




# Real-World Effectiveness of Belimumab in the Treatment of Systemic Lupus Erythematosus: Pooled Analysis of Multi-Country Data from the OBServe Studies

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## ABSTRACT

**Introduction:** The real-world effectiveness of belimumab for systemic lupus erythematosus (SLE) in six countries was evaluated in the OBServe program. The aim of this post hoc analysis (GSK study 206351) was to pool individual patient OBServe data to further evaluate the effectiveness of belimumab in a large sample of patients with SLE.

**Methods:** OBServe (Argentina, Canada, Germany, Spain, Switzerland, and the USA)

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Christopher E. Collins: at the time of study MedStar Washington Hospital Center.

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enrolled adults  $\geq 18$  years of age with SLE, who were prescribed belimumab as part of standard therapy (index: date of belimumab initiation). Endpoints (month 6 vs. index) included physician-assessed overall clinical response to belimumab in the overall population (primary) and high disease activity subgroups (secondary; patients with a SLEDAI-2K/SELENA-SLEDAI score  $\geq 10$  or patients with high anti-dsDNA or low complement at index); other secondary endpoints included changes in glucocorticosteroid (GCS) use and changes in disease activity. Factors associated with physician-assessed overall clinical response were also evaluated.

**Results:** In total, 830 patients were included in the overall population (mean [standard deviation (SD)] age: 41.9 [12.57] years; female: 89.3%; 60.4% from the USA). Nearly half (48.1%) of belimumab-treated patients experienced a

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≥ 50% physician-assessed improvement in their overall manifestations, and 13% achieved a near normalization of their condition (equal to ≥ 80% improvement). Initiating belimumab while on high-dose (> 7.5 mg/day) GCS use was associated with ≥ 50% clinical improvement at month 6 (OR: 1.9,  $p = 0.003$ ). Most (78.1%;  $n = 518/663$ ) patients were able to reduce or discontinue their oral GCS dose after 6 months of belimumab, with a mean (SD) change of  $-8.5$  (10.74) mg/day prednisone-equivalent. The mean (SD) change from belimumab initiation in disease activity score (SLEDAI-2K/SELENA-SLEDAI) was  $-5.7$  (4.5;  $n = 344$ ).

**Conclusions:** Belimumab improves clinical manifestations of SLE and is associated with GCS dose reductions in a real-world clinical setting, supporting the real-world effectiveness of belimumab for SLE.

**Keywords:** Belimumab; Glucocorticosteroid sparing; Real-world effectiveness; Real-world experience; SLE; Systemic lupus erythematosus

### Key Summary Points

#### Why carry out this study?

The efficacy and safety of belimumab in patients with systemic lupus erythematosus (SLE) have been demonstrated in several randomized clinical trials. However, strict eligibility criteria and inflexible concomitant medication management can narrow study populations, limiting the generalizability and interpretation of these findings to real-world clinical practice populations.

The real-world effectiveness of belimumab in patients with SLE in six countries was evaluated in the OBSErve program.

The aim of this post hoc analysis was to pool individual patient data from these six OBSErve studies to further evaluate the real-world effectiveness of belimumab in a large sample of patients with SLE.

#### What was learned from the study?

Belimumab treatment for at least 6 months improves clinical manifestations of SLE in the majority of patients and enables glucocorticosteroid dose reductions, with over half of patients achieving doses ≤ 7.5 mg, and is well tolerated in a real-world clinical setting.

These results support the real-world effectiveness of belimumab in the management of SLE.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13020566>.

## INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with various clinical presentations and typically a relapsing–remitting course [1]. To manage disease activity, patients with SLE often require lifelong medications such as antimalarials, and immunosuppressive agents, in addition to oral glucocorticosteroids (GCS) to prevent and treat flares [2]. Repeated cumulative treatment with these therapies, particularly high-dose (≥ 7.5 mg/day) GCS, is associated with significant morbidity and irreversible damage accrual, and a reduction in GCS exposure is an important treatment goal in SLE [2].

Patients with SLE have elevated levels of B-cell-activating factor (BAFF; also known as B-lymphocyte stimulator [BLyS]), which promotes abnormal B-cell activation and differentiation [3]. Belimumab is a human immunoglobulin G1λ monoclonal antibody that inhibits the activity of BAFF [4] and is

licensed for the treatment of adult and pediatric patients with active autoantibody-positive SLE who are receiving standard SLE therapy [5, 6]. The efficacy and safety of belimumab in patients with SLE has been demonstrated in several randomized clinical trials [7–10]. However, the strict inclusion and exclusion criteria and requirements for consistent concomitant medication use can limit the generalizability and interpretation of the findings of clinical trials to the real-world SLE patient population treated in everyday clinical practice. Furthermore, determining whether improvements in clinical trial composite endpoints translate into benefits in routinely assessed clinical outcomes based on physician judgment provides valuable information for physicians and patients when making treatment decisions. Consequently, the real-world effectiveness and utilization patterns of intravenous (IV) belimumab in patients with SLE have been evaluated in several countries in the OBServe (evaluation Of use of Belimumab in clinical practice SETtings) program [11–16]. In these observational studies, adult patients with SLE treated with belimumab in a clinical practice setting demonstrated consistent clinical improvements. However, with the exception of the USA, which included  $\geq 500$  patients, sample sizes were small (50–100 patients), [11–16] limiting the ability to explore patient subgroups or factors associated with treatment effects.

The aim of this post hoc analysis was to pool individual patient data from the OBServe studies [11–16] to further evaluate the real-world effectiveness and utilization of belimumab in a large sample of patients with SLE.

