Efficacy and safety of sequential therapy with subcutaneous belimumab and one cycle of rituximab in patients with systemic lupus erythematosus: The phase 3, randomised, placebo-controlled BLISS-BELIEVE study

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Supplementary materials

Treatment failure

Patients were regarded as treatment failures for the efficacy endpoints for any of the following reasons:

- Received a protocol-prohibited medication or medication dose
    - Other investigational agents (biologic or non-biologic)
    - Anti-TNF therapy (e.g., adalimumab, etanercept, infliximab)
    - Other biologics with effects on the immune system (e.g., abatacept, interleukin-1 receptor antagonist [anakinra])
    - Intravenous (IV) immunoglobulin
    - IV cyclophosphamide and oral cyclophosphamide (for Germany only)
    - Plasmapheresis
    - Live vaccines
- If patients in the BEL/PBO or BEL/RTX treatment groups received immunosuppressants after the Week 4 visit
- If patients in the BEL/ST treatment group required increased doses of their baseline immunosuppressants or the addition of new immunosuppressants after Week 12
- If a 7-day average prednisone-equivalent dose of >5 mg/day was required at any time after Week 26
- If patients in the BEL/PBO or BEL/RTX treatment groups could not tolerate discontinuation of immunosuppressants or taper of corticosteroids or, in the opinion of the investigator, required added therapy during the 52-week double-blind phase
- If patients in the BEL/ST group could not tolerate the corticosteroid taper or, in the opinion of the investigator, required increased doses of their baseline immunosuppressants or the addition of a new immunosuppressant

- If patients received (at the investigator's discretion) additional treatment of open-label belimumab, corticosteroids (>5 mg/day) and/or immunosuppressants during Weeks 53 to 104
- If patients required a new antimalarial treatment (e.g., hydroxychloroquine, chloroquine, quinacrine) after the start of the study

Patients from any treatment group who were regarded as treatment failures at any time during the study were encouraged to remain in the study and continue to have all efficacy and safety assessments.

Additional statistical analysis

For the post hoc proteinuria analysis, when the protein value was too small to be detected, a character result of '<50' was stored in the dataset and the protein:creatinine ratio was not calculated by the laboratory. Instead, a protein value of 49.999999999 (representing the most conservative value) was imputed to allow the calculation of the ratio using the following formula:

$$Protein{:}\,creatinine\ ratio\ (mg/mg) = \frac{Protein\ (mg/l)/10}{Creatinine\ (\mu mol/l) * 0.0113096584483149}$$

Supplementary tables

Table S1. Components of disease control* at Week 52, based on IBA assessment (mITT population[†], N=263)

Components	Observed response rate, n (%)			BEL/RTX vs BEL/PBO		
	BEL/PBO (n=72)	BEL/RTX (n=144)	BEL/ST[‡] (n=47)	Observed treatment difference (%)	OR (95% CI)[§]	p-value
Clinical SLEDAI-2K ≤2	15 (20.8)	40 (27.8)	18 (38.3)	6.94	1.52 (0.76, 3.03)	0.2358
No study discontinuation	64 (88.9)	126 (87.5)	43 (91.5)	−1.39	0.86 (0.35, 2.09)	0.7360
Not a treatment failure due to immunosuppressant use	62 (86.1)	126 (87.5)	42 (89.4)	1.39	1.13 (0.48, 2.64)	0.7811
Not a treatment failure due to corticosteroid use >5 mg/day	52 (72.2)	112 (77.8)	35 (74.5)	5.56	1.42 (0.74, 2.75)	0.2947
Not a treatment failure due to use of prohibited medications	67 (93.1)	125 (86.8)	44 (93.6)	−6.25	0.48 (0.17, 1.35)	0.1653

*Disease control defined as SLEDAI-2K score ≤2 achieved without immunosuppressants and with a prednisone-equivalent dose of ≤5 mg/day.
[†]mITT population excludes 29 patients from the BEL/ST group, due to independent blinded assessors being potentially unblinded.
[‡]ST included corticosteroids, antimalarials, immunosuppressants, and NSAIDs.
[§]OR (95% CI) and p-value are from a logistic regression model with covariates: baseline SLEDAI-2K, baseline immunosuppressants, baseline prednisone-equivalent dose, and treatment group.
BEL, belimumab; CI, confidence interval; IBA, independent blinded assessor; mITT, modified intention-to-treat; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; PBO, placebo; RTX, rituximab; SLEDAI-2K, SLE Disease Activity Index-2000; SLE, systemic lupus erythematosus; ST, standard therapy.

