A Phase 3, long-term, open-label extension period of safety and efficacy of belimumab in patients with systemic lupus erythematosus in China, for up to 6 years

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SUPPLEMENTARY MATERIALS

Supplementary Methods

Key patient eligibility criteria

Inclusion and exclusion criteria for the double-blind BEL113750 study have been previously reported.[1] Additionally, patients enrolling in the open-label period of the BEL113750 study met the following criteria:

- Have completed the double-blind BEL113750 Protocol through Week 48.
- Be able to receive the first dose of belimumab for the open-label period 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in the double-blind BEL113750 period.

Key exclusion criteria

Have developed clinical evidence of significant, unstable or uncontrolled, acute or chronic diseases not due to SLE, or experienced an adverse event (AE) in the double-blind BEL113750 period that could, in the opinion of the principal investigator, put the patient at undue risk.

Permissible SLE therapy

Once the patient received the first dose of study treatment on Day 0 of the open-label period, the use of permitted concurrent SLE therapy could be adjusted (added, eliminated, changed dose level/frequency) by the investigator as clinically required in response to improving or worsening conditions.

The use of traditional and herbal remedies as part of the local standard therapy for non-SLE illness was permitted (e.g. glycosides of Paeony or Tripterygium).

Prohibited medications and non-drug therapies

The use of the following medications and therapies was prohibited at any time during the study, including the OL period. Patients who started prohibited medications and therapies at any time during the open-label period were withdrawn from open-label treatment with belimumab and entered study follow-up:

- Other investigational agents (biologic and non-biologic)
- Co-enrolment into another study of an investigational agent or non-drug therapy that may have interfered with the conduct of this protocol
- Anti-tumour necrosis factor or anti-interleukin (IL)-6 therapy (e.g. adalimumab, etanercept, or infliximab)
- Other biologics (e.g. rituximab, abatacept, IL-1 receptor antagonist [anakinra])
- Intravenous immunoglobulin
- Intravenous cyclophosphamide
- Plasmapheresis and leukapheresis.

Additionally, live vaccines were not permitted in the study.

Adverse events

Adverse events were coded according to the Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term. Toxicity grades for clinical laboratory parameters were modified from the Division of Microbiology and Infectious Diseases Adverse Event Adult Toxicity Tables.[2]

Definition of proteinuria

Proteinuria was defined as a urine spot protein creatinine ratio >0.5 g/24 hr at baseline.

Definition of SFI flares

SELENA-SLEDAI flare index (SFI) flare: SLE flares were defined as a mild/moderate or severe, according to the modified SFI (excluded severe flares from the SELENA-SLEDAI flare assessment that were triggered only by an increase in SELENA-SLEDAI score to >12).

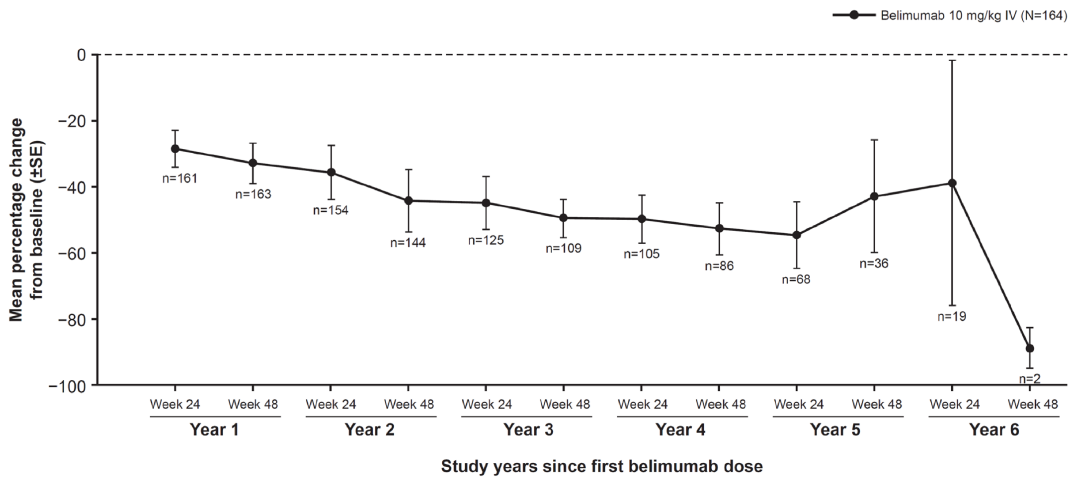
Supplementary references

1. Zhang F, Bae SC, Bass D, et al. A pivotal phase III, randomised, placebo-controlled study of belimumab in patients with systemic lupus erythematosus located in China, Japan and South Korea. Ann Rheum Dis. 2018;77(3): 355−363.

