Efficacy and Safety of Intravenous *Benlysta* in Adult Patients With Active Lupus Nephritis (BLISS-LN)

Summary

- The phase 3, BLISS-LN trial evaluated the efficacy and safety of *Benlysta* (belimumab) intravenous (IV) 10 mg/kg vs placebo, both in combination with standard therapy (ST), in patients ≥ 18 years with biopsy-confirmed Class III, or IV, and/or V active lupus nephritis (LN; N = 448).[1]
- Standard therapy included induction with high-dose corticosteroids (HDCS) plus cyclophosphamide (CYC), followed by azathioprine (AZA) plus low-dose corticosteroids (LDCS) as maintenance therapy, *or* induction with HDCS plus mycophenolate mofetil (MMF), followed by MMF plus LDCS for maintenance.[2]
- At Week 104, significantly more patients treated with *Benlysta* IV plus ST achieved a primary efficacy renal response (PERR; primary endpoint) vs placebo plus ST (43% vs 32.3%, respectively; odds ratio [OR], 1.55 [95% CI, 1.04–2.32]; $P = 0.0311$).[1] Statistically significant differences were also achieved for all 4 major secondary endpoints.
- Overall, adverse events (AEs) occurred in 95.5% of patients who received *Benlysta* IV vs 94.2% on placebo.[2] Serious AEs were reported in 25.9% and 29.9% of patients who received *Benlysta* IV and placebo, respectively. AEs reported in ≥ 15% of patients across groups were upper respiratory tract infection (URTI), diarrhea, urinary tract infection (UTI), and headache.
- Use of *Benlysta* is not recommended in patients with severe active lupus nephritis.[3]
- Important safety information is found in the attached Prescribing Information.

STUDY DESIGN

A phase 3, randomized, double-blind, 104-week trial evaluated the efficacy and safety of *Benlysta* IV 10 mg/kg vs placebo, both in addition to standard therapy, in patients aged ≥ 18 years with auto-antibody positive, biopsy-confirmed, active LN (Figure 1; BeLimumab International Systemic Lupus Erythematosus Study-LN [BLISS-LN]; GSK Study ID: 114054; ClinicalTrials.gov Identifier: NCT01639339).[1] Key inclusion and exclusion criteria are summarized in Table 1. Patients received *Benlysta* IV 10 mg/kg, or placebo, every 2 weeks for the first 3 doses, and then every 4 weeks thereafter.

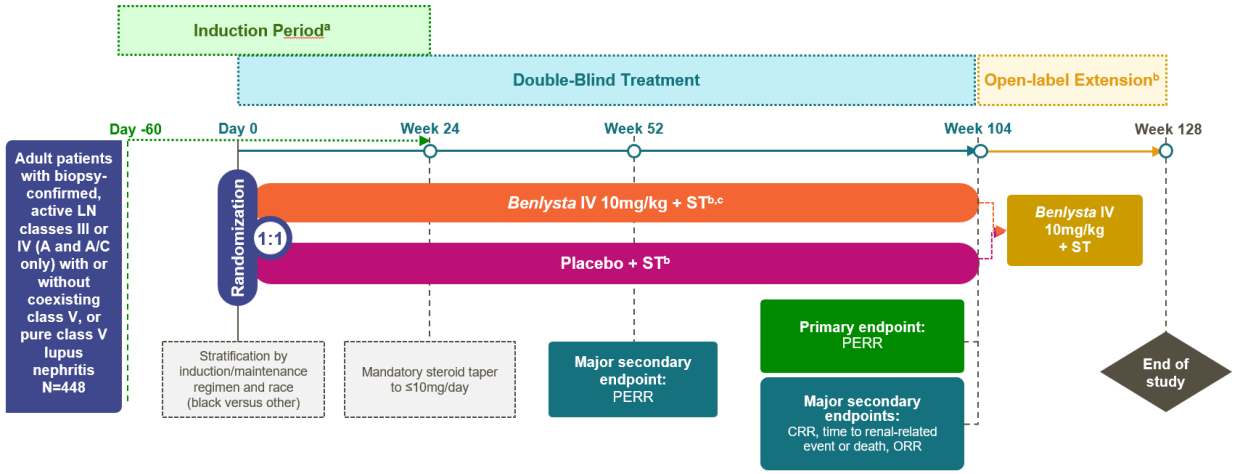
Standard induction therapy consisted of either IV CYC (500 mg every 2 weeks [± 3 days]) for 6 infusions, or MMF (1–3 g/day orally).[2]

- For patients who received CYC induction therapy, AZA maintenance therapy (target dose 2 mg/kg/day [≤ 200 mg/day]) was started approximately 2 weeks after the last CYC dose and administered until study end.[2]
- For patients who received MMF induction therapy, maintenance therapy consisted of MMF doses between 1-3 g/day through study end.[2] After 6 months of MMF therapy, the dose of MMF could have been reduced to 1 g/day, or switched to AZA (target dose 2 mg/kg/day) for tolerability reasons. The use of IV forms of mycophenolate was prohibited.

