KZR-616-002

A PHASE 1B/2 STUDY OF KZR-616 IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS WITH AND WITHOUT NEPHRITIS

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CLINICAL STUDY PROTOCOL

A Phase 1b/2 Study of KZR-616 in Patients with Systemic Lupus Erythematosus with and without Nephritis

Protocol Number:	KZR-616-002
EudraCT Number:	2019-004390-21
Investigational Product:	KZR-616
Phase:	Phase 1b/2
Sponsor:	Kezar Life Sciences 4000 Shoreline Court, Suite 300 South San Francisco, CA 94080
Contract Research Organization:	[redacted]
Original Protocol:	10 OCT 2017, Version 1.0
Protocol Amendment 1:	04 MAY 2018, Version 2.0
Protocol Amendment 2:	23 OCT 2018, Version 3.0
Protocol Amendment 3:	25 OCT 2019, Version 4.0
Protocol Amendment 4:	07 JUL 2020, Version 5.0

Protocol Approval Signatures

Protocol Title: A Phase 1b/2 Study of KZR-616 in Patients with Systemic Lupus Erythematosus with and without Nephritis

Protocol Number: KZR-616-002

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (cGCP), and applicable regulatory requirements.

Sponsor Signatory

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Date

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1 SYNOPSIS

Protocol Number:

KZR-616-002

Title:

A Phase 1b/2 Study of KZR-616 in Patients with Systemic Lupus Erythematosus with and without Nephritis

Investigational Product:

KZR-616

Study Centers:

This study will be conducted in up to approximately 60 investigational sites.

Phase:

Phase 1b/2

Objectives:

***Phase 1b – open-label multiple dose escalation study in systemic lupus erythematosus (SLE)*:**

Primary Objective:

- To evaluate the safety and tolerability of KZR-616 when administered as a subcutaneous (SC) injection weekly for 13 weeks in adult patients with SLE with and without nephritis

Secondary Objectives:

- To select recommended Phase 2 doses (RP2Ds) of KZR-616 when administered as a SC injection
- To characterize the pharmacokinetics (PK) of KZR-616

Exploratory Objectives:

- To explore the efficacy of KZR-616 in patients with SLE
- To explore the pharmacodynamic (PD) effects of KZR-616
- To explore biomarker, immunomodulatory, pharmacogenomic, and proteomic changes following KZR-616 treatment

***Phase 2 – 24 week, open-label study of KZR-616 in patients with lupus nephritis*:**

Primary Objective:

- To assess the number of patients with a 50% reduction in UPCR after 24 weeks of weekly SC injections with KZR-616 when compared to baseline

Secondary Objectives:

- To evaluate the safety and tolerability of KZR-616 when administered as a SC injection weekly for 24 weeks
- To characterize the efficacy of KZR-616 on parameters of renal function when administered as a SC injection weekly for 24 weeks

Exploratory Objectives:

- To explore the PD effects of KZR-616

- To explore the efficacy of KZR-616 in clinical and serological indicators of SLE disease activity
- To explore biomarker, immunomodulatory, pharmacogenomic, and proteomic changes following KZR-616 treatment

Study Design:

This is a Phase 1b/2, multi-center study in which patients will receive KZR-616, administered as a SC injection weekly for 13 (Phase 1b) or 24 weeks (Phase 2).

The study consists of 2 parts. Part 1, Phase 1b, is an open-label multiple dose escalation study to evaluate the safety and tolerability of KZR-616 in patients with SLE with and without nephritis.

Part 2, the Phase 2, is an open-label study of KZR-616 in patients with active proliferative lupus nephritis to assess the number of patients with a 50% reduction in UPCR after 24 weeks of weekly SC injections with KZR-616 when compared to baseline.

Phase 1b:

Phase 1b will evaluate 3 escalating dose levels of KZR-616 (45, 60, and 75 mg). There will be at least 6 patients at each dose level; multiple cohorts could be enrolled at a dose level. Eligible patients will receive 13 weekly SC injections of KZR-616 and then complete follow-up for 12 weeks after the last dose of study drug.

Decisions to escalate, expand, or decrease dose level or frequency following the first 4 weeks of treatment for at least 4 DLT-evaluable patients in a cohort will depend on review of safety data by a Data Monitoring Committee (DMC) comprising participating investigators, the medical monitor, and a Kezar Life Sciences representative and/or designee. Complete details will be provided in a separate DMC charter.

Dose-limiting toxicity (DLT) is defined as any Grade 3 or higher study drug-related adverse event (AE), graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03, that occurs during the 4-week DLT evaluation 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., systemic drug reaction), fatigue, anorexia, chills, 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

Dose Escalation Plan

For each dose level, at least 6 patients may be enrolled to ensure the availability of at least 4 DLT-evaluable patients. Dose escalation guidelines are as follows:

- Each cohort will include 1 sentinel patient who will receive KZR-616 at a selected dose on Day 1/Week 1
- If the sentinel patient does not experience a DLT, as defined above, within 48 hours and based on the clinical judgement of the investigator and medical monitor, the remaining patients in the cohort will be dosed
- If a DLT is experienced in the sentinel patient within 48 hours of injection, a second sentinel patient may be dosed with KZR-616 following a safety review by the DMC. If no DLT is observed after 48 hours in the second sentinel patient, the remainder of the cohort may be enrolled
- If 0 or 1 of 6, 0 or 1 of 5, or 0 of 4 patients (20% or less) in a cohort experience a DLT, the next dose level will be opened for enrollment
- If 1 of 4 (25%) of patients in a cohort, or 2 or more of 5 or 6 patients in a cohort experience a DLT, the maximum tolerated dose will have been exceeded and dose escalation will not continue

If dose escalation is halted due to excessive DLTs, dose escalation may resume if a review by the DMC of all cumulative data identifies a possible mitigating intervention(s) (e.g., corticosteroid pre-medication for injection site reaction). In such an instance, dose escalation may resume by enrolling at least 4 new patients in a new cohort at the same dose level at which escalation ceased, implementing the proposed intervention, and following the dose escalation guidelines above. If successful, any subsequent dose levels must incorporate the new intervention.

Dose escalation will occur after safety data for at least 4 patients, who received KZR-616 for at least 4 weeks, are reviewed and evaluated by the DMC.

Patients who discontinue treatment prior to Week 5 will be considered DLT non-evaluable, unless they experience a DLT prior to Week 5. The DLT non-evaluable patients may be replaced until the necessary number of evaluable patients is achieved per dose level.

Dose escalation increments other than 15 mg may be proposed by the DMC based upon emerging safety, PK, PD, and/or efficacy data. Similarly, emerging data may prompt the DMC to recommend a different safety evaluation period, or alteration of the dosing interval or duration.

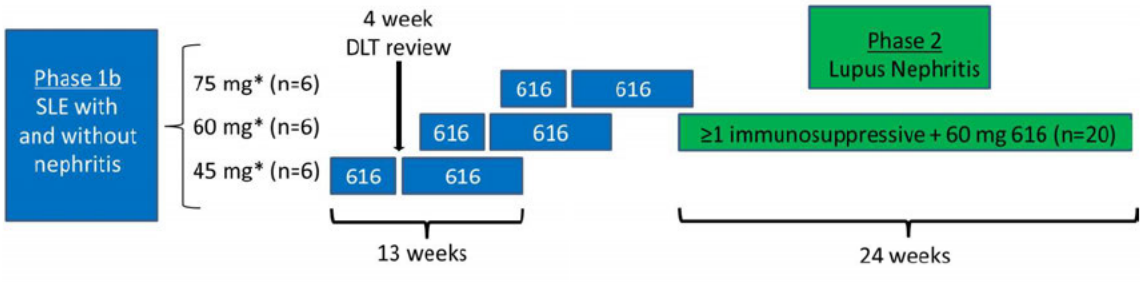
Phase 1b will be completed upon fulfillment of enrollment of the highest dose level that is determined to be tolerated.

Phase 2:

Eligible patients with active proliferative LN who are treated with at least one immunosuppressive agent will receive KZR-616, 60 mg, weekly for 24 weeks.

Patients will be followed for 12 weeks after the last dose of study drug.

Study schematic for Phase 1b and Phase 2:



Abbreviations: DLT = dose limiting toxicity; SLE = Systemic Lupus Erythematosus

Treatment:

KZR-616 is a small molecule, covalent inhibitor of the immunoproteasome.

KZR-616 is supplied as both a frozen solution drug product and a refrigerated lyophilized drug product in single-use vials packaged in multi-vial cartons.

For Phase 1b, patients will receive SC injection of KZR-616 at 45, 60, or 75 mg, respectively, once a week for 13 weeks. Patients must be on a stable regimen of medications for SLE.

For Phase 2, eligible patients will receive KZR-616, 60 mg, via SC injection weekly for 24 weeks. Patients must be on standard therapy including at least one immunosuppressive agent.

Study Duration:

The total study duration for Phase 1b is approximately 28 weeks, including the screening period (up to 28 days), treatment period (13 doses over 12 weeks and 1 day), and follow-up period (12 weeks).

For patients in the Phase 2 portion of the study, screening will last up to 5 weeks, treatment duration is 24 weeks (24 doses) and follow-up will be 12 weeks for a total of up to 41 weeks of participation.

Number of Patients:

Phase 1b: at least 6 patients per cohort and up to 8 cohorts [approximately 48 patients total]

Phase 2: 20 patients

Study Population:

Phase 1b:

Inclusion Criteria:

1. Male or female patients aged 18 to 75 years (inclusive)
2. Body mass index (BMI) of 18 to 40 kg/m^2
3. Fulfills the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE
4. Have at least one of the following at screening per central lab:

a) Positive antinuclear antibody (ANA) test (1:80 or higher); or
b) Anti-double stranded deoxyribonucleic acid (dsDNA) antibodies elevated to above normal (i.e., positive results); or
c) Anti-Smith antibody elevated to above normal (i.e., positive results)

5. Active SLE as indicated by a Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) total score ≥ 4 at screening

6. Must have received 1 or more of the following therapies for SLE, each administered at or higher than the minimum dose indicated for at least 12 weeks (unless discontinued or dose adjusted for documented drug-related toxicity or size/weight):

a) Hydroxychloroquine 200 mg orally daily in combination with prednisone 10 mg daily or equivalent
b) MMF orally 1 g/day or MPA orally 720 mg/day
c) Methotrexate orally or SC 15 mg/wk., or leflunomide orally 10 mg/day
d) Azathioprine (AZA) 100 mg/day or 6-mercaptopurine 50 mg/day (50 or 25 mg/day, respectively, permitted in cases of documented thiopurine methyltransferase [TPMT] polymorphism) orally
e) Cyclosporine or tacrolimus at doses documented to maintain at least 100 or 5 ng/mL during the required duration, respectively
f) Cyclophosphamide 500 mg intravenously (IV) every 2 weeks or 500 mg/m^2 IV once monthly
g) Belimumab 10 mg/kg IV every 2 weeks for 3 doses, followed by 10 mg/kg every 4 weeks; or 200 mg SC weekly
h) Rituximab 1 g IV (may be given as 500 mg twice)

7. Acceptable screening laboratory values of concern, including:

a) Adequate hematologic criteria:
- Absolute neutrophil count ≥ 1.5 × 10^9/L (≥ 1 × 10^9/L if neutropenia is attributable to lupus disease activity)
- White blood cells ≥ 2.0 × 10^9/L (≥ 1.5 × 10^9/L if leukopenia is attributable to lupus disease activity)
- Hemoglobin (Hgb) ≥ 9 g/dL (≥8 g/dL if anemia is attributable to lupus disease activity)
- Platelet count ≥ 100 × 10^9/L (≥ 25 × 10^9/L if thrombocytopenia is attributable to lupus disease activity)

b) Adequate hepatic function:
- Total bilirubin ≤ 1.5 × upper limit of normal (ULN) (3 × ULN for patients with documented Gilbert's syndrome)
- Aspartate aminotransferase (AST) ≤ 2.5 × ULN
- Alanine aminotransferase (ALT) ≤ 2.5 × ULN

c) Estimated glomerular filtration rate (eGFR) ≥ 40 mL/min/1.73 m^2 (estimated based on Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula)
d) Immunoglobulin G (IgG) ≥ 500 mg/dL

8. If taking the following SLE therapies:

a) Oral corticosteroids (up to 20 mg/day prednisone or equivalent): must be on a stable dosage regimen of oral corticosteroid at least 4 weeks prior to screening and maintain stable dosage until randomization

b) Hydroxychloroquine (≤ 400 mg/day) or chloroquine (≤ 500 mg/day) orally or other antimalarials: must be started or stopped at least 12 weeks prior to screening, with stable dosage regimen for at least 4 weeks prior to screening

c) Immunosuppressive agents: must be started or stopped at least 12 weeks prior to screening, with stable dosage regimen, including route of administration, for at least 4 weeks prior to screening:

- MMF (≤ 3 g/day) or MPA (≤ 2.16 g/day) orally
- AZA (≤ 200 mg/day) orally
- Methotrexate (≤ 25 mg/week) orally, SC, or intramuscularly (patients must be on concomitant folic or folinic acid supplementation if using methotrexate)
- Leflunomide (≤ 20 mg/day) orally

9. Women of childbearing potential must have a negative serum beta-human chorionic gonadotropin (hCG) pregnancy test at screening and a negative urine pregnancy test prior to the first dose and must agree to use a highly effective method of birth control from signing the informed consent form (ICF) until their completion of the study (or 30 days following the last dose of study drug in case of early withdrawal). Hormonal contraception may not be effective in women on concomitant MMF/MPA; women on MMF/MPA using hormonal contraception must agree to use a highly effective non-hormonal method of contraception. Abstinence is not an acceptable method of birth control for this study. Women of nonchildbearing potential must be postmenopausal (no menses for at least 2 years before the screening visit), permanently sterilized (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy), or congenitally sterile
10. Male patients must use an effective contraception method (e.g., condom with spermicide) from signing the ICF until their completion of the study (or 12 weeks following the last dose of study drug in case of withdrawal) or be congenitally or surgically sterile (e.g., vasectomy with documented confirmation of post-surgical aspermia)
11. Willing and able to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

Exclusion Criteria:

1. Active central nervous system involvement by autoimmune disease (e.g., neuropsychiatric SLE including seizures, psychosis, acute confusional state or cerebrovascular accident) requiring specific therapeutic intervention within 60 days prior to first day of study treatment. Headache treated only with acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or approved doses of triptans is permitted with medical monitor approval.
2. Presence of another rheumatic (overlap) disease that may confound clinical assessments in the study. Secondary sicca or Sjogren's syndrome, antiphospholipid antibody syndrome, and overlap with rheumatoid arthritis without erosive joint disease ("rhupus") are allowed.
3. 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.
4. Receipt of any of the following treatments within the following timeframes before screening (see Section 14.5, Appendix E, for excluded medications):

a) Systemic corticosteroids ≥ 100 mg prednisone or equivalent: 4 weeks

b) Intra-articular therapies, such as corticosteroids or hyaluronic acid preparations: 4 weeks

c) Intravenous immunoglobulin (IVIg): 4 weeks
d) Other non-biologic immunosuppressive agents, such as cyclosporine and tacrolimus: 4 weeks
e) Cyclophosphamide: 12 weeks
f) Cytokine antagonists, including but not limited to interleukin (IL)-1, IL-6, IL-17, IL-12/23, IL-23, interferon (IFN), integrin, and tumor necrosis factor (TNF)-α antagonists: 12 weeks
g) B-cell-depleting therapies (e.g., rituximab): 24 weeks with levels of circulating cluster of differentiation 19+ (CD19+) B cells within normal limits or 48 weeks if CD19+ count is not available
h) Belimumab, abatacept, or atacicept: 12 weeks
i) Other biologics or investigational drugs: 8 weeks or 5 half-lives, whichever is longer
j) Transfusion with blood, packed red blood cells, platelets or treatment with plasmapheresis or plasma exchange: 6 weeks

5. Patient has had recent serious or ongoing infection, or risk for serious infection, including:
   a) Acute or chronic infections:
      - Requiring systemic antibiotic, antifungal, or antiviral (antimicrobial) therapy within 14 days of Week 1, Day 1
      - Requiring hospitalization or a course of IV antimicrobial therapy within 24 weeks prior to screening
   b) History of severe and/or disseminated viral infections, and/or opportunistic infections
   c) Known seropositivity for or active infection by human immunodeficiency virus (HIV)
   d) Active, chronic, or resolved hepatitis B or hepatitis C infection (see Section 8.2.6.6)
   e) History of progressive multifocal leukoencephalopathy
   f) Active or latent tuberculosis (TB), as suggested by chest x-ray within the 12 weeks prior to screening and/or QuantiFERON®-TB Gold at screening per Section 8.2.6.6
      - Patients with a history of latent TB with documented completed treatment per Centers for Disease Control and Prevention guidelines are allowed
      - A chest x-ray must be performed during screening if one has not been done within 12 weeks prior to the screening visit
   g) Receipt of a live-attenuated vaccine within 12 weeks of first day of study treatment (Week 1, Day 1)
   h) Primary immunodeficiency (unless otherwise considered, in the opinion of the investigator and medical monitor, to confer a clinically insignificant infection risk, such as deficiency in immunoglobulin A (IgA), C1q, C2, or C4 without a history of recurrent infections [3 or more infections in 1 year requiring antimicrobial therapy])
6. History of any concurrent illness, including drug induced SLE, that has required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to signing the ICF
7. Clinical evidence of significant unstable or uncontrolled acute or chronic diseases (e.g., cardiac [including congestive heart failure, hypertension, angina, or history of myocardial infarction], pulmonary [including chronic obstructive pulmonary disease, asthma requiring corticosteroid therapy, pulmonary hypertension, or pulmonary fibrosis], hematologic, gastrointestinal, hepatic, renal, neurological, or infectious diseases) that, in the opinion of the investigator or sponsor, could confound the results of the study, put the patient at undue risk, or interfere with protocol adherence

8. History of cancer, except for in situ cancer that has been completely excised or has been curatively treated with no sign of disease for >5 years
9. Major surgery within 4 weeks before signing the ICF or major surgery planned during the study period

Phase 2:

Inclusion Criteria:

1. Male or female patients aged 18 to 75 years (inclusive)
2. BMI of ≥ 18 kg/m^2
3. Fulfills the 2012 SLICC classification criteria for SLE
4. At least one of the following at Screening per central lab:
    a) Positive ANA test (1:80 or higher) or
    b) Anti-dsDNA antibodies elevated to above normal (i.e., positive results); or
    c) Anti-Smith antibody at screening elevated to above normal (i.e., positive results)
5. Active nephritis with UPCR ≥ 1.0 measured in 24-hour urine collection
6. Currently receiving one or more immunosuppressive agents (see Section 7.2 for allowed background medications and Section 14.5, Appendix E for excluded medications) that has been stable for dose and route of administration for ≥ 8 weeks prior to Baseline. If patient is also on corticosteroids then must be on a stable dose for ≥ 2 weeks prior to Baseline
7. Renal biopsy within 2 years of the Screening visit with a histologic diagnosis of LN (ISN/RPS) Classes III, IV-S or IV-G, (A) or (A/C) +/- Class V; for biopsies > 1 year before the Screening visit, one of the following must also be present at screening: low C3, low C4, or anti-ds-DNA elevated to above normal range.
8. Acceptable screening laboratory values:
    a) Adequate hematologic criteria:
        - Absolute neutrophil count ≥ 1.5 × 10^9/L (≥ 1 × 10^9/L if neutropenia is attributable to lupus disease activity)
        - White blood cells ≥ 2.0 × 10^9/L (≥ 1.5 × 10^9/L if leukopenia is attributable to lupus disease activity)
        - Absolute lymphocyte count ≥ 0.5 × 10^9/L
        - Hgb ≥ 9 g/dL (≥ 8 g/dL if anemia is attributable to lupus disease activity)
        - Platelet count ≥ 100 × 10^9/L (≥ 25 × 10^9/L if thrombocytopenia is attributable to lupus disease activity)
    b) Adequate hepatic function:
        - Total bilirubin ≤ 1.5 × ULN (3 × ULN for patients with known Gilbert's syndrome)
        - AST ≤ 2.5 × ULN
        - ALT ≤ 2.5 × ULN
    c) eGFR ≥ 30 mL/min/1.73 m^2 estimated based on CKD-EPI formula
    d) IgG ≥ 500 mg/dL

9. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline and must agree to employ adequate birth control measures for the duration of the study. Women of childbearing potential (WOCBP) must use highly effective and medically acceptable methods of contraception to prevent pregnancy during Screening and must agree to continue to practice adequate contraception during the study and for 4 weeks after administration of the last dose of the study drug.

