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Background: Belimumab (BEL), a monoclonal antibody that antagonizes B-lymphocyte stimulator, was first approved in 2011 for active, autoantibody-positive systemic lupus erythematosus (SLE). BEL has been studied for over 10 years; and while safety data from individual trials have been informative, a large integrated safety analysis has not yet been conducted.

Objectives: Perform pooled analyses to evaluate the safety of BEL in adult patients with SLE.

Methods: Aggregate analyses were performed using safety data for patients ≥18 years of age pooled from six randomised, placebo (PBO)-controlled BEL clinical trials (GSK studies: LBSL02, 110752, 110751, 112341, 113750, and 115471). Patients from GSK studies LBSL02, 110752, and 110751 received intravenous (IV) BEL 1, 4 (LBSL02 only), or 10 mg/kg, or PBO on Days 1, 14, 28, and every 28 days thereafter. Patients from GSK studies 113750 and 115471 received IV BEL 10 mg/kg or PBO on Days 1, 14, 28, and every 28 days thereafter. Patients from GSK study 112341 received subcutaneous (SC) BEL 200 mg, or PBO weekly. Safety analyses included the incidence of adverse events (AEs), serious AEs (SAEs), severe AEs, AEs of special interest (AESI), and mortality of BEL (all doses and formulations combined) vs PBO at Week 52.

Results: The pooled analysis included 4170 patients. Overall, 81.0% (n=2280/2815) of patients receiving BEL and 76.6% (n=1038/1355) of patients receiving PBO completed their respectively enrolled study; the most common reason for withdrawal was occurrence of an AE in both groups. The majority of patients were female (BEL: 94.5%; PBO: 93.6%), the mean age in both groups was 38 years, and baseline characteristics (race, SLE duration, disease activity, SLE damage, complement levels, anti-dsDNA binding, SLE medication usage) were similar between treatments.

The incidence of patients experiencing ≥1 AE, ≥1 SAE, and mortality was similar across treatments (Table 1); the most commonly reported SAEs in both groups were infections and infestations (BEL: 5.4% [n=151/2815]; PBO: 5.9% [n=80/1355]). The mean duration of treatment exposure was similar between groups (BEL: 334.1 days; PBO: 325.3 days).

A greater proportion of patients experienced AESI with BEL vs PBO for post-infusion/injection systemic reactions (from IV or SC administration) and depression/suicide/self-injury (Table 1). The proportion of patients experiencing an AESI of infections and malignancies was similar between groups.

Conclusion: Consistent with individual studies, BEL demonstrated a similar safety profile to PBO in this large integrated safety analysis of six trials. These results support a positive benefit–risk profile of BEL in the treatment of adult SLE.

Funding: GSK

Table 1. Pooled AE data

N (%)	PBO (IV + SC) N=1355	BEL (IV + SC) N=2815
AE	1184 (87.4)	2440 (86.7)
SAE	230 (17.0)	421 (15.0)
Severe AE (severe or life threatening)	209 (15.4)	377 (13.4)
AE resulting in study drug discontinuation	109 (8.0)	184 (6.5)
Death	6 (0.4)	16 (0.6)
AESI		
Post-infusion/injection systemic reactions*	110 (8.1)	286 (10.2)
Serious	2 (0.1)	13 (0.5)
All infections of special interest (OIs, HZ, TB, sepsis)	97 (7.2)	173 (6.1)
Serious	17 (1.3)	40 (1.4)
All OIs	92 (6.8)	157 (5.6)
Active TB	5 (0.4)	4 (0.1)
All HZ	59 (4.4)	106 (3.8)
All sepsis	10 (0.7)	20 (0.7)
Malignancies excluding NMSC	2 (0.1)	8 (0.3)
Including NMSC	3 (0.2)	12 (0.4)
Depression (inc. mood disorders and anxiety)/suicide/self-injury	92 (6.8)	210 (7.5)
Serious	5 (0.4)	9 (0.3)