## METHODS

### Study Design

This was a post hoc pooled analysis (GSK study 206351) of patient-level data pooled from the six retrospective, observational cohort OBServe studies from 97 study centers based in Argentina (GSK study 201282), Canada (GSK study 117300), Germany (GSK study 117214), Spain (GSK study 200883), Switzerland (GSK study 201232), and the USA (GSK study 117295)

[11–17]. Follow-up times varied between the original studies (OBServe Canada, Germany, Spain, and Switzerland: 6 months; OBServe Argentina and USA: up to 24 months), for the current analysis, patient data collected at belimumab start (index date, between September 2012 and March 2016) and at 6 months after index, or at time of discontinuation, were analyzed, because this was the longest duration of follow-up time for which all countries could contribute data (Supplementary Fig. 1). As the studies were retrospective, study protocols had no influence on the physicians' treatment decisions or collection of patient data.

Ethics committee/institutional review board approval was not required for this analysis, as it used previously published data. All procedures performed in the original OBServe studies were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the original OBServe studies. The reporting of this study conforms to the CONSolidated Standards of Reporting Trials (CONSORT) 2010 guideline [18].

### Physicians

Complete physician eligibility criteria for each individual OBServe study have been published [11–16]. In brief, rheumatologists and/or internal medicine specialists who prescribed belimumab to patients with SLE as part of their usual clinical practice were invited to participate. Physicians extracted patient information about demographics, and disease and treatment characteristics. All patient data were anonymized.

### Patients

The current analysis included all patients from the individual OBServe studies. The following patient eligibility criteria were used in the primary studies: adults  $\geq 18$  years of age with a diagnosis of SLE, who were prescribed

belimumab as part of standard SLE therapy, who initiated their belimumab therapy  $\geq 6$  months prior to study enrollment (Argentina, Germany, Spain, Switzerland), or had received  $\geq 8$  belimumab infusions during the  $\geq 6$  months prior to study enrollment (Canada, USA), and for whom reasons for belimumab initiation could be identified. Patients enrolled in an SLE clinical trial or who had initiated belimumab as part of a clinical trial were not included.

In OBServe Argentina, Canada, Germany, Spain, and Switzerland, physicians examined their patient records to identify all patients with SLE receiving belimumab. To avoid selection bias, all patients who met the eligibility criteria (according to each country's indication) were selected for inclusion. In OBServe US, a random sample of eligible patients was selected by retrospective chart review of all available patients for each individual study center.

### Endpoints and Assessments

The primary endpoint (physician-assessed overall clinical response to belimumab at month 6) was evaluated as worse, no improvement,  $< 20\%$  (minimal) improvement, 20–49% (clear but moderate) improvement, 50–79% (large) improvement, or  $\geq 80\%$  (near normalized) improvement, compared with index.

Patient demographics (e.g., age, gender, country of enrollment), and clinical (disease severity and duration, number and type of SLE manifestations, number of comorbidities) and treatment characteristics (e.g., concomitant medications) at belimumab initiation were described as part of the secondary endpoint. Secondary endpoints (at month 6 vs. date of belimumab initiation) also included physician-assessed overall clinical response among patients in high disease activity subgroups; patient characteristics associated with a  $\geq 50\%$  improvement in physician-assessed overall clinical response to belimumab; change in SLE Disease Activity Index-2000 (SLEDAI-2K)/Safety of Estrogens in Lupus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score (choice based on center preference for each individual patient); reasons for belimumab

initiation and discontinuation (physician-reported) and changes in concomitant GCS use (i.e., mean change in dose, proportion of patients experiencing dose change, and proportion of patients achieving dose reduction to  $\leq 7.5$  mg/day (prednisone-equivalent); and reasons for belimumab initiation and discontinuation (physician-reported).

Exploratory endpoints were also analyzed at month 6, including physician-assessed overall clinical response and concomitant GCS use based on immunomodulator (azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, thalidomide, leflunomide, or tacrolimus) use at belimumab initiation; and physician-assessed improvement in specific clinical manifestations reported as present at belimumab initiation.

For the secondary endpoint of physician-assessed overall clinical response, patients were assigned to one of two high disease activity subgroups to reflect the indicated population in Europe [5]: Subgroup 1, patients with a SLEDAI-2K/SELENA-SLEDAI score  $\geq 10$ ; and Subgroup 2, patients with high anti-dsDNA or low complement (C3 and/or C4,  $<$  lower limit of normal [based on physician's assessment of the medical record]).

### Sample Size and Statistical Analysis

Pre-specified primary and secondary endpoints of the current study were selected based on consistent data reporting/availability across the original OBServe studies. Thus, except for SLEDAI-2K/SELENA-SLEDAI scores, which are not routinely assessed in clinical practice, the extent of missing data was expected to be minimal. Where data were missing, it has been clearly indicated throughout the results, and no imputation was performed for missing data.

Descriptive statistics were used to summarize continuous data (mean, median, standard deviation [SD], 95% confidence intervals [CIs], minimum and maximum, and range) and categorical data (counts and frequencies). The overall clinical response to belimumab was compared between the patients exposed to one immunosuppressant (IM) versus those exposed

