Evaluation Of Use of Belimumab in Clinical Practice SEttings (OBSErve)

Observations from Argentina

Amendment # 2; February 15, 2017

Previous version: Amendment # 1; June 29, 2015
STUDY APPROVAL SHEET

Study Name: Evaluation of the Use of Belimumab in Habitual Clinical Practice ("Estudio OBSERVE"). Observations of Argentina

Protocol number: 201282

This retrospective observational study of review of medical records in our country will respect the Helsinki Declaration in force, the guidelines of Resolution 1480/11 of the Ministry of Health of the Nation and the current local regulations applicable to this type of studies. The study will also respect the confidentiality of patient data according to the laws in force in our country and will be approved by an institutional ethics committee. This study has been approved for implementation in Argentina by the following authorities on the date set forth below.

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<th>Institution</th>
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<td>Tel. F. Medical Manager</td>
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REASON FOR THE AMENDMENT:

This amendment is generated to extend the follow-up period from 18 to 24 months after the date of beginning treatment with Belimumab.
Synopsis of the study

Title of the study:

Evaluation of the Use of Belimumab in the Habitual Clinical Practice ("Estudio OBSERVE"). Observations of Argentina.

Objectives of the study:

Overall objective:

• Describe the global patterns of medical care for systemic lupus erythematosus (SLE) and its clinical response in patients treated with belimumab in clinical centers in Argentina.

Primary Objective:

• Describe the overall clinical response after 6, 12, 18 and 24 months of treatment with belimumab.

Secondary Objectives:

• Describe changes of the SELENA SLEDAI score after 6, 12, 18 and 24 months of treatment with belimumab.

• Evaluate the number and severity of outbreaks of the disease at 6, 12, 18 and 24 months after the start of treatment compared to 6 months before treatment.

• Describe the changes in corticosteroid doses after 6, 12, 18 and 24 months of treatment with belimumab and the treatment patterns with concomitant medication. Including percentage of patients who suspend corticosteroids or who require an increase in dose.

• Describe the use of health resources comparing the 6 months prior to the start of treatment with belimumab with 6, 12, 18 and 24 months after the start of treatment.

• Describe the work condition before and after treatment with belimumab.

• Describe the characteristics of patients treated with belimumab including:

  • Reasons for starting treatment with belimumab
• Reasons for the interruption of treatment with belimumab (including the percentage of abandonment of treatment).

• Describe the percentage of use of the different scales of clinical assessment of Lupus (BILAG, SLAM, ECLAM or others) at the time of initial diagnosis.

Study design:

Multicenter, retrospective and observational cohort study of patients with a diagnosis of SLE and to whom belimumab has been indicated, in selected clinical centers in Argentina.

Study populations:

Physician sample: A sample of 12-18 rheumatologists / internists who treat patients with SLE with belimumab as part of their usual medical care will be recruited from clinical centers in Argentina.

Patient sample: A total of 60-80 patient records will be identified for the extraction of anonymized data in the study. The study population consists of adult patients with SLE who have been prescribed belimumab as part of routine medical care (patients who have received it in the context of a clinical trial will be excluded) and ideally have follow-up records during at least 6, 12, 18 and 24 months after the start of treatment or who have stopped belimumab at any time after receiving at least one dose. Patients with different durations of exposure to belimumab will be included in this study. The inclusion of all patients treated at some time with belimumab (at least one dose as part of the usual medical care) in the participating clinical centers will be considered to avoid a selection bias; This may include patients who have received belimumab but have discontinued its use for any reason. It is expected to include a majority of patients who are at least 6 months and up to 24 months of follow-up after the start of treatment with belimumab.

Methods of data collection:

The physicians acting as study investigators (IE) will be given explicit instructions on the identification of clinical records of patients eligible for the study.
The EIs will collect the clinical data in printed data collection notebooks (CRD). The IE will receive instructions on the data collection procedures. The data will be extracted from the clinical histories of the participating clinical centers of Argentina. It will also seek to gather information from other source documents, including recent inquiries, in order to gather as much information as possible. General information about the clinical center of the doctors (for example, the type and size, geographical location, time of professional practice, affiliations, etc.) will be recorded in a Center Feasibility Questionnaire. In the case of printed CRDs, the data entry will be done by the staff of the doctor's center. These data will be used to create a study database for analysis.

**Evaluation criteria:**

The main endpoint of this study is the overall clinical response at 6, 12, 18 and 24 months of treatment with belimumab, presented as a percentage of patients with specific levels of clinical improvement with respect to baseline (index date: start date of the treatment with belimumab), evaluated through a scale similar to the Physician Global Assessment (PGA) that was used in the pivotal studies of belimumab.

