

TITLE PAGE

Protocol

**A Phase 1b/2a Multicenter Study to Assess the Safety and Tolerability,
Pharmacokinetics, and Preliminary Efficacy of KPG-818 in Patients with
Systemic Lupus Erythematosus**

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Investigational Medicinal Product:
KPG-818

Protocol Reference Number: KPG-818-SLE
IND Number: 136549

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SPONSOR APPROVAL

I have read the protocol and approve it:



25th March 2022

Kai Wei, MD Date (DD-MMM-YYYY)
Vice President, Clinical Development
Kangpu Biopharmaceuticals, Ltd

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INVESTIGATOR AGREEMENT

I have read the protocol and agree to conduct the study as described herein.

Kenneth Kalunian
Kenneth Kalunian

Principal Investigator
Printed Name and Signature

3/30/2022

Date

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STUDY IDENTIFICATION

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Document History

Document	Version Date	Summary of Changes
Protocol Version: 3.0	22 Mar 2022	Phase 2a part of the study is amended with following key points: PK and PD study design and blood sample collection timing were revised. The schedule of events for FSH, Coagulation, PK, and biomarker sample collection has been modified. The changes made throughout the protocol. Number of patients per arm in Phase 2a and approximate patients were revised throughout the protocol. Eligibility criteria for inclusion criteria # 4, 5 and exclusion criteria # 1, 3, and 12 were revised. Minor administrative changes were made to correct typographical errors,

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Document	Version Date	Summary of Changes
		emphasize subtle points, or improve internal consistency with the protocol.
Protocol Version: 2.0	03 Feb 2021	The purpose of this amendment is to make some clarifications and updates to the protocol, including the objectives and endpoints, study design, eligibility criteria, concomitant therapies, and schedule of assessment. Minor administrative changes were made to correct typographical errors, emphasize subtle points, or improve internal consistency with the protocol.
Protocol Version: 1.0	12 Jun 2020	Never distributed or submitted.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and Institutional Review Boards (IRBs)/Ethics Committees (ECs).

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SYNOPSIS

Study Title

A Phase 1b/2a multicenter study to assess the safety and tolerability, pharmacokinetics, and preliminary efficacy of KPG-818 in patients with systemic lupus erythematosus.

Brief Title:

Phase 1b/2a study to evaluate safety and efficacy of KPG-818 in SLE.

Objectives

Phase 1b

The primary objectives of the study are:

- To assess the safety and tolerability of multiple oral doses of KPG-818 in patients with systemic lupus erythematosus (SLE) over a 14-day treatment period.
- To characterize the single and multiple oral dose pharmacokinetics (PK) of KPG-818 and its metabolite, KPG-818H.

The exploratory objective of the study is:

- To evaluate the pharmacodynamics (PD) markers of KPG-818.

Phase 2a

The primary objective of the study is:

- To assess the safety and tolerability of multiple oral doses of KPG-818 in patients with SLE over a treatment period of 12 weeks and a follow-up period of 4 weeks.

The secondary objectives of the study are:

- To evaluate the preliminary efficacy of KPG-818 compared with placebo in adult patients with active SLE on limited background standard-of-care treatment over a treatment period of 12 weeks and a follow up period of 4 weeks.
- To characterize the multiple oral dose PK of KPG-818 and its metabolite, KPG-818H, over a 12-week treatment period.
- To select dosing regimens for Phase 2b study.

The exploratory objectives of the study are:

- To further explore the efficacy of KPG-818.
- To evaluate the PD markers of KPG-818.

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Study Design

This is a Phase 1b/2a multicenter study to evaluate the safety, PK, PD, and clinical efficacy of KPG-818 in patients with SLE. The trial will consist of 2 parts: Phase 1b, a multiple-ascending dose (MAD) study; and Phase 2a, a proof of concept (POC) study.

Eligible patients must have a confirmed diagnosis of SLE according to 2019 European League against Rheumatism (EULAR)/American College of Rheumatology (ACR) Classification criteria for SLE.

Phase 1b

The Phase 1b part of the study is an open-label, multicenter, and multiple dose escalation cohort study. A total of approximately 24 patients will be enrolled into 4 dosing cohorts and receive KPG-818 in an open-label fashion. KPG-818 will be taken orally in the morning approximately every 24 hours for 14 days (up to 14 doses). The total duration of the study is approximately 10 weeks, consisting of 3 periods:

- Screening period: up to 42 days (6 weeks)
- Treatment period: up to 14 days (2 weeks)
- Safety follow-up period: up to 14 days (2 weeks) after the last dose of study treatment

There are 4 dosing cohorts, Cohort A (0.15 mg/day), B (0.6 mg/day), C (2 mg/day), and D (5 mg/day), planned for Phase 1b part of the study. Each cohort will enroll 6 patients to ensure at least 4 evaluable patients to provide an adequate PK profile and safety assessment. The evaluable patient is defined as any patient who completes 14-day treatment and provides blood samples for PK analyses at Day 14.

The first 2 cohorts, Cohort A and Cohort B, will be initiated at the same time, given the very low doses of KPG-818. Patients will be enrolled to Cohort A and Cohort B in sequence. After at least 4 of 6 patients in Cohort B have completed the 14-day treatment, the Safety Review Committee (SRC) will review the accumulated safety and PK data from Cohorts A and B and determine if Cohort C begins dosing. Similarly, the SRC review for dose escalation will occur when at least 4 of 6 patients in Cohort C have completed the 14-day treatment.

A dose-limiting toxicity (DLT) is defined as any Grade 3 or higher study drug-related adverse event (AE), according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, that occurs during the 14-day treatment, with the following exceptions:

- Asymptomatic Grade 3 anemia, neutropenia, or thrombocytopenia returning to baseline or Grade ≤ 2 within 7 days without transfusion, growth factor support, or other active therapeutic intervention
- Grade 3 study drug administration-related reactions (e.g., fatigue, anorexia, nausea, diarrhea, or vomiting) lasting < 1 day
- Asymptomatic, isolated Grade 3 or higher changes in alkaline phosphatase, creatine phosphokinase, gamma-glutamyl transferase, lipase, or lymphocyte count

During the dose escalation review, if 0 of 4 patients in a cohort experiences a DLT, the next dose cohort will be opened for enrollment after SRC review. If 1 of 4 (25%) patients in a

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cohort, or 2 or more of 6 patients in a cohort, experience DLTs, the additional dosing in the current cohort (s) and dose escalation will be withheld until SRC review. The individual patient with a DLT will be discontinued from the study.

The SRC review process will be described in detail in [Section 8.9](#). The SRC's decision may include to proceed to the next planned dose level, to reduce the dose, to add additional patients to the current cohort, to add new dose cohort (s), or to stop the Phase 1b part of the study based on the review of safety and tolerability assessments, clinical efficacy, and PK data. According to the preclinical and early clinical data, the highest dose level will not exceed 10 mg/day.

Safety and tolerability measures will be collected at study visits and include the occurrence of AEs, vital signs, physical examinations, electrocardiograms (ECGs), and clinical laboratory safety tests.

Pharmacokinetics

Blood samples for PK analysis will be collected pre-dose on Day 1; pre-dose on Day 7; at 1, 2, 6, and 10 hours post dose on Day 7; pre-dose on Day 8 (i.e., 24 hours after the pre-dose on Day 7); pre-dose on Day 14; and pre-dose on Day 15 (i.e., 24 hours after the pre-dose on Day 14) (see [Appendix 10](#)).

Pharmacodynamics and biomarkers

Blood samples for biomarkers analysis from each of the 24 patients in Phase 1b will be collected at 3 time points: pre-dose on Day 1, pre-dose on Day 7, and pre-dose on Day 15 (i.e., 24 hours after the pre-dose on Day 14) (see [Appendix 10](#)).

Phase 2a

Phase 2a is planned to be initiated after the completion of Cohort D in Phase 1b, subject to sponsor decision based on the SRC recommendation after a comprehensive review of cumulative safety, PK/PD, and biomarker data.

The Phase 2a study is a randomized, double-blinded, placebo-controlled, parallel group study in patients with active SLE on limited stable background standard-of-care treatment.

The Phase 2a part of the study consists of 3 periods:

- Screening period: up to 28 days (4 weeks)
- Treatment period: up to 12 weeks
- Safety follow-up period: up to 4 weeks post last dose of study drug

Approximately 32 to 48 patients will be randomized (in 1:1:1:1 ratio) to 4 treatment arms. There will be 8 to 12 patients in each arm, with each receiving one of three treatments or placebo: KPG-818 0.15 mg (Treatment Arm E), 0.6 mg (Treatment Arm F), 2 mg (Treatment Arm G), or placebo (Treatment Arm H).

The number of Phase 2a treatment arms and dosing regimen, is subject to the Sponsor's decision based on the SRC's evaluation of the PK, safety, and tolerability data from the

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Phase 1b study. The total daily dose of each Phase 2a arm will not exceed the highest total daily dose shown to be safe and well tolerated in Phase 1b.

In Phase 2a study, patients should be on a stable SLE treatment regimen consisting of at least 1 of following medications (alone or in combination) (see [Section 6.1](#) for details):

- Corticosteroids (prednisone or prednisone equivalent, up to 20 mg/day)
- Immunosuppressants including methotrexate, azathioprine, leflunomide, mycophenolate mofetil, or mycophenolic acid
- Anti-malarials (e.g., hydroxychloroquine, chloroquine, or quinacrine)

Safety measures will be collected at study visits and include the occurrence of AEs, vital signs, physical examinations, ECGs, and clinical laboratory safety tests. Efficacy of KPG-818 will be evaluated by measuring disease biomarkers and using validated SLE outcome measures including the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), Physician Global Assessment (PGA), and Cutaneous Lupus erythematosus disease Area and Severity Index (CLASI) activity score, as well as 28-count tender and swollen joints.

Pharmacokinetics

Blood samples for PK analysis will be collected as follows: pre-dose on Day 1; pre-dose on Day 2; pre-dose on Day 12; pre-dose on Day 13; pre-dose on Day 14 and at 1, 2, 6, 10 and 24 hours post dose on Day 14 (24 hours post dose for Day 14 is drawn on Day 15); and 24 hours after dosing on Day 84 (24 hours post-dose for Day 84 is drawn on Day 85) (See [Appendix 10](#)).

Pharmacodynamics and biomarkers

Blood samples for biomarkers analysis will be collected at 3 time points: pre-dose on Day 1, 24 hours post-dose Day 14 (24 hours post-dose for Day 14 is drawn on Day 15), and 24 hours after the last dose on Day 84 (the 24 hours post-dose Day 84 sample is drawn on Day 85) (See [Appendix 10](#)).

Gene Expression test

The mRNA assay for Aiolos and Type I IFNGS (whole blood sample) targeting the five genes (IKZF3, IFI44, IFI44L, IFI27, and RSAD2) will be taken once, on Day 1 (pre-dose draw).

Number of Patients

Phase 1b: Approximately 24 patients with SLE will be enrolled in 4 cohorts at the proposed KPG-818 dose levels of 0.15, 0.6, 2, and 5 mg/day. Each cohort will enroll at least 6 patients to ensure at least 4 evaluable patients to allow adequate PK and safety profiling.

Phase 2a: Approximately 32 to 48 patients with SLE will be randomized 1:1:1:1 into one of 3 treatment arms (KPG-818 0.15, 0.6, and 2 mg) or a placebo arm.

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Diagnosis and Main Criteria for Inclusion and Exclusion

Male and female patients with a diagnosis of SLE will be included in this study.

Inclusion criteria are listed as follows:

1. Male or female of 18 years of age or older at the time of signing the informed consent form (ICF).
2. Body mass index (BMI) between 18 and 40 kg/m².
3. Able and willing to adhere to the visit schedule and other protocol requirements.
4. Diagnosed with SLE according to the 2019 EULAR/ACR criteria for SLE (See [Appendix 1](#)).
5. Meeting SLE activity requirements as described below:
 - For the Phase 1b part of the study, patients with or without active SLE may be enrolled if, in the opinion of the Investigator, the disease activity is stable and there will be no need for change or increase in SLE therapy anticipated for the study duration. If patients are on stable standard care of SLE treatment, this should comply with inclusion criteria No. 11.
 - For the Phase 2a part of the study, patients must have a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) score of ≥ 6 points at Screening visit with a SLEDAI-2K clinical score ≥ 4 points at Baseline visit. The "clinical" score is the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or blood laboratory results including immunologic measures. Neurologic descriptors of the SLEDAI-2K are not counted towards the SLEDAI study entry criteria. In addition, the patient must be on stable standard care of SLE treatment with at least one of the followings: oral corticosteroids (OCS), anti-malarial, or immunosuppressant (see inclusion criteria No. 11 for allowed medications and doses).
6. Documented history or presence at Screening of positive autoantibodies associated with SLE, which must include at least 1 of the following:
 - Positive antinuclear antibody (ANA) test with a titer of 1:80 or greater
 - Anti-dsDNA antibodies elevated to above normal
 - Anti-Smith antibody elevated to above normal
7. Women of childbearing potential (WOCBP) must:
 - Have 2 negative serum pregnancy tests as verified by the Investigator prior to starting study therapy, 1 at Screening and again within 3 days before taking the first dose of KPG-818, then have a negative urine pregnancy test at Baseline before dosing. WOCBP must agree to ongoing pregnancy testing during the course of the study and after end of study treatment. This applies even if the patient practices true abstinence from heterosexual contact.
 - Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use 2 forms of reliable contraception simultaneously. One must be a highly effective method and 1 additional effective (barrier) method (see [Appendix 5](#) for more details), and both

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must be practiced without interruption, at least 28 days before starting investigational medicinal product (IMP), during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy.

8. Male patients must: Practice true abstinence or agree to use a barrier contraception (male latex condom or non-latex condom NOT made out of natural [animal] membrane [for example, polyurethane]) during sexual contact with WOCBP while participating in the study, and for at least 90 days following IMP discontinuation, even if he has undergone a successful vasectomy. Male patients must agree not to donate semen or sperm during the treatment period and for at least 90 days following the discontinuation of KPG-818.
9. Female patients who are postmenopausal must demonstrate a follicle stimulating hormone (FSH) blood levels of $\geq$ than 40 mIU/mL at the Screening visit. Women aged > 60 years old whose FSH values are not equal to or greater than 40 mIU/mL may be included at the discretion of the Investigator and in consultation with the Sponsor (see [Appendix 5](#) for more details).
10. All patients must:
 - Understand that KPG-818 could have potential teratogenic risk
 - Agree not to share KPG-818 with another person
 - Be counseled about pregnancy precautions and risks of fetal exposure as described in the Pregnancy Prevention Plan
11. In Phase 2a part of the study, the patient must be on stable standard care of SLE treatment with at least one of the followings: oral corticosteroid, anti-malarial, or immunosuppressant:
 - a. If taking OCS, must be on-treatment for ≥ 4 weeks before the Screening visit, and maintained on a stable dose of ≤ 20 mg/day of prednisone or equivalent for at least 4 weeks before the Baseline visit.
 - b. If taking an anti-malarial agent (hydroxychloroquine, chloroquine, or quinacrine), must be on-treatment for ≥ 8 weeks before the Screening visit and be on a stable dose for ≥ 4 weeks before the Screening visit. Anti-malarials at the following doses are allowed:
 - Hydroxychloroquine (≤ 400 mg/day)
 - Chloroquine (≤ 500 mg/day)
 - Quinacrine (≤ 200 mg/day)
 - c. If taking allowed immunosuppressants, must be on-treatment for ≥ 8 weeks prior to the Screening visit and be on a stable dose for ≥ 4 weeks before the Screening visit. Only 1 of the immunosuppressants below is allowed at the indicated doses:
 - Micophenolate mofetil (≤ 2 g/day) or mycophenolic acid (≤ 1.44 g/day)
 - Azathioprine (≤ 200 mg/day)
 - Methotrexate (≤ 20 mg/week)
 - Leflunomide (≤ 20 mg/day)

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- d. If taking NSAIDs or other regularly administered analgesics, these will be allowed if treatment started ≥ 4 weeks before the Baseline visit and dosing has not been changed within the last 2 weeks before the Baseline visit.
 - e. If immunosuppressants, anti-malarial, or OCS is discontinued, the last dose must be more than 4 weeks prior to Screening visit.
12. Patients must agree not to donate blood (or any component of blood) from 3 months before Screening until 3 months after the last dose of KPG-818.
13. Patients must be willing to comply with precautions to reduce the risk of COVID-19 infection in accordance with recommendations from the applicable medical associations and the Investigator for the duration of the study, and to undergo COVID-19 polymerase chain reaction (PCR) test as required based on the Investigator judgment and/or local requirements.

Exclusion criteria are listed as follows:

1. Use of any prohibited medications within the pre-specified time (see Appendix 6 for details on the required washout period for each drug class).
2. Any of the following noted at Screening (within 6 weeks before Week 1 [Day 1] in Phase 1b, within 4 weeks before Week 1 [Day 1] in Phase 2a):
 - Aspartate aminotransferase (AST) $> 2.0 \times \text{ULN}$
 - Alanine aminotransferase (ALT) $> 2.0 \times \text{ULN}$
 - Total bilirubin $> 1.5 \times \text{ULN}$ (unless due to Gilbert's syndrome)
 - Serum creatinine $> 2.5 \text{ mg/dL}$ (or $> 221 \mu\text{mol/L}$)
 - Neutrophil count $< 1500/\mu\text{L}$ (or $< 1.5 \times 10^9/\text{L}$) ($< 1000/\mu\text{L}$ [or $< 1.0 \times 10^9/\text{L}$] if the neutropenia is related to SLE)
 - Platelet count $< 50\,000/\mu\text{L}$ (or $< 50 \times 10^9/\text{L}$) ($< 25\,000/\mu\text{L}$ [or $< 25 \times 10^9/\text{L}$] if the thrombocytopenia is related to SLE)
 - Hemoglobin $< 8 \text{ g/dL}$ (or $< 80 \text{ g/L}$) ($< 7 \text{ g/dL}$ [or $< 70 \text{ g/L}$] if related to SLE)
3. Have an estimated glomerular filtration rate (eGFR) of $< 60 \text{ mL/min/1.73 m}^2$ (CKD-EPI formula) at Screening.
4. Have a spot urine protein to creatinine ratio (sUPCR) $> 2000 \text{ mg/g}$ (226 mg/mmol , as an estimate of approximate proteinuria $> 2 \text{ g/day}$) at Screening.
5. Active and/or unstable neuropsychiatric SLE (e.g., neuropsychiatric SLE including seizures, psychosis, acute confusional state, cerebrovascular accident, aseptic meningitis, or polyneuropathy).
6. Positive serology test for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV-1 and HIV-2) at Screening. In cases of a positive screening test, patient may be enrolled if a confirmatory test is negative (see [Appendix 3](#) for details). Exception: patient who test positive for HCV antibodies may be enrolled if confirmed with cured HCV infection and documented completion of treatment more than 3 months before screening and HCV must not be detectable at screening.