Table S2. Disposition of disease control* based on IBA assessment by first reason for non-response at Weeks 52 and 104 (mITT population†, N=263)

	BEL/PBO (n=72)	BEL/RTX (n=144)	BEL/ST‡ (n=47)
Disease control non-responders at Week 52, n (%)	60 (83.3)	116 (80.6)	35 (74.5)
First reason for disease control non-response at Week 52, n (%)			
SLEDAI-2K score >2	28 (38.9)	50 (34.7)	14 (29.8)
Treatment failure due to average prednisone-equivalent dose >5 mg/day	15 (20.8)	22 (15.3)	10 (21.3)
Study discontinuation§	7 (9.7)	14 (9.7)	4 (8.5)
Treatment failure due to immunosuppressant use	7 (9.7)	13 (9.0)	3 (6.4)
Treatment failure due to other medication‖	2 (2.8)	13 (9.0)	2 (4.3)
SLEDAI-2K score missing	1 (1.4)	4 (2.8)	2 (4.3)
Disease control non-responders at Week 104, n (%)	67 (93.1)	128 (88.9)	37 (78.7)
First reason for disease control non-response at Week 104, n (%)			
Treatment failure due to re-start (or continuation beyond Week 52) of belimumab (BEL/PBO or BEL/RTX group)	24 (33.3)	31 (21.5)	0 (0.0)
Treatment failure due to average prednisone-equivalent dose >5 mg/day	19 (26.4)	27 (18.8)	12 (25.5)
Study discontinuation¶	7 (9.7)	19 (13.2)	6 (12.8)
Treatment failure due to immunosuppressant use	8 (11.1)	15 (10.4)	3 (6.4)
SLEDAI-2K score >2	5 (6.9)	15 (10.4)	10 (21.3)
Treatment failure due to other medication**	3 (4.2)	19 (13.2)	6 (12.8)
SLEDAI-2K score missing	1 (1.4)	2 (1.4)	0 (0.0)

*Disease control defined as SLEDAI-2K score ≤2 achieved without immunosuppressants and with a prednisone-equivalent dose of ≤5 mg/day.
†mITT population excludes 29 patients from the BEL/ST group, due to independent blinded assessors being potentially unblinded.
‡ST included corticosteroids, antimalarials, immunosuppressants, and NSAIDs.
§Patients who withdrew from the study (including death and loss to follow-up) and had no data within 28 days of the target visit date (study day 337 to 393).
‖Patients who took a protocol-prohibited or restricted medication other than immunosuppressant or prednisone-equivalent corticosteroid.
¶Patients who withdrew from the study (including death and loss to follow-up) and had no data within 28 days of the target visit date (study day 701 to 757).

[**]Patients who took a protocol-prohibited or restricted medication other than immunosuppressant, prednisone-equivalent corticosteroid dose >5 mg/day, or re-started belimumab (BEL/PBO or BEL/RTX group).
BEL, belimumab; IBA, independent blinded assessor; mITT, modified intention-to-treat; PBO, placebo; RTX, rituximab; SLEDAI-2K, SLE Disease Activity Index-2000; SLE, systemic lupus erythematosus; ST, standard therapy.

Table S3. Time to disease control or clinical remission*, based on PI assessment (mITT population†, N=263)

	BEL/PBO (n=72)	BEL/RTX (n=144)	BEL/ST‡ (n=47)	BEL/RTX vs BEL/PBO	
				HR (95% CI)§	p-value§
Disease control sustained for at least 24 weeks and maintained through to Week 104					
Patients achieving disease control, n (%)	3 (4.2)	9 (6.3)	5 (10.6)	1.55 (0.42, 5.78)	0.5127
Median (IQR) days to disease control (among patients achieving disease control)	337.0 (141.0, 512.0)	169.0 (114.0, 448.0)	253.0 (184.0, 363.0)		
Clinical remission sustained for at least 24 weeks and maintained through to Week 104					
Patients achieving clinical remission, n (%)	2 (2.8)	3 (2.1)	2 (4.3)	0.83 (0.14, 5.05)	0.8436
Median (IQR) days to clinical remission (among patients achieving clinical remission)	212.5 (88.0, 337.0)	283.0 (171.0, 337.0)	353.5 (342.0, 365.0)		

