Protocol

Study ID: 216989

Official Title of Study: LUNELORD: A descriptive, prospective study to assess demographic, pharmacologic, biomarker, clinical features and QoL of patients with LUpus NEphritis and Long-term ORgan Damage

NCT number: NCT04971590

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NON-INTERVENTIONAL STUDY PROTOCOL

UNIQUE IDENTIFIER	oneCDP: 216989
TITLE	LUNELORD: A descriptive, prospective study to assess demographic, pharmacologic, biomarker, clinical features and QoL of patients with LUpus NEphritis and Long-term ORgan Damage
STUDY ACCOUNTABLE PERSON	PPD
CONTRIBUTING AUTHORS	PPD Dr. PPD Prof. PPD PPD (Phoenix CRO)

ASSET ID	Belimumab
GSK ASSET	Belimumab (Benlysta®)
INDICATION	Lupus Nephritis, systemic lupus erythematosus
PHASE OF DEVELOPMENT	Not applicable

REVISION CHRONOLOGY:

Date	Version	Change(s) since last version
01-03-2021	Original (version 1.0)	N/A
21-03-2021	Version 2.0	Adjusted the protocol based on the comments received from PRC. The PRC comments and

		revisions are provided on the portal.
28-03-2021	Version 3.0	1) Added objective for exploratory analysis of physician profile and treatment. 2) Clarified second secondary objective in section 4.43 on how to proceed with the analysis. 3) In section 3.2.2 clarified the routine laboratories results that will be collected in the prospective and retrospective.
28/06/2021	Version 4.0	1) On page 1 the title on the header should be written as “Non-interventional Study Protocol” 2) For the protocol synopsis on page 9 the correct title is “LUNELORD: A descriptive, prospective study to assess demographic, pharmacologic, biomarker, clinical features and QoL of patients with LUpus NEphritis and Long-term ORgan Damage.” 3) In Appendix 5 on page 48 the title should be “LUNELORD: A descriptive, prospective study to assess demographic, pharmacologic, biomarker, clinical features and QoL of patients with LUpus NEphritis and Long-term ORgan Damage.” 4) Added clarification for inclusion criteria.

SPONSOR SIGNATORY

Dr. Averyan Vasylyev
Medical Director, Gulf

Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:

Investigator Signature

Date

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ABBREVIATIONS

ACR	American College of Rheumatology
ADARRC	Advanced Academic Rheumatology Review Course
AE	Adverse event
anti-dsDNA	Antibody to double-stranded DNA test
Anti-Rib	Antibody to ribosomal P protein
Anti-Scl-70	Anti-topoisomerase I antibody
anti-Sm	Antibody smooth muscles
anti-U1-RNP	Anti-ribonucleoprotein
ARA	American Rheumatism Association
ASE	All subjects enrolled
C3/C4	Complement components 3 and 4
CI	Confidence interval
CRO	Clinical research organisation
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ESR	Emirates Society for Rheumatology
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ESRD	End-stage renal disease
EULAR	European League against Rheumatisms
GFR	Glomerular filtration rate
GP1	anti-beta 2 glycoprotein 1
GPP	Good Pharmacoepidemiology Practice
GSK	GlaxoSmithKline
HCRU	Healthcare resource utilisation
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
ICU	Intensive care unit
IEC	Independent ethics committee
IHD	Individual human data
IRB	Institutional review board
ISN/RPS	International Society of Neurology and the Renal Pathology Society
KAR	Kuwait Association of Rheumatology
LN	Lupus nephritis
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drug
ORS	Orthopaedic Research Society
PPPF	Physician practice profile form
QoL	Quality of life
SAP	Statistical analysis plan
SDI	SLICC/ACR damage index
SELENA	Safety of estrogens in lupus national assessment
SF-36	36-item short form health survey
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus disease activity index

SLEDAI-2K	Systemic lupus erythematosus disease activity index 2000
SLICC	Systemic Lupus International Collaborative Clinics
sPVP	Specific pharmacovigilance plan
TNF	Tumour necrosis factor
UPCR	Urinary protein to creatinine ratio
WHO	World Health Organisation

TRADEMARK INFORMATION

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36-Item Short Form Health Survey (SF-36): used with the permission of RAND corporation
SLEDAI-2K from Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29(2):288-91. PMID: 11838846.

PROTOCOL SUMMARY

Title	LUNELORD: A descriptive, prospective study to assess demographic, pharmacologic, biomarker, clinical features and QoL of patients with LUpus NEphritis and Long-term ORgan Damage
Rationale	Systemic lupus erythematosus (SLE) is a potentially serious, chronic, autoimmune disease, which can affect multiple organs of the body, including the kidneys (lupus nephritis). The high variability and its unpredictable course (flaring/remission), combined with a lack of indicated and integrated treatments, induce a high unmet need within the patient population. Reliable data on LN-related care patterns and resource utilisation in 5 countries in Arabian Gulf (UAE, Kuwait, Qatar, Bahrain, and Oman) region are currently unavailable. The expected key outcomes of this study will be: • Description of clinical characteristics, demographics, and health-related quality of life (HRQoL) of LN patients. • Description of "real-world" standard of care and healthcare resource utilisation (HCRU) associated with LN in the Gulf countries: Bahrain, Kuwait, Oman, Qatar, and United Arab Emirates. The information collected may be used for scientific communication among the expert/physician community and payers with the aim to enhance medical care of lupus nephritis. The study protocol is designed to obtain an accurate, "real-world" picture of LN patients in the Gulf countries.
Study Objectives	• **Primary:** Describe demographics, clinical characteristics, comorbidities, treatments and HRQoL of LN patients across 5 Gulf countries. • **Secondary:** o Describe refractory LN cases, involving rituximab, and to assess changes in serological markers of disease activity (including autoantibodies and complement levels) over the treatment period. o Assess the association between clinical factors, biomarkers, treatment and renal remission. o Assess impact of LN on HRQoL over a one-year period after diagnosis or enrolment. o Describe LN HCRU and direct medical cost, associated with LN management across 5 Gulf countries over a one-year period. o Exploring the difference in treatment patterns by physician profile (physicians in private versus public hospitals).
Study Design	This is a multicentre prospective study with a patient-completed survey and retrospective chart review component. This study will enrol approximately 200 patients with clinician diagnosed LN cases. Staff at participating sites will review their LN patients' medical charts to identify potentially eligible patients who meet the study's preliminary selection criteria. Identified patients who are potentially eligible will be contacted by trained site staff via phone, or approached onsite at the patient's routine care visit, if the visit falls within the study enrolment timelines. When approaching the patient, site staff will review the main study informed consent form (ICF) with patients, explain the study purpose and design, which will include a prospective survey as well as a one-time retrospective data abstraction from their medical chart. Additionally, site staff will answer any questions patients may have about the study. Patients will be asked to confirm their consent to participate in the study by signing the informed consent. • A retrospective phase to collect data from diagnosis or up to one year before enrolment, and • A prospective arm consisting of 5 visits as per routine care of a LN patient: o Visit 1: enrolment o Visit 2: 3-month follow-up after Visit 1 o Visit 3: 6-month follow-up after Visit 1 o Visit 4: 9-month follow-up after Visit 1