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7. Active or history of severe systemic bacterial, viral, fungal, mycobacterial, or parasitic infections (requires hospitalizations or IV antibiotics) within 6 months prior to Screening.
8. Any current or recent (within 4 weeks of Screening) signs or symptoms of infection, except for fungal infections of the nail beds, oral or vaginal candidiasis that has resolved, or minor infections (e.g., common cold, viral gastroenteritis, urinary tract infection) that have in the Investigator's judgement, completely resolved prior to the Baseline visit.
9. Any severe, recurrent, disseminated viral infections, particularly herpes viruses such as HSV-1, HSV-2, VZV, CMV (e.g., herpes encephalitis, ophthalmic herpes, disseminated zoster, CMV colitis) per Investigator's judgment. Recurrent is defined as 2 or more episodes in the past 2 years and/or with an episode within 3 months of Screening.
10. Known history of congenital or acquired immunodeficiency, splenectomy, or any underlying condition that predisposes the patient to infection.
11. Active tuberculosis (TB) or a history of incompletely treated TB, or a positive, QuantiFERON[®]-TB Gold test. If a patient's initial TB test result is indeterminate, the test can be repeated once. If the test result is again indeterminate (or positive), the patient will be excluded from the study. An exception for positive or indeterminate results may be made for patients who have documentation of having completed appropriate standard treatment for latent TB before screening and do not have other risk factors, radiologic findings, or physical evidence supporting latent or active TB.
12. History of malignancy within 5 years of Screening with the exception of basal cell or squamous cell in situ skin carcinomas or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
13. History of antiphospholipid syndrome with thromboembolic event within 12 months of screening or not on an adequate anticoagulation regimen. However, presence of antiphospholipid antibodies alone (without a history of thromboembolic event) is not exclusionary.
14. Other non-SLE driven inflammatory joint or skin disease, mixed connective tissue disease, scleroderma, and/or overlap syndromes. An exception may be allowed for rheumatoid arthritis overlapping with SLE (i.e., RHUPUS) with no erosive joint disease after a discussion with the medical monitor. Patients with SLE and secondary Sjogren syndrome are not exclusionary.
15. Clinically significant or unstable or uncontrolled acute or chronic disease not related to SLE that in the Investigator's opinion would preclude patient participation.
16. Concomitant condition (such as asthma) that required systemic corticosteroid use within 1 year before Screening. Use of inhaled corticosteroid is not exclusionary.
17. History of alcohol or drug abuse within 1 year before screening based on the Investigator's judgement.
18. Have a positive urine drug test at Screening (see [Appendix 3](#)) except if the patient has a valid prescription for an allowed concomitant medication or substance abuse/dependence has been ruled out in the Investigator's judgment.

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19. History of major surgery within 12 weeks prior to Screening or any planned major surgery during the study.
20. Clinically significant ECG abnormalities or have a corrected QT (QTc) interval value > 480 ms at Screening, in the Investigator's opinion would preclude patient participation.
21. Pregnant or breast-feeding female.
22. Signs or symptoms that in the opinion of the Investigator, may be suggestive of COVID-19 infection. The patient may be allowed to enter the study if a COVID-19 PCR test performed during the Screening results in a negative outcome.
23. Known allergic reaction to any of the ingredients for study drug or placebo.

Investigational Medicinal Products, Dose, and Mode of Administration

IMP: KPG-818 capsules.

Proposed Phase 1b dose levels: Cohort A (0.15 mg/day), B (0.6 mg/day), C (2 mg/day), and D (5 mg/day).

Proposed Phase 2a dose levels: Treatment Arm E (0.15 mg/day), F (0.6 mg/day), G (2 mg/day) and H (placebo).

Administration route: KPG-818 capsules will be administered orally approximately every 24 hours with approximately 240 mL of water in the morning at similar time, with or without food.

If patients forget to take KPG-818 in the morning, it is allowed to take the dose within 12 hours. Otherwise, the KPG-818 dose will be skipped, and the patient will proceed with dosing the next day in the morning.

Study drug dosing should occur at the study site on the below days so that PK and or PD samples can be collected:

Phase 1b: Days 1, 7, 8, and 14.

Phase 2a: Days 1, 2, 12, 13, 14, and 15

Reference Product and Mode of Administration

Reference product: placebo capsules.

Administration route: Capsules will be administered orally approximately every 24 hours with approximately 240 mL of water in the morning at similar time, with or without food.

Duration of Patient Participation in the Study

Phase 1b: up to 10 weeks

Planned Screening duration: a maximum of 6 weeks.

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Planned study duration (Baseline to Follow-up): 4 weeks, including a 2-week treatment period and a 2-week safety follow-up.

Phase 2a: up to 20 weeks

Planned Screening duration: a maximum of 4 weeks.

Planned study duration (Baseline to Follow-up): 16 weeks, including a 12-week treatment period and a 4-week safety follow-up.

Endpoints

Phase 1b

Primary endpoints:

- Incidence and severity of AEs and serious AEs (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness
- 12-lead ECGs parameter results at each visit and changes from baseline
- Vital signs (blood pressure [BP], heart rate, and temperature) parameter results at each visit and changes from baseline
- Clinical laboratory results and changes from baseline
- Physical examinations changes from baseline
- Study drug exposure/compliance.
- The PK endpoints for assessment of KPG-818 and KPG-818H (if applicable).

After the plasma concentration reaches a steady state (most likely Day 5), the PK parameters to be assessed include but are not limited to:

- time of the maximum observed plasma concentration (t_{max})
- apparent plasma terminal elimination half-life ($t_{1/2}$)
- mean retention time (MRT)
- trough concentrations at steady state (C_{ss_min})
- peak concentrations at steady state (C_{ss_max})
- the area under the concentration-time curve at steady state (the area under the plasma concentration-time curve over a dosing interval [AUC_{τ}])
- the area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$)
- clearance (CL/F_{ss})
- the apparent volume of distribution (V_z/F_{ss}), and
- accumulation index and/or ratio (AR)

Exploratory endpoints:

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- Mean change from baseline in potential KPG-818 biomarkers (e.g., Aiolos, Ikaros, and CRBN proteins) at Week 2
- Mean change from baseline in absolute counts of CD19⁺ B cells, CD268⁺ B cells, CD3⁺ T cells, T regulatory cells (Treg), and plasmacytoid dendritic cells (pDC) at Week 2
- Mean change from baseline in C3/C4, anti-dsDNA, and immunoglobulins

Phase 2a

Primary endpoint:

- Incidence and severity of AEs and SAEs, related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness.
- 12-lead ECGs parameter results at each visit and changes from baseline.
- Vital signs (BP, heart rate, and temperature) parameter results at each visit and changes from baseline.
- Clinical laboratory results and changes from baseline.
- Physical examinations changes from baseline.
- Study drug exposure/compliance.

Secondary endpoints:

- Mean change from baseline in SLEDAI-2K score at Week 4, 8, 12, and 16.
- The proportion of patients with SLEDAI-2K improvement ≥ 4 points from baseline at Week 4, 8, 12, and 16.
- Mean change from baseline in PGA score at Week 4, 8, 12, and 16.
- Mean change in CLASI activity score from baseline.
- The proportion of patients with a $\geq 50\%$ reduction from baseline in CLASI activity score at Week 12, in patients with baseline CLASI activity score ≥ 10 .
- Mean change in tender and swollen joints from baseline.

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- The PK endpoints for assessment of KPG-818 and KPG-818H (if applicable).
After the plasma concentration reaches a steady state (most likely Day 5), the PK parameters to be assessed include but are not limited to:
 - time of the maximum observed plasma concentration (t_{max})
 - apparent plasma terminal elimination half-life ($t_{1/2}$)
 - mean retention time (MRT)
 - trough concentrations at steady state (C_{ss_min})
 - peak concentrations at steady state (C_{ss_max})
 - the area under the concentration-time curve at steady state (the area under the plasma concentration-time curve over a dosing interval [AUC_{τ}])
 - the area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$)
 - clearance (CL/F_{ss})
 - the apparent volume of distribution (V_z/F_{ss}), and
 - accumulation index and/or ratio (AR)

Exploratory endpoints:

- Mean change in OCS dose from baseline.
- Mean change from baseline in potential biomarkers (e.g., Aiolos, Ikaros, and CRBN proteins) of KPG-818.
- Mean change from baseline in absolute counts of $CD19^+$ B cells, $CD268^+$ B cells, $CD3^+$ T cells, Treg, and pDC.
- Mean change from baseline in C3, C4, anti-dsDNA, anti-SSA, anti-SSB, anti-Smith, antiphospholipid antibodies (APL), and immunoglobulins.

Safety:

AEs; clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis); 12-lead ECGs; vital signs measurements; and physical examinations.

Exploration:

Efficacy of KPG-818 may closely correlate with the 5 gene expression levels. The examination data of the genes will help with the efficacy analysis and stratification and selection of the patients in the future.

Statistical Methods

Pharmacokinetics:

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Individual plasma and PK parameters of KPG-818 and KPG-818H will be listed and summarized using descriptive statistics. Individual and mean KPG-818 and KPG-818H concentration-time profiles will be presented graphically.

Where data are available, KPG-818 dose proportionality will be examined across the dose groups. AUC type PK parameters and $C_{\max}$ will be analyzed for dose proportionality using a power model approach.

Using the trough levels during multiple dose administrations, achievement of steady state may also be evaluated using appropriate statistical methods.

Pharmacodynamics:

The PD population will include all patients who received at least 1 dose of study treatment (KPG-818 or placebo) and for whom PD markers can be evaluated.

Efficacy:

All efficacy parameters will be listed and summarized using descriptive statistics. Comparisons between different dose groups and placebo will be done by exact Fisher-tests and exact confidence intervals. Continuous parameters will be tested by student's t-tests and corresponding confidence intervals.

Safety:

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned.

Biomarkers:

Summary statistics will be provided for the potential biomarkers.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ACR	American College of Rheumatology
ANA	antinuclear antibody
APL	antiphospholipid antibodies
AR	accumulation ratio and/or index
AUC _{0-∞}	area under the plasma concentration-time curve from time zero to infinity
AUC _{0-tlast}	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
AUC ₀₋₂₄	area under the plasma concentration-time curve from time zero to 24 hours post-dose
AUC _{0-τ}	area under the plasma concentration-time curve over a dosing interval
BP	blood pressure
CFR	Code of Federal Regulations
CLASI	Cutaneous Lupus erythematosus disease Area and Severity Index
C _{max}	maximum observed plasma concentration
C _{min}	minimum observed plasma concentration
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
ET	early termination
FDA	Food and Drug Administration
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
IMiDs	immunomodulatory imide drugs
IMP	investigational medicinal product
IRB	Institutional Review Board
MAD	multiple ascending dose
mRNA	messenger RiboNucleic Acid
MTD	maximum tolerated dose
NOAEL	no observed adverse effect level
NSAID	non-steroidal anti-inflammatory drug
OCS	oral corticosteroids

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PD	pharmacodynamic (s)
pDC	plasmacytoid dendritic cells
PGA	Physician Global Assessment
PK	pharmacokinetic (s)
QTc	corrected QT
SAD	single ascending dose
SAE	serious adverse event
SD	Sprague Dawley
SLE	systemic lupus erythematosus
SLEDAI-2K	systemic lupus erythematosus disease activity index 2000
SRC	Safety Review Committee
sUPCR	spot urine protein to creatinine ratio
$t_{1/2}$	apparent plasma terminal elimination half-life
t_{max}	time of the maximum observed plasma concentration
TMF	Trial Master File
Treg	T regulatory cells
ULN	upper limit of normal
V_z/F	apparent volume of distribution
WOCBP	women of childbearing potential

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1. INTRODUCTION

1.1. Overview

Systemic lupus erythematosus (SLE, commonly referred to as lupus) is a clinically heterogeneous, autoimmune disorder of unknown cause. Afflicting approximately 500,000 people in the United States (US), SLE is characterized by considerable mortality and morbidity. For example, with existing therapies, half of patients with organ-threatening disease (for example, cardiopulmonary, hepatic, renal, central nervous system, or autoimmune hemolytic anemia) do not survive 20 years after diagnosis, and the quality of life for those individuals with all forms of SLE is usually seriously compromised. According to the American College of Rheumatology (ACR), 10 times more women than men have lupus, and the disease often starts between the ages of 15 and 44 years.

Treatment of lupus depends on the part of the body being affected by the disease and the severity of the problem. The Food and Drug Administration (FDA) approved the first drug to treat lupus, aspirin, in 1948, and later approved corticosteroids, such as prednisone, which suppress the immune system and reduce inflammation. The agency approved the antimalarial drug Plaquenil (hydroxychloroquine), which helps to relieve some lupus symptoms such as fatigue, rashes, joint pain, or mouth sores. Part of what makes lupus research such a challenge is that the precise problem with the immune system is so different among patients. New research is trying to focus on what the best targets might be.

The FDA approved Benlysta (Belimumab), the first targeted therapy for lupus, in 2011. Benlysta is administered intravenously. It is designed to target a protein called B-lymphocyte stimulator, which may reduce the impact of abnormal cells thought to be a factor in the development of lupus. Benlysta doesn't work for every SLE patient, and not enough research has been done yet to know if it will work in patients with very severe lupus. But it works well for lupus patients with skin and joint involvement.

Advances in the understanding and treatment of lupus over the last several decades have resulted in patients with the disease living longer. Despite these advances, however, there remain many people with lupus who need additional treatment options.

KPG-818 is a novel CRBN (Cereblon) modulator, part of the cullin 4-RING E3 ubiquitin ligase complex CRL4-CRBN.¹ KPG-818 was discovered by Kangpu Biopharmaceuticals, Ltd.'s drug discovery program aiming at the design of novel and next-generation immunomodulatory agents. KPG-818 is structurally similar to Celgene's new investigational drug CC-220, but with greater CRBN binding affinity. Results from in vitro studies in human peripheral blood mononuclear cells (PBMC) demonstrated that KPG-818 significantly inhibits levels of the inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor (TNF)- α , and CRBN substrate proteins Aiolos and Ikaros. Based on these available data, Kangpu Biopharmaceuticals, Ltd. is developing KPG-818 for the treatment of patients with SLE as the intended indication.

1.2. Summary of Nonclinical Pharmacology

In vitro fluorescence polarization binding assay was performed by using recombinant CRBN-DDB1 enzyme. Cy5-conjugated thalidomide served as the substrate, and thalidomide and pomalidomide as positive control compounds. In the assay, KPG-818 exhibited better

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binding affinity to CRBN than CC-220. The data indicated that CRBN is the binding target of KPG-818.

Cytokines are a diverse group of soluble proteins and peptides which act as regulators under both normal and pathological conditions to modulate the functional activities of individual cells and tissues. Many cytokines play critical roles in the development of diseases such as cancer, autoimmune disease, and inflammation. KPG-818 was investigated for the potential immunomodulatory activities on immune cytokines production from healthy human peripheral blood mononuclear cells (PBMCs), which were stimulated with a low concentration of lipopolysaccharide. KPG-818 significantly enhanced production of the anti-inflammatory cytokine IL-10, and inhibited the expression of the proinflammatory cytokines such as TNF- α and IL-6.

1.3. Summary of Safety Pharmacology and Toxicology

To support the investigational new drug opening, a battery of safety pharmacology, general toxicology studies, and genotoxicity panel have been conducted in compliance with US FDA Good Laboratory Practice (GLP) Regulations. These studies included: a hERG assay; a behavioral/central nervous system function study in Sprague Dawley (SD) rats using the functional observational battery; a respiratory function safety pharmacology study in SD rats; a cardiovascular telemetry study in conscious Cynomolgus monkeys; 4-week toxicity and toxicokinetic studies in SD rats and Cynomolgus monkeys with 4-week recovery; a bacterial reverse mutation assay (Ames); an in vitro chromosome aberration assay in human peripheral blood lymphocytes; and an in vivo bone marrow micronucleus assay in rats. Additionally, non-GLP acute and repeat-dose range finding toxicity studies in SD rats and Cynomolgus monkeys were also conducted.

Findings from the preclinical safety studies of KPG-818 are summarized below by body system:

- **Nervous system:** KPG-818 had no effect on the neurobehavioral parameters evaluated in male rats at 5 mg/kg and in female rats at ≤ 60 mg/kg. Low arousal and decreased motor activity were noted in male rats at ≥ 60 mg/kg KPG-818 and in female rats at 600 mg/kg KPG-818.
- **Respiratory system:** Statistically significant decreases in tidal volume at 1-hour post-dose were noted in all treated male rats, although a dose response was not observed. Decreases of minute volume were noted in males given ≥ 60 mg/kg at 1-hour post-dose. There was no dose response relationship. For the treated female rats, in comparison with their own pre-dose data, obvious increases in respiratory rate and minute volume were observed in the 600 mg/kg dose group at 1-hour post-dose, although without statistical significance, the relevance of test article effect could not be excluded. There were no test article-related changes on tidal volume in treated females. Treatment of KPG-818 had no obvious effect on the respiratory rate in all male rats. Treatment of KPG-818 up to 60 mg/kg had no effect on the respiratory parameters in female rats.
- **Cardiovascular system:** KPG-818 at 1, 10, and 50 mg/kg had no effect on the cardiovascular parameters of Cynomolgus monkeys, including systolic BP, diastolic BP, mean arterial BP, body temperature, heart rate, RR interval, PR interval, QRS duration, QT and corrected QT (QTc) intervals. KPG-818 inhibited hERG potassium

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channels expressed in human embryonic kidney (HEK293) cell line with a half-maximal inhibitory concentration (IC₅₀) of 52.14 µmol/L, suggesting that the potential for QT prolongation at clinically relevant concentrations is remote.

In the 28-day repeat-dose toxicity study in Cynomolgus monkeys, there was no effect of KPG-818 on qualitative or quantitative electrocardiogram (ECG) parameters.

- **Blood system:** In the 28-day repeat-dose toxicity study in Cynomolgus monkeys, erythrocyte counts, hematocrit, and hemoglobin values were minimally to mildly decreased in both sexes given ≥ 5 mg/kg/day. These changes were associated with a minimal decrease in erythrocyte volume and hemoglobin. The changes in erythrocyte parameters were associated with an increase in reticulocyte counts in some animals, but this change was inconsistent. Lymphocyte counts were minimally to moderately decreased in both sexes given ≥ 5 mg/kg/day with considerable difference in the changes between animals; decreased lymphocyte counts correlated generally with the group microscopic findings of decreased lymphocytes in lymphoid tissues. Changes in erythroid parameters and lymphocyte counts were not considered adverse because they were not associated with changes in the health of the animals.

In the 28-day repeat-dose toxicity study in rats, a test article-related hematology change occurred in absolute neutrophils in females given 300 mg/kg/day (minimally decreased 41%).

There were no test article-related changes in coagulation parameters in both species tested.