The secondary endpoints are:

- Changes in the SELENA-SLEDAI scale, after 6, 12, 18 and 24 months of treatment compared to the score at the beginning of the same.

- Evaluate the number and severity of outbreaks of the disease at 6, 12, 18 and 24 months after the start of treatment compared to 6 months before treatment.

- Changes in the dose of corticosteroids after 6, 12, 18 and 24 months of treatment compared with the dose at the beginning of the same. Including percentage of patients who suspend corticosteroids or who require an increase in dose. The treatment patterns will also be analyzed with another concomitant medication before and after the 6, 12, 18 and 24 months of use of belimumab.

- Utilization of health resources through the comparison of 6, 12, 18 and 24 months after the use of belimumab compared to the previous 6 months. The scheduled and
unscheduled visits to the rheumatologist, other specialists, the guard and the hospitalizations will be analyzed.

• Condition and work absenteeism through the percentage of work-active patients and days of work absenteeism in the 6, 12, 18 and 24 months after the start of treatment with belimumab compared to the previous 6 months.

• Description of the characteristics of patients treated with belimumab through:
  
  o Reasons for beginning treatment with belimumab.
  
  o Reasons for the interruption of treatment with belimumab (for any reason including administrative) in patients who interrupt such treatment (including the percentage of abandonment of treatment).
  
  o Percentage of use of the different clinical assessment scales of Lupus (BILAG, SLAM, ECLAM or others) at the time of initial diagnosis.

Data analysis:
The data will be collected retrospectively (from patient clinical records) for a period of 36 months comprised between 6 months before, 6, 12, 18 and 24 months after the start of treatment with belimumab.

The analyzes will be carried out mainly using descriptive statistical methods. In general, counts and percentages and 95% confidence intervals for categorical data and the mean, median, standard deviation, minimum and maximum for continuous data will be presented. If necessary, additional descriptive statistics can be calculated. In particular, the median and interquartile range for the non-Gaussian distribution data will be calculated. Bivariate subgroup analyzes will be conducted to determine the effects of the patient's and the patient's underlying characteristics on the study's endpoints.

In addition to descriptive information, statistical tests may be performed to provide inferential summaries of comparisons of endpoints between subgroups when relevant patient strata are observed.
Sample size:

Given the descriptive nature of the study, no formal estimates of sample size were made. It is planned to recruit 12-18 rheumatologists/internists in Argentina and 60-80 patients treated with belimumab.

Limitations:

The study population is composed of patients who have been prescribed belimumab shortly after the approval of the drug, in selected clinical centers in Argentina. Extrapolation of results from this patient population to other patients with SLE should be considered with caution. Data on treatment patterns, clinical endpoints and use of health resources represent only the practice of physicians participating in the study and may be different from those of physicians not participating in the study.
Functions and responsibilities of the study

**Scientific Committee of the Study**

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**Study sponsor**

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<td>Adverse event</td>
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<td>AAI</td>
<td>Serious Adverse event</td>
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<td>AINE</td>
<td>Non-steroid anti-inflammatory</td>
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<td>ANA</td>
<td>Antinuclear antibodies</td>
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<td>Anti-ADN-bc</td>
<td>Antibodies anti-double stranded DNA</td>
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<td>BILAG</td>
<td>British Isles Lupus Assessment Group</td>
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<td>BLyS</td>
<td>B cell estimulator factor</td>
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<td>CE</td>
<td>Ethics Committe</td>
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<td>CEIC</td>
<td>Clinical research ethics committee</td>
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<td>CRD</td>
<td>Case report form</td>
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<td>ECA</td>
<td>Randomized clinical trial</td>
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<td>GSK</td>
<td>GlaxoSmithKline</td>
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<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act</td>
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<tr>
<td>IC</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>IE</td>
<td>Study investigators</td>
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<tr>
<td>LES</td>
<td>Systemic Lupus Erythematosus</td>
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<tr>
<td>NC</td>
<td>Confidence level</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<td>PGA</td>
<td>Physician’s Global Assessment</td>
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<td>SLEDAI</td>
<td>SLE Disease Activity Index</td>
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<td>SRI</td>
<td>SLE Responder Index</td>
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<td>TAC</td>
<td>Commercialization owner</td>
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1. Basic information

Systemic lupus erythematosus (SLE or lupus) is a complex and severe rheumatic disease that presents very diverse clinical manifestations. Global advances in medical care, such as the availability of antibiotics, antihypertensives and renal replacement therapy, together with the judicious use of glucocorticoids, antimalarials and immunosuppressants, have led to an increase in the survival of patients with SLE in recent decades. (Trager 2001). Despite advances in medical care, patients often experience long-term morbidity that can adversely affect their quality of life and their ability to work, which entails substantial direct and indirect costs. It is estimated that between 161,000 and 322,000 people suffer from SLE in the United States, which implies an important potential burden for society (Hemlick 2008, Naleway 2005).

