**SUPPLEMENTARY MATERIALS**

**Predefined belimumab stopping criteria during the study**

Patients recruited into this open-label, continuation study continued to receive treatment with intravenous (IV) belimumab until any of the following occurred:

- Belimumab became commercially available in Japan and South Korea
- The patient elected to participate in another belimumab continuation study for systemic lupus erythematosus (SLE)
- The patient withdrew, or was withdrawn by their physician, from the study
- The sponsor decided to discontinue further development of belimumab for SLE

This study closed when Pharmaceutical and Medical Devices Agency (PMDA) approved belimumab, and patients were transitioned from study supplied belimumab over to commercially available Benlysta. The Korea Food and Drug Administration (KFDA) approved Benlysta in 2015.

**Key patient eligibility criteria**

Inclusion and exclusion criteria for the parent studies have been previously reported.[1,2] Additionally, patients enrolling in BEL114333 study met the following criteria:

- Have completed the BEL113750 Protocol in North East Asia through Week 48 or have completed the open-label extension of BEL112341 in Japan
- Be able to receive the first dose of belimumab for BEL114333 4 weeks (minimum of 2 weeks, maximum of 8 weeks) after the last dose in BEL113750 or be able to receive the first dose of IV belimumab 1 week (plus a 1-week visit window) after the last dose of open-label subcutaneous (SC) belimumab in BEL112341.

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 respective parent studies 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 (BEL114333), 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.

**Prohibited medications and non-drug therapies**

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 Patients who started prohibited medications and therapies were withdrawn from open-label treatment with belimumab and entered study follow-up.

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

Additionally, live vaccines were not permitted in the study.

**Adverse events**

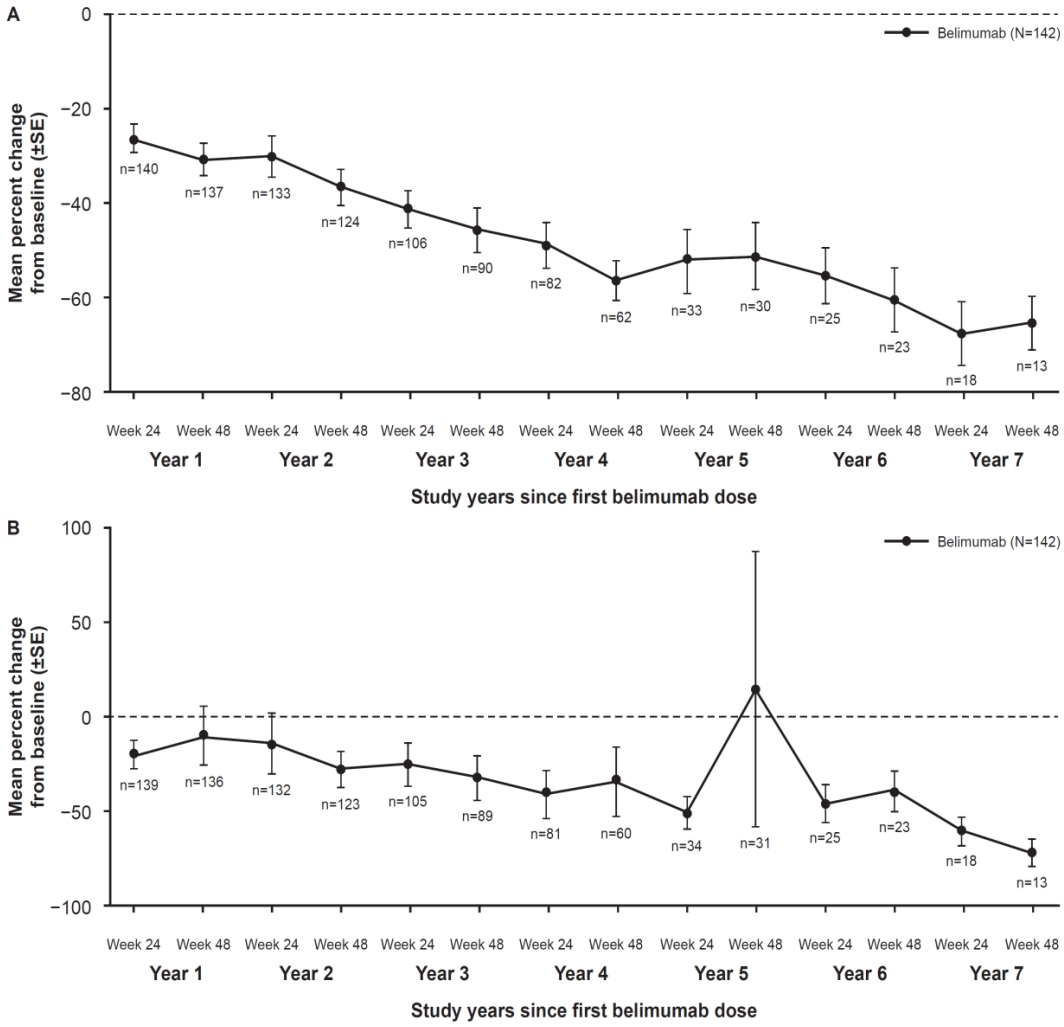
Adverse events were coded according to the Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term. Toxicity grades for clinical laboratory parameters were modified from the Division of Microbiology and Infectious Diseases (DMID) Adverse Event Adult Toxicity Tables.[3]

