Mortality and Adverse Events of Special Interest in Adult Patients With Systemic Lupus Erythematosus Receiving Intravenous Belimumab: A *Post Hoc* Descriptive Summary of Serious Psychiatric Events

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Introduction

- Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease affecting multiple organ systems and reducing health-related quality of life[1,2]
- Intravenous (IV) belimumab, a B-lymphocyte stimulator (BLyS)-specific inhibitor, is approved for the treatment of patients ≥5 years of age with active, autoantibody-positive SLE who are receiving standard therapy[3]
- Results of the BASE study (the largest clinical trial in adult patients with SLE to date: n=4003), demonstrated similar rates of on-treatment all-cause mortality, infection, and malignancy adverse events of special interest (AESI) between belimumab and placebo[4,5]
- However, infrequent but higher incidences of other AESI including serious psychiatric events, fatal infections, and hypersensitivity reactions occurred with belimumab than placebo[5]
- Here we present data for on-treatment observed serious suicidal/self-injury events

Objectives

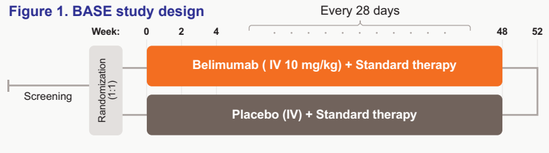
To provide a *post hoc* descriptive summary of the characteristics and disposition of patients who reported on-treatment serious suicide/self-injury events in the BASE study

Methods

Study description

- BASE (GSK Study BEL115467; NCT01705977) was a Phase 4, international, multicenter, randomized, double-blind, placebo-controlled, 52-week safety study in adult patients with SLE treated with belimumab or placebo (**Figure 1**)
- An estimation approach was used for the BASE study analyses, *post hoc* analyses are descriptive

Figure 1. BASE study design



BASE study inclusion criteria

- ≥18 years of age
- Active, autoantibody-positive SLE
- Receiving stable SLE treatment with steroids, immunomodulators, and/or antimalarials
- No minimum SLE disease activity was required; no exclusion based on previous history of psychiatric conditions

Post hoc analysis of psychiatric events

The following were summarized *post hoc* for on-treatment serious suicide/self-injury events:

- On-treatment serious suicidal ideation/behavior and self-injury events as per
  - Columbia-Suicide Severity Rating Scale (C-SSRS)
  - Standardized Medical Dictionary for Regulatory Activities Query (SMQ)
  - Sponsor adjudication
- Prior medical history (PMH) and baseline disease characteristics
- Time to onset
- Whether study treatment was taken after these events occurred
- Treatment and study completion
- Time to recovery
- The C-SSRS score profile
- Outcome

Psychiatric event identification

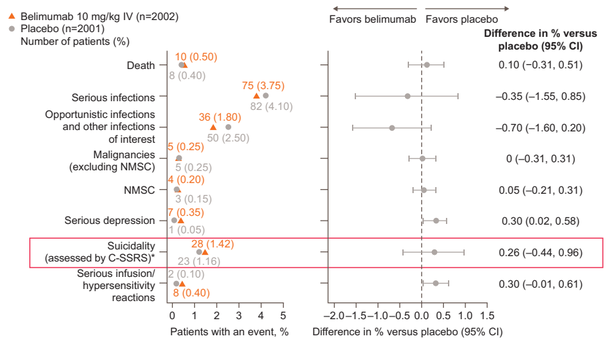
- The C-SSRS is a validated tool designed to screen for the presence and severity of suicidal ideation and behaviour (scores of increasing severity, 1-10)[6]
- Sponsor adjudicated events were identified using SMQ for pre-defined MedDRA preferred terms and subsequently adjudicated at the patient level by a blinded safety review team

Results

BASE population (N=4003)

- A total of 4003 patients with SLE were included in the BASE study (belimumab, n=2002; placebo, n=2001), 92.5% of whom were female, 54.6% were Caucasian, 8.2% of Black African ancestry, and mean age was 40.6 years
- Overall rates of mortality and AESI were similar between the two treatment groups, except for on-treatment serious depression and suicidality events, and serious infusion/hypersensitivity reactions, which were higher with belimumab versus placebo (**Figure 2**)
- PMH of psychiatric disorders were reported for belimumab (8.3%) and placebo (7.5%)
- C-SSRS scores ≥1 for suicidal ideation/behavior at baseline were reported for belimumab (7.5%) and placebo (6.6%)
- No suicide-related deaths were observed as part of this study

Figure 2. Overall BASE study findings related to the primary on-treatment endpoints

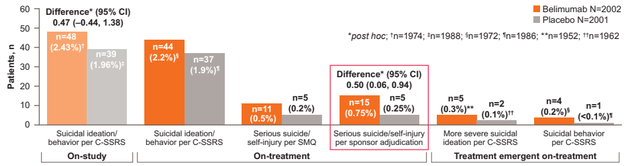


*Treatment-emergent suicidal ideation or behavior.
CI, confidence interval; NMSC, non-melanoma skin cancer

Suicidality events

- In all identification methods used, numerically higher on-treatment suicidality AESI were observed in belimumab-treated patients compared with placebo (**Figure 3**)
- More serious suicidality adverse events were identified through sponsor adjudication compared with SMQ and severe adverse events identified by C-SSRS

