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MOONLIGHT study: the design of a comparative study of the effectiveness of belimumab in patients with a history of lupus nephritis from the post-Marketed effectiveness of belimumab cOhOrt and JapaN Lupus NatIonwide reGistry (LUNA) coHorT

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ABSTRACT

Introduction Lupus nephritis (LN) is more prevalent in patients with SLE of Asian ethnicity than in Caucasian patients. Belimumab became available in Japan in 2017 to treat patients with SLE, including those with LN. In the BLISS-LN trial (NCT01639339), belimumab showed a favourable effect on renal outcomes when combined with standard therapy (ST) starting at the induction treatment phase for active LN, but real-world effectiveness of belimumab in LN has not been extensively studied. Here we describe the protocol for the MOONLIGHT (post-Marketed effectiveness of belimumab cOhOrt and JapaN Lupus Natlonwide ReGistry (LUNA) coHorT) study, which will use data from a Japan postmarketing surveillance study and the Lupus Registry of Nationwide Institutions (LUNA) to evaluate the real-world effectiveness of belimumab plus ST versus ST alone in patients with a history of active LN who are not in the induction phase.

Methods and analysis This multicentre, retrospective, observational study (GSK Study 214710) will enrol adults with SLE and a history of active LN, holding ≥3 years of complete follow-up data from the initiation of belimumab (no continuous treatment required). Data for patients with belimumab plus ST treatment (postmarketing registry data, belimumab cohort) will be compared with those for patients with ST only treatment (LUNA data, comparison cohort). Patients who discontinue/initiate belimumab after the start of the follow-up may be included in the comparison/belimumab cohort, respectively. The primary endpoint will be the occurrence of renal flares, for which belimumab's effectiveness will be estimated using a marginal structural model to consider time-dependent treatment and confounding factors. Secondary endpoints will include change in corticosteroid dose, renal disease activity, extrarenal disease activity, disease severity/activity biomarkers, LN class changes, end-stage kidney disease events and hospitalisations.

Ethics and dissemination This study will be conducted according to the Declaration of Helsinki and the local ethical guidelines. Findings will be submitted to peer-reviewed journals and presented at scientific meetings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The BLISS-LN trial has shown that belimumab im proves renal outcomes in patients with active lupus nephritis (LN) when combined with standard therapy (ST) and started during the induction treatment phase, but belimumab's real-world effectiveness in LN has not been extensively studied.

⇒ Belimumab has been available in Japan since 2017 for the treatment of patients with SLE, including those with active LN.

WHAT THIS STUDY ADDS

⇒ Using data from a postmarketing surveillance study and the Lupus Registry of Nationwide Institutions, the MOONLIGHT study will explore the real-world effectiveness of belimumab plus ST by examining risk reduction in renal flare, the ability to taper corticosteroid treatment and systemic responsiveness for 3 years after the start of belimumab treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ It is anticipated that this study will provide important evidence of the effect of belimumab on renal outcomes when initiated outside the induction treatment phase in Japanese patients, which may be applicable to a wider Asian LN population.

⇒ This study will also provide a touchstone for evaluating relative effectiveness of marketed treatments for SLE through use of a nationwide registry.

INTRODUCTION

Despite recent therapeutic advances, lupus nephritis (LN) remains the most common serious and potentially life-threatening clinical manifestation of SLE. LN occurs more frequently in patients with SLE of Asian ethnicity (30%–40% to as high as 60%–70%) compared with Caucasian patients (29%–38%).[1–4] Approximately, 10%–30% of patients with LN will progress to end-stage kidney disease (ESKD) within 15 years of their LN diagnosis, with the risk being greatest within the first 5 years of diagnosis.[5–7] Importantly, once ESKD has been established, long-term prognosis is poor; the initial clinical progress in reducing ESKD risk plateaued by the mid-1990s, likely reflecting limits of effectiveness of the available therapies.[5 6]

The current standard therapy (ST) for LN includes high-dose corticosteroids plus an immunosuppressive agent, such as cyclophosphamide or mycophenolate mofetil (MMF) for the induction phase, and MMF or azathioprine for maintenance therapy, or as widely used in Japan, tacrolimus and mizoribine.[8–10] However, long-term use of corticosteroids has been shown to pose a significant dose-dependent toxicity and cause irreversible organ damage, which has been associated with increased mortality.[11–13] Thus, there remains an unmet need to identify novel therapies that would improve long-term renal outcomes and minimise treatment-related toxicity.