	○ Visit 5: last 12-month follow-up visit after Visit 1
Study Population	• **Inclusion criteria:** ○ ≥age of 18 years ○ Clinician diagnosed LN patient per physician's discretion ○ At least one visit to the investigational centre, recorded in medical documentation, during the past (12) twelve months prior to enrolment date ○ Literacy in English or Arabic allowing to fully comprehend the written informed consent and study-specific patient reported questionnaires ○ Written informed consent by the patient • **Exclusion criteria:** ○ Incomplete medical records to be able to assess the disease severity or absence of any of the following renal laboratory results from the medical record within the last (12) twelve months: ○ Urinary protein to creatinine ratio (UPCR) or 24-hour proteinuria or urine sediment (activity) ○ Serum creatinine or estimated glomerular filtration rate (eGFR); or measured glomerular filtration rate (GFR), if eGFR is not available ○ Current or medical history of: ○ Congenital or acquired immunodeficiency ○ Malignancy in active treatment phase ○ Acute viral infection, such as HIV infection, requiring hospitalisation
Study Duration	• **Retrospective arm**: medical chart review from diagnosis or up until 12 months prior to enrolment • **Prospective arm:** 12 months after enrolment
Data Collection	• **Retrospective data collection - medical chart review from diagnosis or up till 12 months prior to enrolment** ○ Basic patient demographic characteristics (gender, race/ethnicity, BMI, date of first SLE manifestation, date at SLE diagnosis, date at first LN manifestation, date at LN diagnosis, date at last visit in 2020) ○ LN/SLE treatment medications, including starting dose, current dose, date of treatment start and end, dose at cessation and reasons for medication choice (medications limited to NSAIDs, antimalarials, corticosteroids, immunosuppressants/cytotoxics and biologics) ○ LN treatment history (most recent induction regimen, number of prior treatment failures/relapse(s) [if any], ESRD, and dialysis [current/past and type], listed for transplant/prior transplant conducted) ○ Most recent LN classification including class and histological activity/chronicity based on most recent biopsy (International Society of Neurology and the Renal Pathology Society [ISN/RPS] or World Health Organisation [WHO] classification) ○ LN clinical manifestations ○ Comorbidities (such as antiphospholipid syndrome/thrombotic microangiopathy, obesity, cardiovascular disease, diabetes) ○ Renal laboratory assessments (such as UPCR or 24-hour proteinuria or urine sediment [activity], serum creatinine, and eGFR or measured GFR, if eGFR is not available) ○ Most recent serological findings (such as anti-phospholipid antibodies [anticardiolipin, anti-beta 2 glycoprotein 1 [GP1] and lupus anticoagulant], anti-C1q, low-complement [C3/C4] and positive anti-double-stranded-deoxyribonucleic acid [anti-dsDNA]) ○ Other laboratory tests (haematology, liver function tests, lipid profile, and plasma albumin) ○ Active non-renal clinical manifestations of SLE (such as mucocutaneous, central nervous system, constitutional, cardiopulmonary, gastrointestinal, hematologic, musculoskeletal, vasculitis) ○ Most recent total Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), such as SLEDAI or SLEDAI-2K

	○ Renal remission defined as proteinuria of <0.7 g/d or <0.5g/d or per physicians' discretion • **Prospective data collection from enrolment or diagnosis of LN (0, 3, 6, 9, 12 months)** ○ HRQoL using 36-Item Short Form Health Survey (SF-36) at enrolment (Visit 1) and at 12 months of follow-up (Visit 5) ○ Clinical manifestations at period start with clinical improvement/ worsening assessment at period end ○ Changes in disease activity assessment tools used ○ Any cases presented with refractory LN (defined as inefficacy of cyclophosphamide, use of rituximab, splenectomy, or inefficacy of ≥2 immunosuppressives (methotrexate, leflunomide, abatacept, anti-TNF, azathioprine, mycophenolate mofetil, and/or mycophenolic acid) ○ Renal remission identified (defined as proteinuria of <0.7 g/d or <0.5g/d or per physicians' discretion) ○ Biopsies requested ○ Changes linked to the primary treatment of the disease ○ Renal laboratory assessments (such as UPCR or 24-hour proteinuria or urine sediment [activity], serum creatinine and eGFR or GFR, if eGFR is not available) ○ Most recent serological findings (such as anti-phospholipid antibodies [anticardiolipin, GP1 and lupus anticoagulant], anti-C1q, low complement [C3/C4] and positive anti-dsDNA) ○ Other laboratory tests (haematology, liver function tests, lipid profile, and plasma albumin) ○ HCRU (number of laboratory tests, number of dialyses and use of imaging techniques, ICU hospitalisations/hospitalisations, outpatient visits)
Statistical Methods	Continuous numeric variables will be summarised using the mean, ±standard deviation, median, interquartile range, minimum and maximum. Categorical variables will be summarised using frequency distributions. • **Primary objective:** summary statistics will be used to describe patient profile, demographic features, clinical manifestations, comorbidities, severity, treatments and HRQoL of LN patients across 5 Gulf countries. • **Secondary objective 1:** summary statistics will be used to describe refractory LN cases and the independent t-test or Wilcoxon signed rank test along with repeated measures analysis will be used to test for changes in serological markers of disease activity at one year and over the treatment period. Changes in categorical variables at one-year period will be tested using the McNemar's test. • **Secondary objective 2:** univariate and multivariate logistic regression with renal remission as the dependent variable and clinical factors and treatment as the independent variables. Odds ratios and 95% confidence intervals (CIs) will be presented. • **Secondary objective 3:** paired t-test on the HRQoL scores at enrolment and at one year, or Wilcoxon signed rank test for non-normal distribution. Repeated measures will be used to assess changes over time. • **Secondary objective 4:** for each country, the average HCRU and direct medical cost will be estimated along with its 95%CI. • **Secondary objective 5**: Exploratory analysis of the differences between physician profile and treatment.
Sample Size and Power Calculations	200 patients, a statistical test will ensure the sample size calculation is powered to generate the data. The sample size calculation was computed by PASS® version 2019.

1. BACKGROUND AND RATIONALE

Systemic lupus erythematosus (SLE or lupus) is a complex and severe rheumatic disease with exceedingly diverse clinical manifestations, including renal manifestations. Renal involvement is a frequent aspect of SLE, as 40–75% of SLE patients develop lupus nephritis (LN), most often within five years of the disease onset (1), although some patients do develop this complication later (2).

The risk of developing LN is higher among men, young people, and people of non-European ancestry (3). This risk varies significantly between different regions of the world and different races and ethnicities. For example, black and Hispanic SLE patients develop LN earlier, and have worse outcomes than white patients with SLE, including death and end-stage renal disease (ESRD) (4). As for Arab SLE patients, LN seems to be common and occurring in 37–69% of SLE patients in the Arab dominated groups, particularly among those from Saudi Arabia, and in 50% of the exclusively Arab group (1). Also, LN is more common in patients with anti-dsDNA and it is less frequent in those with positivity for rheumatoid factor and discoid manifestations (2).

LN is recognised as a major cause of morbidity, mortality, health expenditure, and impaired quality of life (QoL) in patients with SLE (1). However, an early diagnosis and treatment are associated with a better prognosis (2). In many patients, LN ends in chronic kidney disease or ESRD despite potent anti-inflammatory and immunosuppressive therapies (4). Also, patients with LN have a higher standardised mortality ratio (6–6.8 versus 2.4) and die earlier than SLE patients without LN (4). Importantly, 10-year survival improves from 46% to 95% if disease remission can be achieved (4). Despite the improvements in care, LN patients often suffer long-term morbidity that can adversely affect their QoL and ability to work (5), resulting in substantial direct and indirect costs. Patients with flares incur higher direct and indirect costs as compared to those without flares. Flares in major organs such as kidneys increase disease costs much more than other organ flares. The high costs associated with LN flare may be reduced by treatments that effectively control disease activity and prevent major organ flares (6,7). Thus, due to both direct and indirect costs, LN leads to a very high burden of disease. Improvement in disease activity and physical health, and prevention of organ damage, may reduce direct and indirect costs in SLE and LN (6,7,8,9,10,11).

LN can be asymptomatic or “silent” (detected by routine renal biopsy), or presenting with trace proteinuria or active urinary sediments (microscopic haematuria, pyuria or cellular casts), or with serious proteinuria (nephrotic syndrome) and acute nephritic syndrome with rapid progression to acute renal failure (5). LN evaluation consists of assessing serum creatinine level, urine dipstick testing, and urine sediment examination (3). Many patients will have findings suggestive of LN at the initial diagnosis of SLE, and patients with SLE should undergo screening for LN at diagnosis, at least yearly thereafter, and any time there is concern for a lupus flare (3). Furthermore, renal biopsy is the gold standard diagnosis and histological classification of LN (3,5). A complete staining pattern for LN consists of finding positive staining for immunoglobulin (Ig) G, A, and M with C1q, C3, and C4 (5). Moreover, patients with LN that is refractory to treatment should be evaluated for other possible causes for the persistence of proteinuria or deterioration in renal function. These include the nephrotoxic side effects of medications (such as the calcineurin inhibitors and nonsteroidal anti-inflammatory drugs [NSAIDs]), renal vein thrombosis, infections, over diuresis, and poorly controlled hypertension. Treatment compliance

should be checked. To help guide further treatment decisions, a repeat renal biopsy should be considered in patients with persistently active serological markers (5,12). Indeed, a second biopsy provides information on: 1) the histological transformation of LN classes; 2) the degree of residual activity in the kidneys; and 3) the extent of chronic irreversible changes and their progression since the initiation of immunosuppressive treatment (5).