- **Clinical chemistry including urinalyses:** In the 28-day repeat-dose toxicity study in Cynomolgus monkeys, minimal test article-related changes occurred in total protein, albumin, cholesterol, blood urea nitrogen, and phosphorus compared to baseline. These changes were considered non-adverse, and not important to the toxicity profile of the test-article.

In the 28-day repeat-dose toxicity study in rats, test article-related changes in clinical chemistry parameters included minimally to mildly increased cholesterol in males and females given ≥ 50 mg/kg/day (14% to 95% increase vs. control mean; not statistically significant in females given 50 mg/kg/day) and minimally increased alanine aminotransferase (ALT) in females given 300 mg/kg/day (40% increase). Test article-related changes noted in females given 300 mg/kg/day were considered to be of little or no toxicological significance and included minimally increased globulin (21% increase), and minimally decreased albumin/globulin (18% decrease), total bilirubin (60% decrease), and phosphorus (13% decrease).

There were no test article-related changes in urinalysis parameters in both species tested.

The maximum tolerated dose (MTD) was greater than 1000 mg/kg in the rat acute study; the no observed adverse effect level (NOAEL) was 300 mg/kg after daily oral KPG-818 administration to SD rats for 4 weeks.

In Cynomolgus monkeys, the MTD was 1000 mg/kg in the acute study; the NOAEL was 25 mg/kg after daily oral KPG-818 administration to Cynomolgus monkeys for 4 weeks.

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The genotoxic potential of KPG-818 was evaluated in the Ames test, chromosomal aberration study, and micronucleus assay, and negative results were obtained from all 3 tests, strongly suggesting that KPG-818 is not mutagenic at clinically relevant concentrations.

KPG-818 is an immunomodulatory agent and drugs in this class typically carry warnings of embryo-fetal toxicity, and venous and arterial thromboembolism.

1.4. Summary of Nonclinical Pharmacokinetics

In vitro studies to establish the metabolite profiles of KPG-818 were performed in liver microsomes of multiple animal species including mouse, rat, dog, monkey, and human. Drug metabolism and pharmacokinetic (PK) studies were also performed in vivo in SD rats and Cynomolgus monkeys. Metabolic stability assays indicated that metabolism of KPG-818 was moderate in mouse, rat, dog, monkey, and human liver microsomes.

Inhibition of KPG-818 on cytochrome P450 (CYP) enzymes was evaluated by the measurement of the IC₅₀ values in pooled human liver microsomes. KPG-818 showed no inhibition against CYP2A6 and CYP2B6 over the concentration range tested (0.15 to 50 µM) and no significant inhibition on CYP1A2, CYP2C8, CYP2C9, and CYP3A4 (midazolam). Inhibition of CYP2C19, CYP2D6, CYP2E1, and CYP3A4 (testosterone) was observed with mean IC₅₀ values of 45.9 µM, >43.1 µM, 7.18 µM, and >46.8 µM, respectively. KPG-818 may have an induction effect on CYP3A4 at the high concentration of 20 µM.

The extent of binding of KPG-818 to mouse, rat, dog, monkey, and human plasma protein was determined in vitro using equilibrium dialysis at concentrations of 0.5 µM, 5 µM, and 50 µM. The mean unbound percentage of KPG-818 in human, monkey, dog, rat, and mouse plasma at the concentration of 0.5 µM was 24.3%, 16.0%, 28.6%, 39.8%, and 26.1%, respectively. The percentage unbound in human, monkey, dog, rat, and mouse plasma at the concentration of 5 µM was 28.6%, 19.2%, 28.8%, 38.3%, and 26.0%, respectively. The percentage unbound in human, monkey, dog, rat, and mouse plasma at the concentration of 50 µM was 26.3%, 28.1%, 31.7%, 36.4%, and 25.4%, respectively.

The transport study results indicate that KPG-818 is a substrate of P-glycoprotein (P-gp) but not a substrate of BCRP nor SLC transporters (OAT1, OAT3, OCT2, OATP1B1, and OATP1B3). The inhibition studies indicated that KPG-818 is not an inhibitor to P-gp, OAT1, OAT3, OCT2, or OATP1B3, but is a very weak inhibitor to OATP1B1 and BCRP with an apparent IC₅₀ value of 29.2 µM and 13.6 µM, respectively.

Following a single intravenous bolus administration of KPG-818 in Cynomolgus monkeys at 5 mg/kg (3/sex), KPG-818 had a mean clearance of 634 mL/hr/kg for male monkeys and 801 mL/hr/kg for female monkeys, with mean apparent plasma terminal elimination half-life (t_{1/2}) of 5.2 hours for males and 7.7 hours for females, respectively.

Following a single oral gavage administration of KPG-818 at 10 or 30 mg/kg (3/sex/dose), the maximum observed plasma concentration (C_{max}) of KPG-818 occurred between 0.5 and 2 hours post-dose. Mean C_{max} and area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{0-tlast}) of KPG-818 increased with increasing dose from 10 to 30 mg/kg. The mean absolute bioavailability of KPG-818 ranged from 25.6% to 25.8% for males and 37.1% to 50.8% for females, respectively.

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Approximately 25% to 30% of KPG-818 converted to KPG-818H. No apparent significant gender difference in PK of KPG-818 following single oral or intravenous administration in Cynomolgus monkeys was observed.

Following a single intravenous bolus administration of KPG-818 in Sprague-Dawley rats at 3 mg/kg (3/sex), KPG-818 had a mean clearance of 2573 mL/hr/kg for male SD rats and 1209 mL/hr/kg for female SD rats, with the average $t_{1/2}$ of 4.1 hours for male SD rats and 4.5 hours for female SD rats, respectively.

Following a single oral gavage administration of KPG-818 at 10 mg/kg, 30 mg/kg, 100 mg/kg, 300 mg/kg, 450 mg/kg, 600 mg/kg, or 1000 mg/kg (3/sex/dose), the plasma concentration of KPG-818 reached a peak of between 0.5 and 6.0 hours post dosing. Mean C_{max} and $AUC_{0-tlast}$ values of KPG-818 increased with increasing dose from 10 mg/kg up to 450 mg/kg, but decreased from 450 mg/kg to 1000 mg/kg. The mean absolute oral bioavailability of KPG-818 was 33.9% to 73.0% for males and 16.2% to 74.4% for females, respectively.

About 40% of KPG-818 converted to KPG-818H. There were marked gender differences in the PK of KPG-818 in SD rats with much larger exposure in female rats than in male rats.

Following 7-day repeat oral doses at 30 mg/kg, the mean $AUC_{0-tlast}$ and C_{max} values of KPG-818 on Day 7 was a little higher than those on Day 1 for male SD rats, while the mean $AUC_{0-tlast}$ and C_{max} values of KPG-818H on Day 7 were very close to those on Day 1 for male SD rats. For female SD rats, the $AUC_{0-tlast}$ and C_{max} values of KPG-818 and KPG-818H on Day 7 were a little lower than those on Day 1.

A detailed description of the chemistry, pharmacology, efficacy, and safety of KPG-818 is provided in the Investigator's Brochure.²

1.5. Summary of Clinical Experience

A Phase 1, first-in-human (FIH), randomized, double-blind, placebo-controlled, sequential parallel group, single ascending dose (SAD) study in healthy subjects was completed in the US in April 2020.

A total of 38 subjects in 5 cohorts dosed with 2 mg, 5 mg, 10 mg, 20 mg, and 30 mg KPG-818 completed the study. There were no safety or tolerability concerns with KPG-818 up to a 30-mg dose, supporting further clinical development in patients.

Summary of Phase 1 PK data: following a single oral dose of KPG-818, KPG-818 displayed biexponential clearance. Inter-individual variability decreased as the KPG-818 doses increased. The mean KPG-818 C_{max} was 13.248 ng/mL at the 2-mg dose, 43.686 ng/mL at the 5-mg dose, 89.450 ng/mL at the 10-mg dose, 176.833 ng/mL at the 20-mg dose, and 315.167 ng/mL at the 30-mg dose under fasted conditions. The median time of the maximum observed plasma concentration (t_{max}) was around 1 to 2 hours for all cohorts under fasted conditions. The mean half-life ($T_{1/2 \lambda_z}$) was 11.341 hours at the 2-mg dose, 24.452 hours at the 5-mg dose, 22.571 hours at the 10-mg dose, 22.324 hours at the 20-mg dose, and 21.777 hours at the 30-mg dose under fasted conditions. The mean KPG-818 Cl/F was 20.41 L/h at the 2-mg dose, 14.71 L/h at the 5-mg dose, 13.25 L/h at the 10-mg dose, 11.89 L/h at the 20-mg dose, and 13.60 L/h at the 30-mg dose under fasted conditions. The mean apparent volume of distribution (V_z/F) was 30.13 L at the 2-mg dose, 48.03 L at the 5-mg dose,

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40.56 L at the 10-mg dose, 38.22 L at the 20-mg dose, and 43.56 L at the 30-mg dose under fasted conditions. KPG-818 C_{max} , the area under the plasma concentration-time curve from time zero to 24 hours post-dose (AUC_{0-24}), $AUC_{0-tlast}$ and the area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) showed more than dose-proportional increase in exposure from 2 mg to 10 mg, and became close to dose-proportional increase from 10 mg to 30 mg.

The metabolite of KPG-818, KPG-818H, displayed biexponential clearance. Inter-individual variability decreased as the KPG-818 doses increased. KPG-818H C_{max} , AUC_{0-24} , $AUC_{0-tlast}$ and $AUC_{0-\infty}$ showed more than dose-proportional increase in exposure from 2 mg to 10 mg of KPG-818 and became close to dose-proportional increase from 10 mg to 30 mg of KPG-818.

In the above completed FIH study, the highest observed exposures of KPG-818 and KPG-818H at a single dose of 30 mg were lower than the exposure in rats and monkeys at NOAEL doses.

1.6. Study Rationale

Preclinical study demonstrated that KPG-818 significantly modulated production of cytokines. The FIH SAD clinical study showed a well-established PK profile of KPG-818 and no safety or tolerability concerns with KPG-818 up to a 30-mg dose. This Phase 1b/2a study will be conducted in patients with SLE as recommended by the FDA. The principal aim of this study is to obtain safety and tolerability data, PK, PD, and preliminary efficacy when KPG-818 is administered orally as multiple doses in patients with SLE. This information will help establish the dosing regimen suitable for future studies, provide further clinical safety and PK data, and allow evaluation of clinical benefit of KPG-818 in patients with SLE. The Phase 1b part of the study is open-label and multiple dose escalation cohort study. The Phase 2a part is a randomized, double-blinded, placebo-controlled, and parallel group study in order to avoid bias in the collection and evaluation of data during its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions.

1.7. Benefit-risk Assessment

KPG-818 is structurally similar to Celgene's new investigational drug CC-220, but with greater CRBN binding affinity. Results from in vitro studies in human PBMC demonstrated that KPG-818 significantly inhibits levels of the inflammatory cytokines IL-6 and TNF- α , and CRBN substrate proteins Aiolos and Ikaros. The risks of participation are primarily those associated with adverse reactions to KPG-818, although there may also be some discomfort from collection of blood samples and other study procedures. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with KPG-818 may be found in the Investigator's Brochure.²

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2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Phase 1b

The primary objectives of the study are:

- To assess the safety and tolerability of multiple oral doses of KPG-818 in patients with SLE over a 14-day treatment period.
- To characterize the single and multiple oral dose PK of KPG-818 and its metabolite, KPG-818H.

The exploratory objective of the study is:

- To evaluate the pharmacodynamics (PD) markers of KPG-818.

2.1.2. Phase 2a

The primary objective of the study is:

- To assess the safety and tolerability of multiple doses of KPG-818 in patients with SLE over a treatment period of 12 weeks and a follow-up period of 4 weeks.

The secondary objectives of the study are:

- To evaluate the preliminary efficacy of KPG-818 compared with placebo in adult patients with active SLE on limited background standard-of-care treatment over a treatment period of 12 weeks and a follow-up period of 4 weeks.
- To characterize the multiple oral dose PK of KPG-818 and its metabolite, KPG-818H, over a 12-week treatment period.
- To select dosing regimens for Phase 2b

The exploratory objectives of the study are:

- To further explore the efficacy of KPG-818.
- To evaluate the PD markers of KPG-818.

2.2. Endpoints

2.2.1. Phase 1b

Primary endpoints:

- Incidence and severity of AEs and serious AEs (SAEs), related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness.
- 12-lead ECGs parameter results at each visit and changes from baseline.

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- Vital signs (BP, heart rate, and temperature) parameter results at each visit and changes from baseline.
- Clinical laboratory results and changes from baseline.
- Physical examinations changes from baseline.
- Study drug exposure/compliance.
- The PK endpoints for assessment of KPG-818 and KPG-818H (if applicable).

After the plasma concentration reaches a steady state (most likely Day 5), the PK parameters to be assessed include but are not limited to:

- time of the maximum observed plasma concentration (t_{max})
- apparent plasma terminal elimination half-life ($t_{1/2}$)
- mean retention time (MRT)
- trough concentrations at steady state (C_{ss_min})
- peak concentrations at steady state (C_{ss_max})
- the area under the concentration-time curve at steady state (the area under the plasma concentration-time curve over a dosing interval [$AUC\tau$])
- the area under the plasma concentration-time curve from time zero to infinity [$AUC_{0-\infty}$]
- clearance (CL/F_{ss})
- the apparent volume of distribution (V_z/F_{ss}), and
- accumulation index and/or ratio (AR)

Exploratory endpoints:

- Mean change from baseline in potential KPG-818 biomarkers (e.g., Aiolos, Ikaros, and CRBN proteins) at Week 2.
- Mean change from baseline in absolute counts of $CD19^+$ B cells, $CD268^+$ B cells, $CD3^+$ T cells, T regulatory cells (Treg), and plasmacytoid dendritic cells (pDC) at Week 2.
- Mean change from baseline in C3/C4, anti-dsDNA, and immunoglobulins.

2.2.2. Phase 2a

Primary endpoint:

- Incidence and severity of AEs and SAEs, related AEs, AEs leading to study drug discontinuation, AEs by severity and relatedness.
- 12-lead ECGs parameter results at each visit and changes from baseline.
- Vital signs (BP, heart rate, and temperature) parameter results at each visit and changes from baseline.
- Clinical laboratory results and changes from baseline.

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- Physical examinations changes from baseline.
- Study drug exposure/compliance.

Secondary endpoints:

- Mean change from baseline in systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) score at Week 4, 8, 12, and 16.
- The proportion of patients with SLEDAI-2K improvement ≥ 4 points from baseline at Week 4, 8, 12, and 16.
- Mean change from baseline in Physician Global Assessment (PGA) score at Week 4, 8, 12, and 16.
- Mean change in Cutaneous Lupus erythematosus disease Area and Severity Index (CLASI) activity score from baseline.
- The proportion of patients with a $\geq 50\%$ reduction from baseline in CLASI activity score at Week 12, in patients with baseline CLASI activity score ≥ 10 .
- Mean change in tender and swollen joints from baseline.
- The PK endpoints for assessment of KPG-818 and KPG-818H (if applicable).

After the plasma concentration reaches a steady state (most likely Day 5), the PK parameters to be assessed include but are not limited to:

- time of the maximum observed plasma concentration (t_{max})
- apparent plasma terminal elimination half-life ($t_{1/2}$)
- mean retention time (MRT)
- trough concentrations at steady state (C_{ss_min})
- peak concentrations at steady state (C_{ss_max})
- the area under the concentration-time curve at steady state (the area under the plasma concentration-time curve over a dosing interval [$AUC\tau$])
- the area under the plasma concentration-time curve from time zero to infinity [$AUC_{0-\infty}$])
- clearance (CL/F_{ss})
- the apparent volume of distribution (V_z/F_{ss}), and
- accumulation index and/or ratio (AR)

Exploratory endpoints:

- Mean change in oral corticosteroids (OCS) dose from baseline.
- Mean change from baseline in potential biomarkers (e.g., Aiolos, Ikaros, and CRBN proteins) of KPG-818.
- Mean change from baseline in absolute counts of $CD19^+$ B cells, $CD268^+$ B cells, $CD3^+$ T cells, Treg, and pDC.

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- Mean change from baseline in C3, C4, anti-dsDNA, anti-SSA, anti-SSB, anti-Smith, antiphospholipid antibodies (APL), and immunoglobulins.

3. INVESTIGATIONAL PLAN

This is a Phase 1b/2a multicenter study to evaluate the safety, PK, PD, and clinical efficacy of KPG-818 in patients with SLE. The trial will consist of 2 parts: Phase 1b, a multiple-ascending dose (MAD) and Phase 2a, proof of concept (POC).

SLE patients to be enrolled must have a confirmed diagnosis according to 2019 European League against Rheumatism (EULAR)/ACR Classification criteria for SLE.

All concomitant therapies must be recorded throughout the study beginning at entry into screening and any changes must be recorded throughout the study.

Given the current worldwide COVID-19 pandemic and the potential risk for COVID-19 viral infection at the time and in the countries of this study, measures are implemented in this protocol to enable identification of patients who are likely to be infected in order to exclude them from enrollment or from subsequent study drug administration. Enrolled patients are required to comply with recommendation for individual protection from COVID-19 infection for the duration of the study. In addition, their condition will be closely monitored so that, in case of suspicion of patients getting infected, administration of study drug can be withhold and further examinations conducted as deemed appropriate by the Investigator. Such measures may need to be modified or implemented in accordance with the pandemic status, availability of a vaccine, relevant national guidelines, or recommendations from medical associations at the time of trial execution.

3.1. Overall Study Design and Plan

3.1.1. Phase 1b

Phase 1b part of the study is an open-label, multicenter, and multiple dose escalation cohort study. A total of approximately 24 patients will be enrolled into 4 dosing cohorts and receive KPG-818 in an open-label fashion. KPG-818 will be taken orally in the morning approximately every 24 hours for 14 days (up to 14 doses). The total duration of the study is approximately 10 weeks, consisting of 3 periods:

- Screening period: up to 42 days (6 weeks)
- Treatment period: up to 14 days (2 weeks)
- Safety follow-up period: up to 14 days (2 weeks) after the last dose of study treatment.

There are 4 dosing cohorts, Cohort A (0.15 mg/day), B (0.6 mg/day), C (2 mg/day), and D (5 mg/day), planned for Phase 1b part of the study. Each cohort will enroll 6 patients to ensure at least 4 evaluable patients to provide an adequate PK profile and safety assessment. The evaluable patient is defined as any patient who completes 14-day treatment and provides blood samples for PK analyses at Day 14.

The first 2 cohorts, Cohort A and Cohort B, will be initiated at the same time, given the very low doses of KPG-818. Patients will be enrolled to Cohort A and Cohort B in sequence. After

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at least 4 of 6 patients in Cohort B have completed the 14-day treatment, the Safety Review Committee (SRC) will review the accumulated safety and PK data from Cohorts A and B and determine if Cohort C begins dosing. Similarly, the SRC review for dose escalation will occur when at least 4 of 6 patients in Cohort C have completed the 14-day treatment.

