients with a proliferative histologic component (Figure 1). There was no observed treatment difference for PERR or CRR in patients with pure class V LN. As this was a small subgroup, it is difficult to draw definitive conclusions about efficacy.

Effect of belimumab on time to kidney-related event or death and LN flares

Overall, the risk of having a kidney-related event or death during BLISS-LN was significantly reduced by belimumab treatment.[9] Kidney-related events were mainly increases in proteinuria, decreases in kidney function, or both or kidney-related treatment failure.[9] When analyzed by ST regimen and LN class, the results were directionally consistent with the overall population results, suggesting positive effects of belimumab in each subgroup (Figure 2).

BLISS-LN had a treatment duration of >2 years, presenting the opportunity to evaluate the effects of belimumab on the LN flare. During the last 18 months of the study, 28 of 194 (14.4%) and 51 of 196 (26.0%) patients had at least 1 LN flare while receiving belimumab or placebo, respectively. Belimumab reduced the risk of an LN flare by 55% relative to placebo (hazard ratio [95% confidence interval] 0.45 [0.28–0.72]; P = 0.0008) (Figure 3). Excluding treatment failure due to kidney disease–related intake of prohibited medications from the LN flare definition (24 fewer patients have flares), belimumab reduced the risk of an LN flare at any time relative to placebo by 59% (hazard ratio [95% confidence interval] 0.41 [0.23–0.73]; P = 0.0023). Consistent with the overall population, a reduction in the risk of an LN flare with belimumab was evident in both ST groups and across all LN classes (Figure 4). Similar trends favoring belimumab were observed in patients who achieved either PERR or uPCR ≤ 0.5 g/g at week 24 (Supplementary Table S1).

Table 3 | Time to 30% and 40% decline in eGFR[a] between baseline and week 104 (mITT population)

Variable	On treatment[b]		On study[c]	
	Placebo (n = 223)	Belimumab 10 mg/kg i.v. (n = 223)	Placebo (n = 223)	Belimumab 10 mg/kg i.v. (n = 223)
30% decrease in eGFR				
n (%)	28 (12.6)	15 (6.7)	38 (17.0)	19 (8.5)
HR (95% CI)	0.52 (0.28–0.98)		0.47 (0.27–0.83)	
P value	0.0429		0.0084	
40% decrease in eGFR				
n (%)	15 (6.7)	6 (2.7)	26 (11.7)	10 (4.5)
HR (95% CI)	0.38 (0.15–0.98)		0.35 (0.17–0.74)	
P value	0.0457		0.0056	

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; mITT, modified intention-to-treat.
[a]Analyses were *post hoc*.
[b]Patients who discontinued treatment and/or withdrew from the study were censored from the first occurrence.
[c]Patients who withdrew from the study were censored from that point.

Table 4 | Sustained 30% and 40% decline in eGFR by the end of study participation (mITT population)[a,b]

Variable	Placebo (n = 223)	Belimumab 10 mg/kg i.v. (n = 223)
Sustained 30% decrease in eGFR		
n (%)	25 (11.2)	8 (3.6)
Observed difference vs. placebo (%)	−7.62	
OR (95% CI)	0.29 (0.13–0.68)	
P value	0.0042	
Sustained 40% decrease in eGFR		
n (%)	15 (6.7)	4 (1.8)
Observed difference vs. placebo (%)	−4.93	
Odds ratio (95% CI)	0.25 (0.08–0.78)	
P value	0.0166	

CI, confidence interval; eGFR, estimated glomerular filtration rate; mITT, modified intention-to-treat; OR, odds ratio.
[a]Analyses were *post hoc*.
[b]As confirmed by the last 2 eGFR measurements in the study.

Effect of belimumab on kidney function

The slope of eGFR was assessed between week 24 and week 104 (Table 2). The annual rate of decline in eGFR appeared to be less in the belimumab-treated group than in the placebo group in both the on-treatment and on-study analyses (Table 2).