To help physicians in diagnosis and care management, new guidelines and recommendations for the management of LN have been proposed by the European League Against Rheumatism (EULAR) and European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) in 2020 (12). Beside the EULAR recommendations, other parameters may be considered such as: patient education, coexisting morbidities, fibromyalgia, stress reduction, and many organ specific complications and aspects of SLE (e.g. autoimmune haemolytic anaemia, and screening for pulmonary hypertension) (13). Patients are usually followed up by rheumatologists and nephrologists in hospital-based physicians in specialised SLE centres (14).

As for the treatment of LN, it depends on disease severity and risk for progressive kidney damage (3). A conservative treatment is used for the non-proliferative forms of LN (class II and V with sub-nephrotic range proteinuria and normal glomerular filtration rate), with treatment focused on blood pressure control with renin-angiotensin system blockade and immunomodulation with antimalarials (e.g. hydroxychloroquine) (3). As for immunosuppressive agents, these are used as needed to treat extrarenal manifestations only. In addition to antimalarials and renin-angiotensin system blockade, proliferative forms of LN (class III, IV, or III/IV+V) and class V with nephrotic syndrome are treated with systemic immunosuppression combined with high-dose corticosteroids to suppress inflammation and control autoimmunity (3). This induction phase of treatment generally lasts 3–6 months and is followed by a prolonged, but less intense maintenance phase, often lasting years. It is not clear when maintenance therapy can be withdrawn. A repeat kidney biopsy showing histologic remission during maintenance in LN patients who have achieved complete clinical remission, or who have stable but persistent proteinuria, may help in making a decision to taper off therapy (4). During the maintenance phase, immunosuppressive/cytotoxic agents are continued but de-escalated slowly over time to limit risk for LN flares. Biological drugs developed more recently show interesting beneficial effects in LN (4). They decrease the level of B lymphocytes which contributes to the decrease in autoantibodies known to play the central role in disease activity and consequently decrease the global inflammation level (15).

There is a paucity of data in the Gulf countries on LN care management (treatment strategies, healthcare pathways, healthcare resource utilisation [HCRU] and costs), especially in moderate and severe cases. In this context, GSK has decided to carry out an observational study mainly to characterise LN patients in 5 Gulf countries who may benefit from early intervention. Also, in order to have an accurate estimation of the costs of LN care management. This study aims at evaluating disease costs according to patients' profile.

1.1. Rationale

SLE is a potentially serious, chronic, autoimmune disease, which can affect multiple organs of the body, including the kidneys (LN). The high variability and its unpredictable course (flaring/remission), combined with a lack of indicated and integrated treatments, induce a high

unmet need within the patient population. Reliable data on SLE- and LN-related care patterns and resource utilisation in the Gulf region are currently unavailable.

The expected key outcomes of this study will be:

- Description of clinical characteristics, demographics, treatment and health-related quality of life (HRQoL) of LN patients.
- Description of "real-world" standard of care and HCRU associated with LN in the Gulf region.

The information collected may be used for scientific interactions with HCP's and payers and for developing a scientific communication plan for Gulf. It can also be used for clinical research, for health planners, for clinical management and education/information for patients/ healthcare professionals/ payers, etc. The study protocol is designed to obtain an accurate, "real-life" picture of LN patients in the Gulf countries.

2. OBJECTIVES

2.1. Primary Objective

Describe patient profile, demographic features, clinical manifestations, comorbidities, severity, treatments and HRQoL of LN patients over one-year period across 5 Gulf countries (UAE, Qatar, Bahrain, Kuwait and Oman).

2.2. Secondary Objectives

1. Describe refractory LN cases, involving rituximab, and to assess changes in serological markers of disease activity (including anti-nuclear antibody, anti-dsDNA antibody and complement levels) over the treatment period.
2. Assess the association between clinical factors, biomarkers, treatment and renal remission.
3. Assess impact of LN on HRQoL over a one-year period after diagnosis or enrolment.
4. Describe LN HCRU and direct medical cost, associated with LN management across 5 Gulf countries over a one-year period.
5. Exploring the difference in treatment patterns by physician profile (physicians in private versus public hospitals).

3. RESEARCH METHODOLOGY

3.1. Study Design

The LUNELORD study is a multicentre prospective study compromising of a patient-completed survey and retrospective chart review (Figure 1).

This study will enrol approximately 200 patients with clinician diagnosed LN cases from 5 different countries in the Gulf (UAE, Bahrain, Qatar, Kuwait and Oman). Enrolment is planned to last for 6 months from June 2021 till November 2021.

Each site is planned to enrol around 16 patients, with the aim to have around 50% of the patients with renal remission and 50% with no renal remission to ensure the study meets the sample size and power assumptions provided below. The recruitment will not be competitive among participating sites for optimal representation of the study population. Since rheumatologists usually play a leading role in the disease management in multidisciplinary setting, clinical sites will predominantly be selected from this clinical specialty. Treatment of flares/ exacerbations/ organ manifestations, recommended by other specialists than rheumatologists / immunologists (for example nephrologists), will be considered and registered during the study by the investigators.

Centres from the private and public sectors will be chosen based on their ability to fulfil the objectives of the study and the ability to enter data onto the electronic case report form (eCRF). The country regulation will not impact the selection criteria of the centre or patient recruitment; major sites in each participating country will be selected and are representative of most patients. All nationalities have also been included as well. Given the ethnic diversity of the region study investigators will ensure to include all ethnicities. Prior to the selection of the sites, feasibility of study in all clinical sites and pilot eCRF will be tested and trainings will be conducted.

GSK study team will choose sites, representing major lupus treatment centres in respective countries, based on availability of sufficient potentially eligible patient population, their competency and experience to conduct research, their ability to fulfil the objectives of the study, ability to enter the data onto the eCRF. Prior to selection feasibility all clinical sites and pilot eCRF will be tested and trainings will be conducted.

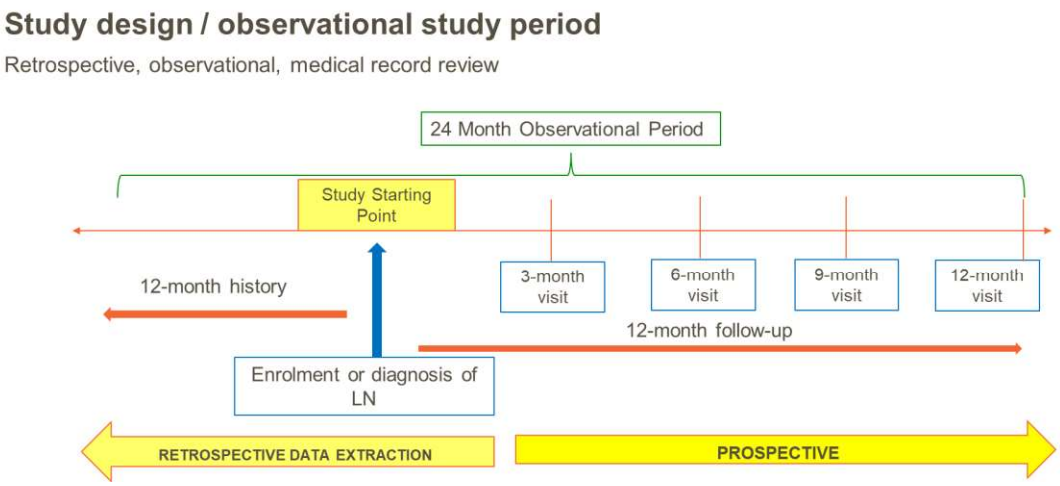

Figure 1. Study schematics.