Belimumab, a human immunoglobulin G1λ monoclonal antibody that binds to and inhibits B lymphocyte stimulator, is approved as an add-on to ST for the treatment of patients ≥5 years of age with active autoantibody-positive SLE and of adults with LN.[14 15] Its approval for SLE was based on several successful phase III trials,[16 17] including one that demonstrated belimumab safety and efficacy in patients from Japan, China and South Korea.[18] A further phase III open-label continuation study demonstrated long-term efficacy and safety of belimumab of up to 7 years in patients with SLE from Japan.[19] A post hoc analysis of patients with SLE and renal involvement, but without active LN, from the phase III BLISS-52/76 studies found belimumab treatment was associated with numerically fewer renal flares and greater renal improvement versus placebo, suggesting belimumab may have a beneficial effect on renal outcomes.[20]

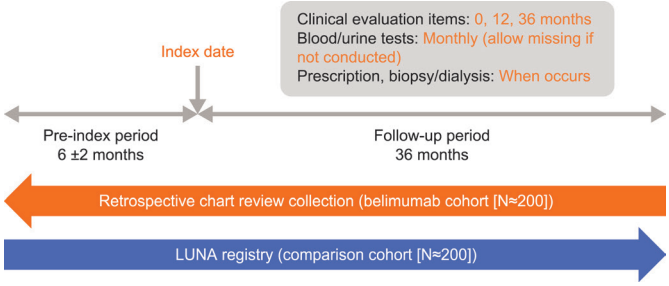

Figure 1 The study cohort and data collection scheme. Index date for belimumab cohort is defined as the date of belimumab initiation. For the comparison cohort, index date is defined as the day of 3 years prior to the last record in the LUNA registry. LUNA, Lupus Registry of Nationwide Institutions.

The favourable effect of belimumab initiated at the induction phase in patients with active LN has been demonstrated through the BLISS-LN study.[21 22] However, the efficacy of belimumab initiated as an add-on treatment during the maintenance phase and later has not been fully explored in clinical trials nor in a real-world clinical setting. The key goal of maintenance therapy in LN is to maintain the response achieved by induction therapy and to prevent disease flares.[8] There remains a gap in knowledge on the understanding of the effect of belimumab when initiated after the start of the induction phase in patients with biopsy-proven LN.

The current study, MOONLIGHT, has been designed to examine the real-world effectiveness of belimumab plus ST, in terms of risk reduction in renal relapse (new LN flares), the ability to taper corticosteroid treatment and systemic responsiveness for 3 years after the start of belimumab treatment, compared with ST alone, in Japanese patients with a history of active LN. To assess these objectives, MOONLIGHT will use the data from the belimumab postmarketing surveillance study (GSK Study 207735, NCT03370263) and the multicentre Lupus Registry of Nationwide Institutions (LUNA).[23 24] Here, we present the design of this ongoing study.

METHODS AND ANALYSIS

Study design

MOONLIGHT is a multicentre, retrospective, longitudinal, observational study of patients with LN who have ≥3 years of complete follow-up data available from initiation of belimumab (it was not required for patients to have continuous treatment, figure 1). Eligible patients with LN will be enrolled into one of two cohorts:

1. The belimumab cohort will include patients from the postmarketing surveillance survey who initiated treatment with belimumab plus ST (index date) ≥3 years prior to study entry (treatment initiation between December 2017 and June 2019). Patients who discontinue belimumab treatment may be included.
2. The comparison cohort will include patients from the LUNA registry who were receiving ST ≥3 years prior to study entry. As the patients in the comparison cohort have likely initiated ST many years ago on the onset of their SLE disease, it was decided to define the index date contemporaneous with that of the belim umab cohort to capture the last 3 years of treatment and avoid missing data. Therefore, the index date for the comparison cohort will be set between January 2016 and December 2019. Patients who initiate belimumab treatment after the start of the follow-up period may be included.

Study population

Detailed inclusion and exclusion criteria are shown in box 1. Briefly, patients must be ≥20 years of age (as per

Box 1 Patient inclusion and exclusion criteria

Inclusion criteria

Apply to both cohorts
⇒ ≥20 years of age.
⇒ SLE diagnosis, using ≥4 of ACR 1997 criteria.
⇒ Biopsy-confirmed diagnosis of LN class III or IV±V, or pure class V before the index date (required a biopsy-proven record).
⇒ Treated with prednisone-equivalent maintenance dose of <20 mg/day at the index date or within 30 days before the index date.