   For the purposes of this study, WOCBP are defined as: all postpubescent female patients, unless the patient is postmenopausal (defined by amenorrhea for at least 2 years or amenorrhea for at least 1 year with confirmatory follicle stimulating hormone [FSH] level in the postmenopausal range as documented historically or measured by the central laboratory at Screening and if patient is not on supplementary hormonal therapy) or if the patient is surgically sterile (i.e., tubal ligation, hysterectomy, bilateral salpingoophorectomy).

   Highly effective contraception is defined as the use of an intrauterine device or hormonal contraceptives (e.g., implant or oral), or having a vasectomized partner. If using a hormonal form of contraception, it must have been stable for at least 4 weeks prior to Screening, and if using concomitant mycophenolate, the patient must use another nonhormonal form of highly effective contraception. Abstinence will be acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation) and withdrawal are not acceptable methods of contraception.

10. Male patients with a partner of childbearing potential must be either congenitally sterile or surgically sterile (by vasectomy) or willing to use a condom in addition to having their female partner use another form of contraception (such as an intrauterine device, barrier method with spermicide, or hormonal contraceptive [e.g., implant, injectable, patch, or oral]) from Screening until 12 weeks after the last dose of study drug, unless their partners are infertile or surgically sterile.

11. Willing and able to provide written informed consent prior to any study-related procedures and to comply with all study requirements

Exclusion Criteria:

1. Any of the following:
   a) Dialysis within 12 months prior to Screening or expected need for renal replacement therapy (dialysis or renal transplant) within a 6-month period after enrollment
   b) Rapidly progressive glomerulonephritis (RPGN) and/or renal disease other than ISN/RPS Classes III, IV-S or IV-G, [A] or [A/C] with or without Class V LN)
   c) Chronic kidney disease not due to LN
   d) > 50% sclerosed glomeruli on most recent renal biopsy
2. Presence of another rheumatic (overlap) disease that may confound clinical assessments in the study. Secondary sicca or Sjogren's syndrome and antiphospholipid antibody syndrome are allowed
3. History of antiphospholipid syndrome with history of thromboembolic event within 12 months of screening
4. Active central nervous system involvement by autoimmune disease (e.g., neuropsychiatric SLE including seizures, psychosis, acute confusional state or cerebrovascular accident) requiring

specific therapeutic intervention within 60 days prior to first day of study treatment. Headache treated only with acetaminophen, NSAIDs, or approved doses of triptans is permitted with medical monitor approval.

5. Active or chronic infection:
    a) Acute or chronic bacterial or fungal infections:
        - Requiring systemic antibiotic or antifungal therapy within 14 days of Screening
        - Receipt of more than a 14-day course of antimicrobial therapy within 12 weeks of Screening to treat sepsis, abscess, osteomyelitis, joint infection, or bacterial endocarditis.
    b) Acute viral illness:
        - Signs and symptoms of acute viral illness must be resolved ≥ 4 weeks prior to Day 1 (Baseline). Patients with history of SARS-CoV-2 must have full resolution of symptoms and no evidence of associated renal injury
        - Symptomatic herpes zoster or herpes simplex infection (HSV) (not including simple oral HSV lesions) within 12 weeks prior to Screening or during the Screening Period
        - Acute hepatitis B or C infection
    c) Chronic viral infection:
        - Patients with chronic herpesvirus infections such as HSV or CMV should be on suppressive therapy at Baseline and during the study.
        - Chronic hepatitis C infection. Patients with prior chronic hepatitis C infection should have received a full treatment course and have documented absence of detectable HCV DNA at the completion of at least 12 weeks of treatment to be enrolled.
        - Chronic hepatitis B infection. Patients who are HBsAg negative and hepatitis B core antibody positive with no detectable DNA will be allowed into the study and will require regular monitoring of hepatitis B virus DNA. (see Section 8.2.6.6).
        - Known seropositivity for or active infection with human immunodeficiency virus (HIV). Those with a positive screening test and negative confirmatory test are eligible.
6. Patient has or had any of the following:
    a) Progressive multifocal leukoencephalopathy
    b) Active or untreated latent TB, per QuantiFERON-TB Gold at screening per Section 8.2.6.6
        - Patients with a history of latent TB with documented completed treatment per Centers for Disease Control and Prevention guidelines are allowed
        - A chest x-ray must be performed during screening if one has not been done within 12 weeks prior to the screening visit
    c) Receipt of a live-attenuated vaccine within 12 weeks of Baseline (Week 1, Day 1)
    d) Primary immunodeficiency (unless otherwise considered, in the opinion of the investigator and medical monitor, to confer a clinically insignificant infection risk, such as deficiency in IgA, C1q, C2, or C4 without a history of recurrent infections [3 or more infections in 1 year requiring antimicrobial therapy])
    e) Primary hematopoietic cell or solid organ transplant

7. Clinical evidence of significant unstable or uncontrolled acute or chronic diseases (e.g., cardiac [including congestive heart failure, hypertension, angina, or history of myocardial infarction], pulmonary [including chronic obstructive pulmonary disease, asthma requiring corticosteroid therapy, pulmonary hypertension, or pulmonary fibrosis], hematologic, gastrointestinal, hepatic, renal, neurological, or infectious diseases) that, in the opinion of the investigator or sponsor, could confound the results of the study, put the patient at undue risk, or interfere with protocol adherence
8. QT interval with Fridericia's correction (QTcF) or Bazett's correction (QTcB) > 480 msec on ECG
9. Major surgery within 12 weeks before signing the ICF or major surgery planned during the study period
10. Any active or suspected malignancy or history of documented malignancy within the last 5 years before Screening. Exceptions include history of appropriately excised and cured cervical carcinoma in situ or excised basal or squamous cell carcinomas of the skin
11. Women who are pregnant or lactating
12. Hypersensitivity to the Investigational Medicinal Products or any of its excipients.
13. Use of investigation medical therapy or device, and/or participation in an investigational trial < 8 weeks or 5 half-lives, whichever is longer, prior to Baseline; Patients who participated in Phase 1b of KZR-616-002 are excluded from Phase 2

Overview of Assessments

Assessments of clinical and laboratory activity of KZR-616 will be performed as detailed in Appendix A and Appendix B, respectively.

Safety: Safety assessments will begin after the patient provides written informed consent and continue through 12 weeks follow-up visit. Severity of AEs will be assessed according to the NCI-CTCAE, Version 4.03.

Efficacy: SLE disease activity (clinical and laboratory assessments and patient reported outcomes) will be assessed approximately every 4 weeks.

Concomitant Medications: concomitant medications will be recorded at start of study and with changes

Pharmacokinetics (Phase 1b only): Blood samples for determination of plasma concentrations of KZR-616 and its metabolites will be collected on Day 1 of Weeks 1 and 5 before dosing and at 5, 15, and 30 minutes and 1, 2, 4, and 8 hours after the injection. Urine samples will be pooled from 0 to 5 hours and 5 to 8 hours.

Pharmacodynamics: Blood samples for the determination of proteasome activity in whole blood and peripheral blood mononuclear cells will be assessed in blood samples collected as follows:

Phase 1b – Day 1 of Week 1 and Week 5, before dosing and 4 hours after

Phase 2 – Day 1 of Week 1, before dosing and 4 hours after injection, and Day 1 of Week 5, before dosing

Biomarkers: Blood samples for the determination of serum cytokine levels and circulating leukocytes will be measured in blood samples collected as follows:

Phase 1b – Day 1 of Weeks 1, 5, 17, and 25

Phase 2 – Day 1 of Weeks 1, 17, 25, and 37

Pharmacogenomics:

Gene expression (RNA) profiling – Blood samples collected as follows:

Phase 1b – Day 1 of Weeks 1, 5, 17, and 25

Phase 2 – Day 1 of Weeks 1, 17, 25, and 37

DNA genotyping – Day 1 of Week 1

Endpoints

Phase 1b:

Primary Endpoint:

- Safety and tolerability of KZR-616 as assessed by incidence, nature, and severity of AEs

Secondary Endpoints:

- The RP2Ds of KZR-616 as determined by evaluation of safety parameters, PK, PD, and DLTs by the DMC
- Plasma PK parameters, including maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration-time curve (AUC), and other applicable parameters will be calculated for KZR-616

Phase 2:

Primary Endpoint:

- The number of patients with a 50% reduction in UPCR after 24 weeks of treatment when compared to baseline

Secondary Endpoints:

- Safety and tolerability of KZR-616 as assessed by the incidence, nature, and severity of AEs
- The number of patients with a partial renal response (PRR) after 24 weeks of treatment as defined by:
    a) A 50% reduction of UPCR and/or reduction of UPCR to < 1.0 if the baseline UPCR was < 3.0 or a 50% reduction of UPCR and/or reduction of UPCR to < 3.0 if the baseline was ≥ 3.0
    b) eGFR of ≥ 60 mL/min/1.73 m^2 or no worsening of eGFR from baseline of ≥ 25%
    c) No use of prohibited medication
- The number of patients with a complete renal response (CRR) after 24 weeks of treatment as defined by:
    a) UPCR of ≤ 0.5
    b) eGFR of ≥ 60 mL/min/1.73 m^2 or no worsening of eGFR from baseline of ≥ 25%

c) Prednisone (or equivalent) ≤ 10 mg
d) No use of prohibited medication

- Time to ≥ 50% reduction in UPCR from baseline
- Time to CRR
- Time to PRR
- The number of patients with UPCR of ≤ 0.5 at 24 weeks
- The number of patients with average daily prednisone (or equivalent) dose ≤ 10 mg
- Change from baseline in levels of autoantibodies (e.g., ANA, anti-dsDNA) and complement at 24 weeks
- Changes in corticosteroid use from baseline

Description of Endpoint Analyses

Safety will be evaluated by the monitoring and assessment of all AEs, physical examinations, vital signs (blood pressure, pulse, body temperature,), electrocardiograms (ECGs), and clinical laboratory tests (hematology, serum chemistry, urinalysis).

Verbatim AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients who experience AEs will be summarized by dose/treatment group and overall.

Laboratory, vital sign, ECG, and efficacy data will be summarized descriptively (mean, median, standard deviation [SD], and minimum and maximum values) by dose/treatment group and overall and will be summarized by protocol specified time point along with a summary of change from baseline at each protocol specified time point. Changes in physical examinations will be listed for each patient and described.

PK analyses will include determination of plasma levels of KZR-616 including C_{max}, T_{max}, and AUC. Urine PK parameters for KZR-616 and its metabolites will include amount excreted (Ae) and fraction of dose excreted (%Fe). Plasma PK parameters, including C_{max}, T_{max}, AUC from time 0 to the last measured concentration (AUC_{last}), and other applicable parameters such as elimination parameters data permitting, will be calculated for KZR-616.

Summary statistics (e.g., total number of patients with observed data, mean, median, SD, min, max for continuous endpoints; for binary endpoints: total number of patients observed, number of patients with the event of interest, percent) will be provided by dose in Phase 1b and for all patients combined in Phase 2.

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LIST OF ABBREVIATIONS

%Fe	fraction of dose excreted
ACE-I	angiotensin converting enzyme inhibitor
ACR	American College of Rheumatology
AE	adverse event
Ae	amount excreted
Ag-Ab	antigen-antibody
ALT	alanine aminotransferase
ANA	antinuclear antibody
APTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{last}	area under the plasma concentration-time curve from time 0 to the last measured concentration
AZA	azathioprine
beta-hCG	beta-human chorionic gonadotropin
BILAG	British Isles Lupus Assessment Group
BLyS	B-lymphocyte stimulator
BMI	body mass index
BNP	B-type natriuretic peptide
CD19+	cluster of differentiation 19+
cGCP	current Good Clinical Practice
CH50	50% hemolytic complement
CK-MB	creatine kinase MB
CLASI	Cutaneous Lupus Erythematosus Disease Index
C-L	caspase-like
C_{max}	maximum plasma concentration
CRO	contract research organization
CRR	complete renal response
CT-L	chymotrypsin-like
CYC	cyclophosphamide
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
dsDNA	double stranded deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
FDA	U.S. Food and Drug Administration
GLP	Good Laboratory Practice
HAQ-DI	Health Assessment Questionnaire-Disability Index
Hgb	hemoglobin
HIV	human immunodeficiency virus
HUS	hemolytic uremic syndrome
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN	interferon

IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
INR	international normalized ratio
IRB	institutional review board
ISN/RPS	International Society of Nephrology/Renal Pathology Society 2003 classification of lupus nephritis
ITT	intent to treat
IV	intravenous; intravenously
IVIg	intravenous immunoglobulin
LMP2	low-molecular mass polypeptide 2
LMP7	low-molecular mass polypeptide 7
LN	lupus nephritis
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MPA	mycophenolic acid
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
NSAID	nonsteroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
PGA	physician global assessment of disease activity
P-gp	P-glycoprotein
PK	pharmacokinetics
ProCISE	proteasome constitutive/immunoproteasome subunit enzyme-linked immunosorbent assay
PRR	partial renal response
RA	rheumatoid arthritis
RNA	ribonucleic acid
RNP	ribonucleoprotein
RP2D	recommended Phase 2 dose
RPGN	rapidly progressive glomerulonephritis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous; subcutaneously
SD	standard deviation
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
Th	T helper
T-L	trypsin-like
TMA	thrombotic microangiopathy
T_{max}	time to maximum plasma concentration
TNF	tumor necrosis factor
TPMT	thiopurine methyltransferase
TTP	thrombicytopenic pupura
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
U.S.	United States of America
VAS	visual analog scale

WHO	World Health Organization

2 BACKGROUND INFORMATION

2.1 Disease Background

2.1.1 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a complex multi-organ autoimmune disease that is characterized by the development of a wide variety of autoantibodies, especially to components of the nucleus, specifically to DNA, RNA, and histones, in addition to red blood cells, platelets, serum proteins, and phospholipids.

SLE affects young adults, occurs more frequently in females than males (9:1 ratio), and is more common in African American, African Caribbean, Hispanic, and Asian populations (approximately 200 cases per 100,000) than in Caucasians (approximately 40 cases per 100,000). It is estimated that there are approximately 250,000 patients with SLE in the United States of America (U.S.). [1, 2]

Clinical manifestations range from relatively mild skin rashes and arthritis to glomerulonephritis, antibody mediated hemolytic anemia and thrombocytopenia, vasculitis, cardiac disease, and central nervous system disorders including seizures, psychosis, and cerebral vascular accidents [3, 4]. Accurate diagnosis of SLE can be difficult because the clinical manifestations vary considerably between patients, and the individual signs and symptoms of SLE can have multiple etiologies. Classification criteria have been developed by the American College of Rheumatology (ACR) [4, 5], with a proposed revision by the Systemic Lupus International Collaborating Clinics (SLICC) [6].

SLE is thought to be the result of dysfunction of multiple components of the immune system, including defective clearance of apoptotic cellular components, a break in T-cell tolerance induction, and generation of antinuclear antibodies (ANAs) such as anti-double stranded DNA (anti-dsDNA) [7]. These ANAs complex with antigens to create antigen-antibody (Ag-Ab) complexes which are deposited in various tissues and initiate inflammatory reactions via complement activation (e.g., arthritis and glomerulonephritis). Type II hypersensitivity reactions can also occur in which antibodies directly target host cells and activate immune effector mechanisms that lead to phagocytosis (e.g., hemolytic anemia or immune thrombocytopenia). These inflammatory reactions lead to excessive complement activation, secretion of inflammatory cytokines, and activation of macrophages and neutrophils.

Currently, there is no cure for SLE. Treatment is targeted at controlling inflammation with a variety of anti-inflammatory and immunosuppressive agents including mycophenolate mofetil (MMF), azathioprine (AZA), cyclophosphamide, corticosteroids, aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), and antimalarials [8]. Of the 3 types of treatments approved for SLE, NSAIDs were approved in 1948; hydroxychloroquine and corticosteroids were approved in 1955; and belimumab, a monoclonal antibody targeting the B-lymphocyte stimulator (BLyS), was approved in 2011 [9].

2.1.2 Lupus Nephritis

Lupus nephritis (LN) is one of the most serious complications of SLE. LN is a disease comprising a spectrum of vascular, glomerular, and tubulointerstitial lesions and develops in about 50% of SLE patients within 10 years of their initial diagnosis [10] (also see: EMA Draft Guideline Feb 2015 [11]). LN is associated with considerable morbidity, including an increased risk of end-stage renal disease requiring dialysis or renal transplantation and an increased risk of death. The prevalence of LN is approximately 74,000 in the U.S. and varies by race, occurring in approximately 20% of Caucasians and up to 60% of Blacks, Hispanics, and Asians with SLE [2, 12, 13].

LN results when Ag-Ab complexes (predominantly DNA-anti-DNA) are deposited in the glomerular mesangium and glomerular basement membrane and activate serum complement. The resulting inflammatory response causes damage to the glomerular epithelium with loss of function. It is often accompanied by mesangial proliferation and subsequent sclerosis of the glomeruli. Histopathologically, LN can take many forms, ranging from a normal glomerular architecture with Ag-Ab complexes identified by immunofluorescence, to proliferative glomerulonephritis or wide-spread sclerosis of the glomeruli associated with end-stage renal disease. The proliferative and membranous forms of glomerulonephritis are most frequently associated with proteinuria which often reaches nephrotic levels. LN is classified according to the International Society of Nephrology/Renal Pathology Society 2003 classification of lupus nephritis (ISN/RPS) (see Section 14.3).[14]

2.2 Treatment of Lupus Nephritis

There are no approved therapies for the treatment of LN. Management typically consists of induction therapy to achieve remission and long-term maintenance therapy to prevent relapse. The ACR and European League Against Rheumatism guidelines [15, 10] recommend treatment with corticosteroids, including an optional initial pulse intravenous (IV) methylprednisolone, then prednisone or equivalent, in combination with either MMF or high- or low-dose cyclophosphamide, followed by maintenance treatment with either MMF or AZA.