3.1.1. Patient Identification Process and Eligibility Verification

Staff at participating sites will consecutively review their LN patients' medical charts to pre-identify potential patients who meet the study's preliminary selection criteria and might be considered eligible to participate in the study. Identified patients who are potentially eligible will be contacted over the phone or approached onsite at the patient's routine care visit if the visit falls within the study enrolment timelines. When contacting the patient, site staff will review the main study informed consent form (ICF) with each patient to explain the study design, which will include a two-time prospective patient survey, prospective data abstraction from medical charts for a period of a year, as well as a one-time retrospective data abstraction from their medical chart. Additionally, site staff will answer any questions patients may have at this time about the study. Patients will be asked to confirm study interest verbally.

Site staff will maintain a master list of patients invited to participate in the study (screening log) to assess the correspondence of the sample to the general population of potentially eligible LN patients at the site.

3.1.2. Patient Consent and Patient Survey

Eligible patients who provide verbal consent will receive a written informed consent form and asked to review and sign following the discussion of the study with the site staff and all queries resolved. Upon signing of the consent form the patient will be asked to complete the first patient survey during their first routine care visit after signing of the consent form. The second patient survey will be completed approximately 12 months after the completion of the first survey. In routine care, this would typically be Visit 5 from the enrolment period.

3.1.3. Retrospective Medical Chart Review

Site staff will perform a one-time data abstraction from the medical charts of patients who sign the consent form and complete the first patient survey. Available data in the charts as part of usual care from diagnosis, or up to (12) twelve months prior to enrolment will be abstracted (as outlined in Section 3.2.2). Data abstracted will be recorded directly in the eCRF.

3.1.4. Prospective Medical Chart Data Collection

Site staff will be asked to abstract data from medical charts of patients who have completed the first patient survey. Data will be abstracted after each patient visit based on their routine care visits. Data abstracted will be recorded directly in the eCRF. A typical LN patient visits the physician every 3 months. In total there will be 5 visits (Figure 1).

a. Visit 1: Enrolment visit

b. Visit 2: 3-month follow-up after Visit 1

c. Visit 3: 6-month follow-up after Visit 1

d. Visit 4: 9-month follow-up after Visit 1

e. Visit 5: last 12-month follow-up visit after Visit 1

We will aim for the data collection visits to be near the 3,6,9,12-month time points, however, since this is a real-world evidence study the frequencies of visits may vary from one patient to another. Therefore, we will take the closest available visit to our study time points. If a patient misses a visit, we will analyse based on available data and assume clinical status did not change. This would allow to minimise the influence of the study procedures on the typical schedule of patient and associated healthcare resource utilisation.

3.1.5. One-Time Physician Survey

A brief, one-time physician survey will be used to collect site-level data on overall practice, population of patients with LN, and LN-related treatment patterns. Sites will be asked to complete and return the survey prior to the last subject last visit date (Appendix 5. Physician Practice Form).

3.1.6. Medical Cost / HCRU

Site staff will be asked to perform abstraction of data on HCRU from the medical charts of patients who sign the consent form and complete the first patient survey. Other data will be collected at enrolment and prospectively. These include number of laboratory tests, number of dialyses and use of imaging techniques, hospitalisations in the intensive care unit (ICU)/hospitalisations. Data abstracted will also be recorded directly in the eCRF.

Data related to the unitary cost of individual healthcare resources will be collected retrospectively at the end of prospective observation. The source of the cost information will be collected for each country separately. For each country, the payer perspective shall be taken (Ministry of Health or the tender price for the relevant payer).

The type of unitary costs will be divided for each country in laboratory tests, biopsy and imaging, medical costs, medical visits costs and hospitalisation costs. More details will be further developed in the statistical analysis plan (SAP).

The cost of illness shall be stratified by disease activity (SELDAI-2K).

The prices will be taken by the end of the year for each country/institution for each resource; if any price modification has occurred during the year, an average price will be considered for the related resource.

Inflation will not be considered since the study period is only for one year.

3.2. Data Source / Data Collection

Data collection will occur by physician abstraction of patient medical chart data onto the study eCRFs which were developed by GSK and the clinical research organisation (CRO). All data instruments are field-tested prior to initiation of data collection.

3.2.1. Physician Practice Profile Form

After being screened for study eligibility and successfully recruited, each physician will be assigned a unique identifier, and the PPPF will be completed. This form will be used to gather specific physician practice information including:

1) Clinical practice and investigator profile

2) Practice setting (community-based, hospital-based or other)

3) Practice type (solo; single specialty group or multi-specialty group with number of rheumatologists quantified)

4) Years in practice

5) Estimated currently managed total patients and SLE and LN patients

6) Patients' role in SLE treatment decisions

3.2.2. Retrospective Data Collection and Prospective Data Collection

Participating physicians will assign a unique identifier to each patient selected for inclusion in the study. This identifier will be used to facilitate follow-up on data queries and data entry validation. The date of chart data abstraction will be tracked separately by the eCRF vendor.

Retrospective data collection - medical chart review from diagnosis or up till 12 months prior to enrolment

As available in the patients' medical charts as part of usual care, the following variables will be collected in the patient eCRF, from diagnosis, or up to (12) twelve months prior to enrolment (Appendix 1).

The patients routine repeated laboratory results will be taken closest to the protocol defined visits 0, 3, 6, 9 and 12. Retrospective data will be collected for both routine laboratory visits and other parameters (i.e. renal biopsies if available). All such additional tests and assessments will be taken for the calculation for the HCRU and associated direct medical costs.

Data include but are not limited to:

1) Basic patient demographic characteristics:
    a. Gender
    b. Race/ethnicity
    c. BMI
    d. Date at first SLE manifestation
    e. Date at SLE diagnosis
    f. Date at first LN manifestation
    g. Date at LN diagnosis
    h. Date at last visit in 2020
2) LN/SLE treatment medications (medications limited to NSAIDs, antimalarials, corticosteroids, immunosuppressants/cytotoxic and biologics):
    a. Starting dose, current dose, date of treatment start and end, dose at cessation and reasons for medication choice
3) LN treatment history:
    a. Most recent induction regimen and number of prior treatment failures/relapse(s), if any
    b. End-stage renal disease (ESRD), and dialysis

c. Date of ESRD diagnosis

d. Type and date of dialysis (current/past)

e. Listed for transplant/prior transplant conducted (date of transplant)

4) Most recent LN classification:

a. Class and histological activity/chronicity based on most recent biopsy (International Society of Neurology and the Renal Pathology Society [ISN/RPS] or World Health Organisation [WHO] classification)

5) LN clinical manifestations

6) Comorbidities (such as, but not limiting with antiphospholipid syndrome/thrombotic microangiopathy, obesity, cardiovascular disease, and diabetes)

7) Laboratory tests:

a. Haematology: white blood cell count ($x10^9$/L]), haemoglobin (g/dL), platelet count ($x10^9$/L), erythrocyte sedimentation rate (mm/hour), C-reactive protein (mg/L)

b. Liver function tests

c. Lipid profile

d. Plasma albumin

e. Most recent serological findings such as: antiphospholipid antibody tests (anticardiolipin, anti-beta 2 glycoprotein 1 [GP1] and lupus anticoagulant), antiC1q, low-complement (C3/C4), positive anti-double-stranded deoxyribonucleic acid (anti-dsDNA) (IU/mL), anti-U1-RNP, anti-Sm antibody, anti-Rib, and anti-Scl-70

f. Renal assessments, such as urinary protein to creatinine ratio (UPCR) or 24-hour proteinuria (mg/24-hr) or urine sediment (activity), serum creatinine (mg/dL), and estimated glomerular filtration rate (eGFR) or measured glomerular filtration rate (GFR) (if eGFR is not available) with date of assessment