Figure 3. C-SSRS, SMQ, and sponsor adjudicated suicidality events



- A total of 20 (0.50%) patients from the BASE study (N=4003) reported on-treatment serious suicidal ideation/behavior and self-injury events per sponsor adjudication, 15 of whom received belimumab and 5 of whom received placebo plus standard SLE therapy (**Figure 3**)
- At baseline, age, weight, race, SLE disease duration, SELENA-SLEDAI score, PMH of psychiatric disorder, Systemic Lupus Erythematosus International Collaborating Clinics/ American College of Rheumatology (SLICC/ACR) Damage Index score, C-SSRS score, and prednisone use differed between patients receiving belimumab and placebo (**Table 1**)
- The median (interquartile range) time to onset of self-injury events per sponsor adjudication was 205 (83, 257) days for belimumab and 204 (173, 229) days for placebo
- In patients who experienced a sponsor adjudicated event, approximately half of belimumab patients (8/15) and 60% of placebo patients (3/5) continued study treatment after experiencing these AESI (**Figure 4**)
- A greater proportion of belimumab patients experiencing an event completed the treatment, compared with placebo (**Figure 4**).The median recovery time (number of days from onset to resolution) was shorter in those who did versus did not receive further study treatment, respectively, and lower in the belimumab group versus the placebo group overall (**Figure 4**)
- The C-SSRS score generally fell to 0 after the AESI for those who received further study treatment (**Figure 4**)
- Resolution occurred in 18/20 patients (**Figure 4**) and 0 patients experienced a recurrent event of suicidal ideation and/or behavior during the study

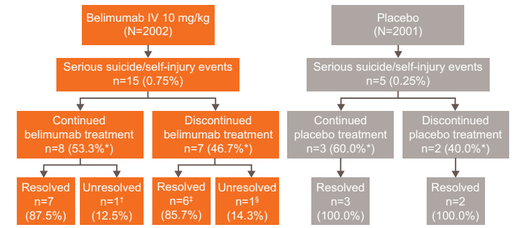
Post hoc population of patients reporting on-treatment suicidal ideation/behavior and self-injury events per sponsor adjudication (n=20)

Table 1. Baseline demographics and patient characteristics

	Belimumab n=15	Placebo n=5
Age, years, mean (SD)	33.5 (11.78)	26.0 (7.97)
Female, % (n)	100 (15)	100 (5)
Weight, kg, mean (range)	70.3 (16.61)	62.6 (19.97)
Race/ethnicity, % (n)		
Caucasian	46.7 (7)	40.0 (2)
Black African ancestry	33.3 (5)	20.0 (1)
Asian	6.7 (1)	20.0 (1)
Alaskan Native/American Native	6.7 (1)	20.0 (1)
Hawaiian Native or Other Pacific Islander	6.7 (1)	0
SLE disease duration, years, mean (SD)	8.4 (11.23)	7.2 (9.93)
SELENA-SLEDAI score, mean (SD)	9.2 (3.91)	6.8 (4.60)
SLICC/ACR Damage Index score, mean (SD)	0.5 (0.64)	0
Patients with PMH of psychiatric disorder, % (n)	46.7 (7)	20.0 (1)
Patients with C-SSRS score ≥1 for suicidal ideation/behavior at baseline, % (n)	33.3 (5)	0
Received prednisone for SLE at baseline, % (n)	100 (15)	80.0 (4)

SD, standard deviation; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index

Figure 4. Serious suicidal/self-injury event and resolution summary per sponsor adjudication *(post hoc)*



	Belimumab		Placebo	
Median recovery time, days¶ (range)	1 (1–919)	3 (1–34)	15 (1–22)	33 (9–56)
C-SSRS score decreased from ≥1 to 0 after event,** n/n (%)	7/8†† (46.7)	—	2/3‡‡ (60.0)	—
Completed treatment, n (%)	7 (46.7)		1 (20.0)	
Completed study, n (%)	8 (53.3)		2 (40.0)	

*Percentages calculated from patients with serious suicide/self-injury events in each treatment group; †lost to follow-up; ‡one patient considered resolved with sequelae; §withdrew from the study upon experiencing an event of major depression and considered recovering/resolving at follow-up; ¶number of days from onset to documented resolution; **in patients that continued study treatment; ††one patient had no further C-SSRS data collected after their event; ‡‡one patient had a C-SSRS score of 0 throughout.

Conclusions

- **In this largest SLE safety study to date, an imbalance with higher on-treatment serious suicidal ideation/behavior and self-injury events was observed with belimumab versus placebo (examined in a defined subpopulation of sponsor-adjudicated serious suicidal/self-injury events)**
- **Mean SLE duration, mean baseline SELENA-SLEDAI score and the proportion of patients with past and/or current history of psychiatric disorder were higher among belimumab-treated patients who reported sponsor-adjudicated serious suicidal/self-injury events than among placebo-treated patients who developed these events, and they were also higher than in the overall BASE patient population. However, conclusions based on these *post hoc* analyses are limited by the small number of patients reporting these events.**
- **The median time to onset of these AESI was similar between belimumab and placebo**
- **The majority of these AESI resolved with no recurrence, regardless of whether study treatment was discontinued**
- **No suicide-related deaths were observed as part of this study**

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