Approximately 50% of patients respond to these treatment regimens with improvement in proteinuria, but only about 25% attain a complete renal response that is frequently defined as normalization of proteinuria and stabilization or improvement in serum creatinine, after 1 year of treatment [16,17]. Attainment of complete renal response leads to a dramatic decrease in risk of end-stage renal disease [18]. Thus, approximately 75% of patients with LN have a sub-optimal response to induction therapy. These patients may subsequently receive treatment with a variety of alternative immunosuppressive or experimental agents, including rituximab, cyclosporine, tacrolimus, or other agents, in combination with long-term corticosteroids [19]. These patients remain at risk for the development of end-stage renal disease, in addition to complications from continued treatment with immunosuppressive agents and long-term corticosteroids.

2.3 Proteasome Background

The 26S proteasome is a ubiquitously expressed protein complex responsible for the homeostatic control of protein turnover and regulated degradation of proteins involved in most cellular functions [20, 21, 22]. Each proteasome contains a 20S core, containing 2 copies of 3 distinct proteolytic enzymes, and 2 regulatory caps forming a 26S complex.

The proteasome exists in 2 forms, the constitutive proteasome and the immunoproteasome. The constitutive proteasome is expressed ubiquitously throughout the body and is responsible for protein degradation in tissues such as the heart, kidney, and liver. In the constitutive proteasome, proteolytic activities are encoded in the β5, β1, and β2 subunits and are characterized based on substrate specificity as chymotrypsin-like (CT-L), caspase-like (C-L) and trypsin-like (T-L), respectively. The immunoproteasome is expressed primarily in hematopoietic cells (e.g., lymphocytes and monocytes) and is induced in cytokine-exposed non-hematopoietic cells [23, 24, 25]. In the immunoproteasome, low-molecular mass polypeptide 7 (LMP7), low-molecular mass polypeptide 2 (LMP2), and multi-catalytic endopeptidase complex-like 1 (MECL1) replace the β5, β1, and β2 subunits of the constitutive proteasome, respectively. LMP7 has a similar substrate preference as β5 and is thus referred to as the CT-L subunit of the immunoproteasome.

The proteasome has been validated as a therapeutic drug target through regulatory approval of 3 compounds, bortezomib (VELCADE®), carfilzomib (KYPROLIS®), and ixazomib (NINLARO®), for use in the treatment of the plasma cell neoplasm, multiple myeloma. These compounds all show equivalent potency for the β5 subunit of the constitutive proteasome and the LMP7 subunit of the immunoproteasome [26, 27]. This dual-targeting nature is necessary for their ability to induce cytotoxicity in multiple myeloma cells and other cell types. Selective inhibitors of LMP7 or β5 alone have no cytotoxic potential [28].

2.3.1 Proteasome Inhibitors for the Treatment of Inflammatory Disorders

The proteasome has been posited as a target for drug development in chronic inflammatory conditions and autoimmune disorders. [29] Bortezomib blocks cytokine release from immune effector cells and has demonstrated anti-inflammatory activity in several animal models of autoimmune disorders including rheumatoid arthritis (RA) [30] and SLE [31]. More recently, bortezomib was shown to have rapid clinical activity in patients with refractory SLE and LN who had failed standard immunosuppressive therapies [32, 33, 34]. However, systemic toxicities associated with dual-targeting proteasome inhibition, such as anemia and thrombocytopenia, restrict chronic administration [35]. Further, bortezomib is associated with a dose-limiting side effect of peripheral neuropathy, likely caused by off-target inhibition of the serine protease HtrA2 in neurons [36]. Peripheral neuropathy is not induced by peptide ketoepoxide proteasome inhibitors such as carfilzomib [36, 37].

The discovery of PR-957 (now called ONX 0914), a selective immunoproteasome inhibitor, demonstrated that the immunomodulatory and anti-inflammatory effects of dual-targeting proteasome inhibitors are due to inhibition of immunoproteasome activity in immune effector cells and inflamed tissues [38, 39]. ONX 0914 is a tripeptide ketoepoxide analog of carfilzomib that selectively inhibits the immunoproteasome in vitro and upon administration to mice.

ONX 0914 exposure inhibited cytokine production in immune effector cells, reduced the number and activity of inflammatory T-cell subsets such as T helper (Th)1 and Th17, increased the number of regulatory T cells, and blocked autoantibody formation [38, 39, 40]. ONX 0914 was shown to be therapeutically active in mouse models of SLE, in which it demonstrated equivalent activity but better tolerability than bortezomib [38, 41]. In addition, treatment of mice with ONX 0914 did not reduce the number of splenic lymphocytes or impair viral clearance in multiple infection models [39, 41].

2.4 KZR-616 Background

KZR-616 is a tripeptide ketoepoxide and is an analog of ONX 0914 and the U.S. Food and Drug Administration (FDA) approved agent carfilzomib. KZR-616 was developed in a medicinal chemistry effort to optimize potency and selectivity for multiple immunoproteasome subunits. KZR-616 demonstrates potent and selective inhibition of the LMP7 subunit of the immunoproteasome and targets multiple subunits of the immunoproteasome at therapeutically relevant concentrations. KZR-616 has no apparent off-target activities, no significant signals in safety pharmacology studies, and no apparent genotoxic potential.

Like ONX 0914, KZR-616 blocks cytokine production across multiple immune cell types, reduces the activity of inflammatory T-helper cell subsets, and blocks plasma cell formation and autoantibody production. In mouse models of SLE and LN, KZR-616 treatment improved renal function in diseased animals and dramatically reduced tissue damage and leukocyte infiltration in kidneys. In addition, combining KZR-616 with MMF improved the therapeutic response versus either treatment alone in the same mouse models. The pharmacokinetics (PK) and metabolic properties of KZR-616 in preclinical models indicate little risk for drug-drug interactions (DDIs) and are similar to carfilzomib, an agent which has been shown to have little to no DDI risk [42]. In both range finding and Good Laboratory Practice (GLP)–compliant toxicity studies, KZR-616 was well tolerated at doses that resulted in selective and potent inhibition of the immunoproteasome.

The safety, PK, and proteasome inhibition level of KZR-616 has been studied in healthy volunteers in two Phase 1 trials, KZR-616-001 and KZR-616-004.

Subcutaneous (SC) administration of KZR-616 was well tolerated at doses that resulted in potent and selective inhibition of the immunoproteasome. Adverse events (AEs) were generally mild and transient and were predominantly injection site reactions such as erythema, induration, and tenderness (pain). Following 4 weeks of treatment KZR-616 appeared not to result in persistent laboratory abnormalities as commonly seen with the dual-targeting proteasome inhibitors (e.g., thrombocytopenia, anemia, and neutropenia).

SC administration of KZR-616 resulted in consistent, dose-proportional PK. At all dose levels tested, KZR-616 was rapidly absorbed and cleared with no accumulation following weekly repeat doses. Drug levels were below limit of quantitation by 24 hours post-dose. The pharmacology was consistent across subjects with low inter-subject variability in both exposure and target inhibition, regardless of concomitant treatment with or without corticosteroids and antihistamines. Though KZR-616 is a weak time-dependent inhibitor of

CYP3A4 and a substrate of P-glycoprotein (P-gp), the rapid clearance and extrahepatic metabolism of KZR-616 by epoxide hydrolases strongly suggest that there is minimal risk for a DDI.

Across doses of 7.5 – 75 mg, SC administration of KZR-616 resulted in selective and dose-dependent inhibition of peripheral blood mononuclear cell (PBMC) CT-L activity (predominantly immunoproteasome), with doses of ≥30 mg resulting in mean inhibition of PBMC CT-L activity >80% and mean inhibition of whole blood CT-L activity (predominantly constitutive proteasome) ≤36%. Data further showed that despite incomplete recovery of immunoproteasome activity on Day 7 (6 days after dosing), there was not an accumulation of proteasome inhibition. From a PK and pharmacodynamic (PD) perspective, weekly SC administration of KZR-616 appeared equivalent to serial episodic dosing.

Following a full safety assessment from multiple cohorts of subjects receiving weekly administration, KZR-616 appears to have an adequate safety profile for use in patients with SLE and LN. For further information, please see the KZR-616 Investigator's Brochure.

2.5 Study Rationale

There remains a significant unmet medical need for new therapeutics for the treatment of SLE and LN. Bortezomib, a dual proteasome inhibitor, has shown promising clinical activity in patients with refractory SLE and LN, including patients who had failed to respond to standard immunosuppressive therapies, but systemic toxicities prevent long-term use in this patient population.

KZR-616 represents a new agent that can be administered as a single agent or, based on animal studies, in combination with background therapy and that may prove beneficial for patients with SLE and LN. We hypothesize that KZR-616 will rapidly induce clinically meaningful improvements in several markers for disease, including a reduction in proteinuria, at well tolerated doses.

Based upon the safety and efficacy in the Phase 2 portion of this study, it is anticipated that pivotal studies in LN will be initiated.

2.5.1 Summary of Potential Risks and Benefits

KZR-616 is expected to induce an anti-inflammatory response in patients with SLE, including those with nephritis. KZR-616 has no apparent off-target activities, no significant signals in safety pharmacology studies, and no apparent genotoxic potential. KZR-616 blocks cytokine production across multiple immune cell types, reduces the activity of inflammatory T-helper cell subsets, and blocks plasma cell formation and autoantibody production. In mouse models of SLE and LN, KZR-616 treatment improved renal function in diseased animals and dramatically reduced tissue damage and leukocyte infiltration in kidneys. In addition, combining KZR-616 with MMF improved the therapeutic response versus either treatment alone in the same mouse models. For these reasons, there is belief that KZR-616 should be efficacious in the treatment of active proliferative LN.

AEs most often associated with KZR-616 treatment to date are injection site reactions (ISRs) that are transient, generally mild, and don't appear to increase in severity or frequency with repeat dosing. All subjects who received repeat doses of ≥ 30 mg experienced ISRs.

Initial SC doses of 60 mg KZR-616 are associated with an AE of adverse drug reaction, with at least one of the following signs or symptoms: hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors, and/or chills. These reactions typically begin within 8 to 24 hours postdose, and usually resolve within 48 hours of dosing. The signs and symptoms can occur with any dose, though they are more likely to occur with initial doses of 60 mg or higher, and when seen, tended to be with the first dose more commonly than subsequent doses. These reactions can be mitigated: single dose administration of up to 75 mg of KZR-616 has been well tolerated following intraparticipant dose escalation initiated with a dose of 30 mg.

In healthy volunteers, occasional, and typically transient NCI-CTCAE Grade 1 abnormalities have been seen, including mild neutropenia, lymphopenia, anemia, thrombocytopenia, mild increases in creatine phosphokinase-transaminases, bilirubin, alkaline phosphatase, and/or elevated urea nitrogen; however, these were not associated with clinical sequelae and required no specific intervention. Complete blood counts, clinical chemistries, and urinalyses will be monitored according to the study protocol.

Thorough monitoring and assessment of all AEs will be performed in this study, and safety assessments according to the protocol will include physical examination, vital sign measurements, ECGs, and clinical laboratory tests. Guidance is provided to monitor for TMA. In addition, related to herpes zoster, patients who have had a recent episode of herpes zoster will be excluded, and vaccinations are recommended to be up to date.

Based on preclinical studies, the potential benefit from anti-inflammatory activity induced by immunoproteasome inhibition includes a reduction in proteinuria, skin lesions and reduced autoantibody levels. These benefits are anticipated to outweigh the known risks of transient, generally mild laboratory abnormalities and injection site reactions.

Following a full safety assessment from multiple cohorts of subjects receiving weekly administration, KZR-616 appears to have an adequate safety profile for use in patients with SLE and LN. For further information, please see the KZR-616 Investigator's Brochure.

2.5.2 Dosing Rationale

KZR-616 will be administered as a SC injection weekly for 13 weeks for patients with SLE with or without LN in the Phase 1b and 24 weeks for patients with active proliferative LN in the Phase 2.

In animal models of RA and SLE/LN, weekly administration of KZR-616 was found to be well tolerated and efficacious at doses that result in potent and selective inhibition of the immunoproteasome. In GLP-compliant repeat dose toxicity studies for 26 weeks in rats and 9 months in monkeys, the NOAELs were determined to be 1.5 mg/kg (9 mg/m^2) and 3 mg/kg (36 mg/m^2), respectively. Due to reduced selectivity for the immunoproteasome in rats vs. monkeys or humans, monkeys likely represent the relevant species for toxicity studies. Total

exposures (i.e., area under the plasma concentration-time curve [AUC]) at the NOAEL for the 9-month monkey study were 1.5-fold higher than the exposure seen in healthy subjects who received 75 mg. Importantly, the exposure in monkeys at the NOAEL is higher than the predicted exposure in humans for all proposed doses in the Phase 1b study (Table 1). Collectively, these data support both the dose escalation and duration of exposure planned for KZR-616-002.

In both Phase 1 studies in healthy volunteers, KZR-616 administration was well tolerated and resulted in consistent PK and consistent and selective inhibition of the immunoproteasome. At all dose levels, no apparent effect from concomitant medication (prednisone and antihistamines) on the exposure or activity of the drug was noted. Based on preclinical data and clinical data with the related molecule carfilzomib, there is little risk for DDIs; therefore, it should be acceptable to administer KZR-616 to patients on a variety of background medications without risk of overexposure.

Based on available data, the starting dose of 45 mg should be safe and tolerable in the Phase 1b portion of the study. In healthy volunteers, doses $\geq$ 30 mg resulted in potent and selective inhibition of the immunoproteasome to levels associated with anti-inflammatory activity in preclinical models at the minimally efficacious dose. Provided that safety and tolerability are demonstrated with the 45 mg dose in the Phase 1b portion of the study, doses that are appropriate for further evaluation in the Phase 2 portion of the study should be able to be recommended to determine if selective inhibition of the immunoproteasome can result in therapeutic benefit to patients with LN.

In animal models, doses above the minimally efficacious dose were well tolerated and resulted in a greater depth of anti-inflammatory response. Further exploration of doses $>$ 45 mg in patients is merited based on anticipated levels of exposure when compared to the NOAELs for rats and monkeys (Table 1), and the potential for increased clinical benefit to patients with SLE who have failed prior therapies, including those with LN, where there remains a significant unmet medical need.

Table 1: Comparison of Maximum Plasma Drug Concentrations (C_{max}) and Systemic Exposures (AUC_{last}) Between Animals and Humans (Mean ± SD)

Species	KZR-616 Dose [formulation]	Pharmacokinetics			
		Parameter	KZR-616	Fold Difference vs. Rats	KZR-59587 (% of KZR-616)
Rats	1.5 mg/kg (9 mg/m^2) [lyophilized]	C_{max} (ng/mL)	325	1	96.4 (30%)
		AUC_{0-6} (ng*hr/mL)	500 ± 33.8*	1	165 ± 12.8* (33%)
Rats	3 mg/kg (18 mg/m^2) [frozen]	C_{max} (ng/mL)	575 ± 62.4	1	66.1 ± 4.26 (12%)
		AUC_{0-6} (ng*hr/mL)	1250 ± 55.7	1	193 ± 9.01 (15%)
Monkeys	3 mg/kg (36 mg/m^2) [lyophilized]	C_{max} (ng/mL)	1820±594	5.6	1050 ± 269 (58%)
		AUC_{0-6} (ng*hr/mL)	776±148	1.6	2180 ± 624 (281%)
Monkeys	4 mg/kg (48 mg/m^2) [frozen]	C_{max} (ng/mL)	1270 ± 369	2.2	950 ± 301 (75%)
		AUC_{0-6} (ng*hr/mL)	1350 ± 172	1.1	2140 ± 481 (158%)
Humans	30 mg Day 1 (19 mg/m^2) [frozen]	C_{max} (ng/mL)	75.1 ± 27.0	0.13	103 ± 29.1 (137%)
		AUC_{last} (ng*hr/mL)	214 ± 44.5	0.17	513 ± 148 (240%)
Humans	30 mg Day 22 (19 mg/m^2) [frozen]	C_{max} (ng/mL)	111 ± 40.7	0.19	98.4 ± 28.0 (88.7%)
		AUC_{last} (ng*hr/mL)	267 ± 54.3	0.21	507 ± 103 (190%)
Humans	45 mg Days 1, 8, 22 (28 mg/m^2) [frozen]	C_{max} (ng/mL)	102 ± 26.7	0.18	119 ± 19.5 (117%)
		AUC_{last} (ng*hr/mL)	354 ± 38.7	0.28	729 ± 164 (206%)
Humans	60 mg (37 mg/m^2)	C_{max} (ng/mL)	160 ± 61.6	0.28	184 ± 43.2 (115%)
		AUC_{last} (ng*hr/mL)	411 ± 85.8	0.33	928 ± 171 (226%)
Humans	75 mg (47 mg/m^2) [lyophilized]	C_{max} (ng/mL)	163 ± 48.4	0.50	160 ± 51.2 (98.2%)
		AUC_{last} (ng*hr/mL)	546 ± 135	1.1	1303± 473 (239%)

Abbreviations: AUC_{last} = area under the plasma concentration-time curve from time 0 to the last measured concentration; AUC_{0-6} = area under the plasma concentration-time curve from time 0 to 6 hours; C_{max} = maximum plasma concentration; hr = hour; ND = not determined; *standard error of the mean.

2.5.3 Design Rationale

The Phase 1b portion of this trial is designed to evaluate the safety and tolerability of escalating doses of KZR-616 when administered in addition to standard-of-care therapy for 13 weeks in patients with SLE. The Phase 2 portion of this trial is designed to evaluate the renal response, safety and tolerability of KZR-616 when administered for 24 weeks in addition to standard therapy in patients with active proliferative LN.

In the Phase 1b portion, at least 6 patients per dose level will be enrolled to receive SC injections of KZR-616. Patients eligible for this part of the study must demonstrate adequate SLE disease activity at screening, be serologically positive, and may currently be on at least one SLE therapy, including oral corticosteroid, immunosuppressant (MMF, AZA, MTX, or leflunomide), and/or antimalarial agents, with stable dosage regimen. As these patients continue to have active SLE disease despite standard of care therapy, they are in need of an effective new treatment. As this is the first multiple dose study of KZR-616 in SLE patients, dose administration and step-wise evaluation is carefully outlined, including a sentinel patient in each dose cohort. Decisions to escalate, expand, or decrease dose level or frequency following the first 4 weeks of treatment for at least 4 evaluable patients in a cohort will depend on review by a Data Monitoring Committee (DMC).

In the Phase 1b portion of the study, a 4-week period of dose-limiting toxicity (DLT) evaluation for at least 4 evaluable patients in each cohort is proposed. Based on nonclinical toxicity studies, tolerability after 4 weeks of treatment is predictive of safety through 13 weeks of treatment. In addition, exposure data in healthy subjects show that KZR-616 is rapidly cleared and has no accumulation. Weekly administration of KZR-616 could be interpreted as serial episodic dosing, with potential AEs and DLTs likely to occur upon initial exposure and with a reduced risk with repeat dosing based on the results of KZR-616-001. These safety data will support the use of the RP2D of KZR-616 in patients with active proliferative LN for which there is a potential to increase the depth or frequency of response to background standard therapy. In addition, these data will be used to inform the design of future studies in non-renal SLE.

In the Phase 2 portion of the study, a total of 20 patients with active proliferative Class III or IV LN (with or without Class V disease) will be enrolled to receive KZR-616 for a total of 24 weeks. Safety will be assessed throughout the 24 weeks of dose administration and the follow-up which will continue for 12 weeks post last dose. As this will be the first study of KZR-616 in patients with active proliferative LN, the data obtained are anticipated to be sufficient to enable design of future development studies for KZR-616.