*Disease control defined as SLEDAI-2K score ≤2 achieved without immunosuppressants and with a prednisone-equivalent dose of ≤5 mg/day; clinical remission defined as a clinical SLEDAI-2K score=0, without immunosuppressants and with corticosteroids at a prednisone-equivalent dose of 0 mg/day.
†mITT population excludes 29 patients from the BEL/ST group, due to independent blinded assessors being potentially unblinded.
‡ST included corticosteroids, antimalarials, immunosuppressants, and NSAIDs.
§HR (95% CI) and p-value are from a Cox proportional-hazards model with covariates: baseline SLEDAI-2K, baseline prednisone-equivalent dose, and treatment group.

BEL, belimumab; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; mITT, modified intention-to-treat; NSAIDs, non-steroidal anti-inflammatory drugs; PBO, placebo; PI, principal investigator; RTX, rituximab; SLEDAI-2K, SLE Disease Activity Index-2000; SLE, systemic lupus erythematosus; ST, standard therapy.

Table S4. Reduction from baseline in SLEDAI-2K ≥4 at Week 52 and duration of disease control by anti-dsDNA antibody and C3/C4 levels at baseline, based on PI assessment (post hoc analyses; mITT population*, N=263)

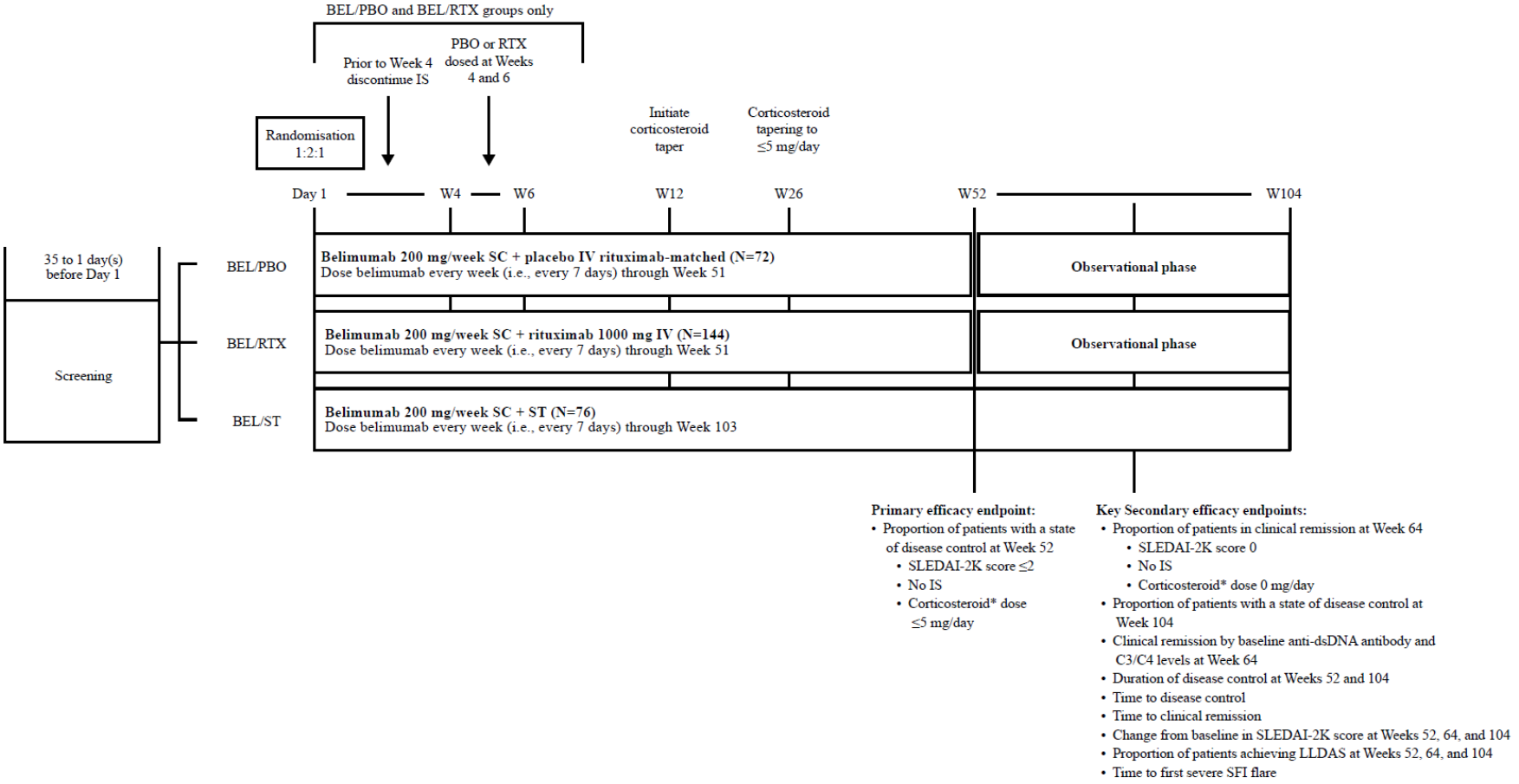
	BEL/PBO (n=72)	BEL/RTX (n=144)	BEL/ST† (n=47)	BEL/RTX vs BEL/PBO		
				Treatment difference (%)	OR (95% CI)‡	p-value
Reduction from baseline in SLEDAI-2K ≥4 at Week 52						
At least one low C3/C4 and anti-dsDNA antibodies ≥30 IU/ml at baseline						
n	27	62	16	15.23	2.0 (0.76, 5.23)	0.1585
Responders, n (%)	12 (44.4)	37 (59.7)	5 (31.3)			
NOT (at least one low C3/C4 and anti-dsDNA antibodies ≥30 IU/ml at baseline)						
n	45	80	31	−3.75	0.83 (0.39, 1.78)	0.6308
Responders, n (%)	18 (40.0)	29 (36.3)	16 (51.6)			
	BEL/PBO (n=72)	**BEL/RTX (n=144)**	**BEL/ST† (n=47)**	**BEL/RTX vs BEL/PBO**		
				Treatment difference (%)§	**95% CI§**	**p-value§**
Duration of disease control						
At least one low C3/C4 and anti-dsDNA antibodies ≥30 IU/ml at baseline						
n‖	8	28	6	39.6	−34.7, 113.8	0.2853
Median (IQR) days	28 (9.0, 72.5)	61.5 (1.0, 142.5)	43.5 (1.0, 92.0)			
NOT (at least one low C3/C4 and anti-dsDNA antibodies ≥30 IU/ml at baseline)						
n‖	26	44	24	55.8	7.6, 103.9	0.0240
Median (IQR) days	29.0 (1.0, 86.0)	110.0 (25.0, 197.0)	85.0 (30.0, 144.5)			

