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

LB0012

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Introduction

- Belimumab is approved as an add-on treatment for active, autoantibody-positive SLE[1,2]
- Phase 2, Phase 3 and long-term extension studies have shown a favourable benefit-risk profile for belimumab[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, the largest SLE clinical study to date, was a 52-week, randomised, double-blind, placebo-controlled safety study to assess these adverse events of special interest (AESI), along with malignancy

Objective

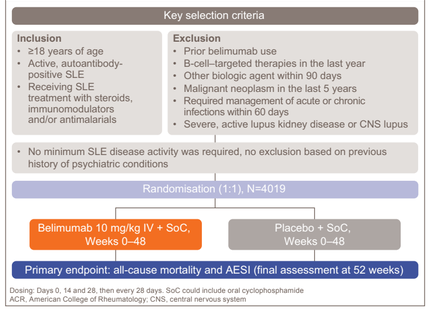
- To evaluate all-cause mortality and AESI in adult patients with active, autoantibody-positive SLE receiving intravenous (IV) belimumab or placebo, plus SoC, over 52 weeks

Methods

Study design and patients

- BASE (BEL115467; NCT01705977) is a multicentre, placebo-controlled, double-blind safety study that randomised adults with SLE (1:1) to monthly belimumab 10 mg/kg IV or placebo, plus SoC, for 48 weeks (**Figure 1**)
- Per-protocol patients were encouraged to continue with study visits if discontinuing treatment early
- Therefore, two study periods were defined for the 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)

Figure 1. BASE study design



Endpoints, assessments and analyses

- Safety analyses were performed on the as-treated population (randomised patients who received ≥1 dose of study drug grouped according to the treatment received for the majority of the time)
- On-treatment differences versus placebo in incidence rates (95% confidence interval [CI]) of all-cause mortality and pre-specified AESIs were calculated (**Figure 2**)

Figure 2. Mortality and protocol-defined AESIs

- **Deaths**
  - All-cause mortality: fatal SAEs, using death date
- **Serious infections**
  - SAEs within the 'Infections and Infestations' system organ class
- **Opportunistic infections and other infections of interest**
  - All (serious and non-serious) infections of interest (opportunistic infections, herpes zoster, tuberculosis, sepsis)
- **Malignancies (excluding non-melanoma skin cancer)**
- **Non-melanoma skin cancer (NMSC)**
- **Serious depression**
  - Psychiatric events (SAEs) suggesting serious mood disorders and anxiety
- **Suicidality**
  - Treatment-emergent suicidal ideation/behaviour, defined as any worsening of C-SSRS assessment relative to the worst pre-treatment scoring
  - C-SSRS ideation and behaviour scales with increasing severity:
    - Any suicidal ideation (C-SSRS items 1–5): 1. Wish to be dead; 2. Non-specific active suicidal thoughts; 3. Active suicidal ideation with any methods (not plan) without intent to act; 4. Active suicidal ideation with some intent to act, without specific plan; 5. Active suicidal ideation with specific plan and intent
    - Any suicidal behaviour (C-SSRS items 6–10): 6. Preparatory acts or behaviour; 7. Aborted attempt; 8. Interrupted attempt; 9. Non-fatal actual suicide attempt; 10. Completed suicide
- **Serious infusion/hypersensitivity reactions**
  - Per Anaphylactic Reaction Broad Search Custom MedDRA query, occurring on or within 3 days of infusion date
- **All SAEs**

C-SSRS, Columbia-Suicide Severity Rating Scale; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event

- Differences (95% CI) versus placebo were calculated *post hoc* for some pre-specified endpoints:
  - On-treatment serious suicidal ideation/behaviour and self-injury events (adjudicated by the sponsor)
  - On-study suicidal ideation/behaviour assessed using the C-SSRS

Results

Patients

- Overall, 4003 randomised patients received ≥1 study dose
  - As-treated population – belimumab: n=2002, placebo: n=2001
- Baseline demographics and disease characteristics were similar between treatment groups (**Table 1**)

Table 1. Patient demographics and baseline characteristics (ITT population*)