2. Diseases DoMaI. Adult Toxicity Table. Available at: https://www.niaid.nih.gov/sites/default/files/dmidadulttox.pdf. Accessed April 2020.

Supplementary figures and tables

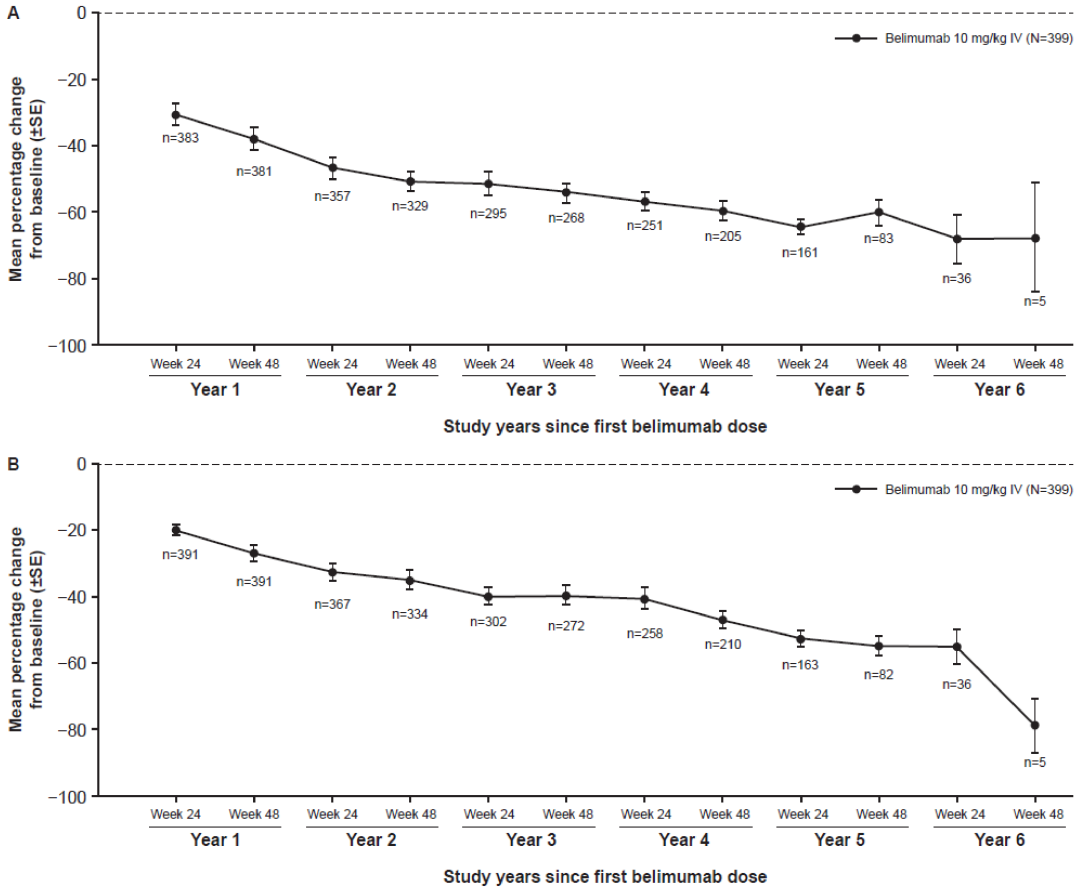
Supplementary Figure 1. Percentage change in proteinuria from baseline by visit among patients with baseline proteinuria >0.5 g/24 hr (Efficacy population; N=399)



Note: Baseline was defined as the last available value prior to belimumab initiation: Day 1 for patients randomised to belimumab in the double-blind period and Week 52 for patients randomised to placebo in the double-blind period.

