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Efficacy and safety of belimumab in patients with active lupus nephritis: a Phase 3, randomised, placebo-controlled trial

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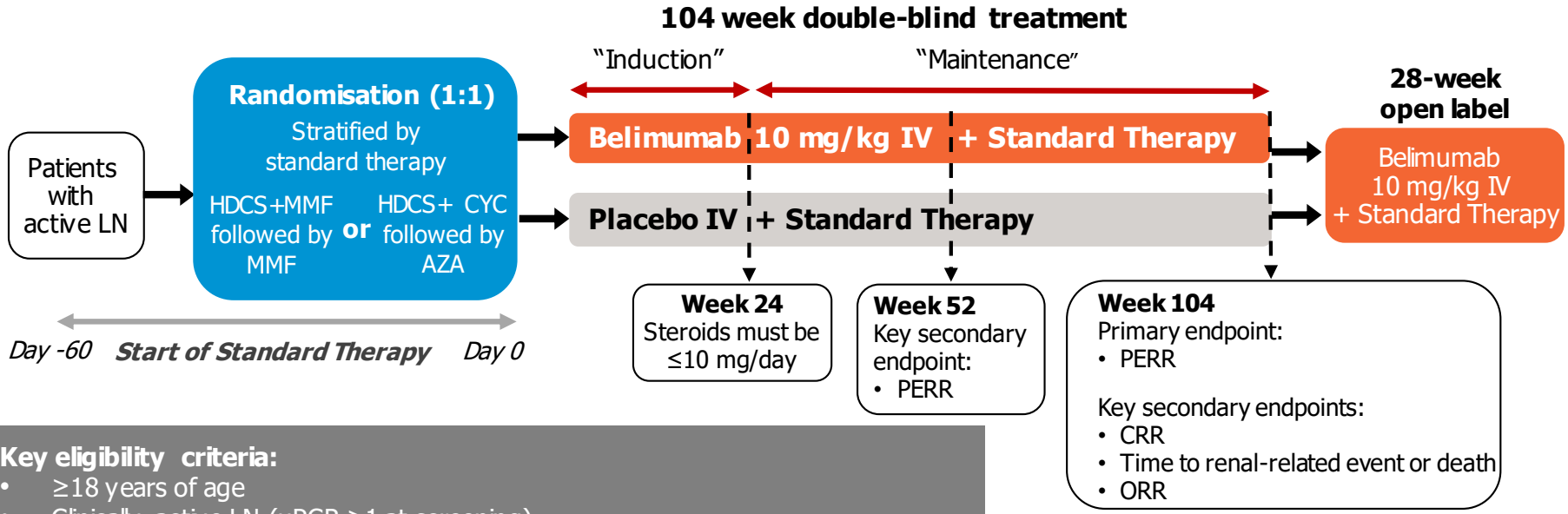
Background and Objectives

- LN is a serious complication of SLE. Despite aggressive treatment, renal response rates remain low, and 10–30% of patients with LN progress to end-stage renal disease[1-4]
- Belimumab is a recombinant human IgG1λ monoclonal antibody that inhibits BAFF and is approved for the treatment of patients with active autoantibody-positive SLE[5]
- *Post hoc* analysis of the BLISS-52 and BLISS-76 Phase 3 trials suggested that belimumab may improve renal parameters in patients with SLE[2]

- BLISS-LN is a Phase 3, randomised, double-blind, placebo-controlled, 104-week trial
- The trial is the largest study in LN to date
- BLISS-LN aimed to assess the efficacy and safety of belimumab in combination with standard therapy in patients with active LN

1. Corapi KM, *et al. Arthritis Res Ther*. 2015; 17: 110; 2. Dooley MA, *et al. Lupus*. 2013; 22(1): 63–72; 3. Hanly JG, *et al. Rheumatology*. 2016; 55(2): 252–62; 4. Almaani S, *et al. Clin J Am Soc Nephrol*. 2017; 12: 825-835; 5. Benlysta Prescribing Information. 2020. Accessed May 13, 2020 (https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Benlysta/pdf/BENLYSTA-PI-MG-IFU-COMBINED.PDF);
BAFF, B-cell–activating factor; BLISS, Belimumab in Subjects With Systemic Lupus Erythematosus; LN, lupus nephritis; SLE, systemic lupus erythematosus

