KZR-616-202

A PHASE 2B, RANDOMIZED, CONTROLLED DOUBLE-BLIND, MULTICENTER STUDY COMPARING THE EFFICACY AND SAFETY OF ZETOMIPZOMIB (KZR-616) 30 MG OR 60 MG WITH PLACEBO IN PATIENTS WITH ACTIVE LUPUS NEPHRITIS

Clinicaltrials.gov Identifier	*NCT05781750*
Date of protocol:	*27 January 2023*

CLINICAL STUDY PROTOCOL

Protocol Title	A Phase 2b, Randomized, Controlled Double-blind, Multicenter Study Comparing the Efficacy and Safety of Zetomipzomib (KZR-616) 30 mg or 60 mg with Placebo in Patients with Active Lupus Nephritis
Protocol Number	KZR-616-202
Investigational Product(s)	Zetomipzomib (KZR-616)
Indication	Lupus Nephritis
Development Phase	2b
US IND Number	[redacted]
EU CT Number	2022-502227-22-00
Sponsor	Kezar Life Sciences, Inc. 4000 Shoreline Court, Suite 300 South San Francisco, CA 94080 Telephone: +1-650-822-5600
Contract Research Organization	[redacted]
Protocol Version and Date	Version 1.0, 27 January 2023

Confidentiality Statement

The concepts and information contained herein are confidential and proprietary and shall not be disclosed in whole or part without the express written consent of the Sponsor.

Compliance Statement

This study will be conducted in accordance with this protocol, the International Council for Harmonisation (ICH), Guideline for Good Clinical Practice (GCP), and the applicable country and regional (local) regulatory requirements.

STUDY PERSONNEL

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* = country exit code

PROTOCOL ACCEPTANCE PAGE

I have read and agree with the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, all local, regional, and national regulatory requirements (including the Code of Federal Regulations [CFR] Title 21 for United States [US] Investigators), requirements of the applicable Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and the clinical trial protocol. I agree to conduct the trial according to these regulations and guidelines, to appropriately direct and assist the staff under my control that will be involved in the trial and ensure that all staff members are aware of their clinical trial responsibilities.

Investigator Name _____

Name of Institution _____

Signature _____

Date _____

PROTOCOL SYNOPSIS

NAME OF INVESTIGATIONAL PRODUCT:

Zetomipzomib (KZR-616)

NAME OF ACTIVE INGREDIENT:

Zetomipzomib maleate (KZR-616 maleate)

CLINICAL CONDITION(S)/INDICATION(S):

Active lupus nephritis

PROTOCOL NUMBER:

KZR-616-202

PROTOCOL TITLE:

A Phase 2b, Randomized, Controlled Double-blind, Multicenter Study Comparing the Efficacy and Safety of Zetomipzomib (KZR-616) 30 mg or 60 mg with Placebo in Patients with Active Lupus Nephritis

SHORT TITLE:

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Zetomipzomib in Patients with Active Lupus Nephritis

Study Phase: Phase 2b

STUDY OBJECTIVES:

The overall study objectives are to evaluate the efficacy and safety of zetomipzomib in patients with active Class III or IV (with or without Class V; Class III/IV +/-V) lupus nephritis (LN) and for those with pure Class V LN.

Efficacy: The primary and secondary efficacy objectives are to evaluate the efficacy of zetomipzomib compared with placebo in patients with active Class III/IV +/-V LN on background mycophenolate mofetil (MMF) or equivalent and corticosteroids based upon current guideline-driven standard of care. Patients with pure Class V LN on similar background therapy will also be evaluated as a subgroup.

Safety: The primary safety objective is to determine the safety and tolerability of zetomipzomib in patients with active LN on background standard of care, MMF or equivalent, and corticosteroids.

STUDY DESIGN:

This is a Phase 2b, randomized, double-blind, placebo-controlled, global, multicenter study to evaluate efficacy and safety of zetomipzomib in patients with active Class III/IV +/-V LN or pure Class V. The study will enroll approximately 279 patients: 249 patients with biopsy-proven Class III/IV +/-V LN with urine protein to creatinine ratio (UPCR) ≥1.0 and up to 30 patients with pure Class V with UPCR ≥2.0. Zetomipzomib will be administered at a dose level of 30 mg or 60 mg (the latter following step-up from an initial Week 1 dose of 30 mg). For each dose group, patients will be randomized in a 2:1 ratio to receive either zetomipzomib or placebo administered as a subcutaneous injection once weekly for 52 weeks, followed by a 4-week safety follow-up visit. Each treatment group (30 mg, 60 mg, or placebo) will include approximately 83 patients per group with Class III/IV +/-V and up to 10 per treatment group with pure Class V LN, for a total of up to 279 patients. During the treatment period, patients will also receive background standard of care therapy consisting of MMF or equivalent for 52 weeks plus corticosteroids tapered over 16 weeks (refer to Section 6.2.1.1).

Patients will be evaluated for eligibility according to the inclusion/exclusion criteria within 5 weeks before the first dose of zetomipzomib or placebo on Day 1 (Week 1). Safety will be assessed

throughout the study by monitoring vital signs, physical examinations, and clinical laboratory tests and by recording and analyzing all treatment emergent adverse events (TEAEs) and serious adverse events (SAEs).

Randomization will occur at Day 1 (Week 1) prior to the first dose of zetomipzomib or placebo and will be stratified by:

- LN Class (Class III/IV +/-V and pure Class V)
- Average 24-hour UPCR at the Screening visit (≤3.0 and >3.0)
- Intravenous (IV) methylprednisolone planned total dose (0 to <500 mg, 500-1000 mg, or >1000 to 3000 mg)
  Note: no more than 20% of the patients may be stratified into the >1000 to 3000 mg group)

Zetomipzomib or placebo will be administered subcutaneously once weekly starting on Day 1 (Week 1) through Week 52, followed by a safety visit 4 weeks after the last dose of zetomipzomib or placebo. Zetomipzomib or placebo injections will either be self-administered by the patient/caregiver or via home health service at patient's location, as appropriate, or by the study personnel at the investigational site.

All patients will receive concomitant MMF or equivalent (target dose of 2 g/day) for 52 weeks and oral corticosteroids (0.3 to 0.5 mg/kg/day, maximum of 40 mg/day), which are to be tapered to ≤5 mg/day over 16 weeks (refer to Section 6.2.1.2). Patients will receive IV methylprednisolone (total dose of 1 g for those weighing >45 kg and 500 mg for those weighing ≤45 kg) on Day 1 (+/- 7 days) unless a patient has had IV methylprednisolone within 3 months prior to Screening or at the Investigator's discretion when a patient has had an inadequate response or adverse effects from prior administration (refer to Section 6.2.1.1). A total dose of IV methylprednisolone up to 3000 mg may be permitted.

Samples for sparse pharmacokinetic (PK) collection will be obtained for all patients 2 hours post dose at Week 25 and 0.5 hours post dose at Week 37. In addition, optional PK samples will be obtained in approximately 30 patients at selected centers at Week 5, pre dose and then at 0.5, 1, 2 and 4 hours post dose.

An interim analysis (IA) is planned during the study when approximately 50% of the randomized patients with Class III/IV +/-V LN have completed or would have completed the Week 37 visit. This IA will serve the following purposes: (1) futility analysis and (2) a potential sample size increase up to 50% for patients with Class III/IV +/-V LN based on conditional power. An Independent Data Monitoring Committee (IDMC) will periodically review unblinded patient safety data and the IA results. A Steering Committee will be formed to receive the IDMC recommendations. Details of the IA will be outlined in the statistical analysis plan (SAP).

ENDPOINTS:

Efficacy Endpoints:

The primary efficacy endpoint is the proportion of patients achieving complete renal response (CRR) at Week 37. CRR is defined as:

- A UPCR ≤0.5 in one 24-hour urine sample (for Weeks 13, 25, 37 [primary endpoint], and 53) or 2 consecutive first morning void urine samples (for all other time points).
- An estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 or no confirmed decrease of >20% from Baseline eGFR.

The key secondary efficacy endpoints will evaluate the proportion of patients achieving the following:

- Partial renal response (PRR) (see Section 2.2.1 for definition) at Week 37
- CRR at Week 53
- PRR at Week 53

- CRR at Week 25
- PRR at Week 25

Safety Endpoint:

The primary safety endpoint is the incidence and severity of AEs for each treatment group and patients treated with zetomipzomib compared with placebo.

INVESTIGATIONAL PRODUCT(S), DOSE, AND MODE OF ADMINISTRATION:

Active Product: Zetomipzomib is the active drug product.

Investigational Medicinal Product: Active zetomipzomib drug product or placebo is supplied as sterile lyophilized solids in single-use glass vials. Zetomipzomib or placebo is reconstituted with sterile water for injection (WFI) diluent prior to administration.

Dose and Dose Frequency: Zetomipzomib or placebo will be administered by subcutaneous injection once weekly. For all patients, the first and second doses of zetomipzomib or placebo will be administered at the clinical site. The first injection will be a 30-mg dose of zetomipzomib or placebo for all randomized patients. For patients randomized to 60 mg of zetomipzomib or placebo, the second and subsequent weekly injections will be at a 60-mg dose of zetomipzomib or placebo. Patients randomized to 30 mg of zetomipzomib or placebo will continue to receive the 30-mg dose of zetomipzomib or placebo at all subsequent weekly injections. After the second dose, zetomipzomib or placebo injections will either be self-administered by the patient/caregiver or via home health service at patient's location, as appropriate, or by study personnel at the investigational site.

Control/Comparator: Placebo is used as the comparator.

PATIENT SELECTION:

Targeted Number of Patients: Approximately 249 patients will be enrolled with Class III/IV +/-V LN. Up to 30 additional patients with pure Class V LN may be enrolled, for a total of up to approximately 279 patients.

Planned Number of Sites: Approximately 250 sites are planned to participate in this study.

Inclusion Criteria:

1. Is able to provide written informed consent before any study-related procedures are performed.
2. Is aged ≥18 years at the time of signing the informed consent.
3. Has a body mass index of ≥18 kg/m^2.
4. Has a diagnosis of systemic lupus erythematosus (SLE) according to the 2019 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) criteria (Aringer et al., 2019).
5. Has an unequivocally positive antinuclear antibody (ANA) test result, defined as an ANA titer ≥1:80 (based on Hep-2 immunofluorescence assay or equivalence by enzyme immunoassay assay) and/or a positive anti-double stranded DNA (anti-dsDNA) (≥30 IU/mL based on the enzyme-linked immunosorbent assay) serum antibody test at the Screening visit.
6. Has a diagnosis of LN according to 2003 or 2018 International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria of either:

a. Class III or IV LN as evidenced by renal biopsy performed within 12 months prior to or during Screening. Patients may co-exhibit Class V disease in addition to either Class III or IV disease. For biopsies >6 months prior to the Screening visit, at least 1 of the following must also be present at Screening: low C3, low C4, or anti-dsDNA elevated above the normal range.

b. Pure Class V LN as evidenced by renal biopsy performed within 12 months prior to or during Screening. In addition, a stable dose of a renin-angiotensin-aldosterone system inhibitor (RAASi) anti-hypertensive medication must be used for at least 1 month prior to screening and a systolic blood pressure of ≤130 mm Hg must be present at Screening.

7. Has confirmed proteinuria defined for
   a. Class III/IV +/-V LN with UPCR of ≥1.0 assessed in two 24-hour urine samples during the Screening period at least 7 days apart (see Section 7.2.2.2).
   b. Pure Class V LN with UPCR of ≥2.0 assessed in two 24-hour urine samples during the Screening period at least 7 days apart (see Section 7.2.2.2).
8. Has an estimated glomerular filtration rate as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation (2021) ≥30 mL/min/1.73 m^2.
9. Is willing to be treated with MMF or equivalent and corticosteroid therapy, as described in Section 6.2.1.
10. Has adequate hematologic, hepatic, and renal function assessed by the following:
    a. Absolute neutrophil count ≥1.5×10^9/L (≥1×10^9/L if neutropenia is attributable to lupus disease activity)
    b. White blood cells (WBC) ≥2.0×10^9/L (≥1.5×10^9/L if leukopenia is attributable to lupus disease activity)
    c. Hemoglobin ≥9 g/dL (≥8 g/dL if anemia is attributable to lupus disease activity)
    d. Platelet count ≥50×10^9/L (≥25×10^9/L if thrombocytopenia is attributable to lupus disease activity)
    e. Total bilirubin ≤1.5× upper limit of normal (ULN) (≤3×ULN for patients with documented Gilbert's syndrome)
    f. Aspartate aminotransferase (AST) ≤2.5×ULN
    g. Alanine aminotransferase (ALT) ≤2.5×ULN

    Note: In cases where transient changes in laboratory values may be suspected, clinical laboratory tests may be repeated once during Screening.
    h. For Screening laboratory parameters not listed above, patient has less than a Grade 3 laboratory abnormality based on the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 toxicity scale, except for the following results that are allowed:
       - prothrombin time secondary to warfarin treatment
       - partial thromboplastin time due to lupus anticoagulant and not related to liver disease or anticoagulant therapy
       - proteinuria
       - hypoalbuminemia due to LN and not related to liver disease or malnutrition

11. Women of childbearing potential (WOCBP) who are engaged in heterosexual intercourse must have a negative urine or serum pregnancy test prior to the first dose of zetomipzomib or placebo and must agree to continue to use a highly effective method of birth control during the study. See Section 7.2.4.7 for additional detailed requirements.
12. Male patients with a sexual partner of childbearing potential must be either congenitally sterile or surgically sterile (by vasectomy with documented confirmation of postsurgical aspermia) or willing to use a condom during the study. In addition, their female partner should use another form of contraception (such as an intrauterine device, barrier method with spermicide, or hormonal contraceptive [eg, implant, injectable, patch, or oral]) during the study, unless their partners are infertile or surgically sterile. See Section 7.2.4.7 for additional detailed requirements.

Exclusion Criteria:

1. Has previously received zetomipzomib or previously enrolled in the study (patients may be rescreened once).
2. Has had rapidly progressive glomerulonephritis (in the absence of acute tubulointerstitial necrosis) in the opinion of the Investigator; patient may enroll if a subsequent biopsy demonstrates recovery.
3. Has greater than 50% of glomeruli with sclerosis on any available renal biopsy, tubular atrophy plus interstitial fibrosis exceeding 60% of the renal cortex, or Class III/IV chronic only lesions.
4. Has had dialysis within the 52 weeks prior to Screening.
5. Has active central nervous system manifestations resulting from SLE.
6. Has any overlapping autoimmune condition for which the condition or treatment of the condition may affect the study assessments or outcomes (eg, systemic sclerosis or any condition for which additional immunosuppression is indicated). Overlapping conditions for which the condition or treatment is not expected to affect assessments or outcomes (eg, Sjogren's syndrome) are not excluded.
7. Has a history of antiphospholipid syndrome with a history of thromboembolic event within 52 weeks of Screening.
8. Has a history of unstable disease with thrombocytopenia or at high risk for developing clinically significant bleeding or organ dysfunction requiring therapies such as plasmapheresis or acute blood or platelet transfusions.
9. Has concomitant chronic conditions (excluding SLE and LN), such as asthma or Crohn's disease, that required systemic corticosteroid use in the 52 weeks prior to Screening.
10. Has clinical evidence of significant unstable or uncontrolled acute or chronic diseases (eg, cardiac [including congestive heart failure, hypertension, angina, or history of myocardial infarction], pulmonary [including chronic obstructive pulmonary disease, asthma requiring systemic corticosteroid therapy, pulmonary hypertension, or pulmonary fibrosis], hematologic, gastrointestinal, hepatic, renal, neurological, or infectious diseases [including a history of severe or serious opportunistic infection, including but not limited to ophthalmologic herpes zoster or *Pneumocystis jiroveci* pneumonia]) 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.

11. Has a QT interval with Fridericia's correction (QTcF) >480 msec at the Screening visit.
12. Has any condition, disease, disorder, or clinically relevant abnormality that, in the opinion of the Investigator, would jeopardize the patient's participation in this study, adherence to the protocol, or obscure the effects of treatment.
13. Has a significant or uncontrolled medical disease in any organ system, not related to SLE or LN, that would preclude patient participation.
14. Has known intolerance to MMF ≤1 g/day or equivalent and corticosteroids or inability to take corticosteroids.
15. Has received any of the following other treatments within the indicated timeframes prior to Screening:
    a. Intraarticular therapies, such as corticosteroids or hyaluronic acid preparations: 4 weeks
    b. IV immunoglobulin: 4 weeks
    c. Other nonbiologic immunosuppressive agents, such as cyclophosphamide, cyclosporine, tacrolimus, voclosporin, kinase inhibitors, such as Janus Kinase inhibitors, and adrenocorticotropic hormone: 4 weeks, except for oral mycophenolic acid (MPA) or mycophenolate in any oral formulation (which is permitted) and azathioprine (AZA), which is excluded for the 4 weeks prior to Baseline (Day 1) (see exclusion criteria No. 17a)
    d. Methotrexate: 8 weeks
    e. Belimumab, anifrolumab, abatacept, or atacicept: 12 weeks (4 weeks, if for extra-renal SLE and with Medical Monitor approval)
    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-α antagonists: 12 weeks
    g. Leflunomide: 12 weeks (4 weeks, if active powdered charcoal or cholestyramine was used)
    h. B-cell-depleting therapies (eg, rituximab): 12 weeks, with levels of circulating cluster of differentiation 19+ (CD19+) B cells within normal limits or at or above pre-treatment levels, or 48 weeks
    i. Other immunosuppressive or immunomodulating biologics or investigational drugs (except for denosumab, insulin, and other approved non-immunosuppressive or modulating biologics, which are permitted): 8 weeks or 5 half-lives, whichever is longer
    j. Transfusion with blood, packed WBC, platelets or treatment with plasmapheresis or plasma exchange: 6 weeks
16. Has received any of the following treatments within 4 weeks prior to Baseline (Day 1):
    a. AZA or 6-mercaptopurine
    b. Cholestyramine or other drugs that may interfere with enterohepatic recirculation of MMF
    c. Change in dose of sodium-glucose cotransporter-2 inhibitors (SGLT2i)
17. Has received a live vaccine within 4 weeks prior to Baseline (Day 1) or plans to receive one during the study (note: non-live vaccines are permitted).
18. Has previous use of non-selective proteasome inhibitors (including, but not limited to, bortezomib, carfilzomib, ixazomib) within 24 weeks of Screening or any previous use of an immunoproteasome inhibitor (including, but not limited to, zetomipzomib).