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

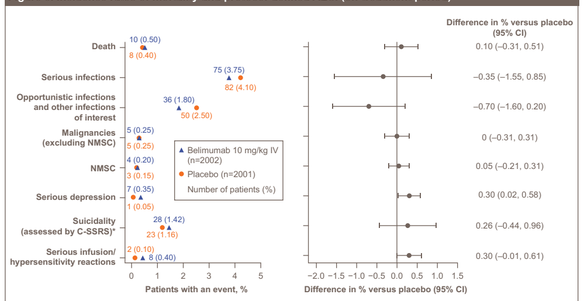
*ITT population: all randomised patients who received ≥1 dose of study drug, according to original allocation; one patient was randomised to placebo but incorrectly received belimumab for >50% of doses, so is included in the belimumab arm for safety analyses (as-treated population); †n=2001; ‡n=2000
dsDNA, double-stranded deoxyribonucleic acid; ITT, intent-to-treat; SD, standard deviation

- In total, 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 (n=128 [6.4%] in each group)
- Study drug was prematurely discontinued by 345 (17.2%) belimumab and 356 (17.8%) placebo patients; the most common reason in both arms was withdrawal by patient (belimumab: n=144 [7.2%], placebo: n=138 [6.9%])
- At Week 52, 88 (2.2%) patients were lost to follow-up or unattainable; therefore, complete mortality and malignancy status to Week 52 was not obtained for these patients

Mortality

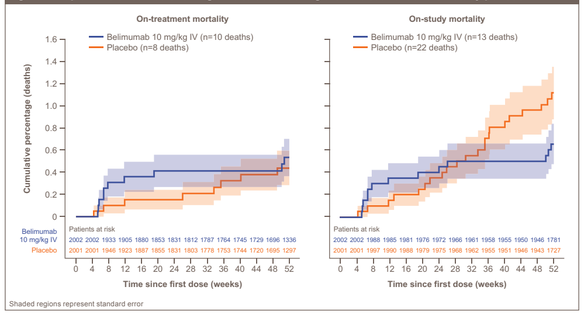
- On-treatment deaths occurred in 10 (0.50%) belimumab and 8 (0.40%) placebo patients
  - Difference versus placebo (95% CI): 0.10 (–0.31, 0.51) (**Figure 3**)
- On-study deaths occurred in 13 (0.65%) belimumab and 22 (1.10%) placebo patients
  - Difference versus placebo (95% CI): –0.45 (–1.03, 0.13)
- On-treatment and on-study deaths were most frequently infection-related (**Table 2**)
- On-treatment mortality was similar between groups, with more post-treatment deaths in the placebo group
- On-treatment and on-study times to death are shown in **Figure 4**

Figure 3. Incidence rates of mortality and protocol-defined AESI (on-treatment period)



*Belimumab: n=1972; placebo: n=1986

Figure 4. Kaplan–Meier curves showing time to death during the on-treatment and on-study periods



Shaded regions represent standard error

Table 2. Deaths by category and preferred term

Number of patients (%)	On-treatment: Belimumab 10 mg/kg IV (n=2002)	On-treatment: Placebo (n=2001)	On-study: Belimumab 10 mg/kg IV (n=2002)	On-study: Placebo (n=2001)
Total	10 (0.50)	8 (0.40)	13 (0.65)	22 (1.10)
Gastrointestinal	0	1 (0.05)	0	2 (0.10)
Cardiopulmonary failure	0	1 (0.05)	0	1 (0.05)
Hypovolaemic shock	0	0	0	1 (0.05)
Infections	9 (0.45)	3 (0.15)	12 (0.60)	8 (0.40)
Pneumonia	5 (0.25)	0	5 (0.25)	2 (0.10)
Septic shock	3 (0.15)	1 (0.05)	4 (0.20)	3 (0.15)
Sepsis	2 (0.10)	0	2 (0.10)	1 (0.05)
Cytomegalovirus infection	1 (0.05)	0	1 (0.05)	0
Gangrene	0	0	1 (0.05)	0
Gastroenteritis	0	1 (0.05)	0	1 (0.05)
Necrotising fasciitis	0	0	1 (0.05)	0
Pulmonary tuberculosis	0	0	1 (0.05)	0
Shrinking lung syndrome	0	1 (0.05)	0	1 (0.05)
Respiratory	0	0	0	2 (0.10)
Respiratory distress	0	0	0	1 (0.05)
Respiratory failure	0	0	0	1 (0.05)
SLE-related	0	0	0	1 (0.05)
Respiratory failure	0	0	0	1 (0.05)
Vascular	1 (0.05)	3 (0.15)	1 (0.05)	6 (0.30)
Cardio-respiratory arrest	1 (0.05)	1 (0.05)	1 (0.05)	2 (0.10)
Acute myocardial infarction	0	0	0	1 (0.05)
Cardiac arrest	0	1 (0.05)	0	1 (0.05)
Cerebral infarction	0	1 (0.05)	0	1 (0.05)
Death	0	0	0	1 (0.05)
Unknown	0	1 (0.05)	0	3 (0.15)
Death	0	0	0	2 (0.10)
Sudden death	0	1 (0.05)	0	1 (0.05)