Conventional treatments for SLE include corticosteroids (the basis of treatment), antimalarials (eg, hydroxychloroquine), nonsteroidal anti-inflammatory drugs (NSAIDs), cytotoxics (such as cyclophosphamide), and immunosuppressants / immunomodulators used in cancer or cancer transplants (eg, azathioprine, cyclosporine, mycophenolate mofetil [MMF], methotrexate, leflunomide, thalidomide, mercaptopurine) (Reveille, 2001; Petri, 2001; Ruiz--Irastorza and cols., 2001; Chatham and Kimberly, 2001; Wallace, 2002; Brocard and cols., 2005; Houssiau, 2004; Ginzler and cols., 2005). Although CNS vasculitis and active lupus nephritis can usually be controlled with several cycles of high-dose steroids and cyclophosphamide for a period of 1 to 2 years, there is a tendency for progressive disease recurrence over time (Houssiau and cols., 2002; Illei and cols., 2001; Petri, 2001; Ruiz--Irastorza and cols., 2001). These treatments can be associated with important adverse reactions. The long-term use of corticosteroids in high doses can cause significant morbidity consisting of osteoporosis, osteonecrosis, metabolic disorders (including exacerbation of diabetes), increased risk of infections, edema, weight gain and hyperlipidemia (Chatham y Kimberly, 2001). Cytotoxic drugs such as cyclophosphamide are immunosuppressants, which is associated with an increased risk of serious infections and certain cancers.

In recent years there has been a great interest in drugs directed to B lymphocytes for the treatment of inflammatory and autoimmune diseases (Sabahi, 2006). Belimumab (also known as LymphoStat-B; BENLYSTA®) is a specific inhibitor of the B lymphocyte stimulator (BLyS) that blocks the binding of soluble BLyS, a factor of survival of B lymphocytes, to its receptors present in the cells. B lymphocytes. Belimumab does not bind to B lymphocytes directly, but, by
binding to BLyS, inhibits the survival of B lymphocytes, including autoreactive B lymphocytes, and reduces the differentiation of B lymphocytes into plasma cells that produce B cells. immunoglobulins. Belimumab is indicated for the treatment of patients with active SLE who are positive for autoantibodies who are receiving conventional treatment, including corticosteroids, antimalarials, immunomodulators and nonsteroidal anti-inflammatory drugs.

Belimumab administered as an intravenous infusion in patients with SLE has been studied in a phase 1 trial (LBSL01), a randomized, double-blind, placebo-controlled phase 2 trial (LBSL02) and two randomized, double-blind, phase 3 trials. placebo-controlled (BLISS 52 [C1057] and BLISS 76 [C1057]); and in patients with rheumatoid arthritis (RA) in a double-blind, placebo-controlled phase 2 trial (LBRA01). The phase 3 trials of belimumab in SLE ended in 2009. Treatment with belimumab at a dose of 10 mg / kg (given intravenously [iv] every 2 weeks for the first 3 doses and every 4 weeks thereafter ) more conventional treatment demonstrated a superiority over placebo treatment plus conventional treatment in the analysis of the main criterion of effectiveness (response rate), assessed using the SRI (Index of patients with response in the LES), in the week 52 in the two phase 3 studies. Benefit data were also obtained in other clinical endpoints, such as reductions in disease activity measured with the SELENA SLEDAI scale, intense exacerbations, and reduced use of steroids. Treatment with belimumab plus conventional treatment was generally well tolerated, with rates of adverse events (AA), severe AA, severe AA, withdrawal-causing AA, and severe / severe infections generally similar to those seen in the placebo plus conventional treatment (Navarra 2011, Furie 2011).

The belimumab in Argentina began its commercialization in October 2012. Although the clinical efficacy of belimumab has been demonstrated in RCTs, its use patterns and clinical benefit have not been studied in real clinical practice in Argentina. Knowing the pattern of use and results of belimumab could help to promote optimal clinical practices, including the identification of obstacles to adherence to treatment / persistence in patient treatment and the characterization of patients in whom treatment with belimumab could be more beneficial.