SE, standard error

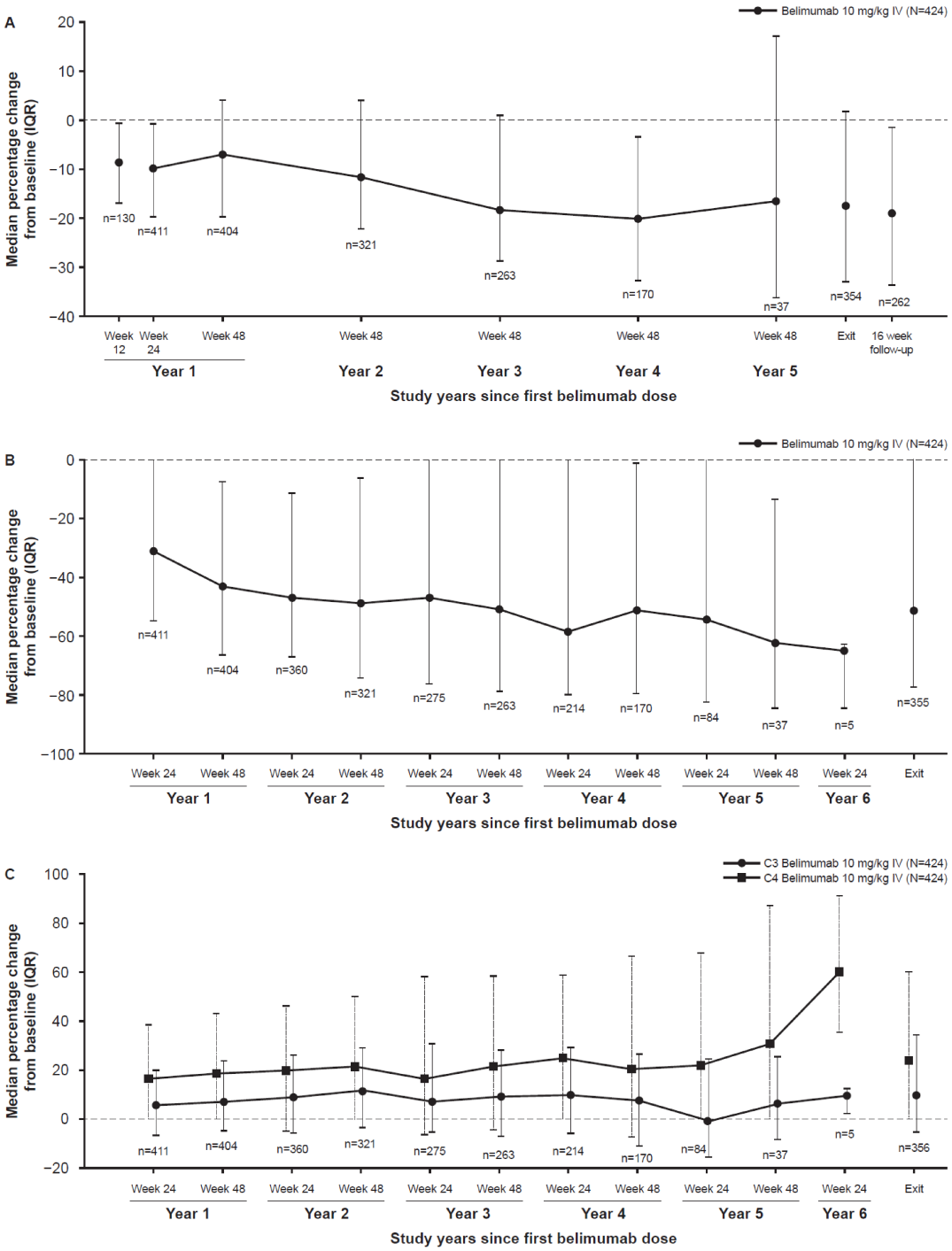
Supplementary Figure 2. Percentage change from baseline in (A) SELENA-SLEDAI score and (B) PGA score by visit (Efficacy population; N=399)



Note: Baseline was defined as the last available value prior to belimumab initiation: Day 1 for patients randomised to belimumab in the double-blind period and Week 52 for patients randomised to placebo in the double-blind period.