**Definition of SFI flares**

Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (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 figures and tables**

**Supplementary Figure 1. Percentage change from baseline in (A) SELENA-SLEDAI and (B) PGA by visit (safety population, N=142)**

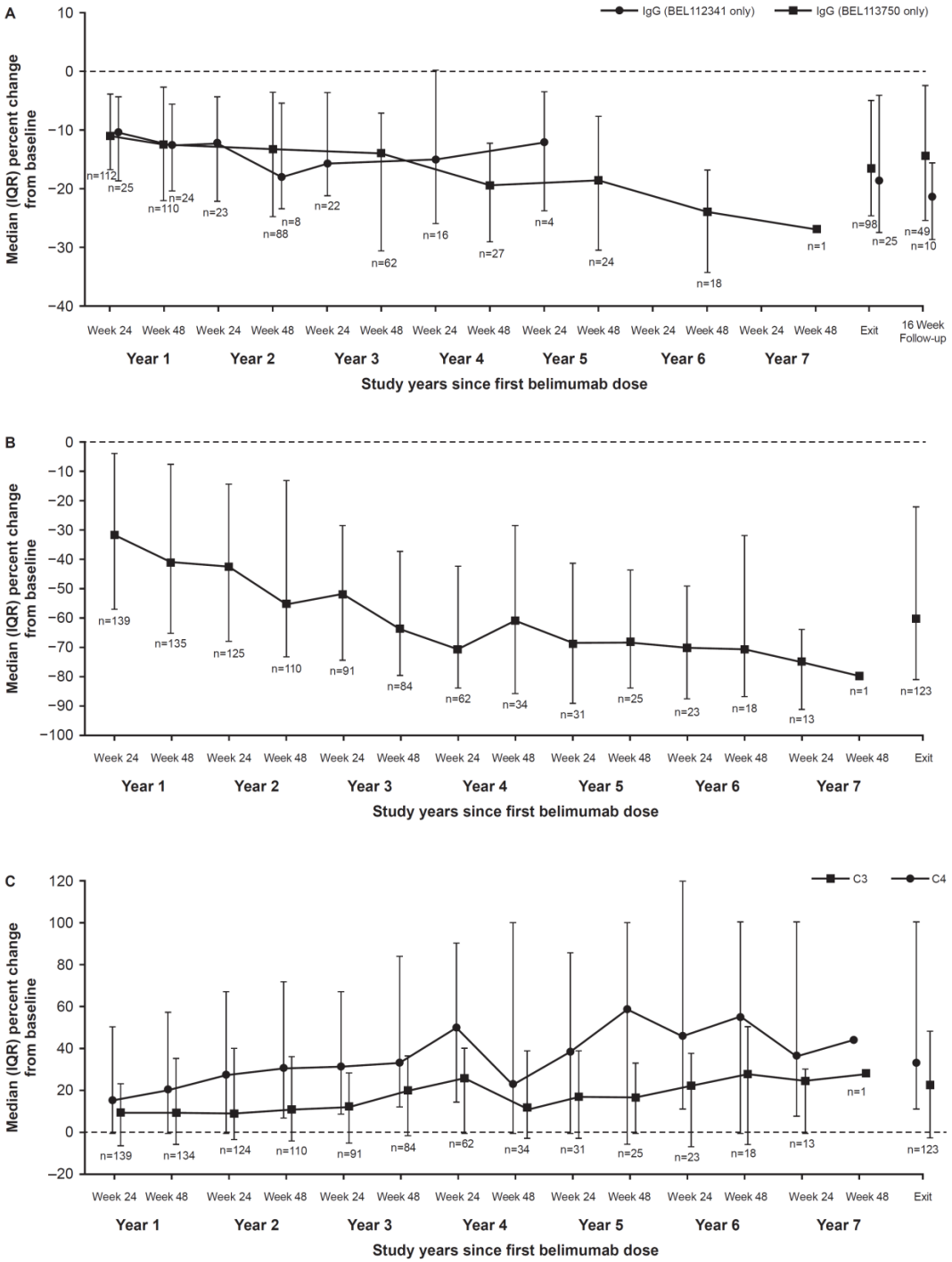



Mean (SD) baseline SELENA-SLEDAI score was 9.3 (3.9) and mean (SD) baseline PGA score was 1.2 (0.6).

Baseline was defined as the last available value prior to belimumab initiation: Day 1 of the parent study for patients randomised to belimumab and Week 52 of the parent study for patients randomised to placebo.

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

**Supplementary Figure 2. Percentage change from baseline by visit for safety population (N=142) in (A) IgG (g/l); (B) anti-dsDNA (IU/ml) levels; (C) C3 and C4 levels (mg/dl)**



Median (IQR) baseline values: IgG 14.1 (11.5, 17.9) g/l from parent study BEL113750 and 14.0 (12.6, 17.4) g/l from parent study BEL112341 (normal range: 6.94−16.18 g/l); anti-dsDNA 110.5 (43.0, 344.0) IU/ml (normal range: <30 IU/ml); C3 65.0 (53.0, 86.0) mg/dl (normal range: 90–180 mg/dl); C4 11.0 (7.0, 15.0) (normal range: 10–40 mg/dl).

Baseline was defined as the last available value prior to belimumab initiation: Day 1 of the parent study for patients randomised to belimumab and Week 52 of the parent study for patients randomised to placebo.

Anti-dsDNA, anti-double stranded deoxyribonucleic acid; C3/C4, complement 3/4; IgG, immunoglobulin G; IQR, interquartile range