8) Active non-renal clinical manifestations of SLE (such as mucocutaneous, central nervous system, constitutional, cardiopulmonary, gastrointestinal, hematologic, musculoskeletal, and vasculitis)

a. Type and date of resolution, if applicable

9) Most recent total Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), such as SLEDAI or SLEDAI-2K (16), Appendix 2

10) Renal remission: defined as proteinuria of <0.7 g/d or <0.5g/d or at physicians' discretion

11) Renal biopsy:

a. Activity index

b. Chronicity index

c. Number of glomeruli

Prospective data collection from enrolment (0, 3, 6, 9, 12 months)

Variables include but are not limited to (Appendix 1):

1) Non-renal and renal clinical manifestations at period start with clinical improvement/ worsening assessment at period end

2) Changes in disease activity assessment tools used (such as SLEDAI-2K)

3) Refractory SLE: defined as inefficacy of cyclophosphamide, use of rituximab, splenectomy, or inefficacy of ≥2 immunosuppressives (methotrexate, leflunomide, abatacept, anti-TNF, azathioprine, mycophenolate mofetil, and/or mycophenolic acid)

4) Renal remission: defined as proteinuria of <0.7 g/d or <0.5g/d or at physician discretion

5) Renal biopsy:

   a. Activity index

   b. Chronicity index

   c. Number of glomeruli

6) Changes linked to the primary treatment of the disease:

   a. Adjustment of the dose by 20% or more, and

   b. Change happening for longer than 1 month, or

   c. Change or addition in the type or group of medication (immunosuppressants, biologics, anti-malarial, and steroids)

7) Laboratory tests:

   a. Haematology: white blood cell count ($x10^9$/L]), haemoglobin (g/dL), platelet count ($x10^9$/L), erythrocyte sedimentation rate (mm/hour), C-reactive protein (mg/L)

   b. Liver function tests

   c. Lipid profile

   d. Plasma albumin

e. Most recent serological findings such as: antiphospholipid antibody tests (anticardiolipin, GP1 and lupus anticoagulant), antiC1q, low-complement (C3/C4), positive anti-dsDNA (IU/mL), anti-U1-RNP, anti-Sm antibody, anti-Rib, and anti-Scl-70

f. Renal assessments, such as UPCR or 24-hour proteinuria (mg/24-hr) or urine sediment (activity), serum creatinine (mg/dL), and eGFR or measured GFR (if eGFR is not available) with date of assessment

8) HCRU (number of laboratory tests, number of dialyses and use of imaging techniques, ICU hospitalisations/hospitalisations, outpatient visits)

3.2.3. Prospective Patient Survey: HRQoL

The 36-Item Short Form Health Survey (SF-36) has been selected as a standard tool, utilized in past studies in patients with lupus nephritis and is widely used in both clinical and real-world research. The tool is comprehensive and recognized by multiple experts in rheumatology as the optimal validate tool to measure quality of life in clinical practice.

The 36-Item Short Form Health Survey (SF-36) is a 36-item QoL questionnaire covering 8 health domains: physical functioning (10 items), bodily pain (2 items), role limitations due to physical health problems (4 items), role limitations due to personal or emotional problems (4 items), emotional well-being (5 items), social functioning (2 items), energy/fatigue (4 items), and general health perceptions (5 items). The questionnaire is available in Arabic and English versions. The average time to complete the questionnaire is 5 to 10 minutes.

Each patient will complete an SF-36 form (17) at enrolment (Visit 1) and at the last visit (Visit 5). It will be completed by the patient in Arabic, or in English in case he/she does not understand Arabic. Once completed, the site staff will enter data in the eCRF.

Scores for each domain range from 0 to 100, with a higher score defining a more favourable health state (Appendix 3 and Appendix 4).

3.3. Study Population

Study participants are patients with lupus nephritis as defined by physician per patient hospital records prior to the enrolment visit or at diagnosis. Retrospective data of patients with diagnosed LN who made at least one centre visit during 12 months prior to the enrolment visit or at diagnosis of LN who fulfil inclusion/exclusion criteria will be abstracted from chart records. The data will be consecutively extracted from paper or electronic records were available. Based on our sample size assumptions and power calculations the study population will aim to recruit 50% of patients with renal remission and 50% of patients with no renal remission at the time of enrolment.

3.3.1. Eligibility Criteria

Patient selection and eligibility for the study at the time of baseline enrolment were determined by the following inclusion/exclusion criteria.

3.3.1.1. Inclusion Criteria

For inclusion into the study, all the following inclusion criteria must be fulfilled by the patients:

1) ≥age of 18 years
2) Clinician diagnosed LN patient
3) At least one visit to the investigational centre during 12 months prior to the baseline visit, recorded in medical documentation
4) Literacy in English or Arabic allowing to fully comprehend the written informed consent and study-specific patient reported questionnaires
5) Written informed consent by the patient

3.3.1.2. Exclusion Criteria

Patients are not eligible for inclusion if they fulfil the following non-inclusion criteria:

1) Incomplete medical records to be able to assess the disease severity or absence of any of the following renal laboratory results from the medical record within the last (12) twelve months:
    a. UPCR or 24-hour proteinuria or urine sediment (activity)
    b. Serum creatinine or eGFR; or measured GFR, if eGFR is not available
2) Current or medical history of:
    a. Congenital or acquired immunodeficiency
    b. Malignancy in active treatment phase
    c. Acute viral infection, such as HIV infection, requiring hospitalisation

3.3.2. Sample Size / Power Calculations

As other similar research recruited a sample size ranging between 200 and 300 patients (18,19) the decision was made to proceed with 200 sample size in this research. This sample size would provide a significant power to interpret the results of the study. In addition, due to overall budget

constraints the maximum number of participants allocated for the study has been determined as 200.

Based on the sample size determination using Slovin's formula and assuming the total SLE population in Gulf countries is 5,600 patients, while 40% of SLE patients manifest with lupus nephritis (LN), the entire LN population size was estimated as 2,240 patients disease onset (1).

The margin of error (significance level), denoting the allowed probability of committing an error in selecting a small representative of the population, is 0.067 for the 93% of confidence that the data are going to be reflective of the entire LN population, given the assumptions of 200 LN patients, required to achieve this significance level (20).

Significance of the adverse factors, impacting the data accuracy and completeness, will be assessed during the data acquisition and may result in respective adjustments to the sample size.

In addition, taking into account our secondary hypothesis on the association between clinical factors, biomarkers, treatment and renal remission, a sample size of 200 observations (of which 65% are in not in renal remission=0 and 35% are in renal remission=1) achieves 80% power at a 0.050 significance level to detect a change in Prob(Y=1) from the baseline value of 0.200 to 0.385 (Table 1). This change corresponds to an odds ratio of 2.508.

Table 1. Tests for the odds ratio in logistic regression with one binary X and other Xs (Wald Test) (21)