Dose-limiting toxicities (DLTs) for KPG-818 are defined in [Section 3.5](#). During the dose escalation review, if 0 of 4 patients in a cohort experiences a DLT, the next dose cohort will be opened for enrollment after SRC review. If 1 of 4 (25%) patients in a cohort, or 2 or more of 6 patients in a cohort, experience DLTs, the additional dosing in the current cohort(s) and dose escalation will be withheld until SRC review. The individual patient with a DLT will be discontinued from the study.

The SRC review process will be described in detail in [Section 8.9](#). The SRC's recommendation to the Sponsor may include to proceed to the next planned dose level, to reduce the dose, to add additional patients to the current cohort, to add new dose cohort (s), or to stop the Phase 1b part of the study based on the review of safety and tolerability assessments, clinical efficacy, and PK data. According to the preclinical and early clinical data, the highest dose level will not exceed 10 mg/day.

Safety and tolerability measures will be collected throughout study visits and include the occurrence of AEs, vital signs, physical examinations, ECGs, and clinical laboratory tests.

Blood samples for PK analysis will be collected pre-dose on Day 1; pre-dose on Day 7; at 1, 2, 6, and 10 hours post-dose on Day 7; pre-dose on Day 8 (i.e., 24 hours after the pre-dose on Day 7); pre-dose on Day 14; and on Day 15 (i.e., 24 hours after the pre-dose on Day 14) (see [Appendix 10](#)).

Blood samples for biomarkers analysis from each of the 24 patients in Phase 1b will be collected at 3 time points: pre-dose on Day 1, pre-dose on Day 7, and on Day 15 (i.e., 24 hours after the pre-dose on Day 14) (see [Appendix 10](#)).

A Schedule of Assessments is presented in [Appendix 9](#).

3.1.2. Phase 2a

Phase 2a is planned to be initiated after the completion of Cohort D in Phase 1b, subject to sponsor decision based on the SRC recommendation after a comprehensive review of cumulative safety, PK/PD, and biomarker data.

The Phase 2a study is a randomized, double-blinded, placebo-controlled, parallel group study in patients with active SLE on limited stable background standard-of-care treatment.

The Phase 2a part of the study consists of 3 periods:

- Screening period: up to 28 days (4 weeks)
- Treatment period: up to 12 weeks
- Safety follow-up period: up to 4 weeks post last dose of study drug

Approximately 32 to 48 patients will be randomized (in 1:1:1:1 ratio) to 4 treatment arms. There will be 8 to 12 patients in each arm, with each receiving one of three treatments or

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placebo: KPG-818 0.15 mg (Treatment Arm E), 0.6 mg (Treatment Arm F), 2 mg (Treatment Arm G), or placebo (Treatment Arm H). KPG-818 or placebo will be taken orally in the morning approximately every 24 hours for 12 weeks.

The number of Phase 2a treatment arms and dosing regimen, is subject to the sponsor's decision based on the SRC's evaluation of the PK, safety, and tolerability data from the Phase 1b study. The total daily dose of each Phase 2a arm will not exceed the highest total daily dose shown to be safe and well tolerated in Phase 1b.

In Phase 2a study, patients should be on a stable SLE treatment regimen consisting of at least 1 of the following medications (alone or in combination) (see [Section 6.1](#) for details):

- Corticosteroids (prednisone or prednisone equivalent, up to 20 mg/day).
- Immunosuppressants including methotrexate, azathioprine, leflunomide, micophenolate mofetil, or mycophenolic acid.
- Anti-malarials (e.g., hydroxychloroquine, chloroquine, or quinacrine).

Safety measures will be collected at study visits and include the occurrence of AEs, vital signs, physical examinations, ECGs, and clinical laboratory safety tests. Efficacy of KPG-818 will be evaluated by measuring disease biomarkers and using validated SLE outcome measures including the SLEDAI-2K, PGA, and CLASI activity score, as well as 28-count tender and swollen joints count.

Blood samples for PK analysis will be collected: pre-dose on Day 1; pre-dose on Day 2; pre-dose on Day 12; pre-dose on Day 13; pre-dose on Day 14 and post-dose Day 14 at 1, 2, 6, 10 and 24 hours (24 hours post-dose for Day 14 is drawn on Day 15), and at 24 hours after the final dose on Day 84 (24 hours post-dose for Day 84 is drawn on Day 85) (See [Appendix 10](#)).

Blood samples for PD and biomarkers will be collected Pre-dose on Day 1, 24 hours post-dose Day 14 (24 hours post-dose for Day 14 is drawn on Day 15), and 24 hours after the final dose on Day 84 (24 hours post-dose for Day 84 is drawn on Day 85) (See [Appendix 10](#)).

The mRNA blood samples for Aiolos and Type I IFNGS assays targeting the five genes (IKZF3, IFI44, IFI44L, IFI27, RSAD2) will be collected once, on Day 1 (pre-dose draw).

A Schedule of Assessments is presented in [Appendix 9](#).

3.2. Study Start and End of Study Definitions

The start of the study is defined as the date the first patient signs the informed consent form (ICF). The end of the study is defined as the date of the last patient's last assessment (scheduled or unscheduled).

3.3. Additional Groups

For Phase 1b part of the study, it is allowed to add additional dose cohorts following review of the safety, tolerability, and PK data by the SRC.

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The requirement for additional cohorts will be agreed with the Sponsor, documented in the Trial Master File (TMF), and the Institutional Review Board (IRB) will be notified of the changes.

3.4. Selection of Doses in the Study

The dose levels for the Phase 1b clinical study are selected based on an evaluation of the SAD study results in healthy subjects, toxicology data, and in vivo efficacy data.

The starting 0.15 mg KPG-818 dose represents a 1333-fold safety margin based on body surface area adjusted dose at the NOAEL dose of 20 mg/kg/day in rats and a 67-fold safety margin based on body surface area adjusted dose at the NOAEL dose of 0.5 mg/kg/day in Cynomolgus monkeys in accordance with scientific standards outlined in the FDA Guidance for Industry ‘Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers.’³

In the SAD study, the interim safety report showed there were no safety or tolerability concerns of KPG-818 in 5 ascending dose levels (2, 5, 10, 20, and 30 mg) in 38 healthy subjects who completed the study. However, based on the 3-month Cynomolgus monkeys’ toxicity data, multiple doses may greatly increase the toxicity.

Administration of the subsequent dose levels of KPG-818 will be based on review of available safety, tolerability, and PK data from the previous doses. In accordance with the SAD study and 3-month Cynomolgus monkeys’ toxicity data, proposed doses in this Phase 1b study are 0.15, 0.6, 2, and 5 mg/day KPG-818. The dose levels might be changed based on the safety review during the study, and the highest dose level will not be greater than 10 mg/day.

Proposed doses in Phase 2a are 0.15, 0.6, and 2 mg/day. The dose levels, dosing frequency, and dosing duration will be decided by the SRC in consultation with the Sponsor, on the basis of data from Phase 1b of the study. The total daily exposure of KPG-818 administered during this part of the study will be planned to not exceed an exposure shown to be safe and well tolerated in Phase 1b.

The proposed KPG-818 dose levels for Phase 1b and Phase 2a are shown in Table 1 and Table 2 respectively.

Details of all doses administered in Phase 1b and Phase 2a of the study will be documented in the TMF.

Table 1. Proposed KPG-818 Dose Levels for Phase 1b

Study Part	Cohort	Dosage
Phase 1b	A	0.15 mg/day
	B	0.6 mg/day
	C	2 mg/day
	D	5 mg/day

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Table 2. Proposed KPG-818 Dose Levels for Phase 2a

Study Part	Treatment Arm	Dosage
Phase 2a	E	0.15 mg/day
	F	0.6 mg/day
	G	2 mg/day

3.5. Stopping Rules

3.5.1. Dose Escalation Stopping Criteria for Phase 1b

For the Phase 1b study, DLT is defined as any Grade 3 or higher study drug-related AE according to CTCAE (version 5.0), that occurs during the 14-day treatment period, with the following exceptions:

- Asymptomatic Grade 3 anemia, neutropenia, or thrombocytopenia returning to baseline or Grade ≤ 2 within 7 days without transfusion, growth factor support, or other active therapeutic intervention.
- Grade 3 study drug administration-related reactions (e.g., fatigue, anorexia, nausea, diarrhea, or vomiting) lasting < 1 day.
- Asymptomatic, isolated Grade 3 or higher changes in alkaline phosphatase, creatine phosphokinase, gamma-glutamyl transferase, lipase, or lymphocyte count.

During the dose escalation review, if 0 of 4 patients in a cohort experiences a DLT, the next dose cohort will be opened for enrollment after SRC review. If 1 of 4 (25%) patients in a cohort, or 2 or more of 6 patients in a cohort, experience DLTs, the additional dosing in the current cohort(s) and dose escalation will be withheld until SRC review. The individual patient with a DLT will be discontinued from the study.

In addition, the following PK considerations will be taken into account with regard to dose escalation evaluation:

- During Phase 1b, multiple administrations of a planned dose level will occur, there is no prior clinical knowledge if the drug will accumulate to a greater extent after multiple doses. So, in case of accumulation occurs, the actual exposure might go higher than anticipated exposure based on the Phase 1a data. As long there are no safety signals which might suggest stopping the dose escalation, the dose escalation will continue.
- There may be periodic PK exposure calculations after certain cohorts from the available plasma samples to check.
- In the case of any correlation between safety signals and higher PK exposures is identified, the SRC will be notified and requested to evaluate or suggest the further dose escalation decisions.

The SRC's recommendation to the Sponsor may include proceeding to the next planned dose level, reducing the dose, adding additional patients to the current dose, adding new dose cohort (s), or stopping the Phase 1b part of the study.

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3.5.2. Stopping and Treatment Resumption Criteria for Phase 2a

If any of the following events occur, administration of study drug to an individual patient should be discontinued

- Any Grade 3 or higher study drug-related AE according to CTCAE (version 5.0), that occurs during the 84-day treatment period, with the following exceptions:
 - Asymptomatic Grade 3 anemia, neutropenia, or thrombocytopenia returning to baseline or Grade ≤ 2 within 7 days without transfusion, growth factor support, or other active therapeutic intervention.
 - Grade 3 study drug administration-related reactions (e.g., fatigue, anorexia, nausea, diarrhea, or vomiting) lasting < 1 day.
 - Asymptomatic, isolated Grade 3 or higher changes in alkaline phosphatase, creatine phosphokinase, gamma-glutamyl transferase, lipase, or lymphocyte count.
- A possibly drug-related serious adverse event (SAE).
- A possibly drug-related significant non serious AE, which in the opinion of the PI and/or Medical Monitor contraindicates further dosing.
- Any other reason that, in the opinion of the investigator, may require discontinuation of the study treatment should be discussed with the Medical Monitor and Sponsor.

The study treatment can be resumed after recovery to baseline or $\leq$ Grade 1 following the AE upon agreement with the PI, Medical Monitor and Sponsor.

Patients prematurely discontinued from study treatment will be encouraged to complete the Early Termination visit within 3 days and return for the Follow-up visit approximately 4 weeks after the receipt of their last dose.

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Male and female patients with a diagnosis of SLE will be included in this study.

Patients for Phase 1b and Phase 2a must satisfy all of the following criteria:

1. Male or female of 18 years of age or older at the time of signing the ICF.
2. BMI between 18 and 40 kg/m².
3. Able and willing to adhere to the visit schedule and other protocol requirements.
4. Diagnosed with SLE according to the 2019 EULAR/ACR criteria for SLE (See Appendix 1).
5. Meeting SLE activity requirements as described below:

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- For the Phase 1b part of the study, patients with or without active SLE may be enrolled if, in the opinion of the Investigator, the disease activity is stable and there will be no need for change or increase in SLE therapy anticipated for the study duration. If patients are on stable standard care of SLE treatment, this should comply with inclusion criteria No. 11.
 - For the Phase 2a part of the study, patients must have a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) score of ≥ 6 points at Screening visit with a SLEDAI-2K clinical score ≥ 4 points at Baseline visit. The "clinical" score is the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or blood laboratory results including immunologic measures. Neurologic descriptors of the SLEDAI-2K are not counted towards the SLEDAI study entry criteria. In addition, the patient must be on stable standard care of SLE treatment with at least one of the followings: OCS, anti-malarial, or immunosuppressant (see inclusion criteria No. 11 for allowed medications and doses).
6. Documented history or presence at Screening of positive autoantibodies associated with SLE, which must include at least 1 of the following:
- Positive antinuclear antibody (ANA) test with a titer of 1:80 or greater.
 - Anti-dsDNA antibodies elevated to above normal.
 - Anti-Smith antibody elevated to above normal.
7. Women of childbearing potential (WOCBP) must:
- Have 2 negative serum pregnancy tests as verified by the Investigator prior to starting study therapy, 1 at Screening and again within 3 days before taking the first dose of KPG-818, then have a negative urine pregnancy test at Baseline before dosing. WOCBP must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the patient practices true abstinence from heterosexual contact.
 - Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use 2 forms of reliable contraception simultaneously. One must be a highly effective method and 1 additional effective (barrier) method (see [Appendix 5](#) for more details), and both must be practiced without interruption, at least 28 days before starting investigational medicinal product (IMP), during the study therapy (including dose interruptions), and for 28 days after discontinuation of study therapy.
8. Male patients must: Practice true abstinence or agree to use a barrier contraception (male latex condom or non-latex condom NOT made out of natural [animal] membrane [for example, polyurethane]) during sexual contact with a WOCBP while participating in the study, and for at least 90 days following IMP discontinuation, even if he has undergone a successful vasectomy. Male patients must agree not to donate semen or sperm during the treatment period and for at least 90 days following the discontinuation of KPG-818.
9. Female patients who are postmenopausal must demonstrate a FSH blood levels of equal to or greater than 40 mIU/mL at the Screening visit. Women aged > 60 years old whose FSH values are not equal to or greater than 40 mIU/mL may be included

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at the discretion of the Investigator and in consultation with the Sponsor(see [Appendix 5](#) for more details).

10. All patients must:

- Understand that KPG-818 could have potential teratogenic risk.
- Agree not to share KPG-818 with another person.
- Be counseled about pregnancy precautions and risks of fetal exposure as described in the Pregnancy Prevention Plan.

11. In Phase 2a part of the study, the patient must be on stable standard care of SLE treatment with at least one of the followings: oral corticosteroid, anti-malarial, or immunosuppressant:

- a. If taking OCS, must be on-treatment for ≥ 4 weeks before the Screening visit, and maintained on a stable dose of ≤ 20 mg/day of prednisone or equivalent for at least 4 weeks before the Baseline visit.
- b. If taking an anti-malarial agent (hydroxychloroquine, chloroquine, or quinacrine), must be on-treatment for ≥ 8 weeks before the Screening visit and be on a stable dose for ≥ 4 weeks before the Screening visit. Anti-malarials at the following doses are allowed:
 - Hydroxychloroquine (≤ 400 mg/day)
 - Chloroquine (≤ 500 mg/day)
 - Quinacrine (≤ 200 mg/day)
- c. If taking allowed immunosuppressants, must be on-treatment for ≥ 8 weeks prior to the Screening visit and be on a stable dose for ≥ 4 weeks before the Screening visit. Only 1 of the immunosuppressants below is allowed at the indicated doses:
 - Micophenolate mofetil (≤ 2 g/day) or mycophenolic acid (≤ 1.44 g/day)
 - Azathioprine (≤ 200 mg/day)
 - Methotrexate (≤ 20 mg/week)
 - Leflunomide (≤ 20 mg/day)
- d. If taking NSAIDs or other regularly administered analgesics, these will be allowed if treatment started ≥ 4 weeks before the Baseline visit and dosing has not been changed within the last 2 weeks before the Baseline visit.
- e. If immunosuppressants, anti-malarial, or OCS is discontinued, the last dose must be more than 4 weeks prior to Screening visit.

12. Patients must agree not to donate blood (or any component of blood) from 3 months before Screening until 3 months after the last dose of KPG-818.

13. Patients must be willing to comply with precautions to reduce the risk of COVID-19 infection in accordance with recommendations from the applicable medical associations and the investigator for the duration of the study and to undergo COVID-19 polymerase chain reaction (PCR) test as required based on the Investigator judgment and/or local requirements.

4.2. Exclusion Criteria

Patients will be excluded from the study if they satisfy any of the following criteria:

1. Use of any prohibited medications within the pre-specified time (refer to Appendix 6 for details on the required washout period for each drug class).
2. Any of the following noted at Screening (within 6 weeks before Week 1 [Day 1] in Phase 1b, within 4 weeks before Week 1 [Day 1] in Phase 2a):
 - Aspartate aminotransferase (AST) $> 2.0 \times$ upper limit of normal (ULN)
 - Alanine aminotransferase (ALT) $> 2.0 \times$ ULN
 - Total bilirubin $> 1.5 \times$ ULN (unless due to Gilbert's syndrome)
 - Serum creatinine > 2.5 mg/dL (or > 221 μ mol/L)
 - Neutrophil count $< 1500/\mu$ L (or $< 1.5 \times 10^9/L$) ($< 1000/\mu$ L [or $< 1.0 \times 10^9/L$] if the neutropenia is related to SLE)
 - Platelet count $< 50\,000/\mu$ L (or $< 50 \times 10^9/L$) ($< 25\,000/\mu$ L [or $< 25 \times 10^9/L$] if the thrombocytopenia is related to SLE)
 - Hemoglobin < 8 g/dL (or < 80 g/L) (< 7 g/dL [or < 70 g/L] if related to SLE)
3. Have an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m² (CKD-EPI formula) at Screening.
4. Have a spot urine protein to creatinine ratio (sUPCR) > 2000 mg/g (226 mg/mmol, as an estimate of approximate proteinuria > 2 g/day) at Screening.
5. Active and/or unstable neuropsychiatric SLE (e.g., neuropsychiatric SLE including seizures, psychosis, acute confusional state, cerebrovascular accident, aseptic meningitis, or polyneuropathy).
6. Positive serology test for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV-1 and HIV-2) at Screening. In cases of a positive screening test, patient may be enrolled if a confirmatory test is negative (see [Appendix 3](#) for details). Exception: patient who test positive for HCV antibodies may be enrolled if confirmed with cured HCV infection and documented completion of treatment more than 3 months before screening and HCV must not be detectable at screening.
7. Active or history of severe systemic bacterial, viral, fungal, mycobacterial, or parasitic infections (requires hospitalizations or IV antibiotics) within 6 months prior to Screening.
8. Any current or recent (within 4 weeks of Screening) signs or symptoms of infection, except for fungal infections of the nail beds, oral or vaginal candidiasis that has resolved, or minor infections (e.g., common cold, viral gastroenteritis, urinary tract infection) that have in the Investigator's judgment, completely resolved prior to the Baseline visit.
9. Any severe, recurrent, disseminated viral infections, particularly herpes viruses such as HSV-1, HSV-2, VZV, CMV (e.g., herpes encephalitis, ophthalmic herpes, disseminated zoster, CMV colitis) per Investigator's judgment. Recurrent is defined

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as 2 or more episodes in the past 2 years and/or with an episode within 3 months of Screening.