Apply to belimumab cohort only
⇒ Recruited at postmarketing surveillance study (GSK Study 207735) and capable of giving signed informed consent.
⇒ Prescription record of belimumab (regardless of the administration route) and medical record (clinical and laboratory) for ≥3 years from initiation of the belimumab treatment (though continuous treatment is not required).

Apply to comparison cohort only
⇒ Enrolled in LUNA registry.
⇒ Prescription record of ST* and medical record (clinical and laboratory) for ≥3 years from index date (continuous treatment is not required and belimumab use during the follow-up period is permitted).

Exclusion criteria

⇒ Pregnant or lactating during study period (from pre-index date).
⇒ A history of major organ transplant (eg, heart, lung, kidney and liver) or haematopoietic stem cell/marrow transplant before the index date.
⇒ Had been on dialysis within 364 days before the index date.
⇒ Malignancy in active and ongoing treatment with antineoplastic therapies during the study period.
⇒ Diagnosis of biopsy-based active LN class III or IV within 60 days before the index date.
⇒ Enrolment in another study involving investigational study treatment intervention or receival of non-approved treatments (eg, rituximab, anifrolumab and voclosporin) or other biologics during the study period.

Apply to comparison cohort only
⇒ Duplicated registration in the belimumab cohort.

*ST comprises corticosteroids, antimalarials and/or immunosuppressants.
ACR, American College of Rheumatology; LN, lupus nephritis; LUNA, Lupus Registry of Nationwide Institutions; ST, standard therapy.

LUNA inclusion criteria), with a clinical diagnosis of SLE according to the American College of Rheumatology (ACR) criteria,[25] and a history of biopsy-proven active LN (ie, with either LN class III or IV with or without coexisting class V, or pure class V). Included patients will be further categorised by the clinical status of renal activity at index into clinically renal active and renal inactive subgroups. A clinically renal active patient is defined as having at least one positive renal involvement in the four-item Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) instrument score, which includes urinary casts (haemgranular or red blood cell (RBC) casts), haematuria (>5 RBC/high power field (hpf), excluding lithiasis, infection or other cause), new onset of proteinuria/recent increase of more than 0.5 g/24 hours and pyuria (>5 white blood cells (WBCs)/hpf, excluding infection).

Patients who were diagnosed with active LN class III or IV within 60 days prior to the index date will be excluded from the study due to the potential impact on the primary endpoint (occurrence of renal flares).

Data source and collection

Belimumab postmarketing surveillance study

Data for the belimumab cohort will be collected from the postmarketing longitudinal surveillance safety study initiated in December 2017 that is ongoing and continues to enrol Japanese patients with SLE who initiated treatment with belimumab (table 1). Data collection from the postmarketing surveillance study will be abstracted from the individual medical charts of study participants. Most variables required for the MOONLIGHT study were collected for the postmarketing surveillance study, but the following additional variables are also required for the MOONLIGHT study and will be abstracted from patients' medical records after obtaining patient consent: Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI), Physician Global Assessment (PGA) and SELENA-SLEDAI score at month 36, British Isles Lupus Assessment Group (BILAG) category and monthly laboratory data.

LUNA registry

Data for the comparison cohort will be collected from the LUNA registry, a national SLE patient registry established in January 2016 and enrolling patients >20 years, fulfilling ≥4 of the ACR criteria for classification of SLE (table 1).[23 24 26 27] The majority of variables required for the MOONLIGHT study are collected for LUNA; additional data required for MOONLIGHT study as monthly laboratory data and prescription records will be collected from medical charts as a LUNA registry expansion.

MOONLIGHT study variables

For the MOONLIGHT study, the following will be collected from each data source: patient demographics, belimumab treatment, concomitant treatments (ACE inhibitors, angiotensin receptor blockers, anticoagulation and non-steroidal anti-inflammatory drugs), prescriptions of treatments for SLE/LN (corticosteroids and immunosuppressants, including route and dosage), laboratory testing (anti-double stranded DNA antibodies (anti-dsDNA Ab), complement C3/C4, total haemolytic complement CH50, serum creatinine, estimated glomerular filtration rate (eGFR) calculated using the following equation: eGFR (mL/min/1.73^2)=194×sCr (mg/dL)$^{-1.094}$×age$^{-0.287}$×0.739 (if female),[28] albumin, urine protein:creatinine ratio (uPCR) and urine sediment), clinical assessments (SELENA-SLEDAI, PGA and SDI, SELENA-SLEDAI Flare Index (SFI)) and changes in BILAG category. Any renal biopsy, dialysis/kidney transplant, and hospitalisation occurring in the 36 months following the index period will also be recorded (table 1).