*Occurring on or within 3 days of infusion/injection date.HZ, herpes zoster; NMSC, non-melanoma skin cancer; OIs, opportunistic infections; TB, tuberculosis

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POS0698 BIIB059 DEMONSTRATED A CONSISTENT THERAPEUTIC EFFECT ON SRI-4 RESPONSE ACROSS SUBGROUPS OF PARTICIPANTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS IN THE LILAC PHASE 2 STUDY

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Background: Type I interferons and other inflammatory mediators derived from plasmacytoid dendritic cells (pDCs) are implicated in systemic lupus erythematous (SLE) pathology. BIIB059 is a humanized monoclonal antibody that targets blood dendritic cell antigen 2 (BDCA2), a pDC-specific receptor. The binding of BIIB059 to BDCA2 leads to rapid internalization of BDCA2 from the surface of pDCs and subsequent inhibition of interferon, cytokine, and chemokine production. In Part A of the 2-part, phase 2 LILAC study (NCT02847598), BIIB059 significantly reduced SLE activity, as evidenced by reduced total active joint count (primary endpoint) and higher SLE Responder Index (SRI-4)[1] response (a secondary endpoint) versus placebo.[2]

Objectives: To evaluate SRI-4 response for BIIB059 versus placebo at Week 24 in SLE participant subgroups.

Methods: Enrollment in LILAC Part A was open to adults fulfilling ≥ 4 of 11 revised 1997 ACR criteria for classification of SLE, with ≥ 4 tender and ≥ 4 swollen joints, active skin disease, and positive lupus antibodies. Participants were randomized to receive either BIIB059 450 mg or placebo subcutaneously every 4 weeks for 20 weeks (with an additional dose at Week 2). SRI-4 response at Week 24 was analyzed in subgroups, though analyses were limited by small sample sizes and were not powered for statistical testing.

Results: In LILAC Part A, 64 and 56 participants were dosed with BIIB059 450 mg and placebo, respectively. At week 24, SRI-4 response rate was observed in favor of BIIB059 regardless of the baseline disease activity, such as SLEDAI-2K <10 versus ≥10, presence of BILAG-2004 grade A or B arthritis, oral corticosteroid usage, positivity for anti-ds DNA autoantibody and/or complement status, with point estimates for least-squares mean differences as well as corresponding 95% CIs consistently favoring BIIB059 (Figure 1). The incidence of adverse events in the overall study population was similar between the placebo and BIIB059 groups.[2]

Conclusion: BIIB059 treatment was associated with greater SRI-4 response rate, consistent among different subgroups of baseline disease activity as measured by SLEDAI-2K and BILAG-2004, glucocorticoid dosage, and serology. These findings provide additional evidence of the potential benefit of BIIB059 for the treatment of patients with active SLE.

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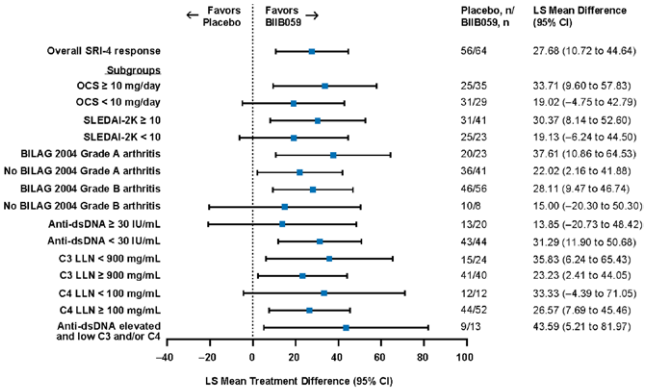
Figure. Subgroup Analysis of SRI-4 Response Between BIIB059 and Placebo at Week 24



BILAG 2004 = British Isles Lupus Assessment Group 2004; dsDNA = double-stranded DNA; LLN = lower limit of normal; LS = least-squares; OCS = oral corticosteroid; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLE = systemic lupus erythematosus; SRI-4 = SLE Responder Index