**Supplementary Table 1. Baseline* disease characteristics by parent study randomisation (safety population, N=142)**

| | Parent study randomised treatment group | | Total (n=142) |
|---|---|---|---|
| | Placebo (n=50) | Belimumab (n=92) | |
| **Mean SLE disease duration (SD)†, years** | 10.2 (7.1) | 7.9 (6.2) | 8.7 (6.6) |
| **Median (min, max)** | 8.9 (1.19, 33.48) | 6.2 (0.03, 29.48) | 7.2 (0.03, 33.48) |
| **BILAG organ domain involvement‡, n (%)** | | | |
| **≥1A or 2B** | 15 (30.0) | 49 (53.3) | 64 (45.1) |
| **≥1A** | 2 (4.0) | 16 (17.4) | 18 (12.7) |
| **≥1B** | 40 (80.0) | 76 (82.6) | 116 (81.7) |
| **No A or B** | 9 (18.0) | 11 (12.0) | 20 (14.1) |
| **BILAG organ system involvement (A or B scores), n (%)** | | | |
| **General** | 0 (0) | 7 (7.6) | 7 (4.9) |
| **Mucocutaneous** | 21 (42.0) | 56 (60.9) | 77 (54.2) |
| **Neurological** | 1 (2.0) | 0 (0) | 1 (0.7) |
| **Musculoskeletal** | 10 (20.0) | 30 (32.6) | 40 (28.2) |
| **Cardiovascular and respiratory** | 0 (0) | 1 (1.1) | 1 (0.7) |
| **Vasculitis** | 5 (10.0) | 17 (18.5) | 22 (15.5) |
| **Renal** | 11 (22.0) | 17 (18.5) | 28 (19.7) |
| **Haematology** | 12 (24.0) | 19 (20.7) | 31 (21.8) |
| **Mean SELENA-SLEDAI score (SD)** | 7.7 (4.0) | 10.2 (3.5) | 9.3 (3.9) |
| **SELENA-SLEDAI category, n (%)** | | | |
| **≤9** | 34 (68.0) | 39 (42.4) | 73 (51.4) |
| **≥10** | 16 (32.0) | 53 (57.6) | 69 (48.6) |
| **SELENA-SLEDAI Flare Index‡,§, n (%)** | | | |
| **≥1 flare** | 8 (16.0) | 19 (20.7) | 27 (19.0) |
| **≥1 severe flare** | 0 | 4 (4.3) | 4 (2.8) |
| **Mean PGA (SD)** | 0.8 (0.7) | 1.4 (0.5) | 1.2 (0.6) |
| **SDI score** | | | |
| **Mean (SD)** | 0.5 (0.7) | 0.5 (0.8) | 0.5 (0.8) |
| **Median (min, max)** | 0 (0, 2) | 0 (0, 4) | 0 (0, 4) |
| **ANA** | | | |

| | | | |
|---|---|---|---|
| **Positive (≥0.80 index or ≥80 titre), n (%)** | 49 (98.0) | 91 (98.9) | 140 (98.6) |
| **Anti-dsDNA** | | | |
| **Positive (≥30 IU/mL), n (%)** | 37 (74.0) | 81 (88.0) | 118 (83.1) |
| **Complement level, n (%)** | | | |
| **Low C3 (<90 mg/dl) and/or low C4 (<10 mg/dl)** | 40 (80.0) | 81 (88.0) | 121 (85.2) |
| **No low C3 or C4** | 10 (20.0) | 11 (12.0) | 21 (14.8) |
| **Mean proteinuria level (SD), g/24 h** | 0.6 (0.8) | 0.8 (1.1) | 0.7 (1.0) |
| **Proteinuria category (g/24 h), n (%)** | | | |
| **≤0.5** | 33 (66.0) | 62 (67.4) | 95 (66.9) |
| **>0.5** | 17 (34.0) | 30 (32.6) | 47 (33.1) |
| **>0.5–<1** | 7 (14.0) | 6 (6.5) | 13 (9.2) |
| **1–<2** | 6 (12.0) | 13 (14.1) | 19 (13.4) |
| **≥2** | 4 (8.0) | 11 (12.0) | 15 (10.6) |

*Baseline was defined as the last available value prior to belimumab initiation: Day 1 of the parent study for patients randomised to belimumab and Week 52 of the parent study for patients randomised to placebo; †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; §SLE flares reported between the last SLE flare assessment and 'baseline'.