PGA, Physician's Global Assessment; SD, standard deviation; SE, standard error; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLE Disease Activity Index; SLE, systemic lupus erythematosus.

Supplementary Figure 3. Median percentage change from baseline by visit (Safety population; N=424) in (A) IgG (g/l) levels*; (B) anti-dsDNA (IU/mL) levels; (C) C3 and C4 levels (mg/dl)



Median (IQR) baseline values: IgG 13.3 (10.9, 16.7) g/l (normal range: 6.94−16.18 g/l); anti-dsDNA 91.0 (33.0, 225.0) IU/ml (normal range: <30 IU/ml); C3 81.0 (67.0, 97.0) mg/dl (normal range: 90–180 mg/dl); and C4 14.0 (10.0, 20.0) mg/dl (normal range: normal range: 10–40 mg/dl).

*At Year 1 Week 12, IgG was only assessed in the placebo group, for patients entering OL period.

Note: Baseline was defined as the last available value prior to belimumab initiation: Day 1 for patients randomised to belimumab in the double-blind period and Week 52 for patients randomised to placebo in the double-blind period.

Anti-dsDNA, anti-double stranded deoxyribonucleic acid; C, complement; Ig, immunoglobulin; IQR, interquartile range; IV, intravenous; OL, open-label.

Supplementary Table 1. Baseline* disease characteristics by double-blind period randomisation (Safety population; N=424)

	Double-blind period randomised treatment group		Total OL population (N=424)
	Placebo (n=134)	Belimumab (n=290)	
Mean SLE disease duration (SD)†, years	6.6 (5.0)	5.7 (4.7)	6.0 (4.8)
Median (minimum, maximum)	5.5 (1.1, 29.5)	4.7 (0.1, 21.4)	5.0 (0.1, 29.5)
BILAG organ domain involvement‡, n (%)			
≥1A or 2B	15 (11.2)	122 (42.1)	137 (32.3)
≥1A	4 (3.0)	16 (5.5)	20 (4.7)
≥1B	55 (41.0)	237 (81.7)	292 (68.9)
No A or B	76 (56.7)	51 (17.6)	127 (30.0)
BILAG organ system involvement (A or B scores), n (%)			
General	1 (0.7)	13 (4.5)	14 (3.3)
Mucocutaneous	21 (15.7)	142 (49.0)	163 (38.4)
Neurological	0 (0)	0 (0)	0 (0)
Musculoskeletal	3 (2.2)	71 (24.5)	74 (17.5)
Cardiovascular and Respiratory	0 (0)	1 (0.3)	1 (0.2)
Vasculitis	2 (1.5)	32 (11.0)	34 (8.0)
Renal	22 (16.4)	75 (25.9)	97 (22.9)
Haematology	23 (17.2)	56 (19.3)	79 (18.6)
Mean SELENA-SLEDAI score (SD)	5.0 (3.3)	9.4 (3.7)	8.0 (4.1)
SELENA-SLEDAI category			
≤9	120 (89.6)	157 (54.1)	277 (65.3)
≥10	14 (10.4)	133 (45.9)	147 (34.7)
SLE flare index‡, n (%)			
≥1 flare	23 (17.2)	40 (13.8)	63 (14.9)
≥1 severe flare	1 (0.7)	8 (2.8)	9 (2.1)
Mean PGA (SD)	1.1 (0.5)	1.6 (0.4)	1.5 (0.5)
SDI score			
Mean (SD)	0.2 (0.4)	0.1 (0.4)	0.2 (0.4)
Median (minimum, maximum)	0 (0, 2)	0 (0, 3)	0 (0, 3)
ANA			
Positive (Index ≥0.80), n (%)	134 (100.0)	290 (100.0)	424 (100.0)
Anti-dsDNA			
Positive (≥30 IU/ml), n (%)	91 (67.9)	233 (80.3)	324 (76.4)
Complement level, n (%)			
Low C3 (<90 mg/dl) and/or low C4 (<10 mg/dl)	81 (60.4)	197 (67.9)	278 (65.6)
No low C3 or C4	53 (39.6)	93 (32.1)	146 (34.4)
Mean proteinuria level (SD), g/24 hr	0.6 (1.2)	0.9 (1.2)	0.8 (1.2)
Proteinuria category (g/24 hr), n (%)			
≤0.5	91 (67.9)	156 (53.8)	247 (58.3)
>0.5	43 (32.1)	134 (46.2)	177 (41.7)
>0.5 to <1	18 (13.4)	39 (13.4)	57 (13.4)
1 to <2	15 (11.2)	56 (19.3)	71 (16.7)
≥2	10 (7.5)	39 (13.4)	49 (11.6)

