A 6-Month Open-label Extension Study of the Safety and Efficacy of Intravenous Belimumab in Patients with Lupus Nephritis

POS0689

Richard Furie[1], Brad H Rovin[2], Frederic Houssiau[3], Gabriel Contreras[4], Paula Curtis[5], Anuradha Madan[6], Angela Jones-Leone[6], Mohamed Okily[5], David A Roth[6]

[1]Northwell Health, Great Neck, NY, USA; [2]The Ohio State University, Columbus, OH, USA; [3]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [4]University of Miami Miller School of Medicine, Miami, FL, USA; [5]GlaxoSmithKline, GSK House, Brentford, Middlesex, UK; [6]GlaxoSmithKline, Collegeville, PA, USA

Introduction

- LN is a serious complication of SLE, and it is associated with a substantial risk of end-stage kidney disease and mortality[1]
- BEL, a recombinant, humanised, IgG1λ monoclonal antibody, is approved for the treatment of patients aged ≥5 years with active, autoantibody-positive SLE and adult patients with active LN who are receiving standard therapy[2]
- BLISS-LN (GSK Study BEL114054; NCT01639339), the largest and longest LN study to date, showed that IV BEL plus standard therapy improved outcomes compared with standard therapy alone in patients with active LN after 104 weeks of treatment[3]

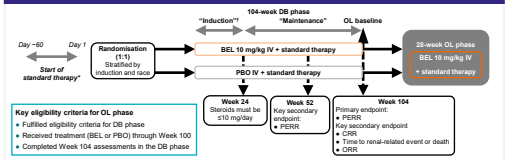
Objective

- To assess additional safety and efficacy data of BEL plus standard therapy in patients with LN in a 28-week OL phase beyond 2 years of DB treatment in BLISS-LN

Methods

- Patients who completed the DB phase of BLISS-LN were assessed for eligibility to participate in a 28-week OL phase, in which all patients received BEL (**Figure 1**)
- The PBO to BEL group included patients who switched from PBO; patients who remained on BEL were included in the BEL to BEL group

Figure 1. BLISS-LN was a Phase 3, DB, randomised, placebo-controlled, 104-week study



*Standard therapy included induction with HDCS + CYC followed by AZA maintenance, or induction with HDCS + MMF followed by MMF maintenance; †Some patients completed induction phase prior to Week 24

Study outcomes (OL phase)

- **Primary endpoint:**
  - Safety: treatment-emergent AEs, SAEs, and AESI (malignancies, post-infusion systemic reactions, opportunistic infections, sepsis, depression/suicide/self-injury)
- **Key secondary endpoints (using OL definitions*):**
  - Proportion of patients with PERR and CRR at OL Week 28
- **Other efficacy endpoints:**
  - Proportion of patients with SLEDAI-S2K score <4 at OL Week 28
  - Average daily prednisone-equivalent dose at OL Week 28
  - Change from OL baseline in biomarkers (anti-dsDNA, anti-C1q, C3/C4) at OL Week 28
- **Post hoc analysis (using DB definitions†):**
  - Proportion of patients with PERR and CRR at OL Week 28

Note: Results are only shown for post hoc PERR and CRR analyses to align with previously presented DB phase results. ***PERR**: criteria met at OL Week 28; uPCR ≤0.7; eGFR no more than 20% below OL baseline GFR or ≥60 ml/min/1.73 m²; no prohibited medications. **CRR**: criteria met at OL Week 28; uPCR <0.5; eGFR no more than 10% below OL baseline GFR or ≥90 ml/min/1.73 m²; no prohibited medications; †**PERR**: criteria met at 2 consecutive visits (i.e. met at OL Week 24 and confirmed at OL Week 28); uPCR ≤0.7; eGFR no more than 20% below DB baseline GFR or ≥60 ml/min/1.73 m²; no prohibited medications. **CRR**: criteria met at 2 consecutive visits (i.e. met at OL Week 24 and confirmed at OL Week 28); uPCR <0.5; eGFR no more than 10% below DB baseline GFR or ≥90 ml/min/1.73 m²; no prohibited medications

