**The efficacy and safety of belimumab in paediatric and adult patients with systemic lupus erythematosus: an across-study comparison**

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**SUPPLEMENTARY MATERIALS**

**Definition of a severe flare[1]**

- A change in Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) >12, or
- new/worse central nervous system-systemic lupus erythematosus (SLE), vasculitis, nephritis, myositis, platelet <60,000 haemolytic anaemia with Hb <7 mg/dl, requiring doubling or >0.5 mg/kg/day prednisone, or
- hospitalisation for SLE, or
- prednisone >0.5 mg/kg/day, or
- new immunosuppressive, or
- increased physician's global assessment to >2.5

Note that the severe flare endpoint (modified SELENA-SLEDAI Flare Index [SFI]) used in these studies excludes severe flares that were triggered only by an increase in SELENA-SLEDAI score to >12.

**Covariates**

Covariates used in selected analyses were:

- **PLUTO:** treatment group, baseline age (5−11 vs 12−17 years), SELENA-SLEDAI score (≤12 vs ≥13).
- **BLISS-52 and BLISS-76:** treatment groups, SELENA-SLEDAI score (≤9 vs ≥10), proteinuria (<2 g/24 hours vs ≥2 g/24 hours equivalent), race/ethnicity (Black African or indigenous American Ancestry vs other).
- **BLISS-NEA:** treatment group, country, SELENA-SLEDAI score, complement levels.
- **EMBRACE:** treatment group, SELENA-SLEDAI with modified SLE Disease Activity Index scoring for proteinuria (incorporates the SLEDAI-2000 [SS-S2K]) score (≤9 vs ≥10), complement levels (≥1 C3/C4 low vs no C3/C4 low), region (USA/Canada vs Rest of World).

**Supplementary tables**

**Supplementary Table 1.** Study design, key eligibility criteria, and primary endpoint in PLUTO, BLISS-52, BLISS-76, BLISS-NEA, EMBRACE studies included in the efficacy comparison

| PLUTO[2] | BLISS-52[3] | BLISS-76[4] | BLISS-NEA[5] | EMBRACE[6] |
|---|---|---|---|---|
| **Study design** | | | | |
| Belimumab: 10 mg/kg IV | Belimumab: 1 and 10 mg/kg IV | Belimumab: 1 and 10 mg/kg IV | Belimumab: 10 mg/kg IV | Belimumab: 10 mg/kg IV |
| Double-blind study phase: 52 weeks | Double-blind phase: 52 weeks | Double-blind phase: 76 weeks | Double-blind phase: 52 weeks | Double-blind phase: 52 weeks |
| Study locations: North America, Latin America, Japan, Europe | Study locations: Latin America, Asia-Pacific, Eastern Europe | Study locations: North America and Europe | Study locations: China, Japan and South Korea | Study locations: Brazil, Colombia, France, South Africa, UK and USA |
| **Eligibility criteria** | | | | |
| ≥5−17 years of age | ≥18 years of age | ≥18 years of age | ≥18 years of age | ≥18 years of age |
| Diagnosis of SLE according to ACR criteria, with ≥4 of 11 criteria being present | Diagnosis of SLE according to ACR criteria, with ≥4 of 11 criteria being present | Diagnosis of SLE according to ACR criteria, with ≥4 of 11 criteria being present | Diagnosis of SLE according to ACR criteria, with ≥4 of 11 criteria being present | Diagnosis of SLE according to ACR criteria, with ≥4 of 11 criteria being present |
| SELENA-SLEDAI ≥6 at screening | SELENA-SLEDAI ≥6 at screening | SELENA-SLEDAI ≥6 | SELENA-SLEDAI ≥8 | SELENA-SLEDAI ≥8 |
| Seropositive for antinuclear antibodies and/or anti-dsDNA antibodies | Seropositive for antinuclear antibodies and/or anti-dsDNA antibodies | Seropositive for antinuclear antibodies and/or anti-dsDNA antibodies | Seropositive for antinuclear antibodies and/or anti-dsDNA antibodies | Seropositive for antinuclear antibodies and/or anti-dsDNA antibodies |
| No severe lupus kidney disease or active CNS lupus | No severe active LN or CNS manifestations | No severe active LN or CNS manifestations or serious intercurrent illness | No severe lupus kidney disease or active nephritis requiring therapy within 90 days of study start or CNS lupus requiring therapy within 60 days of study start | No severe lupus kidney disease or active nephritis requiring acute therapy within 90 days of study start or CNS lupus requiring therapy within 60 days of study start |