Study Design



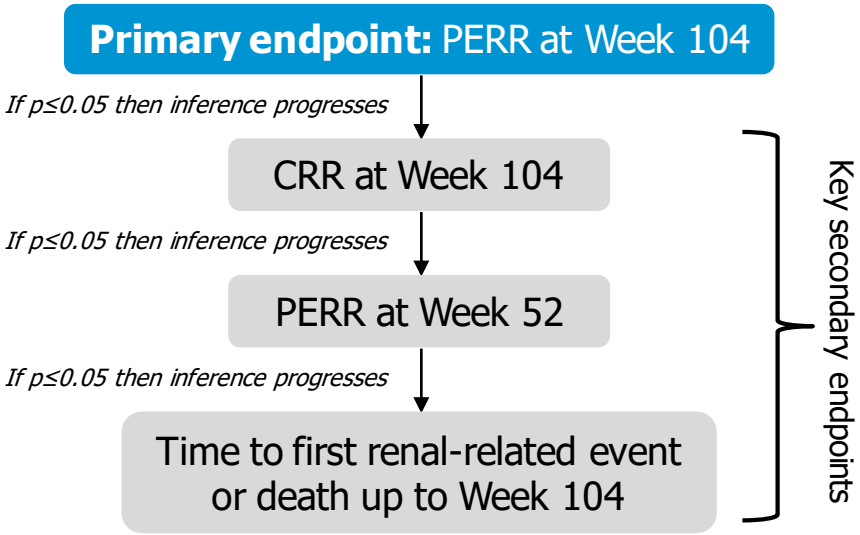
Key eligibility criteria:

- ≥18 years of age
- Clinically active LN (uPCR ≥1 at screening)
- Confirmed by recent* renal biopsy LN (Class III, IV, V or III+V or IV+V) and requiring standard therapy

*Biopsy performed in the 6 months prior to the screening visit or during the screening period.

AZA, azathioprine; BEL, belimumab; CRR, Complete Renal Response; CYC, cyclophosphamide; HDCS, high-dose corticosteroids; IV, intravenous; LN, lupus nephritis; MMF, mycophenolate mofetil; ORR, ordinal renal response; PERR, Primary Efficacy Renal Response; uPCR, urinary protein:creatinine ratio.

Endpoints



Other key endpoints:

- PERR and CRR at Week 104 by induction regimen
- Time to PERR and CRR maintained through Week 104
- PERR and CRR over time
- Proteinuria and eGFR over time
- Safety (assessed via the incidence of AEs)

Definitions:

PERR:
- uPCR ≤0.7
- eGFR ≤20% below pre-flare value or ≥60 ml/min/1.73m^2
- Not a treatment failure

CRR:
- uPCR <0.5
- eGFR ≤10% below pre-flare value or ≥90 ml/min/1.73m^2
- Not a treatment failure

Renal-related event:
- End-stage renal disease
- Doubling of serum creatinine
- Renal worsening
  - Evidenced by increased proteinuria and/or impaired renal function
- Renal disease-related treatment failure

AE, adverse event; CRR, complete renal response; eGFR, estimated glomerular filtration rate; PERR, primary efficacy renal response; uPCR, urine protein:creatinine ratio

Baseline Characteristics

- Of 448 randomised patients, 446 were included in the mITT population; 355 (79.2%) patients completed the study, and 278 (62.3%) patients completed the study treatment
  - Induction regimen for each treatment group: CYC/AZA, n=59 (26.5%); MMF, n=164 (73.5%)

Characteristic	Placebo n=223	Belimumab 10 mg/kg IV n=223
Age (years), mean (SD)	33.1 (10.6)	33.7 (10.7)
Female, n (%)	196 (87.9)	197 (88.3)
LN disease duration (years), median (IQR)	0.2 (0.1, 3.4)	0.2 (0.1, 3.3)
Renal biopsy class, n (%)		
Class III or IV	132 (59.2)	126 (56.5)
Class III + V or Class IV + V	55 (24.7)	61 (27.4)
Class V	36 (16.1)	36 (16.1)
eGFR (mL/min/1.73 m^2), median (IQR)	98.0 (67.0, 127.0)	99.0 (72.0, 124.0)
eGFR <60, n (%)	41 (18.4)	33 (14.8)
uPCR (g/g), median (IQR)	2.5 (1.4, 4.8)	2.6 (1.1, 4.4)
uPCR ≥3, n (%)	92 (41.3)	91 (40.8)

AZA, azacytidine; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; IQR, interquartile range; IV, intravenous; LN, lupus nephritis; mITT, modified intent-to-treat; MMF, mycophenolate mofetil; SD, standard deviation; SLE, systemic lupus erythematosus; uPCR, urinary protein:creatinine ratio.