to at least two IMs at belimumab initiation, using the Wilcoxon rank-sum test. A logistic regression model was fitted to estimate the predictors of  $\geq 50\%$  improvement (combined responses of 50–79% and  $\geq 80\%$  improvement) physician-assessed overall clinical response to belimumab at month 6. The response categories were dichotomized ( $\geq 50\%$  or  $< 50\%$  improvement) to facilitate interpretation by using a generalized linear model specifying a binomial distribution rather than ordinal regression incorporating multiple response levels;  $\geq 50\%$  was selected as this represents a large improvement and used to differentiate patients likely to derive a large benefit from belimumab treatment. The following covariates were included in the model based on clinical understanding of characteristics that influence treatment response: age (reference case: 18–27 years); gender (reference case: female); ethnicity (reference case: Caucasian/white); disease severity at belimumab initiation (reference case: mild); prior IM use (reference case: no prior use); SLE disease duration (reference case:  $\leq 5$  years); GCS dose at belimumab initiation (reference case:  $\leq 7.5$  mg/day); presence of SLE manifestations at belimumab initiation (reference case: no manifestations at belimumab initiation); presence of high anti-dsDNA and/or low complement at belimumab initiation based on physician judgment (reference case: no anti-dsDNA and/or high complement at belimumab initiation). SLEDAI-2K/SELENA-SLEDAI score was not included in the final model due to missing data ( $n = 484$  patients at baseline), which would substantially reduce the number of observations that could be included. Prior to fitting the model, multicollinearity of covariates was assessed using the variance inflation factor (VIF), with  $VIF > 10$  indicative of one covariate being a linear combination of other covariates. A general rule of one covariate for every 20 observations in the smallest response group was applied to eliminate overfitting the model. Odds ratios (OR) and  $p$  values were reported for each covariate included in the model. The Hosmer–Lemeshow test was used to assess whether the observed rates matched the expected rates in the population subgroups (i.e., how well the model predicted overall clinical

response to belimumab treatment). A  $p$  value ( $< 0.05$ ) indicated a poor fit.

## RESULTS

### Patient Demographics and Clinical Characteristics

In total, 830 patients were included in this pooled analysis, with the majority ( $n = 501/830$ , 60.4%) being from the USA, female ( $n = 741/830$ , 89.3%) and Caucasian/white ( $n = 540/830$ , 65.1%); mean (SD) age was 41.9 (12.57) years (Table 1). Most patients were classified as having high disease activity with either a SLEDAI-2K/SELENA-SLEDAI score of  $\geq 10$  ( $n = 208/346$  of patients with available SLEDAI-2K/SELENA-SLEDAI score at belimumab initiation, 60.1%) or were positive for anti-dsDNA or low complement ( $n = 687/830$ , 82.8%). Patients presented with a range of clinical manifestations at belimumab initiation, with musculoskeletal, mucocutaneous, and immunologic being the most common (Table 1).

On a country level, demographic and clinical characteristics at belimumab initiation were broadly similar. However, patients enrolled from OBSERVE Switzerland and USA had a shorter disease duration (45.3 and 55.7%  $< 5$  years, respectively) compared with 23.1% in Canada and 39.7% in Argentina, and more patients from Switzerland had mild disease (43.4%) at belimumab initiation compared with 2.8% in the USA and 10.5% in Argentina. Patients from Switzerland also had the lowest mean number of comorbidities, and lowest proportion of patients with SELENA-SLEDAI scores  $\geq 10$  (32.1%), whereas the USA had the highest proportion of patients with SELENA-SLEDAI scores  $\geq 10$  (77.9%). The majority of patients of Black race were from the USA (Supplementary Table 1).

### Physician-Assessed Clinical Improvements After 6 Months of Belimumab Treatment

At month 6, most ( $n = 791/830$ , 95.3%) patients had an improvement from the date of

**Table 1** Patient demographics and clinical characteristics at date of belimumab initiation (index)

	<b>N = 830</b>
Age <sup>a</sup> , years, mean (SD)	41.9 (12.6)
Female, <i>n</i> (%)	741 (89.3)
Country of enrollment, <i>n</i> (%)	
Argentina	58 (7.0)
Canada	52 (6.3)
Germany	102 (12.3)
Spain	64 (7.7)
Switzerland	53 (6.4)
USA	501 (60.4)
Race/ethnicity, <i>n</i> (%)	
Caucasian/white	540 (65.1)
African American/African origin/West Indian/Black	134 (16.1)
Hispanic	91 (11.0)
Asian	36 (4.3)
Mixed	17 (2.1)
Other	7 (0.8)
American Indian/Native American	5 (0.6)
Disease severity <sup>b</sup> , <i>n</i> (%)	
Mild	58 (7.1)
Moderate	593 (72.1)
Severe	171 (20.8)
Disease duration <sup>c</sup> , <i>n</i> (%)	
≤ 5 years	377 (45.5)
6–10 years	199 (24.0)
> 10 years	252 (30.4)
Low C3 (< lower limit of normal), <i>n</i> (%)	474 (57.1)
Low C4 (< lower limit of normal), <i>n</i> (%)	479 (57.7)
High anti-dsDNA, <i>n</i> (%)	540 (65.1)
SLEDAI-2K/SELENA-SLEDAI score <sup>d</sup> , <i>n</i> (%)	
< 10	138 (39.9)
≥ 10	208 (60.1)
SLEDAI-2K/SELENA-SLEDAI score, mean (SD)	11.0 (5.3)

**Table 1** continued

	<i>N</i> = 830
Clinical manifestations by organ system involvement, <i>n</i> (%)	
Musculoskeletal	598 (72.1)
Mucocutaneous	490 (59.0)
Immunologic	468 (56.4)
Constitutional (fatigue, fever, and/or weight loss)	402 (48.4)
Hematologic	231 (27.8)
Renal	137 (16.5)
Cardiopulmonary	127 (15.3)
Central nervous system	111 (13.4)
Headache	81 (9.8)
Organic brain damage	17 (2.0)
Seizure	13 (1.6)
Cranial nerve neuropathy	8 (1.0)
Cerebrovascular accident	7 (0.8)
Psychosis	7 (0.8)
Vasculitis	37 (4.5)
Gastrointestinal	4 (0.5)
Visual/ocular	1 (0.1)
Other	42 (5.1)
Mucocutaneous and/or musculoskeletal	719 (86.6)
No other organ involvement	81 (9.8)
With renal involvement	114 (13.7)
Without renal involvement	524 (63.1)
No mucocutaneous or musculoskeletal	111 (13.4)
SLE medications, <i>n</i> (%)	
Oral GCS	663 (79.9)
Antimalarial	579 (74.0)
Immunosuppressant	488 (58.8)
Azathioprine	171 (35.0)
Cyclophosphamide	2 (0.4)
Cyclosporine	13 (2.7)
Methotrexate	151 (30.9)