The lack of homogeneity in the modalities of evaluation of clinical benefit in SLE may further complicate the demonstration of the clinical benefit of any intervention in SLE (including belimumab) in different clinical centers.
The premise of the proposed observational cohort study of patients treated with belimumab in clinical centers in Argentina is to understand the current healthcare practices in SLE in clinical centers and to study the clinical benefit attributed to belimumab in its first 2 years of use.

2. Study Objectives

**General Objective:**

- Describe the global patterns of medical care for systemic lupus erythematosus (SLE) and its clinical response in patients treated with belimumab in clinical centers in Argentina.

**Primary Objective:**

- Describe the overall clinical response after 6, 12, 18 and 24 months of treatment with belimumab.

**Secondary Objectives:**

- Describe changes of the SELENA SLEDAI score after 6, 12, 18 and 24 months of treatment with belimumab.

- Evaluate the number and severity of outbreaks of the disease at 6, 12, 18 and 24 months after the start of treatment compared to 6 months before treatment.

- Describe the changes in corticosteroid doses after 6, 12, 18 and 24 months of treatment with belimumab and the treatment patterns with concomitant medication. Including percentage of patients who suspend corticosteroids or who require an increase in dose.

- Describe the use of health resources comparing the 6 months prior to the start of treatment with belimumab with 6, 12, 18 and 24 months later.

- Describe the work condition before and after treatment with belimumab.

- Describe the characteristics of patients treated with belimumab including:
  
  • Reasons for starting treatment with belimumab
• Reasons for the interruption of treatment with belimumab (including the percentage of abandonment of treatment).

• Describe the percentage of use of the different scales of clinical assessment of Lupus (BILAG, SLAM, ECLAM or others) at the time of initial diagnosis.

**Research questions:**

The research questions that will be addressed will be the following:

- What is the overall clinical outcome at 6, 12, 18 and 24 months of use of belimumab?
- What is the clinical result assessed through the SELENA-SLEDAI scale at 6, 12, 18 and 24 months of use of belimumab?
- What were the changes in the dose of corticosteroids and in the concomitant treatment after the 6, 12, 18 and 24 months of use of belimumab?
- What is the use of health resources 6, 12, 18 and 24 months before and after treatment with belimumab?
- What is the impact of the use of blimumab on the condition and absenteeism?
- What are the clinical characteristics and baseline demographic data of patients prescribed belimumab in clinical practice?
- What is the history of treatment for SLE immediately prior to the start of treatment with belimumab?
- What is the reason for starting the treatment of patients with belimumab?
- What are the instruments used by rheumatologists / internists to evaluate clinical outcomes in the participating clinical centers?
- What is the percentage and reason for the interruption of treatment with belimumab in patients who interrupt this treatment?
3. Study design

3.1. Basic design characteristics

The study is a multicentric, retrospective and observational cohort initiative. It is designed to gather information from actual clinical practice from the clinical records of patients in relation to the short-term clinical benefit attributable to the use of belimumab in patients with SLE. The index date (or start of treatment) will be defined as the effective start date (first dose) of the treatment with belimumab. The study period includes a treatment history period that includes at least 6 months prior to the index date and a follow-up period of treatment of about 6, 12, 18 and 24 months after the index date. This will provide an observation time of at least 6, 12, 18 and 24 months after the start of treatment for each patient in the study. It is possible that the duration of the follow-up of the different patients is different. The inclusion of all patients treated with belimumab (as part of the usual medical care) in the participating clinical centers will be considered to avoid a selection bias. Therefore, the inclusion of patients who have discontinued treatment with belimumab in the past will be considered.
Follow up period (≥ 6 months, 12, 18 and 24 months)

Index date (belimumab start date)

Retrospective data capture

3.2. **Data domains**

The data domains that will be evaluated through the retrospective review of clinical histories are:

- Characteristics of the doctor’s center.
- Characteristics / demographics and concomitant diseases of the patient.
- Clinical characteristics and evolution of SLE.
- Treatment of SLE, including the use of belimumab, corticosteroids and other concomitant treatments. In cases of abandonment of treatment with belimumab, the causes of suspension will be sought.
- Use of health resources (scheduled and unscheduled visits to the rheumatology office, visits to other specialists, visits to the hospital guard [not scheduled] and hospitalizations).
- Condition and work absenteeism.