Proof of activity is based on multiple disease response assessments in LN and SLE including evaluation for improvements in kidney function (changes in proteinuria and estimated glomerular filtration rate [eGFR]), changes in lupus disease assessments (Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K] and, for the Phase 1b only, the British Isles Lupus Assessment Group [BILAG]), changes in serum biomarkers of disease (ANA, anti-dsDNA, anti-Smith, anti-ribonucleoprotein [anti-RNP], anti-Ro/La [anti-SSA/SSB], C3/C4, and 50% hemolytic complement [CH50]), and changes in daily corticosteroid use.

3 STUDY OBJECTIVES

3.1 Objectives (Phase 1b)

Primary Objective:

- To evaluate the safety and tolerability of KZR-616 when administered as a SC injection weekly for 13 weeks in adult patients with SLE with and without nephritis

Secondary Objectives:

- To select RP2Ds of KZR-616 when administered as a SC injection
- To characterize the PK of KZR-616

Exploratory Objectives:

- To explore the efficacy of KZR-616 in patients with SLE
- To explore the PD effects of KZR-616
- To explore biomarker, immunomodulatory, pharmacogenomic, and proteomic changes following KZR-616 treatment

3.2 Objectives (Phase 2)

Primary Objective:

- To assess the number of patients with a 50% reduction in UPCR after 24 weeks of weekly SC injections with KZR-616 when compared to baseline

Secondary Objectives:

- To evaluate the safety and tolerability of KZR-616 when administered as a SC injection weekly for 24 weeks
- To characterize the efficacy of KZR-616 on parameters of renal function when administered as a SC injection weekly for 24 weeks

Exploratory Objectives:

- To explore the PD effects of KZR-616
- To explore the efficacy of KZR-616 in clinical and serological indicators of SLE disease activity
- To explore biomarker, immunomodulatory, pharmacogenomic, and proteomic changes following KZR-616 treatment

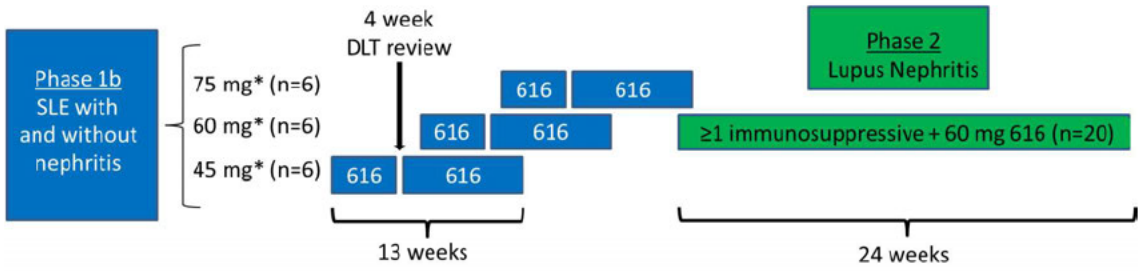
4 STUDY DESIGN

4.1 Overall Study Design

This is a Phase 1b/2, multi-center study in which patients will receive KZR-616, administered as a SC injection weekly for 13 (Phase1b) or 24 weeks (Phase 2).

As shown in Figure 1, the first portion of this trial is designed to evaluate the safety and tolerability of escalating doses of KZR-616 when administered in addition to standard-of-care therapy in patients with SLE (Phase 1b). The second portion of this trial is designed to evaluate the renal response, safety and tolerability of a single dose (60 mg) of KZR-616 when administered in addition to standard therapy in patients with active proliferative LN (Phase 2).

Figure 1 Study schematic for Phase 1b and Phase 2:



Abbreviations: DLT = dose limiting toxicity; SLE = Systemic Lupus Erythematosus

4.1.1 Phase 1b

The Phase 1b is an open-label multiple dose escalation study of KZR-616 to evaluate the safety, tolerability, and PK of KZR-616 in patients with SLE with and without nephritis.

KZR-616 will be administered as a SC injection weekly for up to 13 weeks. Safety assessments will begin after the patient provides written informed consent and continue through 12 weeks of follow-up visits.

4.1.1.1 Dose-Limiting Toxicities

A DLT is defined as any Grade 3 or higher study drug-related AE, according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03, that occurs during the 4-week DLT evaluation 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., systemic drug reaction), fatigue, anorexia, chills, 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

4.1.1.2 Dose Escalation Plan

For each dose level, at least 6 patients may be enrolled to assure the availability of at least 4 DLT-evaluable patients. Dose escalation guidelines are as follows:

- Each cohort within a dose level will include 1 sentinel patient who will receive KZR-616 at a selected dose on Day 1/Week 1
- If the sentinel patient does not experience a DLT, as defined below, within 48 hours and based on the clinical judgement of the investigator and medical monitor, the remaining patients in the cohort will be dosed
- If a DLT is experienced in the sentinel patient within 48 hours of injection, a second sentinel patient may be dosed with KZR-616 following a safety review by the DMC. If no DLT is observed after 48 hours in the second sentinel patient, the remainder of the cohort may be enrolled
- If 0 or 1 of 6, 0 or 1 of 5, or 0 of 4 patients (20% or less) in a cohort experience a DLT, the next dose level will be opened for enrollment after DMC review as below
- If 1 of 4 (25%) patients in a cohort, or 2 or more of 5 or 6 patients in a cohort experience a DLT, the maximum tolerated dose will have been exceeded and dose escalation will not continue

To evaluate tolerability, a minimum of 4 patients should receive KZR-616 at a specified dose level for at least 4 weeks prior to any decision by the DMC to dose escalate.

Patients who discontinue treatment prior to Week 5 will be considered DLT non--evaluable, unless they experience a DLT prior to Week 5. The DLT non-evaluable patients may be replaced until the necessary number of evaluable patients is achieved per dose level.

Escalation is planned to continue in 15 mg increments of KZR-616. Planned dose levels of KZR-616 to be explored are described in Table 2 below. Other dose escalation increments may be proposed by the DMC based upon emerging safety, PK, PD, and/or efficacy data. Similarly, emerging data may prompt the DMC to recommend a different DLT evaluation period, or alteration of the dosing interval or duration. During the dose escalation period, and based on safety evaluation in patients, the DMC may also recommend that patients in subsequent dose cohorts receive prophylactic treatment (e.g., pulse corticosteroid and/or antihistamine) prior to initial doses to prevent AEs and/or intra-patient dose escalation to be employed with an initial tolerizing dose of 30 mg.

Table 2: KZR-616 Dose Levels

Dose of KZR-616 (mg)
45 mg
60 mg
75 mg

4.1.1.2.1 Resumption of Dose Escalation

If dose escalation is halted due to excessive DLTs or other stopping rules for safety being met (Section 9.1), dose escalation may resume if a review by the DMC of all cumulative data identifies a possible mitigating intervention(s) (e.g., corticosteroid pre-medication for injection site reaction). In such an instance, dose escalation may resume, beginning at the same dose level at which escalation ceased, implementing the proposed intervention and following the dose escalation guidelines above. If successful, any subsequent dose levels must incorporate the new intervention.

4.1.1.3 Stopping Rules for Safety (Phase 1b/2)

Please refer to Section 9.1 for detailed information on stopping rules for safety.

4.1.2 Phase 2

Phase 2 is an open-label, single dose level study to evaluate the efficacy and safety of KZR-616 administered weekly in 20 patients with active proliferative LN.

Patients must be on standard therapy including at least one immunosuppressive agent.

KZR-616 at a dose level of 60 mg (including a step-up from an initial week 1 dose of 30 mg), will be administered as a SC injection weekly for 24 weeks. Safety assessments will continue for up to 12 weeks following the last dose of KZR-616.

4.2 Estimated Study Duration

For patients in the Phase 1b, screening will last approximately 4 weeks, treatment will last approximately 12 weeks (13 doses over 12 weeks and 1 day) and follow-up will last 12 weeks for a total of approximately 28 weeks of participation.

For patients in the Phase 2 portion of the study, screening will last up to 5 weeks, treatment duration is 24 weeks (24 doses over 24 weeks), and follow-up will last 12 weeks for a total of up to 41weeks of participation.

4.3 Minimizing Bias

KZR-616-002 is an open-label study.

5 PATIENT SELECTION

5.1 Number of Planned Patients

Approximately 68 patients total, including up to 48 in Phase 1b escalating cohorts.

For Phase 2, the planned number of patients is 20. Any patient in the Phase 2 who withdraws/is withdrawn from the study for any reason prior to Week 14 can be replaced.

5.1.1 Patient Screening

Study participation begins once written informed consent is obtained (see Section 12.3 for details).

Once informed consent is obtained, a sequential patient identification number will be assigned by the site, and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The patient identification number will be used to identify the patient during the screening process and throughout study participation, if applicable.

Screening assessments (see the Schedule of Assessments, Section 14.1, Appendix A, and Section 14.2, Appendix B, for Phase 1b and Phase 2, respectively) for this study should be performed between Day -28 and Day -1. The screening period can be extended to 35 days upon sponsor approval for Phase 1b and without sponsor approval for Phase 2. Patients who fail screening or do not meet inclusion/exclusion criteria may be re-screened one time.

5.2 Inclusion and Exclusion Criteria

5.2.1 Inclusion Phase 1b

1. Male or female patients aged 18 to 75 years (inclusive)
2. Body mass index (BMI) of 18 to 40 kg/m^2
3. Fulfills the 2012 SLICC classification criteria for SLE
4. Have at least one of the following at screening per central lab:
    a) Positive ANA test (1:80 or higher); or
    b) Anti-dsDNA antibodies elevated to above normal (i.e., positive results); or
    c) Anti-Smith antibody elevated to above normal (i.e., positive results)
5. Active SLE as indicated by a SLEDAI-2K total score ≥ 4 at screening
6. Must have received 1 or more of the following therapies for SLE, each administered at or higher than the minimum dose indicated for at least 12 weeks (unless discontinued or dose adjusted for documented drug-related toxicity or size/weight):
    a) Hydroxychloroquine 200 mg orally daily in combination with prednisone 10 mg daily or equivalent
    b) MMF orally 1 g/day or MPA orally 720 mg/day
    c) Methotrexate orally or SC 15 mg/wk., or leflunomide orally 10 mg/day

d) AZA 100 mg/day or 6-mercaptopurine 50 mg/day (50 or 25 mg/day, respectively, permitted in cases of documented thiopurine methyltransferase [TPMT] polymorphism) orally
e) Cyclosporine or tacrolimus at doses documented to maintain at least 100 or 5 ng/mL during the required duration, respectively
f) Cyclophosphamide 500 mg IV every 2 weeks or 500 mg/m^2 IV once monthly
g) Belimumab 10 mg/kg IV every 2 weeks for 3 doses, followed by 10 mg/kg every 4 weeks; or 200 mg SC weekly
h) Rituximab 1 g IV (may be given as 500 mg twice)

7. Acceptable screening laboratory values of concern, including:
   a) Adequate hematologic criteria:
      - Absolute neutrophil count $\geq 1.5 \times 10^9$/L ($\geq 1 \times 10^9$/L if neutropenia is attributable to lupus disease activity)
      - White blood cells $\geq 2.0 \times 10^9$/L ($\geq 1.5 \times 10^9$/L if leukopenia is attributable to lupus disease activity)
      - Hemoglobin (Hgb) ≥ 9 g/dL (≥ 8 g/dL if anemia is attributable to lupus disease activity)
      - Platelet count $\geq 100 \times 10^9$/L ($\geq 25 \times 10^9$/L if thrombocytopenia is attributable to lupus disease activity)
   b) Adequate hepatic function:
      - Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) ($3 \times$ ULN for patients with documented Gilbert's syndrome)
      - Aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN
      - Alanine aminotransferase (ALT) $\leq 2.5 \times$ ULN
   c) eGFR ≥ 40 mL/min/1.73 m^2 (estimated based on Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula)
   d) Immunoglobulin G (IgG) ≥ 500 mg/dL
8. If taking the following SLE therapies:
   a) Oral corticosteroids (up to 20 mg/day prednisone or equivalent): must be on a stable dosage regimen of oral corticosteroid at least 4 weeks prior to screening and maintain stable dosage until randomization
   b) Hydroxychloroquine (≤ 400 mg/day) or chloroquine (≤ 500 mg/day) orally or other antimalarials: must be started or stopped at least 12 weeks prior to screening, with stable dosage regimen for at least 4 weeks prior to screening
   c) Immunosuppressive agents: must be started or stopped at least 12 weeks prior to screening, with stable dosage regimen, including route of administration, for at least 4 weeks prior to screening:
      - MMF (≤ 3 g/day) or MPA (≤ 2.16 g/day) orally
      - AZA (≤ 200 mg/day) orally
      - Methotrexate (≤ 25 mg/week) orally, SC, or intramuscularly (patients must be on concomitant folic or folinic acid supplementation if using methotrexate)
      - Leflunomide (≤ 20 mg/day) orally

9. Women of childbearing potential must have a negative serum beta-human chorionic gonadotropin (hCG) pregnancy test at screening and a negative urine pregnancy test prior to the first dose and must agree to use a highly effective method of birth control from signing the informed consent form (ICF) until their completion of the study (or 30 days following the last dose of study drug in case of early withdrawal). Hormonal contraception may not be effective in women on concomitant MMF/MPA; women on MMF/MPA using hormonal contraception must agree to use a highly effective non-hormonal method of contraception. Abstinence is not an acceptable method of birth control for this study. Women of nonchildbearing potential must be postmenopausal (no menses for at least 2 years before the screening visit), permanently sterilized (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy), or congenitally sterile.
10. Male patients must use an effective contraception method (e.g., condom with spermicide) from signing the ICF until their completion of the study (or 12 weeks following the last dose of study drug in case of early withdrawal) or be congenitally or surgically sterile (e.g., vasectomy with documented confirmation of post-surgical aspermia)
11. Willing and able to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

5.2.2 Exclusion Phase 1b

1. Active central nervous system involvement by autoimmune disease (e.g., neuropsychiatric SLE including seizures, psychosis, acute confusional state or cerebrovascular accident) requiring specific therapeutic intervention within 60 days prior to first day of study treatment. Headache treated only with acetaminophen, NSAIDs, or approved doses of triptans is permitted with medical monitor approval.
2. Presence of another rheumatic (overlap) disease that may confound clinical assessments in the study. Secondary sicca or Sjogren's syndrome, antiphospholipid antibody syndrome, and overlap with RA without erosive joint disease ("rhupus") are allowed.
3. 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.
4. Receipt of any of the following treatments within the following timeframes before screening (see Section 14.5, Appendix E, for excluded medications):
    a) Systemic corticosteroids ≥ 100 mg prednisone or equivalent: 4 weeks
    b) Intra-articular therapies, such as corticosteroids or hyaluronic acid preparations: 4 weeks
    c) Intravenous immunoglobulin (IVIg): 4 weeks
    d) Other non-biologic immunosuppressive agents, such as cyclosporine and tacrolimus: 4 weeks
    e) Cyclophosphamide: 12 weeks

f) Cytokine antagonists, including but not limited to interleukin (IL)-1, IL-6, IL-17, IL-12/23, IL-23, interferon (IFN), integrin, and tumor necrosis factor (TNF)-α antagonists: 12 weeks

g) B-cell-depleting therapies (e.g., rituximab): 24 weeks with levels of circulating cluster of differentiation 19+ (CD19+) B cells within normal limits or 48 weeks if CD19+ count is not available

h) Belimumab, abatacept, or atacicept: 12 weeks

i) Other biologics or investigational drugs: 8 weeks or 5 half-lives, whichever is longer

j) Transfusion with blood, packed red blood cells, platelets or treatment with plasmapheresis or plasma exchange: 6 weeks

5. Patient has had recent serious or ongoing infection, or risk for serious infection, including:

a) Acute or chronic infections:

- Requiring systemic antibiotic, antifungal, or antiviral (antimicrobial) therapy within 14 days of Week 1, Day 1
- Requiring hospitalization or a course of IV antimicrobial therapy within 24 weeks prior to screening

b) History of severe and/or disseminated viral infections, and/or opportunistic infections

c) Known seropositivity for or active infection by human immunodeficiency virus (HIV)

d) Active, chronic, or resolved hepatitis B or hepatitis C infection (see Section 8.2.6.6)

e) History of progressive multifocal leukoencephalopathy

f) Active or latent tuberculosis (TB), as suggested by chest x-ray within the 12 weeks prior to screening and/or QuantiFERON®-TB Gold at screening per Section 8.2.6.6

- Patients with a history of latent TB with documented completed treatment per Centers for Disease Control and Prevention guidelines are allowed
- A chest x-ray must be performed during screening if one has not been done within 12 weeks prior to the screening visit

g) Receipt of a live-attenuated vaccine within 12 weeks of first day of study treatment (Week 1, Day 1)

h) Primary immunodeficiency (unless otherwise considered, in the opinion of the investigator and medical monitor, to confer a clinically insignificant infection risk, such as deficiency in immunoglobulin A (IgA), C1q, C2, or C4 without a history of recurrent infections [3 or more infections in 1 year requiring antimicrobial therapy])

6. History of any concurrent illness, including drug induced SLE, that has required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to signing the ICF

7. Clinical evidence of significant unstable or uncontrolled acute or chronic diseases (e.g., cardiac [including congestive heart failure, hypertension, angina, or history of myocardial infarction], pulmonary [including chronic obstructive pulmonary disease, asthma requiring corticosteroid therapy, pulmonary hypertension, or pulmonary fibrosis], hematologic, gastrointestinal, hepatic, renal, neurological, or infectious diseases) that, in the opinion of the investigator or sponsor, could confound the results of the study, put the patient at undue risk, or interfere with protocol adherence
8. History of cancer, except for in situ cancer that has been completely excised or has been curatively treated with no sign of disease for > 5 years
9. Major surgery within 4 weeks before signing the ICF or major surgery planned during the study period

5.2.3 Inclusion Phase 2

1. Male or female patients aged 18 to 75 years (inclusive)
2. BMI of ≥ 18 kg/m^2
3. Fulfills the 2012 SLICC classification criteria for SLE
4. At least one of the following at Screening per central lab:
    a) Positive ANA test (1:80 or higher) or
    b) Anti-dsDNA antibodies elevated to above normal (i.e., positive results); or
    c) Anti-Smith antibody at screening elevated to above normal (i.e., positive results)
5. Active nephritis with UPCR ≥ 1.0 measured in 24-hour urine collection
6. Currently receiving one or more immunosuppressive agents (see Section 7.2 for allowed background medications and Section 14.5, Appendix E for excluded medications) that has been stable for dose and route of administration for ≥ 8 weeks prior to Baseline. If patient is also on corticosteroids then must be on a stable dose for ≥ 2 weeks prior to Baseline
7. Renal biopsy within 2 years of the Screening visit with a histologic diagnosis of LN (ISN/RPS) Classes III, IV-S or IV-G, (A) or (A/C) +/- Class V; for biopsies > 1 year before the Screening visit, one of the following must also be present at screening: low C3, low C4, or anti-ds-DNA elevated to above normal range.
8. Acceptable screening laboratory values:
    a) Adequate hematologic criteria:
        - Absolute neutrophil count ≥ 1.5×10^9/L (≥ 1×10^9/L if neutropenia is attributable to lupus disease activity)
        - White blood cells ≥ 2.0×10^9/L (≥ 1.5×10^9/L if leukopenia is attributable to lupus disease activity)
        - Absolute lymphocyte count ≥ 0.5×10^9/L
        - Hgb ≥ 9 g/dL (≥ 8 g/dL if anemia is attributable to lupus disease activity)

- Platelet count $\geq 100 \times 10^9$/L ($\geq 25 \times 10^9$/L if thrombocytopenia is attributable to lupus disease activity)

b) Adequate hepatic function:
- Total bilirubin $\leq 1.5 \times$ ULN ($3 \times$ ULN for patients with known Gilbert's syndrome)
- AST $\leq 2.5 \times$ ULN
- ALT $\leq 2.5 \times$ ULN

c) eGFR ≥ 30 mL/min/1.73 m^2 estimated based on CKD-EPI formula

d) IgG ≥ 500 mg/dL

9. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline and must agree to employ adequate birth control measures for the duration of the study. Women of childbearing potential (WOCBP) must use highly effective and medically acceptable methods of contraception to prevent pregnancy during Screening and must agree to continue to practice adequate contraception during the study and for 4 weeks after administration of the last dose of the study drug.