**Table 1** continued

	<i>N</i> = 830
Mycophenolate mofetil	165 (33.8)
Mycophenolate sodium	1 (0.2)
Thalidomide	1 (0.2)
Leflunomide	2 (0.4)
Tacrolimus	1 (0.2)

*C* complement, *GCS* glucocorticosteroids, *SD* standard deviation, *SELENA-SLEDAI* Safety of Estrogens in Lupus National Assessment-SLE Disease Activity Index, *SLE* systemic lupus erythematosus, *SLEDAI-2K* SLE Disease Activity Index 2000

<sup>a</sup> *n* = 778, excluding Canada, in which individual patient data for age were reported as a categorical outcome

<sup>b</sup> *n* = 822

<sup>c</sup> *n* = 828

<sup>d</sup> *n* = 346, data available for a subset of patients in each OBServe study

belimumab initiation in their overall condition. A minimal improvement (< 20%) was observed for 12.5% (*n* = 104/830) of patients, with a further 34.7% (*n* = 288/830), 35.2% (*n* = 292/830), and 12.9% (*n* = 107/830) experiencing an improvement of 20–49%, 50–79%, and ≥ 80%, respectively. Worsening was reported for ten patients (1.2%; Fig. 1a). Similarly, 95.7% of patients with high disease activity defined as SLEDAI-2K/SELENA-SLEDAI ≥ 10 and 95.8% of those with high disease activity defined as high anti-dsDNA or low complement based on physician judgment (C3 and/or C4, < lower limit of normal) demonstrated an improvement in their overall condition, with 11.9–13.5% achieving a near normalization of their condition (≥ 80% improvement from date of belimumab initiation) (Fig. 1b).

#### Characteristics Associated with Physician-Assessed Clinical Improvements

Use of high-dose GCS (> 7.5 mg/day prednisone-equivalent) at belimumab initiation was the only factor significantly associated with ≥ 50% overall clinical improvement (OR: 1.88 [95% CI: 1.23, 2.87]; *p* = 0.003). No other trends in other patient or treatment characteristics were observed. Numerical differences were observed amongst patients with varying manifestations at baseline; the sample size was low

for several organ systems as the majority of patients had mucocutaneous (59%) and musculoskeletal (72%) involvement (Fig. 2).

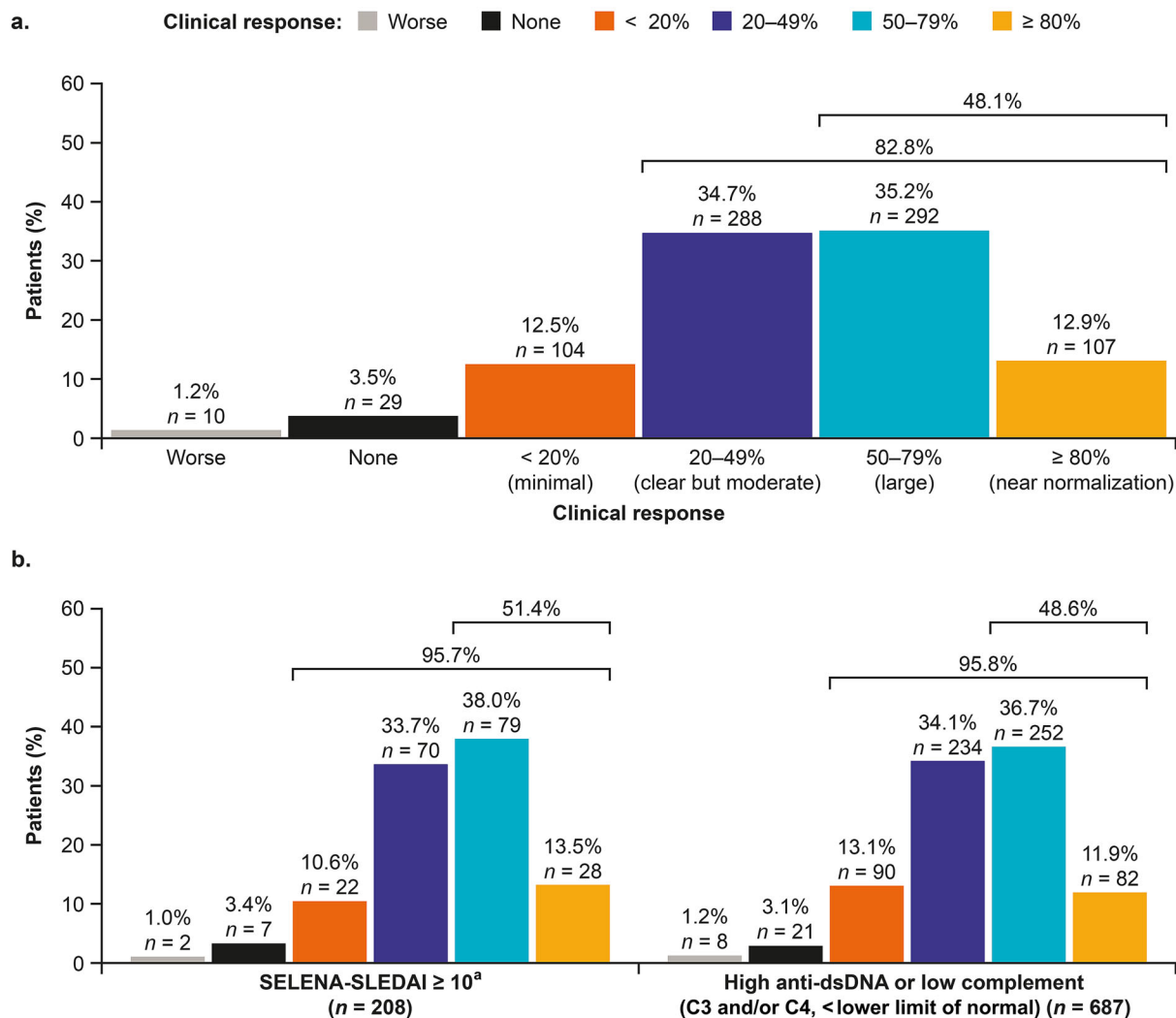
#### Country-Specific Analysis of Clinical Improvement at Month 6