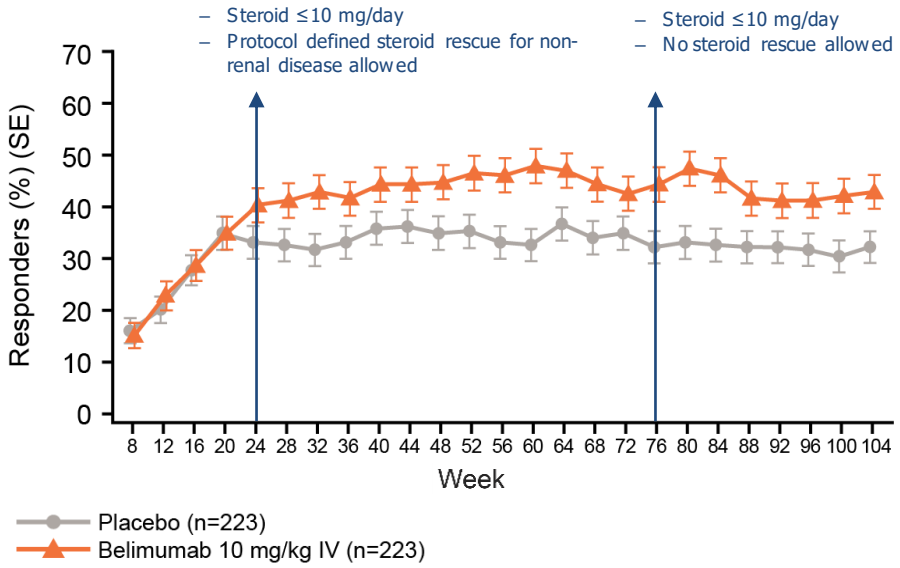
Primary and Key Secondary Efficacy Endpoints

	Patients (%)		OR/HR (95% CI)	p-value
	Placebo n=223	Belimumab 10 mg/kg IV n=223		
PERR* at Week 104	32.3	43.0	OR 1.55 (1.04, 2.32)	0.0311
CRR† at Week 104	19.7	30.0	OR 1.74 (1.11, 2.74)	0.0167
PERR* at Week 52	35.4	46.6	OR 1.59 (1.01, 2.38)	0.0245
Time to first renal-related event or death up to Week 104	28.3	15.7	HR 0.51 (0.34, 0.77)	0.0014

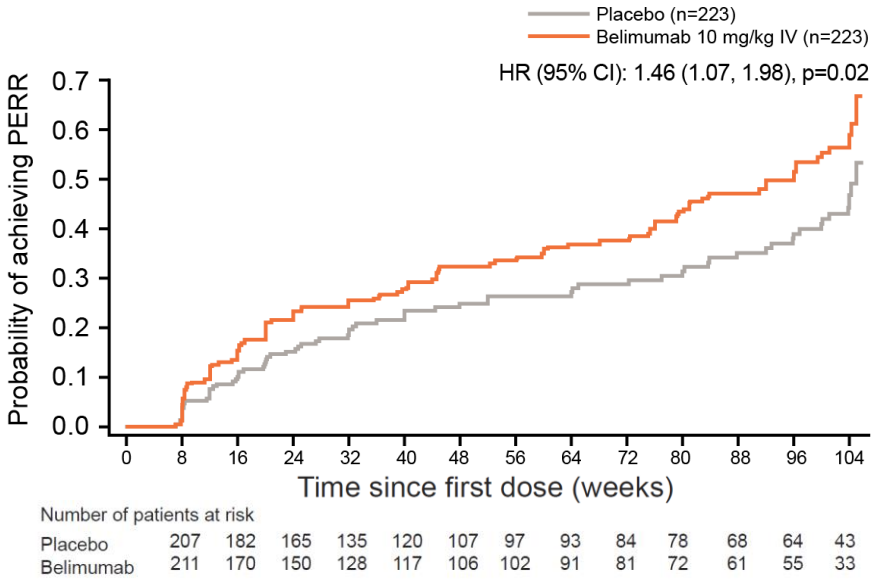
*uPCR ≤0.7, eGFR no more than 20% of the pre-flare value or ≥60 ml/min/1.73m^2, no rescue therapy; †uPCR <0.5, eGFR no worse than 10% below pre-flare value or ≥90 ml/min/1.73m^2, not a treatment failure. CI, confidence interval; CRR, Complete Renal Response; HR, hazard ratio; IV, intravenous; OR, odds ratio; PERR, Primary Efficacy Renal Response; uPCR, urine protein:creatinine ratio

