Supplementary Material

Supplementary methods

Key inclusion criteria

Key inclusion criteria for the studies were: aged ≥18 years; diagnosis of SLE according to American College of Rheumatology (ACR) revised criteria; active disease at screening (defined by most included studies as Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index [SELENA–SLEDAI] score ≥4, 6, or 8); seropositivity (antinuclear antibody titer ≥1:80 and/or anti–double-stranded deoxyribonucleic acid antibody level ≥30 IU/mL; history of measurable autoantibodies was required by Study LBSL02); stable treatment regimen at screening or for ≥30 or ≥60 days, depending on the study, before the first study dose.

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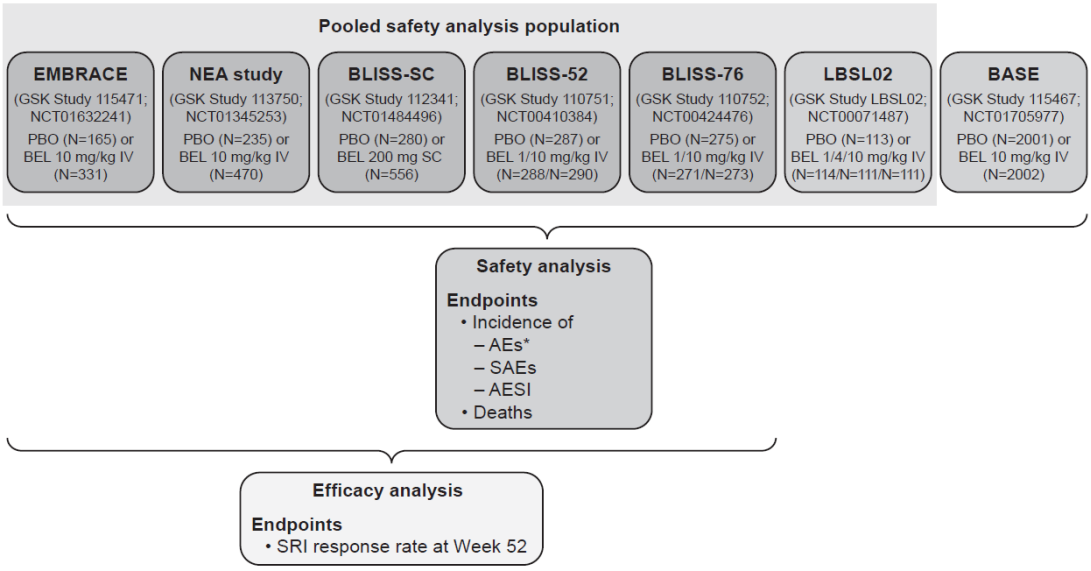
Supplementary Figure 1. Study design



*Only data on SAEs, AESI, and deaths were collected for BASE.[1]

AEs, adverse events; AESI, AEs of special interest; BEL, belimumab; IV, intravenous; SAEs, serious adverse events; SC, subcutaneous; SRI, Systemic Lupus Erythematosus Responder Index.

Supplementary Table 1. AESI and deaths in older adult and the overall populations

	Pooled safety analysis population*				BASE			
	Older adults (N=63)		Overall (N=4170)		Older adults (N=156)		Overall (N=4003)	
n (%)†	**PBO N=27**	**BEL N=36**	**PBO N=1355**	**BEL N=2815**	**PBO N=82**	**BEL N=74**	**PBO N=2001**	**BEL N=2002**
Death‡	0 (0.0)	0 (0.0)	6 (0.4)	16 (0.6)	1 (1.2)	1 (1.4)	11 (0.6)	12 (0.6)
AESI								
PISR§,¶,**	0 (0.0)	2 (5.6)	110 (8.1)	286 (10.2)	-	-	-	-
Serious PISR	0 (0.0)	0 (0.0)	2 (0.1)	13 (0.5)	0 (0.0)	0 (0.0)	2 (<0.1)	8 (0.4)
Infections of special interest (opportunistic, herpes zoster, tuberculosis, sepsis)§	1 (3.7)	0 (0.0)	97 (7.2)	173 (6.1)	0 (0.0)	2 (2.7)	50 (2.5)	36 (1.8)
Serious infections of special interest	0 (0.0)	0 (0.0)	17 (1.3)	40 (1.4)	0 (0.0)	2 (2.7)	17 (0.8)	17 (0.8)
Malignancies (ex. non-melanoma skin cancer)§	0 (0.0)	0 (0.0)	2 (0.1)	8 (0.3)	0 (0.0)	0 (0.0)	5 (0.2)	5 (0.2)
Depression§,,††**	3 (11.1)	3 (8.3)	92 (6.8)	205 (7.3)	-	-	-	-
Serious depression††	1 (3.7)	0 (0.0)	2 (0.1)	6 (0.2)	0 (0.0)	0 (0.0)	1 (<0.1)	7 (0.3)
Suicide/self-injury,‡‡**	0 (0.0)	0 (0.0)	4 (0.3)	8 (0.3)	-	-	-	-
Serious suicide/ self-injury	0 (0.0)	0 (0.0)	4 (0.3)	4 (0.1)	0 (0.0)	1 (1.4)	5 (0.2)	11 (0.5)

*Pooled data from all studies except BASE; [†]patients counted once/category; [‡]BASE: fatal SAEs that started during on-treatment period; death may have occurred after period end. Pooled safety analysis: all deaths during double-blind period; [§]per custom MedDRA query; [¶]occurring on/within 3 days of infusion/injection; **BASE: only serious PISR and serious depression/suicide/self-injury events collected; [††]including mood disorders/anxiety; [‡‡]per standard MedDRA query.

