Efficacy and safety of belimumab in patients of black race with systemic lupus erythematosus: Results from the EMBRACE study

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Disclosures

- Damon Bass, Susan Burriss, Jennifer Gilbride, James Groark, Michelle Miller and Beulah Ji are employees of GlaxoSmithKline (GSK) and hold shares in the company
- David P D’Cruz reports participation in advisory boards and consultancies for GSK and Roche, and has received consulting fees and/or has participated in clinical trials for GSK, Bristol-Myers Squibb, TEVA, Merck Serono, and Eli Lilly
- Kathleen Maksimowicz-McKinnon reports participation in an advisory board for ChemoCentryx and has participated in clinical trials for AstraZeneca, Gilead, GSK, and Merck
- Jim C Oates reports grant funding from the National Institutes of Health and the Department of Veterans Affairs and participation in clinical trials for Gilead, GSK, Merck Serono, and Takeda
- Mittermayer Barreto Santiago reports participation in clinical trials for AstraZeneca, BMS, GSK, Pfizer, and Roche
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Background

- Black patients have an increased prevalence and severity of systemic lupus erythematosus (SLE), alongside higher mortality rates\(^1\)
- The efficacy and safety of belimumab has been demonstrated in three previous Phase 3 intravenous (IV) trials and one Phase 3 subcutaneous trial\(^2\)–\(^5\)
  - The small number of black patients in these trials, along with the conflicting results, made it difficult to draw conclusions regarding efficacy in this population
- In this Phase 3/4, randomized, multicenter, double-blind, placebo-controlled, 52-week trial (EMBRACE study) we evaluated the efficacy and safety of IV belimumab plus standard of care (SoC) in black patients with active, autoantibody-positive SLE
  - Reporting results from 52-week double-blind treatment period
  - Open-label extension is complete (January 28, 2019)

Design and study population

Key selection criteria

Inclusion
• ≥18 years of age
• Self-identified black race
• SLE by ACR criteria
• Active SLE: Screening SELENA-SLEDAI score ≥8
• Autoantibody-positive from two time points
• Stable SoC SLE treatment regimen ≥30 days before Day 0 (first dose)

Exclusion
• Prior belimumab
• Abatacept, B-cell–targeted therapies or any other investigational biologic in the last year

Randomized 2:1 (N=503)

Subjects stratified by:
– Screening SELENA-SLEDAI (8–9 vs ≥10)
– Complement level (C3 or C4 low vs other)
– Region (US/Canada vs Rest of World)

Weeks 0–52

Placebo IV + SoC

Belimumab 10 mg/kg IV + SoC

Dosing schedule:
• Days 0, 14, 28
• Then every 28 days through Week 48
• Final evaluation at Week 52

SoC:
• Corticosteroids
• Immunosuppressives
• Anti-malarials
• Non-steroidal anti-inflammatories

ACR, American College of Rheumatology; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus-National Assessment Trial-Systemic Lupus Erythematosus Disease Activity Index; US, United States.
Responders must meet all 3 criteria

- Drop out/treatment failure = Non-responder

SRI response at Week 52

- ≥4-point SELENA-SLEDAI reduction (with modified SLEDAI-2K scoring for proteinuria)
- No worsening in PGA (defined as an increase of <0.3 points from baseline)
- No new BILAG A or 2 new BILAG B organ domain scores

Responders must meet all 3 criteria
Drop out/treatment failure = Non-responder

Efficacy analyses performed on modified intent-to-treat (mITT) population: defined as all patients from remaining sites* who were randomized and received at least 1 dose of study agent

*Three sites (n=48) excluded from efficacy analyses due to non-compliance.