Table 1 Data source and collection

Belimumab cohort (variables collected in the postmarketing surveillance study and some additional variables*)	
Patient characteristics (at index)	► Patient demographics and clinical characteristics
Disease activity (at index and months 12 and 36*†)	► SELENA-SLEDAI score ► PGA score ► Occurrence of SLE flares ► SDI score ► BILAG category A/B*†
Concomitant treatment (preindex (6±2 months prior to index), at index and afterwards until month 36 if changed during this period)	► Corticosteroids ► Immunosuppressants ► Antimalarials (dosage and route of administration)* ► ACE inhibitors* ► Angiotensin receptor blockers* ► Anticoagulants* ► Non-steroidal anti-inflammatories*
Laboratory testing (preindex if available, at index and every month until month 36)	► Anti-dsDNA Ab ► C3/C4 and total complement activity (CH50) ► uPCR (preindex if available, at index and monthly afterwards) ► Urine sediment*
Procedure	► Renal biopsy (preindex and after index if records existed)* ► Dialysis/transplant (if records existed)* ► Hospitalisations (if records existed)*
Comparison cohort (variables collected through the LUNA registry at baseline and every 12 months thereafter, ongoing, and some variables collected as a LUNA registry expansion)	
Patient characteristics	► Patient demographics, date of disease onset, comorbidities and concomitant treatments, smoking and drinking habits, medical and reproductive history and blood pressure
Disease activity	► SELENA-SLEDAI score ► PGA score ► SDI score ► BILAG category A/B‡
Concomitant treatment	► Corticosteroid dose ► Immunosuppressant use
Laboratory testing	► Complete blood count ► Biochemical examination ► Urinalysis ► C3/C4 levels ► Anti-dsDNA Ab ► Antiphospholipid antibody

*Variables will be abstracted from patients' medical records after obtaining patient consent.
†BILAG category based on the occurrence of a prescription change related to category A/B, with or without renal involvement and collected during the follow-up period (months 1–36).
‡Variables (BILAG category and monthly laboratory data) will be collected from medical charts as a LUNA registry expansion.
BILAG, British Isles Lupus Assessment Group; C3/C4, complement C3/C4; dsDNA Ab, double-stranded DNA antibody; LUNA, Lupus Registry of Nationwide Institutions; PGA, Physician Global Assessment; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index; uPCR, urine protein:creatinine ratio.

OBJECTIVES AND ENDPOINTS

Primary objective and endpoints

The primary objective of this study is to compare the occurrence of renal flares between belimumab and comparison cohorts over 36 months. Renal flare will be defined by either (1) treatment change using modified BILAG category A (defined as clinical features believed to lead to the prescriptions of medium/large doses of corticosteroids (>20 mg/day prednisone-equivalent) and/or starting or increasing immunosuppressants (ie, antimalarials and immunosuppressants other than corticosteroids), or (2) a conventional definition of renal flare based on proteinuric/nephritic renal flares, with proteinuric flares defined by a persistent increase (≥2 consecutive tests results) of ≥1 g/g of uPCR if the index date-baseline is <0.5 g/g, or doubling of uPCR with values if the index date-baseline is ≥0.5 g/g, and nephritic flares defined by the appearance or recurrence of active urinary sediment (RBC 5 hpf not by menstruation, RBC/WBC casts).[29 30]

