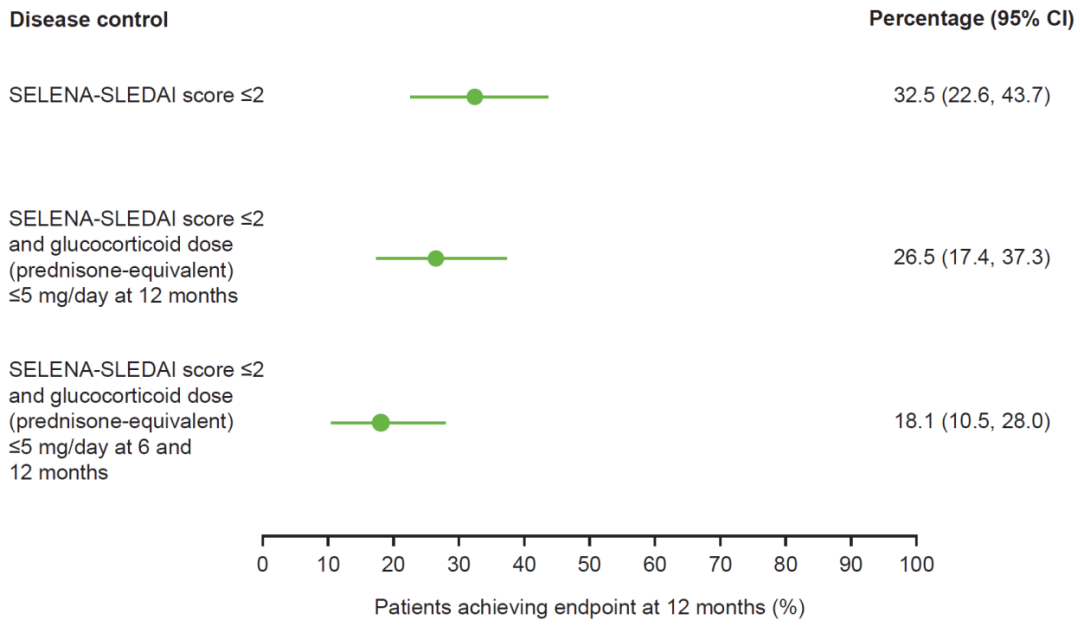
SUPPLEMENTARY MATERIAL

Sensitivity analyses results

In subsequent sensitivity analyses incorporating no immunosuppressant use into the definition of disease control, the overall percentage of patients achieving disease control at 12 months was reduced. In the overall population (N=90), 25.6% (95% confidence interval [CI]: 16.9, 35.8) of patients had a Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score ≤2 without immunosuppressants at 12 months, 21.1% (95% CI: 13.2, 31.0) had a SELENA-SLEDAI score ≤2 and received a glucocorticoid dose (prednisone-equivalent) ≤5 mg without immunosuppressants at 12 months; and 14.4% (95% CI: 7.9, 23.4) had a SELENA-SLEDAI score ≤2 and received a glucocorticoid dose (prednisone-equivalent) ≤5 mg at 6 and 12 months without immunosuppressants at 12 months (**Supplementary Table S2**). Additionally, reductions in the extent of disease control observed at 12 months was also observed for analyses restricted to patients receiving belimumab at baseline, 6, and 12 months with lower glucocorticoid doses at 6 and 12 months (**Supplementary Table S3**); stratified analyses by baseline immunosuppressant use (**Supplementary Table S4**); and stratified analyses by baseline glucocorticoid dose (**Supplementary Table S5**).

Supplementary figures and tables

Supplementary Figure S1. Proportions of patients with SLE achieving disease control at 12 months, according to definitions of increasing stringency, restricted to patients using belimumab at baseline, 6 months, and 12 months (n=83; sensitivity analysis)



CI, confidence interval; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SLE, systemic lupus erythematosus