All patients were on HDCS as part of the induction therapy.[2] The recommended corticosteroid regimen was 0-3 IV pulses of methylprednisolone (500 mg–1000 mg/pulse), followed by oral prednisone 0.5–

1 mg/kg/day with total daily dose ≤ 60 mg/day. Oral corticosteroids were then tapered. A patient was considered a treatment failure if the prednisone dose was not ≤ 10 mg/day by Week 24.

Figure 1. BLISS-LN Study Design[2]



[a]**Standard therapy= induction with HDCS+CYC followed by LDCS+AZA OR induction with HDCS+MMF followed by LDCS+MMF**; [b]Patients who receive treatment with study agent through Week 100 and complete Week 104 assessments in the double-blind period may enter into a 6-month open-label extension; [c]Days 0, 14, 28, and then every 28 days thereafter through 100 weeks, with a final evaluation for the double-blind treatment period at 104 weeks
AZA= azathioprine; CRR= complete renal response; CYC= cyclophosphamide; HDCS= high dose corticosteroids; IV = intravenous; LN= lupus nephritis; LDCS= low dose corticosteroids; MMF= mycophenolate mofetil; ORR= ordinal renal response; PERR= primary efficacy renal response; ST= standard therapy.

Table 1. Key Inclusion and Exclusion Criteria[1,2]

Key Inclusion Criteria	Key Exclusion Criteria
• Diagnosis of SLE by ACR criteria • Auto-antibody positive[a] • Biopsy-proven[b] active LN (Class III, or IV, and/or V using the ISN/RPS criteria) • Active renal disease at Screening requiring induction therapy with HDCS and IV CYC, or HDCS and MMF (or other oral forms of mycophenolate) within 60 days prior to Baseline. Factors used to define active renal disease at Screening were: uPCR of ≥ 1, and: - Active urinary sediment as defined by at least 1 of the following[c]: i) > 5 RBC/hpf[d], ii) > 5 WBC/hpf[d], or iii) cellular casts (RBC or WBC) - Patients without active urinary sediment were eligible if they met at least 1 of the following criteria: i) biopsy-confirmed LN in past 3 months, or ii) proteinuria ≥ 3.5 g/day (or uPCR ≥ 3.5).	• Previously failed both CYC and MMF induction therapies • Dialysis within 364 days of Baseline • eGFR < 30 mL/min/1.73m^2 at Screening • Pre-CYC induction therapy leukocyte count of Grade 3 or 4 • CYC induction therapy in the past 3 months • Severe active CNS lupus requiring therapy within 60 days of Baseline • Treatment with *Benlysta* or any B-cell targeted therapy in the year prior to Baseline • History of malignant neoplasm in the last 5 years[e] • Acute or chronic infections requiring management within 60 days

[a] ANA ≥ 1:80, and/or anti-dsDNA ≥ 30 IU/mL; [b] Biopsy-confirmed in the past 6 months prior to Screening; [c] In absence of menses and genitourinary tract infection; [d] Or above the laboratory reference range; [e] Except for adequately treated cancers of the skin (basal or squamous cell) or carcinoma in situ of the uterine cervix.

ACR = American College of Rheumatology; ANA = anti-nuclear antibody; anti-dsDNA = anti-double stranded deoxyribonucleic acid; CNS = central nervous system; CYC = cyclophosphamide; eGFR = estimated glomerular filtration rate; HDCS = high-dose corticosteroids; HPF = high power field; ISN/RPS = International Society of Nephrology/Renal Pathology Society; LN = lupus nephritis; MMF = mycophenolate mofetil; RBC = red blood cell; SLE = systemic lupus erythematosus; uPCR = urine protein:creatinine ratio; WBC = white blood cell.

Endpoints

The primary endpoint was the PERR at Week 104 (Table 2).[1] Major secondary endpoints were complete renal response (CRR) at Week 104, PERR at Week 52, time to renal-related event or death, and ordinal renal response (ORR) at Week 104. Definitions are summarized in Table 2.