Secondary objectives and endpoints

Secondary objectives include the comparisons of the following between belimumab and comparison cohorts: (1) the change in daily corticosteroid (prednisone-equivalent) dose from index at 36 months, including the proportions of patients achieving average prednisone-equivalent dose of ≤5.0 and ≤7.5 mg/day (among patients receiving >5.0 and >7.5 mg/day dose at index, respectively) at 12 and 36 months; change in average daily prednisone-equivalent dose and cumulative prednisone-equivalent dose, from index to 12 and 36 months; time to average prednisone-equivalent dose of ≤7.5 mg/day, among patients receiving >7.5 mg/day dose at index; (2) the change in renal involvement from index at 36 months, assessed by the proportion of patients with improvement and worsening in renal-related items of the SELENA-SLEDAI index score, which include urinary casts (haem-granular or RBC casts), haematuria (>5 RBC/hpf, excluding lithiasis, infection or other cause), new onset of proteinuria/recent increase of more than 0.5 g/24 hours and pyuria (>5 WBC/hpf, excluding infection) from index to 12 and 36 months; (3) the occurrence of new LN class over 36 months, assessed by the proportion of patients with a newly diagnosed biopsy-proven LN class type; (4) the occurrence of ESKD over 36 months, assessed by the proportion of patients with irreversible eGFR <15 mL/min/1.73 m^2, kidney transplantation, permanent dialysis or semipermanent dialysis (>90 days); (5) the change in extrarenal disease activity and organ damage (all non-renal-related items of SELENA-SLEDAI, BILAG or SDI) and overall disease activity from index at 36 months, assessed by change from index in SELENA-SLEDAI score; proportion of patients with improvement and worsening in extrarenal, each organ items and SELENA-SLEDAI score from index; proportion of patients with BILAG category A/B over 36 months; proportion of patients experiencing any moderate or severe SLE flare (severity defined by SFI); and proportion of patients with worsening SDI

score over 36 months; (6) the changes in systemic and renal serological biomarkers from index date at 36 months, assessed by value changes in complement C3/C4, CH50 and anti-dsDNA Ab (systemic biomarkers), and serum creatinine/eGFR and uPCR (renal biomarkers); and the proportions of patients with a 30% and 40% decline in eGFR; (7) hospitalisations over 36 months, assessed by the proportion of patients, with mean number of and duration of renal-related, non-renal-related, SLE-related and all-cause hospitalisations.

Subgroup analyses

Exploratory subgroup analyses will be performed for the primary endpoint and some secondary endpoints (with a population of at least 10 patients). Subgroup analyses defined a priori will include comparison of (1) patients in the belimumab treatment continuous group to the belimumab treatment discontinuous (90 days or more non-prescription/non-use is considered a discontinuation of belimumab) group, (2) renally active (≥1 of the four renal involvement items in the SELENA-SLEDAI instrument score) patients to renally inactive (no items in the SELENA-SLEDAI instrument score) patients at index, (3) immunosuppressant type at index, (4) histological LN classification (based on most recent preindex biopsy) at index and (5) prednisone-equivalent dose category (≤7.5 mg/day vs >7.5 mg/day) at index.

Statistical analyses

Baseline patient characteristics will be summarised using adequate descriptive statistics. For the primary endpoint, the effect of belimumab on the occurrence of renal flares will be analysed using the marginal structural model (MSM).[31] The MSM is an effective method of causal inference that allows for the control of time-dependent confounding variables (refer to online supplemental file 1 for a list of variables) that influence the effect of treatment on flare.[32] The MSM-based causal inference method is a generalisation of the conventional propensity score weighting method using time-varying weights for adjusting the time-varying confounding factors. An MSM based on generalised estimating equation (GEE) logistic regression analyses will be used to address the repeated measured outcomes, applying the weighted estimating equation based on time varying weights.

In addition, cumulative prednisone-equivalent dose from index will be considered as an intermediate variable between the treatment and outcome variables on the causal pathway, and it will be adequately controlled using the MSM.[33] The estimand of the primary analysis will be the causal treatment effect of belimumab that controls the influence of cumulative prednisone-equivalent dose. The controlled direct effect of belimumab treatment on cumulative prednisone-equivalent dose will be estimated.

In addition, for the primary endpoint, sensitivity analyses will be conducted to assess the influence of theoretical assumptions of the causal inference methods, using the following approaches: univariate GEE logistic regression analysis involving only the treatment variables (ie, belimumab or ST); marginal structural GEE logistic regression analysis without controlling the cumulative prednisone-equivalent dose as an intermediate variable (to estimate the total effect of belimumab on the occurrence of renal flare); and marginal structural GEE logistic regression analysis that controls the cumulative prednisone-equivalent dose as a potential time-varying confounding variable (assuming that it is not on the causal pathway). Stabilised weights for the MSM will be used consistently to estimate the controlled direct effect of belimumab, and a standardised mean difference plot will be used to ensure adequate predictive qualities.[31 33 34]

For the primary and secondary endpoints, comparisons will be made between the belimumab and comparison cohorts. For the four corticosteroid endpoints, propensity score weighting analyses will be used to adjust for potential confounding factors, using the ordinary logistic regression model; the variable selection will be the same as for the analysis of the primary endpoint. Time to average prednisone-equivalent ≤7.5 mg/day dose will be compared between belimumab and comparison cohorts using Kaplan-Meier curves and Cox regression.