The study is designed in a purely retrospective way. Therefore, the start of treatment with belimumab and the respective uses of documented resources must be prior to the study start date. The start date is defined as the day on which the center is initiated after completing the regulatory approval phase that is applicable.
4. Inclusion & exclusion criteria

4.1. Inclusion Criteria of patients

Rheumatologists / internists will select patient records for data extraction; These patients will be considered eligible for inclusion in the study based on the following inclusion criteria:

- Diagnosis of SLE according to the criteria of the treating physician (usually criteria ACR 82/97 and / or SLICC criteria).
- Adults ≥ 18 years of age.
- Initial prescription of belimumab by the attending physician as part of the usual medical care (patients not previously treated with belimumab).
- At the point / time of the investigation, the patient was prescribed treatment with belimumab for at least 6 months and the patient received at least one dose in cases of suspension or discontinuation of treatment.
- The reason for beginning treatment with belimumab can be determined.
- In patients who have discontinued treatment with belimumab, the reason for interruption can be determined.
- The doctor is able to notify the results of the treatment at defined times (eg, 6, 12, 18 and 24 months after the date of treatment initiation or at the time of the suspension of treatment).
- The medical history must be available for the extraction of data from the clinical history according to the study period.

4.2. Exclusion criteria for patients

Physicians will select patient records for data extraction; These patients will be considered unfit for inclusion in the study based on the following exclusion criteria:

- The patient is currently participating in an intervention clinical trial related to SLE.
• The patient has started treatment with belimumab as part of a clinical trial in an intervention group.

4.3. **Physician selection criteria**

The ability of physicians (rheumatologists / internists) to participate in the study will be based on the following general criteria:

- They must currently be treating or treating at least 10 patients with SLE.
- They must have been treating the LES for at least 5 years.
- They should have treated at least 2 patients with belimumab as part of their usual medical care and, if possible, they should currently have at least 1 patient on treatment with belimumab (as part of usual medical care).
- They must accept all the rules of the study, including the resolution of queries for the validation of data.
- They must be validated by the scientific committee of the study.

5. **Study treatment plan**

The study is designed to capture the treatment patterns of real clinical practice for patients with SLE treated with belimumab from 6 months before the date of initiation of treatment with belimumab. No specific treatment plans will be required for patients included in the study other than those indicated in the patient inclusion criteria (ie, having received belimumab as part of usual medical care).

5.1. **Belimumab**

The characteristics of the belimumab treatment plan will be collected from all patients who have received belimumab as part of their usual medical care.
5.2. **Other concomitant medications for SLE**

Information will be collected from the treatment plan for the concomitant medications used to treat SLE during the study period (along with belimumab, as part of usual medical care), with special interest in corticosteroids. Information will be gathered about the drug / class of drug for the SLE, the dose (including modifications) and the frequency of administration. There is no requirement regarding the minimum duration of use of any of these concomitant medications for the LES.

6. **Study Procedures**

6.1. **Selection procedures**

It will undergo a selection process and will be recruited to a sample of about 12-20 rheumatologists / internists who have indicated belimumab, from a list of centers suggested by the study sponsor (GSK). The study provider will document the denials of the doctors and other criteria of non-fitness.

The ability of physicians (rheumatologists / internists) to participate in the study will be based on the criteria indicated in section 4.3 of this protocol.

6.2. **Procedures of study registration**

The doctors’ recruitment will be done by telephone by the study’s provider (after the preselection performed by GSK’s medical teams in Argentina). Physicians must accept all study rules to be eligible to participate in it (including resolving queries for data validation) and to receive retribution for their participation. Before enrollment in the study, physicians will undergo a selection process through a personalized study questionnaire. Once the fitness of the doctors has been confirmed, they will receive specific written instructions on participation and intervention in the study, with detailed information on the selection of patients, the extraction of data from the medical records, the filling in of forms and the contact information of the study administrator for each phase of the study.

Each physician (EI) will be asked to identify the medical records of all patients treated with belimumab fit from their respective centers and to extract data from them to avoid a selection
bias. Only anonymous data will be collected from patients’ medical records. It is expected that the data collection activities will take place during a period of approximately 9 months during the year 2017.

6.3. **Study tools**

**Tool #1: Feasibility form**

Once the doctors have been selected to determine their aptitude for the study, that is, they meet the selection criteria, they will be asked to complete the feasibility form for each participating doctor. The information in this form will gather general information about the physician’s center and its treatment strategies for the LES. It is expected that this instrument will not be extensive and it is estimated that it will take approximately 10 minutes to complete it. At a minimum the following data will be collected (in relation to the doctor):

- Type of center: in particular, whether it is an individual office or a poly-consulting or clinic-Hospital, number of doctors, specialties represented, time of professional practice.
- Volume of patients: total number of patients, number of patients with SLE and number of patients to whom belimumab has been indicated.
- Strategies for the treatment of SLE: systematic use of clinical analyzes and assessments of disease activity, establishment of treatment objectives and inclusion of patients in the clinical decision-making process.