BILAG, British Isles Lupus Assessment Group; PGA, Physician Global Assessment; SRI, Systemic lupus erythematosus (SLE) Responder Index.
### Secondary endpoints and safety

#### A priori sub-group analyses of primary endpoint
- Baseline SELENA-SLEDAI score, low complement, low complement and anti-dsDNA ≥30 IU/mL, and region

#### Major secondary endpoints
1. SRI response rate with SELENA-SLEDAI scoring at Week 52
2. Time to severe flare over 52 weeks
3. Proportion of patients with a reduction in prednisone dose by ≥25% to ≤7.5 mg/day during Weeks 40–52

#### Safety
- Adverse events (AEs)
- AEs of special interest (AESIs): mortality, serious and/or severe infections, opportunistic infections, malignant neoplasms, selected serious psychiatric AEs, suicidality, infusion/hypersensitivity reactions, immunogenicity

- Step-down sequential testing was utilized to control the overall type-1 error rate (2-sided, alpha=0.05)

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dsDNA, double-stranded deoxyribonucleic acid.
Patient disposition

503 patients randomized

496 patients in safety population

448 patients in mITT population

149 patients in placebo arm

299 patients in belimumab 10 mg/kg arm

Withdrawn (n=36, 24.2%) due to:
- Adverse event (n=10, 6.7%)
- Lack of efficacy (n=8, 5.4%)
- Protocol deviation (n=1, 0.7%)
- Lost to follow-up (n=1, 0.7%)
- Physician decision (n=7, 4.7%)
- Patient decision (n=9, 6.0%)

113 patients (75.8%) completed Week 52 visit

Withdrawn (n=67, 22.4%) due to:
- Adverse event (n=16, 5.4%)
- Lack of efficacy (n=14, 4.7%)
- Protocol deviation (n=6, 2.0%)
- Lost to follow-up (n=8, 2.7%)
- Physician decision (n=10, 3.3%)
- Patient decision (n=13, 4.3%)

232 patients (77.6%) completed Week 52 visit

Not treated (n=7, 1.4%)

Excluded from mITT (n=48, 9.7%) due to site non-compliance

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Baseline demographics and disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=149)</th>
<th>Belimumab 10 mg/kg (n=299)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>144 (96.6)</td>
<td>290 (97.0)</td>
</tr>
<tr>
<td>Age, years (mean, SD)</td>
<td>39.3 (12.15)</td>
<td>38.6 (11.05)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US/Canada</td>
<td>65 (43.6)</td>
<td>131 (43.8)</td>
</tr>
<tr>
<td>Rest of World</td>
<td>84 (56.4)</td>
<td>168 (56.2)</td>
</tr>
<tr>
<td>SELENA-SLEDAI-S2K (mean, SD)</td>
<td>10.5 (3.08)</td>
<td>10.2 (3.68)</td>
</tr>
<tr>
<td>SELENA-SLEDAI-S2K category ≥10, n (%)</td>
<td>93 (62.4)</td>
<td>158 (52.8)</td>
</tr>
<tr>
<td>Presence of flare, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of severe flare, n (%)</td>
<td>22 (14.8)</td>
<td>67 (22.4)</td>
</tr>
<tr>
<td>Low C3 and/or C4, n (%)</td>
<td>57 (38.3)</td>
<td>108 (36.1)</td>
</tr>
<tr>
<td>Low C3 and/or C4 and anti-dsDNA ≥30 IU/mL, n (%)</td>
<td>50 (33.6)</td>
<td>91 (30.4)</td>
</tr>
<tr>
<td>Daily prednisone category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 mg/day</td>
<td>22 (14.8)</td>
<td>53 (17.7)</td>
</tr>
<tr>
<td>&gt;0 to ≤7.5 mg/day</td>
<td>32 (21.5)</td>
<td>62 (20.7)</td>
</tr>
<tr>
<td>&gt;7.5 mg/day</td>
<td>95 (63.8)</td>
<td>184 (61.5)</td>
</tr>
<tr>
<td>SLE disease duration, years (mean, SD)</td>
<td>6.9 (7.38)</td>
<td>7.3 (7.08)</td>
</tr>
</tbody>
</table>

*Anytime during the screening period (Day –35 to 0)
SD, standard deviation; SELENA-SLEDAI-S2K, SELENA-SLEDAI with modified SLEDAI-2K scoring for proteinuria.
### Baseline demographics and disease characteristics by region