| | | | | |
|---|---|---|---|---|
| | | | No requirement for new SLE medications other than glucocorticoids within 60 days of study start | No history of a major organ transplant<br>No requirement for new SLE medications other than glucocorticoids within 60 days of study start |
| Stable treatment regimen with glucocorticoids, NSAIDs, antimalarials or immunosuppressives for ≥30 days before study start | Stable treatment regimen with prednisone, NSAIDs, antimalarials or immunosuppressives for ≥30 days before study start | Stable treatment regimen with prednisone, NSAIDs, antimalarials or immunosuppressives for ≥30 days before study start | Stable treatment regimen with glucocorticoids, NSAIDs, antimalarials or immunosuppressives for ≥30 days before study start | Stable treatment regimen with glucocorticoids, NSAIDs, antimalarials or immunosuppressives for ≥30 days before study start |
| SRI-4 response rate at Week 52 | SRI-4 response rate at Week 52 | SRI-4 response rate at Week 52 | SRI-4 response rate at Week 52 | SRI-2K response rate at Week 52 |

ACR, American College of Rheumatology; CNS, central nervous system; dsDNA, double-stranded deoxyribonucleic acid; IV, intravenous; LN, lupus nephritis; NSAID, non-steroidal anti-inflammatory drug; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SLE, systemic lupus erythematosus; SRI, SLE Responder Index.

**Supplementary Table 2.** SRI-4 response at Week 52 by subgroups for PLUTO, pooled BLISS-52 and BLISS-76 and BLISS-NEA studies and SRI-S2K response at Week 52 by subgroups for EMBRACE study (mITT population)