AE, adverse event; AESI, AEs of special interest; BEL, belimumab; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PISR, post-infusion/injection systemic reaction; SAEs, serious adverse events.

Supplementary Table 2. Components of SRI response at Week 52 for older adults and the overall populations

	Treatment, n/N (%)						
	PBO	**Pooled BEL**	**BEL IV 1 mg/kg**	**BEL IV 10 mg/kg**	**BEL SC 200 mg**	**Observed difference vs PBO, %**	**Odds ratio (95% CI) vs PBO***
≥4-point reduction in SELENA-SLEDAI							
Older adults	8/25 (32.0)	12/29 (41.4)	-	-	-	9.38	1.49 (0.49, 4.58)
Overall							
BLISS-76 and	230/562 (40.9)	-	269/559 (48.1)	-	-	7.20	1.40 (1.10, 1.79)
BLISS-52 (pooled)		-	-	297/563 (52.8)	-	11.83	1.68 (1.32, 2.15)
NEA study	91/217 (41.9)	-	-	249/446 (55.8)	-	13.89	2.01 (1.42, 2.86)
EMBRACE	63/149 (42.3)	-	-	149/298 (50.0)	-	7.72	1.46 (0.97, 2.20)
BLISS-SC	137/279 (49.1)	-	-	-	345/554 (62.3)	13.17	1.69 (1.26, 2.27)
No worsening in PGA							
Older adults	17/25 (68.0)	20/29 (69.0)	-	-	-	0.97	1.12 (0.34, 3.67)

Overall							
BLISS-76 and	372/562 (66.2)	-	424/559 (75.8)	-	-	9.66	1.62 (1.24, 2.11)
BLISS-52 (pooled)		-	-	420/563 (74.6)	-	8.41	1.52 (1.17, 1.97)
NEA study	149/217 (68.7)	-	-	345/446 (77.4)	-	8.69	1.57 (1.09, 2.27)
EMBRACE	96/149 (64.4)	-	-	207/298 (69.5)	-	5.03	1.26 (0.82, 1.93)
BLISS-SC	203/279 (72.8)	-	-	-	450/554 (81.2)	8.47	1.61 (1.15, 2.27)
No new 1A/2B BILAG domain scores							
Older adults	18/25 (72.0)	20/29 (69.0)	-	-	-	−3.03	0.85 (0.26, 2.78)
Overall							
BLISS-76 and	389/562 (69.2)	-	429/559 (76.7)	-	-	7.53	1.48 (1.13, 1.94)
BLISS-52 (pooled)		-	-	425/563 (75.5)	-	6.27	1.38 (1.05, 1.80)
NEA study	148/217 (68.2)	-	-	358/446 (80.3)	-	12.07	1.91 (1.32, 2.77)
EMBRACE	93/149 (62.4)	-	-	202/298 (67.8)	-	5.37	1.24 (0.81, 1.88)
BLISS-SC	207/279 (74.2)	-	-	-	448/554 (80.9)	6.67	1.46 (1.04, 2.07)

*In the pooled efficacy analysis (older adults), covariates were treatment and baseline SELENA-SLEDAI score (≤9 vs ≥10). For BLISS-76 and BLISS-52, covariates included treatment, baseline SELENA-SLEDAI score (≤9 vs ≥10), baseline proteinuria level (<2 vs ≥2 g/24 h equivalent), and race (Black African ancestry vs other). For BLISS-SC, covariates were treatment, baseline SELENA-SLEDAI score (≤9 vs ≥10), baseline complement levels (low C3 and/or C4 vs no low C3/C4), and race (Black African ancestry vs other). For the NEA study independent variables were treatment, country, baseline SELENA-SLEDAI score (≤9 vs ≥10), and complement levels (low C3 and/or C4 vs no low C3/C4). For EMBRACE, covariates were treatment, baseline SELENA-SLEDAI score (≤9 vs ≥10), baseline complement levels (low C3 and/or C4 vs no low C3/C4), and region (United States/Canada vs rest of world).

BEL, belimumab; BILAG, British Isles Lupus Assessment Group; CI, confidence interval; IV, intravenous; PBO, placebo; PGA, Physicians Global Assessment; SC, subcutaneous; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index; SRI, Systemic Lupus Erythematosus Responder Index.

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1. Sheikh SZ, Scheinberg MA, Wei JC-C, et al. Mortality and adverse events of special interest with intravenous belimumab for adults with active, autoantibody-positive systemic lupus erythematosus (BASE): a multicentre, double-blind, randomised, placebo-controlled, phase 4 trial. *Lancet Rheumatol* 2021;3:e122-e30. doi: 10.1016/s2665-9913(20)30355-6.