ANA, anti-nuclear antibody; BILAG, British Isles Lupus Assessment Group; C, complement (C3, C4); dsDNA, double-stranded deoxyribonucleic acid; PGA, Physician 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-SLE Disease Activity Index; SLE, systemic lupus erythematosus

**Supplementary Table 2. Allowed concomitant SLE medication by year interval (safety population; N=142)**

| | Number (%) of patients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Any time post first dose of belimumab* (N=142)** | **Year 0–1 (N=142)** | **Year 1–2 (N=136)** | **Year 2–3 (N=108)** | **Year 3–4 (N=79)** | **Year 4–5 (N=32)** | **Year 5–6 (N=24)** | **Year 6+† (N=13)** |
| **Corticosteroids** | 142 (100) | 142 (100) | 135 (99.3) | 106 (98.1) | 74 (93.7) | 30 (93.8) | 23 (95.8) | 12 (92.3) |
| **Antimalarials** | 71 (50.0) | 60 (42.3) | 60 (44.1) | 47 (43.5) | 28 (35.4) | 3 (9.4) | 2 (8.3) | 0 |
| **Immunosuppressants/Immunomodulatory** | 115 (81.0) | 110 (77.5) | 100 (73.5) | 73 (67.6) | 55 (69.6) | 18 (56.3) | 12 (50.0) | 6 (46.2) |
| **Aspirin** | 23 (16.2) | 21 (14.8) | 17 (12.5) | 12 (11.1) | 11 (13.9) | 8 (25.0) | 7 (29.2) | 2 (15.4) |
| **NSAIDs** | 112 (78.9) | 96 (67.6) | 81 (59.6) | 63 (58.3) | 43 (54.4) | 23 (71.9) | 19 (79.2) | 6 (46.2) |
| **Traditional Chinese medication** | | | | | | | | |
| **Glycosides of paeony/*Tripterygium*** | 12 (8.5) | 4 (2.8) | 1 (0.7) | 1 (0.9) | 1 (1.3) | 3 (9.4) | 5 (20.8) | 0 |
| ***Paeonia* (NOS)** | 4 (2.8) | 1 (0.7) | 0 | 1 (0.9) | 1 (1.3) | 1 (3.1) | 1 (4.2) | 0 |
| ***Paeonia officinalis*** | 9 (6.3) | 3 (2.1) | 1 (0.7) | 0 | 0 | 2 (6.3) | 4 (16.7) | 0 |
| ***Paeonia suffruticosa*** | 1 (0.7) | 0 | 0 | 0 | 0 | 1 (3.1) | 1 (4.2) | 0 |

*Post first belimumab dose (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 6+ represents Year 6–7 of belimumab treatment. No patients had exposure >7 years.

Baseline was defined as the last available value prior to belimumab initiation: Day 1 of the parent study for patients randomised to belimumab and Week 52 of the parent study for patients randomised to placebo.

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

**Supplementary Table 3. Percentage change from baseline in levels of B-cell subsets by visit, for patients from Japan (safety population; N=142)**