Time to PERR

PERR* by visit



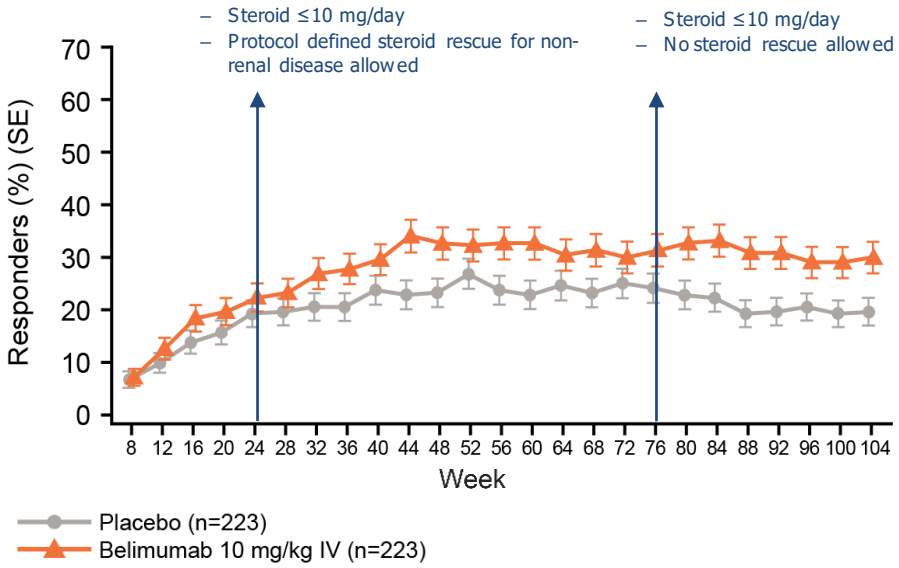
Time to PERR* maintained through to Week 104



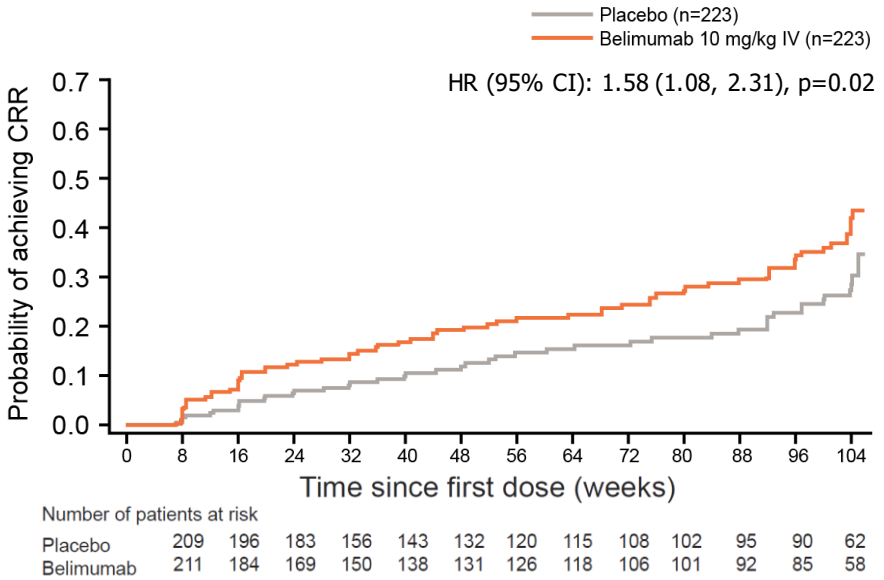
*uPCR ≤0.7; eGFR no worse than 20% below the pre-flare value or ≥60 ml/min/1.73m^2; not a treatment failure.
CI, confidence interval; HR, hazard ratio; IV, intravenous; PERR, Primary Efficacy Renal Response; SE, standard error; uPCR, urinary protein:creatinine ratio.