Table 2. Primary Endpoint and Major Secondary Endpoint Definitions[1,2]

Endpoint	Definition
PERR[a,b]	• uPCR ≤ 0.7, and • eGFR no more than 20% below the pre-flare value or ≥ 60 mL/min/1.73m^2, and • Not a treatment failure
CRR[c]	• uPCR < 0.5, and • eGFR no more than 10% below the pre-flare value or ≥ 90 mL/min/1.73m^2, and • Not a treatment failure
Time to renal-related event or death	First of the following: • Death • ESRD • Doubling of serum creatinine • Renal worsening as evidenced by increased proteinuria[d] and/or impaired renal function[e], or • Renal disease-related treatment failure
ORR (complete, partial or no response)	CRR (as defined above) Partial renal response (PRR) – eGFR no more than 10% below the Baseline value or within normal range, and ≥ 50% decrease in the uPCR with 1 of the following: • a uPCR of < 1, if the Baseline ratio was ≤ 3, or • a uPCR of < 3, if the Baseline ratio was > 3, and • Not a treatment failure No renal response (NRR) – not meeting CRR or PRR criteria

Note: The primary and the 4 major secondary efficacy endpoints were evaluated for statistical significance based on a step-down sequential testing procedure as follows: PERR at Week 104, CRR at Week 104, PERR at Week 52, time to renal-related event or death, and ORR at Week 104.

[a] PERR at Week 104 was defined by a response at Week 100 and confirmed by a repeat measurement at Week 104; [b] PERR at Week 52 was defined by a response at Week 48 and confirmed by a repeat measurement at Week 52; [c] CRR at Week 104 was defined by a response at Week 100 and confirmed by a repeat measurement at Week 104; [d] Defined using spot urine as a reproducible increase in 24-hour urine protein levels (as measured in uPCR) to > 1 g if the Baseline value was < 0.2 g, or > 2 g if the Baseline value was between 0.2 g–1 g, or more than twice the value at Baseline if the Baseline value was > 1 g; [e] Defined as a reproducible decrease in GFR of > 20% accompanied by at least 1 of the following: proteinuria (> 1), RBC casts, WBC casts.

CRR = complete renal response; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; ORR = ordinal renal response; PERR = primary efficacy renal response; RBC = red blood cell; uPCR = urine protein:creatinine ratio; WBC = white blood cell.

RESULTS

In total, 448 patients were randomized, and received at least 1 dose of study medication; the modified Intent-to-Treat (mITT) Population comprised 446 patients (2 patients were excluded due to non-compliance issues but were included in the safety analysis).[2] Key Baseline demographics and disease characteristics are shown in Table 3.

Overall, 16.6% of patients who received *Benlysta* IV, and 24.2% on placebo withdrew.[2] The most common reason for study withdrawal was withdrawal of consent (*Benlysta* IV, 8.5%; placebo, 11.7%).

Randomization of patients to treatment groups was stratified by induction regimen (CYC: 59 patients per group and MMF: 164 patients per group), and race (black race: *Benlysta* IV, n = 31; placebo, n = 32, and non-black race: *Benlysta* IV, n = 192; placebo, n = 191).[2]

Table 3. Baseline Demographics and Disease Characteristics of the mITT Population[1,2]

	***Benlysta* IV 10 mg/kg + ST (n = 223)**	**Placebo + ST (n = 223)**
Female, % (n)	88.3 (197)	87.9 (196)
Mean Age (years)	33.7	33.1
Race, % (n)[a]		
Asian	51.1 (114)	48.9 (109)
White/Caucasian	32.7 (73)	33.6 (75)
Black or African American	13.5 (30)	13.9 (31)
Mean LN disease duration (years)	2.28	2.35
Mean SLE disease duration (years)	5.49	5.14
Renal biopsy class category[b] local reader, % (n)		
Class III or IV	56.5 (126)	59.2 (132)
Class III+V or Class IV+V	27.4 (61)	24.7 (55)
Class V	16.1 (36)	16.1 (36)
uPCR Category (g/g), % (n)		
< 0.5	4 (9)	3.6 (8)
0.5 to < 3	55.2 (123)	55.2 (123)
≥ 3	40.8 (91)	41.3 (92)
≤ 0.7	9.9 (22)	6.7 (15)
Mean uPCR ratio level	3.1982	3.5291
eGFR (mL/min/1.73m^2) category, % (n)		
< 30	1.3 (3)	2.7 (6)
30 to < 60	13.5 (30)	15.7 (35)
60 to < 90	26.5 (59)	22 (49)
≥ 60	85.2 (190)	81.6 (182)
≥ 90	58.7 (131)	59.6 (133)
Mean eGFR (mL/min/1.73m^2)	100	101
Mean pre-flare eGFR (mL/min/1.73m^2)[c,d]	99.6	98.6