   For the purposes of this study, WOCBP are defined as: all postpubescent female patients, unless the patient is postmenopausal (defined by amenorrhea for at least 2 years or amenorrhea for at least 1 year with confirmatory follicle stimulating hormone [FSH] level in the postmenopausal range as documented historically or measured by the central laboratory at Screening and if patient is not on supplementary hormonal therapy) or if the patient is surgically sterile (i.e., tubal ligation, hysterectomy, bilateral salpingoophorectomy).

   Highly effective contraception is defined as the use of an intrauterine device or hormonal contraceptives (e.g., implant or oral), or having a vasectomized partner. If using a hormonal form of contraception, it must have been stable for at least 4 weeks prior to Screening, and if using concomitant mycophenolate, the patient must use another nonhormonal form of highly effective contraception. Abstinence will be acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation) and withdrawal are not acceptable methods of contraception.

10. Male patients with a partner of childbearing potential must be either congenitally sterile or surgically sterile (by vasectomy) or willing to use a condom in addition to having their female partner use another form of contraception (such as an intrauterine device, barrier method with spermicide, or hormonal contraceptive [e.g., implant, injectable, patch, or oral]) from Screening until 12 weeks after the last dose of study drug, unless their partners are infertile or surgically sterile.

11. Willing and able to provide written informed consent prior to any study-related procedures and to comply with all study requirements

5.2.4 Exclusion Phase 2

1. Any of the following:
    a) Dialysis within 12 months prior to Screening or expected need for renal replacement therapy (dialysis or renal transplant) within a 6-month period after enrollment
    b) Rapidly progressive glomerulonephritis (RPGN) and/or renal disease other than ISN/RPS Classes III, IV-S or IV-G, [A] or [A/C] with or without Class V LN)
    c) Chronic kidney disease not due to LN
    d) > 50% sclerosed glomeruli on most recent renal biopsy
2. Presence of another rheumatic (overlap) disease that may confound clinical assessments in the study. Secondary sicca or Sjogren's syndrome and antiphospholipid antibody syndrome are allowed
3. History of antiphospholipid syndrome with history of thromboembolic event within 12 months of screening
4. Active central nervous system involvement by autoimmune disease (e.g., neuropsychiatric SLE including seizures, psychosis, acute confusional state or cerebrovascular accident) requiring specific therapeutic intervention within 60 days prior to first day of study treatment. Headache treated only with acetaminophen, NSAIDs, or approved doses of triptans is permitted with medical monitor approval.
5. Active or chronic infection:
    a) Acute or chronic bacterial or fungal infections:
        - Requiring systemic antibiotic or antifungal therapy within 14 days of Screening
        - Receipt of more than a 14-day course of antimicrobial therapy within 12 weeks of Screening to treat sepsis, abscess, osteomyelitis, joint infection, or bacterial endocarditis.
    b) Acute viral illness:
        - Signs and symptoms of acute viral illness must be resolved ≥ 4 weeks prior to Day 1 (Baseline). Patients with history of SARS-CoV-2 must have full resolution of symptoms and no evidence of associated renal injury
        - Symptomatic herpes zoster or herpes simplex infection (HSV) (not including simple oral HSV lesions) within 12 weeks prior to Screening or during the Screening Period
        - Acute hepatitis B or C infection
    c) Chronic viral infection:
        - Patients with chronic herpesvirus infections such as HSV or CMV should be on suppressive therapy at Baseline and during the study
        - Chronic hepatitis C infection. Patients with prior chronic hepatitis C infection should have received a full treatment course and have documented absence of detectable HCV DNA at the completion of at least 12 weeks of treatment

- Chronic hepatitis B infection. Patients who are HBsAg negative and hepatitis B core antibody positive with no detectable DNA will be allowed into the study and will require regular monitoring of hepatitis B virus DNA (see Section 8.2.6.6).
- Known seropositivity for or active infection with human immunodeficiency virus (HIV). Those with a positive screening test and negative confirmatory test are eligible.

6. Patient has or had any of the following:
    a) Progressive multifocal leukoencephalopathy
    b) Active or untreated latent TB, per QuantiFERON-TB Gold at screening per Section 8.2.6.6
        - Patients with a history of latent TB with documented completed treatment per Centers for Disease Control and Prevention guidelines are allowed
        - A chest x-ray must be performed during screening if one has not been done within 12 weeks prior to the screening visit
    c) Receipt of a live-attenuated vaccine within 12 weeks of Baseline (Week 1, Day 1)
    d) Primary immunodeficiency (unless otherwise considered, in the opinion of the investigator and medical monitor, to confer a clinically insignificant infection risk, such as deficiency in IgA, C1q, C2, or C4 without a history of recurrent infections [3 or more infections in 1 year requiring antimicrobial therapy])
    e) Primary hematopoietic cell or solid organ transplant
7. Clinical evidence of significant unstable or uncontrolled acute or chronic diseases (e.g., cardiac [including congestive heart failure, hypertension, angina, or history of myocardial infarction], pulmonary [including chronic obstructive pulmonary disease, asthma requiring corticosteroid therapy, pulmonary hypertension, or pulmonary fibrosis], hematologic, gastrointestinal, hepatic, renal, neurological, or infectious diseases) that, in the opinion of the investigator or sponsor, could confound the results of the study, put the patient at undue risk, or interfere with protocol adherence
8. QT interval with Fridericia's correction (QTcF) or Bazett's correction (QTcB) > 480 msec on ECG
9. Major surgery within 12 weeks before signing the ICF or major surgery planned during the study period
10. Any active or suspected malignancy or history of documented malignancy within the last 5 years before Screening. Exceptions include history of appropriately excised and cured cervical carcinoma in situ or excised basal or squamous cell carcinomas of the skin
11. Women who are pregnant or lactating
12. Hypersensitivity to the Investigational Medicinal Products or any of its excipients.
13. Use of investigation medical therapy or device, and/or participation in an investigational trial < 8 weeks or 5 half-lives, whichever is longer, prior to Baseline; Patients who participated in Phase 1b of KZR-616-002 are excluded from Phase 2

6 STUDY DRUG

6.1 KZR-616

6.1.1 Physical Description

KZR-616 is a small molecule, covalent inhibitor of the immunoproteasome. Two subcutaneous formulations, described below, have been manufactured for clinical use and formulated as the maleate salt of KZR-616.

1. KZR-616 Maleate SC Injection: A frozen solution drug product that is supplied in vials containing 150 mg/mL KZR-616 (180 mg/mL KZR-616 maleate) in a vehicle of [redacted]. This drug product is shipped on dry ice (-70°C) and stored at -17.5° ± 7.5° C
2. KZR-616 Lyophile: A lyophilized drug product that is supplied in vials containing 125-mg KZR-616 (150-mg KZR-616 maleate) and [redacted] (inactive excipient) per vial. Each vial is reconstituted with sterile water for injection (WFI) prior to administration. This drug product is shipped on dry ice (-70° C) and stored at 2° to 8°C.

6.1.2 Packaging and Labeling

The frozen solution drug product will be supplied in single-use vials packaged in multi-vial cartons.

The lyophilized drug product will be supplied in single-use vials packaged in multi-vial cartons.

All investigational products will be labeled according to appropriate regulatory guidelines.

All packaging and labeling operations will be performed according to Good Manufacturing Practice (GMP) for Medicinal Products and the relevant regulatory requirements.

6.1.3 Storage of KZR-616

Refer to the Investigator's Brochure and Pharmacy Manual for storage conditions for KZR-616.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all investigational product received and any discrepancies are reported and resolved before use of the investigational drug product.

Only participants enrolled in the study may receive investigational product and only authorized site staff may supply or administer investigational product. All investigational products should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions. Access to investigational product must be limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

6.2 Study Drug Accountability

On receipt of the study drug, the investigator (or deputy) will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts. The monitor may check the study supplies at each study center at any time during the study.

It is the responsibility of the study monitor to ensure that the investigator (or deputy) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. The study monitor will perform an inventory of study drug at the closeout visit to the study center. All discrepancies must be accounted for and documented.

7 DOSAGE AND TREATMENT ADMINISTRATION

7.1 KZR-616 Treatment Administration

For both the Phase 1b and the Phase 2 portions of the study, KZR-616 will be administered as a SC injection once weekly for 13 and 24 doses, respectively. Further details regarding drug product formulation, preparation and administration of KZR-616 will be provided in a separate Pharmacy Manual/Investigational Product Handling Manual.

Phase 1b:

At least 6 patients per dose level will be enrolled sequentially to receive SC injection of KZR-616 at 45 mg, 60 mg, and 75 mg, respectively. For dose levels ≥ 60 mg, patients should receive at least one prior dose of 30 mg (i.e., Step-up dosing).

Phase 2:

Patients in the Phase 2 portion will receive KZR-616, 60 mg. Dose administration will include a Week 1 dose of 30 mg followed by an increase to 60 mg (i.e., Step-up dosing) for Week 2-Week 24 unless dose is reduced.

7.1.1 Dosing Criteria

All patients must meet the following criteria before each dose, based on the most recent laboratory testing:

- ANC ≥ 1.0×10^9/L
- Hemoglobin ≥ 7.5 g/dL
- Platelet count ≥ 75×10^9/L [≥ 25×10^9/L in patients with known lupus-related immune thrombocytopenia]
- AST and ALT ≤ 3 x ULN and bilirubin < 2 x ULN (except for Gilbert's syndrome where bilirubin will not be used to hold dosing)
- Non-ISR AEs ≤ Grade 2

7.1.2 Administrative Site

A different injection site should be used for each administration. If sites are to be rotated (i.e., 4 abdominal quadrants), a minimum of 4 weeks should separate injections to the same site.

7.1.3 Monitoring of Dose Administration

Systemic injection reactions have been observed in healthy volunteer studies with KZR-616; the following guidance is based on these known experiences.

In KZR-616-001, 4 of 12 healthy volunteer subjects who received 60 mg KZR-616 SC experienced a "systemic drug reaction" consisting of hypotension, tachycardia, nausea, vomiting, rigors, and chills, associated with an acute phase-like response, including

leukocytosis and elevated C-reactive protein (CRP), which occurred approximately 8 to 12 hours after dosing.

Using dual proteasome inhibitors as a reference point, systemic injection reactions included a number of signs and symptoms including fever, chills, myalgia, facial swelling or flushing, vomiting, weakness, hypotension, chest tightness, and shortness of breath, as well as abnormalities in laboratory values (e.g., creatinine, transaminases) and blood pressure.[43, 44] However, the relative roles of the immunoproteasome versus constitutive proteasomes to these specific events are not known. The individual signs/symptoms of systemic injection reactions must be reported as AEs of special interest within 24 hours in the AE eCRF (RAVE) (refer to Section 10.5.1).

With other proteasome inhibitors, prophylactic measures have been demonstrated to reduce the incidence and severity of infusion-related reactions. Therefore, upon the development of signs and/or symptoms suggestive of a systemic drug reaction, the following interventions are suggested:

- Supportive measures, including the administration of oral and/or IV fluids, antiemetics, acetaminophen, antihistamines and/or systemic corticosteroids (e.g., prednisone 25 mg – equivalent to 4 mg of dexamethasone)
- Collection of serum and/or plasma samples for analysis of potentially elevated levels of cytokines, histamines, etc.
- For patients who develop signs and/or symptoms that may be consistent with a cardiac etiology (e.g., hypo- and/or hypertension, tachycardia, arrhythmia, or abnormal cardiac enzymes), the following should be obtained to rule out cardiac toxicity which has been described with proteasome inhibitors:
    - Serial ECGs, cardiac enzymes (e.g., creatine kinase MB [CK-MB], troponins, B-type natriuretic peptide [BNP]) to rule out myocardial infarction
    - Echocardiogram, unless heart failure can otherwise be ruled out by the preceding investigations
- Prophylactic measures may be considered at the time of the first dose, or with subsequent doses if signs and/or symptoms consistent with a systemic drug reaction develop, including:
    - Fluid hydration, e.g., 30 mL/kg orally at least 48 hours prior to dosing; and/or 250 to 500 mL IV after dosing if symptoms are present
    - Antiemetics, acetaminophen, and antihistamines
    - Systemic corticosteroids (e.g., dexamethasone 4 mg or prednisone 25 mg) prior to subsequent doses. Use of systemic corticosteroids should be discussed in advance with the medical monitor as their use could confound efficacy assessments.

7.1.4 Dose Modification Guidelines for KZR-616

Dose Reductions

During Phase 1b and Phase 2, patients who experience a KZR-616-related AE, not otherwise subject to Individual Stopping Rules (Section 9.1), are permitted to undergo dose reduction of 15 mg for subsequent doses at the discretion of the investigator and with medical monitor and/or sponsor approval.

- Patients must continue to fulfill the Dosing Criteria in Section 7.1 prior to each dose
- If the AE does not recur at the lower dose level for at least 2 doses, the original dose may be resumed with medical monitor and/or sponsor approval. If the AE then recurs, dose reduction may be attempted once more with medical monitor and/or sponsor approval. Only one attempt to resume the original dose is allowed per patient
- If the AE recurs at the reduced dose level with the same grade, it should be considered whether or not KZR-616 must be permanently discontinued

Otherwise, intra-patient dose escalations are not allowed.

Missed Doses

Patients who do not fulfill Dosing Criteria (Section 7.1) may miss up to 2 consecutive doses in Phase 1b or Phase 2 or patients may miss up to 4 total doses in Phase 1b or up to 6 total doses in Phase 2 for any reason (e.g. AE, scheduling, emergency). Upon resumption of dosing, subsequent doses should be timed according to the original dosing schedule based on Day 1. Patients who cannot resume dosing within 2 weeks of the first missed dose or who miss more than 4 total doses in Phase 1b or 6 total doses in Phase 2 must permanently discontinue KZR-616 unless the doses in question were missed based on Study Stopping Rules (Section 9.1). If doses were missed due to implementation of Study Stopping Rules, then the patient should be discussed with the medical monitor to evaluate if KZR-616 should be discontinued. Any dose modifications should be discussed with the medical monitor and documented in the eCRF.

If study medication is permanently discontinued due to an AE, standard therapy and planned assessments (see Schedule of Assessments, Section 14.1, Appendix A, and Section 14.2, Appendix B, for Phase 1b and Phase 2, respectively) should continue for the protocol specified time period.

7.2 Prior and Concomitant Medications

A concomitant medication is any prescription or over-the-counter preparation, including vitamins and supplements. Any concomitant therapies must be recorded on the eCRF. Except as described below, prior and concomitant medication use will be recorded for the 60 days prior to screening until the last follow-up visit.

All prior SLE treatment (e.g., immunosuppressants, antimalarials, biologics) will be recorded, including corticosteroid use, from at least the previous 24 weeks prior to screening. When possible, all prior biologics should be recorded.

SLE Disease-Related Concomitant Medications

Patients should continue all concomitant medications related to SLE therapy throughout the study, as outlined in Inclusion/Exclusion Criteria (Section 5.2), this section (Section 7.2), and Table 3.

- All immunosuppressant therapies and antimalarial agents should be continued at a stable dose except when change is deemed necessary by the treating physician or clinical investigator, or if access is limited due to supply issues (see also Section 7.2.2).
- In Phase 1b, if the baseline prednisone dose is ≥ 10 mg/day, tapering is strongly encouraged, and at the investigator's discretion. However, stable prednisone dose is required between Week 9 and Week 13.
- In Phase 2, if the baseline prednisone dose is ≥ 10 mg/day, tapering is strongly encouraged, and at the investigator's discretion to a goal of prednisone ≤ 10 mg/day (or prednisone equivalent) by Week 16. Stable prednisone dose is preferred between Week 16 and Week 24.
- Prednisone (or other corticosteroid) can be initiated or increased to treat a non-renal SLE flare when deemed necessary by the treating physician or clinical investigator.
- Intra-articular or intra-bursal corticosteroid injections are permitted when deemed necessary by the treating physician or clinical investigator.

Other Concomitant Medications

Other concomitant therapies for comorbid conditions, such as antihypertensives or lipid lowering agents, are permitted. The patient should be advised to maintain stable dosage regimen for antihypertensive medication(s) (such as angiotensin receptor blocker [ARB]/angiotensin-converting enzyme inhibitor [ACE-I]), lipid lowering agents (such as statins), NSAIDs unless the dosage adjustment is clinically necessary, e.g., to control hypertension or for intolerance.

KZR-616 is a substrate of the P-gp transporter. Given the rapid clearance of the drug (half-life < 2 hours), it is unlikely that inhibitors of P-gp will affect drug exposure. However, no formal interaction studies with P-gp inhibitors have been performed. Therefore, KZR-616 should be administered at least 6 hours before or 4 hours after drugs that are known inhibitors of P-gp (e.g., cyclosporine, atorvastatin, azithromycin, colchicine, omeprazole).

Vaccinations

It is strongly recommended that patients be up-to-date on immunizations per current 2015 ACR guidelines for RA.[45] Vaccinations received at any time documenting that the patient is up-to-date on vaccines should be recorded in the eCRF.

7.2.1 Excluded Concomitant Medications

The use of any investigational agents or devices is prohibited.

Plasma exchange/plasmapheresis and live-attenuated vaccines are excluded.

Please refer to Section 14.5, Appendix E, for a list of excluded medications and associated wash-out periods.

7.2.2 Required Concomitant Medications

Phase 1b:

Patients should remain stable on their medications during the treatment period, per inclusion and exclusion criteria, Section 7.2, and Section 14.5, Appendix E.

Phase 2:

Patients should remain stable on their medications during the treatment period, per inclusion and exclusion criteria, Section 7.2, (including Table 3) and Section 14.5, Appendix E.

Permitted therapy for LN for study entry is listed in Table 3 and should include at least one non-corticosteroid immunosuppressant. Additionally, one antimalarial and up to 60 mg prednisone or prednisone equivalent are permitted.

For those on a EuroLupus CYC regimen at study entry, once treatment course is complete (500 mg every 2 weeks for 6 doses, or similar), an appropriate immunosuppressive regimen should be initiated with a goal of stable dosing by Week 16, and stable dosing between Weeks 16 and 24.

Once enrolled, treatment regimens should not be changed except as above (including steroid taper) or for reasons of unavailability. Immunosuppressant(s) should not be added to current regimen except as above after completion of a EuroLupus CYC regimen. Corticosteroids should not be added during the study except when needed to treat an SLE flare, and antimalarials should not be added during the study except when they were previously not available, and then are able to be obtained.