Time to CRR

CRR* by visit



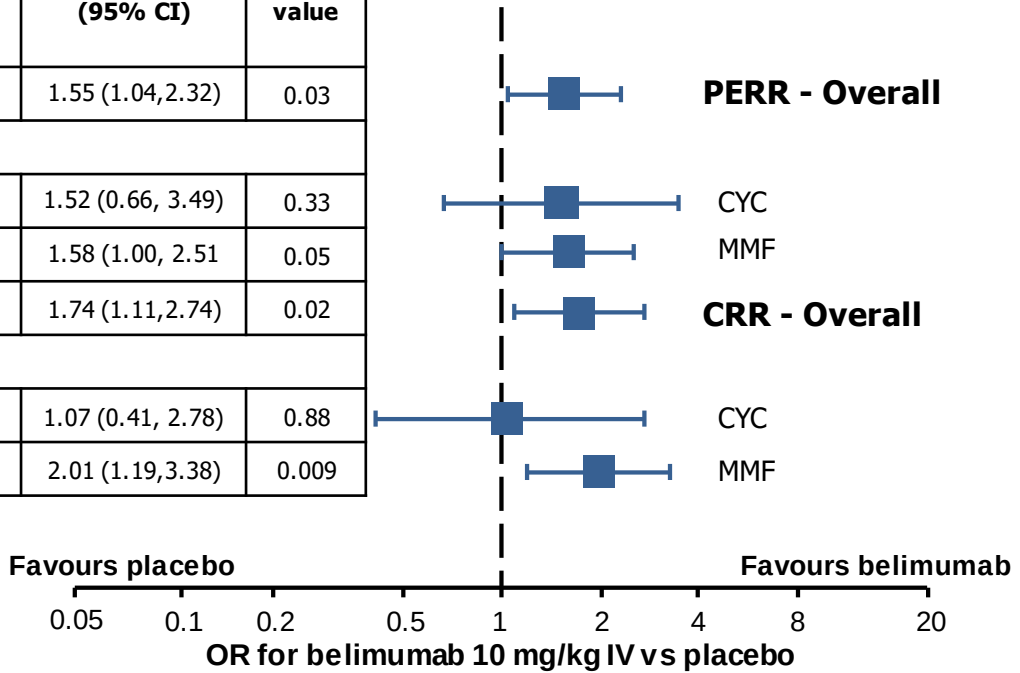
Time to CRR* maintained through to Week 104



*uPCR <0.5; eGFR no worse than 10% below pre-flare value or ≥90 ml/min/1.73m^2; not a treatment failure; CI, confidence interval; CRR, Complete Renal Response; HR, hazards ratio; IV, intravenous; NR, non-responder; PERR, Primary Efficacy Renal Response; SE, standard error; uPCR, urinary protein:creatinine ratio.

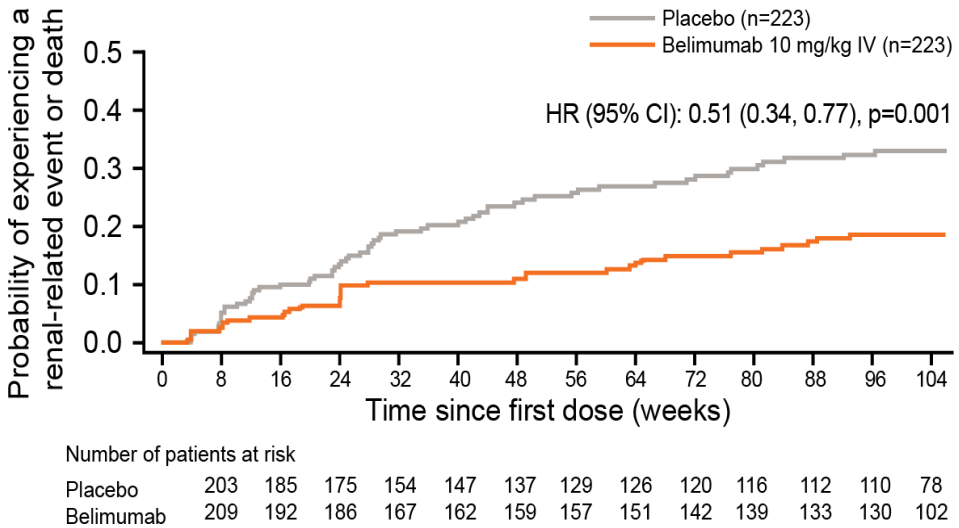
PERR and CRR at Week 104 by Standard Therapy