**Tool # 2: CRD of patient treated with belimumab**

The second research instrument that will be developed is the CRD, which will be used to collect anonymized data from the clinical records of patients treated with belimumab who are suitable for the study. This CRD will be used to document data related to treatment, clinical results and the use of health resources of these patients. IE will be instructed to assign an exclusive identification code to each patient enrolled in the study. This CRD will contain the following general data domains:

- Demographic data of the patient (age, sex, race / ethnic group, weight, work).
- Patient characteristics (concomitant diseases).
• Characteristics of SLE (time elapsed since diagnosis, intensity of the disease measured through different scales including SELENA SLEDAI, clinical manifestations) at the beginning of treatment with belimumab.
• Clinical results in relation to clinical manifestations, assessments of the intensity of the disease (if available) and the overall clinical response according to the doctor's criteria (6 and / or 12 and / or 18 and / or 24 months after the start of treatment).
• Characteristics of treatment with belimumab including use of corticosteroids and other concomitant medications and reasons for discontinuation of treatment as applicable.
• Use of health resources in the 6 months prior to the start of treatment with belimumab and for about 6, 12, 18 and 24 months of follow-up.
  o Office visits scheduled and not scheduled, visits to specialists and visits to the hospital.
  o Hospitalizations, visits to emergency services, clinical analysis.
  o History of treatment of SLE (drug / pharmacological group, dose, frequency and route of administration).
  o History of treatment for disorders other than SLE (indicators to indicate the use of drugs in a specific time frame).
6.4. **Study withdrawal**

The participating IE can withdraw from the study at any time.

Due to the retrospective nature of the data collection (anonymized) of the study using only patient records, they will have already received treatments for SLE (including belimumab) as part of routine medical care, and the study protocol does not establish any treatment model. A review by the CE / CEIC accompanied by an exemption from obtaining the patient's consent will be requested. Given the nature of this design of observational study, the withdrawal of patients from the study is not applicable in the centers where CEIC is obtained exemption from obtaining the consent of the patient. In centers in which the consent of the patient is required, the patient may withdraw his consent and, therefore, withdraw from the study at any time, without this decision affecting the medical care he is receiving for the LES.

7. **Adverse event reporting**

Notification to GSK of information regarding safety

7.1. **Definitions**

- **Adverse event**: any harmful, unwanted response related to the use of a medication.

- **Serious adverse event**: adverse event that causes death, can endanger life, requires hospitalization of the patient or prolongation of hospitalization, causes disability or persistent or important disability or is an anomaly or congenital defect. For notification purposes, suspicions of serious adverse events that are considered important from the medical point of view, but that do not meet the above criteria, for example, those that endanger the patient or require intervention, will also be treated as such. to prevent one of the previous outcomes and all cases of suspected transmission of an infectious agent through a medication.
7.2. Notification

During the clinical study, if the investigators identify an adverse event (AD) or a serious adverse event (EAS) that meets the following criteria:

El evento se manifieste en un paciente identificable individual.

a) It takes place while the patient receives a GSK product.

b) Is notified by a source (for example, health professional).

c) There is a reasonable belief that the product / drug / vaccine caused the event (attribution of causality by the health professional, the study researcher or the GSK doctor).

They must complete the EA / EAS report form and send it by mail to the Medical Department of GSK Argentina in less than 24 hours after they became aware of it.

If during the review of medical records you are aware that a patient, while pregnant, has been exposed to a product of GSK, you must notify this circumstance to the medical department of GSK Argentina within 24 hours of being aware of it. Pregnancy cases will be reflected in specific forms.

Only EA, EAS, pregnancy reports that are explicitly attributed to GSK products should be collected.

7.3. Report to GSK of safety data

Suspects of serious adverse events should be notified to the Pharmacovigilance Unit in the specific notification form by sending them by email to:

GSK Medical Department

e-mail: PPD
8. Statistical analysis and valuation criteria

8.1. Primary endpoint

The primary endpoint of this study is:

- Overall clinical response to 6, 12, 18 and 24 months of treatment with belimumab, reported as a percentage of patients with specific levels of clinical improvement with respect to baseline (index date or start of treatment), assessed through a scale similar to the Physician Global Assessment (PGA) that was used in the pivotal studies of belimumab.

The secondary endpoints of this study are:

- Changes in the SELENA-SLEDAI scale, evaluated as a score after 6, 12, 18 and 24 months of treatment compared to the score at the beginning of the same.

- Evaluate the number and severity of outbreaks of the disease at 6, 12, 18 and 24 months after the start of treatment compared to 6 months before treatment, using the BLISS study outbreak criteria.