Supplementary Table S1. Outcome definitions: SLE disease control and remission

Sequentially restrictive definitions	SLE DISEASE CONTROL		SLE COMPLETE DISEASE REMISSION
	Initial analyses	**Subsequent sensitivity analyses**	
1	***SELENA-SLEDAI score ≤2 at 12 months***	SELENA-SLEDAI score ≤2 and ***no immunosuppressant use at 12 months***	***SELENA-SLEDAI score=0 at 12 months***
2	SELENA-SLEDAI score ≤2 and ***glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 12 months***	SELENA-SLEDAI score ≤2, glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 12 months, and ***no immunosuppressant use at 12 months***	SELENA-SLEDAI score=0 and ***glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 12 months***
3	SELENA-SLEDAI score ≤2 and glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at ***6 and 12 months***	SELENA-SLEDAI score ≤2, glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 6 and 12 months, and ***no immunosuppressant use at 12 months***	SELENA-SLEDAI score=0 and glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at ***6 and 12 months***

SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus

Supplementary Table S2. Proportions of patients with SLE achieving disease control at 12 months, for all eligible patients (N=90; subsequent sensitivity analysis incorporating no immunosuppressant use into outcome definitions)

Outcome	Percentage of patients (95% CI)
Sensitivity analysis: SELENA-SLEDAI score ≤2 and no immunosuppressant use at 12 months	25.6 (16.9, 35.8)
Sensitivity analysis: SELENA-SLEDAI score ≤2 and glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 12 months and no immunosuppressant use at 12 months	21.1 (13.2, 31.0)
Sensitivity analysis: SELENA-SLEDAI score ≤2 and glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 6 and 12 months and no immunosuppressant use at 12 months	14.4 (7.9, 23.4)

CI, confidence interval; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SLE, systemic lupus erythematosus

Supplementary Table S3. Proportions of patients in a state of SLE disease control at 12 months, among patients receiving belimumab at baseline, 6 months, and 12 months AND who received a glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 6 and 12 months (n=39; subsequent sensitivity analysis incorporating no immunosuppressant use into outcome definitions)

Outcome	Percentage of patients (95% CI)
Sensitivity analysis: SELENA-SLEDAI score ≤2 and no immunosuppressant use at 12 months	30.8 (17.0, 47.6)*
Sensitivity analysis: SELENA-SLEDAI score ≤2 and glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 12 months and no immunosuppressant use at 12 months	30.8 (17.0, 47.6)*
Sensitivity analysis: SELENA-SLEDAI score ≤2 and glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 6 and 12 months and no immunosuppressant use at 12 months	30.8 (17.0, 47.6)*

*Percentages are the same across definitions because all patients in this analysis had to have glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 6 and 12 months.

CI, confidence interval; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus

Supplementary Table S4. Proportions of patients in a state of SLE disease control at 12 months, stratified by baseline immunosuppressant use (n=90; subsequent sensitivity analysis incorporating no immunosuppressant use into outcome definitions)

	Percentage of patients (95% CI)*	
Outcome	**Patients using IS at baseline (n=43)**	**Patients not using IS at baseline (n=47)**
Sensitivity analysis: SELENA-SLEDAI score ≤2 and no immunosuppressant use at 12 months	14.0 (5.3, 27.9)	36.2 (22.7, 51.5)
Sensitivity analysis: SELENA-SLEDAI score ≤2 and glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 12 months and no immunosuppressant use at 12 months	14.0 (5.3, 27.9)	27.7 (15.6, 42.6)
Sensitivity analysis: SELENA-SLEDAI score ≤2 and glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 6 and 12 months and no immunosuppressant use at 12 months	11.6 (3.9, 25.1)	17.0 (7.6, 30.8)

*All percentages are column percentages (i.e., the denominator is the number of persons being treated with immunosuppressants OR without immunosuppressants at baseline).

CI, confidence interval; IS, immunosuppressant; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus

Supplementary Table S5. Proportions of patients in a state of SLE disease control at 12 months, stratified by baseline glucocorticoid dose (n=90; subsequent sensitivity analysis incorporating no immunosuppressant use into outcome definitions)

	Percentage of patients (95% CI)*	
Outcome	**Patients receiving ≤5 mg/day glucocorticoids (prednisone-equivalent) at baseline (n=11)**	**Patients receiving >5 mg/day glucocorticoids (prednisone-equivalent) at baseline (n=79)**
Sensitivity analysis: SELENA-SLEDAI score ≤2 and no immunosuppressant use at 12 months	36.4 (10.9, 69.2)[†]	24.1 (15.1, 35.0)
Sensitivity analysis: SELENA-SLEDAI score ≤2 and glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 12 months and no immunosuppressant use at 12 months	36.4 (10.9, 69.2)[†]	19.0 (11.0, 29.4)
Sensitivity analysis: SELENA-SLEDAI score ≤2 and glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 6 and 12 months and no immunosuppressant use at 12 months	27.3 (6.0, 61.0)	12.7 (6.2, 22.0)

*All percentages are column percentages (i.e., the denominator is the number of persons being treated with ≤5 mg/day glucocorticoid dose (prednisone-equivalent) at baseline OR >5 mg/day glucocorticoid dose (prednisone-equivalent) at baseline; [†]percentages and 95% CIs are the same across definitions because all patients in this analysis had to have glucocorticoid dose (prednisone-equivalent) ≤5 mg/day at 6 and 12 months.