10. Known history of congenital or acquired immunodeficiency, splenectomy, or any underlying condition that predisposes the patient to infection.
11. Active tuberculosis (TB) or a history of incompletely treated TB, or a positive, QuantiFERON®-TB Gold test. If a patient's initial TB test result is indeterminate, the test can be repeated once. If the test result is again indeterminate (or positive), the patient will be excluded from the study. An exception for positive or indeterminate results may be made for patients who have documentation of having completed appropriate standard treatment for latent TB before screening and do not have other risk factors, radiologic findings, or physical evidence supporting latent or active TB.
12. History of malignancy within 5 years of Screening with the exception of basal cell or squamous cell in situ skin carcinomas or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
13. History of antiphospholipid syndrome with thromboembolic event within 12 months of screening or not on an adequate anticoagulation regimen. However, presence of antiphospholipid antibodies alone (without a history of thromboembolic event) is not exclusionary.
14. Other non-SLE driven inflammatory joint or skin disease, mixed connective tissue disease, scleroderma, and/or overlap syndromes. An exception may be allowed for rheumatoid arthritis overlapping with SLE (i.e., RHUPUS) with no erosive joint disease after a discussion with the medical monitor. Patients with SLE and secondary Sjogren syndrome are not exclusionary.
15. Clinically significant or unstable or uncontrolled acute or chronic disease not related to SLE that in the Investigator's opinion would preclude patient participation.
16. Concomitant condition (such as asthma) that required systemic corticosteroid use within 1 year before Screening. Use of inhaled corticosteroid is not exclusionary.
17. History of alcohol or drug abuse within 1 year before screening based on the Investigator's judgment.
18. Have a positive urine drug test at screening (see [Appendix 3](#)) except if the patient has a valid prescription for an allowed concomitant medication or substance abuse/dependence has been ruled out in the Investigator's judgment.
19. History of major surgery within 12 weeks prior to Screening or any planned major surgery during the study.
20. Clinically significant ECG abnormalities or have a QTc interval value > 480 ms at Screening, in the Investigator's opinion would preclude patient participation.
21. Pregnant or breast-feeding female.
22. Signs or symptoms that in the opinion of the Investigator may be suggestive of COVID-19 infection. The patient may be allowed to enter the study if a COVID-19 PCR test performed during the Screening results in a negative outcome.
23. Known allergic reaction to any of the ingredients for study drug or placebo.

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4.3. Patient Number and Identification

Patients will have a unique identification number assigned by the site at Screening. In Phase 1b, patient numbers start with the site number followed by a sequential, three-digit number starting with 0, e.g., 001, 002, ...00n. In Phase 2a, the patient number assigned by the site will be the site number followed by a sequential number starting with 2, e.g., 201, 202,...20n. This will remain the patient's identification number throughout screening and after randomization. Patients who are re-screened will be assigned a new number in normal sequence. In addition to the screening identification number assigned by the site, patients will have a randomization number assigned by the IWRS, which will be recorded in eCRF and will not be used to identify the patient. Patients will always be identified only by the identification number assigned at screening.

4.4. Patient Withdrawal and Replacement

A patient is free to withdraw from the study at any time without providing reason (s) for withdrawal and without prejudice to further treatment. In addition, a patient may be withdrawn if any of the following criteria are met:

- AE/SAE
- Protocol deviation
- Lost to follow up
- Pregnancy
- Decision by Investigator
- Decision by Sponsor

For patients in Phase 1b, if meeting stopping criteria (See [Section 3.5](#)), the patient will be withdrawn.

If a patient is withdrawn, the Sponsor will be notified and the date and reason (s) for the withdrawal will be documented in the patient's electronic Case Report Form (eCRF). If a patient is withdrawn, efforts will be made to perform all follow-up assessments, if possible. Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. If the patient is in-house, these procedures should be performed before the patient is discharged from the clinic. The Investigator (or designee) may also request that the patient return for an additional Follow-up visit. All withdrawn patients will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

In Phase 1b, patients who are withdrawn for reasons not related to study treatment may be replaced following discussion between the Investigator and the Sponsor. Replacement for patients withdrawn as a result of AEs thought to be related to the study treatment will be decided by the SRC.

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4.5. Study Termination

The AEs based on the expected mechanism of action of IMP are to be monitored as part of the safety and tolerability assessment during the entire study and will be taken into consideration for possible termination of the study.

Other criteria for study termination include:

- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Cancellation of drug development.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

KPG-818 capsules (0.15 mg, 1 mg, and 5 mg) and placebo capsules will be supplied by the Sponsor (or designee), along with the batch numbers and Certificates of Analysis. KPG-818 and placebo capsules for oral administration will be provided in high-density polyethylene (HDPE) bottle capped with HDPE cap (HDPE in compliance with 21 Code of Federal Regulations [CFR] Part 177 and 21CFR Part 175 regulations) and stored according to the instructions on the label.

All IMPs will be stored at the study site in a location that is locked with restricted access.

The IMP kits in Phase 2 and unit dose containers will be labeled in accordance with national laws and regulations. Study Treatment Administration

5.2. Investigational Medicinal Products, Dose, and Mode of Administration

IMP: KPG-818 capsules.

Proposed dose levels for Phase 1b: Cohort A (0.15 mg/day), B (0.6 mg/day), C (2 mg/day), and D (5 mg/day).

Proposed Phase 2a dose levels: Treatment Arm E (0.15 mg/day), F (0.6 mg/day), G (2 mg/day) and H (placebo). The study design for Phase 2a, including the number of treatment arms and dosing regimen, may be modified, in consultation with the Sponsor, on the basis of data from Phase 1b of the study. The total daily exposure of KPG-818 administered during this part of the study will be planned to not exceed an exposure shown to be safe and well tolerated in Phase 1b.

Administration route: KPG-818 capsules will be administered orally approximately every 24 hours with approximately 240 mL of water in the morning at similar time, with or without food.

If patients forget to take KPG-818 in the morning, it is allowable to take the dose within 12 hours. Otherwise, the KPG-818 dose will be skipped and the patient will proceed with dosing the next day in the morning.

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Study drug administration should occur at the study site on the below dates so that PK and PD samples can be collected at designated time points:

Phase 1b: Days 1, 7, 8, and 14.

Phase 2a: Days 1, 2, 12, 13, 14, and 15.

Study drug administration may be withheld in case of suspicion of current COVID-19 infection based on the Investigator's clinical judgment.

Reference Product and Mode of Administration

Reference product: placebo capsules.

Administration route: Capsules will be administered orally approximately every 24 hours with approximately 240 mL of water in the morning at similar time, with or without food.

Patients should be administered the IMP while standing or sitting and should not be permitted to lie supine for 2 hours after dosing, except as necessitated by the occurrence of an AE (s) and/or study procedures.

5.3. Randomization

The Phase 1b part of the study is open-label.

Randomization to placebo/KPG-818 will be performed in Phase 2a using an interactive voice/web response system (IXRS) randomization service.

5.4. Blinding

5.4.1. Phase 1b

The Phase 1b part is open-label therefore no procedures for blinding are applicable.

5.4.2. Phase 2a

The following controls will be employed to maintain the double-blind status of the Phase 2a part:

- The placebo capsules will be identical in appearance to the KPG-818 capsules.
- The Investigator and other members of staff involved in the study will remain blinded to the treatment randomization code during the assembly procedure.
- IMP will be packaged in a blinded manner and assigned by an IXRS using a randomization scheme.
- Identical number of capsules will be taken daily for each arm.
- Lab results or other data that could be unblinding will not be able to be viewed or presented to the blinded investigator, CRO or Sponsor teams.
- IMP assigned by the IXRS will be dispensed, logged and accounted for on Day 1, Day 28, and Day 56 of treatment, and final accountability will be completed at end of

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treatment. Each arm will receive the same number of bottles in each kits when IP is dispensed per assignment by IXRS.

In case of an emergency, in order to manage patient safety, the decision to unblind resides with the Investigator in consultation with the Medical Monitor and Sponsor. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Medical Monitor and/ or sponsor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. The Investigator should discuss breaking the blind in IXRS with the Medical Monitor and Sponsor. If it becomes necessary to break the blind in IXRS during the study, the date, time, and reason will be recorded in the patient's source data and completed in IXRS by the PI or Sub investigator.

5.5. Drug Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each patient and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each IP kit, the empty or used IP kit containers will be discarded upon satisfactory completion of the compliance and accountability procedures.

Overall satisfactory compliance is defined as subject taking 80% to 120% of dispensed IP.

Any unused IP kits will be retained until completion of the study.

At the completion of the study, all unused IP kits will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

All pre-study therapies (including prescription, over-the-counter, herbal and/or supplements) administered up to 90 days before entry into Screening must be recorded at Screening. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a patient into the study. All concomitant therapies must be recorded throughout the study, beginning at entry into Screening, and any changes must be recorded throughout the study.

Every reasonable effort should be made to keep concomitant medications stable as defined in the protocol. A concomitant medication may be reduced or medication temporarily discontinued because of abnormal laboratory values, side effects, concurrent illness, or the performance of a surgical procedure, but the change and reason for the medication change should be clearly documented in the patient's medical record.

The initiation and/or addition of concomitant medications during the study is generally prohibited without prior approval of the Investigator (or designee), unless its use is deemed

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necessary for treatment of an AE. Any medication taken by a patient during the course of the study and the reason for its use will be documented in the source data.

6.1.1. Corticosteroids

Oral Corticosteroids

If using OCS for SLE treatment, patients must be receiving this medication for at least 4 weeks before the Screening visit and on a stable dose equivalent to an average dose of ≤ 20 mg/day of prednisone for at least 4 weeks before the Baseline visit. See [Appendix 7](#) for equivalent dose of oral prednisone.

The dose of OCS must remain stable throughout the study for patients enrolled in the Phase 1b part of the study unless the dose adjustment is clinically necessary.

For patients enrolled in the Phase 2a part of the study and taking OCS at a dose level ≤ 7.5 mg/day of prednisone or equivalent at baseline, the OCS dose should maintain stable or taper down at the Investigator's discretion. If the baseline OCS dose is > 7.5 mg/day prednisone or equivalent, tapering of OCS dose must be attempted starting from Week 2 as clinically allowed. An indicative tapering schedule could be represented by reducing the OCS dose of 5 mg/day prednisone equivalent every other week or of 2.5 mg/day every week. If such tapering schedule is not considered appropriate for the individual patient by the Investigator, a different tapering regimen can be used. The goal is to reduce the daily prednisone equivalent dose to 7.5 mg/day or lower by Week 8 of the study. Patients achieving a dose of 7.5 mg/day or lower earlier than Week 8 may remain on this dose or continue to taper at the discretion of the Investigator. Patients who cannot fulfill the taper should remain in the study and receive corticosteroids at an appropriate dose as determined by the Investigator. In any case, the achieved OCS dose must be maintained stable between Week 9 to Week 12.

If a patient experiences increased SLE disease activity after randomization, OCS dose increase (up to 40 mg/day of prednisone equivalent) will be allowed if clinically indicated between Day 1 and Week 6. OCS dose should be tapering down to baseline level within 2 weeks as possible.

If OCS is required for treatment of non-SLE indication, a single course of oral prednisone equivalent up to 40 mg/day for 14 days is permitted, though it should be completed prior to Week 8 as possible. No long acting steroid injections are permitted.

Corticosteroids administered via bronchial or nasal inhalation for treatment of conditions other than SLE may be given as needed.

IV, IM, intra-lesional, or intra-articular injection of corticosteroids is prohibited during the course of the study.

Topical corticosteroid should maintain stable regimen if the medication is used prior to Screening. PRN use is not considered stable regimen. Initiation of topical corticosteroids is prohibited during the course of the study.

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6.1.2. Immunosuppressants

Immunosuppressants, including methotrexate (maximum 20 mg/week), azathioprine (maximum 200 mg/day), leflunomide (maximum 20 mg/day), micophenolate mofetil (maximum 2 g/day), or mycophenolic acid (maximum 1.44 g/day) will be allowed if treatment starts ≥ 8 weeks before the Screening visit and if the dose regimen is stable for at least 4 weeks before the Screening visit and is expected to remain stable for the duration of the study.

During the study, dose modification is not allowed except for reasons of documented intolerance, toxicity or unavailability. Initiation of immunosuppressive agent is not allowed during the course of the study.

6.1.3. Anti-malarials

Stable treatment with either hydroxychloroquine (maximum 400 mg/day), chloroquine (maximum 500 mg/day), or quinacrine (maximum 200 mg/day) will be allowed if treatment starts ≥ 8 weeks before the Screen visit and if the dose regimen is stable for at least 4 weeks before the Screening visit and is expected to remain stable for the duration of the study and is permitted through the safety follow-up period. Anti-malarials produced by a licensed compounding pharmacy (e.g., quinacrine) in the country of administration and using pharmaceutical grade components are allowed.

During the study, dose modification is not allowed except for reasons of documented intolerance, toxicity or unavailability. Initiation of anti-malarial agent is not allowed during the course of the study.

6.1.4. Non-steroidal Anti-inflammatory Drugs and Other Analgesics

Patients treated with NSAIDs, including aspirin and selective cyclooxygenase-2 (COX-2) inhibitors, and other analgesics should receive the usual marketed doses approved in the country in which the study is being conducted. Prescriptions of NSAIDs and other regularly administered analgesics will be allowed if treatment starts ≥ 4 weeks before the Baseline visit and should not be adjusted for at least 2 weeks before the Baseline visit and through the study, and may be changed only if the patient develops unacceptable side effects. Besides, NSAIDs will be withheld within 24 hours of the visit date in Phase 2a to minimize confounding factors to efficacy assessment. The addition of new NSAIDs to the treatment regimen is not permitted. Minor adjustments in NSAID therapy are allowed during the treatment period although it is recommended that the use of any NSAIDs remain as stable as possible, and any notable changes should be recorded.

6.2. Restrict and Prohibited Therapies

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting the Investigator (refer to [Appendix 6](#) for details on the required washout period for each drug class).

6.2.1. Immunomodulatory Drugs

Immunomodulatory imide drugs (IMiDs), a class of immunomodulatory drugs containing an imide group, are structural and functional analogues of thalidomide, including thalidomide,

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lenalidomide, pomalidomide, and iberdomide (cc-220). These drugs may also be referred to as Cereblon modulators. IMiDs are prohibited throughout the study.

6.2.2. Biologics disease-modifying antirheumatic drugs

Biologics disease-modifying antirheumatic drugs (bDMARDs) including, but not limited to, belimumab, abatacept, rituximab, ustekinumab, or IFN therapy (alpha 2a and 2b, beta 1a and 1b, and pegylated IFNs alpha 2a and 2b) are prohibited throughout the study.

6.2.3. Targeted synthetic disease-modifying antirheumatic drugs

Targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), comprising phosphodiesterase inhibitors (apremilast) and kinase inhibitors (including but not limited to Janus Kinase inhibitors, e.g., tofacitinib and baricitinib) are prohibited throughout the study.

6.2.4. Estrogen-derived products

Caution is recommended in the administration of estrogen-derived products (e.g., hormone replacement therapy) due to the risk of thromboembolic events.

6.2.5. Others

Plasmapheresis and any immunoglobulin (Ig) therapy are prohibited throughout the study.

Live or attenuated vaccines, including BCG vaccine, are prohibited throughout the study.

Any investigational agents and other therapies for SLE which are not described above should be discussed with and approved by the medical monitor or designee.

6.3. Exercise

Patients are required to refrain from strenuous exercise from 7 days before Screening until the Follow-up visit, and will otherwise be allowed to maintain their normal level of physical activity during this time (i.e., will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

6.4. Blood Donation

Patients are required to refrain from donation of blood (or any component of blood) from 3 months before Screening until 3 months after the last dose of KPG-818.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Study Procedures in Phase 1b

The procedures to be performed during the study are listed by visit in the Schedule of Assessments in [Appendix 9](#). Specific procedures to be performed during the study are described in detail by visits in this section.

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7.1.1. Visit 1 (Screening period)

Visit 1 will occur within 42 days before the Baseline visit (Visit 2). At Visit 1, the following procedures are to be performed:

- Obtain signatures for the ICF prior to performing any protocol related procedures
- Obtain signatures for the pregnancy ICF prior to performing any protocol related procedures (female patients only)
- Assess patient eligibility based on inclusion and exclusion criteria
- Collect demographic data
- Document SLE classification criteria
- Record complete medical history, all prior medications (prescription medications and over-the-counter preparations within the last 3 months), and prior surgeries/procedures
- Measure vital signs, body weight, and height
- Perform physical examination (including a questionnaire for COVID-19 in accordance with applicable local Health Authority requirements)
- Perform 12-lead ECGs
- Perform a chest X-ray (Only required for patient who has not had a chest X-ray within 12 weeks prior to signing the ICF)
- Collect blood samples for the following assessments:
 - QuantiFERON[®]-TB Gold test
 - Routine hematology
 - Clinical chemistry
 - Serum pregnancy test (One at Screening and again within 3 days before taking the first dose of KPG-818)
 - FSH
 - Serum virology (HBV, HCV, and HIV)
- Coagulation profile
- Collect urine for the following assessments:
 - Urinalysis
 - Spot urine protein to creatinine ratio (sUPCR)
 - Urine drug screening
- Collect blood samples for the following serological markers assessments:
 - Complement C3 and C4
 - ANA, anti-dsDNA, anti-Smith, anti-SSA, anti-SSB, and APL antibodies
 - Immunoglobulins (IgG, IgM)

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7.1.2. Visit 2 (Baseline)

At Visit 2 (Week 1, Day 1), the following procedures are to be performed:

- Assess patient eligibility based on inclusion and exclusion criteria
- Conduct pregnancy counselling
- Dispense study medications and provide dosing instructions (first dose of study drug to be taken at the site)
- Measure vital signs and body weight
- Perform physical examination (including a questionnaire for COVID-19 in accordance with applicable local Health Authority requirements)
- Perform 12-lead ECGs
- Collect blood samples for the following assessments:
 - Routine hematology
 - Clinical chemistry
- Coagulation profile
- Collect urine for the following assessments:
 - Urinalysis
 - sUPCR
 - Urine pregnancy test (β hCG for female patients of childbearing potential)
- Record AEs
- Record current medications and surgeries/procedures
- Collect blood samples for the following PK assessments (see [Appendix 10](#) for blood samples collection time points):
 - Plasma KPG-818 and KPG-818H
- Collect blood samples for the following biomarkers assessments (see [Appendix 10](#) for blood samples collection time points):
 - Potential biomarkers of KPG-818
 - Absolute counts of CD19⁺ B cells, CD268⁺ B cells CD3⁺ T cells, Treg, and pDC

7.1.3. Visits 3 and 4

Visits 3 and 4 are to be scheduled at Days 7 and 8, relative to Visit 2 (Week 1, Day 1). The following procedures are to be performed:

- Conduct pregnancy counselling (Visit 4 only)
- Study drug administration (study drug to be taken at the site)
- Assess compliance with study medication dosing instructions per protocol (Visit 4 only)

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- Measure vital signs
- Perform physical examination (including a questionnaire for COVID-19 in accordance with applicable local Health Authority requirements)
- Collect blood samples for the following assessments (Visit 4 only):
 - Routine hematology
 - Clinical chemistry
- Coagulation profile
- Collect urine for the following assessments (Visit 4 only):
 - Urinalysis
 - sUPCR
 - Urine pregnancy test (β hCG for female patients of childbearing potential)
- Record AEs
- Record current medications and surgeries/procedures
- Collect blood samples for the following PK assessments (see [Appendix 10](#) for blood samples collection time points):
 - Plasma KPG-818 and KPG-818H
- Collect blood samples for the following biomarkers assessments (Visit 3 only, see [Appendix 10](#) for blood samples collection time points):
 - Potential biomarkers of KPG-818
 - Absolute counts of CD19⁺ B cells, CD268⁺ B cells CD3⁺ T cells, Treg, and pDC

7.1.4. Visit 5 (End of Treatment Visit/Early Termination Visit)

Visit 5 is to occur at Day 14 (± 1). Patients who withdraw from the study prior to completion of Visit 5 are to arrive at the site for an early termination (ET) visit and to complete ET procedures which will be the same as in Visit 5 in a timely manner.