*mITT population excludes 29 patients from the BEL/ST group, due to IBAs being potentially unblinded.
†ST included corticosteroids, antimalarials, immunosuppressants, and NSAIDs.
‡OR (95% CI) and p-value are from a logistic regression model with covariates: baseline SLEDAI-2K, baseline immunosuppressants, baseline prednisone-equivalent dose, and treatment group.
§All statistics are from ANCOVA model with covariates: baseline SLEDAI-2K, baseline immunosuppressants, baseline prednisone-equivalent dose and group.

[l]Subgroup of patients with ≥1 assessment where disease control was met.
ANCOVA, analysis of covariance; BEL, belimumab; C3/4, complement 3/4; CI, confidence interval; IBA, independent blinded assessor; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; PBO, placebo; PI, principal investigator; RTX, rituximab; SLEDAI-2K, SLE Disease Activity Index-2000; SLE, systemic lupus erythematosus; ST, standard therapy.

Supplementary Figures

Figure S1. Study design

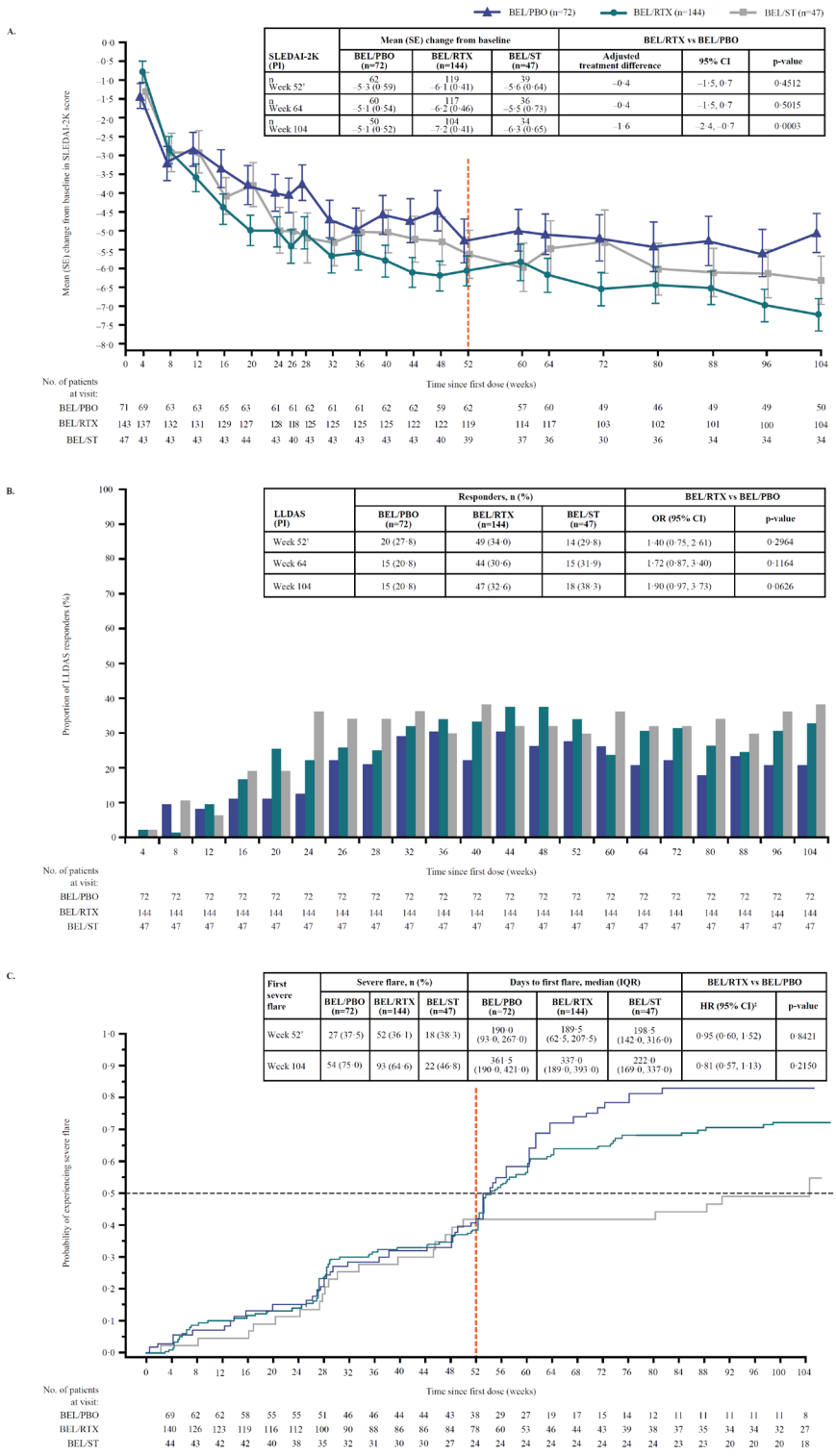


The figure was reproduced from ‘Phase III, multicentre, randomized, double-blind, placebo-controlled, 104-week study of subcutaneous belimumab administered in combination with rituximab in adults with systemic lupus erythematosus (SLE): BLISS-BELIEVE study protocol’ Teng YKO, et al. *BMJ Open* 2019;9:e025687 with copyright permission (2023) from BMJ Publishing Group.

*Prednisone-equivalent.

BEL, belimumab; IS, immunosuppressants; IV, intravenous; LLDAS, Lupus Low Disease Activity State; PBO, placebo; RTX, rituximab; SC, subcutaneous; SFI, Safety of Estrogens in Lupus Erythematosus National Assessment- Systemic Lupus Erythematosus Disease Activity Index flare index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000; ST, standard therapy; W, week.