During the study, dose modification is not permitted except for reasons of documented toxicity or unavailability, except for up-titration of immunosuppressive therapy after a EuroLupus CYC regimen, and taper of corticosteroids as below.

Corticosteroids should be tapered as per local standard of care or practice to a goal of $\leq$ 10 mg of prednisone by Week 16.

Table 3: Permitted LN Medications During Study

Permitted Medications during study	Max dose	Therapeutic Agent Stability prior to Baseline	Required washout if not continued during study, from Baseline
Prednisone (or other corticosteroid)	60 mg qd (or prednisone equivalent)	14 days	6 weeks
Mycophenolate mofetil	N/A	8 weeks	8 weeks
Mycophenolic acid	N/A	8 weeks	8 weeks
Leflunomide	N/A	8 weeks	8 weeks
Azathioprine	N/A	8 weeks	8 weeks
Cyclosporine	N/A	8 weeks	8 weeks
Tacrolimus	N/A	8 weeks	8 weeks
Methotrexate	N/A	8 weeks	8 weeks
Other oral immunosuppressants/ immunomodulators	N/A	8 weeks	8 weeks
EuroLUPUS Cyclophosphamide	500 mg IV q2 weeks, or similar	8 weeks	8 weeks, unless course completed and oral immunosuppressant(s) started; a minimum of 14-days should separate last dose of CYC and first dose of KZR-616
Hydroxychloroquine or other antimalarial	N/A	2 weeks	2 weeks
ARB/ACE	N/A	2 weeks	4 weeks
Topical medications	N/A	2 weeks	2 weeks

Abbreviations: ARB/ACE = angiotensin receptor blocker/angiotensin-converting enzyme

8 STUDY PROCEDURES

8.1 Schedule of Study Procedures

A schedule of study procedures for the screening, treatment periods, and the follow-up period (or end of study) is presented in the Schedule of Assessments (Section 14.1, Appendix A, and Section 14.2, Appendix B, for Phase 1b and Phase 2, respectively).

Please refer to the Laboratory Manual and Collection Flow Chart for details regarding the specific blood draw requirements for each visit.

For details regarding visit windows, refer to the Schedule of Assessments (Section 14.1, Appendix A, and Section 14.2, Appendix B, for Phase 1b and Phase 2, respectively).

8.2 Description of Study Procedures

The following section provides details of the procedures to be performed.

8.2.1 Medical History

Documentation of the patient's medical history should contain the patient's full medical history including past and concomitant illnesses/diseases, concomitant medications, and demographic data (race, ethnicity, date of birth, and gender). Historical SLE disease data and diagnostic information should include the following:

- Year of diagnosis
- SLICC Classification Criteria for SLE diagnosis
- Historical medications for SLE treatment (biologic, immunosuppressive agents, antimalarials), including start/stop date, dosage, reasons for discontinuation, etc.
- History of disease specific measurements (e.g. UPCR, eGFR)
- Date and results of renal biopsy or biopsies

8.2.2 Vital Signs

Vital signs will include systolic and diastolic blood pressure, pulse, and body temperature. Vital signs should be checked after patient has been resting quietly in either a sitting or supine position for 10 minutes and should be checked prior to blood draws or study drug administration, but after ECG.

8.2.3 Physical Examination

Complete physical exam conducted at screening visit only should include at least assessments of these systems: head & neck, dermatological, respiratory, cardiovascular, abdomen, extremities, neurological, musculoskeletal. Body weight and height will be collected at screening.

Brief physical examination will be performed at post-screening visits, as directed by the patient complaints and the clinical judgment of the investigator. Medically significant

changes from physical examination will be recorded as AEs. SLE signs captured in the SLE assessment instruments will not be recorded for the brief physical examination unless they are classifiable as SAEs.

8.2.4 Electrocardiogram

A 12-lead electrocardiogram (ECG) is to be performed prior to vital signs, following 10 minutes of supine rest. The investigator or qualified designee will review and indicate if the ECG is normal or abnormal, and whether clinically significant. Any medically significant changes from the screening ECG will be recorded as an AE.

8.2.5 Chest X-ray

A chest x-ray will be obtained during the screening period if there is no previous chest x-ray performed within the 12 weeks prior to signing informed consent. A chest x-ray that has no evidence of malignancy, active infection, or clinically significant abnormalities (unless due to SLE) is required for enrollment.

8.2.6 Clinical Laboratory Evaluations

Clinical laboratory tests for safety (hematology, serum chemistries, urinalyses, coagulation tests, serum pregnancy) and other tests during scheduled visits will be performed at a central laboratory. Urine pregnancy tests may be performed at the site using a licensed test. Abnormal safety laboratory results that are considered clinically significant (or potentially clinically significant) should be repeated as soon as possible (preferably within 24-48 hours).

Unscheduled or additional laboratory samples may be collected and analyzed by local laboratories if immediate results are necessary for management of treatment-emergent AEs or dosing determination. Unless otherwise noted, when scheduled simultaneously with a dosing visit, samples for laboratory evaluations should be collected prior to administration of study medications.

Detailed instructions for sample collection, processing, storage and shipment will be provided in the Laboratory Manual.

8.2.6.1 Hematology

Hematology tests will be performed according to standard methods at a central laboratory according to the schedule detailed in the Schedule of Assessments (Section 14.1, Appendix A, and Section 14.2, Appendix B for Phase 1b and Phase 2, respectively) and will include:

Hematology Tests
• Hemoglobin • Hematocrit • White blood cell (WBC) count (total and differential) • Red blood cell (RBC) count • Reticulocyte count • Platelet count • Mean cell volume (MCV) • Mean cell hemoglobin (MCH) • MCH concentration (MCHC)

8.2.6.2 Serum Chemistry

The clinical chemistry laboratory tests will be performed according to standard methods at a central laboratory according to the schedule detailed in the Schedule of Assessments (Section 14.1, Appendix A, and Section 14.2, Appendix B, for Phase 1b and Phase 2, respectively) and will include:

Serum Chemistry Tests (Non-Fasting)	
• Creatinine	• Bicarbonate
• Creatine kinase	• Potassium
• Urea (or blood urea nitrogen)	• Chloride
• Aspartate transferase (AST)	• Glucose
• Alanine transferase (ALT)	• Uric acid
• Gamma-glutamyltransferase (GGT)	• Total cholesterol
• Alkaline phosphatase	• Triglycerides
• Lactate dehydrogenase (LDH)	• Lipids
• Total bilirubin	• Magnesium (Mg)
• Albumin	• Calcium
• Total protein	• Phosphorus
• Sodium	

8.2.6.3 Estimated Glomerular Filtration Rate

Patients will have eGFR calculated based on CKD-EPI formula. $eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

Where:
S_{cr} is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1

For BILAG scoring purposes, eGFR is also calculated using the Modification of Diet in Renal Disease (MDRD) formula.

$$eGFR = 175 \times (S_{cr})^{-1.154} \times (age)^{-0.203} \times 0.742 \text{ [if female]} \times 1.212 \text{ [if black]}$$

8.2.6.4 Urinalysis

The urinalysis laboratory tests include pH, glucose, ketones, blood, protein, creatinine, and microscopy and will be performed according to standard methods at a central laboratory.

8.2.6.5 Proteinuria Evaluation

Proteinuria will be assessed via spot UPCR (should be first morning void in all patients with nephritis) and 24-hour urine collection (Phase 1b patients with nephritis and all Phase 2 patients).

Patients should be given specific instructions on the 24-hour urine collection. At a minimum, patients should be instructed to collect urine over a 24-hour period, to keep the sample cold during the collection period and until the sample is returned to the study site, and to return the sample (within 7 days after collection completed for screening).

At screening, patients will be instructed to collect two 24-hour urine collection samples, at least 7 days apart. Both samples must demonstrate UPCR levels meeting protocol inclusion in order to be eligible for Phase 2 study entry. If one of these samples fails to demonstrate UPCR levels meeting protocol inclusion for Phase 2, one additional 24-hour urine collection sample may be obtained at least 7 days from the last sample taken. In addition, a first morning void sample will also be collected at these same time points for a spot UPCR.

Once enrolled into the Phase 2 portion, 24-hour urine samples will be collected at Weeks 1, 5, 9, 13, 17, 21, 25, 29, 33, and 37. Patients should be instructed to return the chilled 24-hour urine sample to the clinic following its collection, which should occur during the 48 hours prior to the visit. A first morning void sample should also be collected at these same time points for a spot UPCR.

The 24-hour urine collection sample will be used to assess UPCR level at the specified visits. If the laboratory test results indicate a urine collection sample is inadequate at any time point, the spot UPCR obtained from the first morning void sample may be used instead for assessments performed at randomization and onward.

8.2.6.6 Other Screening Tests

Screening for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, and HIV will be performed at screening visit only. Positive screens may require additional testing.

8.2.6.7 TB Tests

Evaluation of all patients by QuantiFERON®-TB Gold/Gold Plus test will be performed by the central clinical laboratory or per local laboratory as per the schedule of study procedures. Use of the T-SPOT® TB will be permitted locally also.

History of active TB infection is excluded regardless of treatment history.

If the screening QuantiFERON-TB Gold/Gold Plus (or T-SPOT TB test is negative and there is no known history of recent exposure to individuals with active TB, and chest radiograph shows no evidence of active TB, the patient may be enrolled. If the screening QuantiFERON-TB Gold/Gold Plus (or T-SPOT TB) test is positive at screening and/or the patient is diagnosed with latent TB, they must have documentation confirming completion of appropriate treatment prior to being permitted to enroll.

An indeterminate QuantiFERON-TB Gold test (or borderline T-SPOT TB test) at screening must be repeated at least one time by the central laboratory (QuantiFERON-TB Gold/Gold Plus test) or local laboratory (QuantiFERON-TB Gold/Gold Plus or T-SPOT TB) and must be repeated as soon as possible. If the result remains indeterminate (or borderline), the patient is not eligible for enrollment into the study or randomization. The site, if it has performed the T-SPOT TB locally and if it has the appropriate equipment and laboratory kits, may perform the QuantiFERON-TB Gold Plus test centrally if a repeat test needs to be performed.

8.2.6.8 Immunological Variables

Patients will be tested for autoantibodies and complement levels according to the schedule detailed in the Schedule of Assessments (Section 14.1, Appendix A, and Section 14.2, Appendix B, for Phase 1b and Phase 2, respectively) and will include:

Immunological
• ANA • Anti-dsDNA • Anti-Sm • Anti-RNP • Anti-Ro/La (anti-SSA/SSB) • Complement (C3, C4) • 50% hemolytic complement (CH50) • Quantitative immunoglobulins (IgM, IgG, IgA) • Antiphospholipid antibodies

8.2.6.9 Coagulation

Patients will be tested for coagulation according to the schedule detailed in the Schedule of Assessments (Section 14.1, Appendix A, and Section 14.2, Appendix B, for Phase 1b and Phase 2, respectively) and will include:

Coagulation
• International normalized ratio (INR) • Activated partial thromboplastin time (APTT) • Fibrinogen (FIB) • Lupus anticoagulant panel

8.2.6.10 Pregnancy Evaluation

Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at the screening visit, which is confirmed to be negative by urine testing prior to the first dose of study drug at Week 1 and prior to further dosing at each study visit thereafter. WOCBP are defined as: all postpubescent female patients, unless the patient is postmenopausal (defined by amenorrhea for at least 2 years or amenorrhea for at least 1 year with confirmatory follicle stimulating hormone [FSH] level in the postmenopausal range as documented historically or measured by the central laboratory at Screening and if patient is not on supplementary hormonal therapy) or if the patient is surgically sterile (i.e., tubal ligation, hysterectomy, bilateral salpingoophorectomy).

Please refer to Inclusions 9 and 10 for both the Phase 1b and Phase 2 studies for contraception requirements.

8.2.6.11 Disease Activity Assessments

SLEDAI-2K

The SLEDAI-2K is an instrument that measures disease activity in SLE patients at the time of the visit and in the previous 30 days. 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 and LN. 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. The SLEDAI-2K has been shown to be a valid and reliable disease activity measure in multiple patient groups. A SLEDAI-2K of 6 or more generally represents moderately to severely active disease.

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 (e.g., chart, worksheet, clinic notes, and labs) at each visit.

BILAG-2004 (Phase 1b only)

The BILAG-2004 is an organ-specific 97-question assessment based on the principle of the doctor's intent to treat (ITT). Only clinical features attributable to SLE disease activity are to be recorded and based on the patient's condition in the last 4 weeks compared with the previous 4 weeks. Scored as not present (0), improved (1), the same (2), worse (3), or new (4). Disease activity is graded separately for 9 body systems to 5 different grades (A to E) as follows: A ("Active") is very active disease, B ("Beware") is moderate activity, C ("Contentment") is mild stable disease, D ("Discount") is inactive now but previously active, and E ("excluded") indicates the organ was never involved. A shift from BILAG-2004 Grade A or B to a lower grade indicates a clinically relevant change in disease activity as the BILAG-2004 grades mirror the decision points for treatment interventions.

Preferably, the same investigator should evaluate the patient at each BILAG-2004 assessment from screening to study completion. The investigator must maintain documentation with descriptive details supporting the BILAG scoring (e.g., chart, worksheet, clinic notes, and labs) at each visit. Note: The BILAG will only be done for the Phase 1b portion of the study.

28-Joint Count

The joint assessment will be carried out on 28 joints, including the shoulders, elbows, wrists (radiocarpal, carpal, and carpometacarpal bones were considered as a single unit), metacarpophalangeal (MCP) joints (MCP 1, 2, 3, 4, and 5), thumb interphalangeal (IP) joint, proximal interphalangeal (PIP) joints (PIP 2, 3, 4, and 5), and the knees.

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

CLASI

The CLASI consists of 2 scores; the first summarizes the activity of the disease and the second is a measure of the damage done by the disease [46]. Activity is scored on the basis of erythema, scale/hypertrophy of skin and mucous membranes, acute hair loss, and nonscarring alopecia. Damage is scored in terms of dyspigmentation and scarring, including scarring alopecia. Patients are asked whether dyspigmentation due to cutaneous lupus erythematosus lesions usually remains visible for more than 12 months, which is taken to be permanent. If so, the dyspigmentation score is doubled. The scores are calculated by simple addition based on the extent of the symptoms. 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.

Physician Global Assessment of Disease Activity

The Physician Global Assessment of Disease Activity (PGA) is used to quantify disease activity and is measured using an anchored visual analog scale (VAS). The PGA will be determined on a continuous VAS that asks the investigator to assess the patient's current disease activity from a score of 0 (none) to 3 (severe) on a 100-mm VAS, with the assessment 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 assessor should always look back at the score from the previous visit. This assessment by the investigator must be blinded to the Patient Global Assessment of Disease Activity performed at the same visit.

Patient Reported Outcomes

Patient Global Assessment of Disease Activity

Patients will rate their global assessment of their SLE disease activity for the day of the visit in response to the statement "Considering all the ways your SLE affects you, please mark a vertical line on the scale below for how you are feeling today" using a 100-mm VAS where 0 is "very good, no symptoms" and 100 is "very poor, very severe symptoms."

Patient Global Assessment of Pain

Patients are asked to assess the severity of pain in the past week on a 100-mm VAS with 0 being no pain and 100 being severe pain. The assessment should be completed prior to the painful, tender, and swollen joint count examination. This assessment is part of the Health Assessment Questionnaire-Disability Index (HAQ-DI).

Health Assessment Questionnaire-Disability Index

The HAQ-DI will be used to assess the functional status of each patient.[47] This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks of daily living in 8 functional areas (domains; i.e., dressing, arising, eating, hygiene, walking, reaching, grip, and outside activities) over the past week. Scores range from 0 (without any

difficulty) to 3 (unable to do). The highest scoring item in each domain is chosen. If an aid or device is used, or if assistance is required from another individual, then minimum score for that functional area/domain is 2. The final scores are equal to the mean of these 8 highest scores and range from 0-3, with higher scores indicating greater functional disability.

8.3 Pharmacokinetic Measurements

Phase 1b only:

Blood and urine samples will be collected from all patients to measure the blood and urine concentration of KZR-616 (and its metabolites, e.g., KZR-59587) as outlined in the Schedule of Assessments (Section 14.1, Appendix A).

Blood samples will be collected as outlined in the Schedule of Assessments (Section 14.1, Appendix A) to measure the plasma concentration of KZR-616 (AUC, maximum concentration [C_{max}], time to maximum plasma concentration [T_{max}]), and other PK calculations, etc.). At the visits and times specified, blood samples of approximately 4 mL will be collected.

Urine samples will be collected over 0 to 5 and 5 to 8 hours and then pooled for analysis to measure amount of KZR-616 and its metabolites.

Samples collected to measure investigational product concentration and metabolism and/or protein binding will be retained for as long as legally permitted in the country of origin.

8.4 Pharmacodynamics

Phase 1b and Phase 2:

The extent of proteasome activity in whole blood and isolated PBMCs will be assessed in blood samples collected as outlined in the Schedule of Assessments (Section 14.1, Appendix A, and Section 14.2, Appendix B, for Phase 1b and Phase 2, respectively).

CT-L peptidase activity will be measured by a cleavable fluorogenic substrate enzymatic activity assay.

KZR-616 occupancy of individual subunits of the proteasome in whole blood and PBMCs is measured by the Proteasome Constitutive/Immunoproteasome Subunit enzyme-linked immunosorbent assay (ELISA) (ProCISE), a subunit-specific proteasome active site ELISA.

8.5 Biomarker Measurements

8.5.1 Cytokine Activity

Phase 1b and Phase 2:

Blood samples will be collected for assessment of cytokine activity and circulating leukocytes as outlined in the Schedule of Assessments (Section 14.1, Appendix A, and Section 14.2, Appendix B, for Phase 1b and Phase 2, respectively).

8.5.2 Gene Expression/Pharmacogenomics

Phase 1b and Phase 2:

Gene expression (RNA) profiling and genomic DNA genotyping will be assessed in blood samples. A whole blood sample will be collected for pharmacogenomic analysis for storage and analysis at a later date as specified in the Schedule of Assessments (Section 14.1, Appendix A, and Section 14.2, Appendix B, for Phase 1b and Phase 2, respectively) and to the extent permitted by the national and/or local laws and regulations.

Samples will be used to conduct retrospective disease or population genetic research as a separate analysis not included in this study. Samples will be used to investigate variable response to KZR-616 and to investigate genetic variants thought to play a role in the diseases under investigation in this study. Assessment of variable response may include evaluation of AEs or differences in efficacy. The results may be reported in the separate report.

8.5.3 Urine Biomarkers

Phase 1b (LN only)/Phase 2 (all):

For patients who provide separate written consent, a portion of 24-hour urine collections will be utilized by the central laboratory to identify biomarkers for response and/or safety.

8.5.4 Sample Management/Future Research

All samples will be coded with the patient number. Samples and any data generated can be linked back to the patient as detailed in Section 4.3.

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 sponsor or its designee following study completion.

9 STUDY DISCONTINUATION

9.1 Individual and Study Stopping Rules for Safety (Phase 1b/2)

Study Stopping Rules

If any of the following events occur, administration of study drug will be temporarily discontinued until a thorough review of the accumulated safety data is undertaken by the DMC.