<table>
<thead>
<tr>
<th></th>
<th>US/Canada (n=196)</th>
<th>Rest of World (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean, SD)</td>
<td>40.0 (11.49)</td>
<td>37.9 (11.29)</td>
</tr>
<tr>
<td>SLE disease duration, years (mean, SD)</td>
<td>7.8 (7.35)</td>
<td>6.6 (7.01)</td>
</tr>
<tr>
<td>SLE disease duration, years (median; min, max)</td>
<td>6.2 (0, 36)</td>
<td>4.1 (0, 35)</td>
</tr>
<tr>
<td>SELENA-SLEDAI-S2K category ≥10, n (%)</td>
<td>125 (63.8)</td>
<td>126 (50.0)</td>
</tr>
<tr>
<td>SLICC/ACR damage index score = 0, n (%)</td>
<td>110 (56.1)</td>
<td>180 (71.4)</td>
</tr>
<tr>
<td>Proteinuria ≤0.5 g/24 hr, n (%)</td>
<td>167 (85.2)</td>
<td>195 (77.4)</td>
</tr>
<tr>
<td>Any steroid, n (%)</td>
<td>141 (71.9)</td>
<td>232 (92.1)</td>
</tr>
<tr>
<td>Average daily prednisone dose &gt;7.5 mg/day, n (%)</td>
<td>101 (51.5)</td>
<td>178 (70.6)</td>
</tr>
<tr>
<td>Low C3 (&lt;90 mg/dL), n (%)</td>
<td>59 (30.1)</td>
<td>91 (36.1)</td>
</tr>
<tr>
<td>Low C4 (&lt;10 mg/dL), n (%)</td>
<td>25 (12.8)</td>
<td>59 (23.4)</td>
</tr>
<tr>
<td>Low C3 and/or C4, n (%)</td>
<td>63 (32.1)</td>
<td>102 (40.5)</td>
</tr>
<tr>
<td>Low C3 and/or low C4 and anti-dsDNA ≥30 IU/mL, n (%)</td>
<td>53 (27.0)</td>
<td>88 (34.9)</td>
</tr>
</tbody>
</table>

SLICC, Systemic Lupus International Collaborating Clinics.
Primary endpoint: SRI-S2K response at Week 52*

- SRI-S2K response was numerically greater in belimumab compared with placebo patients

*SELENA-SLEDAI component with modified SLEDAI-2K scoring for proteinuria; †covariates were treatment group, baseline SELENA-SLEDAI-S2K score (≤9 vs ≥10), baseline complement levels (at least one C3/C4 low vs no C3/C4 low) and region (US/Canada vs Rest of World). CI, confidence interval; OR, odds ratio; SE, standard error.
Primary endpoint: SRI-S2K response over time*

*SELENA-SLEDAI component with modified SLEDAI-2K scoring for proteinuria; †p<0.05 vs placebo; ‡p<0.01 vs placebo.
Subgroup analyses: SRI-S2K response at Week 52*

Overall (n=298 vs 149)
SELENA-SLEDAI-S2K score at baseline
SELENA-SLEDAI-S2K score ≥10 (n=158 vs 93) 52.5 vs 40.9 1.76 (1.03, 3.00) †
SELENA-SLEDAI-S2K score ≤9 (n=140 vs 56) 44.3 vs 42.9 0.97 (0.51, 1.85)
C3 and/or C4 at baseline
Low C3 and/or C4 (n=108 vs 57) 47.2 vs 24.6 3.00 (1.45, 6.23) ‡
Without low C3 and/or C4 (n=190 vs 92) 49.5 vs 52.2 0.92 (0.55, 1.54)
C3/C4 and anti-dsDNA at baseline
Low C3 and/or C4 and anti-dsDNA ≥30 IU/mL (n=91 vs 50) 45.1 vs 24.0 3.00 (1.35, 6.68) ‡
Without C3 and/or C4 and anti-dsDNA ≥30 IU/mL (n=207 vs 99) 50.2 vs 50.5 1.01 (0.62, 1.66)
Region
US/Canada (n=131 vs 65) 37.4 vs 38.5 0.97 (0.52, 1.81)
Rest of World (n=167 vs 84) 57.5 vs 44.0 1.81 (1.05, 3.13) †