SRI-4 was defined as a reduction from baseline of ≥ 4 points in SLEDAI-2K, no new BILAG-2004 Grade A domain score or no more than 1 new BILAG-2004 Grade B domain score, no worsening from baseline in Physician's Global Assessment (< 10%), and no violations of protocol-specified medication rules. Participants who were considered as treatment failures or discontinued treatment were considered as nonresponders at visits after treatment failure or discontinuation. Participants who completed treatment but had a missing score at a primary timepoint were classified as nonresponders for that timepoint. Results are based on a generalized linear regression model adjusted for treatment using an identity link function (linear probability model) for the LS mean differences. Only BIIB059 450 mg and placebo are included in the statistical modeling.

Disclosure of Interests: Ronald van Vollenhoven Consultant of: AbbVie, AstraZeneca, Biotest, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Lilly, Medac, Merck, Novartis, Pfizer, Roche, UCB, Grant/research support from: AbbVie, Arthrogen, Bristol Myers Squibb, GlaxoSmithKline, Lilly, Pfizer, UCB, Richard Furie Consultant of: Biogen, Grant/research support from: Biogen, Kenneth Kalunian Consultant of: AbbVie, Amgen, AstraZeneca, Biogen, Bristol Myers Squibb, Eli Lilly, Equillium, Genentech, Gilead, ILTOO, Janssen, Nektar, Roche, Viela, Grant/research support from: Lupus Research Alliance, Pfizer, Sanford Consortium, Sandra Navarra Speakers bureau: Astellas, Johnson & Johnson, Novartis, Pfizer, Consultant of: Biogen, Grant/research support from: Biogen, Juanita Romero-Diaz Consultant of: Biogen, Boehringer Ingelheim, Victoria Werth Consultant of: AbbVie, Amgen, AstraZeneca, Biogen, Bristol Myers Squibb, Eli Lilly, EMD Serono, Gilead, GlaxoSmithKline, Janssen, Kyowa Kirin, Resolve, Viela, Grant/research support from: Biogen, Celgene, Gilead, Janssen, Viela, XIAOBI HUANG Shareholder of: Biogen, Employee of: Biogen, HUA CARROLL Shareholder of: Biogen, Employee of: Biogen, Cristina Musselli Shareholder of: Biogen, Employee of: Biogen, Catherine Barbey Shareholder of: Biogen, Employee of: Biogen, NATHALIE FRANCHIMONT Shareholder of: Biogen, OMass Therapeutics, Employee of: Biogen
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POS0699

GREATER REDUCTION IN CLASI-A SCORES ACHIEVED WITH BIIB059 VERSUS PLACEBO INDEPENDENTLY OF DISEASE SEVERITY AT BASELINE

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Background: Patients with cutaneous lupus erythematosus (CLE) experience symptoms including photosensitivity, rash, pain, and skin damage that can impact their quality of life. No targeted therapies are approved for CLE. BIIB059 is a humanized monoclonal antibody that targets blood dendritic cell antigen-2 (BDCA2), expressed exclusively on the surface of plasmacytoid dendritic cells (pDCs). The binding of BIIB059 to BDCA2 leads to rapid internalization of BDCA2 from the cell surface of pDCs, thereby inhibiting the production of pDC-derived type I interferons, cytokines, and chemokines, which are involved in CLE pathology. In Part B of the 2-part, phase 2 LILAC study (NCT02847598), the primary endpoint was met: BIIB059 significantly reduced CLE activity, as evidenced by a statistically significant dose response and statistically significant differences in least-squares mean percent changes in Cutaneous Lupus Erythematosus Disease Area and Severity Index – Activity (CLASI-A) score[1] versus placebo.[2]

Objectives: To determine the proportion of patients with CLE who presented at baseline with moderate or severe disease (CLASI-A ≥ 10) or with the higher category of mild disease (CLASI-A < 10 [i.e., 8 or 9]) and experienced a shift in CLASI-A score to a mild skin disease category or clear/almost clear skin status.