Numeric Results

Power	N	Pcnt N X=1	P0	P1	Odds Ratio	R Squared	Alpha	Beta
0.80000	200	35	0.200	0.385	2.508	0.000	0.050	0.20000
0.80000	200	35	0.200	0.409	2.770	0.200	0.050	0.20000
0.80000	200	35	0.200	0.444	3.199	0.400	0.050	0.20000
0.80000	200	35	0.200	0.504	4.065	0.600	0.050	0.20000
0.80000	200	35	0.200	0.643	7.200	0.800	0.050	0.20000
0.90000	200	35	0.200	0.418	2.871	0.000	0.050	0.10000
0.90000	200	35	0.200	0.446	3.216	0.200	0.050	0.10000
0.90000	200	35	0.200	0.487	3.791	0.400	0.050	0.10000
0.90000	200	35	0.200	0.555	4.985	0.600	0.050	0.10000
0.90000	200	35	0.200	0.707	9.644	0.800	0.050	0.10000
0.80000	200	35	0.300	0.501	2.342	0.000	0.050	0.20000
0.80000	200	35	0.300	0.525	2.582	0.200	0.050	0.20000
0.80000	200	35	0.300	0.561	2.981	0.400	0.050	0.20000
0.80000	200	35	0.300	0.620	3.808	0.600	0.050	0.20000
0.80000	200	35	0.300	0.752	7.094	0.800	0.050	0.20000
0.90000	200	35	0.300	0.533	2.666	0.000	0.050	0.10000
0.90000	200	35	0.300	0.561	2.984	0.200	0.050	0.10000
0.90000	200	35	0.300	0.602	3.524	0.400	0.050	0.10000
0.90000	200	35	0.300	0.668	4.685	0.600	0.050	0.10000
0.90000	200	35	0.300	0.808	9.836	0.800	0.050	0.10000
0.80000	200	35	0.400	0.606	2.308	0.000	0.050	0.20000
0.80000	200	35	0.400	0.630	2.554	0.200	0.050	0.20000
0.80000	200	35	0.400	0.665	2.972	0.400	0.050	0.20000
0.80000	200	35	0.400	0.721	3.877	0.600	0.050	0.20000
0.80000	200	35	0.400	0.843	8.080	0.800	0.050	0.20000
0.90000	200	35	0.400	0.637	2.634	0.000	0.050	0.10000
0.90000	200	35	0.400	0.664	2.965	0.200	0.050	0.10000
0.90000	200	35	0.400	0.703	3.543	0.400	0.050	0.10000
0.90000	200	35	0.400	0.764	4.859	0.600	0.050	0.10000
0.90000	200	35	0.400	0.891	12.225	0.800	0.050	0.10000

Report Definitions

Power is the probability of rejecting a false null hypothesis. It should be close to one. N is the size of the sample drawn from the population. Pcnt N X=1 is the percentage of the population in which X = 1. P0 is the response probability at the mean of X. P1 is the response probability when X is increased to one standard deviation above the mean. Odds Ratio is the odds ratio when P1 is on top. That is, it is [P1/(1-P1)]/[P0/(1-P0)]. R-Squared is the R2 achieved when X is regressed on the other independent variables in the regression. Alpha is the probability of rejecting a true null hypothesis. Beta is the probability of accepting a false null hypothesis (21).

The sample size calculation was computed by PASS® version 2019.

4. DATA ANALYSIS CONSIDERATIONS

4.1. Analysis Population

Analyses will be based on the "all subjects enrolled (ASE)" population. This includes all subjects who meet the inclusion or exclusion criteria

4.2. Protocol Deviation

No per-protocol population is included in this study.

Any protocol deviations will be documented and tracked by the study team. Any lost to follow up will not be replaced if it happens after the third month of recruitment. All efforts will be done by the investigator to reach out to the patient who is lost to follow up. Analysis of data associated with visits will happen according to data analysis planned, expect for HCRU.

The number of patients who do not meet the inclusion and exclusion criteria will be reported.

4.3. Interim Analysis

No interim analysis is planned for this study.

4.4. Data Analyses

4.4.1. General Considerations for Data Analysis

Variables will be summarised using the mean±standard deviation along with the median, interquartile range, smallest and largest observations for continuous numeric variables such as age, body weight at SLE diagnosis, and HRQoL. For categorical variables such as gender, race, and current diagnosis, frequency distributions (basically the frequency and percentage in each category) will be used.

4.4.2. Primary Analysis

The primary objective is to describe patient profile, demographic features, clinical manifestations, comorbidities, severity, treatments and HRQoL of LN patients across 5 Gulf countries. The analysis of the primary objective will be carried out on the ASE population and includes using summary statistics as described above in Section 4.4.1. General Considerations for Data Analysis at each time point the variables are collected.

4.4.3. Secondary Analysis

The first secondary objective is to describe refractory LN cases, involving rituximab, and to assess changes in serological markers of disease activity (including anti-nuclear antibody, anti-dsDNA antibody and complement levels) over the treatment period. This will be achieved by first using summary statistics as per the general consideration of data analysis section at each time point. To assess one-year changes in numeric variables, the paired t-test or Wilcoxon signed rank test will be used while the McNemar's test will be used for changes in categorical variables. In addition, repeated measures analysis will be used to look at changes over the whole time period.

The second secondary objective is to assess the association between clinical factors (disease activity), biomarkers (inflammatory markers and hematological markers), treatment (type and duration of therapy) and renal remission. The variables included in the model will be taken from the measures closest to the time of enrolment. For continuous variables, the nonparametric Wilcoxon test will be used for assessing differences between the patients who attained renal remission verses patients who did not attain renal remission, while the chi-square test will be used for dichotomized variables. Statistically significant factors will be included in the multivariate logistic regression models with renal remission as the dependent variable. Odds ratio and corresponding 95% confidence intervals (CIs) will be presented.

The third secondary objective is to assess impact of LN on HRQoL over a one-year period after diagnosis or enrolment. This will be achieved by looking at changes in the SF-36 physical and mental components, and the total score at one year using the paired t-test or Wilcoxon signed rank test for non-normal distribution. Changes over all the time period will be assessed using repeated measures analysis.

The fourth secondary objective is to estimate HCRU and direct medical cost, associated with LN management across 5 Gulf countries over a one-year period. This will be carried out as per Section 4.5. Cost Evaluation. Generating an estimate for the average HCRU and direct medical cost and creating the 95% CIs for those will be carried out for each country.

The number and proportion of patients with missing data will be presented. Listwise missing will be used during data analysis. All data analyses will be done using IBM-SPSS (version 26, Armonk NY). A *p*-value of 0.05 or less will be considered statistically significant.

4.5. Cost Evaluation

Direct medical costs of LN management will be assessed per country based on laboratory analyses, medication and duration of hospitalisation during 2020.

In each country cost analysis will be determined by considerations outlined in the SAP of the study.

Direct costs will be calculated for each patient on annual basis.

The annual direct medical cost will be calculated considering resources used and unitary costs at local level, in local currencies and United States Dollars. Direct medical cost evaluation considerations are outlined in the study SAP.

To compute total cost, the direct cost components listed in Appendix 1 will be summed.

Major cost drivers associated with LN management will be identified by multivariate adjusted models.

The relevance of health status, disease severity, disease activity, symptoms and organs involved, disease duration since diagnosis, number of flares endured, age/severity at disease onset, treatments used, etc as predictor variables will be established. Multiple linear regression analysis will be used to determine the best model.

Details about model specifications, parameter estimation and assumption validity will be outlined in the study SAP.

4.6. Data Handling Conventions

Details about the methods of handling missing data and the analysis methods will be documented in a separate SAP.

4.7. Exploratory Analysis

Supplementary exploratory data will be analysed regarding physicians' profile (public versus private) and treatment of patients.

5. LIMITATIONS

Study limitations are as follows:

- In routine practice, limited retrospective clinical SLE/LN data are available in the participating countries. Doctors in routine practice often do not indicate SLE and LN activity scores (SELENA-SLEDAI, SLEDAI-2K) in medical documentation. Lack of data to perform the full SLE activity scales completion will not limit inclusion of patients. Investigator will capture data of SLE and LN activity scales optionally, if possible.

- HCRU and costs:

    - Relevant data will be collected in local currency, as US$ and local currency are used based on a fixed annual rate.

    - In order to map the costs at Governmental hospitals, these hospitals will be asked to list the costs of their services and to describe consultation fees of their salaried healthcare practitioners.

    - Assumptions should also be made on out-of-pocket expenses that are not recorded.

- The participating centres will be selected based on the feasibility of providing adequate data. Given regional variations in LN risk factors and in healthcare provision (including access to specialised SLE/LN centres) within the participating countries, the data should only be extrapolated to general populations with caution.

- Since the number of patients to be recruited from each country is not prefixed, analyses by countries from where the number of patients recruited is very small will lack precision.

- Sample size of the patient population in the study may not allow to generalize the data and perform comparisons between countries and some stratified analyses. However, the data from this research will be extremely important to inform future research of lupus nephritis in larger populations.

6. STUDY CONDUCT, MANAGEMENT & ETHICS

6.1. Ethical and Regulatory Submissions

This study protocol and any amendments will be submitted to a properly constituted IEC/ IRB and/or Regulatory Authorities, in agreement with applicable regulatory requirements, for formal approval of the study conduct. A copy of these approvals will be submitted to GSK before initiation of the study and each centre will keep a copy of these documents.