*SELENA-SLEDAI component with modified SLEDAI-2K scoring for proteinuria; †p<0.05 vs placebo; ‡p<0.01 vs placebo.
Subgroup analyses: SRI-S2K response at Week 52*
High disease activity subgroups

Overall (n=298 vs 149)
SELENA-SLEDAI-S2K score at baseline
SELENA-SLEDAI-S2K score ≥10 (n=158 vs 93)
C3 and/or C4 at baseline
Low C3 and/or C4 (n=108 vs 57)
C3/C4 and anti-dsDNA at baseline
Low C3 and/or C4 and anti-dsDNA ≥30 IU/mL (n=91 vs 50)

Belimumab 10 mg/kg vs placebo, %

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Belimumab 10 mg/kg vs placebo, %</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=298 vs 149)</td>
<td>48.7 vs 41.6</td>
<td>1.40 (0.93, 2.11)</td>
</tr>
<tr>
<td>SELENA-SLEDAI-S2K score at baseline</td>
<td>52.5 vs 40.9</td>
<td>1.76 (1.03, 3.00) †</td>
</tr>
<tr>
<td>C3 and/or C4 at baseline</td>
<td>47.2 vs 24.6</td>
<td>3.00 (1.45, 6.23) ‡</td>
</tr>
<tr>
<td>C3/C4 and anti-dsDNA at baseline</td>
<td>45.1 vs 24.0</td>
<td>3.00 (1.35, 6.68) ‡</td>
</tr>
</tbody>
</table>

*SELENA-SLEDAI component with modified SLEDAI-2K scoring for proteinuria; †p<0.05 vs placebo; ‡p<0.01 vs placebo.
Subgroup analyses: SRI-S2K response at Week 52*

Region

Overall (n=298 vs 149)

Region
US/Canada (n=131 vs 65)
Rest of World (n=167 vs 84)

- At baseline (no statistical analyses completed):
  - Longer SLE disease duration, fewer patients with SLICC/ACR score of 0 and more patients with SELENA-SLEDAI-S2K ≥10 in US/Canada versus Rest of World
  - Greater steroid use and higher levels of serological activity in Rest of World versus US/Canada

*SELENA-SLEDAI component with modified SLEDAI-2K scoring for proteinuria; †p<0.05 vs placebo.
Major secondary endpoint: SRI response at Week 52

SELENA-SLEDAI proteinuria scoring rule

- SRI response was numerically greater in belimumab compared with placebo patients

OR 1.42
(95% CI 0.94, 2.15)
p=0.0937*

*Sequential testing; therefore, nominal p-value.
Major secondary endpoint: time to severe flare over 52 weeks

Modified SFI*

- Patients who received belimumab had a 23% lower risk of experiencing a severe flare, at any time point, compared with placebo

HR 0.77  
(95% CI 0.51, 1.17)  
p=0.2264†

*SFI, SELENA-SLEDAI Flare Index (excludes severe flares triggered only by an increase in SELENA-SLEDAI to >12); †sequential testing; therefore, nominal p-value. HR, hazard ratio.
Major secondary endpoint: prednisone dose reduction
Reduction of ≥25% from baseline to ≤7.5 mg/day, during Weeks 40 through 52

- There was a numerically greater proportion of patients with a prednisone dose reduction in the belimumab group compared with placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Belimumab 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with reduction in prednisone (%)</td>
<td>12.6</td>
<td>14.7</td>
</tr>
<tr>
<td>12/95</td>
<td>27/184</td>
<td></td>
</tr>
</tbody>
</table>

OR 1.30
(95% CI 0.61, 2.80)
p = 0.4996*

*Sequential testing, therefore nominal p-value.
The percentage of patients who experienced an AE or SAE was similar between groups