Protocol-defined AESIs

Infections

- Rates of on-treatment serious infections were similar between groups (**Figure 3**)
- Details of opportunistic infections and other infections of interest are shown in **Table 3**

Table 3. On-treatment opportunistic infections and other infections of interest

Number of patients (%)	Belimumab 10 mg/kg IV (n=2002)	Placebo (n=2001)
Total (serious and non-serious)	36 (1.80)	50 (2.50)
Serious infections of special interest (opportunistic infections, herpes zoster, tuberculosis, sepsis)	17 (0.85)	17 (0.85)
All adjudicated opportunistic infections	11 (0.55)	15 (0.75)
Adjudicated opportunistic infections excluding tuberculosis and herpes zoster	6 (0.30)	2 (0.10)
Active tuberculosis	4 (0.20)	4 (0.20)
All herpes zoster	18 (0.90)	36 (1.80)
Sepsis	10 (0.50)	7 (0.35)

Malignancies

- Rates of on-treatment malignancies were similar between groups (**Figure 3**)
  - There were 9 (0.45%) malignancies overall in the belimumab group: 4 solid tumours, 1 haematologic malignancy and 4 NMSC
  - There were 8 (0.40%) malignancies in the placebo group: 5 solid tumours and 3 NMSC

Psychiatric events

- There were 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) (**Figure 3**)
- On-treatment serious suicidal ideation/behaviour and self-injury sponsor-adjudicated events were reported for 15 (0.75%) belimumab and 5 (0.25%) placebo patients: difference versus placebo calculated *post hoc* (95% CI): 0.50 (0.06, 0.94) (**Table 4**)
- No suicide-related deaths were reported

Table 4. On-treatment serious suicidal ideation/behaviour and self-injury events*

Number of patients (%)	Belimumab 10 mg/kg IV (n=2002)	Placebo (n=2001)
Total	15 (0.75)	5 (0.25)
Suicidal behaviour	4 (0.20)	1 (0.05)
Suicidal ideation	10 (0.50)	3 (0.15)
Self-injurious behaviour without suicidal intent	1 (0.05)	1 (0.05)

*Sponsor-adjudicated

Suicidality

- On-study suicidal ideation/behaviour (C-SSRS) occurred in 48/1974 (2.43%) belimumab and 39/1988 (1.96%) placebo patients: difference versus placebo calculated *post hoc* (95% CI): 0.47 (–0.44, 1.38)
  - Suicidal ideation occurred in 47 (2.38%) belimumab and 39 (1.96%) placebo patients
  - Suicidal behaviour occurred in 5 (0.25%) belimumab and 2 (0.10%) placebo patients
- Treatment-emergent suicidality (C-SSRS) was reported for 28/1972 (1.42%) belimumab and 23/1986 (1.16%) placebo patients: difference versus placebo (95% CI): 0.26 (–0.44, 0.96) (**Figure 3**)
  - Suicidal ideation occurred in 27/1952 (1.38%) belimumab and 23/1962 (1.17%) placebo patients relative to pre-treatment (among patients without a pre-treatment suicidal behaviour)
  - Suicidal behaviour occurred in 4/1972 (0.20%) belimumab patients and 1/1986 (0.05%) placebo patient, relative to pre-treatment

Infusion and hypersensitivity reactions

- Higher rates of serious infusion and hypersensitivity reactions were reported with belimumab versus placebo (8 [0.40%] belimumab, 2 [0.10%] placebo; **Figure 3**)

Serious adverse events (on-treatment)

- SAEs were reported by 220 (11.0%) belimumab and 222 (11.1%) placebo patients (294 and 310 events, respectively)

Conclusions

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

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Disclosures

- **RAL**, **DB**, **RP**, **JH**, **KST**, **BJ** and **DR:** employees of GSK and hold shares in the company. **JRT** was a GSK employee at the time of study and holds shares in the company. **SS:** paid consultant for GSK. **CCW:** 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 and UCB. **WS:** research funding from GSK and paid consultant for Janssen. **TM:** research funding from Amgen, Eli Lilly, GSK, Janssen, Pfizer and Roche; paid consultant for Janssen, Novartis, Roche and UCB; paid speaker for Abbvie, Janssen, Novartis, Pfizer, Roche and UCB. **MAS** and **DT:** nothing to disclose.

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