CI, confidence interval; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus

Supplementary Table S6. Extent of patients with SLE achieving disease control, LLDAS, or LDA at 52 weeks following the initiation of belimumab or comparator medications: results from previous studies

Author	Study	Outcome	Operationalization of disease activity state			% achieving outcome (stratified by study and treatment [if relevant])		
			Disease activity	Prednisone dose	IS allowed			
Post hoc analyses of prior randomized clinical trials*								
Oon 2019* [1]	BLISS-52 (NCT00424476), BLISS-76 (NCT00410384)†	LLDAS	SLEDAI-2K ≤4‡ and PGA ≤1	≤7.5 mg/day	Yes§	BLISS-52	Placebo‖	5.8%
							Belimumab 10 mg/kg IV‖	12.5%[1]
						BLISS-76	Placebo‖	7.8%
							Belimumab 10 mg/kg IV‖	14.4%[1]
Parodis 2019* [2]	BLISS-52 (NCT00424476), BLISS-76 (NCT00410384)†	LLDAS	SLEDAI-2K ≤4¶ and PGA ≤1	≤7.5 mg/day	–	BLISS-52	Placebo (n=227)	6.2%
							Belimumab 10 mg/kg IV (n=243)	11.9%[1]
						BLISS-76	Placebo (n=203)	6.4%
							Belimumab 10 mg/kg IV (n=206)	8.3%
						Pooled	Placebo (n=430)	6.3%
							Belimumab 10 mg/kg IV (n=449)	10.2%[1]

		cSLEDAI-2K=0	cSLEDAI-2K=0	–	–	BLISS-52	Placebo (n=227)	33.0%
							Belimumab 10 mg/kg IV (n=243)	44.0%[1]
						BLISS-76	Placebo (n=203)	26.6%
							Belimumab 10 mg/kg IV (n=206)	34.5%
						Pooled	Placebo (n=430)	30.0%
							Belimumab 10 mg/kg IV (n=449)	39.6%[2]
Observational studies evaluating belimumab and low disease activity states								
Gatto 2020 [3]	BERLiSS, a prospective cohort study of SLE patients initiating belimumab from 24 Italian centers (n=466)	LDA	cSLEDAI-2K ≤2	–	–		Real-world use of belimumab 10 mg/kg IV	71.7%
Sbeih 2020 [4]	Single French center prospective cohort study of patients with refractory SLE	LLDAS (without relapse up to 12 months)**	Not reported	Not reported	Not reported		Real-world use of belimumab 10 mg/kg IV	58.1%

	initiating belimumab (n=50)

[1]Statistically different from placebo p<0.05

[2]Statistically different from placebo p<0.01

*Oon et al. 2019 and Parodis et al. 2019 both quantified the extent of LLDAS in BLISS-52 and BLISS-76; however, the extent of LLDAS achieved across treatment arms differed. This is most likely driven by differences in how LLDAS was operationalized (e.g., Oon et al. 2019 used the BILAG to assess disease activity and Parodis et al. 2019 used the SELENA-SLEDAI Flare Index); see Parodis and Nikpour 2021 for further discussion on other possible differences [5]; [†]BLISS-52 and BLISS-76 were not initially designed to assess LDA states; patients were not required to discontinue immunosuppressants or taper glucocorticoid dose during follow-up as in BLISS-BELIEVE. Note: only the placebo and belimumab 10 mg/kg IV treatment arm are summarized because the 10 mg/kg IV dose is the current marketed dose; results for belimumab 1 mg/kg IV arm are not shown; [‡]in addition to a SLEDAI-2K ≤4, patients were required to have no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever), no hemolytic anemia or gastrointestinal activity, no new features of lupus disease activity (defined as no new SELENA-SLEDAI item score >0 and no new BILAG activity compared with the previous assessment); [§]standard maintenance doses of immunosuppressive drugs and approved biologics were allowed; [‖]patient numbers not reported; [¶]in addition, Parodis et al. 2019 required no activity in the renal descriptors (proteinuria, pyuria, hematuria, and cellular casts), no pleurisy, no pericarditis, and no fevers, with no new features of SLE disease activity (defined as no new moderate or severe flares on the SELENA-SLEDAI Flare Index compared with baseline); **for LLDAS, Sbeih et al. 2020 reference Franklyn et al. 2016 [6], but do not discuss how LLDAS was operationalized in their study.