In both the on-treatment and on-study analyses, belimumab reduced the risk of having a 30% and 40% decline in eGFR during 104 weeks relative to placebo (Table 3). Sustained 30% and 40% decline in eGFR (as confirmed by the last 2 observed eGFR measurements) was less commonly reported with belimumab treatment relative to placebo (Table 4). These eGFR thresholds are considered predictors of future kidney insufficiency or failure.[15]

Effect of baseline proteinuria on the efficacy of belimumab

Because the level of proteinuria at flare may affect the rapidity and completeness of the kidney response in LN,[16–18] analyses were performed on subgroups of patients with baseline uPCR < 3 g/g (n = 263) and uPCR ≥ 3 g/g (n = 183). The effects of belimumab favoring PERR and CRR were driven by the response in patients with baseline uPCR < 3 g/g (Figure 5). There were no observed differences between belimumab and placebo in PERR and CRR in patients with higher baseline proteinuria (≥3 g/g). The results of the time to kidney-related event or death analysis across baseline proteinuria subgroups were consistent with the results in the overall population, suggesting positive effects of belimumab treatment on the reduction of the risk of kidney-related events or death in patients with both low and high baseline proteinuria levels (Figure 6). Kidney-related events were predominantly driven by increased proteinuria, decreased kidney function, or kidney disease–related treatment failure (Supplementary Table S2).

To further understand the effects of belimumab on kidney function in patients with different levels of proteinuria, we reanalyzed eGFR slopes and the time to a 30% or 40% decline in eGFR by baseline level of proteinuria. These data suggest that the risk of reaching a 30% or 40% decline in eGFR at any time during the study was reduced in patients treated with belimumab for high and low baseline proteinuria levels, with a greater magnitude of risk reduction observed in patients with low baseline proteinuria (Supplementary Table S3). For the eGFR slope from week 24 to week 104, these data suggest that belimumab lowered the rate of annual eGFR decline for both baseline proteinuria level groups in the on-treatment analysis (Supplementary Table S4). In the on-study analysis, there was no observed benefit of belimumab in patients with baseline proteinuria (uPCR of ≥ 3 g/g; Supplementary Table S4).

In patients with an LN flare, increased proteinuria leads to increased kidney elimination of belimumab, resulting in decreased systemic exposure to the drug early in treatment. However, from week 24 onward there was no appreciable

Response type	Baseline proteinuria level[b]	Responders, *n* (%) Placebo (n = 223)	Belimumab 10 mg/kg i.v. (n = 223)	Treatment difference (%)	Odds ratio (95% CI)	*P* value
PERR	Overall	72 (32.3)	96 (43.0)	10.8	1.55 (1.04, 2.32)	0.0311
	Low[c]	44 (33.6)	72 (54.5)	21.0	2.44 (1.46, 4.08)	
	High[d]	28 (30.4)	24 (26.4)	−4.1	0.85 (0.44, 1.63)	
CRR	Overall	44 (19.7)	67 (30.0)	10.3	1.74 (1.11, 2.74)	0.0167
	Low[c]	29 (22.1)	51 (38.9)	16.5	2.18 (1.26, 3.78)	
	High[d]	15 (16.3)	16 (17.6)	1.3	1.20 (0.54, 2.64)	