Methods: Adults with histologically confirmed CLE with or without systemic manifestations were enrolled if they had CLASI-A ≥ 8 at baseline, despite prior use of or intolerance to topical corticosteroids (CS) and/or antimalarials, in addition to ≥ 1 lesion diagnostic of subacute CLE (CLASI-A erythema score ≥ 2) and/or chronic CLE (CLASI-A erythema score ≥ 2 and CLASI-Damage scarring score ≥1). Concomitant CLE/SLE therapy was allowed if doses were initiated ≥ 12 weeks and kept stable ≥ 4 weeks before randomization and throughout the treatment period. Systemic corticosteroid doses could not exceed 15 mg/day of prednisone (or equivalent). BIIB059 (50, 150, 450 mg) or placebo was subcutaneously administered once every 4 weeks for 12 weeks, with an additional dose at Week 2. An ad hoc analysis was conducted to determine the proportion of participants (CLASI-A ≥ 10 or < 10 at baseline) with a shift in CLASI-A score to ≤ 1, ≤ 3, ≤ 6, and ≤ 8 at Week 16.

Results: In this ad hoc analysis from LILAC Part B, 106 (80.3%) and 26 (19.7%) of participants had a baseline CLASI-A score ≥ 10 and < 10, respectively. Compared with placebo, higher proportions of participants treated with BIIB059 achieved a shift in CLASI-A score from either ≥ 10 or < 10 at baseline to ≤ 1, ≤ 3, ≤ 6, and ≤ 8 at Week 16 (Figure 1). Treatment with BIIB059 resulted in higher proportions of participants achieving reduced scores, indicating shifts to more mild disease activity, compared with placebo. A score ≤ 1 (clear or almost clear skin) at Week 16 was achieved by 0.0% (0/25), 5.0% (1/20), 14.3% (3/21), and 12.5% (5/40) of participants with baseline CLASI-A ≥ 10 who were treated with placebo and BIIB059 50, 150, and 450 mg, respectively. Two of 26 participants with baseline CLASI-A < 10 achieved a score ≤ 1 (both received BIIB059 150 mg).

Conclusion: A greater proportion of participants achieved milder skin disease or clear/almost clear skin status in the BIIB059 groups as compared with the placebo group. This effect was observed in participants with moderate or severe disease as well as in those in the higher range of the mild category of disease severity at baseline, indicating the ability of BIIB059 to improve skin lesions in patients with a broad range of cutaneous disease activity.

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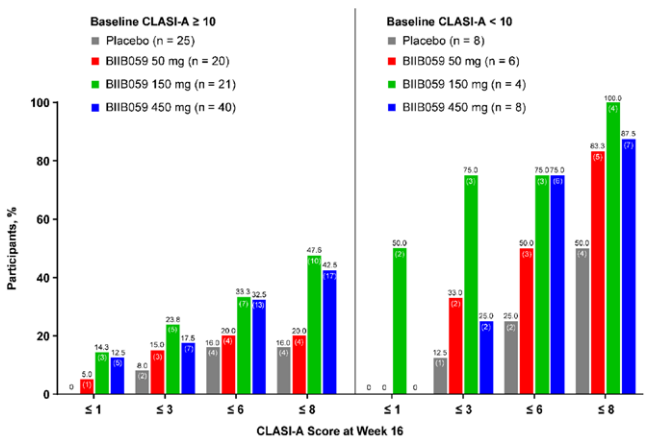
Figure. Percentage of Participants With Baseline CLASI-A ≥ 10 and < 10 Achieving a Decrease to CLASI-A Score Thresholds ≤ 1, ≤ 3, ≤ 6, and ≤ 8 at Week 16



CLASI-A = Cutaneous Lupus Erythematosus Disease Area and Severity Index – Activity

The denominator is the number of participants who had a CLASI-A score ≥ 10 or < 10 at baseline and a non-missing CLASI-A score at Week 16. Participants who were treatment failures or who discontinued treatment were considered nonresponders at visits after the treatment failure or discontinuation. Participants who completed treatment but had a missing score at the primary timepoint were classified as nonresponders for that timepoint.