| | PLUTO | | BLISS-52 and BLISS-76 | | BLISS-NEA | | EMBRACE | |
|---|---|---|---|---|---|---|---|---|
| | **Placebo (n=40)** | **Belimumab 10 mg/kg IV (n=53)** | **Placebo (n=562)** | **Belimumab 10 mg/kg IV (n=563)** | **Placebo (n=226)** | **Belimumab 10 mg/kg IV (n=451)** | **Placebo (n=149)** | **Belimumab 10 mg/kg IV (n=299)** |
| **mITT population** | | | | | | | | |
| N | 39 | 53 | 562 | 563 | 217 | 446 | 149 | 298 |
| Response, n (%) | 17 (43.6) | 28 (52.8) | 218 (38.8) | 285 (50.6) | 87 (40.1) | 240 (53.8) | 71 (47.7) | 157 (52.7) |
| Treatment difference vs placebo, % | - | 9.24 | - | 11.83 | - | 13.72 | - | 5.03 |
| OR (95% CI) | - | 1.49 (0.64, 3.46) | - | 1.68 (1.32, 2.15) | - | 1.99 (1.40, 2.82) | - | 1.28 (0.85, 1.92) |
| **Baseline SELENA-SLEDAI score ≥10** | | | | | | | | |
| N | 25 | 31 | 299 | 296 | 123 | 233 | 90 | 153 |
| Response, n (%) | 12 (48.0) | 18 (58.1) | 132 (44.1) | 187 (63.2) | 58 (47.2) | 164 (70.4) | 36 (40.0) | 81 (52.9) |
| Treatment difference vs placebo, % | - | 10.06 | - | 19.03 | - | 23.23 | - | 12.94 |
| OR (95% CI) | - | 1.50 (0.52, 4.33) | - | 2.22 (1.59, 3.10) | - | 2.66 (1.69, 4.19) | - | 1.90 (1.10, 3.29) |
| **Baseline SELENA-SLEDAI score ≤9** | | | | | | | | |
| N | 14 | 22 | 263 | 267 | 94 | 213 | 59 | 145 |
| Response, n (%) | 5 (35.7) | 10 (45.5) | 86 (32.7) | 98 (36.7) | 29 (30.9) | 76 (35.7) | 26 (44.1) | 65 (44.8) |
| Treatment difference vs placebo, % | - | 9.74 | - | 4.00 | - | 4.83 | - | 0.76 |
| OR (95% CI) | - | 1.50 (0.38, 5.95) | - | 1.16 (0.81, 1.67) | - | 1.24 (0.74, 2.09) | - | 0.92 (0.48, 1.73) |
| **Baseline low C3/C4* and anti-dsDNA ≥30 IU/ml** | | | | | | | | |
| N | 16 | 22 | 287 | 305 | 135 | 291 | 50 | 91 |
| Response, n (%) | 6 (37.5) | 8 (36.4) | 91 (31.7) | 157 (51.5) | 46 (34.1) | 156 (53.6) | 12 (24.0) | 41 (45.1) |
| Treatment difference vs placebo, % | - | -1.14 | - | 19.77 | - | 19.53 | - | 21.05 |
| OR (95% CI) | - | 0.95 (0.25, 3.61) | - | 2.73 (1.91, 3.89) | - | 2.24 (1.46, 3.42) | - | 3.00 (1.35, 6.68) |
| **Baseline normal/high C3/C4 and anti-dsDNA <30 IU/ml** | | | | | | | | |
| N | 23 | 31 | 275 | 258 | 82 | 155 | 99 | 207 |
| Response, n (%) | 11 (47.8) | 20 (64.5) | 127 (46.2) | 128 (49.6) | 41 (50.0) | 84 (54.2) | 50 (50.5) | 104 (50.2) |
| Treatment difference vs placebo, % | - | 16.69 | - | 3.43 | - | 4.19 | - | -0.26 |

| | PLUTO | | BLISS-52 and BLISS-76 | | BLISS-NEA | | EMBRACE | |
|---|---|---|---|---|---|---|---|---|
| | **Placebo (n=40)** | **Belimumab 10 mg/kg IV (n=53)** | **Placebo (n=562)** | **Belimumab 10 mg/kg IV (n=563)** | **Placebo (n=226)** | **Belimumab 10 mg/kg IV (n=451)** | **Placebo (n=149)** | **Belimumab 10 mg/kg IV (n=299)** |
| OR (95% CI) | - | 1.98 (0.66, 5.96) | - | 1.12 (0.78, 1.59) | - | 1.18 (0.69, 2.02) | - | 1.01 (0.62, 1.66) |

*Low C3 defined as <90 mg/dl and low C4 defined as <10 mg/dl.

C, complement; CI, confidence interval; dsDNA, double-stranded DNA; mITT, modified intention-to-treat; OR, odds ratio; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index.

**Supplementary references**

1. Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. *Lupus* 1999;8:685-691.
2. Brunner HI, Abud-Mendoza C, Viola DO, *et al*. Safety and efficacy of intravenous belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial. *Ann Rheum Dis* 2020;79:1340-1348.
3. Navarra SV, Guzman RM, Gallacher AE, *et al*. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet (London, England)* 2011;377:721-731.
4. Furie R, Petri M, Zamani O, *et a*l. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011;63:3918-3930.
5. 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;77:355-363.
6. Ginzler E, Guedes Barbosa LS, D'Cruz D, et al. EMBRACE: Phase 3/4, Randomized, 52-Week Study of Belimumab Efficacy and Safety in Patients of Black African Ancestry With Systemic Lupus Erythematosus. *Arthritis Rheumatol* 2021 doi: 10.1002/art.41900