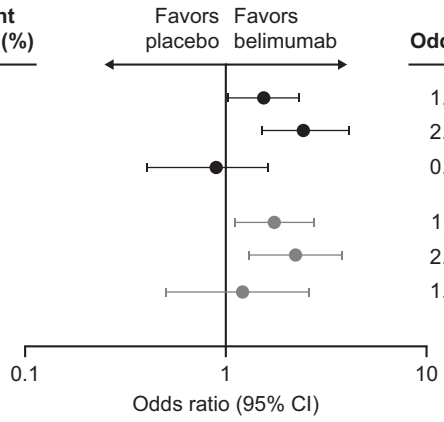
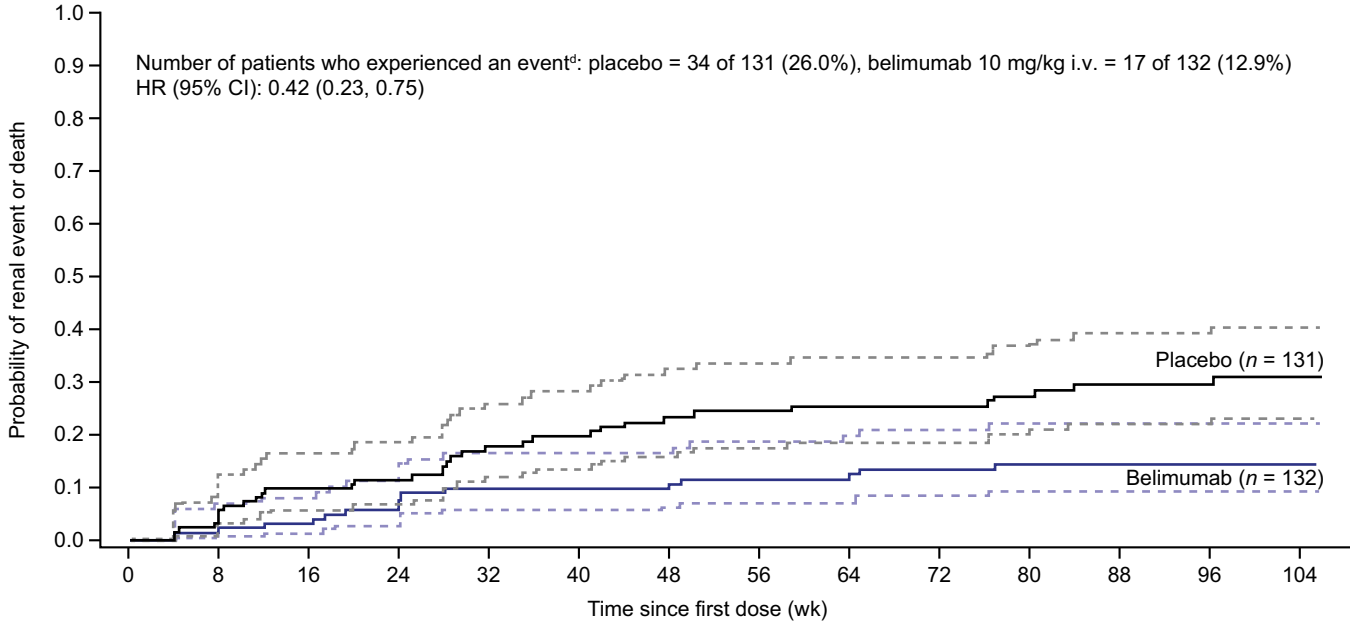


Figure 5 | Primary efficacy renal response (PERR) and complete renal response (CRR) at week 104 by baseline proteinuria[a] (modified intention-to-treat population). [a]Analyses were *post hoc*. [b]*Low/high baseline proteinuria levels* were defined as urine protein/creatinine ratio < 3 g/g and ≥ 3 g/g, respectively. [c]Placebo, n = 131; belimumab, n = 132. [d]Placebo, n = 92; belimumab, n = 91. CI, confidence interval.