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Placebo (N=165) n (%)</th>
<th>Belimumab 10 mg/kg (N=331) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥1 AE</td>
<td>144 (87.3)</td>
<td>277 (83.7)</td>
</tr>
<tr>
<td>Patients with an SAE by system organ class (≥2%)*</td>
<td>31 (18.8)</td>
<td>36 (10.9)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>13 (7.9)</td>
<td>11 (3.3)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>7 (4.2)</td>
<td>9 (2.7)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>3 (1.8)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>3 (1.8)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>4 (2.4)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>4 (2.4)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>AEs leading to discontinuation by system organ class (≥1%)*</td>
<td>12 (7.3)</td>
<td>22 (6.6)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>2 (1.2)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>2 (1.2)</td>
<td>6 (1.8)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>2 (1.2)</td>
<td>2 (0.6)</td>
</tr>
</tbody>
</table>

*Patients only counted once per system organ class.  
SAE, serious adverse event.
# Safety: AESI

<table>
<thead>
<tr>
<th>AESIs</th>
<th>Placebo (N=165) n (%)</th>
<th>Belimumab 10 mg/kg (N=331) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All malignancies (no cases of NMSC)</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Post-infusion systemic reactions per anaphylactic reaction CMQ</td>
<td>8 (4.8)</td>
<td>21 (6.3)</td>
</tr>
<tr>
<td>broad search</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious acute post-infusion systemic reactions/hypersensitivity*†</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All infections of special interest (serious: 1 each)</td>
<td>13 (7.9)</td>
<td>19 (5.7)</td>
</tr>
<tr>
<td>All opportunistic infections (none serious)*</td>
<td>2 (1.2)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Active tuberculosis</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>All herpes zoster‡ (none serious)</td>
<td>4 (2.4)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>Opportunistic</td>
<td>2 (1.2)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (1.2)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Depression/suicide/self-injury</td>
<td>17 (10.3)</td>
<td>26 (7.9)</td>
</tr>
<tr>
<td>Suicide/self-injury</td>
<td>2 (1.2)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Suicide/self-injury per GSK adjudication</td>
<td>2 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>2 (0.6)</td>
</tr>
</tbody>
</table>

- Reasons for deaths: pneumonia and meningitis, neither established as directly related to belimumumab

*Per sponsor adjudication; †acute: onset ≤1 day; delayed acute: onset 2–3 days; ‡not all herpes zoster recurrent or disseminated.

CMQ, Custom Medical Dictionary for Regulatory Activities Queries; NMSC, non-melanoma skin cancer.
EMBRACE and other Phase 3 studies: SRI response at Week 52
SELENA-SLEDAI proteinuria scoring rule (major secondary endpoint in EMBRACE)

OR (95% CI), belimumab 10 mg/kg vs placebo

EMBRACE (n=298 vs 149) 1.42 (0.94, 2.15)
BLISS-76 (n=273 vs 275) 1.52 (1.07, 2.15) *
BLISS-52 (n=290 vs 287) 1.83 (1.30, 2.59) †
BLISS-SC (n=554 vs 279) 1.68 (1.25, 2.25) ‡

*p<0.05 vs placebo; †p<0.01 vs placebo; ‡p<0.001 vs placebo.
Summary

- The study did not achieve the primary endpoint
  - Numerical trends were observed in favor of belimumab
  - Significant improvements were observed in subgroups with characteristics of high disease activity at baseline (SELENA-SLEDAI-S2K ≥10, low C3 and/or C4, and low C3/C4 and anti-dsDNA ≥30 IU/mL), which is consistent with previous studies
- There were numerical trends in favor of belimumab for secondary endpoints (SRI response at Week 52, time to severe flare over 52 weeks, and prednisone dose reduction)
- Study withdrawals were similar between groups (placebo 24.2%; belimumab 22.4%)
  - AEs were the primary reason for withdrawals (placebo 6.7%; belimumab 5.4%)
- The percentage of patients who experienced an AE or SAE was similar between groups
  - AEs: placebo 87.3%; belimumab 83.7%
  - SAEs: placebo 18.8%; belimumab 10.9%
- The safety profile was consistent with previous studies
  - Low numbers of opportunistic infections and psychiatric events
Thank you

Questions?