Changes to the study protocol must be made in the form of an amendment that has the prior written approval of GSK and – as applicable – of the appropriate IEC/IRB and regulatory authority.

The study will be performed according to the legal requirements of the national law(s) of the participating countries considering the principles of Good Pharmacoepidemiological Practice (GPP; 22) and the ethical principles that guided development of the Declaration of Helsinki.

6.2. Patient Information

The patient and/or - if applicable - legally acceptable representative will be informed about the study according to the requirements of the GPP and the legal requirements of the country in which the patient is recruited.

The study, its objectives, possible benefits and risks, and its consequences will be verbally explained to the patient and/or his/her legally acceptable representative. Moreover, the patient and/or legally acceptable representative is/are provided with written information about the study. Enough time will be allowed for the information to be read and for questions to be asked. The patient and/or legally acceptable representative must be told that refusal to participate in the study does not cause any disadvantages to their treatment; similarly, withdrawal of written informed consent is possible at any time, without stating a reason and without prejudice to further medical management.

Patients and/or legally acceptable representative should be informed and should agree that medical data may be reviewed by authorised persons during monitoring and during an audit or an inspection by the appointed regulatory authority or ethics committee, but that personal data will be treated with absolute confidentiality.

The patient' and/or legally acceptable representative's written informed consent will be filed at the investigator's site.

6.3. Declaration of Informed Consent

The patient and/or - if applicable - legally acceptable representative must give written consent to participate in the study by signing and personally dating the informed consent form. Informed consent to the proposed data handling and to data inspection must also be documented in written form. Written informed consent must be obtained from each patient or legally acceptable representative before any study-related procedures are performed. A duplicate of the signed and dated written informed consent form must be handed over to the patient and/or – if applicable - legally acceptable representative.

6.4. Legal Basis for Processing Individual Human Data

The authors confirm that study data are Individual Human Data (IHD) not owned by GSK, but that the proposed use of the IHD aligns with the 'purpose of use' outlined in the source contract and/or the terms and conditions of use of the data source and will it comply with any specified prohibitions of use.

6.5. Adverse Event (AE), Pregnancy Exposure, and Incident Reporting

All serious and non-serious AEs, pregnancy exposures, or incidents related to any GSK products will be collected and reported by Investigators as described in the study-specific pharmacovigilance plan (sPVP) reviewed by GSK Pharmacovigilance accordingly. This plan will include the following elements to ensure a comprehensive approach to safety event collection and reporting:

- CRO pharmacovigilance training
- Investigator and site staff pharmacovigilance training
- Safety-specific roles
- AEs, pregnancy exposures, and incidents collection and reporting processes
- AE, pregnancy exposure, and incident collection forms

- Frequency of data review
- Reporting process and timelines
- Interim reports
- Reconciliation process
- Study-specific PVP monitoring process
- Provision of final study report

6.6. Study Scientific Advisory Committee

This study is developed and governed under the guidance of a scientific advisory committee, composed of academic members experienced in SLE research and clinical practice (maximum 2 from each country) and 2 methodologists.

Its role will be:

- To review and provide credible scientific input for the essential study documents (protocol, CRF, SAP etc.);
- To review and comment on the study results;
- To review and provide input on the study report;
- To review and provide input into the data dissemination plan for the study results;
- To provide input into the selection of manuscript(s) authors as per ICMJE recommendations;
- To participate in medical writing and lead potential publications from the study results;
- To appoint an external audit, if considered necessary;
- To communicate results both internationally and locally upon explicit written approval from the study sponsor prior to such data disclosure in the public domain.

7. EXTERNAL INVOLVEMENT (THIRD PARTY SUPPLIER, EXTERNAL EXPERT/HCPS)

Quality control and Quality Assurance

This study will be conducted according to GSK SOP52213 (Conducting Quality Control Review of Study Results generated using Existing Data in VEO and USVEO).

8. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A report will be generated at the end of the study. GSK will provide the competent authority and IEC/IRB with a summary of the study report within 6 months after the end of the study, where required.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

Neither the complete report nor any part of the study report may be used without the approval of GSK.

Publication plan to support the dissemination of study results will be developed to seek publication of the research results (primary manuscript) in the indexed peer-reviewed scientific literature within 18 months of LSLV. Secondary manuscripts and congress abstracts, posters and oral presentations will provide important scientific knowledge around the study methodology, design, additional analyses of study data, country-specific data analysis and findings, arising from this research and provide additional scientific insight and/or release important new data into the public domain.

For all publication authors will follow authorship criteria of the ICMJE or, if more stringent, the criteria of the target journals.

Oral presentation and associated abstract on the primary and key secondary outcomes from the study will be aimed for the disclosure at the international (e.g. EULAR or ACR) or regional (e.g., ADARRC, ESR, KAR, ORS) congresses.

Primary manuscript primary and key secondary outcomes from the study will be aimed for the publication in Lupus or equivalent scientific journals (e.g., Journal of Rheumatology, Current Opinion in Rheumatology, or Journal of Clinical Rheumatology).

Secondary manuscripts with country-specific data analysis and findings, arising from this research will be aimed for publication in similar scientific journals.

Study data around HCRU and direct medical cost, associated with LN management across 5 Gulf countries will be aimed for dissemination at respective leading Middle East and North Africa conferences for Health Economics and Outcomes Research or Public Health (e.g. ISPOR, Public Health Conference Dubai), followed by the publication in local or regional Health Economics and Outcomes Research journals (e.g. Journal of Medical Economics).

Each investigator is obligated to keep data pertaining to the study confidential. He/she must receive an explicit written approval from the study sponsor before any study data are published.

The study protocol will be disclosed at the GSK study register and other study registries.

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10. APPENDIX 1: DATA TABLE

Variables	Retro-spective	Enrolment* (Visit 1)	Pro-spective
Demographics			
Gender		x	
Race/ethnicity		x	
BMI		x	
Date at first SLE manifestation		x	
Date at SLE diagnosis		x	
Date at first LN manifestation		X	
Date at LN diagnosis		X	
Date at last visit in 2020		X	
Comorbidities		X	
SLE Characteristics			
SLEDAI-2K	x		x
Refractory SLE			x
Lupus Nephritis Characteristics			
LN Pathological type (Class I-V)	x		x
Active Non-Renal Clinical Manifestations of SLE			
Mucocutaneous	x		x
Central nervous system	x		x
Constitutional	x		x
Cardiopulmonary	x		x
Gastrointestinal	x		x
Hematologic	x		x
Musculoskeletal	x		x
Vasculitis	x		x
LN Clinical Manifestations			
Arthritis	x		x
Arthralgia	x		x
Photosensitisation	x		x
Skin rash	x		x
Malar rash	x		x
Neuropsychiatric disorders	x		x
Oral ulcer	x		x
Haematological abnormality	x		x
Serositis	x		x
Anti-dsDNA	x		x
Anti-U1-RNP	x		x
Anti-Sm	x		x
Anti-Rib	x		x
Anti-Scl-70	x		x
Lupus anticoagulant	x		x
Antiphospholipid	x		x
Anti-cardiolipin	x		x
C3/C4	x		x
Laboratory Tests			
White blood cell	x		x
Haemoglobin	x		x
Platelet count	x		x
Erythrocyte sedimentation rate	x		x

Variables	Retro-spective	Enrolment* (Visit 1)	Pro-spective
C-reactive protein	x		x
Serum creatinine	x		x
24-proteinuria	x		x
Urinary protein to creatinine ratio	x		x
Urine sediment	x		x
eGFR	x		x
Measured glomerular filtration rate (if eGFR is not available)	x		x
Liver function tests	x		x
Lipid profile	x		x
Plasma albumin	x		x
Renal remission	x		x
Renal Biopsy			
Activity index	x		x
Chronicity index	x		x
Number of glomeruli	x		x
Treatment			
Oral glucocorticoids	x		x
Daily dose of methylprednisolone	x		x
Daily dose of prednisolone	x		x
Antimalarial drugs	x		x
Immunosuppressants/cytotoxic	x		x
NSAIDs	x		x
Biological therapy	x		x
Quality of Life			
SF-36		x	x
Healthcare Resources/ Medical Costs			
Immunological tests			x
Haematology tests			x
Blood chemistry tests			x
Urine analysis: creatinine			x
Other fluid analysis			x
Kidney biopsy			x
Dialysis			x
Imaging tests			x
MRI			x
Computer tomography			x
Ultrasound			x
X-ray			x
Hospitalisations			x
ICU hospitalisations			x
Outpatient visits			x
Other			x

*Enrolment or diagnosis of LN

Note: Data will be collected only if available.