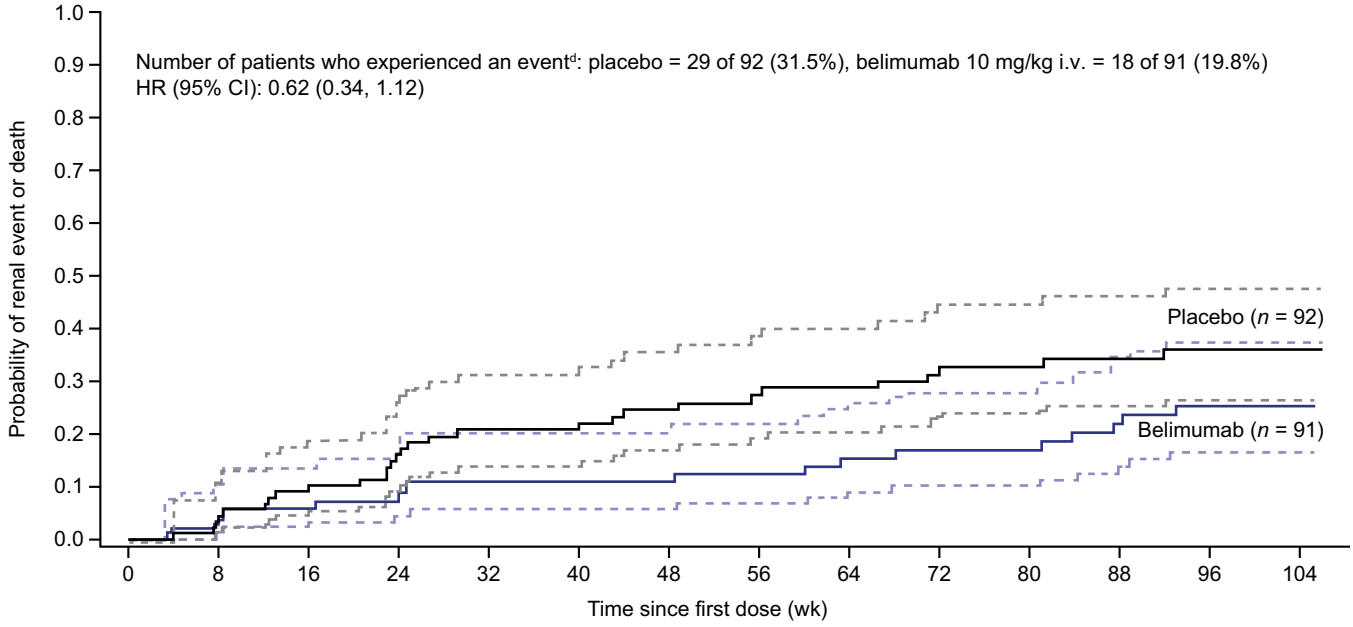
a **Low baseline proteinuria level**[c]



Number of patients at risk

Placebo	119	107	104	89	84	79	76	75	73	70	67	66	54
Belimumab	126	118	114	103	101	99	98	96	90	88	86	85	67

b **High baseline proteinuria level**[c]



Number of patients at risk

Placebo	84	78	71	65	63	58	53	51	47	46	45	44	24
Belimumab	83	74	72	64	61	60	59	55	52	51	47	45	35

Figure 6| Time to kidney-related event or death by baseline proteinuria[a,b] (modified intention-to-treat population). [a]Analyses were *post hoc*. [b]Dashed lines show 95% confidence intervals (CIs). [c]*Low/high baseline proteinuria levels* were defined (continued)

difference in exposure to belimumab between patients with high and low proteinuria at baseline (data not shown). Although it may seem plausible that lower exposure in the early stage of the treatment may negatively affect efficacy, the exposure-response analyses provided no evidence that increasing early belimumab exposure would change efficacy outcomes in patients with nephrotic range proteinuria (data not shown).

DISCUSSION

A key goal of the management of LN is preservation of kidney function and may be achieved by controlling disease activity and preventing LN flares.[2,19] BLISS-LN demonstrated that adding belimumab to ST significantly improved kidney responses (PERR and CRR) compared with ST alone, but did not increase adverse events.[9] We performed a *post hoc* analysis of BLISS-LN and found that the risk of an LN flare over time decreased in patients given ST plus belimumab versus ST alone. Furthermore, positive effects on validated surrogates of ESKD progression were observed in belimumab-treated patients. Although eGFR declined in patients treated with belimumab plus ST and ST alone, those treated with belimumab tended to lose eGFR more slowly. The magnitude of the observed difference in eGFR decline would be sufficient to delay progression to ESKD.[14] Additionally, the risk of having a 30% or 40% decline in eGFR was higher in patients treated only with ST than in patients also given belimumab; moreover, more patients treated with ST alone sustained this 30% to 40% decline in eGFR compared with belimumab-treated patients through the end of study participation. Sustained 30% or 40% decline in eGFR over 2 to 3 years of follow-up strongly correlates with ESKD development and is accepted as a surrogate end point for clinical trials in chronic kidney disease.[15] These data demonstrate that adding belimumab to ST not only facilitates control of disease activity but also prevents LN flares and may help preserve kidney function.