	Response Type	Response Rate (%)		Treatment Difference (%)	OR (95% CI)	p-value
		Placebo	Belimumab 10 mg/kg IV			
PERR*	Overall	32.3	43.0	10.8	1.55 (1.04,2.32)	0.03
	Induction/maintenance					
	CYC/AZA	27.1	33.9	6.8	1.52 (0.66, 3.49)	0.33
	MMF	34.1	46.3	12.2	1.58 (1.00, 2.51	0.05
CRR†	Overall	19.7	30.0	10.3	1.74 (1.11,2.74)	0.02
	Induction/maintenance					
	CYC/AZA	18.6	18.6	0	1.07 (0.41, 2.78)	0.88
	MMF	20.1	34.1	14.0	2.01 (1.19,3.38)	0.009



*uPCR ≤0.7, eGFR no worse than 20% below pre-flare value or ≥60 ml/min/1.73m2, not a treatment failure; †uPCR <0.5, eGFR no worse than 10% below pre-flare value or ≥90 ml/min/1.73 m^2, not a treatment failure.
AZA, azacytidine; CI, Confidence interval; CRR, Complete Renal Response; CYC, cyclophosphamide; IV, intravenous; MMF, mycophenolate mofetil; PERR, Primary Efficacy Renal Response.

Time to Renal-Related Event or Death

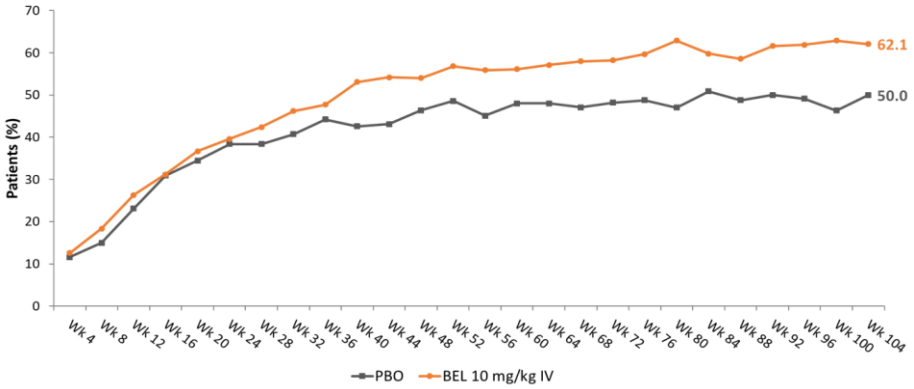


	Placebo n=223	Belimumab 10 mg/kg IV n=223
Total events*	63	35
Renal worsening†	39	17
Treatment failure related to renal event‡	20	16
Doubling of serum creatine from baseline	1	1
Progression to ESRD	1	0
Death for any reason	2	1

*First event for each patient with an event. †Defined by increased proteinuria (a reproducible increase in uPCR to >1 g if the baseline value was <0.2 g, to >2 g if the baseline value was 0.2–1 g, or more than twice the value at baseline if the baseline value was >1 g), or impaired renal function (a reproducible decrease in GFR of >20%, accompanied by proteinuria >1 g), and/or cellular [RBC/WBC]] casts).‡Based on adjudication of treatment failures.
ESRD, end-stage renal disease; GFR, glomerular filtration rate; HR, hazards ratio; IV, intravenous; RBC, red blood cell; uPCR, urinary protein:creatinine; WBC, white blood cell.