- Changes in the dose of corticosteroids after 6, 12, 18 and 24 months of treatment compared with the dose at the beginning of the same. Including percentage of patients who suspend corticosteroids or who require an increase in dose. The treatment patterns will also be analyzed with another concomitant medication before and after the 6, 12, 18 and 24 months of use of belimumab.

- Utilization of health resources through the comparison of 6, 12, 18 and 24 months after the use of belimumab compared to the previous 6 months. The scheduled and unscheduled visits to the rheumatologist, other specialists, the guard and hospitalizations will be analyzed.

- Condition and labor absenteeism through the percentage of active labor patients and days of absenteeism in the 6, 12, 18 and 24 months after the use of belimumab compared to the previous 6 months.
• Description of the characteristics of patients treated with belimumab through the following variables:

  o Reasons for the start of treatment with belimumab and the reasons for discontinuing treatment with belimumab in patients who discontinue such treatment (including the percentage of abandonment of treatment).

  o Percentage of use of the different clinical assessment scales of Lupus (BILAG, SLAM, ECLAM or others) at the time of initial diagnosis.

8.2. General Considerations

The primary and secondary objectives are descriptive in nature and will be treated by collecting the variables indicated in the data domains section.

The extraction of the data from the medical records will be done by the doctors who care for the patients; in this way, the possible limitation of the study that is normally observed in other studies of review of clinical histories in which the information can be interpreted incorrectly is eliminated. In case an electronic data collection tool is used, logical verifications will be programmed in the tool that will minimize the incidence of variables with atypical data, as well as the loss of information of the key data variables.

A study database will be generated with records for each patient. All the analyzes will be carried out in a combined manner (pooled analyzes that will include all study centers) and will be notified in the same way. A first analysis of the data will be performed, including follow-up up to 6 months after the start of treatment, a second subsequent analysis that will include follow-up up to 12 months after the start of treatment and a third subsequent analysis that will cover the follow-ups of 18 and 24 months after the start of treatment.
8.3. **Sample size**

Given the descriptive nature of the study, no formal estimates of sample size were made. In the participating study centers, data from 60 to 80 clinical histories of patients eligible for the study will be extracted.

8.4. **Statistic analysis**

The analyzes will be carried out mainly using descriptive statistical methods. We will consider a safety population that will include all patients who have received at least one dose of medication and one population per protocol that will include all patients who have completed 6, 12, 18 and 24 months of treatment with belimumab. The safety population will be used to describe the baseline conditions, collect the potential adverse reactions to the medication according to what is stated in section 7 and to determine the percentage of patients who abandon the treatment. The population per protocol will be used for the assessment of the primary and secondary objectives of response at 6, 12, 18 and 24 months of treatment. In general, counts and percentages and 95% confidence intervals for categorical data and the mean, median, standard deviation, minimum and maximum for continuous data will be presented. If necessary, additional descriptive statistics may be calculated. In particular, the median and interquartile range for the non-Gaussian distribution data will be calculated. Bivariate subgroup analyzes will be conducted to determine the effects of the patient's and the patient's underlying characteristics on the study's endpoints.

The main subgroups that will be analyzed, in addition to the total population per protocol, will be the following:

- Subgroups of High Illness Activity ("High Disease Activity" or "HDA") at the beginning of treatment, defined as:
  
  a) Low complement and High Anti-DNA-dc. Or
  
  b) SELENA SLEDAI> 10. or
  
  c) Corticosteroids ≥ 7.5mg / day.
Clinical effect on the five most frequent manifestations of disease: Arthritis, skin rash; Fatigue; Under Complement; Elevation of the anti DNA-ds.

Subgroups according to educational and socio-economic level.

In addition to descriptive information, statistical tests may be performed to provide inferential summaries of comparisons of endpoints between subgroups when relevant patient strata are observed, such as the baseline intensity of the disease or specific demographic data. The t test for two samples, the analysis of variance (ANOVA) or the Mann-Whitney test for quantitative variables as appropriate, and the chi-square test or Fisher's exact test for qualitative variables may be used. Or use tests for paired data if applicable. For multiple comparisons (> 2) the Kruskal-Wallis test or the corresponding one may be applied.

The possibility of multivariate analysis may be considered to identify factors that influence specific treatment outcomes, if the sample size allows such evaluations.

The possibility of using relevant statistical software (such as SAS or SPSS) to support the planned analyzes will be considered.

Anonymized patient data obtained in this OBSErve initiative in Argentina may be combined with similar OBSErve study data / protocols from other countries (such as the United States, Canada and Germany) to perform a combined multinational assessment.