[a] Patients were counted in 1 category; [b] Based on the presence of class III, IV, and V results although other classes may have also been present; [c] Pre-flare was defined as most recent values obtained prior to Screening and before first manifestations of the current renal flare, as reported by investigator if available; [d] Derived from pre-flare serum creatinine.

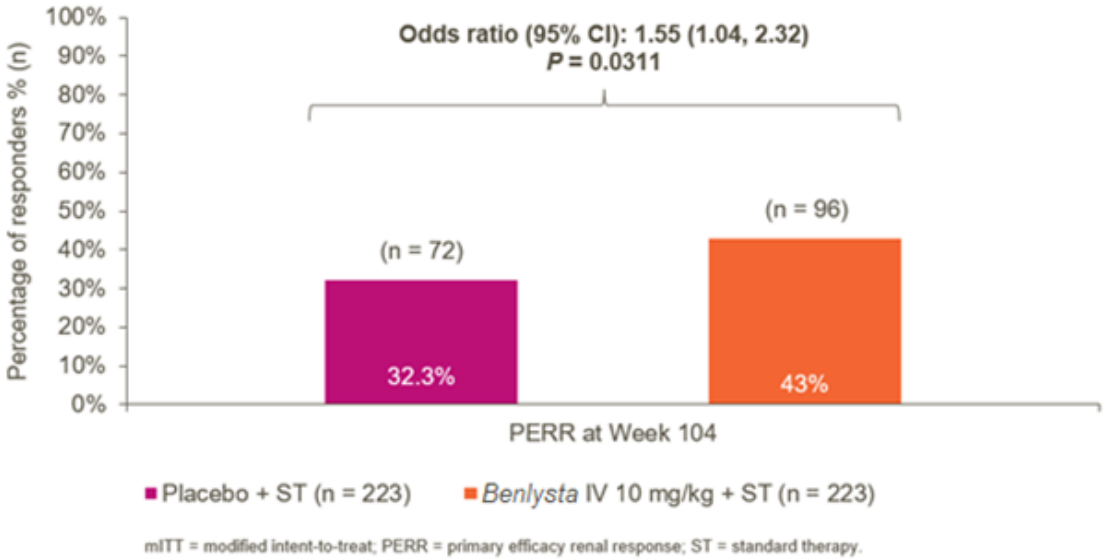
eGFR = estimated glomerular filtration rate; LN = lupus nephritis; mITT = modified intent-to-treat; SLE = systemic lupus erythematosus; ST = standard therapy; uPCR = urine protein:creatinine ratio.

Efficacy Results

Primary Endpoint

The primary endpoint was met; significantly more patients treated with *Benlysta* IV plus ST had a PERR compared with placebo plus ST at Week 104 (Figure 2).[1]

Figure 2: PERR at Week 104 (mITT Population)[2]



mITT = modified intent-to-treat; PERR = primary efficacy renal response; ST = standard therapy.

Major Secondary Endpoints

In addition, statistically significant differences were achieved between *Benlysta* IV plus ST and placebo plus ST for all 4 major secondary endpoints (Table 4).[2]

Table 4. Major Secondary Endpoint Results (mITT Population)[2]

	***Benlysta* IV 10 mg/kg + ST (n = 223)**	**Placebo + ST (n = 223)**	**OR/HR (95% CI) vs Placebo**	***P*-value**
Major Secondary Endpoint, % (n)				
CRR at Week 104, responders	30 (67)	19.7 (44)	1.74[a] (1.11–2.74)	0.0167
PERR at Week 52, responders	46.6 (104)	35.4 (79)	1.59[a] (1.06–2.38)	0.0245
Time to renal-related event or death[b], patients with an event	15.7 (35)	28.3 (63)	0.51[c] (0.34–0.77)	0.0014
ORR at Week 104				
CRR, responders	30 (67)	19.7 (44)	–	0.0096
PRR, responders	17.5 (39)	17 (38)	–	
Non-responders[d]	52.5 (117)	63.2 (141)	–	

[a] Odds ratio; [b] Events were defined as the first event experienced among the following: death, progression to ESRD, doubling of serum creatinine from Baseline, renal worsening, or renal-related treatment failure. Patients who discontinued randomized treatment, withdrew from the study, or were lost to follow-up were censored on the date of the event. Patients who completed the 104-week treatment period were censored at the Week 104 visit. Time to event was defined as (event date – treatment start date +1); [c] Hazard ratio; [d] Non-responders = IPD/TF/WD.