- Death in any patient, unless the cause of death is due to obvious alternative etiology
- Unexpected life-threatening event in any patient, unless due to obvious alternative etiology.
- Three (3) or more of the same Grade 3 or higher AE (judged by the investigator, medical monitor, or sponsor's representative), including injection site reactions, occurring in 20% or more individuals in any dose group, unless due to obvious alternative etiology
- Any event which, in the opinion of the investigator, medical monitor, DMC or sponsor's representative, contraindicates further dosing of additional patients

Individual Patient Stopping Rules

If any of the following events occur, administration of study drug to an individual patient should be discontinued until a review of the accumulated safety data is undertaken by the DMC.

- Any event which fulfills criteria for DLT, within or outside the DLT (see Section 4.1.1.1) in Phase 1b or Phase 2, evaluation period
- Any unexpected SAE, unless due to obvious alternative etiology
- Any event which fulfills criteria for a Study Stopping Rule, including any life-threatening or SAE, unless due to obvious alternative etiology
- Any event which, in the opinion of the investigator, medical monitor, DMC or sponsor's representative, contraindicates further dosing

After such a review, resumption of dosing may be considered at the same or lower dose including consideration for any prophylactic interventions (e.g. as per Section 7.1.3).

9.2 Early Withdrawal of Patients from Study

Patients may stop study drug for any of the following reasons:

- Patient request/withdraw consent due to an AE
- Patient request/withdraw consent for any reason other than an AE
- Patient becomes pregnant
- Use of non-permitted concurrent therapy
- Non-compliance with the study drug or study schedule
- AE of ≥ Grade 4
- Lost to follow-up
- Occurrence of AEs not compatible with the continuation of patient participation in the study, in the investigator's or sponsor's opinion, or unacceptable to the patient to continue
- Investigator request
- Sponsor request

For Phase 1b, patients who do not comply with the protocol or who withdraw consent may be replaced. For Phase 2, only patients who withdraw before the Week14 injection may be replaced.

Patients are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the eCRF. If a patient withdraws consent, all samples obtained will be retained for analysis unless the patient confirms that he or she wishes the samples to be discarded.

Patients withdrawing from the study treatment will be encouraged to complete the Early Withdrawal Visit within 7 days and return for an EOS Visit approximately 12 weeks after receipt of their last dose to complete the final evaluations according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for patients who completed the study.

Reasonable efforts will be made to contact patients who are lost to follow-up. These efforts must be documented in the patient's file.

9.3 Early Withdrawal (or Discontinuation) Visit

The Early Withdrawal Visit will take place within 7 days after withdrawal. The following procedures will be performed at the Early Withdrawal Visit:

- Record any AEs that have occurred since the last visit and any changes in concomitant medication
- Record vital signs
- Record any changes from baseline in physical examination as AEs
- Collect samples for hematology, clinical chemistry, and urinalysis tests

9.4 Study Termination

The sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the study drug or the company itself occur that makes further treatment of patients impossible. In this event, the investigator(s) will be informed of the reason for study termination.

10 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

10.1 Adverse Event Reporting

10.1.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical study patient administered a medicinal product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs will be elicited by asking the patient a nonleading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?” AEs should be reported on the appropriate page of the eCRF.

10.1.2 Assessment of Severity

Severity of AEs will be graded according to NCI-CTCAE version 4.03. If there is a change in severity of an AE, it must be recorded as a separate event.

10.1.3 Assessment of Causality

AEs will be deemed related to study medication unless clearly unrelated to study medication.

The principal investigator will assess the causal relationship. One of the following categories should be selected based on medical judgment, considering the definitions below and all contributing factors.

Related	A clinical event, including laboratory test abnormality, occurs in a plausible time relationship to treatment administration and which concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the treatment (dechallenge[a]) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge[b] procedure if necessary.
Unrelated	A clinical event, including laboratory test abnormality, with little or no temporal relationship with treatment administration. May have negative dechallenge and rechallenge information. Typically explained by extraneous factors (e.g., concomitant disease, environmental factors, or other drugs or chemicals).

[a] Dechallenge: Upon discontinuation of a drug suspected of causing an AE, the symptoms of the AE disappear partially or completely, within a reasonable time from drug discontinuation, (positive dechallenge), or the symptoms continue despite withdrawal of the drug (negative dechallenge). Note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (for example, as in bone marrow suppression, fixed drug eruptions, or tardive dyskinesia).

[b] Rechallenge: Upon re-administration of a drug suspected of causing an AE in a specific patient in the past, the AE recurs upon exposure (positive rechallenge), or the AE does not recur, (negative rechallenge).

10.1.4 Action Taken

The investigator will describe the action taken with study drug in the appropriate section of the eCRF, as follows:

- None
- Study drug stopped
- Study drug temporarily interrupted
- Study dose modification
- Other, specify

10.1.5 Follow-up of Adverse Events

AEs are intended to be collected according to the procedures outlined above from the time of informed consent and to continue for 12 weeks following the last dose.

All investigators should follow up with patients with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

10.1.6 Documentation and Reporting of Adverse Events

AEs (including SAEs) should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Diagnosed or description of the symptom if diagnosis is not established

- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken with study drug
- Causal relationship with study drug
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

10.2 Serious Adverse Events

10.2.1 Serious Adverse Events Definition

An SAE is any untoward medical occurrence or affect that, at any dose,

- Results in death
- Is life-threatening (an AE is life-threatening if the patient was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form)
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF)
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions)
- Results in a congenital anomaly/birth defect

In addition, medical and scientific judgement is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the patient or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

10.2.2 Serious Adverse Event Reporting and Documentation Requirements

Any SAE must be reported as detailed above (Documentation and Reporting of Adverse Events) by the investigator if it occurs from the time of signed consent through 30 days after the last dose of study drug (KZR-616), whether or not the SAE is considered to be related to the investigational product. After the reporting period, SAEs should be reported throughout the 12 week follow-up if the investigator assesses the event to be related to study drug. An SAE report consists of the SAE form, provided separately, along with requested additional source documentation as considered necessary.

SAEs that occur during the reporting period must be reported by the investigator to the Safety Reporting e-mail address, or dedicated fax (see below) and entered into electronic data capture (EDC) within 24 hours from the point in time when the investigator becomes aware of the SAE.

A copy of the SAE form should also be emailed or faxed **within 24 hours** for the attention of the study safety lead:

Contact Information:

SAE Reporting E-mail: [redacted]

Fax: [redacted]

The investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the study monitor.

The sponsor and/or the CRO will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of patients, impact on the conduct of the study or alter the DMC/independent ethics committee (IEC)/institutional review board (IRB) approval/favorable opinion of the study. In addition, the CRO and the sponsor, will expedite the reporting to all concerned investigators, to the DMC/IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

10.3 Pregnancy Reporting

Pregnancy occurring during a clinical investigation must be reported to safety within 24 hours on a Pregnancy Monitoring Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse. Infants should be followed for a minimum of 8 weeks and all findings should be reported to the sponsor. Study drug is to be discontinued immediately.

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE—spontaneous abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly—the investigator should repeat the procedures for expedited reporting of SAEs as outlined above.

Full details will be recorded on the withdrawal page of the eCRF, or an SAE report will be completed if the patient has completed the study.

10.4 New or Worsening Disease Manifestations

New or worsening manifestation(s) of SLE should not be recorded as AEs unless they are assessed as serious.

10.5 AEs of Special Interest

An AE of special interest (AESI) is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a product or compound. Systemic injection reactions and thrombotic microangiopathy (TMA) have been identified as AESI and should be reported within 24 hours using the AE eCRF ([redacted]). These will not be reported to [redacted] unless they become SAEs.

10.5.1 Systemic Injection Reactions

Systemic injection reactions have been observed with KZR-616 and other proteasome inhibitors and are considered AESIs.

Systemic injection reactions have included a number of signs and symptoms including fever, chills, myalgia, facial swelling or flushing, dizziness, headache, nausea, vomiting, weakness, hypotension, chest tightness, and shortness of breath, as well as abnormalities in laboratory values (e.g., creatinine, transaminases) and blood pressure. However, the relative roles of the immunoproteasome versus constitutive proteasomes to these specific events are not known. Therefore, terms such as the NCI-CTCAE terms of 'infusion-related reaction,' 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or hypersensitivity reaction' should not be used. Instead, each sign or symptom should be recorded as an individual AE. If multiple signs or symptoms occur with a given systemic injection-related event, each sign or symptom should be recorded separately with its own level of severity.

Management of systemic injection reactions is described in Section 7.1.3.

10.5.2 Thrombotic Microangiopathy (TMA)

Cases of TMA, including TTP and HUS, have been described with the nonspecific proteasome inhibitors, bortezomib, carfilzomib, and ixazomib. The clinical presentation of TMA typically includes fever, microangiopathic hemolytic anemia (with schistocytes on blood smear), thrombocytopenia, renal failure, purpura, and neurological manifestations. Patients should be monitored for signs and symptoms of TTP/HUS. If the diagnosis is suspected, interrupt treatment with study drug and evaluate (refer to Section 9.1). Missed doses should be addressed as per Section 7.1.4. If the diagnosis of TTP/HUS is excluded, study drug may be resumed. If the diagnosis is confirmed, study drug must be permanently discontinued (refer to Section 9.2).

10.6 Unexpected Adverse Reactions

10.6.1 Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose and that is not consistent with the applicable product information (e.g., investigators brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

All suspected unexpected serious adverse reactions (SUSARs) will be subject to expedited reporting. The sponsor and/or the CRO shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC/IRB within 7 days after knowledge by the sponsor of such a case and that relevant follow-up information is communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and IEC/IRB within 15 days after knowledge by the sponsor of such a case. All investigators should follow up SUSARs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Post study SUSARs that occur prior to completion of the 12 weeks follow-up must be reported by the investigator to the sponsor.

10.7 Data Monitoring Committee

To enhance the safety and integrity of the study data, a study-specific DMC consisting of principal investigators, medical monitors, and Kezar Life Sciences (hereafter, Kezar) designees will be convened to review the accumulating safety data for the study.

For Phase 1b, safety review will occur for each cohort as it completes the first 4 weeks of treatment. The first safety review by the DMC will occur after the first 6 patients have been enrolled and received study drug and progressed to Week 4. Decisions to escalate, expand, or modify dose level(s) or frequency will depend on review of safety data by the DMC.

The DMC will review cumulative Phase 1b study data and provide a recommendation for the Phase 2 dose.

For Phase 2, the DMC will convene and review cumulative data on a periodic basis to be defined in a separate DMC charter.

The specific responsibilities and composition of the DMC are outlined in a separate DMC Charter. In addition, the details of outputs provided for the meetings will be referenced in the separate document.

11 STATISTICS

11.1 Endpoints

11.1.1 Phase 1b Endpoints

Primary Endpoints:

- Safety and tolerability of KZR-616 as assessed by changes in physical examination, safety laboratory findings, 12-lead ECGs; incidence and severity of AEs and SAEs; and the evaluation of other safety information collected and summarized by protocol specified time points along with a summary of change from baseline at each protocol specified time point

Secondary Endpoints:

- The RP2Ds of KZR-616 as determined by evaluation of safety parameters, PK, PD, and DLTs by the DMC
- Plasma PK parameters, including C_{max}, T_{max}, AUC, and other applicable parameters will be summarized for KZR-616 and its metabolites

Exploratory Endpoints:

- The efficacy of KZR-616 in patients with SLE with and without nephritis will be assessed through changes in lupus disease assessments and changes from baseline in laboratory measures
- The level of proteasome inhibition in whole blood and PBMCs, as measured by both a cleavable fluorogenic substrate enzymatic assay and a subunit-specific proteasome active site ELISA
- The proteomic and pharmacogenomic activity of KZR-616 will be assessed through ex vivo analysis of whole blood and PBMC samples
- Serum cytokine levels and circulating leukocytes will be measured in blood samples collected on Day 1 of Weeks 1, 5, 17, and 25

11.1.2 Phase 2 Endpoints

Primary Endpoint:

- The number of patients with a 50% reduction in UPCR after 24 weeks of treatment when compared to baseline

Secondary Endpoints:

- Safety and tolerability of KZR-616 as assessed by the incidence, nature, and severity of AEs

- The number of patients with a partial renal response (PRR) after 24 weeks of treatment as defined by:
    a) A 50% reduction of UPCR and/or reduction of UPCR to < 1.0 if the baseline UPCR was < 3.0 or a 50% reduction of UPCR and/or reduction of UPCR to < 3.0 if the baseline was ≥ 3.0
    b) eGFR of ≥ 60 mL/min/1.73 m^2 or no worsening of eGFR from baseline of ≥ 25%
    c) No use of prohibited medication
- The number of patients with a complete renal response (CRR) after 24 weeks of treatment as defined by:
    a) UPCR of ≤ 0.5
    b) eGFR of ≥ 60 mL/min/1.73 m^2 or no worsening of eGFR from baseline of ≥ 25%
    c) Prednisone (or equivalent) < 10 mg
    d) No use of prohibited medication
- Time to ≥ 50% reduction in UPCR from baseline
- Time to CRR
- Time to PRR
- Time to UPCR of ≤ 0.5 from baseline
- The number of patients with UPCR of ≤ 0.5 at 24 weeks
- The number of patients with daily prednisone (or equivalent) dose ≤ 10 mg
- Change from baseline in levels of autoantibodies (e.g. ANA, anti-dsDNA) and complement at 24 weeks
- Changes in corticosteroid use from baseline

Exploratory Endpoints:

- The level of proteasome inhibition in whole blood and PBMCs, as measured by both a cleavable fluorogenic substrate enzymatic assay and a subunit-specific proteasome active site ELISA
- Change from baseline in SLEDAI-2K score, CLASI, and 28 joint count and changes from baseline in laboratory measures
- The proteomic and pharmacogenomic activity of KZR-616 will be assessed through ex vivo analysis of whole blood and PBMC samples
- Serum cytokine levels and circulating leukocytes will be measured in blood samples collected on Day 1 of Weeks 1, 5, 17 and 25

11.2 Statistical Methods

11.2.1 Methods of Analysis

Verbatim AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients who experience AEs and SAEs will be summarized by dose/treatment group and overall.

Laboratory, vital sign, ECG, and efficacy data will be summarized descriptively (mean, median, standard deviation [SD], and minimum and maximum values) by dose/treatment group and overall and will be summarized by protocol specified time point along with a summary of change from baseline at each protocol specified time point. Changes in physical examinations will be listed for each patient and described.

PK analyses will include determination of plasma levels of KZR-616 including C_{max}, T_{max}, and AUC.

All patients who receive any amount of study drug (Safety Population) will be included in the safety analyses. Descriptive statistics, including the numbers and percentages for categorical variables and the numbers, means, SDs, medians, minimums and maximums for continuous variables will be provided by dose/treatment group overall.

11.2.2 Analysis Population

Safety Population

All patients who receive any amount of study drug will be included in the safety analyses.

PK Analysis Population

All patients who receive the Day 1 dose of KZR-616 and who have at least one post-dose concentration of KZR-616 measured will be included in the PK analysis population. Any protocol deviations affecting PK analyses may result in exclusion from summaries for individual time point concentrations, complete profiles, and/or PK parameters. These exclusions will be reviewed before database lock and confirmed with the sponsor before the implementation.

Pharmacodynamics Analysis Population

All patients who receive any amount of study drug and who have any measured results for PD assessment will be included in the PD analysis population. Any protocol deviations affecting PD analyses may result in exclusion from summaries for individual time point concentrations and/or complete profiles. These exclusions will be reviewed before database lock and confirmed with the sponsor before the implementation.

11.3 Assessments

11.3.1 Criteria for Evaluation – Safety Analysis

Safety and tolerability is the primary endpoint for Phase 1b and a secondary endpoint for Phase 2.

Safety for the study will be evaluated through monitoring and assessment of all AEs, physical examination findings, vital sign measurements (blood pressure, pulse, and body temperature), ECGs, and clinical laboratory test results (hematology, serum chemistry, urinalysis) including quantitative serum immunoglobulins.

Severity of AEs will be assessed using the NCI-CTCAE, Version 4.03.

All AEs occurring on or after treatment on Week 1, Day 1 through Week 25, Day 169 for Phase 1b and through Week 37, Day 253 for Phase 2 will be summarized by MedDRA system organ class, preferred term, grade, and investigator assessment of causality.

In addition, all SAEs, including deaths, will be listed separately and summarized. Extent of exposure to the study treatment will be summarized using descriptive statistics.

Full details of the analyses will be specified in the statistical analysis plan (SAP). With regard to inconsistencies, the SAP will take precedence over the protocol.

11.3.2 Criteria for Evaluation – Pharmacokinetic Analyses

Phase 1b:

Assessment of the Secondary Endpoint:

Blood samples will be collected from all patients to measure the plasma concentration of KZR-616 on Days 1 and 29 of Weeks 1 and 5, respectively. Blood samples will be collected before dosing and 5, 15, 30 minutes and 1, 2, 4, and 8 hours after the injection. Plasma PK parameters, including C_{max}, T_{max}, AUC from time 0 to the last measured concentration (AUC_{last}), and other applicable parameters such as elimination parameters data permitting, will be calculated for KZR-616. The PK parameters will be listed and summarized by dose/treatment group and type of the disease as applicable. Dose proportionality assessments and other comparisons such as effect of the type of disease may be performed.

Concentrations will be listed and summarized for all patients by dose level and type of the disease as applicable. The excluded data will be flagged and explained in the footnotes.

Urine PK of the drug will be analyzed from urine samples pooled from 0 to 8 hours post-dose (see Section 8.3). Total amount of excreted unchanged and metabolized drug (Ae) and percent fraction of dose excreted (%Fe) will be listed and summarized by dose/treatment group and type of disease, where applicable. Exploratory correlation between %Fe and eGFR may be evaluated.

The PK results will be presented graphically as individual and mean plasma concentration plots. Statistical models will be presented by regression plots vs dose and box plots for different treatments. The details of the analysis will be further described in the SAP.

11.3.3 Criteria for Evaluation – Pharmacodynamic Analyses

Pharmacodynamic analyses will be performed in both Phase 1b and Phase 2. The extent of proteasome activity in whole blood and isolated PBMCs will be assessed in blood samples collected.

The PD effects of KZR-616 will be assessed by evaluating levels of proteasome activity. Proteasome CT-L peptidase activity will be measured by a cleavable fluorogenic substrate enzymatic activity assay. The inhibition of proteasome activity will be expressed relative to

individual patient matched pre-dose levels in whole blood and PBMCs, representing selective inhibition of constitutive proteasome and immunoproteasome, respectively.

KZR-616 occupancy of individual subunits of proteasome in whole blood and PBMCs is measured by subunit-specific proteasome active site ELISA (ProCISE). KZR-616 occupancy/ inhibition of constitutive and immune-proteasome specific subunits will be expressed relative to individual patient matched pre-dose levels. ProCISE will further confirm selective inhibition of constitutive proteasome and immunoproteasome by KZR-616.

11.3.4 Criteria for Evaluation – Biomarker and Other Analyses

Obtain material to assess gene transcriptional and proteomic changes following KZR-616 treatment including (i.e., RNA) profiling through ex vivo analysis of whole blood and PBMC samples. In the Phase 1b, blood samples will be collected on Day 1 of Weeks 1, 5, 17, and 25 (For DNA genotyping a sample will be collected only on Day 1, Week 1). In the Phase 2, blood samples will be collected on Day 1 of Weeks 1, 17, 25, and 37 (For DNA genotyping a sample will be collected only on Day 1, Week 1).