The distribution of the degree of physician-assessed clinical improvement in response to belimumab from date of belimumab initiation at month 6 between countries was statistically significant (*p* < 0.0001; Supplementary Table 2). Patients from Switzerland had a smaller clinical improvement from the date of belimumab initiation to month 6 compared with other countries, with 17.0% (*n* = 9/53) having no improvement compared with 0.6% from the USA and 9.4% from Spain. Spain and Argentina had the largest proportion of patients with ≥ 80% clinical improvement from date of belimumab initiation (*n* = 17/64, 26.6% and *n* = 12/58, 20.7%, respectively), compared with 8.8% from Germany and 17.3% from Canada.

#### Change from Date of Belimumab Initiation in SLEDAI-2K/SELENA-SLEDAI at Month 6

In total, 346 patients had a SLEDAI-2K/SELENA-SLEDAI score at belimumab initiation (mean





**Fig. 1** Physician-assessed overall clinical response at month 6 in the overall population (a) and patients with SLEDAI-2K/SELENA-SLEDAI score  $\geq 10$  and those with serologically active disease (b). C complement, dsDNA double-stranded deoxyribonucleic acid, SLEDAI-

2K/SELENA-SLEDAI Safety of Estrogens in Lupus National Assessment-SLE Disease Activity Index, SLE systemic lupus erythematosus

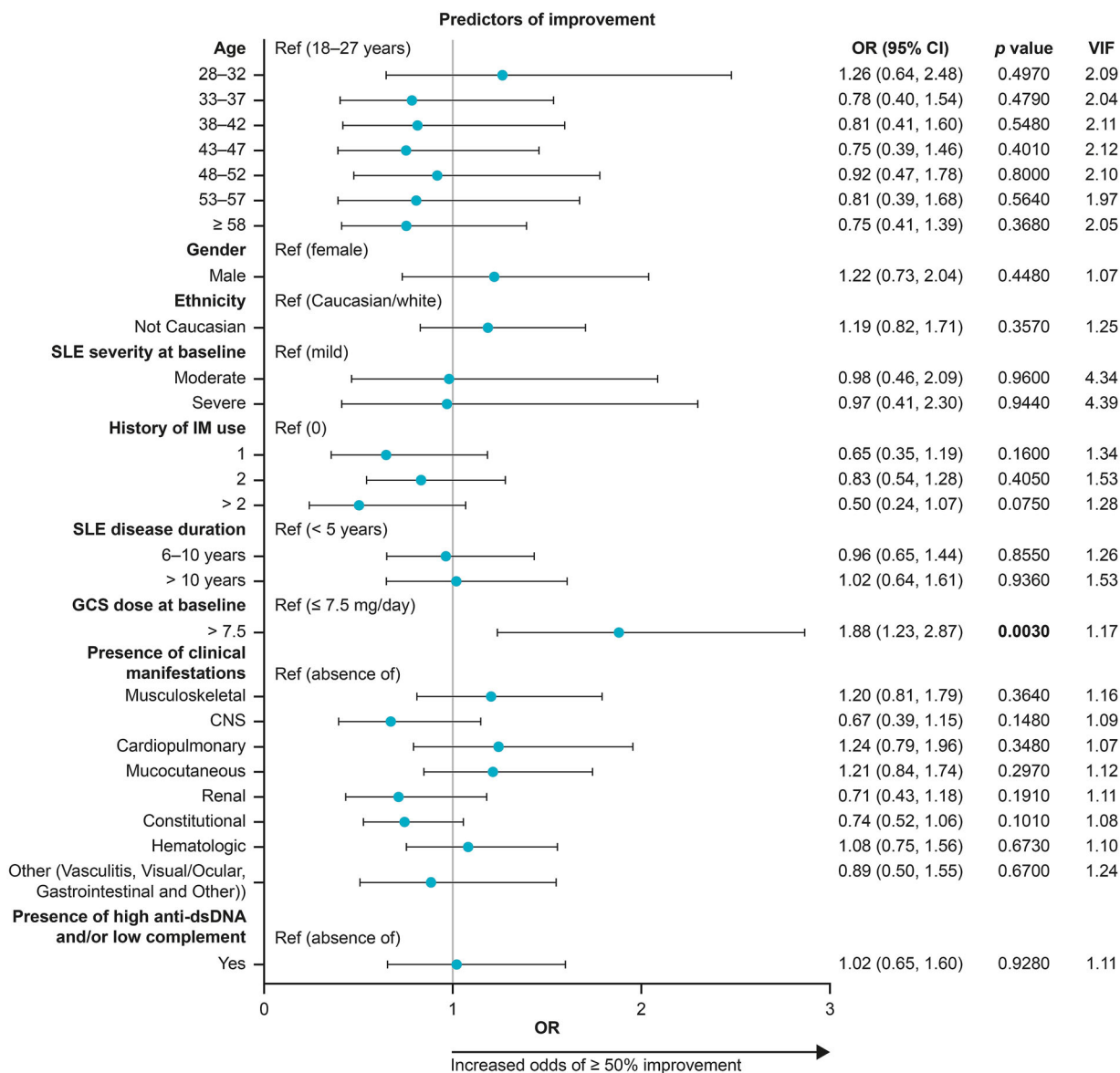
<sup>a</sup>SLEDAI-2 K/SELENA-SLEDAI scores were only available for 42% (n = 346) of the pooled cohort