*Baseline was defined as the last available value prior to belimumab initiation: Day 1 for patients randomised to belimumab in the double-blind period and Week 52 for patients randomised to placebo in the double-blind period; †duration defined as (date of first belimumab dose – date of SLE diagnosis + 1)/365.25; ‡patients may have been counted in more than one category.

ANA, anti-nuclear antibody; Anti-dsDNA, anti-double stranded deoxyribonucleic acid; BILAG, British Isles Lupus Assessment Group; C, complement; OL, open-label; PGA, Physician's Global Assessment; SD, standard deviation; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage

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

Supplementary Table 2. Allowed concomitant SLE medication by year interval (Safety population; N=424)

	Number (%) of patients					
	Any time post-first dose of belimumab* (N=424)	**Year 0–1 (N=424)**	**Year 1–2 (N=404)**	**Year 2–3 (N=319)**	**Year 3–4 (N=251)**	**Year 4+† (N=130)**
Corticosteroids	420 (99.1)	419 (98.8)	400 (99.0)	311 (97.5)	242 (96.4)	123 (94.6)
Antimalarials	355 (83.7)	343 (80.9)	327 (80.9)	255 (79.9)	200 (79.7)	99 (76.2)
Immunosuppressants/Immunomodulatory	314 (74.1)	284 (67.0)	267 (66.1)	203 (63.6)	151 (60.2)	75 (57.7)
Aspirin	84 (19.8)	54 (12.7)	63 (15.6)	51 (16.0)	46 (18.3)	21 (16.2)
NSAIDs	72 (17.0)	32 (7.5)	28 (6.9)	23 (7.2)	24 (9.6)	11 (8.5)
Traditional Chinese medication						
Glycosides of Paeony/Tripterygium	109 (25.7)	83 (19.6)	82 (20.3)	59 (18.5)	45 (17.9)	26 (20.0)
Paeonia (NOS)	9 (2.1)	1 (0.2)	4 (1.0)	3 (0.9)	0	0
Paeonia extract (NOS)	64 (15.1)	56 (13.2)	56 (13.9)	40 (12.5)	27 (10.8)	17 (13.1)
Paeonia Rubra	1 (0.2)	1 (0.2)	0	0	0	0
Paeonia Suffruticosa	14 (3.3)	7 (1.7)	7 (1.7)	5 (1.6)	6 (2.4)	3 (2.3)
Paeonia Alba	9 (2.1)	4 (0.9)	3 (0.7)	1 (0.3)	1 (0.4)	0
Paeonia Alba extract	14 (3.3)	10 (2.4)	10 (2.5)	9 (2.8)	8 (3.2)	6 (4.6)
Tripterygium (NOS)	1 (0.2)	0	1 (0.2)	0	0	0
Tripterygium Wilfordii	13 (3.1)	11 (2.6)	10 (2.5)	7 (2.2)	5 (2.0)	1 (0.8)
Tripterygium Wilfordii extract	3 (0.7)	1 (0.2)	3 (0.7)	1 (0.3)	0	0

*Post-first dose of belimumab (baseline) includes time on study up to the 16-week follow-up visit post-last dose. Data from Year 0 to a patient's Exit visit (4 weeks post-last dose) are shown by years of study participation; †Year 4+ represents Year 4–5 and Year 5–6 of belimumab treatment.

Baseline was defined as the last available value prior to belimumab initiation: Day 1 for patients randomised to belimumab in the double-blind period and Week 52 for patients randomised to placebo in the double-blind period.

NSAIDs, non-steroidal anti-inflammatory drugs; NOS, not otherwise specified; SLE, systemic lupus erythematosus.