Figure S2. (A) Change from baseline in SLEDAI-2K, (B) proportion of LLDAS responders*, and (C) time to first modified severe SFI flare†§ through Week 104 (mITT population, N=263)



SLEDAI-2K (PI)	Mean (SE) change from baseline			BEL/RTX vs BEL/PBO		
	BEL/PBO (n=72)	BEL/RTX (n=144)	BEL/ST (n=47)	Adjusted treatment difference	95% CI	p-value
n Week 52‡	62 −5·3 (0·59)	119 −6·1 (0·41)	39 −5·6 (0·64)	−0·4	−1·5, 0·7	0·4512
n Week 64	60 −5·1 (0·54)	117 −6·2 (0·46)	36 −5·5 (0·73)	−0·4	−1·5, 0·7	0·5015
n Week 104	50 −5·1 (0·52)	104 −7·2 (0·41)	34 −6·3 (0·65)	−1·6	−2·4, −0·7	0·0003

LLDAS (PI)	Responders, n (%)			BEL/RTX vs BEL/PBO	
	BEL/PBO (n=72)	BEL/RTX (n=144)	BEL/ST (n=47)	OR (95% CI)	p-value
Week 52‡	20 (27·8)	49 (34·0)	14 (29·8)	1·40 (0·75, 2·61)	0·2964
Week 64	15 (20·8)	44 (30·6)	15 (31·9)	1·72 (0·87, 3·40)	0·1164
Week 104	15 (20·8)	47 (32·6)	18 (38·3)	1·90 (0·97, 3·73)	0·0626

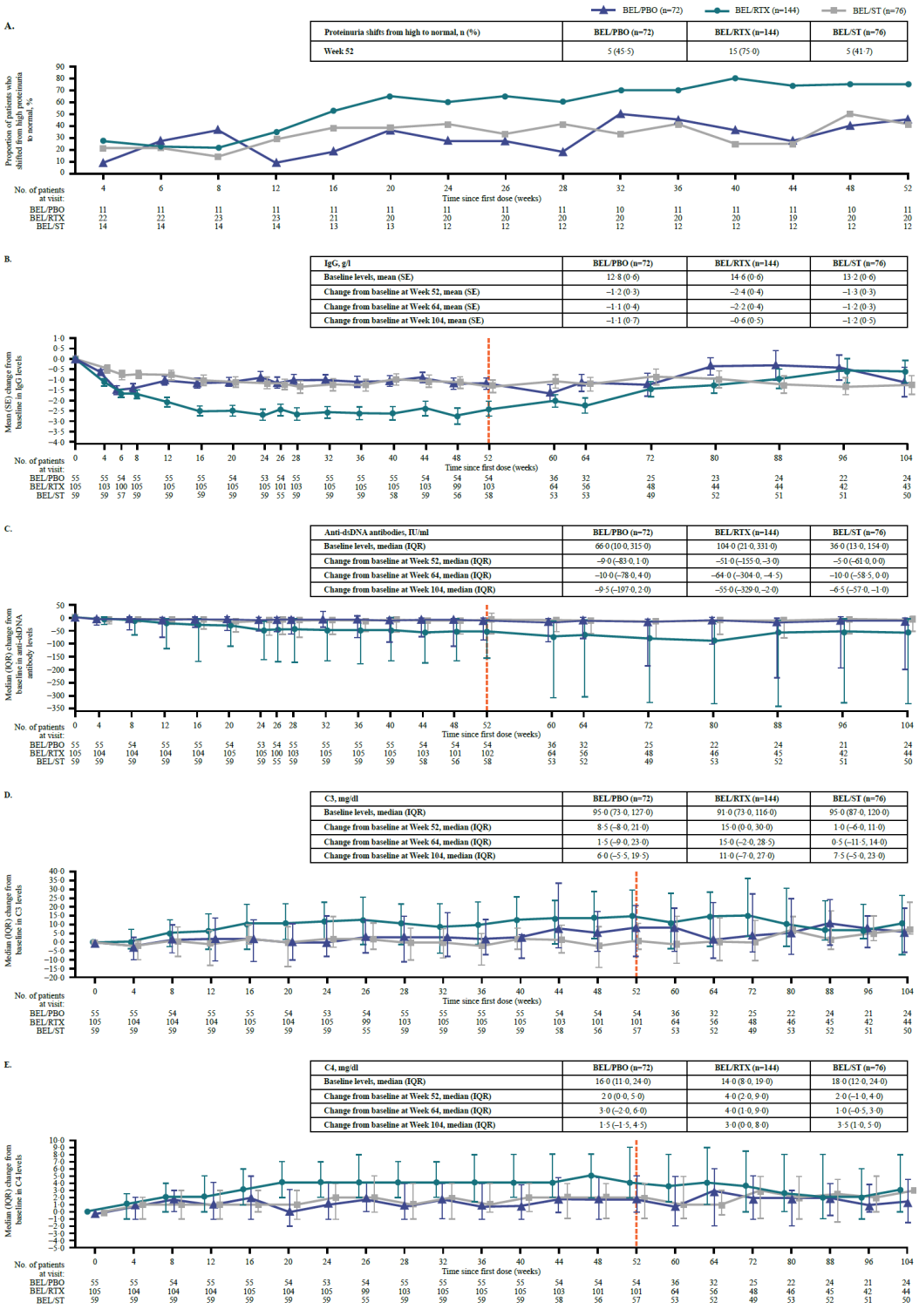
First severe flare	Severe flare, n (%)			Days to first flare, median (IQR)			BEL/RTX vs BEL/PBO	
	BEL/PBO (n=72)	BEL/RTX (n=144)	BEL/ST (n=47)	BEL/PBO (n=72)	BEL/RTX (n=144)	BEL/ST (n=47)	HR (95% CI)‖	p-value
Week 52‡	27 (37·5)	52 (36·1)	18 (38·3)	190·0 (93·0, 267·0)	189·5 (62·5, 207·5)	198·5 (142·0, 316·0)	0·95 (0·60, 1·52)	0·8421
Week 104	54 (75·0)	93 (64·6)	22 (46·8)	361·5 (190·0, 421·0)	337·0 (189·0, 393·0)	222·0 (169·0, 337·0)	0·81 (0·57, 1·13)	0·2150