Every effort should be made to schedule ET procedures within 1 day of the last dose of study medication and before initiation of any new treatments.

The following procedures are to be performed at Visit 5/ET visit:

- Conduct pregnancy counselling
- Study drug administration (study drug to be taken at the site)
- Assess compliance with study medication dosing instructions per protocol
- Measure vital signs and body weight
- Perform physical examination (including a questionnaire for COVID-19 in accordance with applicable local Health Authority requirements)
- Perform 12-lead ECGs

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- Collect blood samples for the following assessments:
 - Routine hematology
 - Clinical chemistry
- Coagulation profile
- Collect urine for the following assessments:
 - Urinalysis
 - sUPCR
 - Urine pregnancy test (β hCG for female patients of childbearing potential)
- Record AEs
- Record current medications and surgeries/procedures
- Collect blood samples for the following PK assessments (see [Appendix 10](#) for blood samples collection time points):
 - Plasma KPG-818 and KPG-818H
- Collect blood samples for the following serological markers assessments:
 - Complement C3 and C4
 - ANA, anti-dsDNA, anti-Smith, anti-SSA, anti-SSB, and APL antibodies
 - Immunoglobulins (IgG, IgM)

7.1.5. Visits 6 and 7 (Follow-up)

Visits 6 and 7 are to be scheduled at Days 15 (± 1) and 28 (± 3), relative to Visit 2 (Week 1, Day 1). The following procedures are to be performed:

- Measure vital signs
- Perform physical examination (including a questionnaire for COVID-19 in accordance with applicable local Health Authority requirements) (Visit 7 only)
- Perform 12-lead ECGs (Visit 7 only)
- Collect blood samples for the following assessments (Visit 7 only):
 - Routine hematology
 - Clinical chemistry
- Coagulation profile
- Collect urine for the following assessments (Visit 7 only):
 - Urinalysis
 - sUPCR
 - Urine pregnancy test (β hCG for female patients of childbearing potential)
- Record AEs

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- Collect blood samples for the following PK assessments (Visit 6 only, see [Appendix 10](#) for blood samples collection time points):
 - Plasma KPG-818 and KPG-818H
- Collect blood samples for the following biomarkers assessments (Visit 6 only, see [Appendix 10](#) for blood samples collection time points):
 - Potential biomarkers of KPG-818
 - Absolute counts of CD19⁺ B cells, CD268⁺ B cells CD3⁺ T cells, Treg, and pDC

7.2. Study Procedures in Phase 2a

7.2.1. Visit 1 (Screening Period)

Visit 1 will occur within 28 days prior to randomization (Visit 2). At Visit 1, the following procedures are to be performed:

- Obtain signatures for the ICF prior to performing any protocol related procedures
- Obtain signatures for the pregnancy ICF prior to performing any protocol related procedures (female patients only)
- Assess patient eligibility based on inclusion and exclusion criteria
- Collect demographic data
- Document SLE classification criteria
- Record complete medical history, all prior medications (prescription medications and over-the-counter preparations within the last 3 months), and prior surgeries/procedures
- Measure vital signs, body weight, and height
- Perform physical examination (including a questionnaire for COVID-19 in accordance with applicable local Health Authority requirements)
- Perform 12-lead ECGs
- Perform a chest X-ray (Only required for patient who has not had a chest X-ray within 12 weeks prior to signing the ICF)
- Collect blood samples for the following assessments:
 - QuantiFERON[®]-TB Gold test
 - Routine hematology
 - Clinical chemistry
 - Coagulation profile
 - Serum pregnancy test (One at Screening and again within 3 days before taking the first dose of KPG-818)
 - FSH
 - Serum virology (HBV, HCV, and HIV)

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- Collect urine for the following assessments:
 - Urinalysis
 - sUPCR
 - Urine drug screening
- Perform SLE disease activity assessments:
 - SLEDAI-2K (see [Appendix 11](#))
 - PGA (see [Appendix 12](#))
 - CLASI (see [Appendix 13](#))
 - Tender and swollen joints assessment (See [Appendix 14](#))
- Collect blood samples for the following assessments:
 - Complement C3 and C4
 - ANA, anti-dsDNA, anti-Smith, anti-SSA, anti-SSB, and APL antibodies
 - Immunoglobulins (IgG, IgM)

7.2.2. Visit 2 (Baseline)

At Visit 2 (Week 1, Day 1), the following procedures are to be performed:

- Assess patient eligibility based on inclusion and exclusion criteria
- Randomize eligible patients
- Conduct pregnancy counselling
- Dispense study medications and provide dosing instructions (first dose of study drug to be taken at the site)
- Measure vital signs and body weight
- Perform physical examination (including a questionnaire for COVID-19 in accordance with applicable local Health Authority requirements)
- Perform 12-lead ECGs
- Collect blood samples for the following assessments:
 - Routine hematology
 - Clinical chemistry
 - Coagulation profile
- Collect urine for the following assessments:
 - Urinalysis
 - sUPCR
 - Urine pregnancy test (β hCG for female patients of childbearing potential)
- Record AEs

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- Record current medications and surgeries/procedures
- Perform SLE disease activity assessments:
 - SLEDAI-2K (see [Appendix 11](#))
 - PGA (see [Appendix 12](#))
 - CLASI (see [Appendix 13](#))
 - Tender and swollen joints assessment (See [Appendix 14](#))
- Collect blood samples for the following PK assessments (see [Appendix 10](#) for blood samples collection time points):
 - Plasma KPG-818 and KPG-818H
- Collect blood samples for the following biomarkers assessments (see [Appendix 10](#) for blood samples collection time points):
 - Leukocytes (total B cells (CD19+), Activated B cells (CD268+), total T cells (CD3+), T regulatory cells (Treg), and plasmacytoid dendritic cells (pDC))
 - PD markers (Aiolos [intracellular protein], Ikaros [intracellular protein], CRBN [intracellular protein], IFN- α , IFN- β , and IL-2)
- Collect mRNA blood sample for Aiolos and Type I IFNGS assay targeting the five genes (IKZF3, IFI44, IFI44L, IFI27, RSAD2)
- Collect blood samples for the following immunological assessments:
 - Complement C3 and C4
 - ANA, anti-dsDNA, anti-Smith, anti-SSA, anti-SSB, and APL antibodies
 - Immunoglobulins (IgG, IgM)

7.2.3. Visits 3, 4, 5, and 7 (± 0 Days)

Visits 3, 4, 5, and 7 are to be scheduled at Day 2, Day 12, Day 13, and Day 15. The following procedures are to be performed:

- Collect blood samples for the following PK assessments (see [Appendix 10](#) for blood sample collection time points) 30 minutes pre-dose;
 - Plasma KPG-818 and KPG-818H
- At Visit 7 (Day 15), biomarkers will be drawn as follows:
 - 30 minutes pre-dose at Visit 7 (Day 15)
- Study drug administration will be completed in the office
- Assess compliance with study medication dosing instructions at Visits 3, 4, 5, and 7
- Record AEs
- Record current medications and surgeries/procedures

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7.2.4. Visit 6, Day 14 (± 0)

Visit 6 is to be scheduled at Day 14 (± 0) relative to Visit 2 (Week 1, Day 1). The following procedures are to be performed:

- Conduct pregnancy counselling
- Study drug administration (study drug to be taken at the site on Visit 6)
- Assess compliance with study medication dosing instructions per protocol and complete IP accountability
- Measure vital signs
- Perform physical examination (including a questionnaire for COVID-19 in accordance with applicable local Health Authority requirements)
- Collect blood samples for the following assessments:
 - Routine hematology
 - Clinical chemistry
 - Coagulation profile
- Collect urine for the following assessments:
 - Urinalysis
 - sUPCR
 - Urine pregnancy test (β hCG for female patients of childbearing potential)
- Record AEs
- Record current medications and surgeries/procedures
- Collect blood samples for the following PK assessments (see Appendix 10 for blood sample collection time points) pre-dose and 1, 2, 6, 10 and 24 hours post-dose, which is drawn on Day 15. For 24 hours post-dose sample, see [Section 7.2.3](#) for Day 15
 - Plasma KPG-818 and KPG-818H

7.2.5. Visits 8 and 9 (Day 28 and Day 56) (± 2 Days)

Visits 8 and 9 are to be scheduled at Day 28 (± 2), and Day 56 (± 2), respectively, relative to Visit 2 (Week 1, Day 1). The following procedures are to be performed:

- Conduct pregnancy counselling
- Dispense medication and review dosing instructions
- Study drug administration (study drug may be taken at the site at Visits 8 and 9)
- Assess compliance with study medication dosing instructions and perform drug accountability
- Measure vital signs
- Perform physical examination (including a questionnaire for COVID-19 in accordance with applicable local Health Authority requirements)

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- Collect blood samples for the following assessments:
 - Routine hematology
 - Clinical chemistry
 - Coagulation profile
- Collect urine for the following assessments:
 - Urinalysis
 - sUPCR
 - Urine pregnancy test (βhCG for female patients of childbearing potential)
- Record AEs
- Record current medications and surgeries/procedures
- Perform SLE disease activity assessments:
 - SLEDAI-2K (see [Appendix 11](#))
 - PGA (see [Appendix 12](#))
 - CLASI (see [Appendix 13](#))
 - Tender and swollen joints assessment (see [Appendix 14](#))
- Collect blood samples for the following assessments:
 - Complement C3 and C4
 - ANA, anti-dsDNA, anti-Smith, anti-SSA, anti-SSB, and APL antibodies
 - Immunoglobulins (IgG, IgM)

7.2.6. Visit 10 (Day 84) (± 2 Days)

Visit 10 is to be scheduled at Day 84 (± 2), this will be phone call Visit, to remind subject to take study medication KPG-818 or placebo.

7.2.7. Visit 11 (Day 85/End of Treatment Visit/Early Termination Visit)

Visit 11 is to occur at Day 85 (± 0). Patients who withdraw from the study treatment prior to completion of Visit 11 are to arrive at the site for an ET visit and to complete ET procedures, which are the same as in Visit 11, in a timely manner.

Every effort should be made to schedule ET procedures within 3 days of the last dose of study medication and before initiation of any new treatments.

The following procedures are to be performed at Visit 11 /ET visit:

- Conduct pregnancy counselling
- Patient to return all study medication for final IP accountability
- Assess compliance with study medication dosing instructions per protocol
- Measure vital signs and body weight

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- Perform physical examination (including a questionnaire for COVID-19 in accordance with applicable local Health Authority requirements)
- Perform 12-lead ECGs
- Collect blood samples for the following assessments:
 - Routine hematology
 - Clinical chemistry
 - Coagulation profile
- Collect urine for the following assessments:
 - Urinalysis
 - sUPCR
 - Urine pregnancy test (β hCG for female patients of childbearing potential)
- Record AEs
- Record current medications and surgeries/procedures
- Perform SLE disease activity assessments:
 - SLEDAI-2K (see [Appendix 11](#))
 - PGA (see [Appendix 12](#))
 - CLASI (see [Appendix 13](#))
 - Tender and swollen joints assessment (See [Appendix 14](#))
- Collect blood samples for the following PK assessments (see [Appendix 10](#) for blood sample collection time points)
 - Plasma KPG-818 and KPG-818H
- Collect blood samples for the following biomarkers assessments (see [Appendix 10](#) for blood samples collection time points): where collection is 24 hours after final dose on Day 84;
 - Leukocytes (total B cells (CD19+), Activated B cells (CD268+), total T cells (CD3+), T regulatory cells (Treg), and plasmacytoid dendritic cells (pDC))
 - PD markers (Aiolos (intracellular protein), Ikaros (intracellular protein), CRBN (intracellular protein), IFN- α , IFN- β , and IL-2)
- Collect blood samples for the following immunological assessments:
 - Complement C3 and C4
 - ANA, anti-dsDNA, anti-Smith, anti-SSA, anti-SSB, and APL antibodies
 - Immunoglobulins (IgG, IgM)

7.2.8. Visit 12 (Day 112, Follow-up) ($\pm$ 5 Days)

Visit 12 is to be scheduled at Day 112 ($\pm$ 5), relative to Visit 2 (Week 1, Day 1). The following procedures are to be performed:

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- Measure vital signs
- Perform physical examination (including a questionnaire for COVID-19 in accordance with applicable local Health Authority requirements)
- Perform 12-lead ECGs
- Collect blood samples for the following assessments:
 - Routine hematology
 - Clinical chemistry
 - Coagulation profile
- Collect urine for the following assessments:
 - Urinalysis
 - sUPCR
 - Urine pregnancy test (β hCG for female patients of childbearing potential)
- Record AEs
- Perform SLE disease activity assessments:
 - SLEDAI-2K (see [Appendix 11](#))
 - PGA (see [Appendix 12](#))
 - CLASI (see [Appendix 13](#))
 - Tender and swollen joints assessment (See [Appendix 14](#))
- Collect blood samples for the following assessments:
 - Complement C3 and C4
 - Anti-dsDNA antibodies

7.3. Efficacy Assessments

7.3.1. SLEDAI-2K

The SLEDAI-2K is an established and validated SLE activity index. The SLEDAI-2K is a global index and includes 24 clinical and laboratory variables that are weighted by the type of manifestation, but not by severity. The total score falls between 0 and 105, with higher scores representing increased disease activity (see [Appendix 11](#)). A SLEDAI-2K of 6 or more generally represents moderately to severely active disease.

For the purposes of this study, the SLEDAI-2K will be assessed using a 4-week interval which is a common approach in clinical trials of SLE. Preferably, the same Investigator should evaluate the patient at each SLEDAI-2K assessment from Screening to study completion. The Investigator must maintain documentation with descriptive details supporting the SLEDAI-2K scoring at each visit.

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7.3.2. Physician Global Assessment of Disease Activity

The assessments will be recorded on a visual analogue scale (VAS; 0 to 10 cm or 0 to 100 mm). The scale for the assessment ranges from 0 representing “no Lupus activity”, 1 representing mild disease activity, 2 representing moderate disease activity, to 3 representing “extremely active Lupus” (see [Appendix 12](#)). The PGA evaluation is made relative not to the patient’s most severe state but the most severe state of SLE per the Investigator’s assessment.

When scoring the PGA, the Investigator should always look back at the score from the previous visit. The Investigator should preferably be the same person at every study visit for a given patient.

7.3.3. CLASI

Cutaneous lupus erythematosus disease activity will be measured by the CLASI. The CLASI is an instrument the Investigator will use to assess the disease activity and damage caused to the skin for SLE patients with or without systemic involvement. The CLASI consists of 2 scores; the first summarizes the activity of the disease, while the second is a measure of the damage done by the disease (see [Appendix 13](#)). Activity is scored on the basis of erythema, scale/hyperkeratosis, mucous membrane involvement, acute hair loss, and non-scarring alopecia.

Damage is scored in terms of dyspigmentation and scarring, including scarring alopecia.

The extent of involvement for each of the skin symptoms is documented according to specific anatomic areas that are scored according to the worst affected lesion within that area for each symptom. The scores are calculated by simple addition based on the extent of the symptoms. Higher scores indicate worsening disease activity and greater damages.

7.3.4. Tender and swollen joints assessment

The joint assessment for tenderness and swelling will be carried out on 28 joints (see [Appendix 14](#)). Artificial and ankylosed joints will be excluded from tenderness and swelling assessments. The joint assessment should be performed by an adequately trained assessor. Training on how the joint count will be performed will be provided by the Sponsor.

It is strongly recommended that the same joint assessor perform the assessments at every visit within the same patient whenever possible.

7.4. Pharmacokinetic Assessments

7.4.1. Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the time points indicated in [Appendix 10](#). Blood volumes withdrawn for each patient is in [Appendix 4](#). Any changes to the scheduled times of PK assessments will be agreed with the Sponsor and documented in the TMF. Samples taken from patients who received placebo will not be analyzed.

Procedures for collection, processing, and shipping of PK blood samples will be detailed in a separate document.

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7.4.2. Analytical Methodology

Collection schedules for PK samples are shown in [Appendix 10](#).

Plasma concentrations of KPG-818 and its metabolite KPG-818H will be determined using validated analytical procedures. Specifics of the analytical methods will be provided in separate documents.

7.5. Safety and Tolerability Assessments

7.5.1. Adverse Events

AE definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in [Appendix 2](#).

The condition of each patient will be monitored from the time of signing the ICF to final discharge from the study. Patients will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?”, at least once each day while resident at the study site and at each study visit. Patients will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All nonserious AEs and SAEs, whether reported by the patient voluntarily or upon questioning, or noted on physical examination, will be recorded from initiation of study treatment until study completion. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to study treatment.

AEs recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator’s (or designee’s) discretion.

7.5.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedule of Assessments in [Appendix 9](#). Clinical laboratory evaluations are listed in [Appendix 3](#).

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

For all female patients, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in [Appendix 9](#). Pregnancy tests are only required for women with childbearing potential.

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

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7.5.3. Vital Signs

Blood pressure, pulse rate, respiratory rate, and body temperature will be assessed at the times indicated in the Schedule of Assessments in [Appendix 9](#). Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All vital Signs will be measured singularly and repeated once if outside the relevant clinical reference ranges.

Patients must be rested for at least 5 minutes before BP and pulse rate measurements.

7.5.4. 12-Lead Electrocardiograms

Resting 12-lead ECGs will be recorded after the patient has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in [Appendix 9](#).

All 12-lead ECGs will be performed singularly and repeated once if outside the relevant clinical reference ranges.

The 12-lead ECGs will be repeated twice, and an average of the 3 readings will be taken, only if either of the following criteria apply:

- QTc interval value > 500 ms
- QTc change from baseline (pre-dose) is > 60 ms.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECG is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.5.5. Physical Examination

A full physical examination will be performed at the time points specified in the Schedule of Assessments in [Appendix 9](#).