19. Has an active or chronic infection:
    a. Acute or chronic bacterial or fungal infections:
        - Requiring systemic antibiotic or antifungal therapy during the Screening period
        - Requiring hospitalization or a course of IV antimicrobial therapy within 12 weeks prior to Screening
    b. Acute viral illness:
        - Signs and symptoms of acute viral illness must be resolved ≥4 weeks prior to Day 1 (Week 1)
        - If mandated by local conditions and requirements, has a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test (real-time polymerase chain reaction) at Screening and/or Day 1, Week 1. 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 (not including simple oral herpes simplex infection lesions) within 12 weeks prior to Screening or during the Screening period
20. Has a positive test at Screening for human immunodeficiency virus (HIV), hepatitis B (surface antigen, core antibodies), or hepatitis C (anti-hepatitis C virus [HCV] antibody confirmed with hepatitis C ribonucleic acid [RNA]).
    a. Patients with a history of positive testing for HIV are not eligible.
    b. Patients who are hepatitis B virus (HBV) surface antigen (HBsAg) positive are not eligible.
    c. Patients who are HBsAg negative and hepatitis B core antibody (HBcAb) positive will be tested for HBV surface antibody (HBsAb) and HBV DNA:
        - Patients with HBsAb titer ≥100 IU/L and negative hepatitis B DNA may be enrolled.
        - Patients with HBsAb titer <100 IU/L or positive hepatitis B DNA will be excluded.
    d. Patients with Hepatitis C antibodies, with or without treatment, with a positive Hepatitis C RNA will be excluded.
21. Has a positive interferon-gamma release assay (IGRA) (eg, T-SPOT tuberculosis [TB] Test, QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus), at Screening, unless the patient has latent TB, and all the following 3 conditions are true:
    a. Chest x-ray does not show evidence suggestive of active TB disease
    b. No clinical signs and symptoms of pulmonary and/or extrapulmonary TB disease
    c. Completion of an appropriate course of therapy (according to regional/national standards at the time of disease/therapy) prior to Screening that is well documented in the source

    If a QuantiFERON®-TB Gold/Gold Plus is indeterminate for any reason and a local blood test or T-SPOT TB test is negative, the patient may be enrolled using the local result upon approval of the Sponsor. On a case-by-case basis, after discussion and approval by the Sponsor, a local TB test that is negative and is considered equivalent to 1 of the above tests may be used for eligibility. Without a negative test, unless treated as noted above, 1 or more indeterminant tests are not sufficient for the patient to be enrolled.
22. Has a history of malignancy of any type, except for the following:
    a. Surgically excised nonmelanoma skin cancers
    b. In situ cervical cancer fully excised >5 years

c. Prostate cancer considered cured with a normal prostate specific antigen >5 years after prostatectomy
d. Colon cancer considered cured >5 years after surgical treatment
e. Lymphoma with >5 years complete remission

23. Current active drug or alcohol abuse or has a history of drug or alcohol abuse within the 52 weeks prior to Screening, in the opinion of the Investigator.
24. Female patients who are pregnant, planning to get pregnant, or nursing during the study.
25. Has a history of solid organ transplant or planned transplant during the study period.
26. Has not recovered from a previous surgery or has a planned surgery during study period.
27. Has a hypersensitivity to the zetomipzomib or placebo or any of its excipients.

STATISTICAL ANALYSIS:

Study Populations

The intent-to-treat (ITT) population consists of all patients who are randomized in the study. The ITT population will be the primary analysis population used for the efficacy analyses.

The safety population includes all randomized patients (with Class III/IV+/- V and pure Class V LN) who receive at least 1 dose of zetomipzomib or placebo. The safety population will be the population used for the safety analyses.

The per-protocol (PP) population consists of all patients included in the ITT population who have no protocol deviations that may substantially affect the efficacy results. The PP population will be used in efficacy analyses to support the primary efficacy analyses based on the ITT population.

Interim Analysis, Primary Endpoint Analysis and Final Analysis

An IA is planned when approximately 50% of the randomized patients with Class III/IV+/- V LN have completed or would have completed the Week 37 visit.

The primary endpoint analysis will be performed when all patients with Class III/IV+/- V LN have completed or would have completed the Week 37 visit.

The final analysis will be conducted after all patients have completed the study including the safety follow-up visits.

Efficacy Analysis

The primary analysis of each efficacy endpoint will be carried out for randomized patients with Class III/IV+/- V LN (N=249).

A sensitivity analysis for each of the selected efficacy endpoints (i.e., primary, key secondary and selected other efficacy endpoints) will be carried out for all randomized patients including Class III/IV+/- V and pure Class V LN (N= up to 279) and nominal p-values will be presented for hypothesis tests.

For time-to-event variables (eg, time to death or renal-related event, time to CRR, time to PRR, and time to UPCR ≤0.5), the Kaplan-Meier method will be used to estimate survival function, median survival time, and confidence interval (CIs). The log-rank test will be used to compare between 2 survival curves. Cox's proportional hazards model may be performed to assess differences between treatment groups. The model will include terms for treatment and selected Baseline parameters including stratification factors. Binary efficacy endpoints (eg, CRR and PRR) will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors. Patients who have insufficient data for response determination for the time point under consideration will be handled using an estimand approach for intercurrent events or non responder imputation (NRI), where appropriate for that time point. Continuous efficacy endpoints (eg, change or percentage change from Baseline in UPCR by visit) will be analyzed using the longitudinal data analysis method

based on a mixed model for repeated measures (MMRM) approach. All statistical tests will be 2-sided, unless otherwise noted.

In the primary analysis of the primary estimand, the proportion of patients with Class III/IV +/- V LN achieving CRR at Week 37 for the treatment comparison between zetomipzomib and placebo (separately for each of the 2 dose groups and pooled placebo) will be carried out in the ITT population using CMH test at 2-sided 5% level of significance, stratified by the randomization stratification factors (3 factors). Results will be expressed as the number of patients achieving CRR, CRR proportion, weighted difference in CRR proportions, odds ratio, associated 2-sided 95% CI, and p-value (for each pairwise comparison between zetomipzomib and placebo).

Safety Analysis

All TEAEs will be summarized by system organ class, preferred term, severity, and relationship to zetomipzomib or placebo. TEAEs leading to death or to discontinuation from treatment and serious TEAEs will also be tabulated. Summary statistics including cumulative incidence rates of TEAEs and exposure-adjusted incidence rates within each treatment group, and pairwise differences between zetomipzomib and placebo with point estimates and 95% CIs may be provided. Laboratory, vital signs, weight, and electrocardiogram (ECG) data will be summarized descriptively by time point. In addition, shift tables showing the number of patients with values low, normal, and high compared to the normal ranges at Baseline versus post-Baseline will be provided for laboratory tests.

Pharmacokinetic Analysis

Blood samples for assay of zetomipzomib plasma concentrations will be collected periodically. The plasma concentrations of zetomipzomib and its metabolite, KZR-59587, and PK parameters will be listed and summarized by appropriate summary statistics (eg, geometric means, natural log-scale standard deviation [SD], medians, quartiles).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
AE	adverse event
AESI	adverse event of special interest
Ag-Ab	antigen-antibody
AIS	Aggregate Improvement Score
ALT	alanine aminotransferase
ANA	antinuclear antibody
anti-dsDNA	anti-double stranded DNA
ARB	angiotensin receptor antagonist/blocker
AST	aspartate aminotransferase
AZA	azathioprine
BID	twice daily
BLyS	B-lymphocyte stimulator
CBC	complete blood count
CD19+	circulating cluster of differentiation 19+
CEC	Clinical Endpoints Committee
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	coronavirus disease 2019
CMH	Cochran-Mantel-Haenszel
CRR	complete renal response
CWS	Cumulative Worsening Score
CYC	cyclophosphamide
CYP	cytochrome P450
DDI	drug-drug interaction
DM	dermatomyositis
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture

Abbreviation	Definition
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study
EQ-5D-5L	EuroQol 5-Dimension 5-Level
EQ-VAS	EuroQol visual analog scale
ESRD	end-stage renal disease
ETV	Early Termination Visit
EULAR	European Alliance of Associations for Rheumatology
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GTI	Glucocorticoid Toxicity Index
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B virus surface antibody
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IA	interim analysis
ICF	informed consent form
ICH	International Council on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	interferon
IFU	instructions for use
IGRA	interferon-gamma release assay

Abbreviation	Definition
IL	interleukin
IP	investigational product
IRB	Institutional Review Board
ISN	International Society of Nephrology
ITT	intention-to-treat
IV	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KZR-616	zetomipzomib
LDL	low-density lipoprotein
LMP	low molecular mass polypeptide
LN	lupus nephritis
MCP	metacarpophalangeal
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMF	mycophenolate mofetil
MMRM	mixed model for repeated measures
MNAR	missing not at random
MP	methylprednisolone
MPA	mycophenolic acid
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NRI	non-responder imputation
NIH	National Institutes of Health
NSAID	nonsteroidal anti-inflammatory drug
OCT	organic cation transporter
PFS	prefilled syringe
PGA	physician global assessment of disease activity
P-gp	P-glycoprotein
PIP	proximal interphalangeal
PK	pharmacokinetic(s)
PM	polymyositis
PP	per-protocol
PRO	Patient Reported Outcome

Abbreviation	Definition
PRR	partial renal response
QID	four times daily
QTcF	QT interval with Fridericia's correction
RAASi	renin-angiotensin-aldersterone system inhibitor
RBC	red blood cell
RNA	ribonucleic acid
RPS	Renal Pathology Society
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SGLT2i	sodium-glucose cotransporter-2 inhibitor
SIR	systemic injection reaction
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SOP(s)	Standard Operating Procedure(s)
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAE	treatment-emergent adverse event
TID	three times daily
TMA	thrombotic microangiopathy
TNF	tumor necrosis factor
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
US	United States
VAS	visual analog scale
WBC	white blood cell
WFI	water for injection
WHO	World Health Organization
WOCBP	women of childbearing potential

1. INTRODUCTION

Study KZR-616-202 is a Phase 2b, randomized, double-blind, placebo-controlled, global, multicenter study to evaluate the efficacy and safety of zetomipzomib (KZR-616) in patients with active lupus nephritis (LN). In this study, patients will receive subcutaneous injections of zetomipzomib or placebo once weekly for 52 weeks, while receiving background standard of care therapy consisting of mycophenolate mofetil (MMF) or equivalent for 52 weeks and corticosteroids tapered over 16 weeks. In addition, intravenous (IV) methylprednisolone will be administered on Day 1 (+/- 7 days), unless a patient has had IV methylprednisolone within 3 months prior to Screening or at the Investigator's discretion when a patient has had an inadequate response or adverse effects from prior administration (Refer to Section 6.2.1.1). Patients will receive zetomipzomib or placebo at a dose level of 30 mg or 60 mg (the latter following a step-up from an initial Week 1 dose of 30 mg).

1.1. Disease Background

1.1.1. 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 deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and histones, in addition to red blood cells (RBCs), platelets, serum proteins, and phospholipids.

SLE often 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 (US) (Feldman et al., 2013; Helmick et al., 2008; Stojan and Petri, 2018).

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 (Tsokos, 2011; Wallace and Gladman, 2020). 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) (Hochberg, 1997; Tsokos, 2011), with a proposed revision by the Systemic Lupus International Collaborating Clinics (SLICC) (Petri et al., 2012).

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) (Kaul et al., 2016). These ANAs complex with antigens to create antigen-antibody (Ag-Ab) complexes that are deposited in various tissues and initiate inflammatory reactions via complement activation (eg, 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 (eg, 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 nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antimalarials, MMF, azathioprine (AZA), cyclophosphamide (CYC), and aspirin (Hahn, 2011). Among the 3 types of treatments approved for SLE, NSAIDs were approved in 1948; hydroxychloroquine and corticosteroids were approved in 1955; and monoclonal antibodies including belimumab, which targets the B-lymphocyte stimulator (BLyS), and anifrolumab, which targets the type I interferon receptor, were approved in 2011 and 2021, respectively (Lamore et al., 2012; Burki, 2021).

1.1.2. Lupus Nephritis

Lupus nephritis is one of the most serious complications of SLE. Lupus nephritis 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 (Aringer et al., 2019) as described in the European Medicines Agency (EMA) Draft Guideline February 2015 for the treatment of SLE and LN (EMA-Guideline, 2015). Lupus nephritis is associated with considerable morbidity, including an increased risk of end-stage renal disease (ESRD) requiring dialysis or renal transplantation and an increased risk of death. In the US, the prevalence of LN is approximately 4.8 to 78.5 per 100,000(Almaani et al., 2017; Danchenko et al., 2006).

Lupus nephritis 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 widespread sclerosis of the glomeruli associated with ESRD. 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 (ISN/RPS) 2018 classification of LN (Weening et al., 2004; Bajema et al., 2018) (also see Section 13, Appendix 1). Class III and IV, which comprise the targeted population of the current study, are the more aggressive forms of the disease that may lead to poor outcomes. Those with pure Class V LN tend to have more resistant disease and a high rate of complications secondary to nephrotic syndrome.

Management of LN typically consists of induction therapy to achieve remission and long-term maintenance therapy to prevent relapse. European Alliance of Associations for Rheumatology (EULAR) /European Renal Association–European Dialysis and Transplant Association guidelines (Aringer et al., 2019; Hahn et al., 2012) recommend treatment with corticosteroids, including an initial pulse IV methylprednisolone, then oral corticosteroids, in combination with either MMF or low-dose CYC, followed by maintenance treatment with either MMF or AZA (Fanouriakis et al., 2020). These guidelines recommend MMF/mycophenolic acid (MPA) induction to be followed by MMF/MPA maintenance and CYC induction to be followed by either MMF/MPA or AZA; AZA is preferred if pregnancy is contemplated (Fanouriakis et al., 2020). The Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Disease Guideline, Section 10.2.3 on Class III or IV LN has generally similar recommendations for treatment of LN, with a range of glucocorticoid dosing, including a reduced-dose scheme (KDIGO, 2021).

Approximately 50% of patients respond to these treatment regimens with improvement in proteinuria, but only about 25% attain a complete renal response (CRR) that is frequently defined as reduction of urine protein to creatinine ratio (UPCR) to ≤0.5 and stabilization or improvement in serum creatinine, after 1 year of treatment (Rovin et al., 2012; Wofsy et al., 2012). Thus, approximately 75% of patients with LN have a suboptimal 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 (eg, voclosporin or belimumab), in combination with long-term corticosteroids (Dall'Era, 2017; LUPKYNIS, 2021; BENLYSTA, 2022). These patients remain at risk for the development of ESRD, in addition to complications from continued treatment with immunosuppressive agents and long-term corticosteroids.

1.2. Zetomipzomib

Zetomipzomib is a tripeptide ketoepoxide selective inhibitor of the immunoproteasome. It is an analog of ONX 0914 and structurally similar to the US Food and Drug Administration (FDA) approved agent, carfilzomib (KYPROLIS®, 2021). Zetomipzomib demonstrates potent and selective inhibition of the low molecular mass polypeptide 2 and 7 (LMP2 and LMP7) subunits of the immunoproteasome at therapeutically relevant concentrations. Zetomipzomib has no described off-target activities, no significant signals in safety pharmacology studies, and no apparent genotoxic potential.

Selective inhibition of the immunoproteasome 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 both range finding and Good Laboratory Practice (GLP)-compliant toxicity studies, zetomipzomib was well tolerated at doses that resulted in selective and potent inhibition of the immunoproteasome. For further information, refer to the zetomipzomib Investigator's Brochure.

The pharmacokinetics (PK) and pharmacodynamics of zetomipzomib administered by subcutaneous injection have been studied in healthy volunteers and patients with SLE with or without LN, and there were no appreciable differences. Zetomipzomib was approximately 100% bioavailable, and there was low (~25%) inter-subject variability in total exposure. Zetomipzomib is enzymatically metabolized via the ubiquitously expressed microsomal epoxide hydrolase and the major metabolite is an inactive diol. There is limited potential for drug-drug interactions given the rapid clearance of zetomipzomib, the epoxide hydrolase-mediated metabolism, and minimal inhibition of cytochrome P450 (CYP) enzymes. In addition, though zetomipzomib is a weak substrate for P-glycoprotein (P-gp) (MDR1) and organic cation transporter (OCT)1, the rapid clearance likely eliminates concern for co-administration with inhibitors of these pump proteins. There is no observed drug accumulation with weekly dosing. The overall pharmacokinetic profile is consistent with chronic weekly administration in patients with complex disease and/or comorbid conditions.

Once weekly zetomipzomib dosing elicits anti-inflammatory activity without continuous inhibition of immunoproteasome activity as immunoproteasome activity returns to baseline levels in 3 to 7 days after administration. Thus, weekly administration of zetomipzomib, demonstrates anti-inflammatory effects without altering the overall function of the immune system. There are no observed reductions in circulating leukocytes, normal antibody responses to

vaccination and viral clearance following infection are observed in animal models, and no reduction in immunoglobulins are seen in patients.

Safety of zetomipzomib has also been evaluated in studies of patients with SLE with or without LN, and patients with dermatomyositis (DM) and polymyositis (PM). To date, zetomipzomib has been well tolerated in these studies at weekly doses of 45, 60, and 75 mg. Initial subcutaneous doses of zetomipzomib are occasionally associated with at least 1 of the following signs/symptoms regarded as systemic injection reactions (SIRs): hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors, and/or chills. The events are associated with an acute phase-like response, including leukocytosis and elevated C-reactive protein, typically begin within 8 to 24 hours after dosing, and usually resolve within 48 hours of dosing. Although the numbers are small, the percentage of patients reporting treatment-emergent adverse events (TEAEs) of the above-mentioned signs/symptoms appears to be lower in patients who received zetomipzomib as step-up doses and/or with pre/post dose prophylaxis, suggesting that these methods are effective at tolerizing patients to higher doses of zetomipzomib. The most common adverse events (AEs), at any dose, were predominantly injection site reactions such as erythema, induration, and tenderness (pain), which were generally mild and transient in nature. Following 4 weeks of treatment, zetomipzomib did not result in persistent laboratory abnormalities as commonly seen with the dual-targeting proteasome inhibitors (eg, thrombocytopenia, anemia, and neutropenia). Overall, subcutaneous administration of zetomipzomib was well tolerated at doses that resulted in potent and selective inhibition of the immunoproteasome.

In the Phase 1b portion of Study KZR-616-002 in SLE patients with and without nephritis, a total of 47 patients were enrolled across 6 dose-escalation cohorts and improvements from baseline were seen across all efficacy measures analyzed at Week 13. Biomarkers that were abnormal in patients with LN at screening also improved or normalized, including urine protein to creatinine ratio (UPCR) (2 of 2 patients), anti-dsDNA, C3, and C4.

In the Phase 2 portion of Study KZR-616-002, all enrolled patients had active proliferative LN with UPCR ≥1 g/g despite standard of care. Twenty-one patients enrolled, of which 17 received zetomipzomib (30 mg initial step-up dose, followed by 60 mg weekly) for 24 weeks (end of treatment visit at Week 25) and completed through the end of the study (Week 37). Of the 21 patients, 11 of 21 (52.4%) achieved a ≥50% reduction from baseline in UPCR, and 6 of 21 (28.6%) patients achieved a CRR. The treatment benefit was maintained or deepened following cessation of treatment through Week 37, with 15 of 21 (71.4%) patients achieving ≥50% reduction from baseline in UPCR at Week 37. Renal response was observed as early as Week 13 with 10 of 21 (47.6%) patients achieving a reduction of UPCR ≥50% from baseline and CRR in 5 of 21 (23.8%) patients. At Week 37, there were 7 of 21 patients (33.3%) that achieved a CRR (6 patients maintained a CRR from Week 25 and one additional CRR was observed). The primary efficacy endpoint was defined as a responder analysis for at least a 50% reduction in UPCR at Week 25 (1 week following last dose).

Zetomipzomib treatment was associated with clinically meaningful reductions in proteinuria in patients with difficult-to-treat LN. Treatment with zetomipzomib also appears to ameliorate signs and symptoms of SLE. These results were achieved not only in the absence of IV pulse methylprednisolone induction therapy, but also with tapering corticosteroid background therapy despite not being protocol mandated. In addition, since no serious or opportunistic infections and

immune cell depletion were reported, the hypothesis is that treatment with zetomipzomib induces immunomodulation rather than immunosuppression. For detailed information on safety and efficacy of zetomipzomib, refer to the current Investigator's Brochure.

1.3. Rationale for Use of Zetomipzomib in the Proposed Study Populations and Rationale for the Study

It is estimated that about 50% of SLE patients will develop LN within 10 years of their initial diagnosis, which can evolve to ESRD requiring dialysis or renal transplantation and an increased risk of death (Hahn et al., 2012). The use of prednisone or equivalent at a 1 mg/kg initial induction dose with a taper over 6 to 12 months and MMF at 2 g/day is considered standard of care for LN (Almaani and Rovin, 2019). Furthermore, long-term maintenance therapy to prevent relapse using immunosuppressive agents and long-term corticosteroids can lead to complications due to continued treatment. Many patients cannot tolerate the AEs associated with these treatments, especially those of corticosteroids. Therefore, there is a considerable unmet medical need for developing targeted selective and steroid-sparing treatments for patients with LN.

The rationale for the study design is that zetomipzomib, may, in combination with MMF or equivalent and corticosteroids, inhibit LN-associated renal damage mediated by autoantibodies, complement, oxidation, and cell-mediated cytotoxicity.

The Phase 2 portion of Study KZR-616-002 (Phase 1b/2 MISSION; NCT 03393013) examined open-label zetomipzomib 60 mg (following an initial dose of 30 mg) administered as a subcutaneous injection once weekly for 24 weeks in a generally similar population of patients (n=21) with active LN. In this completed study, improvement in UPCR was demonstrated in patients who were on stable background immunosuppressive agents (predominantly MMF and decreasing doses of oral corticosteroids; the average starting dose was approximately 19 mg/day tapered to approximately 9 mg/day). This improvement was maintained for 4 weeks after the last dose of zetomipzomib, 15 of 21 patients achieving ≥50% improvement in UPCR at Week 37. Zetomipzomib treatment was well tolerated, with generally mild to moderate AEs, predominantly injection site reactions, pyrexia, headache, and nausea with or without vomiting. At a lower dose of 30 mg, the pharmacodynamic effect upon immunoproteasome inhibition is still >80%; thus, it is reasonable to also examine this dose. Lower doses with <80% immunoproteasome inhibition are not anticipated to have sufficient inhibition to be effective. Weekly dosing with zetomipzomib 60 mg has shown preliminary evidence of efficacy in patients with LN.

As a response to induction, immunosuppressive agents can take several months to occur in LN and may vary widely; thus, placebo is a necessary comparator. Although it is anticipated that onset of a beneficial effect may be rapid with zetomipzomib, 52 weeks is planned for dosing placebo to determine when the effect first occurs and if the effect increases over the year.

1.4. Rationale for Study Endpoints

The primary efficacy endpoint in this study is CRR, defined as:

- UPCR ≤0.5 in one 24-hour urine sample (for Weeks 13, 25, 37 [primary endpoint], and 53) or 2 consecutive first morning void urine samples (for all other time points).
- An estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2 or no confirmed decrease of >20% from Baseline eGFR.

To be a responder, a patient must complete the study and not be a treatment failure (see Section 2.2.5). UPCR is an objective laboratory measure that is predictive of renal outcome. Reduced UPCR has been associated with repair of renal damage as well as decreased progression to dialysis and ESRD (Dall'Era, 2017).

1.5. Summary of Potential Risks and Benefits

Despite evidence-based care guidelines and increasing therapeutic options, LN poses therapeutic challenges with increased risk of morbidity and mortality (Fanouriakis et al., 2020). Therefore, there is a considerable unmet medical need in LN for developing targeted selective treatments which will reduce renal inflammation and damage, be safe to use as maintenance therapy, and that could reduce or obviate the need for immunosuppressive therapies, including corticosteroids.

The nonclinical pharmacologic, PK, and toxicologic properties of zetomipzomib have been thoroughly evaluated. The nonclinical data supports investigation of zetomipzomib as a selective and irreversible inhibitor of the immunoproteasome, which controls key intracellular processes in immune effector cells in patients with autoimmune diseases, including SLE and SLE-induced nephritis. Zetomipzomib could provide a meaningful potent anti-inflammatory treatment potentially without immunosuppression or significant off-target effects found with currently available therapies.

Zetomipzomib has shown evidence of clinical activity in adult patients with LN (KZR-616-002), showed improvement in proteinuria, reduction in autoantibodies (anti-ds-DNA antibodies), and improvements in extra-renal disease activity.

Patients will be closely monitored for safety. For adult patients with autoimmune diseases who were treated with zetomipzomib, systemic injection reaction is an important potential risk. Systemic injection reaction has presented as hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors, and/or chills. In addition, the most common AE, at any dose were predominantly injection site reactions such as erythema, induration, and tenderness (pain), which were generally mild and transient in nature and did not appear to increase in severity or frequency with repeat dosing of zetomipzomib. Injection site reaction is an identified risk for zetomipzomib. Patients will be monitored for the aforementioned signs and symptoms.

The effects of zetomipzomib on embryogenesis, reproduction, and spermatogenesis in humans are unknown. No formal studies have been conducted with zetomipzomib in pregnant women or during breastfeeding. In nonclinical studies, zetomipzomib tested positive for mammalian chromosomal aberration, but did not have clastogenic activity in animal studies and was not found to have direct teratogenic effects in rats and rabbits. In addition, zetomipzomib had no toxicological effect on mating or fertility in male and female rats. Study patients should be advised to use effective contraception during and after zetomipzomib treatment as described in respective protocols.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of zetomipzomib may be found in the current Investigator's Brochure.

The potential risks identified in association with zetomipzomib are justified by the anticipated benefits that may be afforded to subjects with lupus nephritis.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

The overall study objectives are to evaluate the efficacy and safety of zetomipzomib in patients with active Class III or IV (with or without Class V; Class III/IV +/-V) LN and for those with pure Class V LN. The primary, secondary, and exploratory objectives and endpoints are summarized below.

The primary and secondary efficacy objectives are to evaluate zetomipzomib compared with placebo in patients with active Class III/IV +/-V LN on background MMF or equivalent, and corticosteroids based upon current guideline-driven standard of care. Patients with pure Class V LN on similar background therapy will also be evaluated as a subgroup.

The primary safety objective is to determine the safety and tolerability of zetomipzomib in patients with active LN on background standard of care, MMF or equivalent, and corticosteroids.

The exploratory objectives include the following, each on background standard of care:

- To evaluate the speed of action of zetomipzomib compared with placebo
- To evaluate the clinical benefit of zetomipzomib compared with placebo
- To evaluate changes in serum levels of selected parameters in zetomipzomib compared with placebo
- To evaluate the efficacy of zetomipzomib compared with placebo on clinical lupus disease assessments
- To evaluate the efficacy of zetomipzomib compared with placebo on improving patient's quality of life
- To evaluate relapse in zetomipzomib compared with placebo
- To evaluate glucocorticoid-related AEs in zetomipzomib compared with placebo
- To evaluate renal histopathology and immunohistopathology (at selected sites based on feasibility)
- To evaluate biomarkers
- To evaluate the pharmacokinetics of zetomipzomib

2.2. Study Endpoints

2.2.1. Definitions Related to Efficacy Endpoints

Baseline values for 24-hour UPCR and all other endpoints are defined in Section 10.6.

CRR:

- A UPCR ≤0.5 in one 24-hour urine sample (for Weeks 13, 25, 37 [primary endpoint], and 53) or 2 consecutive first morning void urine samples (for all other time points).

- An eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease of >20% from Baseline eGFR.
- Partial renal response (PRR):
- A ≥50% reduction of UPCR from Baseline, and to <1.0 if the Baseline UPCR was <3.0 or to <3.0 if the Baseline value was ≥3.0.

Responder requirements:

- Should not have received more than 10 mg prednisone or equivalent for ≥3 consecutive days or for ≥7 days in total during the 8 weeks prior to a CRR assessment.
- No use of rescue medication (see Section 6.2.3) or concomitant medication, except those required or permitted (see Sections 6.2.1 and 6.2.2, respectively) sufficient to be a treatment failure (see Section 2.2.5) as determined by the Clinical Endpoints Committee (CEC, see Section 9.10).
- Patient has data available for endpoint assessment.

Relapse: loss of CRR at 2 consecutive time points

Proteinuric flare: doubling from lowest UPCR and (if CRR then >1 or if PRR then >2) at 2 consecutive time points

Time to death or renal-related events: defined as the first occurrence among the following:

1. Death
2. Doubling of serum creatinine
3. Proteinuric flare
4. Renal event-related treatment failure

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients achieving CRR at Week 37.

CRR will be adjudicated by the CEC (Section 9.10). The estimand description is provided in Section 10.6.1.1.

2.2.2.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints will evaluate the proportion of patients achieving the following:

- PRR at Week 37
- CRR at Week 53
- PRR at Week 53
- CRR at Week 25
- PRR at Week 25

2.2.2.3. Other Secondary Endpoints

The other secondary efficacy endpoints include the following:

- Percentage change from Baseline in UPCR by visit
- Time to CRR
- Time to PRR
- Time to death or renal-related events
- Proportion of patients achieving CRR (at Weeks 25, 37, and 53) with successful taper of prednisone or equivalent to ≤5 mg by Week 17
- Proportion of patients achieving CRR (at Weeks 25, 37, and 53) with no use of prednisone or equivalent during the 8 weeks prior to the renal response assessment
- Proportion of patients with UPCR ≤0.5 at Weeks 13, 25, 37, and 53
- Proportion of patients achieving CRR with UPCR ≤ upper limit of normal (ULN) at Weeks 25, 37, and 53
- Change from Baseline in clinical Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, excluding complement and anti-dsDNA components
- Change from Baseline in EuroQol 5-Dimension 5-Level (EQ-5D-5L)

2.2.3. Exploratory Endpoints

The exploratory endpoints for patients treated with zetomipzomib compared with placebo include the following:

- Proportion of patients achieving PRR with successful taper of prednisone or equivalent to ≤5 mg by Week 17
- Proportion of patients achieving PRR with no use of prednisone or equivalent during the 8 weeks prior to the renal response assessment
- Proportion of patients who develop doubling of Baseline serum creatinine, kidney failure (receiving dialysis or kidney transplantation), or death
- Change from Baseline in antibodies (anti-dsDNA antibody, C1q autoantibody) and time to antibodies normalization or negative status (anti-dsDNA antibody normalization, anti-C1q antibody negative status)
- Change from Baseline in complement (C3, C4) and time to complement (C3, C4) normalization status
- Change from Baseline in 24-hour urine protein
- Change from Baseline in serum albumin
- Change from Baseline in serum creatinine
- Change from Baseline in eGFR

- Change from Baseline in serum lipids (serum low-density lipoprotein [LDL] cholesterol, serum total cholesterol, serum triglycerides)
- Change from Baseline in blood hemoglobin A1c (HbA1c)
- Change from baseline in the Glucocorticoid Toxicity Index (GTI) as measured by the Cumulative Worsening Score (GTI-CWS) and the Aggregate Improvement Score (GTI-AIS)
- Proportion of patients with Baseline SLEDAI-2K, excluding renal components, ≥6 with at least a 4-point improvement
- Change from Baseline in SLEDAI-2K
- Change from Baseline in 28-joint counts
- Change from Baseline in physician global assessment of disease activity (PGA) score
- Proportion of patients with relapse or proteinuric flare
- Time to relapse or proteinuric flare
- Proportion of patients with SLE Flare Index of severe, moderate, or mild
- Time to SLE Flare Index of severe, moderate, or mild
- Change from Baseline in renal biopsy histopathology and immunohistopathology (optional)
- Pharmacogenomics profile (ribonucleic acid [RNA] sequencing) and biomarkers, such as serum cytokine levels and circulating leukocytes to be determined in blood samples and urinary biomarkers
- Pharmacokinetics profile

2.2.4. Safety Endpoint

The primary safety endpoint is the incidence and severity of AEs for each treatment group and patients treated with zetomipzomib compared with placebo.

2.2.5. Treatment Failures

The following criteria define treatment failure:

- Prednisone or equivalent beyond that permitted (see Section 6.2.1.2)
- Prednisone or equivalent >10 mg/day for ≥3 consecutive days or for ≥7 days in total during the 8 weeks prior to the renal response assessment
- MMF or equivalent >2 g/day after Week 25
- Requiring rescue therapy (see Section 6.2.3 for details)
- Use of prohibited medications (see Section 6.2.4 and Section 13, Appendix 2 for details)
- Discontinuation of zetomipzomib or placebo

Whenever possible, a complete disease activity assessment (eg, SLEDAI-2K, SLE flare index, PGA) and laboratory assessments (hematology, chemistry, urinalysis, anti-dsDNA, and C3 and C4) should be performed to document flare prior to initiating treatment that results in a treatment failure designation. Treatment failure does not necessarily require discontinuation of zetomipzomib or placebo, thus please refer to Section 8.1.2 for individual patient stopping rules.

3. STUDY DESIGN

3.1. Type and Design of Study

This is a Phase 2b, randomized, double-blind, placebo-controlled, global, multicenter study to evaluate efficacy and safety of zetomipzomib in patients with active Class III/IV +/-V LN or pure Class V LN. The study will enroll approximately 279 patients: 249 patients with biopsy-proven Class III/IV +/-V LN with urine protein to creatinine ratio (UPCR) ≥1.0 and up to approximately 30 patients with pure Class V with UPCR ≥2.0. Zetomipzomib or placebo will be administered at a dose level of 30 mg or 60 mg (the latter following step up from an initial Week 1 dose of 30 mg). For each dose group, patients will be randomized in a 2:1 ratio to receive either zetomipzomib or placebo administered as a subcutaneous injection once weekly for 52 weeks, followed by a 4-week safety follow-up visit. Each treatment group (30 mg, 60 mg, or placebo) will include approximately 83 patients per group with Class III/IV +/-V and up to 10 per treatment group with pure Class V LN, for a total of up to 279 patients. During the treatment period, patients will also receive background standard of care therapy consisting of MMF or equivalent for 52 weeks plus oral corticosteroids tapered over 16 weeks. In addition, all patients will also receive IV methylprednisolone on Day 1 (+/- 7 days), unless a patient has had IV methylprednisolone within 3 months prior to Screening or at the Investigator's discretion when a patient has had an inadequate response or adverse effects from prior administration (refer to Section 6.2.1.1).

Patients will be evaluated for eligibility according to the inclusion/exclusion criteria (Sections 4.2 and 4.3) within 5 weeks before the first dose of zetomipzomib or placebo on Day 1 (Week 1). Safety will be assessed throughout the study by monitoring vital signs, physical examinations, and clinical laboratory tests and by recording and analyzing all TEAEs and serious adverse events (SAEs). Time points for all efficacy and safety assessments are detailed in Appendix 3.

Zetomipzomib or placebo will be administered subcutaneously once weekly starting on Day 1 (Week 1) through Week 52, followed by a safety visit 4 weeks after the last dose of treatment. Zetomipzomib or placebo injections will either be self-administered by the patient/caregiver or via home health service at patient's location, as appropriate, or by study personnel at the investigational site.

All patients will receive concomitant MMF or equivalent (target dose of 2 g/day) for 52 weeks, and oral corticosteroids (0.3 to 0.5 mg/kg/day, maximum of 40 mg/day), which are to be tapered to ≤5 mg/day over 16 weeks.

Patients who have taken MMF or equivalent prior to and upon entering the Screening period will continue to take it at the pre-existing dose, with a target dose of MMF 2 g/day or equivalent (see Section 6.2.1.3 for MMF dosing guidance). Patients who are taking other oral forms of mycophenolate may be switched to MMF after randomization at the Investigator's discretion. All other patients will begin taking MMF at a dose of 1 g/day, which will be increased to 2 g/day after 1 week.

The MMF dose can be increased up to 3 g/day or equivalent (taken as a divided dose, 2 or 3 times a day) if needed for up to 24 weeks in total, up to Week 25, per the Investigator's discretion and after consultation with the Medical Monitor based on the patient's treatment

history and condition. If the patient cannot tolerate the MMF dose, the dose can be decreased to 1 g/day or equivalent per the Investigator's discretion.

Patients will receive IV methylprednisolone (total dose of 1 g for those weighing >45 kg and 500 mg for those weighing ≤45 kg) on Day 1 (+/- 7 days) unless a patient has had IV methylprednisolone within 3 months prior to Screening or at the Investigator's discretion when a patient has had an inadequate response or adverse effects from prior administration (refer to Section 6.2.1.1). A total dose of IV methylprednisolone up to 3000 mg may be permitted.

All patients will also receive 0.3 to 0.5 mg/kg oral prednisone or equivalent, with a dose based upon Investigator's judgment up to a maximum dose of 40 mg/day, on Day 1 (Week 1). For patients who have already been taking prednisone or equivalent at a dose of 40 mg/day or higher at Screening, the dose must be tapered to ≤40 mg/day by Day 1 (Week 1). All patients will initiate a tapering of this prednisone or equivalent dose, starting on Day 15 (Week 3) and should reduce the dose to ≤5 mg/day by Week 17 (Table 2) (see Section 6.2.1.1).

Those patients who exceed a dose greater than 10 mg/day prednisone or equivalent for ≥3 consecutive days or for ≥7 days in total during the 8 weeks prior to the CRR assessment will be considered a treatment failure. Other reasons for which a patient would be considered a treatment failure in this study are defined in Section 2.2.5.

If a disease flare occurs during the study, patients may receive rescue therapy (see Section 6.2.3 for additional details). These patients will be discontinued from zetomipzomib or placebo but will be encouraged to remain in the study as outlined in the Schedule of Assessments (Appendix 3) through End of Study (EOS). Similarly, patients who do not receive rescue therapy but undergo a permanent discontinuation of zetomipzomib or placebo will also be encouraged to remain in the study through EOS. If the patient cannot continue with the planned assessments, the Early Termination Visit (ETV) and the 4-week safety follow-up (EOS) visit will be accomplished at a minimum.

Samples for sparse PK collection will be obtained for all patients at the following time points:

- 2 (±15 minutes) hours post dose at Week 25
- 0.5 (±10 minutes) hours post dose at Week 37

Optional PK samples will be obtained in approximately 30 patients at selected centers at Week 5 at the following time points:

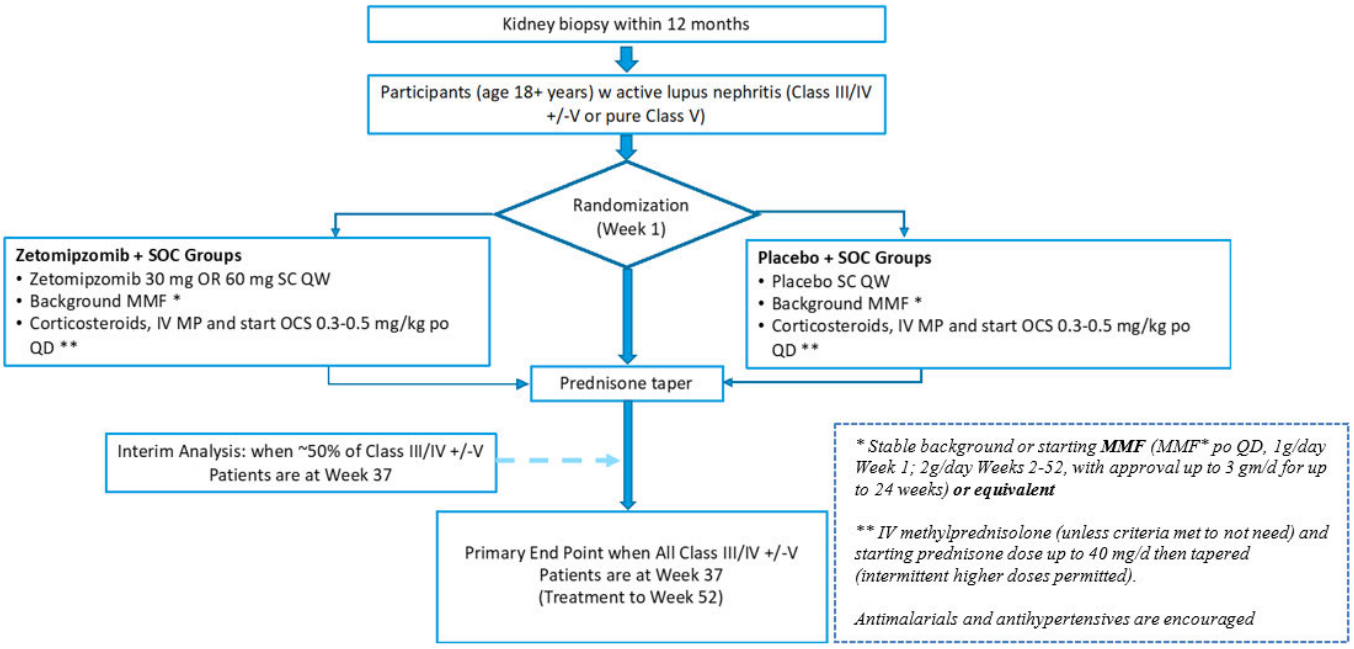
- pre dose and then at 0.5 (±10 minutes), 1 (±10 minutes), 2 (±15 minutes), and 4 (±15 minutes) hours post dose.

There will be an interim analysis (IA) when approximately 50% of the randomized patients with Class III/IV +/-V LN have completed or would have completed the Week 37 visit. This IA will serve the following purposes: (1) futility analysis and (2) a potential sample size increase up to 50% for patients with Class III/IV +/-V LN based on conditional power. An Independent Data Monitoring Committee (IDMC) will periodically review unblinded patient safety data and the IA results. A Steering Committee will be formed to receive the IDMC recommendations. Details of the IA will be outlined in the statistical analysis plan (SAP).

3.1.1. Study Design Schema

The study design schema is presented in Figure 1.

Figure 1: Study KZR-616-202 Study Design Schema



Note: patients will be randomized 2:1 (zetomipzomib 30 mg: placebo) 2:1 (zetomipzomib 60 mg: placebo) with N=83 Class III/IV +/-V patients per dose group (zetomipzomib 30 mg, zetomipzomib 60 mg, and placebo) and up to approximately N=10 pure Class V patients per treatment group. Patients will be stratified by: LN Class, average 24-hour UPCR at the Screening visit, and IV methylprednisolone planned total dose.
IV=intravenous; LN=lupus nephritis; MMF=mycophenolate mofetil; MP=methylprednisolone; OCS=oral corticosteroid; po=oral; QD=once daily; QW=once weekly; SOC=standard of care; SC=subcutaneous; UPCR=urine protein to creatinine ratio.

3.1.2. Study Design Rationale

This is a Phase 2b, randomized, double-blind, placebo-controlled, global, multicenter study to evaluate efficacy and safety of zetomipzomib in patients with active Class III or IV +/- V LN or pure Class V LN. The study is designed to evaluate the efficacy and safety of subcutaneous injections of zetomipzomib once weekly for 52 weeks, in addition to background standard of care therapy consisting of MMF or equivalent and corticosteroids tapered to ≤5 mg/day over 16 weeks.

Patients will be randomized to receive either zetomipzomib or placebo (as described in Section 3.2.1). The study is "double-blind," which means patients, investigators, site staff, and the Sponsor will not know who takes zetomipzomib or placebo (Section 3.2.2).

A placebo-controlled design is scientifically appropriate as it will allow for robust evaluation of any treatment effect of zetomipzomib and characterization of any potential adverse drug reactions. Patients will have close medical observation throughout the study, and rescue

medications will be prescribed if indicated. In addition, only patients for whom it is considered safe to participate in the study, in the opinion of the Investigator, will be permitted to participate.

The study will evaluate efficacy and safety as primary objectives in addition to secondary and exploratory objectives to evaluate other potential clinical benefits and pharmacokinetics. The study is also being conducted using two doses of zetomipzomib (30 mg and 60 mg), each of which will be compared to placebo for efficacy. Based on the efficacy results at each dose, safety data, and PK, the results from this study will also help inform the dose selection for Phase 3.

3.2. Randomization, Blinding, and Unblinding Procedures

3.2.1. Randomization

Study KZR-616-202 is a randomized, double-blind, placebo-controlled study in which patients will be randomized to receive active or placebo treatment.

Once informed consent is obtained, a sequential identification number will be assigned by the site, and the Screening evaluations may begin to assess study inclusion/exclusion criteria (Sections 4.2 and 4.3). The identification number will be used to identify the patient during the Screening process and throughout study participation.

Patients will be randomized to receive either zetomipzomib (30 mg or 60 mg) or placebos in a 2:1:2:1 ratio (zetomipzomib 30 mg: placebo: zetomipzomib 60 mg: placebo). Randomization will occur at Day 1 (Week 1) prior to the first dose of zetomipzomib or placebo and will be stratified by:

- LN Class (Class III/IV +/- V and pure Class V)
- Average 24-hour UPCR at the Screening visit (≤3.0 and >3.0)
- IV methylprednisolone planned total dose (0 to <500 mg, 500-1000 mg, or >1000 to 3000 mg) Note: no more than 20% of the patients may be stratified into the >1000 to 3000 mg group.

3.2.2. Blinding

To preserve the double-blind design, patients randomized to the placebo group will receive a subcutaneous injection in an equivalent volume to the active zetomipzomib (Section 5.1). The dosing schedule in the placebo group will be the same as that of zetomipzomib. All study personnel and patients may know if the patient is on the low dose (30 mg or placebo) or the high dose (60 mg or placebo) of zetomipzomib. Thus, the double-blind nature of this study preserves the blind with respect to active treatment and placebo.

The randomization code key will not be available to the study monitors, project statisticians, or the project team at the Sponsor or its representatives. The study site staff, monitors, and patients will remain blinded until the end of the study. In case of emergency, the unblinding process in Section 3.2.3 should be followed.

3.2.3. Unblinding

In the rare event that a TEAE or pregnancy occurs for which knowledge of the treatment (zetomipzomib or placebo) administered is necessary to manage the patient's condition, the code

for that patient may be broken and the test substance identified. Procedures for unblinding will be provided.

If emergency unblinding is required, the Investigator should contact the Medical Monitor prior to unblinding whenever possible. The Investigator is strongly advised to discuss options with the Medical Monitor or appropriate Sponsor study personnel prior to unblinding. The reason for unblinding must be documented prior to the unblinding. Patients who have been unblinded for pharmacovigilance reporting purposes only will not be discontinued from further receipt of zetomipzomib or placebo.

3.3. Number of Sites

Approximately 250 sites are planned to participate in this study.

4. PATIENT SELECTION AND ENROLLMENT

4.1. Number of Patients

Male and female patients aged ≥18 years with a diagnosis of SLE and biopsy-proven active Class III or IV +/-V LN performed within 12 months prior to or during Screening with UPCR ≥1.0 will be enrolled. Patients may co-exhibit Class V disease in addition to either Class III or IV disease. Approximately 249 patients (83 per treatment group) with Class III/IV +/-V LN with UPCR ≥1.0 will be enrolled. Approximately 30 additional patients (10 per treatment group) with pure Class V LN with UPCR ≥2.0 will also be enrolled for a total of 279 patients.

Patients will be evaluated for eligibility in the study according to the inclusion/exclusion criteria. Patients who fail Screening or do not meet inclusion/exclusion criteria may be rescreened once. The Investigator will ensure that the patient has provided written informed consent before any study-related procedures are performed and before administration of zetomipzomib or placebo.

4.2. Inclusion Criteria

1. Is able to provide written informed consent before any study-related procedures are performed.
2. Is aged ≥18 years at the time of signing the informed consent.
3. Has a body mass index of ≥18 kg/m^2.
4. Has a diagnosis of SLE according to the 2019 ACR/EULAR criteria (Aringer et al., 2019).
5. Has an unequivocally positive ANA test result, defined as an ANA titer ≥1:80 (based on Hep-2 immunofluorescence assay or equivalence by enzyme immunoassay assay) and/or a positive anti-dsDNA (≥30 IU/mL based on enzyme-linked immunosorbent assay) serum antibody test at the Screening visit.
6. Has a diagnosis of LN according to 2003 or 2018 ISN/RPS criteria of either:
    a. Class III or IV LN as evidenced by renal biopsy performed within 12 months prior to or during Screening. Patients may co-exhibit Class V disease in addition to either Class III or IV disease. For biopsies >6 months prior to the Screening visit, at least 1 of the following must also be present at Screening: low C3, low C4, or anti-dsDNA elevated above the normal range.
    b. Pure Class V LN as evidenced by renal biopsy performed within 12 months prior to or during Screening. In addition, a stable dose of a renin-angiotensin-aldosterone system inhibitor (RAASi) anti-hypertensive medication must be used for at least 1 month prior to screening and a systolic blood pressure of ≤130 mm Hg must be present at Screening.
7. Has confirmed proteinuria defined for
    a. Class III/IV +/-V LN with UPCR of ≥1.0 assessed in two 24-hour urine samples during the Screening period at least 7 days apart (see Section 7.2.2.2).
    b. Pure Class V LN with UPCR of ≥2.0 assessed in two 24-hour urine samples during the Screening period at least 7 days apart (see Section 7.2.2.2).

8. Has an eGFR as calculated by the Chronic Kidney Disease Epidemiology Collaboration equation (2021) ≥30 mL/min/1.73 m^2.
9. Is willing to be treated with MMF or equivalent and corticosteroid therapy, as described in Section 6.2.1.
10. Has adequate hematologic, hepatic, and renal function assessed by the following:
    a. Absolute neutrophil count ≥1.5×10^9/L (≥1×10^9/L if neutropenia is attributable to lupus disease activity)
    b. White blood cells (WBC) ≥2.0×10^9/L (≥1.5×10^9/L if leukopenia is attributable to lupus disease activity)
    c. Hemoglobin ≥9 g/dL (≥8 g/dL if anemia is attributable to lupus disease activity)
    d. Platelet count ≥50×10^9/L (≥25×10^9/L if thrombocytopenia is attributable to lupus disease activity)
    e. Total bilirubin ≤1.5×ULN (≤3×ULN for patients with documented Gilbert's syndrome)
    f. Aspartate aminotransferase (AST) ≤2.5×ULN
    g. Alanine aminotransferase (ALT) ≤2.5×ULN

       Note: In cases where transient changes in laboratory values may be suspected, clinical laboratory tests may be repeated once during Screening.
    h. For Screening laboratory parameters not listed above, patient has less than a Grade 3 laboratory abnormality based on the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 toxicity scale, except for the following results that are allowed:
       - prothrombin time secondary to warfarin treatment
       - partial thromboplastin time due to lupus anticoagulant and not related to liver disease or anticoagulant therapy
       - proteinuria
       - hypoalbuminemia due to LN and not related to liver disease or malnutrition
11. Women of childbearing potential (WOCBP) who are engaged in heterosexual intercourse must have a negative urine or serum pregnancy test prior to the first dose of zetomipzomib or placebo and must agree to continue to use a highly effective method of birth control during the study. See Section 7.2.4.7 for additional detailed requirements.
12. Male patients with a sexual partner of childbearing potential must be either congenitally sterile or surgically sterile (by vasectomy with documented confirmation of postsurgical aspermia) or willing to use a condom during the study. In addition, their female partner should use another form of contraception (such as an intrauterine device, barrier method with spermicide, or hormonal contraceptive [eg, implant, injectable, patch, or oral]) during the study, unless their partners are infertile or surgically sterile.
    See Section 7.2.4.7 for additional detailed requirements.

4.3. Exclusion Criteria

1. Has previously received zetomipzomib or previously enrolled in the study (patients may be rescreened once).
2. Has had rapidly progressive glomerulonephritis (in the absence of acute tubulointerstitial necrosis) in the opinion of the Investigator; patient may enroll if a subsequent biopsy demonstrates recovery.
3. Has greater than 50% of glomeruli with sclerosis on any available renal biopsy, tubular atrophy plus interstitial fibrosis exceeding 60% of the renal cortex, or Class III/IV chronic only lesions.
4. Has had dialysis within the 52 weeks prior to Screening.
5. Has active central nervous system manifestations resulting from SLE.
6. Has any overlapping autoimmune condition for which the condition or treatment of the condition may affect the study assessments or outcomes (eg, systemic sclerosis or any condition for which additional immunosuppression is indicated). Overlapping conditions for which the condition or treatment is not expected to affect assessments or outcomes (eg, Sjogren's syndrome) are not excluded.
7. Has a history of antiphospholipid syndrome with a history of thromboembolic event within 52 weeks of Screening.
8. Has a history of unstable disease with thrombocytopenia or at high risk for developing clinically significant bleeding or organ dysfunction requiring therapies such as plasmapheresis or acute blood or platelet transfusions.
9. Has concomitant chronic conditions (excluding SLE and LN), such as asthma or Crohn's disease, that required systemic corticosteroid use in the 52 weeks prior to Screening.
10. Has clinical evidence of significant unstable or uncontrolled acute or chronic diseases (eg, cardiac [including congestive heart failure, hypertension, angina, or history of myocardial infarction], pulmonary [including chronic obstructive pulmonary disease, asthma requiring systemic corticosteroid therapy, pulmonary hypertension, or pulmonary fibrosis], hematologic, gastrointestinal, hepatic, renal, neurological, or infectious diseases [including a history of severe or serious opportunistic infection, including but not limited to ophthalmologic herpes zoster or *Pneumocystis jiroveci* pneumonia]) 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.
11. Has a QT interval with Fridericia's correction (QTcF) >480 msec at the Screening visit.
12. Has any condition, disease, disorder, or clinically relevant abnormality that, in the opinion of the Investigator, would jeopardize the patient's participation in this study, adherence to the protocol, or obscure the effects of treatment.
13. Has a significant or uncontrolled medical disease in any organ system, not related to SLE or LN, that would preclude patient participation.
14. Has known intolerance to MMF ≤1 g/day or equivalent and corticosteroids or inability to take corticosteroids.

15. Has received any of the following other treatments within the indicated timeframes prior to Screening:
    a. Intraarticular therapies, such as corticosteroids or hyaluronic acid preparations: 4 weeks
    b. IV immunoglobulin: 4 weeks
    c. Other nonbiologic immunosuppressive agents, such as cyclophosphamide, cyclosporine, tacrolimus, voclosporin, kinase inhibitors, such as Janus Kinase inhibitors, and adrenocorticotropic hormone: 4 weeks, except for oral MPA or mycophenolate in any oral formulation (which is permitted) and AZA, which is excluded for the 4 weeks prior to Baseline (Day 1) (see exclusion criterion No. 17a)
    d. Methotrexate: 8 weeks
    e. Belimumab, anifrolumab, abatacept, or atacicept: 12 weeks (4 weeks, if for extra-renal SLE and with Medical Monitor approval)
    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. Leflunomide: 12 weeks (4 weeks, if active powdered charcoal or cholestyramine was used)
    h. B-cell-depleting therapies (eg, rituximab): 12 weeks, with levels of circulating cluster of differentiation 19+ (CD19+) B cells within normal limits or at or above pre-treatment levels, or 48 weeks
    i. Other immunosuppressive or immunomodulating biologics or investigational drugs (except for denosumab, insulin, and other approved non-immunosuppressive or modulating biologics, which are permitted): 8 weeks or 5 half-lives, whichever is longer
    j. Transfusion with blood, packed WBC, platelets or treatment with plasmapheresis or plasma exchange: 6 weeks
16. Has received any of the following treatments within 4 weeks prior to Baseline (Day 1):
    a. AZA or 6-mercaptopurine
    b. Cholestyramine or other drugs that may interfere with enterohepatic recirculation of MMF
    c. Change in dose of sodium-glucose cotransporter-2 inhibitors (SGLT2i)
17. Has received a live vaccine within 4 weeks prior to Baseline (Day 1) or plans to receive one during the study (note: non-live vaccines are permitted).
18. Has previous use of non-selective proteasome inhibitors (including, but not limited to, bortezomib, carfilzomib, ixazomib) within 24 weeks of Screening or any previous use of an immunoproteasome inhibitor (including, but not limited to, zetomipzomib).
19. Has an active or chronic infection:
    a. Acute or chronic bacterial or fungal infections:
        - Requiring systemic antibiotic or antifungal therapy during the Screening period
        - Requiring hospitalization or a course of IV antimicrobial therapy within 12 weeks prior to Screening

b. Acute viral illness:
    - Signs and symptoms of acute viral illness must be resolved ≥4 weeks prior to Day 1 (Week 1)
    - If mandated by local conditions and requirements, has a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test (real-time polymerase chain reaction) at Screening and/or Day 1, Week 1. 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 (not including simple oral herpes simplex infection lesions) within 12 weeks prior to Screening or during the Screening period

20. Has a positive test at Screening for human immunodeficiency virus (HIV), hepatitis B (surface antigen, core antibodies), or hepatitis C (anti-hepatitis C virus [HCV] antibody confirmed with hepatitis C RNA).
    a. Patients with a history of positive testing for HIV are not eligible.
    b. Patients who are hepatitis B virus (HBV) surface antigen (HBsAg) positive are not eligible.
    c. Patients who are HBsAg negative and hepatitis B core antibody (HBcAb) positive will be tested for HBV surface antibody (HBsAb) and HBV DNA:
        - Patients with HBsAb titer ≥100 IU/L and negative hepatitis B DNA may be enrolled.
        - Patients with HBsAb titer <100 IU/L or positive hepatitis B DNA will be excluded.
    d. Patients with Hepatitis C antibodies, with or without treatment, with a positive Hepatitis C RNA will be excluded
21. Has a positive interferon-gamma release assay (IGRA) (eg, T-SPOT tuberculosis [TB] Test, QuantiFERON®-TB Gold, or QuantiFERON®-TB Gold Plus), at Screening, unless the patient has latent TB, and all the following 3 conditions are true:
    a. Chest x-ray does not show evidence suggestive of active TB disease
    b. No clinical signs and symptoms of pulmonary and/or extrapulmonary TB disease
    c. Completion of an appropriate course of therapy (according to regional/national standards at the time of disease/therapy) prior to Screening that is well documented in the source

    If a QuantiFERON®-TB Gold/Gold Plus is indeterminate for any reason and a local blood test or T-SPOT TB test is negative, the patient may be enrolled using the local result upon approval of the Sponsor. On a case-by-case basis, after discussion and approval by the Sponsor, a local TB test that is negative and is considered equivalent to one of the above tests may be used for eligibility. Without a negative test, unless treated as noted above, 1 or more indeterminant tests are not sufficient for the patient to be enrolled.

22. Has a history of malignancy of any type, except for the following:
    a. Surgically excised nonmelanoma skin cancers
    b. In situ cervical cancer fully excised >5 years
    c. Prostate cancer considered cured with a normal prostate specific antigen >5 years after prostatectomy
    d. Colon cancer considered cured >5 years after surgical treatment
    e. Lymphoma with >5 years complete remission
23. Current active drug or alcohol abuse or has a history of drug or alcohol abuse within the 52 weeks prior to Screening, in the opinion of the Investigator.
24. Female patients who are pregnant, planning to get pregnant, or nursing during the study.
25. Has a history of solid organ transplant or planned transplant during the study period.
26. Has not recovered from a previous surgery or has a planned surgery during study period.
27. Has a hypersensitivity to zetmipzomib or placebo or any of the excipients.

5. INVESTIGATIONAL PRODUCT INFORMATION

Active zetomipzomib drug product or placebo will be provided. A prefilled syringe (PFS) containing diluent for zetomipzomib or placebo reconstitution may also be supplied as an investigational product (IP). Instructions for the receipt, inspection, storage, preparation, administration, and disposal of the IPs (including zetomipzomib or placebo and PFS) at clinical sites will be provided in a separate Pharmacy Manual.

5.1. Physical Description of Investigational Medicinal Product

Zetomipzomib or placebo is supplied as sterile lyophilized solids in single-use glass vials. Zetomipzomib or placebo is reconstituted with sterile water for injection (WFI) diluent prior to administration. Details of the formulation of zetomipzomib or placebo are provided in the Investigator's Brochure.

Placebo control will be reconstituted with sterile water for injection (WFI) diluent to an equivalent volume as the reconstituted zetomipzomib doses as per the Pharmacy Manual.

5.2. Diluent for Investigational Medicinal Product Reconstitution - Sterile Water for Injection

Commercially available sterile WFI formats may be used as diluent for zetomipzomib or placebo reconstitution. Alternatively, custom-manufactured and Sponsor-supplied PFS containing sterile WFI may be provided.

5.3. Ancillary Items

Ancillary items required for or used to facilitate the at-home reconstitution and administration of zetomipzomib or placebo such as vial adapters, alcohol wipes/swabs, syringes, and needles will be provided by a pharmacy, provided by the clinical site, supplied by the Sponsor, or prescribed by the Investigator.

5.4. Packaging and Labeling

Zetomipzomib or placebo will be packaged in cartons. PFS containing sterile WFI diluent will be packaged in pouches or cartons. All IP and ancillary items will be manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) and relevant regulatory requirements.

5.5. Supply, Dispensing, Storage, and Accountability

Refer to the most current version of the Pharmacy Manual for storage conditions of zetomipzomib or placebo. The current recommended storage condition for zetomipzomib or placebo is 2°C to 8°C. The current recommended storage condition for PFS is controlled room temperature.

Upon receipt of zetomipzomib or placebo, the Investigator (or designee) will conduct an inventory of the supplies and verify that they have been received in acceptable condition and in the correct amounts. The clinical site monitor (Monitor) may verify the study supplies at each study center at any time during the study.

The Investigator (or designee) must confirm that appropriate temperature conditions have been maintained during transit for all zetomipzomib or placebo received and that any discrepancies are reported to sponsor and resolved before their use.

Zetomipzomib or placebo should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions. Unless communicated as permissible by the Sponsor, excursions from labeled storage conditions must be reported to the Sponsor and resolved before use. Access to zetomipzomib or placebo must be limited to the Investigator and delegated authorized site personnel.

Only patients enrolled in the study may receive zetomipzomib or placebo.

The Investigator/Institution is responsible for the accurate and complete accountability and related record maintenance of zetomipzomib or placebo (eg, receipt, dispensing, use, reconciliation, and final disposition records). The Investigator/Institution may delegate some or all of the duties for zetomipzomib or placebo accountability to an appropriate pharmacist or another appropriate individual under the Investigator's supervision.

It is the responsibility of the Monitor to ensure that the Investigator (or designee) has correctly documented the amount of zetomipzomib or placebo received, dispensed, and returned/destroyed. Full IP accountability will be maintained by the site at all times. The Monitor will perform an inventory of zetomipzomib or placebo during the study and at the closeout visit to the site. All discrepancies must be accounted for and documented.

6. DOSAGE AND INVESTIGATIONAL MEDICINAL PRODUCT ADMINISTRATION

6.1. Zetomipzomib or Placebo Administration

Zetomipzomib or placebo will be administered by subcutaneous injection once weekly from Week 1 to Week 52 according to the Schedule of Assessments (Appendix 3). For all patients, the first and second doses of zetomipzomib or placebo will be administered at the clinical site. The first injection will be a 30-mg dose of zetomipzomib or placebo for all randomized patients. For patients randomized to 60 mg of zetomipzomib or placebo, the second and subsequent weekly injections will be at a 60-mg dose level of zetomipzomib or placebo. Patients randomized to 30 mg of zetomipzomib or placebo will continue to receive the 30 mg dose of zetomipzomib or placebo at all subsequent weekly injections.

After the second dose, zetomipzomib or placebo injections will either be administered by the patient/caregiver at home following training or via home health service at the patient's location, as appropriate, or by study personnel at the investigational site.

Proper handling, storing, reconstitution, administration, and disposal of zetomipzomib or placebo must be performed as described in the pharmacy manual or the Instructions for Use (IFU).

Patients/caregivers will be provided with the IFU to ensure proper handling, storage, reconstitution, administration, and disposal of zetomipzomib or placebo and ancillary items dispensed.

6.1.1. Administration Site

Subcutaneous injection sites should be rotated (eg, 4 abdominal quadrants, posterior upper arms, and anterior thighs), and a minimum of 4 weeks should separate injections to the same anatomic site, if possible.

6.1.2. Suggested Measures to Improve Tolerance to Systemic Injection Reactions (SIRs)

Initial subcutaneous doses of zetomipzomib are occasionally associated with at least 1 of the following signs/symptoms regarded as SIRs: hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors, and/or chills. The events are associated with an acute phase-like response, including leukocytosis and elevated C-reactive protein, typically begin within 8 to 24 hours after dosing, and usually resolve within 48 hours of dosing.

Although the numbers are small, the percentage of patients reporting TEAEs of the above signs/symptoms appears to be lower in patients who received zetomipzomib as step-up doses and/or with pre/post dose prophylaxis, suggesting that these methods are effective at tolerizing patients to higher doses of zetomipzomib.

Step-up dosing

All patients randomized to 60 mg in this study will receive an initial dose of 30 mg to be followed weekly by the target dose of 60 mg.

Pre/Post dose prophylaxis

Prophylactic measures may be considered if any of the aforementioned signs and/or symptoms develop and may be used as treatment, either while the patient is at the study site or after the patient leaves the study site. Measures that have been demonstrated to reduce the incidence and severity of infusion-related reactions with other proteasome inhibitors include the following:

- **fluid hydration is strongly encouraged**, eg, 250 to 500 mL oral (or IV, if necessary) of an electrolyte solution up to 48 hours prior to dosing or up to 24 hours after dosing (if symptoms are present)
- antiemetics, nonsedating antihistamines, and/or acetaminophen

If additional guidance for improving initial tolerability symptoms is required, the Medical Monitor should be consulted. Home health service staff do not provide or administer any of the fluids or medications listed above.

6.1.3. Dose Modification Guidelines

6.1.3.1. Dose Reduction

Patients who experience a treatment-related AE at the 60-mg dose of zetomipzomib or placebo will be permitted to undergo dose reduction to the 30-mg dose of zetomipzomib or placebo for subsequent doses at the discretion of the Investigator, in consultation with the Medical Monitor. Patients on the 30-mg dose are not able to have a dose reduction. Approval from the Medical Monitor should be obtained in advance of implementing dose reduction, when possible. After dose reduction is implemented, patients should remain on the reduced dose for at least 2 doses, after which re-escalation to the patient's originally assigned dose should be attempted/ encouraged. If the original dose is not tolerated after re-escalation, a reduced dose may be continued for the remainder of the study at a minimum 30-mg dose of zetomipzomib or placebo, or re-escalation may be reattempted after written approval from the Medical Monitor. Any dose modifications should be documented in the electronic case report form (eCRF) as per Section 9.1.4.

6.1.3.2. Missed Doses

Doses should be administered within the visit windows as per the Schedule of Assessments (Appendix 3). Any doses administered outside the visit window will be considered a protocol deviation; however, if necessary to avoid missing a dose, doses may be administered up to 3 days from the date of the scheduled administration with a minimum of 4 days required between doses.

Patients who meet individual patient stopping rules (Section 8.1.2) may resume administration of zetomipzomib or placebo after discussion between the Investigator and Medical Monitor. Upon resumption of dosing, subsequent doses should be timed according to the original dosing schedule based on Day 1 (Week 1). Patients who are discontinued for missed doses should have their discontinuation recorded in the eCRF based on the reason the doses were missed (eg, AE or protocol non-compliance). The Investigator should contact the Medical Monitor if a patient missed >3 consecutive doses or >7 total doses to determine if the patient should resume administration of zetomipzomib or placebo.

If zetomipzomib or placebo is permanently discontinued due to an AE, the planned assessments (Appendix 3) should continue for the protocol-specified time period. If the patient cannot continue with the planned assessments, the ETV and the 4-week safety follow-up (EOS) visit should be accomplished at a minimum.

6.2. Prior and Concomitant Medications

A concomitant medication is any prescription or over-the-counter preparation, including vitamins and supplements. Any concomitant medications 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 patient's last follow-up visit.

All prior systemic SLE treatment (eg, immunosuppressive agents, antimalarials, and biologics) will be recorded, including corticosteroid use and any topical use from at least the previous 24 weeks prior to Screening. When possible, all prior CYC, MMF, IV methylprednisolone, calcineurin inhibitors (eg voclosporin and tacrolimus), and biologics (eg, belimumab and rituximab) should be recorded. Details to be recorded include, but are not limited to, the concomitant medication generic name, dose, route, frequency of administration, and indication.

Patients should remain stable on their medications during the treatment period, as outlined in the inclusion/exclusion criteria (Sections 4.2 and 4.3) and in this section.

6.2.1. Required Concomitant Medications and Therapies

This section reviews medications that are required or allowed provided the guidelines below are followed. If the concurrent medication requirements are not followed, the patient will be considered a treatment failure (see Section 2.2.5).

Comprehensive education and guidance regarding the use of concurrent standard of care medications (including escalations and tapers, as appropriate) must be provided to the patient at Day 1 (Week 1) and at each scheduled visit. Patient compliance with concurrent medications is essential and will be monitored and recorded in the eCRF. Guidance for patient education and instructions regarding monitoring patient compliance will be provided separately.

Received doses for all systemic corticosteroids are considered as prednisone equivalent. As such, when "prednisone" is used throughout this protocol, it refers to prednisone dose or equivalent.

Patients who deviate from these requirements will be considered treatment failures, as described in Section 2.2.5, except for minor differences (eg, ≤20% deviations) with approval of the Medical Monitor.

6.2.1.1. IV Methylprednisolone

IV methylprednisolone (1 g in a patient weighing >45 kg and 500 mg in a patient weighing ≤45 kg) is to be administered on Day 1 (+/- 7 days) unless already administered in the 3 months prior to screening or at the Investigator's discretion if the patient had:

- a <25% decline in proteinuria (UPCR in a spot or 24-hour urine collection, or total protein in a 24-hour urine collection) >3 months after IV methylprednisolone, or
- a <50% decline in proteinuria (UPCR in a spot or 24-hour urine collection, or total protein in a 24-hour urine collection) >6 months after IV methylprednisolone, or

- sufficiently severe adverse effects from prior IV methylprednisolone (in which case, lower doses may be used).

The dosing of IV methylprednisolone should occur on Day 1 (+/- 7 days) and may be administered in 1 dose or divided into 2 doses (e.g., 500 mg IV twice for those weighing >45 kg and 500 mg once a patient weighing ≤45 kg or 250 mg IV twice in a patient weighing ≤45 kg). Up to 3000 mg divided into up to 3 doses (e.g., 1 g three times) may be administered at the Investigator's discretion with approval of the Medical Monitor.

Earlier dosing of IV methylprednisolone during screening is permitted and dosing should be completed within 14 days. If IV methylprednisolone dosing is given during screening, every effort should be made so that a dose is not administered prior to collection of the Screening 24-hour urine collections, unless deemed to be in the patient's best interest by the Investigator.

6.2.1.2. Oral Corticosteroids

Oral prednisone or equivalent is a required concomitant medication during this study (Table 1). Enteric-coated corticosteroids are not permitted. Patients should be informed of and follow appropriate local practice for this medication including monitoring for adverse effects.

A daily dose of prednisone or equivalent is preferred.

At Day 1 (Week 1), a prednisone or equivalent dose of 0.3 to 0.5 mg/kg/day is required for all patients, with a dose based on Investigator's judgment up to a maximum of 40 mg/day. A dose lower than 0.3 mg/kg/day can be used if higher doses are not in the best interest of the patient, in the opinion of the Investigator, and if below 20 mg/day after consultation with the Medical Monitor. For patients who have already been taking prednisone or equivalent at a dose higher than 40 mg at Screening, the dose must be tapered to 40 mg/day or less (0.3 to 0.5 mg/kg/day) by Day 1 (Week 1). Oral corticosteroids should not be taken on a day that a patient is receiving IV methylprednisolone.

Beginning on Day 15 (Week 3), the prednisone or equivalent dose is to be tapered every 2-4 weeks to ≤5 mg/day by Week 17, as outlined in Table 2. Decreases in dosing per the taper schedule should be done within ±3 days of planned timeframe. Phone calls by site personnel can be made between the scheduled on-site visits to facilitate the taper.

A 4-week stable dose or an increase to the prior prednisone or equivalent dose is permitted for lack of response (no or minimal improvement in UPCR per Investigator discretion over 2 visits separated by at least 4 weeks). In addition, the dose can be tapered faster due to adverse effects experienced due to the corticosteroid or due to clinical or renal improvement as assessed by the Investigator, including a tapering of the prednisone or equivalent dose to zero (discontinue).

While the recommended taper is to ≤5 mg/day by Week 17, the overall goals are for the patient to be at a dose of prednisone or equivalent dose to be ≤10 mg/day by Week 25, and for 8 weeks prior to the primary endpoint (Week 37) and ideally to the end of treatment (Week 53).

Investigators are encouraged to taper to discontinuation if clinically appropriate throughout the study.

Table 1: Summary of Prednisone Equivalents

Corticosteroid	Prednisone Equivalent (mg)
Prednisone	20
Betamethasone	2.4
Cortisone acetate	100
Dexamethasone	3
Hydrocortisone	80
Methylprednisolone	16
Prednisolone	20

Note: If other oral corticosteroids are used, then Medical Monitor approval is required to determine the prednisone equivalents

Table 2: Recommended Oral Corticosteroid Taper Schedule

Study Week (±3 days)	Prednisone or Equivalent Dose if starting at 20 mg/day	Prednisone or Equivalent Dose Maximum (mg/day)
1	20	0.3 to 0.5 mg/kg/day, maximum of 40 mg/day
2	20	40
3[a]	17.5	35
4	17.5	35
5	15	30
6	15	30
7	12.5	25
8	12.5	25
9	10	20
10	10	20
11	10	15
12	10	15
13	7.5	10
14	7.5	10
15	7.5	7.5
16	7.5	7.5
17	5	5

[a] All patients will initiate a tapering of the prednisone or equivalent dose, starting on Day 15 (Week 3) and continuing every 2-4 weeks. The taper should start at the line/row where the patient's current dose resides.
Faster tapering is permitted.
Note: On a day when IV methylprednisolone is administered, oral corticosteroid should not be taken.

Up to 2 additional treatment courses of any systemic corticosteroids separate from the initial dose and recommended taper are permitted if:

- There is an interval of at least 12 weeks between each additional treatment (>10 mg/day)
- The treatment is for SLE (not LN) at a dose of ≤20 mg/day for up to 7 days
- The treatment is for reasons other than SLE or LN ≤100 mg/day (oral or injection) for up to 3 days
- Following treatment with higher doses, the dose returns to ≤10 mg/day over 14 days or less
- Medical Monitor approval has been received for minor differences as described above (eg, ≤20% deviations)

6.2.1.3. Mycophenolate Mofetil

Patients will receive background standard of care of "MMF or equivalent," which refers to MMF, MPA, and mycophenolate sodium. MMF 1 g is equivalent to mycophenolate sodium 720 mg.

Oral MMF is a required concomitant medication after randomization, unless the patient is taking equivalent doses of other oral forms, such as MPA and mycophenolate sodium. Patients who are taking other oral forms of mycophenolate may be switched to MMF after randomization at the Investigator's discretion. Patients should be informed of and follow appropriate local practice for this medication, including laboratory monitoring and contraception. MMF will be provided at the sites, or the costs of MMF up to 3 g/day or equivalent will be reimbursed.

Twice daily (BID), 3 times daily (TID) and 4 times daily (QID, if needed due to gastrointestinal AEs) dosing are permitted. The target dose is 2 g/day (e.g., 1 g BID), with doses from 1 g/day to 3 g/day permitted with consultation of the Medical Monitor.

Patients receiving MMF should continue their current dose or, if receiving >2 g/day, will decrease the dose to 2 g/day on Day 1 (Week 1) unless a higher dose (up to 3 g/day) is approved by the Medical Monitor. If >2 g/day is permitted, this dose will not be continued for more than 24 weeks in total nor after Week 25.

For patients who are not currently receiving MMF or equivalent, they will start MMF during the first week (after Week 1 dose of zetomipzomib or placebo) at 1 g/day (0.5 g BID) and increase to 2 g/day (e.g., 1 g BID) during the second week (after Week 2 dose of zetomipzomib or placebo). A complete blood count (CBC) must be performed locally after starting or dose increases. In patients who were not already taking MMF or equivalent at Screening and thus started MMF after randomization, a CBC must additionally be done locally at approximately Weeks 2, 3, and 4 and as per local practice thereafter. After dose increases of MMF or equivalent, CBC must be monitored as per local practice. To aid in distinguishing possible gastrointestinal adverse effects, such as nausea, it is recommended to wait 2 days after the first and second doses of zetomipzomib or placebo, before MMF is started (Day 3) or increased (Day 10), respectively. If a MMF dose of at least 1 g/day is not tolerated, then the patient may be switched to other equivalent forms of mycophenolate at the Investigator's discretion. If a dose of MMF or

equivalent <1 g/day is use, then the Medical Monitor should be contacted to assess the appropriateness of continuing zetomipzomib or placebo.

Changes to the dose of MMF are not permitted after Week 25, unless for tolerability issues.

6.2.2. Permitted Concomitant Medications and Therapies

Patients should continue all concomitant medications related to SLE therapy throughout the study as outlined in the inclusion/exclusion criteria (Sections 4.2 and 4.3) and in this section.

- All permitted agents including antimalarials should be continued at a stable dose except when change is deemed necessary by the treating physician or Investigator, or if access is limited due to supply issues.
- Intraarticular or intrabursal corticosteroid injections are permitted when deemed necessary by the treating physician or the Investigator.
- Topical corticosteroids, topical calcineurin inhibitors, and other topical agents are permitted.
- Inhaled corticosteroids and other inhaled treatments are permitted.

Other concomitant medications for comorbid conditions, such as antihypertensives, SGLT2i, or lipid lowering agents, are permitted. The patient should be advised to maintain a stable dosage regimen for antihypertensive medication(s) (such as angiotensin receptor antagonist/blocker [ARB]/angiotensin converting enzyme [ACE] inhibitor), SGLT2i (gliflozins), lipid lowering agents (such as statins), and NSAIDs unless the dosage adjustment is clinically necessary (eg, to control hypertension or for intolerance).

6.2.2.1. Antimalarials

Antimalarials (eg, hydroxychloroquine, chloroquine, and quinacrine) are encouraged and permitted as per local dosing guidelines if they are started on or before Week 25. One antimalarial at a time is permitted. The dose and type should remain stable unless due to tolerability/AEs or availability, but it may be changed if started on or before Week 25.

6.2.2.2. Antihypertensives

RAASi including ACE inhibitor, ARB and DRI use is allowed in this study. Investigators are encouraged to consider whether the patient might benefit from ACE inhibitors, ARBs or DRIs, or a combination therapy that includes these agents, to treat hypertension or SLE-related nephropathy. Since these medications may confound efficacy assessment by mimicking renal deterioration (eg, increased serum creatinine) or improving renal function (eg, beneficial remodeling of renal parenchyma), the following guidelines should be applied.

The target blood pressure for patients in this study is systolic blood pressure ≤130 mmHg and diastolic blood pressure ≤80 mmHg. Thus, titration of dose to obtain therapeutic effect on blood pressure is allowed.

ACE inhibitors, ARBs and DRIs, which are considered interchangeable for this study, are encouraged and permitted for the treatment of hypertension. An ACE inhibitor, ARB or DRI will

be considered new if started after Week 25. The dose and type should remain stable unless due to tolerability/AEs or availability, but these may be changed if started on or before Week 25.

Other antihypertensive agents are permitted, but it is strongly recommended to include an ACE inhibitor, ARB or DRI in combination with other agents.

Initiation of new antihypertensive agents other than ACE or ARB is permitted.

6.2.3. Rescue Therapies

Rescue therapy is defined as any modification to the background LN treatment, including dose or frequency increases in concomitant medications, or initiation of a new medication, except as permitted (Section 6.2.2).

If disease flare occurs during the study, patients may receive rescue therapy including, but not limited to, cytotoxic therapy (such as CYC), IV methylprednisolone (see Section 6.2.1 for permitted doses), B-cell targeting monoclonal antibodies (such as rituximab), calcineurin inhibitors (such as tacrolimus and voclosporin) if the Investigator believes that it is in the best interest of the patient. Any rescue therapy administered should be recorded in the eCRF as concomitant medications. These patients should be discontinued from zetomipzomib or placebo, but will be encouraged to remain in the study as outlined in the Schedule of Assessments (Appendix 3) through the EOS visit. If the patient cannot continue with the planned assessments, the ETV and the 4-week safety follow-up (EOS) visit will be accomplished at a minimum.

6.2.4. Prohibited Concomitant Medications and Therapies

The use of any investigational agents or devices is prohibited. Plasma exchange/plasmapheresis and live-attenuated vaccines are also excluded. Please refer to Section 13, Appendix 2, for a list of prohibited medications and their associated wash-out periods prior to Baseline.

Concomitant use of any immunosuppressive agent other than corticosteroids and those listed in Sections 6.2.1 and 6.2.2 is prohibited during the study. Patients who require other immunosuppressive agents during the study will be discontinued from the zetomipzomib or placebo but will be encouraged to remain in the study as outlined in the Schedule of Assessments (Appendix 3) through EOS. If the patient cannot continue with the planned assessments, the ETV and the 4-week safety follow-up (EOS) visit will be accomplished at a minimum.

Cholestyramine or other drugs that may interfere with enterohepatic recirculation of MMF are prohibited.

6.2.5. Potential Drug-Drug Interactions

Zetomipzomib has a half-life of less than 5 hours in humans and is metabolized extra-hepatically by the ubiquitously expressed epoxide hydrolase. A very weak inhibition of CYP P-gp has been observed but is unlikely to be of clinical significance. No formal interaction studies with P-gp inhibitors have been performed; however, no drug-drug interactions (DDIs) are predicted. All efforts will be made to observe if any occur.

6.2.6. Vaccinations

Zetomipzomib is not anticipated to impact the response to vaccinations. It is strongly recommended that patients be up to date on immunizations per current 2022 ACR guidelines for

rheumatoid arthritis (Singh et al., 2016) and to follow local guidelines for SARS-CoV-2 vaccination prior to Screening. If vaccinations are recommended and received during the study, they should be recorded in the eCRF. Live-attenuated vaccinations are not permitted during the study or within 4 weeks prior to Baseline (Day 1). If vaccination against herpes zoster is required during the study, Shingrix or other non-live vaccine (if available) is preferred over live vaccines. Similarly, vaccination against influenza virus with inactivated vaccine is preferred.

If a patient requires the SARS-CoV-2 vaccine during the study, no interruption of zetomipzomib or placebo is required for the purpose of vaccination. If it is possible to schedule SARS-CoV-2 vaccine administration with respect to zetomipzomib or placebo administration, the following is recommended when feasible:

- If zetomipzomib or placebo is administered in an extremity, the vaccine should be administered in an extremity other than the one used for zetomipzomib or placebo injection that week.
- If symptoms related to zetomipzomib or placebo administration are present, it is recommended to administer the vaccine when the symptoms are resolved or resolving.
- For patients who have received at least 3 doses of zetomipzomib or placebo, ideally 2 days should separate administration of zetomipzomib or placebo and the vaccination to permit sufficient time to distinguish potential adverse effects.
- For patients who have received less than 3 doses of zetomipzomib or placebo, ideally 3 days should separate administration of zetomipzomib or placebo and the vaccination to permit sufficient time to distinguish potential adverse effects.

7. STUDY EVALUATIONS

7.1. Schedule of Assessments

Efficacy and safety assessments will be performed, and zetomipzomib or placebo will be administered according to the Schedule of Assessments (Appendix 3). A safety follow-up visit will occur 4 weeks after the last dose of zetomipzomib or placebo (EOS visit). In addition, monthly visits at Weeks 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53, as well as the EOS visit (Week 56) and the ETV, must all be performed at the investigational site. All other study visits may occur either at the investigational site or the patient's location.

The first and second doses of zetomipzomib or placebo must be administered at the investigational site on Day 1 (Week 1) and Week 2. Following Week 2, zetomipzomib or placebo injections will either be self-administered by the patient/caregiver or via home health service at patient's location, as appropriate, or by study personnel at the investigational site.

7.1.1. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing following abnormal clinical laboratory results, for follow-up of AEs, or for other reasons, as warranted. During an unscheduled visit, information regarding concomitant medications and AEs (at a minimum) will be collected. A brief physical examination should also be performed. Any of the other procedures listed for the Week 53 visit may also be performed at the Investigator's discretion.

Additional contact with the patients may occur, and is encouraged, during the initial dose, subsequent taper, or after other changes to the corticosteroid dose. Similarly, additional contact and laboratory testing to monitor patients after starting or changing the dose of MMF or equivalent should be done per local practice, especially at Weeks 2 through 4.

7.1.2. Telehealth Visits

While the study visits in Appendix 3 are mandatory, sites may optionally elect to use a combination of telemedicine and/or home health services (as permitted by their institutions and/or local regulations) to conduct these visits. With the exception of the visits listed in Section 7.1, all other weekly zetomipzomib or placebo injections may occur at the investigational site or optionally at the patient's location.

For telehealth visits, weight will not be measured, and a brief physical examination will be performed. All other assessments will be performed, if feasible. Samples for clinical laboratory tests will be collected by home health services and sent to the central laboratory.

7.2. Study Procedures and Assessments

All patients must be provided an informed consent form (ICF) describing the study with sufficient information for them to make an informed decision regarding their participation as per Section 11.3. Informed consent must be signed prior to any procedures for the study. All study procedures and assessments should be performed according to the Schedule of Assessments presented in Appendix 3.

If a patient is not able to come to the site for an on-site visit as per the Schedule of Assessments (Appendix 3), a telehealth visit should occur (see Section 7.1.2).

7.2.1. 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 sex). Historical SLE disease data and diagnostic information should include the following:

- Year of diagnosis
- EULAR/ACR classification criteria for SLE diagnosis
- Historical medications for SLE treatment (eg, immunosuppressive agents, antimalarials, and biologics) including start/stop date, dosage, and reasons for discontinuation, etc.
- History of disease-specific measurements (eg, UPCR and eGFR)
- Date and results of renal biopsy or biopsies

7.2.2. Efficacy Assessments

Efficacy assessments will be performed at the visits specified in the Schedule of Assessments (Appendix 3).

7.2.2.1. Estimated Glomerular Filtration Rate

Patients will have eGFR calculated based on the following Chronic Kidney Disease Epidemiology Collaboration formula (Inker et al., 2021).

$eGFR = 142 \times \min(\text{standardized } S_{cr}/\kappa,1)^{\alpha} \times \max(\text{standardized } S_{cr}/\kappa,1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female]

Where:

- S_{cr} is serum creatinine in mg/dL
- κ is 0.7 for females and 0.9 for males
- α is -0.241 for females and -0.302 for males
- min indicates the minimum of S_{cr}/κ or 1
- max indicates the maximum of S_{cr}/κ or 1

7.2.2.2. Proteinuria Evaluation

Proteinuria will be evaluated via spot UPCR (first morning void) and 24-hour urine collection.

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 criteria in order to be eligible. If 1 of these samples fails to demonstrate UPCR levels meeting protocol inclusion criteria, then an additional 24-hour urine collection sample may be obtained at least 7 days from the last sample taken. At least one 24-hour urine collection should be within 14 days

of randomization; an additional 7 days (up to 21 days total) may be permitted if approved by the Medical Monitor or the Sponsor. In addition, a first morning void sample will also be collected at these same time points for a spot UPCR.

Baseline UPCR will be determined by the average of the 24-hour collections at Screening.

Once enrolled, 24-hour urine samples will be collected according to the Schedule of Assessments (Appendix 3). Patients should be instructed to return the chilled 24-hour urine sample to the site 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.

After Day 1 (Week 1), the 24-hour urine collection sample will be used to assess UPCR level at the specified visits. If the clinical laboratory test results indicate that a urine collection sample is inadequate at any time point, then the spot UPCR obtained from the first morning void sample may be used instead for assessments performed after Day 1 (Week 1).

The 24-hour urine collection sample may be postponed up to 14 days at the discretion of the Investigator if menstrual bleeding or a genitourinary tract infection is present at time of urinalysis or anytime during the collection.

In the case that any 24-hour urine collection is missed after randomization, it is suggested to collect a replacement 24-hour urine within 4 weeks from the missed collection date.

7.2.2.3. Immunological Variables and Biomarkers

Along with serum albumin, serum creatinine, serum LDL cholesterol, serum total cholesterol, serum triglycerides, HbA1c, and urine protein, patients will be tested for serum levels of the following immunological variables:

- Anti-dsDNA
- Complement (C3 and C4)
- C1q autoantibody
- Quantitative immunoglobulins (immunoglobulins M, G, and A)

7.2.2.4. Clinical Lupus Disease Assessments

7.2.2.4.1. Systemic Lupus Erythematosus Disease Activity Index and Flare Index

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. 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. An 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 (eg, chart, worksheet, clinic notes, and

laboratory results) at each visit. The SLEDAI-2K will have a minimal requirement for 2 inflamed joints to score arthritis.

An SLE Flare Index based on SLEDAI-2K and Investigator assessment for mild, moderate, and severe flares will be assessed.

Additional details for SLEDAI-2K and SLE Flare index will be provided.

7.2.2.4.2. 28-Joint Count

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

7.2.2.4.3. Physician Global Assessment of Disease Activity

The Physician Global Assessment (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 PGA performed at the same visit.

7.2.2.5. EuroQol 5-Dimension 5-Level (Patient Reported Outcome Measure)

The EQ-5D-5L is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D-5L consists of a descriptive system and the EuroQol visual analog scale (EQ-VAS).

The descriptive system comprises 5 levels of severity for each of 5 dimensions (ie, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The EQ-VAS records the patient's self-rated health on a vertical VAS. This can be used as a quantitative measure of health outcome that reflects the patient's own judgment. The scores on these 5 dimensions can be presented as a health profile or converted to a single summary index number (utility) reflecting preferability compared to other health profiles. Collection of Patient Reported Outcome (PRO) measures may be performed using technology other than EDC.

7.2.2.6. Renal Histopathology and Immunohistopathology

Renal histopathology and immunohistopathology, including, but not limited to, hematoxylin and eosin staining, and immunohistochemical pathology with T-, B-, and other immune effector cells markers must be performed during the Screening period if it was not performed 12 months prior the study.

Optional renal histopathology and immunohistopathology may be performed at Week 53 (EOT visit) or ETV.

Local reports of the renal biopsy are sufficient for inclusion. A central review of renal biopsies may also be performed as part of exploratory analyses. Additional details of the central review will be provided.

7.2.2.7. Biomarker Measurements

7.2.2.7.1. Cytokine Activity

Blood samples will be collected for assessment of cytokine activity and circulating leukocytes as specified in the Schedule of Assessments (Appendix 3).

7.2.2.7.2. Gene Expression/Pharmacogenomics

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 (Appendix 3) 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 zetomipzomib 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. These results may be reported in the separate report.

7.2.2.7.3. Urine Biomarker

A portion of 24-hour urine and urinalysis collections will be utilized by the central laboratory to identify biomarkers for response and/or safety. Urine collections are specified in the Schedule of Assessments (Appendix 3), and a urine sample will be separated for storage and analysis at a later date to the extent permitted by the national and/or local laws and regulations.

7.2.2.8. Glucocorticoid Toxicity Index

The GTI is a comprehensive, outcome-based glucocorticoid toxicity monitoring instrument developed by a multidisciplinary team of international experts (Jayne et al., 2021).
The instrument calculates a composite index score from data captured related to the following domains: body mass index, glucose tolerance, blood pressure, lipids, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection. In addition, reports of any of the following toxicities are included in the index: endocrine (adrenal insufficiency), gastrointestinal (perforation, peptic ulcer disease), musculoskeletal (ruptured tendon, avascular necrosis), and ocular (retinopathy, increase in ocular pressure, posterior subcapsular cataract).
Additional details will be provided.

The GTI instrument uses 2 GTI scores: the Cumulative Worsening Score and the Aggregate Improvement Score, referred to as GTI-CWS and GTI-AIS, respectively.

7.2.3. Pharmacokinetic Assessments

Blood samples will be drawn on a subset of ~50 patients as outlined in the Schedule of Assessments (Appendix 3). Samples will be used to measure the plasma concentration of zetomipzomib and its metabolite KZR-59587 (area under the time-concentration curve [AUC],

maximum concentration [C_{max}], time to maximum plasma concentration [T_{max}]), and other PK calculations). At the visits and times specified, blood samples of approximately 4 mL will be collected. Additional information regarding sample collection and handling are outlined in the Laboratory Manual.

Samples collected to measure investigational product concentration and metabolism will be retained for as long as legally permitted in the country of origin or until Sponsor decision to destroy.

7.2.4. Safety Assessments

Safety will be assessed throughout the study by monitoring of vital signs, physical examinations, and clinical laboratory tests and by recording and analyzing all AEs and SAEs.

7.2.4.1. Vital Sign Measurements

Systolic and diastolic blood pressure, pulse rate, and body temperature will be measured at the visits specified in the Schedule of Assessments (Appendix 3). Blood pressure and pulse rate should be collected after the patient has had at least 10 minutes of rest in the supine position. If the blood pressure is elevated on the first measurement at Screening and Day 1 (Week 1), then it should be repeated after at least an additional 5 minutes of rest. It is recommended that blood pressure is measured using the same arm at each assessment. When the time of vital signs measurement coincides with a blood sample collection, the vital signs will be measured before blood sample collection or zetomipzomib or placebo administration. A second set of vital signs must be obtained on the Day 1 (Week 1) visit 30 minutes (±15 minutes) after zetomipzomib or placebo has been administered.

7.2.4.2. Body Weight and Height

When possible, body weight will be recorded at the visits specified in the Schedule of Assessments (Appendix 3). Body weight, with the patient wearing light clothing and the shoes and jacket or coat removed, will be measured and recorded in kilograms.

Height will be measured at the Screening visit only, and body weight will be collected throughout the study.

7.2.4.3. Physical Examination

A full physical examination will be performed at the Screening visit. A complete physical examination should include assessments of at least the following systems: general appearance, head, ears, eyes, nose and throat, neck, dermatological, respiratory, cardiovascular, abdomen, extremities, neurological, and musculoskeletal.

At other visits specified on the Schedule of Assessments (Appendix 3) (including unscheduled visits), a symptom-directed brief physical examination will be completed. Medically significant changes from the physical examination will be recorded as AEs. Muscle evaluation findings captured in the muscle assessment instruments will not be recorded unless they are classifiable as SAEs, as per Section 9.2.1.

7.2.4.4. Electrocardiogram

A 12-lead electrocardiogram (ECG) with QTcF interval should be completed at Screening, Week 25, Week 53, and ETV, prior to vital signs, following 10 minutes of supine rest. At Week 25, the ECG should be completed between 30 minutes to 4 hours post dose. Additional (optional) 12-lead ECGs may be performed at other visits, as indicated per the Investigator's discretion.

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 ECG at the Screening visit will be recorded as an AE.

7.2.4.5. 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 90 days prior to signing informed consent form. A chest x-ray that has no evidence of malignancy, active infection, or unexpected clinically significant abnormalities (unless due to SLE) is required for enrollment.

7.2.4.6. Clinical Laboratory Tests

Clinical laboratory tests for safety (eg, hematology, serum chemistry, urinalysis, and coagulation) and clinical laboratory tests for efficacy measures such an assessment of immunological variables and biomarkers will be performed at a central laboratory at the visits specified in the Schedule of Assessments (Appendix 3).

A listing of the clinical laboratory tests evaluated for safety is provided in Table 3.

Table 3: Clinical Laboratory Tests for Safety

Hematology	Serum chemistry (non-fasting)	Urinalysis	Coagulation and Other
hemoglobin hematocrit WBC count (total and differential) RBC count reticulocyte count platelet count MCV MCH MCHC	creatinine creatine kinase urea (or BUN) AST ALT GGT alkaline phosphatase LDH total bilirubin albumin total protein sodium bicarbonate potassium chloride glucose	pH glucose ketones blood protein creatinine microscopy leukocyte esterase nitrite	INR APTT fibrinogen lupus anticoagulant panel HbA1c

Hematology	Serum chemistry (non-fasting)	Urinalysis	Coagulation and Other
	uric acid total cholesterol LDL cholesterol triglycerides magnesium calcium phosphorus C-reactive protein		

ALT=alanine aminotransferase; APTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma-glutamyl transferase; HbA1c=hemoglobin A1c; INR=international normalized ratio; LDH=lactate dehydrogenase; LDL=low-density lipoprotein; MCH=mean cell hemoglobin; MCHC=mean cell hemoglobin concentration; MCV=mean cell volume; RBC=red blood cell; WBC=white blood cell.

Other infectious disease blood tests screening for HBsAg, HBcAb, hepatitis C antibody, and HIV will be performed at the Screening visit only. Positive screens may require additional testing. For those HBcAb-positive patients permitted to enter the study (HBcAb positive, HBsAg negative, HBsAb titer ≥100 IU/L, and negative hepatitis B DNA), additional assessments for hepatitis B DNA should be performed at the visits indicated in the Schedule of Assessments (Appendix 3).

HbA1c, total cholesterol, LDL cholesterol and triglycerides will also be performed for the GTI at the visits indicated in the Schedule of Assessments (Appendix 3).

Unscheduled or additional laboratory samples may be collected and analyzed by local laboratories if immediate results as necessary for management of TEAEs or dosing determination. Urine pregnancy tests will be performed locally.

When scheduled simultaneously with a dosing visit, samples for clinical laboratory tests should be collected prior to administration of zetomipzomib or placebo.

Clinical laboratory results that the Investigator deems clinically significantly abnormal should be repeated within 48 to 72 hours or as clinically appropriate from when the result became available, when possible.

7.2.4.6.1. Tuberculosis 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 Assessments (Appendix 3). 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 the chest x-ray 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 and/or the patient is diagnosed with latent TB, they must have a chest x-ray that shows no evidence of active TB, no clinical signs and

symptoms of TB, and documentation confirming completion of appropriate prophylactic 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 once as soon as possible by the central laboratory (QuantiFERON-TB Gold/Gold Plus test) or local laboratory (QuantiFERON-TB Gold/Gold Plus or T-SPOT TB). If the result remains indeterminate (or borderline), the patient is not eligible for enrollment into the study, unless already treated for latent TB as described above for a positive test. The site, if it has performed the T-SPOT TB test 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.

7.2.4.7. Contraception Requirements and Pregnancy Testing

Women of childbearing potential (WOCBP) who are engaged in heterosexual intercourse must have a negative urine or serum pregnancy test before the administration of zetomipzomib or placebo as specified in Appendix 3 and must agree to continue to use highly effective and medically acceptable methods of contraception to prevent pregnancy during the study and for 12 weeks after the last dose of MMF or equivalent. For the purposes of this study, WOCBP are defined as 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 or local laboratory and if the patient is not on supplementary hormonal therapy) or surgically sterile (ie, tubal ligation, hysterectomy, or bilateral salpingoophorectomy).

Highly effective contraception is defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. Examples of such methods include the use of an intrauterine device or hormonal contraceptives (eg, implant, injectable, patch, or oral), bilateral tubal occlusion, or having a vasectomized partner. In regions where it is considered highly effective contraception, 2 barrier methods (eg, female diaphragm and male condom) may be used.

If using a hormonal form of contraception, use must have been stable for at least 4 weeks prior to Day 1 (Week 1), and the patient must use a second highly effective nonhormonal form of contraception during the study, until 4 weeks after the last dose of zetomipzomib or placebo and for 6 weeks after the last dose of MMF or equivalent. Abstinence from heterosexual intercourse will be acceptable only if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence from heterosexual intercourse (eg, calendar, ovulation) and withdrawal are not acceptable methods of contraception.

For WOCBP, urine pregnancy testing will be performed at the time points specified in Appendix 3. Zetomipzomib or placebo should not be administered prior to confirmation of a negative test at visits at which pregnancy tests are performed. Positive urine pregnancy tests should be confirmed by a serum pregnancy test.

Samples for FSH testing may be collected at any time during the study to confirm postmenopausal status in female patients whose childbearing potential status has changed since the Screening visit. Only after confirmation of postmenopausal status is pregnancy testing not required.

Male patients must continue to use an effective contraception method (eg, condom with spermicide) during the study and for 12 weeks after the last dose of MMF or equivalent or be congenitally or surgically sterile (eg, vasectomy with documented confirmation of postsurgical aspermia). The requirement for contraception for male patients is based upon guidelines for background agents (MMF or equivalent). It is also supported by the short half-life of zetomipzomib (<5 hours), full recovery of immunoproteasome inhibition within 3 days of dosing, lack of mutagenic potential as determined in vitro and in vivo non-clinical studies, and lack of reproductive organ findings in the 6- and 9-month rodent and monkey repeat-dose toxicity studies. Additionally, no teratogenic effects were found in the definitive embryofetal toxicity studies in rats and rabbits. As per International Council for Harmonisation (ICH) M3 guidance, lack of reproductive and teratogenic findings in general toxicity and embryofetal toxicity studies is sufficient to support the treatment of male patients in Phase 1 and 2 studies prior to conducting fertility studies.

8. STUDY DISCONTINUATION

The Investigator must make every reasonable effort to keep each patient on study for the duration of the study, including through the safety follow-up, lost to follow-up, consent withdrawal, or EOS, whichever occurs first (see Section 8.2 for additional details).

8.1. Study and Individual Patient Stopping Rules

8.1.1. Termination or Suspension of the Study

The Sponsor has the right to terminate the study at any time, for any reason, including safety or administrative reasons. In all cases, all necessary measures will be taken to guarantee appropriate safety follow-up of patients already included in the trial. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory, and the Sponsor wishes to stop the study.
- IDMC recommendation due to safety concerns.

The IDMC will hold periodic meetings to undertake thorough reviews of the accumulated safety data. The IDMC can recommend stopping the study based on their review and findings. Further information about the IDMC's role and oversight will be detailed in the IDMC charter.

In the event that the Sponsor terminates the study, Investigators will be informed of the reason for study termination. Should the study be terminated due to safety reasons, the Investigator must contact all study patients promptly, complete the EOS procedures, and return the zetomipzomib or placebo.

8.1.2. Individual Patient Stopping Rules

The Investigator and Sponsor may discontinue the patient from zetomipzomib or placebo administration or study participation at any time if discontinuation would be in the patient's best interest. In the event that zetomipzomib or placebo is discontinued, the patient should be encouraged, where possible, to remain in the study.

Reasons for discontinuing a patient from zetomipzomib or placebo administration include, but are not necessarily limited to, any one of the criteria listed below.

- Receipt of a kidney transplant or initiation of dialysis
- Grade 4 (life-threatening) TEAE, unless due to an obvious alternative etiology
- Confirmed thrombotic microangiopathy (TMA)
- Serious allergic reaction to zetomipzomib or placebo, including anaphylaxis
- HIV/acquired immune deficiency syndrome or viral hepatitis (B or C) infection occurring during the study
- Pregnancy

- Any medical condition or personal circumstance that, in the opinion of the Investigator, exposes the patient to risk if the patient continues with zetomipzomib or placebo or that prevents the patient's adherence to the protocol
- Protocol deviation involving inclusion or exclusion criteria or concomitant medications (Section 6.2) that, in the Investigator or the Sponsor's judgment, would significantly compromise data interpretation or patient safety

The Investigator must contact the Medical Monitor to discuss further continuation if after 12 weeks of treatment, at 2 consecutive visits at least 4 weeks apart, either of the following criteria is met:

- UPCR does not decrease >25% from the last Screening result
- eGFR <60 mL/min/m^2 and decreases of >20% from the last Screening result

  Note: If the patient is not discontinued, and UPCR or eGFR thresholds are subsequently met but remain stable in the judgment of the Investigator and Medical Monitor, then the Investigator must also contact the Medical Monitor to discuss further continuation at least every 12 weeks.

Furthermore, zetomipzomib or placebo should be interrupted, and the patient should be evaluated if there is a suspected diagnosis of thrombotic microangiopathy, such as with any acute changes in renal function, thrombocytopenia, or intravascular hemolytic anemia.

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 study participation will be encouraged to complete the ETV within 14 days and return for a safety follow-up (EOS) visit 4 weeks after the last dose of zetomipzomib or placebo.

8.2. Lost to Follow-up

The Investigator must make reasonable efforts to contact patients who fail to return for scheduled visits so that they will not be declared lost to follow-up. Patients will be considered lost to follow-up only after reasonable, documented attempts to reach the patient prove unsuccessful. These attempts include, but are not limited to, the following:

- Attempt contact at all telephone numbers for the patient and his/her listed contacts (to be collected in the source documents at the patient's entry into the study), as applicable.
- Contact the patient's primary care physician, referring specialist, or other healthcare professional, as applicable.
- Send emails, texts, and certified letters through the postal service to all the patient's addresses and contacts, as applicable.
- Review available medical records/notes for details of hospitalizations, clinic visits, or other procedures that may indicate the status of the patient, as applicable.

- Perform an internet search for additional contact information, as applicable.
- Check local, regional, and national public records to locate the patient or search for mortality status as allowed by law, as applicable.

The information and dates of attempted contact must be recorded in the patient's records and the patient's final status recorded in the appropriate eCRF. Once all attempts to contact the patient have been exhausted and documented, the Sponsor or Sponsor's designee should be contacted for additional guidance.

9. ADVERSE EVENTS

9.1. Adverse Event Reporting

This study will be conducted in accordance with the European Medicines Agency (EMA) "Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic" as well as the FDA Guidance for Industry, Investigators, and Institutional Review Boards "Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency."

9.1.1. Definitions of an Adverse Event

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

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 such as, "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.

9.1.2. Assessment of Severity

Severity of AEs will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. If a new version is released during the conduct of the study, the impact will be assessed, and a determination will be made regarding which version to follow. If there is a change in severity of an AE, it must be recorded as a separate event.

9.1.3. Assessment of Causality

AEs will be deemed related to zetomipzomib or placebo unless clearly unrelated to zetomipzomib or placebo. The Investigator will assess the causal relationship between zetomipzomib or placebo and the AE. One of the categories listed in Table 4 should be selected based on medical judgment, considering the definitions and all contributing factors.

Table 4: Adverse Event Causality Categories

Related	A clinical event, including clinically significant laboratory test abnormality, that occurs in a plausible time relationship to zetomipzomib or placebo administration, and that concurrent disease or other drugs or chemicals cannot explain. The response to withdrawal of the zetomipzomib or placebo (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 clinically significant laboratory test abnormality, with little or no temporal relationship to zetomipzomib or placebo administration. May have negative dechallenge[a] and rechallenge[b] information. Typically explained by extraneous factors (eg, concomitant disease, environmental factors, or other drugs or chemicals).

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

[b] Rechallenge: upon readministration of zetomipzomib or placebo 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).

AE=adverse event.

9.1.4. Action Taken with Regard to Zetomipzomib or Placebo

The Investigator will describe the action taken with zetomipzomib or placebo in the appropriate section of the eCRF, as one of the following:

- None
- Dose stopped
- Dose temporarily interrupted
- Dose reduced (with written approval from the Medical Monitor)
- Other (specify)

9.1.5. Follow-up of Adverse Events

AEs are intended to be collected, according to the procedures outlined, from the time of informed consent and continuing for 30 days following the last dose of zetomipzomib or placebo or the EOS visit, whichever occurs later.

All Investigators should follow patient 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.

9.1.6. Documenting and Reporting of Adverse Events

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

- Diagnosis, or description of the symptoms if a diagnosis is not established
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken with regard to zetomipzomib or placebo
- Outcome of the event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

9.2. Serious Adverse Events

9.2.1. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence or effect 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, ie, 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 considered 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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.2.2. Serious Adverse Event Reporting and Documentation Requirements

An SAE must be reported (see Section 9.1.6) by the Investigator if it occurs from the time of signed consent through 30 days after the last dose of zetomipzomib or placebo or the EOS visit, whichever occurs later, whether or not the SAE is considered to be related to treatment. After the

reporting period, SAEs should only be reported if the Investigator assesses the event to be related to study treatment.

Every SAE that occurs during the reporting period regardless of suspected causality must be reported by the Investigator in the electronic data capture (EDC) system (AE/SAE eCRF) within 24 hours from the time the Investigator becomes aware of the SAE. If there are any issues with EDC, a completed paper SAE report form should be emailed [redacted] or faxed [redacted] within 24 hours for the attention of the [redacted] Project Manager (see Study Personnel page). Additional source documents can be requested, if deemed necessary.

The Investigator should not wait for additional information to fully document the event before notification of an SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained. Follow-up information should be submitted in the same way as the original SAE report.

Instances of death, congenital abnormality, any SAEs, or an event 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 zetomipzomib or placebo administration and considered by the Investigator to be related to participation in this study, should be reported to the Medical Monitor and to [redacted].

The Sponsor and/or designee will promptly notify all relevant Investigators and the regulatory authorities of findings that could adversely affect the safety of patients, impact the conduct of the study, or alter the IDMC (or appropriate alternative)/Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favorable opinion of the study. In addition, the Sponsor or designee will expedite the reporting of all adverse reactions that are both serious and unexpected to all concerned Investigators, to the IDMC (or appropriate alternative)/IRBs/IECs where required, and to relevant regulatory authorities.

For SAEs that have been reported in the zetomipzomib development program, refer to the most current zetomipzomib (KZR-616) Investigator's Brochure.

9.3. Pregnancy Reporting

Pregnancy occurring in female patients or female partners of male patients participating in the study or during a clinical investigation must be reported to the [redacted] via the Pregnancy Report Form within 24 hours and entered into the EDC. The outcome of a pregnancy should be followed up carefully, and any abnormal outcome for the mother or the child should be reported. Infants should be followed for a minimum of 8 weeks, and all findings should be reported to [redacted] via the Pregnancy Report Form. Zetomipzomib or placebo is to be discontinued immediately upon Investigator knowledge of the pregnancy in a female patient or a female partner of a male participant and reported as per Section 8.1.2.

If the outcome of the pregnancy meets a criterion for immediate classification as an SAE (ie, spontaneous abortion [for which any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for expedited reporting of SAEs as outlined in Section 9.2.2.

Any SAE experienced by a subject during pregnancy must be reported as an SAE.

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.

9.4. New or Worsening Disease Manifestations

New or worsening manifestation(s) of SLE should not be recorded as AEs unless they are assessed as serious. New or worsening manifestation(s) of SLE should be captured on the clinical lupus disease assessments (see Appendix 3 and Section 7.2.2.4).

9.5. Adverse Events of Special Interest

An adverse event of special interest (AESI) is one that is of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of zetomipzomib or placebo.

SIRs and thrombotic microangiopathy have been identified as AESIs. Any Grade 3 or higher AESIs should be reported within 24 hours using the AE eCRF.

9.5.1. Systemic Injection Reactions

In clinical studies of zetomipzomib, SIRs associated with subcutaneous injections have been reported, consisting of 1 or more of the following signs/symptoms: hypotension, tachycardia, nausea, vomiting, dizziness, headache, pyrexia, rigors, and/or chills. The events are associated with an acute phase-like response, including leukocytosis and elevated C-reactive protein, occur within 8 to 24 hours after dosing, and usually resolve within 48 hours of dosing. While most commonly associated with an initial subcutaneous dose of zetomipzomib 60 mg and reduced in frequency when initially dosed with 30 mg, any or all of these events could occur with lower doses of zetomipzomib or with subsequent higher doses of zetomipzomib. The events are similar to those described for infusion-related reactions observed with the currently approved proteasome inhibitor carfilzomib, which generally occur in the first cycle of dosing.

In reporting TEAEs related to zetomipzomib or placebo tolerability, 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 TEAE. 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 these symptoms is described in Section 6.1.2.

9.5.2. Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombocytopenic purpura and hemolytic uremic syndrome, have been described with the proteasome inhibitors, bortezomib, carfilzomib, and ixazomib. The clinical presentation of thrombotic microangiopathy 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 thrombocytopenic purpura/hemolytic uremic syndrome. If the diagnosis is suspected, such as with any acute changes in renal function, thrombocytopenia or intravascular hemolytic anemia, interrupt zetomipzomib or placebo administration and evaluate (refer to Section 8.1.2). Missed doses should be addressed as per Section 6.1.3.2. If the diagnosis of thrombocytopenic purpura/hemolytic uremic syndrome is excluded, zetomipzomib or placebo may be resumed. If the diagnosis is confirmed, zetomipzomib or placebo must be permanently discontinued (refer to Section 8.1.2).

9.6. Unexpected Adverse Reactions

9.6.1. Definition of an Unexpected Adverse Reaction

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of zetomipzomib or placebo at any dose, which is not consistent with the applicable product information (eg, the Reference Safety information of the zetomipzomib Investigator's Brochure).

All suspected unexpected serious adverse reactions (SUSARs) will be subject to expedited reporting. The Sponsor or designee shall ensure that all relevant information about an SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IRB/IEC 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 IRB/IEC within 15 days after knowledge by the Sponsor of such a case. All Investigators should follow 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 after the patient has completed the clinical study must be reported by the Investigator to the Sponsor.

9.7. Hypersensitivity Reactions

Hypersensitivity reactions are exaggerated or inappropriate immunologic responses occurring in response to an antigen or allergen. Drugs may cause allergic reactions by any mechanism of hypersensitivity. For example, penicillin may cause anaphylaxis, which is IgE-mediated, but most responses are trivial. Hypersensitivity reactions to zetomipzomib are not anticipated given its structure and mechanism of action; however, potential hypersensitivity to an excipient could occur. Studies in compound ONX 0914, an analog of zetomipzomib, demonstrated inhibition of T-helper 2 cell response and allergic reactions in foreign ovalbumin and house dust mite induced allergic airway inflammation in mouse models.

Known risk factors for developing a hypersensitivity reaction include allergic reaction history, concomitant diseases such as chronic respiratory diseases, cardiovascular diseases, mastocytosis or clonal mast cell disorders, and severe atopic disease. Some concurrent medications such as beta-adrenergic blockers and ACE inhibitors might also increase the risk. Patients in this study should be closely monitored. Should any signs and symptoms of suspected hypersensitivity reactions occur, the Investigator will diagnose per clinical guideline and zetomipzomib or placebo may be temporarily withheld. If the diagnosis of hypersensitivity is confirmed, zetomipzomib or placebo must be permanently discontinued, and the patient will be treated per clinical guidelines.

9.8. Infections

The usual clinical care for patients with LN who use chronic immunosuppressives includes surveillance for severe or opportunistic infections, given the increased incidence in this setting. Patients with recent serious or ongoing infections are excluded from the study (Section 4.3). While zetomipzomib has not been associated with new onset or more severe infections to date in patients with similar risk factors, patients will be monitored for new infections, and potential infections (bacterial, viral, or fungal) will be fully evaluated. The periodic physical assessments in this study include capturing new onset signs and symptoms. Patients should be encouraged to contact the Investigator if they develop any new signs or symptoms between physical assessments. Clinical care will be provided for any newly diagnosed infection. Patients who use chronic prophylactic or suppressive therapy (eg, chronic antivirals for herpes simplex virus) as part of their usual care are permitted to continue with their usual therapies. Infections will be captured as AEs. In addition to inclusion in the safety database, the data on infections will be analyzed as part of the GTI (Section 7.2.2.8).

9.9. Independent Data Monitoring Committee

A study-specific IDMC will be used to enhance the safety and integrity of the study data for interim safety monitoring. The specific responsibilities and composition of the IDMC will be outlined in a separate IDMC Charter. The IDMC will be convened regularly, at least twice a year, and ad hoc.

It is the responsibility of the IDMC to weigh the risks and benefits throughout the study's duration. Specifically, this role includes the following: monitoring evidence for treatment harm (eg, toxicity, AEs, SAEs, and deaths) and requesting additional data analyses as necessary for the review process.

The IDMC will also examine efficacy and safety from the IA. Adjudication of CRR will be done by the Clinical Endpoint Committee (CEC) (see Section 9.10) and overseen by the IDMC, as described in the IDMC Charter. In addition, a Steering Committee will be formed to receive the IDMC recommendations.

9.10. Clinical Endpoint Committee

A CEC will adjudicate CRR (primary efficacy endpoint) by reviewing blinded data for patients in this study. The CEC will also assess treatment failure based on the criteria outlined in Section 2.2.5 The Sponsor will establish a CEC Charter describing the working procedures and responsibilities of the CEC. All adjudication decisions of the CEC will be appropriately documented.

10. STATISTICAL ANALYSES

10.1. Overview

Key elements of the statistical analyses for this study are described in this section; full details will be documented in a statistical analysis plan (SAP). The statistical analyses for this study will be the responsibility of the Biostatistics department of the Sponsor or its designee ([redacted]).

The SAP will be written and approved prior to the first IDMC data review meeting and IA. The SAP may be revised or amended in accordance with subsequent protocol amendments or whenever deemed necessary. For the purpose of the primary endpoint and final data analyses, the primary endpoint and final database will not be unblinded until medical/scientific review has been conducted, protocol deviations have been identified, the data have been declared final and complete, and the SAP has been approved.

The following sections include a summary of the planned statistical analyses of the primary and secondary endpoints. Any substantive changes to the planned analysis procedures relative to those described in the protocol will be explained in the SAP and included in the clinical study report.

Baseline value:

Baseline UPCR will be determined by the average of the 24-hour collections at Screening.

Unless specified otherwise, baseline value for eGFR and other parameters including laboratory data is defined as the last value prior to the 1st dose of the zetomipzomib or placebo.

10.2. Study Population Definitions

The following is a list of the main analysis populations.

ITT Population: The intent-to-treat (ITT) population consists of all patients who are randomized to the study. The ITT population will be the primary analysis population used for the efficacy analyses.

Safety Population: The safety population includes all randomized patients who receive at least 1 dose of zetomipzomib or placebo. The safety population will be the population used for the safety analyses.