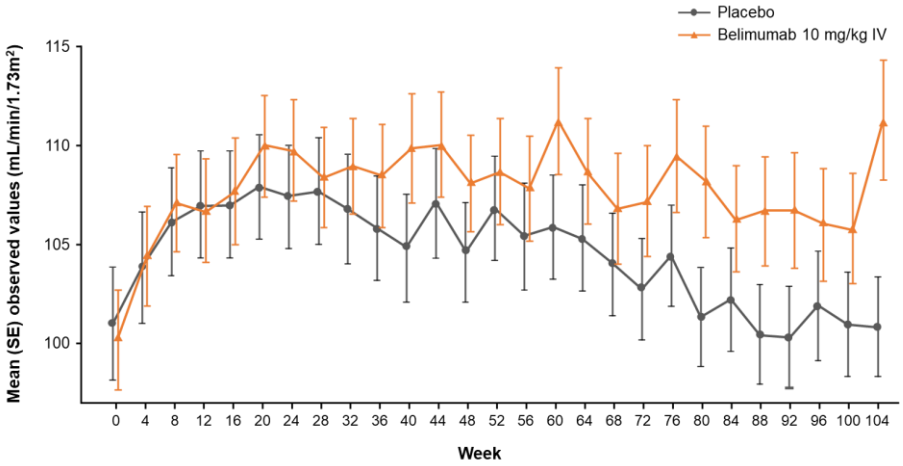
Proteinuria Shift and eGFR Over Time

Proportion of patients with proteinuria shift from ≥0.5 at baseline to <0.5 during study



- A greater proportion of belimumab-treated patients had a proteinuria shift from ≥0.5 to <0.5 at Week 104 versus placebo

Mean (SE) observed eGFR values over time by visit while on treatment



- In the belimumab-treated group, eGFR values remained stable from Week 52 onwards, versus a decline over this period in the placebo group

BEL, belimumab; eGFR, estimated glomerular filtration rate; IV, intravenous; PBO, placebo; SE, standard error; Wk, week

Safety – Incidence of AEs, AESI and Suicidality

n (%)	Placebo (n=224)	Belimumab 10 mg/kg IV (n=224)
≥1 AE	211 (94.2)	214 (95.5)
≥1 treatment-related AE	119 (53.1)	123 (54.9)
≥1 SAE	67 (29.9)	58 (25.9)
≥1 treatment-related SAE	**25 (11.2)**	**23 (10.3)**
AE resulting in study drug discontinuation	29 (12.9)	29 (12.9)
AESI		
Malignancies excluding NMSC	0	2 (0.9)
Malignancies including NMSC	0	3 (1.3)
Post-infusion reactions	29 (12.9)	26 (11.6)
All infections of special interest (OI, HZ, TB, sepsis)	**34 (15.2)**	**30 (13.4)**
Serious infections	7 (3.1)	9 (4.0)
Depression/suicide/self-injury†	16 (7.1)	11 (4.9)
All deaths	**5 (2.2)**	**6 (2.7)**
On-treatment fatal SAE	3 (1.3)	4 (1.8)
Post-treatment fatal SAE	2 (0.9)	2 (0.9)
C-SSRS suicidal ideation or behavior on-treatment	12 (5.4)	7 (3.1)

*Placebo group, n=224; belimumab group, n=224; †One attempted suicide in a patient receiving belimumab with pre-existing depression and self-discontinuation of an anti-depressant; AE, adverse event; AESI, adverse event of special interest; C-SSRS, Columbia-Suicide Severity Rating Scale; HZ, herpes zoster; IV, intravenous; NMSC, non-melanoma skin cancer; OI, opportunistic infection; SAE, serious adverse event; TB, tuberculosis.

Conclusions

- A greater proportion of patients treated with belimumab plus standard therapy achieved and maintained CRR and PERR compared with placebo plus standard therapy.
- Belimumab significantly reduced the risk of renal-related events over 104 weeks versus placebo.
- Improvement in renal outcomes was achieved on background of sustained reduction in corticosteroid use.
- Safety profile for belimumab plus standard therapy was similar to standard therapy alone and was as expected for the LN population.

CRR, complete renal response; CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; MMF, my cophenolate mofetil; PERR, Primary Efficacy Renal Response.