BILAG, British Isles Lupus Assessment Group; CNS, central nervous system; cSLEDAI-2K, clinical SLE Disease Activity Index 2000; IS, immunosuppressant; IV, intravenous; LDA, low disease activity; LLDAS, low lupus disease activity state; PGA, Physician's Global Assessment; SC, subcutaneous; SLE, systemic lupus erythematosus, SLEDAI-2K, SLE Disease Activity Index 2000; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index

Supplementary Table S7. Extent of patients with SLE achieving remission at 52 weeks following the initiation of belimumab or comparator medications: results from previous studies

Author	Study	Outcome	Operationalization of disease activity state			% achieving outcome (stratified by study and treatment [if relevant])		
			Disease activity	Prednisone dose	IS allowed			
Post hoc analyses of prior randomized clinical trials								
Parodis 2019* [7]	BLISS-52 (NCT00424476) BLISS-76† (NCT00410384)	DORIS remission 1a – on therapy at Week 52*	cSLEDAI-2K=0 and PGA ≤0.5 at Week 52	≤5 mg/day at Week 52	Yes‡	BLISS-52	Placebo (n=227)	8.8%
							Belimumab 10 mg/kg IV (n=243)	12.3%
						BLISS-76	Placebo (n=204)	11.3%
							Belimumab 10 mg/kg IV (207)	10.1%
						Pooled	Placebo (n=431)	10.0%
							Belimumab 10 mg/kg IV (n=540)	11.3%
		Sustained DORIS remission 1a – on therapy at Week 52*	cSLEDAI-2K=0 and PGA ≤0.5 at Weeks 26 and 52	≤5 mg/day at Weeks 26 and 52	Yes‡	BLISS-52	Placebo (n=255)	2.0%
							Belimumab 10 mg/kg IV (n=267)	4.5%
						BLISS-76	Placebo (n=240)	2.5%

						Belimumab 10 mg/kg IV (n=239)	4.6%
					Pooled	Placebo (n=495)	2.2%
						Belimumab 10 mg/kg IV (n=506)	4.5%[1]
Observational studies evaluating belimumab and low disease activity states							
Gatto 2020 [3]	BERLiSS, a prospective cohort study of SLE patients initiating belimumab from 24 Italian centers (n=466)	Remission	cSLEDAI-2K=0	≤5.0 mg/day	Yes	Real-world use of belimumab 10 mg/kg IV	41.1%
Sbeih 2020 [4]	Single center prospective cohort study of patients with refractory SLE initiating belimumab (n=50)	Remission (without relapse up to 12 months)[§]	Not reported	Not reported	Not reported	Real-world use of belimumab 10 mg/kg IV	37.1%

[1]Statistically different from placebo p<0.05

*Parodis et al. 2019 considered multiple remission definitions based on the DORIS criteria; however, only a subset of definitions was examined in analyses stratified by treatment arms in BLISS-52 and/or BLISS-76; [†]for BLISS-52 and BLISS-76, only the placebo and belimumab 10 mg/kg IV treatment arm are summarized because the 10 mg/kg IV dose is the current marketed dose; results for belimumab 1 mg/kg IV arm are not shown; [‡]maintenance immunosuppressive therapies, and stable (maintenance) doses of biologic agents were allowed; [§]for remission, Sbeih et al. 2020 referenced van Vollenhoven et al. 2017 [8], but did not describe how remission was operationalized in their study

cSLEDAI-2K, clinical SLE Disease Activity Index 2000; DORIS, Definitions of Remission In Systemic Lupus Erythematosus; IS, immunosuppressant; IV, intravenous; PGA, Physician's Global Assessment; SLE, systemic lupus erythematosus

Supplementary references

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