During each physical examination the following activities related to COVID-19 infection will be conducted:

- Questionnaire for potential exposure, close contact, signs and/or symptoms suggestive of COVID-19 infection, including elevated body temperature in accordance with applicable local Health Authority requirements.
- Compliance with the precautions to reduce the risk of getting COVID-19 infection (in accordance with recommendations from the applicable medical associations and the Investigator for the duration of the study).

7.5.6. Body Weight

Body weight (in underclothes) will be recorded at the time points indicated in the Schedule of Assessments in [Appendix 9](#).

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7.6. Serologic Markers

Sample for autoantibodies (including ANA, anti-dsDNA, anti-Smith, anti-SSA, anti-SSB, and APL), complement C3, C4, and other analytes will be collected as described in the Schedule of Assessments in [Appendix 9](#).

7.7. Exploratory Biomarkers Evaluations

The selected biomarkers listed in [Table 3](#).

In Phase 1b, blood samples from each of the 24 patients will be collected at 3 time points: pre-dose on Day 1, pre-dose on Day 7, and on Day 15 (i.e., 24 hours after the pre-dose on Day 14).

Biomarkers in Phase 2a, will be collected from each of the 32-48 patients at 3 time points: pre-dose on Day 1, 24 hours post-dose Day 14 (drawn on Day 15), and 24 hours after the last dose on Day 84 (drawn on Day 85).

Table 3. Biomarkers for testing in Phase 1b and Phase 2a

Biomarkers for testing in Phase 1b and Phase 2a	
Leukocytes	Total B cells (CD19 ⁺)
	Activated B cells (CD268 ⁺)
	Total T cells (CD3 ⁺)
	T regulatory cells (Treg)
	Plasmacytoid dendritic cells (pDC)
PD markers	Aiolos (intracellular protein)
	Ikaros (intracellular protein)
	CRBN (intracellular protein)
	IFN- α , IFN- β , and IL-2

Abbreviations: IFN = interferon, PD = pharmacodynamics.

7.8. Gene Expression

Efficacy of KPG-818 may closely correlate with the 5 gene expression levels. The examination data of the genes will help with the efficacy analysis and stratification and selection of the patients in the future.

For Phase 2a, mRNA assay for Aiolos and Type I IFNGS (whole blood sample) targeting the five genes (IKZF3, IFI44, IFI44L, IFI27, RSAD2) will be collected once, on Day 1 (pre-dose).

Biomarker samples donated for future research may be retained by the Sponsor or its designee indefinitely or as permitted by the applicable laws and regulations in the relevant country in which the study is conducted. Additional consent for storage of samples will be requested as a separate approval line on the ICF. Remaining de-identified unused clinical samples (blood/urine) will be retained by the Sponsor and used for the Sponsor's future research, including but not limited to the evaluation of immunoproteasome activity and of additional targets for novel therapeutic agents, the biology of the immunoproteasome, and to identify biomarkers for response and/or safety.

If additional written consent is not provided, any remaining biological samples will be destroyed by the Sponsor or its designee following study completion.

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8. SAMPLE SIZE AND DATA ANALYSIS

8.1. Determination of Sample Size

Phase 1b: Approximately 24 patients with SLE will be enrolled in 4 cohorts with 4 proposed dose levels of 0.15, 0.6, 2, and 5 mg/day. Each cohort will enroll 6 patients to ensure at least 4 evaluable patients to provide an adequate PK profile and safety assessment.

Phase 2a: Approximately 32 to 48 patients with SLE will be randomized 1:1:1:1 into 3 treatment arms of 3 proposed dose levels (0.15, 0.6, and 2 mg/day) and 1 placebo arm.

No formal statistical assessment, in terms of sample size, has been conducted. However, the number of patients in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study.

8.2. Analysis Populations

8.2.1. Efficacy Population

The efficacy population will include all patients who received at least 1 dose of KPG-818 and have baseline and at least 1 post-baseline efficacy data in Phase 2a part of the study.

8.2.2. Pharmacokinetic Population

The PK population will include all patients in Phase 1b and Phase 2a who received at least 1 dose of KPG-818 and have evaluable PK data.

8.2.3. Pharmacodynamic Population

The PD population will include all patients in Phase 1b and Phase 2a who received at least 1 dose of study treatment (KPG-818 or placebo) and for whom PD markers can be evaluated.

8.2.4. Safety Population

The safety population will include all patients who received at least 1 dose of study treatment (KPG-818 or placebo).

8.3. Efficacy Analyses

All efficacy parameters will be listed and summarized using descriptive statistics.

For the proportion of patients with SLEDAI-2K improvement ≥ 4 points from baseline at Week 4, 8, 12, and 16, the proportion of patients with a $\geq 50\%$ reduction from baseline in CLASI activity score at Week 12, in patients with baseline CLASI activity score ≥ 10 , comparisons between different dose groups and placebo will be done by exact Fisher-tests and exact confidence intervals. The difference between active groups and placebo, the two-sided 95% confidence interval of the difference will be presented at each individual visit.

The mean change from baseline in SLEDAI-2K, PGA, CLASI score, and tender and swollen joints should be analyzed using student's t-tests and corresponding confidence intervals will be presented.

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8.4. Pharmacokinetic Analyses

Noncompartmental PK analysis will be performed on individual plasma concentration data, using commercial software such as Phoenix[®] WinNonlin[®]. Plasma concentrations of KPG-818 and KPG-818H (if applicable), and plasma PK parameters will be listed and summarized using descriptive statistics. Individual and mean KPG-818 concentration-time profiles will also be presented graphically.

In Phase 1b and 2a, the PK parameters on scheduled time points (see [Appendix 10](#)) of KPG-818 dose proportionality will be examined across dose groups. The PK parameters will be analyzed for dose proportionality using a power model approach or analysis of variance (ANOVA) model as appropriate.

Achievement of steady state may be determined using appropriate statistical methods using the trough levels collected during the multiple dosing.

8.5. Pharmacodynamic Analyses

PD data on biomarkers will be listed and summarized using descriptive statistics. No formal statistical analysis of PD data is planned.

8.6. Safety Analysis

Safety parameters will be listed and summarized using descriptive statistics. No formal statistical analysis of safety data is planned. Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 or later and graded for severity according to CTCAE version 5.0.

8.7. Interim Analysis

No formal interim analyses are planned for this study.

8.8. COVID-19

Given the current COVID-19 pandemic, per regulatory guidance, a listing of all patients either experiencing COVID-19 or at least possibly affected by COVID-19 related measures will be produced where applicable.

Every effort will be taken to document where clinical trial conduct is affected by COVID-19 infection or related measures. Where applicable, the proposed statistical analyses will attempt to assess any effects on the validity and integrity of the data collected, as well as any impact on the results of the study.

Utilizing the data collected, continuing review will occur to ascertain the status of patients with respect to missing data and/or other significant information. Analyses may include (not exhaustive):

- Additional sensitivity analyses to adjust for population-level or record-level decisions made on a by-patient basis.
- Additional missing data summaries (by-patient summary of visits attended/missed) and current study status (i.e. able to attend clinic or not, discontinued etc.)

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- Additional subgroup analyses as exploratory.

All summaries may be investigated by form/domain, country, region, site, endpoint etc. Patterns of missingness should be investigated as part of the above.

Further details relating to additional populations and subgroup analyses, handling of protocol deviations, handling of missing data (including use of virtual assessments and/or switches from local to centralized labs), and any other considerations related to COVID-19 and related measures will be detailed further in the statistical analysis plan, finalized before unblinding. Any decisions made pertaining to inclusion/exclusion of patients from populations, or of record-level data from analyses will be documented during Blind Data Review discussions, prior to unblinding. The corresponding results of investigation will be documented in the Clinical Study Report (CSR).

8.9. Safety Review Committee

A SRC will be established to monitor safety and PK data on an ongoing basis for the Phase 1b portion of the study. During scheduled meetings, the SRC will review relevant study data for safety or benefit-risk concern.

During the Phase 1b part of the study, the SRC may provide the following recommendations to the Sponsor:

- Expanding a cohort at a specific dosing level or repeating a lower dose in a subsequent cohort.
- Continuing a dose level for a given cohort.
- Escalating a dose level for a subsequent cohort.
- Termination of current or previous cohort (s).

The coordinating principal Investigator or his/her designee, medical monitor, and pharmacovigilance monitor will comprise the voting members of the SRC. In addition, an independent arbitrator will receive the same information reviewed by the SRC and will attend the SRC meetings as an observer. Additional reviewers with expertise in clinical pharmacology, PK, statistics, or other clinical disciplines may be included, as deemed appropriate.

During the Phase 2a part of the study, sponsor and CRO Medical Monitor will provide oversight of safety considerations for the study and determine actions necessary for continuing protection of the study participants as well as for maintaining validity and scientific integrity of the study results. Details regarding management and schedule of review of safety data will be detailed in the Safety Monitoring Plan

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9. REFERENCES

1. Matyskiela, ME, Zhang W, Man HW, et al. J. Med. Chem. 2018, 61(2): 535-542.
2. Kangpu Biopharmaceuticals, Ltd. KPG-818 – Investigator’s Brochure. (Version 1.0). July 6, 2018.
3. Food and Drug Administration. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers [Internet]. Food and Drug Administration; 2005. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078932.pdf>
4. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. July 2005.

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10. APPENDICES

APPENDIX 1: 2019 EULAR/ACR CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS

Entry criterion			
Antinuclear antibodies (ANA) at a titer of $\geq 1:80$ on HEp-2 cells or an equivalent positive test (ever)			
↓			
If absent, do not classify as SLE If present, apply additive criteria			
↓			
Additive criteria			
Do not count a criterion if there is a more likely explanation than SLE. Occurrence of a criterion on at least one occasion is sufficient. SLE classification requires at least one clinical criterion and ≥ 10 points. Criteria need not occur simultaneously. Within each domain, only the highest weighted criterion is counted toward the total score [§] .			
Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		Antiphospholipid antibodies	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti- $\beta 2$ GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	Complement proteins	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	SLE-specific antibodies	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5 g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		
Total score:			
↓			
Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.			

Reference

Aringer M, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol. 2019; 71(9): 1400-12.

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APPENDIX 2: ADVERSE EVENT REPORTING

Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study treatment, whether or not related to the study treatment.

The definition of an AE includes an exacerbation of pre-existing medical conditions, intercurrent illnesses, drug interaction and exacerbation or the significant worsening of the indication under investigation (SLE) that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study (SLE), that do not represent a clinically significant exacerbation or worsening need not be considered an AEs.

Non-serious SLE manifestations or abnormal laboratory results related to SLE disease activity would not be recorded as AEs unless they meet the definition for SAEs.

Assessment of Severity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study referencing the CTCAE v5.0. The general CTCAE definitions of Grade 1 through Grade 5 are in the Table 5.

Table 4. Severity Grade of CTCAE version 5.0

Grade	Clinical Description of Severity
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL ^a .
Grade 3	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; Limiting selfcare ADL ^b .
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Abbreviations: ADL = Activities of Daily Living, AE = Adverse Events, CTCAE = Common Terminology Criteria for Adverse Events.

Notes:

- ^a. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- ^b. Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Relationship to Study Treatment

The Investigator (or designee) will make a determination of the relationship of the AE to the study treatment using a 4-category system according to the following guidelines:

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- **Not Related:** The AE is definitely caused by the patient's clinical state or the study procedure/conditions.
- **Unlikely Related:** The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related:** The AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the patient's clinical state or the study procedures/conditions.
- **Related:** The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Follow-up of Adverse Events

Every reasonable effort will be made to follow up with patients who have AEs. Any patient who has an ongoing AE that is possibly related or related to the IMP or study procedures at the Follow-up visit will be followed up, where possible, until resolution or until the unresolved AE is judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator's (or designee's) discretion. Any patient who has an ongoing AE that is not related or unlikely related to the IMP or study procedures at the Follow-up visit can be closed out as ongoing at the Investigator's discretion.

Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose either:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- Results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Instances of death or congenital abnormality, if brought to the attention of the Investigator at any time after cessation of the study treatment and considered by the Investigator to be possibly related to the study treatment, will be reported to the Sponsor.

Definition of Life-threatening

An AE is life-threatening if the patient was at immediate risk of death from the event as it occurred (i.e., does not include a reaction that might have caused death if it had occurred in a

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more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Definition of Hospitalization

AEs requiring hospitalization should be considered serious. In general, hospitalization signifies that the patient has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not be considered AEs, but such event should be recorded on a Clinical Assessment Form and added to the electronic Case Report Form. If anything untoward is reported during the procedure, this must be reported as an AE and either 'serious' or 'nonserious' attributed according to the usual criteria.

Serious Adverse Event Reporting

An SAE occurring from the initiation of study treatment until study completion must be reported to the Sponsor (or the designated CRO). Any such SAE due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event.

The event must be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the IMP. The Investigator must report all additional follow-up evaluations within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the Investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the patient's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

Suspected Unexpected Serious Adverse Reactions

AEs that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- Serious
- Unexpected (i.e., the event is not consistent with the safety information in the IB[or summary of product characteristics for noninterventional studies])
- There is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

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The Investigator will assess whether an event is causally related to study treatment. The Sponsor (or the designated CRO) will consider the Investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the IEC/IRBs (where required) within 7 days after the Sponsor (or the designated CRO) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor (or the designated CRO) first has knowledge of them.

The Sponsor (or the designated CRO) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

Pregnancy

If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate forms (pregnancy report form and pregnancy follow-up form) and submit to the Sponsor within 24 hours of learning of the pregnancy.

Females suspicious of or confirmed to be pregnant during the study must stop study drug immediately. Even though pregnancy is not considered as an AE, any complication during pregnancy and adverse outcome (to the mother and/or fetus or infant) should be reported as AE/SAE. All pregnancy should be followed up until final outcome. If live born, the infant will be followed at least 8 weeks after born.

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APPENDIX 3: CLINICAL LABORATORY EVALUATIONS

Clinical chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Creatine kinase Gamma-glutamyl transferase eGFR Glucose Lipase Potassium Serum creatinine Sodium Total bilirubin ^a Total protein	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count RBC distribution width White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Coagulation profile: Activated partial thromboplastin time International normalized ratio Prothrombin time	Bilirubin Blood Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive) Microscopic examination spot urine protein to creatinine ratio (sUPCR)
Serology:	Drug screen:	Hormone panel - females only ^d :
Anti-hepatitis B core antibody Hepatitis B surface antigen (HBsAg) Hepatitis B virus DNA ^b Hepatitis C antibody Hepatitis C virus RNA ^c Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen ANA Anti-dsDNA Anti-Smith antibody Anti-SSA Anti-SSB Antiphospholipid antibodies (APL) C3 and C4 Complement Ig isotype profile (IgG and IgM)	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/cannabinoids Cotinine test	Follicle-stimulating hormone (postmenopausal females only) Serum pregnancy test (human chorionic gonadotropin) (women of childbearing potential) Urine pregnancy test (women of childbearing potential) mRNA QuantiFERON [®] -TB Gold test

Notes:

^a. Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.

^b. Patients who test negative to hepatitis B surface antigen (HBsAg) and positive to Hepatitis B core (HBc) antibody should further undergo hepatitis B virus DNA titer detection to exclude active hepatitis B virus

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infection. If patients are negative to viral DNA, they can be enrolled. If patients are positive to HBsAg, they are excluded.

- c. Patient with hepatitis C virus antibody positive test results must be further tested for hepatitis C virus RNA to exclude active hepatitis C virus infection.
- d. Pregnancy tests are only required for women with childbearing potential.

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APPENDIX 4: TOTAL BLOOD VOLUME

The following blood volumes will be withdrawn for each patient.

	Volume per blood sample (mL)	Maximum number of blood samples	Total amount of blood (mL)
Clinical chemistry	~5		
Hematology	~5		
Coagulation	~5		
Serology	~5		
QuantiFERON®-TB Gold test	~4		
Pregnancy test	~2		
KPG-818 pharmacokinetics	~4	Phase 1b: 9 Phase 2a: 11	Phase 1b: 36 Phase 2a: 44
PD*	~2	Phase 1b: 6 Phase 2a: 6	Phase 1b: 12 Phase 2a: 12
mRNA	~2	Phase 2a: 1	Phase 2a: 2
Total: The exact volume of blood for each test and in total will follow the laboratory manual.			
*For PD, two 2-mL samples are taken at each of 3 visits, for a total of 6 blood samples and 12 ml of blood for both Phase 1b and Phase 2a.			

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APPENDIX 5: CONTRACEPTION GUIDANCE

Definitions

Women of Childbearing Potential: premenopausal females who are anatomically and physiologically capable of becoming pregnant following menarche.

Women of Nonchildbearing Potential:

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Postmenopausal:** Females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels of ≥ 40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators. Women aged >60 years old whose FSH values are not ≥ 40 mIU/mL may be included at the discretion of the Investigator and in consultation with the Sponsor.

Fertile male: a male that is considered fertile after puberty.

Infertile male: permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Patients

Female patients who are of nonchildbearing potential will not be required to use contraception. Female patients of childbearing potential must be willing to use 2 methods (1 primary and 1 secondary method) of birth control at least 28 days before starting IMP until 28 days after discontinuation of study therapy. Primary (non-barrier) methods of contraception include:

- Hormonal injection (as prescribed)
- Combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- Combined hormonal patch (as prescribed)
- Combined hormonal vaginal ring (as prescribed)
- Surgical method performed at least 3 months prior to the Screening visit:
 - Bilateral tubal ligation
 - Essure[®] (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- Hormonal implant

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- Hormonal or non-hormonal intrauterine device
- Vasectomized male partner (sterilization performed at least 90 days prior to the Screening visit, with documented confirmation of surgical success, and the sole partner for the female patient)

Secondary (barrier) methods of contraception include:

- Male condom with spermicide
- Female condom with spermicide
- Over-the-counter sponge with spermicide
- Cervical cap with spermicide (as prescribed)
- Diaphragm with spermicide (as prescribed)

Male Patients

Male patients must practice true abstinence or agree to use a barrier contraception (male latex condom or non-latex condom NOT made out of natural [animal] membrane [for example, polyurethane]) during sexual contact with a WOCBP while participating in the study, and for at least 90 days following IMP discontinuation, even if he has undergone a successful vasectomy.

Male patients must agree not to donate semen or sperm during the treatment period and for at least 90 days following the discontinuation of KPG-818.

Sexual Abstinence and Same-sex Relationships

Patients who practice true abstinence because of the patient's lifestyle choice (i.e., the patient should not become abstinent just for the purpose of study participation) are exempt from contraceptive requirements. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a patient who is abstinent at the time of signing the ICF becomes sexually active, they must agree to use contraception as described previously.