| | Baseline | Percent change from baseline* | | | | | |
|---|---|---|---|---|---|---|---|
| | | Year 1, Week 48 | Year 2, Week 48 | Year 3, Week 48 | Year 4, Week 48 | Year 5, Week 48 | Year 6, Week 48 |
| **Japanese patients from parent BEL113750 study†** | | | | | | | |
| **CD19+ (cells/µl), n** | 46 | 41 | 34 | 28 | 18 | 14 | 17 |
| **Median** | 56.50 | −43.24 | −57.98 | -56.54 | −63.67 | −68.52 | −70.59 |
| **(IQR)** | (29.00, 93.00) | (−69.75, −15.38) | (−70.36, −36.00) | (−70.67, −36.64) | (−74.17, −30.00) | (−82.00, −60.00) | (−79.33, −52.63) |
| **CD20+ (cells/µl), n** | 45 | 39 | 34 | 27 | 18 | 15 | 16 |
| **Median** | 49.00 | −46.15 | −57.80 | −53.57 | −63.64 | −71.05 | −73.03 |
| **(IQR)** | (28.00, 83.00) | (−69.74, −8.33) | (−70.27, −33.33) | (−71.43, −33.93) | (−74.42, −37.50) | (−79.52, −57.69) | (−83.42, −58.57) |
| **Naïve CD19+CD20+CD27- (cells/µl), n** | 45 | 39 | 34 | 27 | 18 | 15 | 16 |
| **Median** | 39.00 | −66.67 | −70.73 | −65.38 | −68.99 | −79.25 | −79.47 |
| **(IQR)** | (23.00, 73.00) | (−82.05, −39.13) | (−82.31, −54.55) | (−77.78, −50.00) | (−78.48, −45.83) | (−83.54, −62.50) | (−85.88, −68.31) |
| **Memory CD19+CD20+CD27+ (cells/µl), n** | 45 | 39 | 34 | 27 | 18 | 15 | 16 |
| **Median** | 7.00 | 37.50 | 11.81 | 0.00 | −9.09 | −20.00 | −12.14 |
| **(IQR)** | (5.00, 11.00) | (−16.67, 100.00) | (−30.00, 90.91) | (−35.29, 71.43) | (−40.00, 50.00) | (−51.72, 30.00) | (−63.60, 9.09) |
| **Activated CD19+CD20+CD69+ (COUNT/ml), n** | 46 | 40 | 34 | 28 | 18 | 14 | 17 |
| **Median** | 58.12 | −75.52 | −70.96 | −73.95 | −79.08 | −55.07 | 52.16 |
| **(IQR)** | (35.35, 163.06) | (−90.85, −47.72) | (−85.84, −19.77) | (−92.40, 7.87) | (−93.85, −12.71) | (−88.35, 48.69) | (−29.51, 351.05) |
| **Plasma CD19+CD20+CD138+ (COUNT/ml), n** | 46 | 40 | 33 | 28 | 17 | 13 | 16 |
| **Median** | 236.22 | −82.29 | −79.18 | −84.95 | −84.68 | −75.32 | −33.14 |
| **(IQR)** | (103.45, 575.25) | (−91.62, −42.97) | (−91.33, −45.48) | (−95.18, −73.51) | (−93.05, −21.15) | (−83.94, −63.21) | (−76.58, 68.46) |
| **Plasmacytoid CD19+CD20+CD138+ (COUNT/ml), n** | 46 | 41 | 34 | 28 | 18 | 14 | 17 |
| **Median** | 70.92 | −75.13 | −62.20 | −85.28 | −64.89 | −75.10 | −34.68 |
| **(IQR)** | (41.90, 120.55) | (−91.16, −52.24) | (−88.66, −13.26) | (−93.22, −26.59) | (−86.93, −40.34) | (−87.08, 34.76) | (−60.84, 28.09) |
| **Short-lived plasma CD19+CD20+CD27b+ (COUNT/ml), n** | 46 | 41 | 34 | 28 | 18 | 14 | 17 |
| **Median** | 1003.40 | −53.36 | −40.08 | −60.78 | −70.21 | −59.05 | −33.01 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **(IQR)** | (466.29, 2110.85) | (−81.57, −21.25) | (−66.09, 20.97) | (−84.79, −15.21) | (−93.84, 41.46) | (−80.39, 10.65) | (−68.22, 14.05) |
| **SLE subset CD19+CD38b+CD27b+ Lymph (COUNT/ml), n** | 46 | 41 | 34 | 28 | 18 | 14 | 17 |
| **Median** | 1023.16 | −52.23 | −36.49 | −58.58 | −69.40 | −62.25 | −43.99 |
| **(IQR)** | (466.29, 2095.58) | (−80.55, −29.43) | (−70.85, 23.06) | (−84.65, −4.12) | (−95.49, 19.80) | (−80.85, −10.97) | (−66.38, 10.53) |
| | **Baseline** | **Year 1, Week 24** | **Year 2, Week 24** | **Year 3, Week 24** | **Year 4, Week 24** | **Year 5, Week 24** | |
| **Japanese patients from parent BEL112341 study‡** | | | | | | | |
| **CD19+ (cells/µl), n** | 25 | 25 | 21 | 19 | 13 | 3 | |
| **Median** | 72.00 | −45.90 | −64.53 | −63.95 | −77.78 | −64.53 | - |
| **(IQR)** | (48.00, 149.00) | (−61.54, −9.01) | (−80.00, −43.75) | (−83.80, −50.00) | (−84.69, −48.84) | (−66.67, −56.00) | |
| **CD20+ (cells/µl), n** | 25 | 25 | 20 | 18 | 12 | 3 | |
| **Median** | 70.00 | −42.86 | −64.29 | −64.39 | −81.42 | −65.68 | - |
| **(IQR)** | (46.00, 142.00) | (−63.31, −8.41) | (−81.88, −43.48) | (−84.29, −50.00) | (−87.42, −39.42) | (−68.57, −62.50) | |
| **Naïve CD19+CD20+CD27- (cells/µl), n** | 25 | 25 | 20 | 18 | 12 | 3 | - |
| **Median** | 59.00 | −52.27 | −76.07 | −80.74 | −84.18 | −72.73 | |
| **(IQR)** | (41.00, 130.00) | (−77.78, −20.69) | (−86.43, −56.80) | (−87.79, −65.52) | (−91.85, −65.65) | (−79.37, −62.02) | |
| **Memory CD19+CD20+CD27+ (cells/µl), n** | 25 | 25 | 20 | 18 | 12 | 3 | - |
| **Median** | 7.00 | 71.43 | 0.00 | −18.33 | −47.41 | 14.29 | |
| **(IQR)** | (5.00, 18.00) | (0.00, 128.57) | (−35.22, 66.67) | (−45.45, 25.00) | (−62.50, 8.93) | (−77.50, 20.00) | |
| **Activated CD19+CD20+CD69+(COUNT/ml), n** | 25 | 22 | 18 | 16 | 12 | 3 | - |
| **Median** | 45.58 | −59.40 | −77.90 | 77.88 | 299.31 | 58.26 | |
| **(IQR)** | (17.32, 75.56) | (−92.24, 13.64) | (−99.14, −40.25) | (−71.07, 752.56) | (−69.51, 592.07) | (−37.54, 132.97) | |
| **Plasma CD19+CD20+CD138+ (COUNT/ml), n** | 25 | 22 | 18 | 15 | 12 | 3 | - |
| **Median** | 72.49 | −62.78 | −59.73 | 9.03 | 180.21 | −71.87 | |
| **(IQR)** | (20.21, 282.76) | (−87.81, −3.45) | (−90.20, 84.69) | (−55.21, 218.77) | (−41.35, 601.85) | (−77.71, −45.35) | |
| **Plasmacytoid CD19+CD20+CD138+ (COUNT/ml), n** | 25 | 22 | 18 | 16 | 11 | 3 | - |
| **Median** | 29.25 | −21.31 | −15.55 | 10.57 | 61.76 | 91.29 | |
| **(IQR)** | (10.87, 86.58) | (−88.49, 64.94) | (−75.01, 182.15) | (−71.73, 339.57) | (−66.22, 1276.61) | (50.72, 747.17) | |
| **SLE subset CD19+CD38b+CD27b+** | | | | | | | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Lymph (COUNT/ml), n** | 25 | 25 | 21 | 18 | 13 | 3 | |
| **Median** | 1144.23 | −53.02 | −60.56 | −46.08 | −55.06 | −22.66 | |
| **(IQR)** | (903.61, 1749.46) | (−71.86, −12.85) | (−88.60, −19.39) | (−73.53, −9.27) | (−68.05, −8.33) | (−26.51, 30.45) | |

*Percent change from baseline was calculated as 100*(visit value – baseline value)/baseline value. Patients with a baseline of 0 were excluded from the change from baseline summaries; [†]Only presents data for patients who enrolled into this study, at selected sites in Japan, as per protocol BEL114333; [‡]All Japanese patients who enrolled into this study from BEL112341, at selected sites in Japan. B-cell samples from parent BEL112341 study patients were not analysed for the short-lived plasma subset.

IQR, interquartile range; SLE, systemic lupus erythematosus

**Supplementary references**

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