Statistical analyses

- Pre-defined analyses were descriptive, based on observed data, and summarised relative to the OL baseline. No follow-up data were collected post study
- OL baseline was defined as the last available value prior to the first dose of OL treatment (Day 1)

Results

Baseline characteristics

- Of 257 patients enrolled in the OL phase, 2 patients did not receive OL study treatment and 255 were treated and included in the safety population; 96.5% of patients completed the OL phase, and 3.5% withdrew, mainly due to AEs (2.0%)
- Baseline patient characteristics were similar across both groups (**Table 1**)

Table 1. Baseline patient characteristics (OL mITT population*)

	PBO to BEL 10 mg/kg IV N=122	BEL to BEL 10 mg/kg IV N=132
Female, n (%)	110 (90.2)	118 (89.4)
Age (years), mean (SD)	35.5 (10.3)	36.2 (10.3)
SLE duration (years), median (IQR)	5.3 (2.2, 10.0)	5.2 (2.2, 10.9)
LN duration (years), median (IQR)	2.2 (2.1, 4.7)	2.2 (2.1, 5.1)
uPCR (g/g), median (IQR)	0.37 (0.14, 1.05)	0.26 (0.09, 0.74)
eGFR (ml/min/1.73 m²), median (IQR)	105.0 (84.0, 123.0)	108.0 (88.0, 130.0)
SLEDAI-2K score, median (IQR)	4.0 (2.0, 8.0)	4.0 (1.0, 6.0)
Average daily prednisone-equivalent dose (mg/day), median (IQR)	7.5 (5.0, 10.0)	5.0 (2.5, 10.0)

*Safety population, excluding 1 patient due to non-compliance

Safety

- Overall, OL safety findings were consistent with those seen in the DB phase of BLISS-LN, with no new AEs of clinical concern (**Table 2**)

Table 2. Summary of AEs and AESI* (OL Safety population)

n (%)	PBO to BEL 10 mg/kg IV (N=123)	BEL to BEL 10 mg/kg IV (N=132)
≥1 AE	76 (61.8)	92 (69.7)
≥1 treatment-related AE	25 (20.3)	24 (18.2)
≥1 SAE	5 (4.1)	10 (7.6)
≥1 severe AE	6 (4.9)	5 (3.8)
AE resulting in study drug discontinuation/withdrawal from study	1 (0.8)	4 (3.0)
AESI		
Malignancies	0 (0.0)	0 (0.0)
Post-infusion systemic reactions†	4 (3.3)	5 (3.8)
Infections of special interest (OI, HZ, TB, sepsis)	2 (1.6)	6 (4.5)
Serious	0 (0.0)	2 (1.5)
All adjudicated OI	0 (0.0)	2 (1.5)
Active TB	0 (0.0)	1 (0.8)
HZ‡	2 (1.6)	3 (2.3)
Serious	0 (0.0)	1 (0.8)
Disseminated	0 (0.0)	1 (0.8)
Sepsis	0 (0.0)	0 (0.0)
Depression (inc. mood disorders and anxiety) /suicide/self-injury	2 (1.6)	4 (3.0)§
Death	1 (0.8)¶	0 (0.0)

*Only treatment-emergent AEs are reported (i.e. post-first OL infusion); †No serious post-infusion systemic reactions were reported; ‡No recurrent HZ infections were reported; §There was 1 SAE of suicidal behaviour in a patient diagnosed with an adjustment disorder that occurred 12 days after the first OL infusion. This patient recovered and completed BEL treatment throughout the OL phase; ¶Occurred 85 days after the first OL infusion. Death was associated with a fatal SAE of multiple organ dysfunction syndrome, sepsis secondary to healthcare-associated pneumonia, and chronic kidney disease

Efficacy

- At OL Week 28, 52.3% of BEL to BEL patients and 52.5% of PBO to BEL patients achieved PERR, and 40.9% of BEL to BEL patients and 35.2% of PBO to BEL patients achieved CRR (**Table 3**)
- Among patients who had an intercurrent event (18.2%), non-response was mainly due to treatment failures as a result of taking prohibited medications (13.6%) and discontinuations and drop outs (4.5%)
- All but one of the treatment failures were for non-renal reasons, indicating that the reductions in rates of PERR and CRR achievement were not due to renal worsening