All missing covariates in the multivariate analyses will be handled by multiple imputations using 200 imputed data generated based on the chained equation.[35] All statistical tests will be performed at significance level 0.05, and confidence levels of confidence intervals will be set to 0.95. Statistical calculations will be performed using R (R Foundation for Statistical Computing, Vienna, Austria).

Sample size/power calculations

As of March 2020, among the 1024 patients with SLE, the number of eligible patients with LN from belimumab postmarketing surveillance study was estimated at around 250, and from the LUNA registry, at around 230.

Based on outcomes from the BLISS-52 trial (GSK Study BEL110752; NCT00424476),[17] and epidemiological data,[36–40] the rate of renal flare was estimated to be 0.05 per year per patient and belimumab can protect 1/4 to 1/3 of placebo/comparison treatment groups. This sample size provides a target power of 80% at a 5% level of significance.

Dissemination

The results of this study will be submitted for publication in relevant peer-reviewed journals and key findings presented at national and international scientific meetings. The study-related information (ie, protocol and results summary, statistical analysis plan and clinical study report) was registered in GSK internal and external public posting (jRCT1031210522 (niph.go.jp)) on 26 December 2021.

Patient and public involvement

Patients and/or public were not involved in the design of this study.

DISCUSSION

The efficacy of belimumab administered alongside induction therapy in a population of patients of varied ethnicities with active LN was previously demonstrated in the BLISS-LN study.[21] The MOONLIGHT study was designed to address the gap in understanding the real-world effectiveness of belimumab when initiated after the induction phase in Japanese patients with a history of biopsy-proven active LN.

Previous studies demonstrated that Asian patients with SLE exhibit higher rates of renal involvement (18%–100%) than Caucasian patients (14%–30%).[4 41] However, higher 10-year survival (overall or renal) rates were reported in Asian patients with LN (81%–98.2%) than in Caucasian patients (68%–92.2%),[42–46] possibly due to the high response rates to immunosuppressive therapies observed in Asian patients with LN.[47–50] In addition, class IV-G LN, which is associated with decreased renal function and higher frequency of nephrotic syndrome (compared with Class III [±V] or V), was found to be the predominant class in Japanese patients, occurring in 31.1% of patients with LN from the Japan Renal Biopsy Registry.[51] In Japan, compared with patients with SLE only, patients with SLE and renal involvement experience poor quality of life[52] and have a significantly greater disease burden, requiring more healthcare resource uses and incurring significantly greater medical costs.[53] Therefore, due to high severity and current knowledge gaps, it is important to examine the real-world effectiveness of belimumab in patients with LN, particularly of Asian ethnicity.

Current treatment guidelines for the management of SLE (and LN) in Japan are similar to the guidelines provided by the British Society for Rheumatology and the European Alliance of Associations for Rheumatology for the ST of LN, including the use of hydroxychloroquine and corticosteroids before the use of immunosuppressants, followed by biologics such belimumab and rituximab.[53–56] Importantly, maintenance therapies such as intravenous cyclophosphamide, oral MMF or oral azathioprine are associated with considerable adverse effects.[57] Prior to the approval of belimumab, common treatment options for patients with LN included MMF or cyclophosphamide in combination with corticosteroids, in the induction phase, followed by lower doses of MMF or azathioprine and tapered corticosteroids in the maintenance phase.[58] Therefore, it is advantageous to assess the effectiveness of belimumab alongside current standard practice, which in Japan also includes tacrolimus and mizoribine,[9] for the treatment of LN in Japanese patients, as well as in the wider population.