CRR = complete renal response; ESRD = end stage renal disease; HR = hazard ratio; IPD = investigational product discontinuation; mITT = modified intent-to-treat; OR = odds ratio; ORR = ordinal renal response; PERR = primary efficacy renal response; PRR = partial renal response; ST = standard therapy; TF = treatment failure; WD = withdrawal.

Safety

Overall, AEs occurred in 95.5% of patients who received *Benlysta* IV plus ST vs 94.2% on placebo plus ST.[2] Serious AEs were reported in 25.9% and 29.9% of patients who received *Benlysta* IV and placebo, respectively. In both groups, 12.9% of patients experienced ≥ 1 AE resulting in study treatment discontinuation.

Eleven deaths occurred during the study (*Benlysta* IV, n = 6; placebo, n = 5), the most common cause was infections (3 patients/group).[1] The listing of deaths by preferred term and adjudicated category is shown in Appendix Table 5.

Serious infections occurred in 13.8% of patients who received *Benlysta* IV plus ST vs 17% on placebo plus ST.[2] Adverse events of special interest (AESI) are summarized in Table 6, and AEs reported in ≥ 15% of patients in any group are shown in Table 7.

Table 6. AESI (Double-Blind, Safety Population)[2]

	***Benlysta* IV 10 mg/kg + ST (n = 224)**	**Placebo + ST (n = 224)**
AESI, % (n)		
All infections of special interest (opportunistic infections, herpes zoster, tuberculosis, sepsis)	13.4 (30)	15.2 (34)
Post-infusion reactions	11.6 (26)	12.9 (29)
Depression/suicide/self-injury	4.9 (11)	7.1 (16)
Malignancies excluding NMSC	0.9 (2)	0
Malignancies including NMSC	1.3 (3)	0

AESI = adverse event of special interest; NMSC = non-melanoma skin cancer; ST = standard therapy.

Table 7. AEs reported in ≥ 15% of Patients (Double-Blind, Safety Population)[2]

	***Benlysta* IV 10 mg/kg + ST (n = 224)**	**Placebo + ST (n = 224)**
AEs (≥ 15% in any group), % (n)		
URTI	32.1 (72)	31.3 (70)
Diarrhea	18.8 (42)	20.1 (45)
UTI	19.2 (43)	15.6 (35)
Headache	13.4 (30)	15.6 (35)

AE = adverse event; ST = standard therapy; URTI = upper respiratory tract infection; UTI = urinary tract infection.

Some information contained in this response is outside the approved Prescribing Information. This product is not approved for the use described. This response is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling.

In order for GlaxoSmithKline to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249.

Please consult the attached Prescribing Information. This response was developed according to the principles of evidence-based medicine and, therefore, references may not be all-inclusive.

REFERENCES

1. Furie R, Rovin BH, Houssiau F, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. *N Eng J Med.* 2020;383(12):1117-1128. doi:http://dx.doi.org/10.1056/NEJMoa2001180.
2. Data on File. Study 114054 (NCT01639339). GSK Study Register. Study entry at https://www.gsk-studyregister.com/study/114054.
3. Prescribing Information for Benlysta.

APPENDIX

Table 5. Total Number of Deaths and Listing by Preferred Term and Adjudicated Category (Double-Blind, Safety Population)[2]

		Benlysta IV 10 mg/kg + ST (n = 224)	Placebo + ST (n = 224)
	Total Number of Deaths (n)	6	5
	Preferred Term/Adjudicated Death Category (n)		
Fatal SAE started on-treatment[a]	Pneumonia/infectious	2	1
	Dsypnea (hypertension)/unknown	1	–
	Pneumonia/vascular	1	–
	Encephalopathy/unknown	–	1
	Sepsis/infectious	–	1
Fatal SAE started off-treatment	Septic shock/infectious	1	–
	Cardiac failure congestive/SLE related	1	–
	Hemorrhage intracranial/infectious	–	1
	Seizure/unknown	–	1

[a] although death may have occurred anytime thereafter.

AE = adverse event; SAE = serious AE; ST = standard therapy.