The immunomodulatory activity of KZR-616 will be assessed by evaluating levels of cytokines, including change from baseline.

11.3.5 Criteria for Evaluation – Efficacy Analyses

Phase 2:

Assessment of Primary and/or Secondary Endpoints

Please see Section 11.1.2 for a listing of secondary endpoints for Phase 2.

Rate of renal response will be assessed at 24 weeks. Renal response will be classified as complete, partial [50% reduction in UPCR], or no renal response. Summary statistics (e.g., total number of patients with observed data, mean, median, SD, min, max for continuous endpoints; for binary endpoints: total number of patients observed, number of patients with the event of interest, percent) will be provided by dose in Phase 1b and for all patients combined in Phase 2. The primary efficacy endpoint in Phase 2 is percent of patients with 50% reduction in UPCR after 24 weeks of treatment when compared to baseline. The null hypothesis is that the percentage is < = 20%; the alternative hypothesis is that the percentage is > 20%. The test of hypotheses will be carried out with an exact binomial test. The KZR-616-002 Statistical Analysis Plan contains details of the planned analysis.

Phase 1b and Phase 2: Exploratory Endpoints:

The efficacy of KZR-616 on SLE will be assessed using changes from baseline in study administered questionnaires/disease assessment tools and changes from baseline in laboratory measures.

11.3.6 Handling of Missing Data

All withdrawals will be included in all analyses up to the time of withdrawal. Patients who are withdrawn prematurely from investigational product and/or the study will be included in all analyses regardless of the duration of treatment. There will be no imputation for missing data, unless otherwise specified.

11.4 Determination of Sample Size

The study is not powered using statistical hypothesis testing.

11.5 Interim Analysis

Review of safety data will be carried out after each cohort in Phase 1b as explained above. There is no formal statistical interim analysis planned.

12 ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

12.1 Compliance Statement

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (cGCP), and the applicable national and local laws and regulatory requirements.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

12.2 Institutional Review Board or Independent Ethics Committee

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study (i.e., amendments to the protocol, the ICF, or other study documentation). The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

12.3 Informed Consent and Human Patient Protection

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to current Good Clinical Practice (GCP).

Patients will provide written informed consent before any study-related procedures are performed.

The investigator is responsible for ensuring that no patient undergoes any study-related examination or activity before that patient has given written informed consent to participate in the study.

The investigator or designated personnel will inform the patient of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The patient should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the patient will be given ample time to consider the study. Patients will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the

investigator's study file. A signed and dated copy of the patient ICF will be provided to the patient or their authorized representative.

It should be emphasized that the patient may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the patient is otherwise entitled. Patients who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the patient's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study patients will be informed about this new information and reconsent will be obtained.

12.4 Direct Access to Source Data, Source Documents, and Study Records

Kezar or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Kezar and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable review boards with direct access to the original source documents.

12.5 Data Collection and Handling

An EDC system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of patient personal information collected will be provided in a written document to the patient by the sponsor.

12.6 Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study patients' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the patients to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the patients' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of

those data, and in accordance with the Health Insurance Portability and Accountability Act, applicable to national and/or local laws and regulations on personal data protection.

12.7 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between the CRO and the sponsor.

12.8 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

12.9 Monitoring

Data for each patient will be recorded on an eCRF. Data collection must be completed for each patient who signs an ICF and is administered study drug.

In accordance with cGCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The investigator must permit the monitor, the IEC/IRB, the sponsor's internal auditors, and representatives from regulatory authorities' direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

12.10 Data Management and Coding

The sponsor or the CRO will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the data management and biostatistics departments of sponsor or the CRO.

Study centers will enter data directly into an EDC system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be FDA CFR 21 Part 11 compliant.

Medical coding will use MedDRA for concomitant diseases and AEs with World Health Organization (WHO) drug classifications being used for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

12.11 Reporting and Publication, Including Archiving

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last patient), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-related documentation. In addition, all patient medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately

13 REFERENCES

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14 APPENDICES

14.1 APPENDIX A: SCHEDULE OF ASSESSMENTS – PHASE 1B

Assessments	Screening (-28 days)* *Visit 1*	Week 1 (D1) *Visit 2*								Week 2-Week 4 (D8/15/22 ±1 day) *Visits 3/4/5*	Week 5 (D29 ±1 day) *Visit 6*								Week 6-8 (D36/43/50 ±1 day) *Visits 7/8/9*	Week 9 (D57 ±1 day) *Visit 10*	Week 10-12 (D64/71/78 ±1 day) *Visits 11/12/13*	Week 13 (D85 ±1 day) *Visit 14*	Week 17 and 21 (D113 and D141 ±3 days) *Visits 15/16*	Week 25 (D169 ±3 days) *Visit 17*
		Pre-dose		5 min	15 min	30 min	1 hr	2 hr	4 hr	8 hr		Pre-dose		5 min	15 min	30 min	1 hr	2 hr	4 hr	8 hr					*1m and 2m follow-up*	*EOS/ 12-week follow-up*
Informed consent	X																									
Medical History	X																									
Screening blood tests [a]	X																									
QuantiFERON®-TB Gold test	X																									
Physical Examination [b]	X	X								X	X								X	X	X	X	X	X	X	X
28 Joint Count	X	X									X									X		X	X	X	X	X
Chest X-ray [c]	X																									
SLICC Criteria for SLE	X																									
Vital Signs [d]	X	X				X			X		X	X				X			X		X	X	X	X	X	X	X
12-lead ECG [e]	X	X				X			X			X				X			X							X
Hematology (see Section 8.2.6.1)	X	X									X	X									X			X	X	X
Serum chemistry (see Section 8.2.6.2)	X	X									X	X									X			X	X	X
Urinalysis (see Section 8.2.6.4)	X	X									X	X									X			X	X	X
Urine pregnancy test [f]		X									X	X									X	X	X	X		
24-hour urine test (all nephritis patients) [g]	X	X										X									X			X	X	X
Quantitative Igs (IgM, IgG, IgA)	X											X												X	X	X
Serology [h]	X	X									X [i]	X									X			X	X	X
CRP and ESR [j]	X	X									X [i]	X									X			X	X	X
Coagulation [k]	X	X									X [i]	X									X			X	X	X
SLEDAI-2K, BILAG, CLASI, PGA [l]	X	X										X									X			X	X	X
PtGP, PtGA, HAQ-DI	X	X										X									X			X	X	X
KZR-616 administration [f]			X								X		X								X	X	X	X		
Blood sample - Plasma PK assessment		X		X	X	X	X	X	X	X		X		X	X	X	X	X	X	X						
Pooled urine samples – Urine PK assessment		X		0 to 5 hr					5-8 hr																	

Assessments	Screening (-28 days)* *Visit 1*	Week 1 (D1) *Visit 2*								Week 2-Week 4 (D8/15/22 ±1 day) *Visits 3/4/5*	Week 5 (D29 ±1 day) *Visit 6*								Week 6-8 (D36/43/50 ±1 day) *Visits 7/8/9*	Week 9 (D57 ±1 day) *Visit 10*	Week 10-12 (D64/71/78 ±1 day) *Visits 11/12/13*	Week 13 (D85 ±1 day) *Visit 14*	Week 17 and 21 (D113 and D141 ±3 days) *Visits 15/16*	Week 25 (D169 ±3 days) *Visit 17*
		Pre-dose		5 min	15 min	30 min	1 hr	2 hr	4 hr	8 hr		Pre-dose		5 min	15 min	30 min	1 hr	2 hr	4 hr	8 hr					*1m and 2m follow-up*	*EOS/ 12-week follow-up*
Blood sample – Plasma PD - proteasome inhibition		X							X			X							X						
Blood sample – cytokine activity/circulating eukocytes		X										X												X [m]	X
Blood sample – Plasma RNA gene expression profiling		X										X												X [m]	X
Blood sample - Genomic DNA genotyping		X																							
AEs and prior and concomitant medications [n]	X	X																							

* The screening period can be extended to 35 days upon sponsor approval only.

[a] Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis C antibody, HIV, pregnancy test for FCBP. Screening serum pregnancy testing is required within the 28-day screening period.

[b] Physical exam conducted at screening visit only and should include at least assessment of these systems: head and neck, dermatological, respiratory, cardiovascular, abdomen, extremities, neurological, and musculoskeletal. Body weight and height will also be collected at screening visit. Brief physical to be completed post screening visit.

[c] If not available from within 90 days prior to signing informed consent form.

[d] Vital signs: Systolic and diastolic blood pressure, pulse, and body temperature. Vital signs should be checked after patient has been resting quietly in a supine position for 10 minutes, and should be checked prior to blood draws or study drug administration.

[e] ECG done prior to vital signs during supine rest as detailed in the protocol.

[f] KZR-616 dose administration on day one of each week from Week 1 up to Week 13. Negative urine pregnancy test required prior to dose administration.

[g] Urine biomarkers from 24-hour urine (LN patients).

[h] ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-Ro/La (anti-SSA/SSB), C3/C4, and CH50 at all visits specified. Antiphospholipid antibodies will be evaluated only at baseline.

[i] Week 3, Day 1 only.

[j] ESR performed locally.

[k] INR, APTT, and fibrinogen at all visits specified. Lupus anticoagulant panel will be evaluated only at baseline.

[l] When needed for SLEDAI-2K/BILAG assessments and scoring, a Coombs test could be performed locally to confirm hemolytic anemia, and ultrasound or other evaluation (e.g., chest radiograph, echocardiogram) could be performed as needed to confirm pleuritis (pericarditis or pneumonitis).

[m] Week 17 only.

[n] All AEs must be recorded on the patient's electronic case report form (eCRF), starting at the time of informed consent and continuing through 12 weeks post last dose. Prior medications will be collected at the screening visit. Concomitant medications will be collected at each visit.

Abbreviations: AEs = adverse events; ANA = antinuclear antibody; APTT = activated partial thromboplastin time; BILAG = British Isles Lupus Assessment Group; C3/C4 = complement 3 and 4; CH50 = 50% hemolytic complement; CRP = C-reactive protein; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOS = End of Study; ESR = erythrocyte sedimentation rate; FCBP = females of child bearing potential; HAQ-DI = Health Assessment Questionnaire-Disability Index; HIV = Human immunodeficiency virus; hr = hour; Immunoglobulin (Ig); INR = international normalized ratio; min = minutes; m = month; PD = pharmacodynamics; PGA = Physician Global Assessment of Disease Activity; PK = pharmacokinetic; PtGA = Patient Global Assessment of Disease Activity; PtGP = Patient Global Assessment of Pain; SLE = Systemic Lupus Erythematosus (includes lupus nephritis); SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC = Systemic Lupus International Collaborating Clinics; TB = tuberculosis; UPCR = Urine Protein to Creatinine Ratio.

14.2 APPENDIX B: SCHEDULE OF ASSESSMENTS – PHASE 2

Assessment	Screening	Week 1			Week 2-Week 4	Week 5	Week 6-Week 8	Week 9	Week 10-Week 12	Week 13	Week 14-Week 16	Week 17	Week 18-Week 20	Week 21	Week 22-Week 24	Week 25	Week 29	Week 33	Week 37
Day	D-28* to D-1	D1			D8/15/22 ±1 day	D29 ±1 day	D36/43/50 ±1 day	D57 ±1 day	D64/71/78 ±1 day	D85 ±1 day	D92/99/106 ±1 day	D113	D120/127/ 134 ±1 day	D141 ±1 day	D148/155/162 ±1 day	D169 ±1 day	D197 ±3 days	D225 ±3 days	D253 ±3 days
Visit	1	2 Pre-dose		Post-dose	*3/4/5*	6	7/8/9	10	11/12/13	14	15/16/17	18	19/20/21	22	23/24/25	26	27	28	29 EOS/ETV
Informed consent	X																		
Medical History	X																		
Screening blood tests [a]	X																		
QuantiFERON®-TB Gold test	X																		
Physical Examination [b]	X				X	X		X		X		X		X		X	X	X	X
28 Joint Count	X	X				X		X		X		X		X		X	X	X	X
Chest X-ray [c]	X																		
SLICC Criteria for SLE	X																		
Vital Signs [d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG with QTc interval [e]	X	X		X															X
Hematology (see Section 8.2.6.1)	X	X				X		X		X		X		X		X	X	X	X
Serum chemistry (see Section 8.2.6.2)	X	X				X		X		X		X		X		X	X	X	X
Urinalysis (see Section 8.2.6.4)	X	X				X		X		X		X		X		X	X	X	X
Urine pregnancy test [f]		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour urine test [g]	X	X				X		X		X		X		X		X	X	X	X
Quantitative Igs (IgM, IgG, IgA)	X					X				X		X		X		X	X	X	X
Serology [h]	X	X				X		X		X		X		X		X	X	X	X
Coagulation[i]	X	X				X		X		X		X		X		X	X	X	X
SLEDAI-2K, CLASI, PGA [j]	X	X				X		X		X		X		X		X	X	X	X
PtGP, PtGA, HAQ-DI	X	X				X		X		X		X		X		X	X	X	X
KZR-616 administration [f]			X		X	X	X	X	X	X	X	X	X	X	X				
Blood sample – Plasma PD assessment of proteasome inhibition		X		X [k]		X [k]													
Blood sample – cytokine activity/circulating leukocytes		X										X				X			X
Blood sample – for gene expression (RNA) profiling		X										X				X			X
Blood sample – Genomic DNA genotyping		X																	

Assessment	Screening	Week 1			Week 2-Week 4	Week 5	Week 6-Week 8	Week 9	Week 10-Week 12	Week 13	Week 14-Week 16	Week 17	Week 18-Week 20	Week 21	Week 22-Week 24	Week 25	Week 29	Week 33	Week 37
Day	D-28* to D-1	D1			D8/15/22 ±1 day	D29 ±1 day	D36/43/50 ±1 day	D57 ±1 day	D64/71/78 ±1 day	D85 ±1 day	D92/99/106 ±1 day	D113	D120/127/134 ±1 day	D141 ±1 day	D148/155/162 ±1 day	D169 ±1 day	D197 ±3 days	D225 ±3 days	D253 ±3 days
Visit	1	2 Pre-dose e		Post-dose	3/4/5	6	7/8/9	10	11/12/13	14	15/16/17	18	19/20/21	22	23/24/25	26	27	28	29 EOS/ETV
AEs and prior and concomitant medications [l]	X																		

*The screening period can be extended to 35 days if needed at discretion of Principal Investigator without Sponsor approval

[a] Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis C antibody, HIV, pregnancy test for FCBP. Screening serum pregnancy testing is required within the 35-day screening period.

[b] Physical exam conducted at screening visit only and should include at least assessment of these systems: head and neck, dermatological, respiratory, cardiovascular, abdomen, extremities, neurological, and musculoskeletal. Body weight and height will also be collected at screening visit. Brief physical to be completed post screening visit.

[c] If not available from within 90 days prior to signing informed consent form.

[d] Vital signs: Systolic and diastolic blood pressure, pulse, and body temperature. Vital signs should be checked after patient has been resting quietly in a supine position for 10 minutes, and should be checked prior to blood draws or study drug administration.

[e] ECG done prior to vital signs during supine rest.

[f] KZR-616 dose administration on day one of each week from Week 1 up to Week 24. Negative urine pregnancy test required prior to dose administration.

[g] Urine biomarkers from 24-hour urine.

[h] ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-Ro/La (anti-SSA/SSB), C3/C4, and CH50 at all visits specified. Antiphospholipid antibodies will be evaluated at baseline only.

[i] INR, APTT, and fibrinogen at all visits specified. Lupus anticoagulant panel will be evaluated at baseline only.

[j] When needed for SLEDAI-2K assessments and scoring, a Coombs test could be performed locally to confirm hemolytic anemia, and ultrasound or other evaluation (e.g., chest radiograph, echocardiogram) could be performed as needed to confirm pleuritis (pericarditis or pneumonitis).

[k] Week 1, Day 1, predose and 4 hours post-dose; Week 5, Day 29 pre-dose only.

[l] All AEs must be recorded on the patient's electronic case report form (eCRF), starting at the time of informed consent and continuing through after 12 weeks post last dose. Prior medications will be collected at the screening visit. Concomitant medications will be collected at each visit.

Abbreviations: AEs = adverse events; ANA = antinuclear antibody; APTT = activated partial thromboplastin time; C3/C4 = complement 3 and 4; CH50 = 50% hemolytic complement; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOS = End of Study; FCBP = females of child bearing potential; HAQ-

DI = Health Assessment Questionnaire-Disability Index; hr = hour; Immunoglobulin (Ig); INR = international normalized ratio; min = minutes; PGA = Physician Global Assessment of Disease Activity; PK = pharmacokinetic; PtGA = Patient Global Assessment of Disease Activity; PtGP = Patient Global Assessment of Pain; SLE = Systemic Lupus Erythematosus (includes lupus nephritis); SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SJC-28 = Swollen 28-Joint Count; TJC-28 = Tender 28-Joint Count; SLICC = Systemic Lupus International Collaborating Clinics; TB = tuberculosis; UPCR = Urine Protein to Creatinine Ratio.

14.3 APPENDIX C: INTERNATIONAL SOCIETY OF NEPHROLOGY/RENAL PATHOLOGY SOCIETY (ISN/RPS) 2003 CLASSIFICATION OF LUPUS NEPHRITIS

Full text of the ISN/RPS article (The ISN/RPS 2003 classification of lupus nephritis: an assessment at 3 years. Markowitz GS, D'Agati VD, Kidney Int. 2007 Mar;71(6):491-5. Epub 2007 Jan 31) is available from Elsevier here:

http://www.kidney-international.com/article/S0085-2538(15)52418-6/pdf

14.4 APPENDIX D: INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 1b/2 Study of KZR-616 in Patients with Systemic Lupus Erythematosus with and without Nephritis

Protocol Number: KZR-616-002

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/IRB, I will not modify this protocol without obtaining prior approval of Kezar Life Sciences and of the IEC/IRB. I will submit the protocol amendments and/or any ICF modifications to Kezar Life Sciences and IEC/IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the patients' state of health will be regarded as confidential. No patients' names will be disclosed. All patients will be identified by assigned numbers on all CRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the patient before disclosure of patient information to a third party.

Information developed in this clinical study may be disclosed by Kezar Life Sciences, to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

_____ _____

Investigator Signature Date

_____

Printed Name

_____

Institution

14.5 APPENDIX E: EXCLUDED MEDICATIONS

Besides the medications listed below, plasma exchange/plasmapheresis and live -attenuated vaccines are excluded.

Treatment	Wash-out period Prior to *Baseline*
Intravenous, intramuscular, or subcutaneous immunoglobulin	2 weeks
Any cytokine antagonist, including but not limited to IL-6, IL-17, IL-12/23, IL-23, IFN, integrin, BL*y*S, or TNF-alpha antagonists	12 weeks
B-cell-depleting therapies: e.g., rituximab (Rituxan®), ofatumumab (Arzerra®), obinutuzumab (Gazyva®), ocrelizumab, veltuzumab	24 weeks
Other biologic therapies	12 weeks
NIH (high-dose) cyclophosphamide or oral cyclophosphamide	8 weeks
Investigational drugs	8 weeks or 5 half-lives, whichever is longer

Abbreviations: BLyS = B-lymphocyte stimulator; IL = interleukin; NIH=National Institutes of Health; TNF = tumor necrosis factor.