Since becoming available in Japan, patients with LN are included in the indicated population for treatment with belimumab.[15 48 57–59] The approval of the use of belimumab in Japan alongside standard induction therapy for LN was based on the recently published phase III BLISS-LN study.[21] However, few studies have evaluated the effect of belimumab when administered during the maintenance phase and later in patients with a history of biopsy-proven active LN. One recent study in patients with SLE, of which just under half had LN class I–V, reported that belimumab, in combination with ST, during maintenance therapy significantly reduced corticosteroid dose and prevented relapse of LN when compared with ST, in a real-world clinical setting.[60]

There remains a knowledge gap on whether belimumab is superior to ST for maintaining the response achieved during induction therapy and preventing renal flares, which is an important goal of maintenance therapy in LN.[8] To address this, the MOONLIGHT study will evaluate the real-world clinical effectiveness of belimumab in combination with ST in Japanese patients with a history of biopsy-diagnosed active LN using real-world clinical data from a nationwide surveillance study and a multicentre registry. The MOONLIGHT study will compare renal and systemic outcomes in patients with LN treated with belimumab and ST with those treated with ST alone, with the primary objective to assess if belimumab is superior to ST in reducing the occurrence of renal flares. Additional important and clinically relevant renal endpoints will also be captured, such as improvement/worsening in urinary casts, haematuria, proteinuria and pyuria, occurrence of new LN class and ESKD, and changes in renal serological biomarkers.

Prolonged use of high-dose oral corticosteroids has been shown to lead to toxicity and organ damage in patients with SLE.[11–13] Over the course of the last decade, belimumab demonstrated a trend towards greater corticosteroid reduction in the SLE trials, which, in part, led to inclusion of a mandatory corticosteroid taper and examination of belimumab's role in reducing corticosteroids in the recent BLISS-LN trial.[16–18 21 61] Current SLE and LN guidelines also recommend therapies that have a corticosteroid-sparing effect.[55] MOONLIGHT will explore corticosteroid endpoints commonly evaluated in clinical trials, such as changes in daily and cumulative corticosteroid doses, and proportions of patients with dose reductions to below 7.5 and 5.0 mg/day, among belimumab-treated and ST-treated patients. Hospitalisations due to renal-related events will also be evaluated. Belimumab's effect on these outcomes will be assessed longitudinally over 3 years of treatment, providing evidence for its enduring effectiveness.

This study will use MSMs to estimate unbiased treatment effectiveness while addressing time-dependent confounding variables (ie, cumulative corticosteroid dose), which conventional statistical analyses, such as regression model adjustment, fail to do. MSMs can be used to account for the relationship between confounding variables and the effectiveness of belimumab, and in this way, a better estimate of belimumab's direct effect can be elucidated.[31 33 34] We will also use a robust renal flare definition, which considers treatment change as a clinically significant decision, for clinically meaningful and reproducible measurement of flares.[59]

Primary limitations of the MOONLIGHT study design include the estimated small population sample

for the belimumab and comparison cohorts, and the high number of patient characteristics with weighting. However, the appropriateness of this weighting will be evaluated during the study analysis. This limits the power to reach statistically significant conclusions. In addition, patients for each cohort will not have been randomly selected from the same overall population, and there may be a population selection bias as eligible patients are restricted to those with ≥3 years of follow-up. Patients who have initiated belimumab treatment may potentially be in the active SLE or LN state, which may lead to the confounding by indication of the observed increased risk of flares; however, this study will attempt to exclude this confounder by including confounders as weighting factors. The duration of exposure to belimumab among patients in the belimumab cohort may differ as patients can initiate or discontinue the treatment after the start of the follow-up period; thus, the patients may not exhibit a true effect of belimumab treatment. Finally, retrospective collection of outcome data may result in missing data, and differences in practice and data collection among study sites may act as potential confounding factors.

To conclude, this study may provide important comparative real-world evidence of the effect of belimumab on risk reduction of renal flare, corticosteroid tapering and other renal parameters following 3 years of treatment, as well as providing a touchstone for evaluating postmarketing treatments for SLE through the use of a nationwide registry.

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Ethics approval This study involves human participants. This study will be conducted according to the Declaration of Helsinki and the local guideline 'Ethical Guidelines for Medical and Life Science Research Involving Human Subjects'. The institutional review board/independent ethics committees' favourable opinion/approval to conduct the study will be obtained before data extraction, if required. For the belimumab cohort, a signed informed consent will be obtained from each patient prior to data collection. For the comparison cohort, signed informed consent will not be required as this study uses LUNA registry data as secondary data. Findings will be submitted to peer-reviewed journals and presented at scientific meetings.

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