Preservation of kidney function by belimumab treatment is explained, in part, by its salutary effects on kidney worsening and the rate of an LN flare. LN flares or ongoing disease activity, even if low grade, increase the risk of chronic kidney disease in patients with LN that may progress to ESKD.[1,3,20,21] As shown here, belimumab prevented kidney worsening and overt LN flares across LN background therapies, LN histologic classes, and baseline proteinuria levels.

Preliminary data suggest that belimumab may have direct antifibrotic effects that could contribute to preservation of kidney function. A small study in patients with systemic sclerosis examined transcript expression in skin biopsies from patients who had clinical improvement with belimumab.[22] Belimumab downregulated pathways related to matrix expression and inflammation, raising the possibility that belimumab may attenuate fibrosis.[22] Additionally, in a murine model of bleomycin-induced pulmonary fibrosis, lung injury was attenuated by blocking or knocking out BLyS, the target of belimumab.[23] In this model, pulmonary fibrosis was interleukin-17A dependent, and interleukin-17A expression was enhanced by exogenous BLyS.[23] These data are consistent with a role of BLyS in the fibrosis that occurs during inflammatory tissue injury. BLyS inhibition by belimumab could, therefore, directly block the development of fibrosis. Although speculative, this may potentially translate to preventing or slowing chronic kidney damage in patients with LN treated with belimumab.

PERR and CRR at week 104 did not demonstrate a difference between ST alone versus ST plus belimumab in patients who had baseline proteinuria $\geq$ 3 g/g. Although the kidney clearance of belimumab is increased in patients with high proteinuria,[24] the exposure-response analyses in BLISS-LN provided no evidence that increased clearance of belimumab early in the treatment was responsible for the lack of treatment effect on PERR and CRR. In contrast, these *post hoc* subgroup analyses of time to kidney-related event or death and eGFR decline end points suggested that belimumab may reduce the risk of kidney disease progression regardless of baseline proteinuria level.

This discordance between PERR/CRR and the apparent beneficial effects of belimumab on the LN flare rate and eGFR in patients with different baseline levels of proteinuria demonstrates some of the difficulties of using end points based largely on an absolute threshold of proteinuria in clinical trials for LN.[25] A proteinuria level of $<$0.5 g/d is required for most definitions of CRR. The studies that established PERR as a reasonable end point in LN trials demonstrated good long-term kidney outcomes if patients achieved a proteinuria level of 0.7 to 0.8 g/d after 1 year of treatment.[26–28] Even this more relaxed proteinuria cutoff may be too strict. Although reaching a proteinuria level of $\leq$0.7 to 0.8 g/d by 1 year had a high positive predictive value for preservation of kidney function, this threshold had a low negative predictive value. Many patients who did not realize a decrease in proteinuria to this level after 1 year of treatment still had good long-term kidney outcomes.[26,27] There may be several reasons for this. One potentially important issue not generally considered in clinical trials is that resolution of immune kidney injury is not always reflected by resolution of proteinuria, and vice versa.[29,30] Addressing this issue would require a kidney biopsy end point or a validated noninvasive biomarker of kidney histology to evaluate whether histologic activity had resolved. Nonetheless, maintenance of kidney function exceeds the

Figure 6 | (continued) as urine protein/creatinine ratio $<$ 3 g/g and $\geq$ 3 g/g, respectively. [d]*Events* were defined as the first incidence of the following: death, progression to end-stage kidney disease, doubling of serum creatinine from baseline, kidney worsening, or kidney-related treatment failure. Patients who discontinued study treatment, withdrew from the study, have treatment failure unrelated to a kidney event, or were lost to follow-up were censored on the date of the event. Patients who completed the study were censored at week 104. HR, hazard ratio.

proteinuria level in importance in patient-reported outcomes of glomerular diseases.[31]

In a small subgroup of patients with pure class V LN, belimumab did not improve PERR or CRR rates relative to ST, although the level of baseline proteinuria in patients with pure class V LN was not different from that in those with proliferative LN with or without a class V component. The pathogenesis of class V LN is likely different from that of class III or IV. Most trials to date have included a mixed population of patients with proliferative or membranous LN[32,33] because of the practical need of adequate trial enrollment but also because nonspecific immunosuppressants (MMF, AZA, and CYC) have been used to treat all LN classes.[34,35] As more targeted therapeutic agents for LN are evaluated, it may be reasonable to enrich trial enrollment with patients who may be more likely to benefit from the novel agents. This will provide more insight into the pathogenic mechanisms of LN phenotypes. Importantly, and despite the considerations just discussed, positive effects of belimumab treatment on reducing the risk of kidney-related events or death and prevention of LN flares in patients with pure class V LN were observed, consistent with the results in other LN classes.