Note: mITT population excludes 29 patients from the BEL/ST group, due to independent blinded assessors being potentially unblinded.

*A modified LLDAS definition was used in this study: 1) SLEDAI-2K ≤4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity; 2) no new features of lupus disease activity compared with the previous assessment; 3) PGA (scale 0–3) ≤1; 4) current prednisone-equivalent dose ≤7.5 mg/day; 5) well-tolerated standard maintenance doses of immunosuppressants and approved biological agents, excluding investigational drugs; 6) not study withdrawal (including death and lost to follow-up).
†Modified severe SFI flare did not consider severe flares triggered only by an increase in SLEDAI-2K score to >12 to be severe flares, but did impute patients who met the study's treatment failure definition as having a severe flare.
‡Week 52 results from a model that includes all Week 52 (Year 1) and Week 104 (Year 2) data; figure relates to Year 1 and Year 2 data.
§Severe flare hazard ratios are from analysis of time to event. Time to first flare is defined as (event date − treatment start date + 1). Statistics are missing when the number of events is too low to estimate the value.

BEL, belimumab; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; LLDAS, Lupus Low Disease Activity State; mITT, modified intention-to-treat; OR, odds ratio; PBO, placebo; PI, principal investigator; RTX, rituximab; SE, standard error; SFI, Safety of Estrogens in Lupus Erythematosus National Assessment- Systemic Lupus Erythematosus Disease Activity Index flare index; SLEDAI-2K, SLE Disease Activity Index-2000; SLE, systemic lupus erythematosus; ST, standard therapy.