Table 3. PERR and CRR responses at OL baseline and OL Week 28 (OL mITT population; post hoc analysis)

		PBO to BEL 10 mg/kg IV (N=122)		BEL to BEL 10 mg/kg IV (N=132)	
		OL baseline*	OL Week 28	OL baseline*	OL Week 28
PERR† (using DB phase definition)‡	n	122	122	132	132
	Responders, n (%)	66 (54.1)	64 (52.5)	87 (65.9)	69 (52.3)
CRR† (using DB phase definition)‡	n	122	122	132	132
	Responders, n (%)	41 (33.6)	43 (35.2)	60 (45.5)	54 (40.9)

*DB Week 104 visit and the OL baseline visit were the same visit; †To be PERR and CRR responders, the results had to be replicated across two consecutive visits; ‡All patients were included in the analysis. Withdrawal from the trial, treatment failure, and discontinuation of BEL were imputed as a non-response

- The proportion of patients who attained SLEDAI-S2K score <4 decreased slightly from OL baseline to OL Week 28 in the PBO to BEL group and increased slightly in the BEL to BEL group (**Table 4**)

Table 4. Proportion of patients with SLEDAI-S2K score <4 at OL baseline and OL Week 28 (OL mITT population)

		PBO to BEL 10 mg/kg IV (N=122)		BEL to BEL 10 mg/kg IV (N=132)	
		OL baseline	OL Week 28	OL baseline	OL Week 28
SLEDAI-S2K score <4	n	122	120	132	122
	Responders, n (%)	44 (36.1)*	40 (33.3)	64 (48.5)*	64 (52.5)

*Post hoc analyses

- Among patients receiving average daily prednisone-equivalent doses of ≤5 mg/day, ≤7.5 mg/day or ≤10 mg/day, the dose was maintained from OL baseline to OL Week 28 (**Table 5**)

Table 5. Average daily prednisone-equivalent dose at OL baseline and OL Week 28 (OL mITT population)

		PBO to BEL 10 mg/kg IV (N=122)		BEL to BEL 10 mg/kg IV (N=132)	
		OL baseline	OL Week 28	OL baseline	OL Week 28
Average daily prednisone-equivalent dose	n	122	121	132	128
	≤5 mg/day, n (%)	59 (48.4)	60 (49.6)	78 (59.1)	75 (58.6)
	≤7.5 mg/day, n (%)	62 (50.8)	66 (54.5)	85 (64.4)	83 (64.8)
	≤10 mg/day, n (%)	122 (100)	120 (99.2)	132 (100)	126 (98.4)

- Among patients with positive anti-dsDNA and anti-C1q levels at OL baseline, anti-dsDNA and anti-C1q levels decreased from OL baseline to OL Week 28 in both groups (**Table 6**)
- Among patients with low C3/C4 levels at OL baseline, C3/C4 levels increased from OL baseline to OL Week 28 in both groups (**Table 6**)

Table 6. Levels of biomarkers at OL baseline and OL Week 28 (OL mITT population)

	PBO to BEL 10 mg/kg IV (N=122)		BEL to BEL 10 mg/kg IV (N=132)	
	OL baseline*	OL Week 28	OL baseline*	OL Week 28
Anti-dsDNA (IU/ml)†				
n	85	81	64	61
Median (IQR) levels	107.0 (49.0, 212.0)	-	65.5 (42.5, 126.5)	-
Median (IQR) % change from baseline	-	−30.2 (−46.3, −6.8)	-	−10.7 (−27.2, 9.1)
Anti-C1q (U/ml)‡				
n	64	58	60	54
Median (IQR) levels	71.7 (36.6, 167.5)	-	47.1 (33.0, 75.7)	-
Median (IQR) % change from baseline	-	−23.0 (−41.5, 0.5)	-	−16.5 (−33.0, 6.1)
C3 (mg/dl)§				
n	45	44	37	35
Median (IQR) levels	78.0 (72.0, 83.0)	-	80.0 (71.0, 84.0)	-
Median (IQR) % change from baseline	-	0.2 (−4.2, 14.6)	-	4.7 (−4.8, 16.9)
C4 (mg/dl)§				
n	18	18	12	11
Median (IQR) levels	7.5 (6.0, 8.0)	-	7.0 (7.0, 8.5)	-
Median (IQR) % change from baseline	-	23.6 (11.1, 37.5)	-	11.1 (0.0, 57.1)