11. APPENDIX 2: SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX 2000 (SLEDAI-2K)

Name/ID: _____ **Date of Birth:** _____ **Date of Assessment:** _____

(**Circle in "SLEDAI Score" column** if descriptor is present at the time of the visit or in the preceding 10 days.)

SLEDAI Score	Descriptor	Definition
8	Seizure	Recent onset. Exclude metabolic, infectious, or drug causes.
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, and bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function (with rapid onset and fluctuating clinical features), inability to sustain attention to environment, and at least two (2) of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, and increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, and optic neuritis. Exclude hypertensive, infectious, or drug causes.
8	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	Lupus headache	Severe, persistent headache. May be migrainous, but must be nonresponsive to narcotic analgesia.
8	CVA	New onset cerebrovascular accident(s). Exclude arteriosclerosis.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages or biopsy, and angiogram proof of vasculitis.
4	Arthritis	≥2 joints with pain and signs of inflammation (i.e., tenderness, swelling, or effusion).
4	Myositis	Proximal muscle aching/weakness associated with elevated creatinine phosphokinase (CK)/aldolase or EMG changes or a biopsy showing myositis.
4	Urinary casts	Heme-granular or RBC casts.
4	Hematuria	>5 RBC/high-power field. Exclude stone, infection, or other cause.
4	Proteinuria	>0.5 gram/24 hours.
4	Pyuria	>5 WBC/high-power field. Exclude infection.
2	Rash	Inflammatory-type rash.
2	Alopecia	Abnormal, patchy, or diffuse loss of hair.
2	Mucosal ulcers	Oral or nasal ulcerations.
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	Pericarditis	Pericardial pain with at least one (1) of the following: rub, effusion, or ECG or echocardiogram confirmation.
2	Low complement	Decrease in CH50, C3, or C4 below lower limit of normal for testing laboratory.
2	Increased DNA binding	Increased DNA binding above normal range for testing laboratory.
1	Fever	>38° C. Exclude infectious cause.
1	Thrombocytopenia	<100 x 10^9 platelets/L. Exclude drug causes.
1	Leukopenia	<3 x 10^9 WBC/L. Exclude drug causes.

TOTAL SCORE:

12. APPENDIX 3: 36-ITEM SHORT FORM HEALTH SURVEY (SF-36) – ENGLISH VERSION

Choose one option for each questionnaire item

1. In general, would you say your health is:

☐1 - Excellent

☐2 - Very good

☐3 - Good

☐4 - Fair

☐5 – Poor

2. Compared to one year ago, how would you rate your health in general now?

☐1 - Much better now than one year ago

☐2 - Somewhat better now than one year ago

☐3 - About the same

☐4 - Somewhat worse now than one year ago

☐5 - Much worse now than one year ago

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
5. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
6. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
7. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
8. Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
9. Walking more than a mile	☐ 1	☐ 2	☐ 3
10. Walking several blocks	☐ 1	☐ 2	☐ 3
11. Walking one block	☐ 1	☐ 2	☐ 3
12. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
13. Cut down the amount of time you spent on work or other activities	☐ 1	☐ 2
14. Accomplished less than you would like	☐ 1	☐ 2
15. Were limited in the kind of work or other activities	☐ 1	☐ 2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the amount of time you spent on work or other activities	☐ 1	☐ 2
18. Accomplished less than you would like	☐ 1	☐ 2
19. Didn't do work or other activities as carefully as usual	☐ 1	☐ 2

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

☐1 - Not at all

☐2 - Slightly

☐3 - Moderately

☐4 - Quite a bit

☐5 – Extremely

21. How much bodily pain have you had during the past 4 weeks?

☐1 - None

☐2 - Very mild

☐3 - Mild

☐4 - Moderate

☐5 - Severe

☐6 - Very severe

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐1 - Not at all

☐2 - A little bit

☐3 - Moderately

☐4 - Quite a bit

☐5 – Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
24. Have you been a very nervous person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
26. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
27. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
28. Have you felt downhearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
29. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
30. Have you been a happy person?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
31. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

☐1 - All of the time

☐2 - Most of the time

☐3 - Some of the time

☐4 - A little of the time

☐5 - None of the time

How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

13. APPENDIX 4: 36-ITEM SHORT FORM HEALTH SURVEY (SF-36) – ARABIC VERSION

PPD

PPD

PPD

PPD

PPD

PPD

PPD

14. APPENDIX 5: PHYSICAN PRACTICE PROFILE FORM

PHYSICIAN PRACTICE PROFILE FORM

LUNELORD: A descriptive, prospective study to evaluate demographic, pharmacologic, biomarker, QoL, and clinical features of patients with SLE, LUpus NEphritis, refractory SLE and Long term ORgan Damage

SPONSOR:

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VENDOR/COLLABORATOR:

Phoenix Clinical Research

COORDINATING INVESTIGATOR:

XX

Clinical Practice and Investigator Profile

1. Years in practice: |___|___|
2. Estimated currently managed total patients |___|___|___|___|
3. Estimated currently managed SLE patients |___|___|___|___|
4. Estimated currently managed LN patients |___|___|___|___|
5. Consultation fees |___|___|___|___|
6. Estimated burden of disease severity on SLE patients:

Health-related burden	☐ Low	☐ Moderate	☐ High
Cost-related burden	☐ Low	☐ Moderate	☐ High
Healthcare utilisation-related burden	☐ Low	☐ Moderate	☐ High

8. Patient's involvement in SLE treatment decisions ☐ Total ☐ Partial ☐ None

Practice Setting

		No	Yes
1.	Community-based	☐	☐
2.	Hospital-based	☐	☐
3.	If other, please specify: _____		

Practice Type

		No	Yes
1.	Solo	☐	☐
2.	Single specialty group	☐	☐
3.	Multi-specialty group including a quantified number of rheumatologists	☐	☐

Disease Assessment tools/Laboratory Tests for SLE/LN Patient Monitoring

		No	Yes
1.	**Disease activity assessment**		

The European Consensus Lupus Activity Measurements, Systemic Lupus Activity Measure Revised (SLAM-R)	☐	☐
Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)	☐	☐
Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)	☐	☐
Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)–SLEDAI	☐	☐
The British Isles Lupus Assessment Group Index (BILAG)	☐	☐
Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)–SLEDAI	☐	☐
Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) score	☐	☐
Systemic Lupus Activity Questionnaire for Population Studies (SLAQ)	☐	☐
European Consensus Lupus Activity Measurement (ECLAM)	☐	☐

Other, please specify: _____

2. **Laboratory assessment**

2.1	Hematology		
	White blood cell count	☐	☐
	Hemoglobin count	☐	☐
	Platelet count	☐	☐
	Erythrocyte sedimentation rate	☐	☐
	C-reactive protein	☐	☐
2.2	Renal function	☐	☐
	serum creatinine	☐	☐
	estimated 24-hour urinary protein	☐	☐
	spot protein/creatinine ratio	☐	☐
2.3	Complement protein system components	☐	☐
	C3	☐	☐
	C4	☐	☐
2.4	Immunology	☐	☐
	Anti-dsDNA test	☐	☐
	ANA	☐	☐
	Anti-Sm antibody	☐	☐
2.5	Antiphospholipid (APL) antibody tests	☐	☐
	lupus anticoagulant (LAC)	☐	☐
	anticardiolipin (ACL) antibodies	☐	☐
	anti-β2-glycoprotein I antibodies	☐	☐