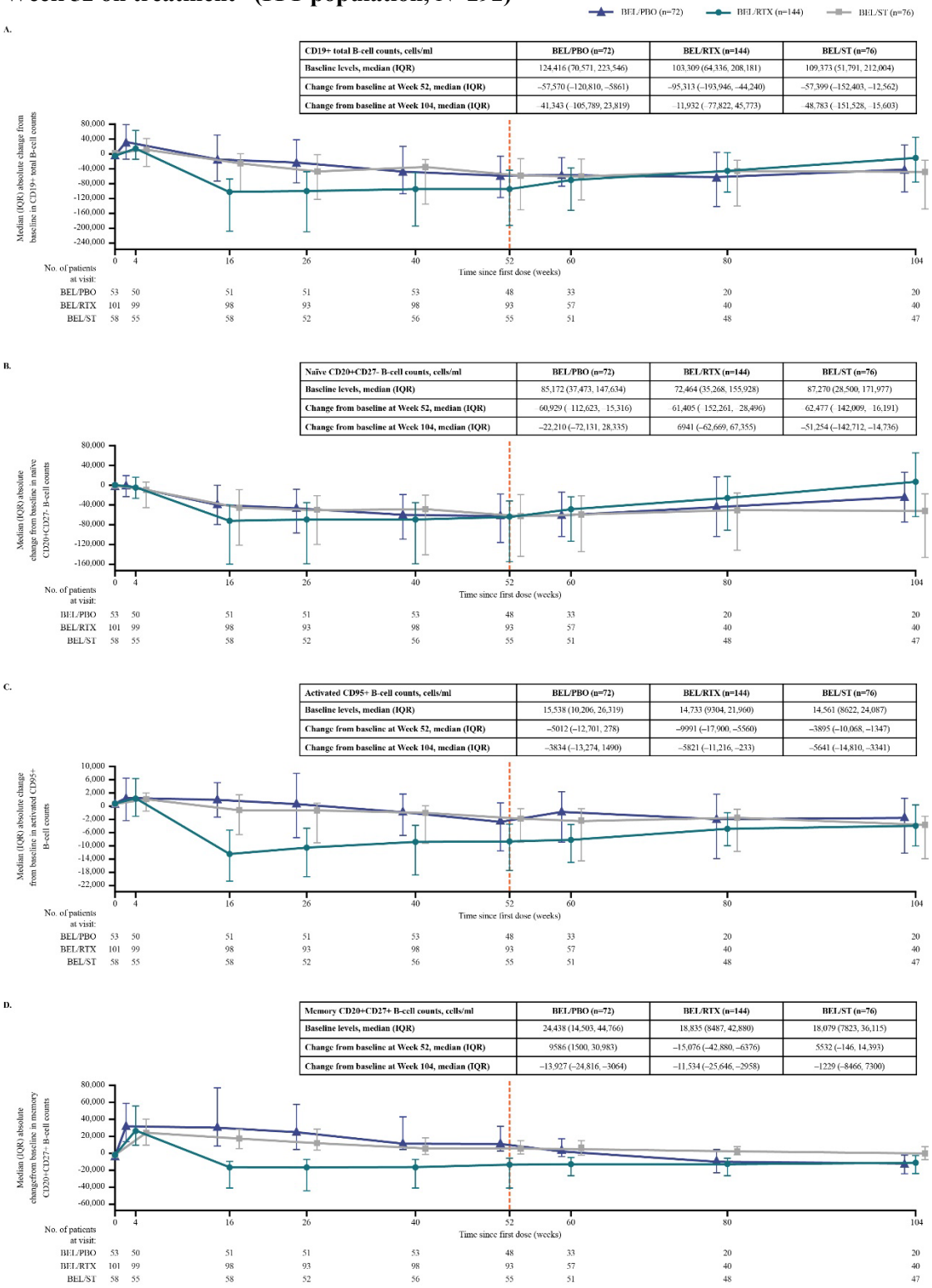
Figure S3. (A) Shift from high proteinuria at baseline to normal proteinuria (g/24 h) at Week 52* and change from baseline in (B) IgG (g/l), (C) anti-dsDNA antibodies (IU/ml)†, (D) C3 (mg/dl)†, and (E) C4 (mg/dl)† by visit through Week 104 (ITT population, N=292)



*Shifts from high (>0.5 g/24 h) to normal (≤0.5 g/24 h) proteinuria values were assessed via post hoc analysis and are shown only for those patients with high proteinuria at baseline (n=50).
†Anti-dsDNA antibody and C3/C4 outcomes were analysed among patients who completed Week 52 on treatment.

BEL, belimumab; C3/C4, complement 3/4; IQR, interquartile range; ITT, intention-to-treat; PBO, placebo; RTX, rituximab; SE, standard error; ST, standard therapy.

Figure S4. Absolute change from baseline in (A) CD19+ total B-cell counts, (B) naïve CD20+CD27- B-cell counts, (C) activated CD95+ B-cell counts, and (D) memory CD20+CD27+ B-cell counts by visit through to Week 104 among patients who completed Week 52 on treatment* (ITT population, N=292)



Note: LLOQ, 2.5 cells/µl.

P-value for Week 52 analysis was calculated using an ANCOVA model with baseline SLEDAI-2K score, baseline IS dose, baseline prednisone-equivalent dose, and treatment group as covariates. P-value for Week 104 analysis was calculated using a rank ANCOVA model with baseline level and treatment group as covariates.
*The data for patients in the BEL/PBO and BEL/RTX groups who re-started belimumab after Week 52 and for patients in the BEL/ST group who withdrew belimumab after Week 52 were excluded from the analysis.

ANCOVA, analysis of covariance; BEL, belimumab; IQR, interquartile range; IS, immunosuppressant; PBO, placebo; RTX, rituximab; ST, standard therapy.