9. Study administration

9.1. Informed Consent

Due to the nature of the collection of anonymized data (retrospectively) from patient medical records in which the confidentiality of information will be respected according to local laws for the protection of personal data and in accordance with resolution 1480 / 11 of the Ministry of Health of the Nation, it will not be necessary to obtain the informed consent of the patient unless the intervening ethics committee so requires. In these cases, the clinical research ethics committee (CEIC) of the principal investigator will be consulted to confirm this exemption.
situation. If in any of the participating centers it is considered necessary to obtain the patient's consent to facilitate the extraction of data from the medical records, the IE (or its staff) will be instructed to carry out the necessary process of obtaining the patient's consent before start collecting data.

9.2. **Review and approval by the clinical research ethics committee**

Because it is a retrospective observational study, review of medical records, which will respect the confidentiality of information according to local laws for the protection of personal data, as indicated in resolution 1480/11 of the Ministry of Health of the Nation and the 6677/10 provision of the ANMAT this study does not require the approval of the national regulatory authority for application, but it is necessary to obtain approval from an ethics committee before its initiation.

We plan to carry out the study in accordance with the standards of good pharmacoepidemiological practice.

The study is designed in a purely retrospective way. Therefore, the initiation of treatment with belimumab and the respective uses of documented resources must be prior to the date of review of the source documents. The start date is defined as the day on which the center is initiated after completing the regulatory approval phase that is applicable.

9.3. **Confidentiality of patients**

Information on the identity of patients will be considered confidential for all purposes and purposes. The identity of the patients will not be disclosed or published under any circumstances. The data of the patients registered in the CRD will be documented anonymously, coded with a patient number so that only the researcher and the staff of the center can associate specific data with an identified or identifiable person or with their clinical history. All other parties involved in the administration, analysis and preservation of the data will receive, and subsequently analyze, non-identifiable patient data. All the regulations in force in our country regarding the protection of personal data will be complied with.
9.4. **Collection and administration of data**

The study sponsor will prepare a Feasibility Form and a CRD in collaboration with the study provider. The Feasibility Form and the CRD will be used by physicians to gather information pertinent to this study.

The doctors will complete the printed CRD. All data will be collected anonymously. Internet-based research tools will also be tested in advance. For the collection of data, physicians will extract from the clinical histories the clinical data related to the treatments and results of interest. CRDs completed manually will be returned in sealed envelopes to the study provider. All CRD data (on paper) will be combined for the final analysis of the study.

With respect to the raw database, patient data will be anonymized and delivered in the format preferred by the promoters. In particular, the delivery of the raw database will be accompanied by a schema of the data fields that will contain a detailed description of each data field. This database will reside on the studio provider’s server for a maximum of two years unless otherwise required.

The participation of physicians is an important and essential feature of the study. Physicians are recruited to participate in the study with the understanding that they will act as study investigators with responsibility in the selection of patients, the extraction of data from medical records and the validation / resolution of the data (if necessary). This responsibility and direct participation of physicians improves the quality of the data by minimizing inaccurate, omitted or incomplete data and the incorrect interpretation of the data that often occurs in this type of studies. However, if the doctor does not have time to collect data / extract data from the medical records, the center's support staff can be used for some parts of the data collection tasks.

The recruitment of the study centers and the extraction of data from patients' medical records will be closely monitored to reach the proposed sample sizes. The study physicians will be asked to extract the data from the medical records of all patients treated with belimumab suitable for the study in their respective centers. The study provider will follow up with the centers during the data collection process when appropriate to ensure a rapid completion of the data collection process.
9.5. **Risks**

This study is a retrospective observational review of medical records. The study protocol does not establish any direct intervention of patients (prospectively) in relation to clinical analyzes, explorations or pharmacological treatments. Patients will not be exposed to any additional risk for participating in the study, since the inclusion in it does not imply any additional action of an evaluative or therapeutic nature.

9.6. **Premature termination of study center**

After center / EI recruitment, if an EI can not complete the assigned study tasks (including data extraction through the printed CRD), the EI and the center's participation in the study may be terminated prematurely.

9.7. **Record keeping**

The IE will keep all original records and documents related to the study. They shall be kept for the maximum period required by the national standards and the center in which the study is conducted or during the period specified by the promoter at the time of completion, premature termination or interruption of the study, whichever is longer.

If the IE leaves the center, the records will be transferred to an appropriate designated person who accepts responsibility for the preservation of records. The notice of such transfer will be documented in writing and sent to the developer.
10. Bibliography