Several limitations to these analyses should be considered. BLISS-LN was not designed to detect treatment differences in the subgroups or for the outcomes evaluating decline in kidney function. The smaller sample sizes often lacked sufficient power for definitive resolution of the questions posed. Most of the analyses were performed *post hoc* and were exploratory in nature. LN flare and eGFR slope analyses were performed for the subset of patients who remained on treatment at week 24, which could be a potential source of bias as discontinuations during the first 6 months of treatment may have been nonrandom.

In conclusion, these data suggest that the addition of belimumab to ST may be effective in preserving long-term kidney function in patients with LN. This likely occurs through several pathways, with prevention of kidney worsening and LN flares of undoubted importance. BLISS-LN and this *post hoc* analysis also highlight the discordance between proteinuria and established surrogate end points for kidney failure, such as 30% to 40% decline in eGFR and eGFR slope. LN is a chronic kidney disease; therefore, preservation of kidney function as opposed to achieving a specific level of proteinuria is the main goal of therapy. BLISS-LN demonstrated that a 30% and 40% decline in eGFR and an eGFR slope end point may be feasible for a 2-year LN trial and could be considered as a model for efficacy evaluation in future LN studies.

DISCLOSURE

BHR has received advisory fees from Aurinia Pharmaceuticals, Calliditas Therapeutics, ChemoCentryx, Retrophin, Novartis, Omeros, MorphoSys, EMD Serono, Bristol Myers Squibb, Janssen Pharmaceuticals, AstraZeneca, and GlaxoSmithKline and research funding from the National Institutes of Health. RF has received advisory board fees, travel support, and consulting fees from GlaxoSmithKline. YKOT has received grant support from GlaxoSmithKline and Aurinia Pharmaceuticals and consulting fees from Kezar Life Sciences, GlaxoSmithKline, Aurinia Pharmaceuticals, and Novartis. GC has received 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. AM has received advisory board fees from GlaxoSmithKline. XY has received grant support from Baxter Healthcare, Wanbang Biopharmaceuticals, Kyowa Kirin, AstraZeneca, and GlaxoSmithKline. BJ, YG, TG-R, DB, JG, C-HT, and DAR are employed by and own shares and stock options of GlaxoSmithKline. JG is a volunteer member of the PSI Scientific Committee who organizes webinars, meetings, and the annual conference. PSI is a not-for-profit professional organization.

DATA STATEMENT

Anonymized individual patient data and study documents can be requested for further research from https://www.clinicalstudydatarequest.com/.

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AUTHOR CONTRIBUTIONS

BHR, RF, BJ, YG, DB, and DAR conceived of and designed the study. BHR, RF, YKOT, GC, AM, and XY acquired the data. BHR, RF, YKOT, GC, AM, XY, BJ, YG, TG-R, DB, JG, C-HT, and DAR analyzed and interpreted the data.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Time to first lupus nephritis (LN) flare from week 24 in primary efficacy renal response (PERR) responders and patients with a urine protein/creatinine ratio (uPCR) $\leq$ 0.5 at week 24[a,b] (modified intention-to-treat [mITT] population).

Table S2. First renal-related events or death by proteinuria category[a,b] (modified intention-to-treat [mITT] population).

Table S3. Time to confirmed 30% and 40% decrease in estimated glomerular filtration rate (eGFR) from baseline by baseline proteinuria level[a] (modified intention-to-treat [mITT] population).

Table S4. Estimated glomerular filtration rate (eGFR) slope from week 24 to week 104 by baseline proteinuria level[a] (modified intention-to-treat [mITT] population).

Figure S1. Patient disposition.

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