For patients who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a patient who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

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APPENDIX 6: WASHOUT PERIODS FOR EACH CLASS OF MEDICATIONS

Medications	Washout periods
Intra-articular, intralesional, subcutaneous, intradermal, intramuscular or intravenous pulse corticosteroids (≥ 250 mg prednisone equivalent/day for 1 or more days)	6 weeks before the Baseline visit
Immunomodulatory imide drugs (IMiDs) including thalidomide, lenalidomide, pomalidomide, and iberdomide (cc-220)	Not allowed at any time
Abatacept, ustekinumab, or interferon (IFN) therapy (alpha 2a and 2b, beta 1a and 1b, and pegylated IFNs alpha 2a and 2b)	12 weeks or 5 PK half-lives, whichever is longer, before the Screening visit
Rituximab and belimumab	24 weeks before the Screening visit
Adalimumab, infliximab, certolizumab pegol, golimumab, abatacept, IL-6 inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, and IL-23 inhibitors	8 weeks before the Screening visit
Denosumab and romosozumab	3 months or 5 PK half-lives, whichever is longer, before the Screening visit
Azathioprine, mycophenolate mofetil or mycophenolic acid, methotrexate or antimalarials	4 weeks before the Screening visit unless ongoing at screening at stable allowed dose
Other immunosuppressant drugs, e.g., leflunomide, calcineurin inhibitors	4 weeks before the Screening visit For leflunomide, 8 weeks before the Screening visit unless ongoing at Screening visit at stable allowed dose.
Targeted synthetic disease-modifying antirheumatic drug (tsDMARDs), including, but not limited to apremilast, tofacitinib and baricitinib	4 weeks before the Screening visit
Cytotoxic medications (e.g., cyclophosphamide)	24 weeks before the Screening visit
Blood products	24 weeks before the Screening visit
Topical preparations (e.g., corticosteroids, calcineurin inhibitors) for cutaneous manifestations of SLE	Must be stable for at least 4 weeks before the Screening visit
Live vaccine	4 weeks before the Screening visit
Other non-biologic investigational products	5 PK half-lives or 30 days, whichever is longer, before the Screening visit

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APPENDIX 7: EQUIVALENT DOSE OF ORAL PREDNISONE

Active Principle	Equivalent Dose (mg)
Prednisone	5
Cortisone acetate	25
Hydrocortisone	20
Prednisolone	5
Triamcinolone	4
Methylprednisolone	4
Betamethasone	0.75
Dexamethasone	0.75

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APPENDIX 8: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments (if applicable), ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of serious adverse events or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European Directive 2001/20/EC for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each patient will be provided with a study-specific ICF giving details of the study treatments, procedures, and potential risks of the study.

Patients will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Patients will be given an opportunity to ask questions about the study prior to providing written consent for participation.

Following discussion of the study with CRU personnel, patients will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving

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their informed consent. One copy will be given to the patient, and the other will be maintained in the patient's records.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

Patient Data Protection

Patients will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Patient and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual patients or Investigators will be redacted according to applicable laws and regulations.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient. The patient must also be informed that his/her study-related data may be examined by Sponsor or CRO auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All relevant patient data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections, and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being

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protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c), unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, patient-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (e.g., laboratory and bioanalytical data), and transmitted to the Sponsor or designee electronically, will be integrated with the patient's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each enrolled patient who undergoes any screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

Publications

Publications will be addressed in a separate agreement. The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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APPENDIX 9: SCHEDULE OF ASSESSMENT

Table 5. Schedule of Assessments - Phase 1b

Trial Period	Screening	Treatment period ^a				Follow-up	
Week	-6 ~ -1	1		2		3	4
Trial Day	-42~-1	1/Baseline	7	8	14/ET	15	28/ES
Visit	1	2	3	4	5/ET	6	7
Visit window (± day)	0	0	0	0	±1	0	±3
ICF	X						
Inclusion/exclusion criteria	X	X					
Pregnancy ICF	X						
Demographic data	X						
Documentation of SLE classification criteria	X						
SLE & other medical history, prior medications, prior surgery/procedures	X						
Pregnancy counselling		X		X	X		
IMP		Once a day throughout the treatment period (Day 1 to 14)					
IMP accountability				X	X		
Vital signs	X	X	X	X	X	X	X
Body Weight	X	X			X		
Height	X						
Physical examination	X	X	X	X	X		X
12-lead ECGs	X	X			X		X
Chest X-ray ^b	X						
QuantiFERON [®] -TB Gold test	X						
FSH ^c	<u>X</u>						
Routine hematology, chemistry, urinalysis	X	X		X	X		X
<u>Coagulation profile</u>	<u>X</u>	<u>X</u>		<u>X</u>	<u>X</u>		<u>X</u>

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Trial Period	Screening	Treatment period ^a				Follow-up	
Week	-6 ~ -1	1		2		3	4
Trial Day	-42~-1	1/Baseline	7	8	14/ET	15	28/ES
Visit	1	2	3	4	5/ET	6	7
Visit window (± day)	0	0	0	0	±1	0	±3
Spot urine protein to creatinine ratio	X	X		X	X		X
Urine drug screening	X						
Serum virology (HBV, HCV, HIV)	X						
Serum pregnancy test	<u>X</u> ^d						
Urine pregnancy test		X		X	X		X
Adverse event collection		Continuous throughout trial					
Current medications and surgeries/procedures		Continuous throughout trial					
Pharmacokinetics							
Plasma KPG-818, KPG-818H ^e		X	X	X	X	X	
Pharmacodynamics							
Biomarkers ^f		X	X			X	
Serologic markers							
C3, C4	X				X		
ANA, anti-dsDNA, anti-Smith, anti-SSA, anti-SSB, APL antibodies, and immunoglobulins (IgG, IgM)	X				X		

Abbreviations: ANA = antinuclear antibodies, ECG = electrocardiogram, ET = early termination, FSH = follicle stimulating hormone, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, ICF = informed consent form, IMP = investigational medicinal product, SLE = Systemic Lupus Erythematosus.

Notes:

^a The first dose date (Baseline visit) is counted as Day 1/Week 1, the day immediately after the first dose date will be counted as Day 2 and the date immediately before will be counted as Day -1 (skipped Day 0).

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- b. The chest X-ray is only required for patient who has not had a chest X-ray within 12 weeks prior to signing the ICF.
- c. FSH is only required for postmenopausal women
- d. There are 2 serum pregnancy tests. One is at Screening and again within 3 days before taking the first dose of KPG-818.
- e. Blood samples for PK analysis will be collected pre-dose on Day 1; pre-dose on Day 7; at 1, 2, 6, and 10 hours post-dose on Day 7; pre-dose on Day 8 (i.e., 24 hours after the pre-dose on Day 7); pre-dose on Day 14; and pre-dose on Day 15 (i.e., 24 hours after the pre-dose on Day 14) (see [Appendix 10](#)).
- f. Blood samples for biomarkers analysis will be collected at 3 time points: pre-dose on Day 1, pre-dose on Day 7, and pre-dose on Day 15 (i.e., 24 hours after the pre-dose on Day 14) (see [Appendix 10](#)).

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Table 6. Schedule of Assessments - Phase 2a

Trial Period	Screening	Baseline	Treatment period ^a									Follow-up
Week	-4 ~ -1	1	1	2	2	2	2	4	8	12	12	16
Trial Day	-28~-1	1	2	12	13	14	15	28	56	84	85	112
Visit	1	2	3	4	5	6	7	8	9	10/Call	11/EoT	12
Visit window (± day)	0	0	0	0	0	0	0	±2	±2	±2	±0	±5
ICF	X											
Inclusion/exclusion criteria	X	X										
Pregnancy ICF	X											
Demographic data	X											
Documentation of SLE classification criteria	X											
SLE & other medical history, prior medications, prior surgery/procedures	X											
Randomization		X										
Pregnancy counselling		X				X		X	X		X	
IMP dispensation		X						X	X	Reminder call to patient		

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Trial Period	Screening	Baseline	Treatment period ^a									Follow-up
Week	-4 ~ -1	1	1	2	2	2	2	4	8	12	12	16
Trial Day	-28~-1	1	2	12	13	14	15	28	56	84	85	112
Visit	1	2	3	4	5	6	7	8	9	10/Call	11/EoT	12
Visit window (± day)	0	0	0	0	0	0	0	±2	±2	±2	±0	±5
IMP dosing			Once a day throughout the treatment period (Day 1 to 84)									
IMP accountability		X	X	X	X	X	X	X	X		X	
Vital signs	X	X				X		X	X		X	X
Body Weight	X	X									X	
Height	X											
Physical examination	X	X				X		X	X		X	X
12-lead ECGs	X	X									X	X
Chest X-ray ^b	X											
QuantiFERON®-TB Gold test	X											
FSH ^c	X											
Routine hematology, chemistry, urinalysis	X	X				X		X	X		X	X
Coagulation profile	X	X				X		X	X		X	X
Spot urine protein to creatinine ratio	X	X				X		X	X		X	X
Urine drug screening	X											

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Trial Period	Screening	Baseline	Treatment period ^a									Follow-up
Week	-4 ~ -1	1	1	2	2	2	2	4	8	12	12	16
Trial Day	-28~-1	1	2	12	13	14	15	28	56	84	85	112
Visit	1	2	3	4	5	6	7	8	9	10/Call	11/EoT	12
Visit window (± day)	0	0	0	0	0	0	0	±2	±2	±2	±0	±5
Serum virology (HBV, HCV, HIV)	X											
Serum pregnancy test	X ^d											
Urine pregnancy test		X				X		X	X		X	X
Adverse Event collection	Continuous throughout trial											
Current medications and surgeries/ procedures	Continuous throughout trial											
	SLE disease activity assessment											
SLEDAI-2K, PGA, CLASI	X	X						X	X		X	X
Tender and swollen joints assessment	X	X						X	X		X	X
	Pharmacokinetics											
Plasma KPG-818, KPG-818H ^e		X	X	X	X	X	X				X	
	Pharmacodynamics											
Biomarkers ^f		X					X				X	
	Serologic markers											

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Trial Period	Screening	Baseline	Treatment period ^a									Follow-up
Week	-4 ~ -1	1	1	2	2	2	2	4	8	12	12	16
Trial Day	-28~-1	1	2	12	13	14	15	28	56	84	85	112
Visit	1	2	3	4	5	6	7	8	9	10/Call	11/EoT	12
Visit window (± day)	0	0	0	0	0	0	0	±2	±2	±2	±0	±5
C3, C4	X	X						X	X		X	X
Anti-dsDNA antibodies	X	X						X	X		X	X
ANA, anti-Smith, anti-SSA, anti-SSB, APL antibodies, and immunoglobulins (IgG, IgM)	X	X						X	X		X	
mRNA		X										

Abbreviations: ANA = antinuclear antibodies, CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index, ECG = electrocardiogram, ET = early termination, FSH = follicle stimulating hormone, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, ICF = informed consent form, IMP = investigational medicinal product, PGA = Physician Global Assessment of Disease Activity, SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

Notes:

- The first dose date (Randomization) is counted as Day 1/Week 1, the day immediately after the first dose date will be counted as Day 2 and the date immediately before will be counted as Day -1 (skipped Day 0).
- The chest X-ray is only required for patient who has not had a chest X-ray within 12 weeks prior to signing the ICF.
- FSH is only required for postmenopausal women.
- There are 2 serum pregnancy tests. One is at Screening and another within 3 days before taking the first dose of KPG-818.
- Blood samples for PK analysis will be collected as follows: pre-dose on Day 1; pre-dose on Day 2; pre-dose on Day 12; pre-dose on Day 13; pre-dose on Day 14 and at 1, 2, 6, 10 and 24 hours post dose on Day 14 (24 hours post-dose for Day 14 is drawn on Day 15); and - 24 hours after dosing on Day 84 (24 hours post-dose for Day 84 is drawn on Day 85). (see [Appendix 10](#)).
- Blood samples for ambient biomarkers analysis in Phase 2a will be collected at 3 time points: pre-dose on Day 1, 24 hours post-dose Day 14 (24 hours post-dose for Day 14 is drawn on Day 15), and 24 hours after the last dose on Day 84 (the 24 hours post-dose Day 84 sample is drawn on Day 85).(see

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[Appendix 10](#)). Biomarkers from prematurely discontinued patients will be collected at Early Termination visit. Please note that two samples are drawn for PD analysis at each visit.

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Protocol Reference: KPG-818-SLE**APPENDIX 10: BLOOD COLLECTION TIME POINTS FOR PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENT****Table 7. Phase 1b Blood Collection Time Points for Pharmacokinetic Assessment**

Dosing Day (Acceptable Limit)	Blood Collection Point (Acceptable Limit)	Blood Volume (4 mL/Sample)
Day 1 (± 0 days)	within 30 minutes pre-dose	4 mL
Day 7 (± 0 days)	within 30 minutes pre-dose 1 hour (± 15 minutes) post-dose 2 hours (± 15 minutes) post-dose 6 hours (± 20 minutes) post-dose 10 hours (± 40 minutes) post-dose	20 mL
Day 8 (± 0 days)	within 30 minutes pre-dose ^a	4 mL
Day 14 (± 1 days)	within 30 minutes pre-dose	4 mL
Day 15 (± 0 days)	within 30 minutes pre-dose ^b	4 mL

Notes:

^a. Pre-dose on Day 8 (i.e., 24 hours after the pre-dose on Day 7).^b. Pre-dose on Day 15 (i.e., 24 hours after the pre-dose on Day 14).**Table 8. Phase 2a Blood Collection Time Points for Pharmacokinetic Assessment**

Dosing Day (Acceptable Limit)	Blood Collection Point	Blood Volume (4 mL/Sample)
Day 1 (± 0 days)	within 30 minutes pre-dose	4 mL
Day 2 (± 0 days)	within 30 minutes pre-dose	4 mL
Day 12 (± 0 days)	within 30 minutes pre-dose	4 mL
Day 13 (± 0 days)	within 30 minutes pre-dose	4 mL
Day 14 (± 0 days)	within 30 minutes pre-dose 1 hour (± 15 minutes) post-dose 2 hours (± 15 minutes) post-dose 6 hours (± 20 minutes) post-dose 10 hours (± 40 minutes) post-dose	4 mL
Day 15 (± 0 days)	24 hours after Day 14 dose	4 mL
Day 85 (± 0 days)	24 hours after dose taken on Day 84	4 mL

Table 9. Phase 1b Blood Collection Time Points for Pharmacodynamic Assessment

Dosing Day (Acceptable Limit)	Blood Collection Point	Blood Volume (2 mL/sample)
Day 1 (± 0 days)	within 30 minutes pre-dose	4 mL
Day 7 (± 0 days)	within 30 minutes pre-dose	4 mL
Day 15 (± 0 days)	within 30 minutes pre-dose ^a	4 mL

^a. Pre-dose on Day 15 (i.e., 24 hours after the pre-dose on Day 14).

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Table 10. Phase 2a Blood Collection Time Points for Pharmacodynamic Assessment

Dosing Day (Acceptable Limit)	Blood Collection Point	Blood Volume (2 mL/sample)
Day 1 (± 0 days)	within 30 minutes pre-dose	4 mL
Day 15 (± 0 days)	24 hours after Day 14 dose	4 mL
Day 85 (± 0 days)	24 hours after Day 84 dose	4 mL

Biomarkers from prematurely discontinued patients will be collected at Early Termination visit.

Table 11. Phase 2a Blood Collection Time Point for Gene Expression test

Dosing Day (Acceptable Limit)	Blood Collection Point	Blood Volume (2 mL/sample)
Day 1 (± 0 days) mRNA sample	within 30 minutes pre-dose	2 mL

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Protocol Reference: KPG-818-SLE**APPENDIX 11: SLEDAI-2K: DATA COLLECTION SHEET**Study No.: _____ Patient Name: _____ Visit Date: _____
d m yr

(Enter weight in SLEDAI-2K Score column if descriptor is present at the time of the visit or in the preceding 4 weeks)

SLEDAI 2K Weight	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, 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, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, 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 of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or 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 creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours.
4	_____	Pyuria	>5 white blood cells/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 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.

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SLEDAI 2K			
Weight	SCORE	Descriptor	Definition
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38° C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / x10 ⁹ /L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / x10 ⁹ /L, exclude drug causes.
TOTAL			
SCORE _____			

Reference

Dafna D Gladman 1, Dominique Ibañez, Murray B Urowitz. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002; 29(2):288-91.

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APPENDIX 12: PHYSICIAN GLOBAL ASSESSMENT OF DISEASE ACTIVITY

PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY

Was the questionnaire completed? ☐ Yes ☐ No, (*specify*) _____



PGA Visual Analogue Scale Measurement = _____ mm (measure to the nearest 1/10 of 1 mm)

Physician's Signature: _____ Date: ____ - ____ - 20 ____
day month year

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APPENDIX 13: CLASI

Cutaneous LE Disease Area and Severity Index (CLASI)

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

activity			damage		
Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentation	0 – absent 1 – scarring 2 – severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Dyspigmentation

Mucous membrane lesions (examine if patient confirms involvement)		Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)
0-absent; 1-lesion or ulceration		☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains) ☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia

Recent Hair loss (within the last 30 days / as reported by patient)		NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both	
1-Yes 0-No			
Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.			
Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score

(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)

Total Damage Score

(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)

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APPENDIX 14: TENDER AND SWOLLEN JOINTS ASSESSMENT

The joint assessment will be carried out on 28 joints, including the shoulders, elbows, wrists, metacarpophalangeal (MCP) joints (MCP 1, 2, 3, 4, and 5), thumb interphalangeal (IP) joints, proximal interphalangeal (PIP) joints (PIP 2, 3, 4, and 5), and knees,

Artificial and ankylosed joints will be excluded from tenderness and swelling assessments.

28 JOINT COUNT ASSESSMENT

Please circle all that apply.

Query the subject at the start of the joint count about pain (prior to assessment of tenderness and swelling) as to whether they have experienced or are experiencing pain in any of the 28 joints. Artificial joints and joints that have ever had surgery performed on them should be scored as "NA".

	Joint #	Left Side			Right Side		
		Tenderness		Swelling	Tenderness		Swelling
Upper Extremity							
Shoulder	1	Y	N	NA	Y	N	NA
Elbow	2	Y	N	NA	Y	N	NA
Wrist	3	Y	N	NA	Y	N	NA
MCP I	4	Y	N	NA	Y	N	NA
MCP II	5	Y	N	NA	Y	N	NA
MCP III	6	Y	N	NA	Y	N	NA
MCP IV	7	Y	N	NA	Y	N	NA
MCP V	8	Y	N	NA	Y	N	NA
IP	9	Y	N	NA	Y	N	NA
PIP II	10	Y	N	NA	Y	N	NA
PIP III	11	Y	N	NA	Y	N	NA
PIP IV	12	Y	N	NA	Y	N	NA
PIP V	13	Y	N	NA	Y	N	NA
Lower Extremity							
Knee	14	Y	N	NA	Y	N	NA

Are there any other joints (not listed above) that are significantly affected by SLE?

No Yes

If Yes, list and describe: