Headline results for a Phase 4, 52-week, randomised, double-blind, placebo-controlled study to assess adverse events of special interest (AESI) in adults with active, autoantibody-positive systemic lupus erythematosus (SLE) receiving belimumab

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*At the time of the study
Disclosures

• Roger A Levy, Damon Bass, Raj Punwaney, Julia Harris, Kevin S Thorneloe, Beulah Ji and David Roth are employees of GlaxoSmithKline (GSK) and hold shares in the company

• Jorge Ross Terrés was an employee of GSK at the time of study and holds shares in the company

• Saira Sheikh has worked as a paid consultant for GSK

• Cheng-Chung Wei has received research funding from AbbVie, BMS, Celgene, Janssen, Novartis, Pfizer, TSH Biopharm and UCB, and has worked as a paid consultant for AbbVie, BMS, Celgene, Chugai, Eisai, Janssen, Novartis, Pfizer, Sanofi-Aventis, TSH Biopharm and UCB

• William Stohl has received research funding from GSK and worked as a paid consultant for Janssen

• Tamara Mucenic has received research funding from Amgen, Eli Lilly, GSK, Janssen, Pfizer and Roche, has worked as a paid consultant for Janssen, Novartis, Roche and UCB, and has been a paid speaker for AbbVie, Janssen, Novartis, Pfizer, Roche and UCB

• Morton A Scheinberg and Dana Tegzova have nothing to disclose

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Background

• Belimumab is approved as an add-on treatment for active, autoantibody-positive SLE\textsuperscript{1,2}

• Phase 2, Phase 3, and long-term extension studies have shown a favourable benefit-risk profile for belimumab\textsuperscript{3-8}

• However, there were numerical differences between belimumab and placebo on background standard of care (SoC), in the incidence of mortality, infections, hypersensitivity reactions and some psychiatric events

• BASE was a 52-week, randomised, double-blind, placebo-controlled safety study to assess these adverse events of special interest (AESI), along with malignancy

Objective: To evaluate all-cause mortality and AESI in adult patients with active, autoantibody-positive SLE receiving IV belimumab or placebo, plus standard of care, over 52 weeks

Methods: A multicentre, placebo-controlled safety study

Key selection criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
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<tbody>
<tr>
<td>• ≥18 years of age</td>
<td>• Prior belimumab use</td>
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<tr>
<td>• Active, autoantibody-positive SLE</td>
<td>• B-cell-targeted therapies in the last year</td>
</tr>
<tr>
<td>• Receiving SLE treatment with steroids, immunomodulators and/or antimalarials</td>
<td>• Other biologic agent within 90 days</td>
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<tr>
<td>• No minimum SLE disease activity was required; no exclusion based on previous history of psychiatric conditions</td>
<td>• Malignant neoplasm in the last 5 years</td>
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<td></td>
<td>• Required management of acute or chronic infections within 60 days</td>
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<td></td>
<td>• Severe, active lupus kidney disease or CNS lupus</td>
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Randomisation (1:1), N=4019

Belimumab 10 mg/kg IV + SoC (Weeks 0–48) | Placebo + SoC (Weeks 0–48)

Primary endpoint: all-cause mortality and AESI (final assessment at 52 weeks)

Dosing: Days 0, 14 and 28, then every 28 days. SoC could include oral cyclophosphamide
AESI, adverse events of special interest; CNS, central nervous system; IV, intravenous; SLE, systemic lupus erythematosus; SoC, standard of care
Methods: Data analyses

Two study periods defined for 52-week analyses

- On-treatment (primary analysis):
  First dose to last dose + 28 days

- On-study (supportive analysis):
  On-treatment and off-treatment (i.e. if patient was followed after discontinuing study drug)

- All safety analyses carried out in **as-treated population** (n=4003 randomised and treated)*
- Differences (95% CI) versus placebo were calculated
  - For all-cause mortality and pre-specified AESI
  - *Post hoc* for on-treatment serious suicidal ideation/behaviour and self-injury events (per sponsor adjudication), and on-study suicidal ideation/behaviour (C-SSRS) (pre-specified endpoints)

*All randomised patients who received ≥1 dose of study drug, grouped according to the actual treatment administered for majority of time
AESI, adverse events of special interest; CI, confidence interval; C-SSRS, Columbia-Suicide Severity Rating Scale
Results: Study population

• Baseline demographics and disease characteristics were similar between treatment groups (n=4003)

<table>
<thead>
<tr>
<th>Baseline characteristics: ITT population*</th>
<th>Belimumab 10 mg/kg IV (n=2001)</th>
<th>Placebo (n=2002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>40.4 (12.8)</td>
<td>40.8 (12.7)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1848 (92.4)</td>
<td>1853 (92.6)</td>
</tr>
<tr>
<td>SLE disease duration, years, median (range)</td>
<td>5.1 (0–54)</td>
<td>5.3 (0–48)†</td>
</tr>
<tr>
<td>SELENA-SLEDAI, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>7.8 (4.7)‡</td>
<td>7.9 (4.5)</td>
</tr>
<tr>
<td>≤9, n (%)</td>
<td>1363 (68.1)</td>
<td>1369 (68.4)</td>
</tr>
<tr>
<td>≥10, n (%)</td>
<td>638 (31.9)</td>
<td>633 (31.6)</td>
</tr>
<tr>
<td>Low complement and high anti-dsDNA binding, n (%)</td>
<td>568 (28.4)</td>
<td>584 (29.2)</td>
</tr>
</tbody>
</table>

• 258 (12.9%) belimumab and 271 (13.5%) placebo patients withdrew from the study prior to Week 52; the most common reason was withdrawal by patient (6.4% in each group)

*All randomised patients who received ≥1 dose of study drug according to original allocation; one patient was randomised to placebo but incorrectly received belimumab for >50% of doses, so is included in the belimumab arm for safety analyses (as-treated population); †n=2001; ‡n=2000. dsDNA, double-stranded deoxyribonucleic acid; ITT, intent-to-treat; IV, intravenous; SD, standard deviation; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment - SLE Disease Activity Index; SLE, systemic lupus erythematosus
Results: Incidence rates of mortality and protocol-defined AESI
Primary analysis (on-treatment period)

- Overall rates of mortality and AESI were similar between groups, except for serious depression and serious infusion/hypersensitivity reactions.

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=2001)</th>
<th>Belimumab 10 mg/kg IV (n=2002)</th>
<th>Patients with an event, %</th>
<th>Difference in % versus placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>8 (0.40)</td>
<td>10 (0.50)</td>
<td>-</td>
<td>0.10 (−0.31, 0.51)</td>
</tr>
<tr>
<td>Serious infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious depression</td>
<td>1 (0.05)</td>
<td>7 (0.35)</td>
<td>-</td>
<td>0.30 (0.02, 0.58)</td>
</tr>
<tr>
<td>Opportunistic infections and other infections of interest</td>
<td>5 (0.25)</td>
<td>5 (0.25)</td>
<td>-</td>
<td>0 (-0.31, 0.31)</td>
</tr>
<tr>
<td>Malignancies (excluding NMSC)</td>
<td>4 (0.20)</td>
<td>3 (0.15)</td>
<td>-</td>
<td>0.05 (-0.21, 0.31)</td>
</tr>
<tr>
<td>NMSC</td>
<td>3 (0.15)</td>
<td>2 (0.10)</td>
<td>-</td>
<td>-0.70 (-1.60, 0.20)</td>
</tr>
<tr>
<td>Serious infusion/hypersensitivity reactions</td>
<td>82 (4.10)</td>
<td>75 (3.75)</td>
<td>-</td>
<td>-0.35 (-1.55, 0.85)</td>
</tr>
</tbody>
</table>

*Treatment-emergent suicidal ideation/behaviour was assessed in patients with ≥1 on-treatment and a pre-treatment C-SSRS assessment (placebo: n=1986, belimumab: n=1972).

AESI, adverse events of special interest; CI, confidence interval; C-SSRS, Columbia-Suicide Severity Rating Scale; IV, intravenous; NMSC, non-melanoma skin cancer.
Results: All-cause mortality

On-treatment deaths
- Occurred in 10 (0.50%) belimumab and 8 (0.40%) placebo patients
  - Difference versus placebo (95% CI): 0.10 (−0.31, 0.51)
  - Most frequently infection-related – Belimumab: n=9 (0.45%), placebo: n=3 (0.15%)

On-study deaths
- Occurred in 13 (0.65%) belimumab and 22 (1.10%) placebo patients
  - Difference versus placebo (95% CI): −0.45 (−1.03, 0.13)
  - Most frequently infection-related – Belimumab: n=12 (0.60%), placebo: n=8 (0.40%)
Results: Serious psychiatric events and suicidality

### Serious psychiatric events*

- Higher rates of serious depression events for belimumab (7 [0.35%]) versus placebo (1 [0.05%])
  - Difference versus placebo (95% CI): 0.30 (0.02, 0.58)

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Belimumab 10 mg/kg IV (n=2002)</th>
<th>Placebo (n=2001)</th>
<th>Difference vs placebo (95% CI) – post hoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious suicidal ideation/behaviour and self-injury, sponsor-adjudicated events</td>
<td>15 (0.75)</td>
<td>5 (0.25)</td>
<td>0.50 (0.06, 0.94)</td>
</tr>
<tr>
<td>Suicidal behaviour</td>
<td>4 (0.20)</td>
<td>1 (0.05)</td>
<td></td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>10 (0.50)</td>
<td>3 (0.15)</td>
<td></td>
</tr>
<tr>
<td>Self-injurious behaviour without suicidal intent</td>
<td>1 (0.05)</td>
<td>1 (0.05)</td>
<td></td>
</tr>
</tbody>
</table>

On-study C-SSRS assessment

- Suicidal ideation/behaviour occurred in 48/1974 (2.43%) belimumab and 39/1988 (1.96%) placebo patients
  - Difference (95% CI): 0.47 (−0.44, 1.38) (post hoc analysis)

Treatment-emergent C-SSRS assessment†

- Suicidality reported for 28/1972 (1.42%) belimumab and 23/1986 (1.16%) placebo patients
  - Difference (95% CI): 0.26 (−0.44, 0.96)

No suicide-related deaths were reported

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*On-treatment and on-study rates are the same; †on-treatment C-SSRS: Suicidal ideation/behaviour occurred in 44/1972 (2.2%) belimumab and 37/1986 (1.9%) placebo patients
CI, confidence interval; C-SSRS, Columbia-Suicide Severity Rating Scale; IV, intravenous
Conclusions

• This double-blind, placebo-controlled, 4003-patient safety study is the largest SLE clinical study to date

• On-treatment rates were similar between belimumab and placebo for:
  – All-cause mortality
  – Serious infections
  – Opportunistic infections/other infections of interest (serious or non-serious)
  – Malignancy

• Higher rates were observed on belimumab versus placebo for the following events, although the numbers of cases were low:
  – Serious psychiatric events
  – Serious infusion and hypersensitivity reactions

We would like to acknowledge all study participants and the BASE study group