*DB Week 104 visit and the OL baseline visit were the same visit; †Among anti-dsDNA positive patients at OL baseline (≥30 IU/ml); ‡Among anti-C1q positive patients at OL baseline (≥22.2 U/ml); §Among patients with low C3 (<90 mg/dl)/C4 (<10 mg/dl) levels at OL baseline

Conclusions

- The safety profile of BEL in this OL phase was consistent with that observed in the DB phase of BLISS-LN, with no new safety signals of clinical concern
- In the PBO to BEL group, PERR and CRR were 54.1% and 33.6% at the DL phase entry and 52.5% and 35.2% at OL Week 28
- In the BEL to BEL group, PERR and CRR were 65.9% and 45.5% at the OL phase entry and 52.3% and 40.9% at OL Week 28
- Without any protocol mandated thresholds, the proportion of patients receiving average daily prednisone-equivalent doses of ≤5 mg, ≤7.5 mg, or ≤10 mg was maintained throughout the OL phase in both groups
- Improvements in levels of biomarkers were observed, especially in patients who switched from PBO to BEL
- Limitations:
  - The duration of the OL phase was short, and the sample of patients included in this OL phase was self-selected and potentially more likely to respond well to belimumab over time
  - The DB randomised treatment groups were no longer random by the start of the OL phase as drop-outs during the 104-week DB phase may have impacted treatment groups differently; any comparisons during the OL phase should be treated with caution
  - At OL baseline, patients were not required to be in LN flare and, as such, baseline characteristics were different when patients entered the DB phase

Abbreviations

AE, adverse event; AESI, AE of special interest; AZA, azathioprine; BEL, belimumab; CRR, Complete Renal Response; CYC, cyclophosphamide; DB, double-blind; eGFR, estimated glomerular filtration rate; HDCS, high-dose corticosteroids; HZ, herpes zoster; IQR, interquartile range; IV, intravenous; LN, lupus nephritis; mITT, modified intention-to-treat; MMF, mycophenolate mofetil; OI, opportunistic infections; OL, open-label; ORR, Ordinal Renal Response; PBO, placebo; PERR, Primary Efficacy Renal Response; SAE, serious AE; SD, standard deviation; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; TB, tuberculosis; uPCR, urine protein:creatinine ratio

References

1. Hanly JG, *et al. Rheumatol* 2016;55:252–62.
2. Benlysta Prescribing Information. GlaxoSmithKline; 2021. Available from: https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Benlysta/pdf/BENLYSTA-PI-MG-IFU.PDF [last accessed April 2021].
3. Furie R, *et al. N Engl J Med* 2020;383(12):1117–28.

Disclosures

RF has received grant/research support and consulting fees from GSK. **BHR** has received consulting fees from GSK. **FH** has received grant/research support from UCB and consulting fees from GSK. **GC** has received grant/research and consulting fees support from Genentech and Merck. **PC, AM, AJL, MO,** and **DAR** are employees of GSK and hold stocks and shares in the company.

Acknowledgements

This study was funded by GlaxoSmithKline (GSK Study BEL114054).

Medical writing support with poster development was provided by Olga Conn, PhD, of Fishawack Indicia Ltd, UK, part of Fishawack Health, and was funded by GSK.

Please find the online version of this poster by scanning the QR code or via http://tago.ca/_EULAR1

Author email address: RFurie@northwell.edu

Poster presented at the EULAR 2021 E-Congress, 2–5 June 2021 | Online