[SD]: 11.0 [5.3]) and 349 patients at month 6 (5.3 [3.8]). The mean (SD) change between these two time points, calculated for 344 patients, was  $-5.7$  (4.5).

### Treatment Patterns Associated with Belimumab

The most common reason for belimumab initiation was due to the previous treatment

regimen not being effective (n = 617/830, 74.3%), followed by the desire to decrease GCS use (n = 460/830, 55.4%) and the patient’s condition worsening (n = 451/830, 54.3%; Table 2). In total, 28.3% of patients in Switzerland initiated treatment due to condition worsening versus 50% from both Canada and Argentina, and 60.8% from Germany. Of those from whom discontinuation data were available (n = 277), only 12 (4.3%) patients discontinued



**Fig. 2** Predictors of a large ( $\geq 50\%$ ) physician-assessed overall clinical improvement at month 6 based on patient characteristics at date of belimumab initiation (index). *CI* confidence interval, *CNS* central nervous system, *dsDNA* double-stranded deoxyribonucleic acid, *GCS* glucocorticosteroid, *OR* odds ratio, *SLE* systemic lupus erythematosus, *VIF* variance initiation factor. The OR represents the odds of achieving an overall clinical improvement

of  $\geq 50\%$  will occur given a particular characteristic, compared with the odds of an overall clinical improvement of  $\geq 50\%$  in the reference case  $OR > 1$ : characteristic is associated with higher odds of a large ( $\geq 50\%$ ) improvement;  $OR < 1$ : the characteristic is associated with lower odds of a large ( $\geq 50\%$ ) improvement. *Black horizontal lines* represent 95% CIs

belimumab during the 6 months of treatment (Table 2). The most common reasons for belimumab discontinuation were patient request and ineffective treatment (both  $n = 4$ , 33.3%),

and adverse event and disease progression (both  $n = 3$ , 25.0%).

At belimumab initiation, 663 (79.9%) patients were receiving oral GCS (Table 3) at a

**Table 2** Reasons for belimumab initiation and discontinuation

Reason for initiating belimumab <sup>a</sup> , <i>n</i> (%)	<i>N</i> = 830
Previous treatment regimen not effective	617 (74.3)
To decrease use of GCS	460 (55.4)
Patient condition worsening	451 (54.3)
Previous treatment regimen not well tolerated	186 (22.4)
Patient request	58 (7.0)
Previous treatment regimen inconvenient	29 (3.5)
Drug-to-drug interactions with previous medication	9 (1.1)
Other	5 (0.6)
Reasons for discontinuing belimumab <sup>ab</sup> , <i>n</i> (%)	<i>n</i> = 277
Total number of discontinuations	12 (4.3)
Medication not effective	4 (33.3)
Patient request	4 (33.3)
Disease progression	3 (25.0)
Adverse event	3 (25.0)
Loss of insurance or reimbursement	2 (16.7)
Lack of compliance	1 (8.3)
Death	1 (8.3)
Other	2 (16.7)

GCS glucocorticosteroids

<sup>a</sup> Categories are not mutually exclusive

<sup>b</sup> Data from Argentina, Germany, Spain, and Switzerland only

mean (SD) prednisone-equivalent dose of 16.7 (12.67; median, 15.0 [range, 2, 100]) mg/day. The majority ( $n = 518/663$ , 78.1%) of patients were able to reduce or discontinue their oral GCS dose after 6 months of belimumab treatment (Table 3). At month 6, the mean (SD) prednisone-equivalent dose was 8.3 (6.16) mg/day, a decrease from the date of belimumab initiation of  $-8.5$  (10.74) mg/day. Among the 526 patients receiving  $> 7.5$  mg/day dose of oral GCS at belimumab initiation, 52.6% of those with data for month 6 ( $n = 258/491$ ) reduced their dose to  $\leq 7.5$  mg/day at month 6 (Table 3).

### Patient Response to Belimumab Based on Patient History of IM Use

Physician-assessed response to belimumab at month 6 was similar in patients with prior and/or concomitant exposure to 0, 1, 2, or  $> 2$  IMs during the 6 months prior to the date belimumab initiation (inclusive) (disease-modifying anti-rheumatic drugs, excluding hydroxychloroquine; Supplementary Table 3). There was no clear trend in the changes in GCS use or dose based on patient history of IM use (Supplementary Table 3).

**Table 3** Oral GCS use at date of belimumab initiation (index) and during 6 months of belimumab treatment

	<i>N</i> = 830
Oral GCS use at index, <i>n</i> (%)	663 (79.9)
Oral GCS dose (prednisone-equivalent) at index, <i>n</i> (%)	
≤ 7.5 mg/day	137 (20.7)
> 7.5 mg/day	526 (79.3)
Oral GCS use at month 6, <i>n</i> (%)	
Discontinued	50 (7.5)
Reduced dose	468 (70.6)
No change in dose	124 (18.7)
Increased dose	21 (3.2)
Oral GCS dose (prednisone-equivalent), mg/day; mean (SD)	
Index	16.7 (12.7)
Month 6	8.3 (6.2)
Change between index and month 6	– 8.5 (10.7)
Oral GCS dose (prednisone-equivalent) at month 6, <i>n</i> (%)	<i>n</i> = 613
≤ 7.5 mg/day	375 (61.2)
> 7.5 mg/day	238 (38.8)
Reduction to ≤ 7.5 mg/day <sup>a</sup>	258 (52.6)

GCS glucocorticosteroids

<sup>a</sup> From > 7.5 mg/day at index; *n* = 491

### Physician-Assessed Clinical Improvements in Organ-Specific Manifestations

Of the 598 and 490 patients with musculoskeletal and mucocutaneous manifestations at belimumab initiation, 311 (51.8%) and 269 (54.7%) patients experienced ≥ 50% improvement from the date of belimumab initiation at month 6, respectively. Similarly, of the 127 patients with cardiopulmonary manifestations at belimumab initiation, 70 (55.1%) experienced improvement from belimumab initiation to month 6 of ≥ 50% and 37 (29.1%) had improvement ≥ 80% (data not shown).

The most common (≥ 100 patients) individual manifestations are shown in Supplementary Fig. 2. Of these, over half of the patients demonstrated at least a 50%

improvement in manifestations of arthritis and mucosal ulcer. In the 137 patients with renal manifestations at belimumab initiation, 132 (15.9%) had proteinuria and 11 (1.3%) had pyuria; the degree of improvement in these specific manifestations was evenly distributed amongst the response categories; similar results were seen for alopecia and leukopenia (Supplementary Fig. 2).

### DISCUSSION

This post hoc pooled analysis of real-world medical data pooled from six OBSERVE studies provides important insights into clinical outcomes and concomitant medication use in a large global sample of patients with SLE treated

with belimumab. Following 6 months of belimumab IV treatment, most patients demonstrated clinical improvements in SLE, and reductions in GCS dose, consistent with the primary studies conducted in Argentina, Canada, Germany, Spain, Switzerland, and the USA [11–16]. As assessed by their physicians, nearly half of belimumab-treated patients experienced  $\geq 50\%$  improvement in their overall manifestations, and 13% achieved a near normalization of their condition (equal to  $\geq 80\%$  improvement). The results were consistent between the overall population and subgroups of patients with a SLEDAI-2K/SELENA-SLEDAI score of  $\geq 10$  and those positive for anti-dsDNA or low complement. These results are also consistent with a post hoc analysis of the BLISS IV studies, which defined high disease activity as a SELENA-SLEDAI score of  $\geq 10$ , low complement levels, anti-dsDNA 30 IU/ml, and GCS use [19].

Similar to the original OBSERVE studies, this pooled analysis confirmed improvements in SLEDAI scores and reductions in GCS use after 6 months of belimumab treatment. As noted in the 2019 update of the European League Against Rheumatism recommendations for the management of SLE, GCS should be discontinued or daily dose reduced to  $\leq 7.5$  mg to avoid organ damage accrual associated with prolonged high-dose GCS intake [2]. A steroid-sparing effect of belimumab has previously been indicated in post hoc analyses and long-term continuation studies of belimumab clinical trials [19–21]. In the current study, 71% of patients were able to reduce and 8% to discontinue their oral GCS during the first 6 months of belimumab treatment, in addition to 53% reducing their dose to  $\leq 7.5$  mg/day. Furthermore, the mean GCS dose reduction of 8.5 mg/day in this study was similar to that observed in an independent, investigator-initiated, prospective study in Italy (7.6 mg/day) of patients with active SLE [22].

In the current study, compared with patients receiving  $\leq 7.5$  mg/day dose at belimumab initiation (21%), a high ( $> 7.5$  mg/day) GCS dose at date of belimumab initiation was significantly ( $p = 0.003$ ) associated with almost twice the odds of a patient achieving an overall

clinical improvement  $\geq 50\%$  at month 6. This is similar to a post hoc analysis of the BLISS-52 and BLISS-76 randomized clinical trials, which included a more restricted group of patients and found that there was a significant association between GCS dose at baseline and response to belimumab [19]. This post hoc analysis also found that SELENA-SLEDAI scores  $\geq 10$  also predicted better belimumab responses; investigation of this relationship was precluded in the current study by more than half of the patients having missing SLEDAI-2K/SELENA-SLEDAI scores [19]. Together, these results suggest that real-world patients who are receiving high-dose oral GCS ( $> 7.5$  mg/day), which indicates that they have a higher degree of disease activity, are likely to have a greater degree of improvement from belimumab treatment than those on lower doses.

OBSERVE did require patients to have a previous treatment history and/or active disease. Consequently, differences were observed in the characteristics of the patients included in the individual OBSERVE studies, which likely contributed to between-country differences in degree of improvement since belimumab treatment. For example, many more patients in Switzerland than in any of the other countries were initiated with belimumab when their disease severity was considered mild (as assessed by the physician). The capacity of patients with already mild disease to have a large degree of improvement is lower than those with severe disease, and accordingly this was reported in OBSERVE Switzerland [14]. Indeed, of all the countries assessed in OBSERVE, Switzerland had the highest proportion of patients with no or  $< 20\%$  improvement, which reflects a desirable outcome for patients whose mild, and presumably well-controlled, disease is sought to be maintained rather than further improved. In the primary OBSERVE Switzerland study, reductions from baseline in SELENA-SLEDAI score and GCS dose ( $- 5.7$  mg/day reduction from baseline at 6 months) were also observed [14]. More mild patients receiving belimumab in Switzerland compared with other countries may suggest that belimumab is being used to prevent future flares and damage over the long term rather than to intervene when patients are

progressing or are less well controlled. This is further supported by the finding that only 28% of patients in Switzerland compared with 50 to 61% in other countries initiated belimumab due to disease worsening. The largest proportion of patients experiencing near normalization of their SLE was in Spain, where > 25% had a  $\geq 80\%$  improvement since belimumab initiation. The highest proportion of patients with severe disease at belimumab initiation was also observed in Spain. Consequently, these data also provide insights into the differing treatment approaches between countries, although it should be noted that sample sizes for individual countries were small, meaning between-country comparisons should be interpreted with caution.

Physician-assessed improvement in specific clinical manifestations was broadly consistent with their assessment of their overall response. In this cohort, 72% of patients had musculoskeletal involvement at date of belimumab initiation and more than half of these patients were reported to have  $\geq 50\%$  improvement in this organ system by month 6. Improvement at the level of individual, specific clinical manifestations is dependent upon the baseline severity of that manifestation, which has not been analyzed here, and the inherent ability of each to improve. For example, patients with proteinuria may be expected to have stable, low levels of proteinuria given that patients with active nephritis and uncontrolled proteinuria were less likely to receive belimumab prior to initiation of the BLISS-LN study in 2012 (NCT01639339) [23]. However, this cannot be confirmed in the absence of renal laboratory parameters, and without a definition/cutoff for proteinuria, which were not collected and defined in the OBSErve studies, respectively. The results of the regression analysis may imply that there are lower odds of a large ( $\geq 50\%$ ) improvement in patients with renal, central nervous system, and constitutional manifestations at date of belimumab initiation. However, this does not suggest that these patients are achieving no or a poor response since patients assessed as having had 20–49% improvement at month 6, pre-defined as a clear but moderate improvement are not included in the outcome

variable of the binomial regression. Therefore, results of the regression analysis should be considered conservative.

This study has a number of limitations inherent to this type of observational study. Although validated SLE assessment scores were reported where available from patient medical records, the primary outcome of the overall clinical response was based on the subjective clinical physician judgment. As such, the accuracy of the physician judgment cannot be compared with validated disease activity measures such as the SELENA-SLEDAI or British Isle Lupus Assessment Group instruments, nor was it verified by another physician, which poses a potential for misclassification bias. Selection bias may be present, introduced by the use of convenience sampling by most of the individual OBSErve country studies, although some studies included random sampling of patients. Additionally, treatment patterns, clinical outcomes, and resource use data represent only the medical sites of physicians participating in the study and may vary from those of non-participating physicians. The study population was predominantly Caucasian/white with other races and ethnicities in whom SLE is generally more severe with higher disease activity and more damage accrual (i.e., people of Hispanic, Black, and Asian race) [24] largely underrepresented. Subgroup analysis by race/ethnicity was not conducted as part of our pooled analysis; however, because 92% of the patients of Black race were in OBSErve US, the results published in that specific individual study are of note [15]. In OBSErve US, the change in overall clinical response at 0–6 months did not significantly differ between ethnic subgroups ( $p = 0.2622$ ), with 46.8% and 45.5% of patients of Caucasian or African-American origin, respectively, reporting  $a \geq 50\%$  improvement in clinical response. Neither the subgroup analysis according to IM use nor the regression analysis were specified in the individual OBSErve studies and should be interpreted with some caution. Additionally, data on SLEDAI score were missing for over half of the included patients, which may have increased or decreased mean changes from baseline, although it should be noted that improvements from the date of belimumab

initiation in SLEDAI score are in line with previous clinical trials [7, 9, 10].

As the current study analyzed outcomes only following 6 months of belimumab treatment, the results of this study will not fully reflect belimumab's clinical effectiveness. Both the USA and Argentina OBServe studies included follow-up to 24 months after belimumab initiation. Additional analysis with a longer follow-up time could be considered on a pooled cohort of these patients to explore predictors of clinical outcomes over a longer belimumab treatment period. Patient-reported outcomes were not collected in the individual OBServe studies, which would have provided further insights into belimumab treatment outcomes from the patients' perspective. While cross-sectional survey studies provide important confirmation of treatment satisfaction [25], real-world assessment of improvements in health-related quality of life or fatigue are limited. Finally, as was the case with the individual OBServe studies, the results of this pooled analysis may not be generalizable outside the countries included. Nonetheless, this study provides important additional validation of the real-world effectiveness of belimumab in a large sample of patients with SLE in a real-world setting.

## CONCLUSIONS

In conclusion, this pooled analysis demonstrated that belimumab improves clinical manifestations of SLE and enables a reduction in GCS  $\leq$  7.5 mg/day in over half of the patients in a real-world clinical setting. The results of this study corroborate the conclusions of the individual OBServe studies and confirm the real-world effectiveness of belimumab IV in the management of SLE.

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**Compliance with Ethics Guidelines.** An ethics committee/institutional review board

approval was not required for this analysis, as it used previously published data. All procedures performed in the original OBSERVE studies were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the original OBSERVE studies. The reporting of this study conforms to the CONSOLIDATED Standards of Reporting Trials (CONSORT) 2010 guideline [18].

**Data Availability.** Information on GSK's data sharing commitments and requesting access to anonymized individual participant data and associated documents can be found at [www.clinicalstudydatarequest.com](http://www.clinicalstudydatarequest.com).

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