Per-Protocol Population: The per-protocol (PP) population consists of all patients included in the ITT population who have no protocol deviations that may substantially affect the efficacy results. The final determination on protocol deviations, and thereby the composition of the PP population, will be made prior to the unblinding of the database and will be documented separately. The PP population will be used in efficacy analyses to support the primary efficacy analyses based on the ITT population.

10.3. Sample Size and Power Considerations

A sample size of 249 patients with Class III/IV +/-V LN or 83 per treatment group (randomized in a 2:1:2:1 ratio for zetomipzomib 30 mg: placebo: zetomipzomib 60 mg: placebo) will have 80% power to detect a 20% difference (40% versus 20%) in CRR between zetomipzomib and placebo at Week 37 (9 months), using a 2-group binomial test (for pooled estimate of variance)

with a 0.05 2-sided α level. The assumption of 20% for CRR in the placebo group was made based on the evaluation of relevant published data (Furie et al., 2020; Rovin et al., 2021).

The sample size calculation is intended for pairwise comparisons for zetomipzomib 60 mg versus the pooled placebo group and for zetomipzomib 30 mg versus the pooled placebo group, respectively. There is no statistical comparison between the 2 zetomipzomib dose groups. This sample size also reflects a planned IA for futility when approximately 50% of the randomized patients with Class III/IV +/-V LN have or would have completed the Week 37 visit (Section 10.3.1).

In addition to the 249 patients with Class III/IV +/-V LN, the study will also enroll up to 30 patients with pure Class V LN across the 3 treatment groups, for a total of up to 279 patients. The 30 patients with pure Class V LN were not included in the power calculation, as well as the assessments for type 1 error and multiplicity.

10.3.1. Futility Boundary and Assessment

A futility assessment will be performed through an IA that is planned when approximately 50% of the randomized patients with Class III/IV +/-V LN have completed or would have completed the Week 37 visit with the primary endpoint assessment and prior to the completion of the target enrollment. The futility boundary using the Lan-DeMets (O'Brien and Fleming, 1979; DeMets and Gordon Lan, 2014) is non-binding and is shown in Table 5. The calculation was performed using [redacted]. The futility boundary of Δ=5.4% (4.7% conditional power at the observed value), will be assessed for the pairwise comparisons of zetomipzomib and placebo using an Intersection-Union approach. In this approach, futility will be declared if both Δ1 ≤5.4% and Δ2 ≤5.4% are true. Otherwise, futility will not be declared if either Δ1 >5.4% or Δ2 >5.4% is true. Here, Δ1 and Δ2 are pairwise differences in CRR at Week 37 between zetomipzomib 30 mg and pooled placebo and between zetomipzomib 60 mg and pooled placebo, respectively. A decision to stop the study for futility or to continue as planned will be reached after careful review of the data by the IDMC and the Sponsor's designated members (Steering Committee).

Table 5: Futility Boundary

Information Fraction	Cumulative β Spent at final analysis	Futility Boundary for Treatment Difference (Δ) in CRR at Week 37
50% randomized patients with Class III/IV +/-V LN	0.19786 (80.2% power)	5.4% (conditional power at the observed value according to [redacted]=4.7%)

CRR=complete renal response; IA=interim analysis; LN=lupus nephritis; N=number of patients.

10.4. Background and Demographic Characteristics

Age, height, body weight, and other continuous variables will be summarized using descriptive statistics, while sex, race, age group, ethnicity, region, and other categorical variables will be provided using frequency tabulations. Medical history data will be summarized using frequency tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

10.5. Patient Disposition

Patient disposition (analysis population allocation, entered, completed, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percentages. A summary of patients enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

10.6. Efficacy Analysis

The ITT will be the primary analysis population used for the efficacy analyses. Patients will be included in the treatment group to which they were randomized for the efficacy analysis using the ITT.

The primary analysis of each efficacy endpoint will be carried out for randomized patients (ITT) with Class III/IV+/- V LN (N=249). A supportive analysis using the PP population (Class III/IV+/- V LN) will be performed for key efficacy endpoints.

A sensitivity analysis for each of the selected efficacy endpoints (i.e., primary, key secondary and selected other efficacy endpoints) will be carried out for all randomized patients (ITT) including Class III/IV+/- V and pure Class V LN (N= up to 279) and nominal p-values will be presented for hypothesis tests.

Descriptive statistics for continuous variables will be summarized using the number of non-missing values (n), mean, standard deviation (SD), median, minimum, and maximum. Summaries will be presented for the change from Baseline, when appropriate. Categorical variables will be summarized using counts, percentages, and confidence intervals (CIs). All percentages will be based on the number of patients in the treatment group unless specified otherwise.

For time-to-event variables (eg, time to CRR, time to PRR, and time to UPCR ≤0.5), the Kaplan-Meier method will be used to estimate survival function, median survival time, and CIs. The log-rank test (stratified for the randomization stratification factors) will be used to compare between 2 survival curves. Cox's proportional hazards model will be performed to assess differences between treatment groups. The model will include terms for treatment and selected Baseline parameters including stratification factors. All statistical tests will be 2-sided, unless otherwise noted.

Binary efficacy endpoints (eg, CRR and PRR) will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by the randomization stratification factors (Section 3.2.1). Patients who have insufficient data for response determination for the time point under consideration will be handled using an estimand approach for intercurrent events or non-responder imputation (NRI), where appropriate for that time point.

Continuous efficacy endpoints (ie, change or percentage change from Baseline in UPCR by visit) will be analyzed using the longitudinal data analysis method based on a mixed model for repeated measures (MMRM) approach. This model will include fixed effect terms for randomized treatment, timepoint (ie, visit) and randomized treatment by timepoint interaction. Within subject error will be modelled by use of an unstructured variance-covariance matrix. Baseline value will be included as a covariate and the randomization stratification factors will be included as class terms. Treatment effect (ie, the difference in least-square mean values between

each zetomipzomib dose and placebo and the 2 zetomipzomib doses combined vs placebo) estimates will be extracted from the model by timepoint along with the associated 95% CIs and 2-sided p-values. A sensitivity analysis of this model by using multiple imputation (MI) for handling missing data will be performed. The influence of missing data over time will be assessed using multiple imputation techniques, specifically assuming missing at random and missing not at random (MNAR); for the latter both jump to placebo and tipping point MI analyses will be employed.

The Baseline value for 24-hour UPCR is defined as the average of non-missing 24-hour UPCR results from the Screening visit. Repeat test results will not be used to replace non-missing original test data. When only 1 non-missing sample 24-hour UPCR results from the Screening visit is available, then that single value will be used for the Baseline. Unless specified otherwise, baseline value for eGFR and other parameters including laboratory data is defined as the last value prior to the 1st dose of zetomipzomib or placebo.

In this study, all analyses involving treatment comparisons will be performed based on pairwise comparisons for zetomipzomib 60 mg versus the pooled placebo group and for zetomipzomib 30 mg versus the pooled placebo group. No statistical comparisons will be performed between the 2 zetomipzomib dose groups.

All analyses will be performed in SAS® v9.4 for Microsoft® Windows®.

10.6.1. Analysis of the Primary Efficacy Endpoint

10.6.1.1. Primary Estimand and Analysis

According to ICH E9 (R1), an estimand is defined by the following 4 attributes: population of interest, endpoints of interest (variables), population-level summary, and intercurrent events (ICH-E9, 1998). A list of potential intercurrent events is specified below, while the primary estimand for the primary efficacy endpoint is described in Table 6. Details of supportive estimands, sensitivity analyses, and supplemental analyses will be described in the SAP.

Intercurrent events:

- Treatment failure, defined as meeting any of the criteria outlined in Section 2.2.5 (eg, use of prohibited medications, use of rescue therapy or alternative treatments, or discontinuation of zetomipzomib or placebo)
- Increased dose for background medications and/or corticosteroids
- Change in background medications

Note: Study discontinuation, loss to follow-up, and other missing data are not intercurrent events and are not reflected in estimands, but instead represent limitations to the data to be addressed in the analysis via missing data handling.

Table 6: Estimand for Comparative Analysis between Zetomipzomib and Placebo

Attribute	Primary Estimand	Secondary Estimand(s)/ Sensitivity Analysis
Population of interest	ITT for randomized patients with Class III/IV+/- V LN	ITT for randomized patients with Class III/IV+/- V LN and pure Class V (sensitivity analysis) PP population for randomized patients with Class III/IV+/- V LN
Endpoints of interest	CRR at Week 37	Same as primary estimand
Population-level summary	Difference in proportion of patients in CRR at Week 37 between zetomipzomib and pooled placebo	Same as primary estimand
Intercurrent events[a]	Use Composite method • Treatment failure (non-responder) • Discontinuation of zetomipzomib or placebo (non-responder)[b] • Use of rescue therapy or alternative treatments (non-responder) • Use of prohibited medications (non-responder) • Increased dose for background medications and/or corticosteroids (non-responder) • Change in background medications (non-responder, unless permitted per Sections 6.2.1 and 6.2.2 where observed efficacy data will be used for analysis)	(1) Use Treatment Policy method • For patients who had an IE and remained in the study, the observed efficacy data at Week 37 will be included in the analysis of CRR at Week 37, respectively (2) Use Principal stratum • For patients in the strata of the ITT population who do not require additional medication (including rescue therapy and protocol prohibited medications) and change in background medications • For patients who reach EOT
Missing data	NRI will be applied to the primary estimand for missing data at Week 37 (ie, early discontinuation of study, lost to follow-up, or due to other intercurrent events)	Other missing data handling methods (such as tipping point analysis, MI for binary endpoints [ie, CRR, PRR], and MI for continuous endpoints [ie, percentage change from Baseline in UPCR]) may be applied.

[a] Prior to the Week 37 visit.
[b] Exception: For patients who discontinue zetomipzomib or placebo without using any rescue therapy or protocol prohibited medications and remain in the study, their observed efficacy data will be included in the analysis.
CRR=complete renal response; EOT=end of treatment; ITT=intent-to-treat population; LN=lupus nephritis; MI=multiple imputation; NRI=non-responder imputation; PP=per-protocol; PRR=partial renal response; UPCR=urine protein to creatinine ratio.

In the primary analysis of the primary estimand, the proportion of patients achieving CRR at Week 37 for the treatment comparison between zetomipzomib and placebo (separately for each of the 2 dose groups and pooled placebo) will be carried out in the ITT using CMH test at 2-sided 5% level of significance, stratified by the randomization stratification factors (3 factors

for this study; see Section 3.2.1). Results will be expressed as the number of patients achieving CRR, CRR proportion, weighted difference in CRR proportions, odds ratio, associated 2-sided 95% CI, and p-value (for each pairwise comparison between zetomipzomib and placebo). A bar graph showing the proportion of patients achieving CRR by treatment group with the weighted treatment difference and CMH p-value will be produced. For patients whose CRR at Week 37 cannot be adequately determined (including missing data, early study discontinuation, or lost to follow-up), their CRR will be imputed using an NRI approach. For patients meeting the treatment failure criteria prior to the Week 37 visits, their CRR after discontinuation and at the Week 37 visit, respectively, will be imputed using NRI.

The primary analysis of the primary estimand and secondary estimand(s) will be carried out for randomized patients (ITT) with Class III/IV+/- V LN (N=249).

A sensitivity analysis for each estimand (primary and secondary) will be carried out for all randomized patients (ITT) including Class III/IV+/- V and pure Class V LN (N= up to 279).

Sensitivity analyses of the primary endpoint will be performed using other missing data handling approaches, specifically MI and tipping point analysis.

Supplemental analyses on the primary and selected key secondary endpoints may be performed using logistic regression models. These analyses will include covariates for treatment, UPCR at baseline (stratification factor), biopsy class, IV methylprednisolone use at Baseline (stratification factor), and region and other selected baseline parameters.

Details on which of these analyses will include patients with Class III/IV+/- V LN, or patients with Class III/IV+/- V and pure Class V LN will be provided in the SAP.

As indicated in Section 9.10, a CEC will adjudicate CRR (primary efficacy endpoint) by reviewing blinded data for patients in this study. All adjudication decisions of the CEC will be appropriately documented. The adjudication covers cases of treatment failure as well.

10.6.1.2. Primary Endpoint Analysis and Final Analysis

The primary endpoint analysis will be performed when all randomized patients have completed or would have completed the Week 37 visit. The analysis will include treatment comparison for CRR at Week 37. As discussed in Section 10.6.3, treatment comparison for CRR at Week 37 will be done statistically at a significance level of 2-sided 0.05. In addition, point estimates and 95% CIs will be generated for PRR at Week 37, CRR at Week 53, and PRR at Week 53.

The final analysis will be performed when all patients have completed the study including the safety follow-up visits.

10.6.2. Analysis of the Secondary Efficacy Endpoints

The secondary efficacy endpoint analyses will evaluate the proportion of patients treated with zetomipzomib compared with pooled placebo (in pairwise comparison) achieving the following:

- PRR at Week 37
- CRR at Week 53
- PRR at Week 53

- CRR at Week 25
- PRR at Week 25
- Percentage change from Baseline in UPCR by visit
- Time to CRR
- Time to PRR
- Time to death or renal-related events
- Proportion of patients achieving CRR (at Weeks 25, 37, and 53) with successful taper of prednisone or equivalent to ≤5 mg by Week 17
- Proportion of patients achieving CRR (at Weeks 25, 37, and 53) with no use of prednisone or equivalent during the 8 weeks prior to the renal response assessment
- Proportion of patients with UPCR ≤0.5 at Weeks 13, 25, 37, and 53
- Proportion of patients achieving CRR with UPCR ≤ upper limit of normal (ULN) at Weeks 25, 37, and 53
- Change from Baseline in clinical Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score, excluding complement and anti-dsDNA components.
- Change from Baseline in EuroQol 5-Dimension 5-Level (EQ-5D-5L)

Time to death or renal-related events is defined as the first event occurring among the following:

1. Death
2. Doubling of serum creatinine
3. Proteinuric flare
4. Renal event-related treatment failure

The primary analysis of certain key secondary endpoints (ie, CRR at Week 53, PRR at Week 37 and Week 53) will follow the primary estimand principle, using the same approach as described in Section 10.6.1 and Table 6.

For a continuous endpoint such as percentage change from Baseline in UPCR by visit, data will either be observed or missing (ie, no NRI will be applied). The missing data will be handled by the following 2 approaches: (1) using MMRM model and (2) using MI to impute missing data and then applying MMRM model for analysis. The MMRM model (ie, Approach #1) will be the primary analysis method.

10.6.3. Controlling for Type I Error

Formal statistical tests are planned for the primary and the following key secondary efficacy endpoints. The analyses will be performed based on the ITT for randomized patients with Class III/IV+/- V LN. Patients with pure Class V LN will not be included in the analyses involving hypothesis testing of the following endpoints.

Primary endpoint

- CRR at Week 37

Key secondary endpoints

1. CRR at Week 53
2. PRR at Week 37
3. PRR at Week 53
4. CRR at Week 25
5. PRR at Week 25

The testing sequence will be performed independently for each zetomipzomib treatment group versus placebo (pooled).

Analysis of the primary endpoint will involve in three pairwise comparisons:

- zetomipzomib 60 mg vs placebo
- zetomipzomib 30 mg vs placebo
- [(zetomipzomib 30 mg + zetomipzomib 60 mg) /2] vs placebo

The above treatment comparisons can be tested under the following hypotheses:

- Null hypothesis H_0: P0=P1=P2=0.20
- Alternative hypothesis (a): P1=P2=0.40, P0=0.20
- Alternative hypothesis (b): P1=0.20, P2=0.40, P0=0.20

where P0, P1 and P2 are the true CRR at Week 37 for placebo, and 2 zetomipzomib doses (30 mg, 60 mg).

We use the approach such that each of the above three comparisons is assessed at the 2-sided α=0.05, as such the overall Type 1 error rate across the three comparisons will become higher but controlled at 2-sided level of 0.096716. The overall power for the three comparisons under Alternative hypothesis (a) and Alternative hypothesis (b) would be 94.98% and 82.27%, respectively.

For each of the above 3 pairwise comparisons, a family-wise type I error rate at the α=0.05 level (2-sided) will be used for the analysis of endpoints (primary & 5 key secondary) starting from the primary endpoint, so that statistical significance for any of the 5 key secondary endpoints can only be declared if the same comparison on the primary endpoint (primary estimand) achieves statistical significance at 2 sided α=0.05. The Hochberg step-up method (Hochberg, 1988) will be applied to adjust for hypothesis testing of each pairwise comparison on all 5 key secondary endpoints and maintain the overall type I error rate at 0.05 level for each of pairwise comparison. Results from all statistical analyses, regardless of the level of significance, will be provided.

For statistical tests that are planned but not performed as a result of the multiplicity adjustment procedure (ie, other secondary endpoints), as well as for any other comparisons that are not subjected to multiplicity adjustment, nominal 2-sided p-values (without adjustment for multiplicity) will be provided as a measure of the strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

Exploratory endpoints will be analyzed without controlling for the global family-wise type I error rate.

10.6.4. Handling of Missing Data

Sensitivity analyses of the primary and key secondary endpoints including CRR and PRR will be performed to support their primary analyses. These analyses will use missing data handling methods including MI (for both binary and continuous endpoints), all observed data, and tipping point analysis as well as NRI (for binary endpoint only). Further details will be provided in the SAP.

10.7. Safety Analysis

The safety analysis will be based on the safety population. Patients will be included in the treatment group corresponding to the treatment they actually received for the analysis using the safety population.

AEs will be classified using the MedDRA classification system. AE data will be coded to system organ class and preferred term using the most current MedDRA version available at the time of entry.

All TEAEs will be summarized and reported by system organ class, preferred term, severity, and relationship to zetomipzomib or placebo. TEAEs leading to death or to discontinuation from treatment and serious TEAEs will also be tabulated. In the by-patient analysis, a patient having the same event more than once will be counted only once and by greatest severity. Summary statistics including cumulative incidence rates of TEAEs and exposure-adjusted incidence rates within each treatment group, and pairwise differences between zetomipzomib and placebo with point estimates and 95% CIs may be provided. A TEAE is defined as an AE that emerges during treatment having been absent pre-treatment or an AE that worsens relative to the pre-treatment state (ICH-E9, 1998).

Laboratory, vital signs, weight, and ECG data will be summarized descriptively by time point. In addition, shift tables showing the number of patients with values low, normal, and high compared to the normal ranges at Baseline versus post-Baseline will be provided for laboratory tests.

Concomitant medications will be coded using the most current World Health Organization (WHO) drug dictionary.

10.8. Other Analysis

10.8.1. Exploratory Analysis

Details of the exploratory analyses will be specified in the SAP.

10.8.2. Subgroup Analysis

Prespecified subgroup analyses of the primary and selected key secondary endpoints may be conducted for stratification factors: average 24-hour UPCR at Screening visit (≤3.0 and >3.0), LN Class (Class III/IV +/- V vs. pure Class V), IV methylprednisolone on Day 1 +/- 7 days (0 to <500 mg, 500-1000 mg, or >1000 to 3000 mg), maximum MMF dose (≤2 g versus >2 g); and

other baseline data including sex, race, age group, ethnicity, region, patients who have received IV methylprednisolone within 3 months prior to Screening (yes/no), current use of MMF or equivalent at the Screening visit (yes/no), classes of pathology on biopsy, and others (eg, pure Class V LN patients). Additional details will be provided in the SAP.

10.9. Interim Analysis

No IAs are planned for the purpose of stopping the study early for success in efficacy endpoints.

An IA is planned when approximately 50% of the randomized patients with Class III/IV +/-V LN have completed or would have completed the Week 37 visit with the primary endpoint assessment and prior to the completion of the target enrollment. This IA will serve the following purposes: (1) futility analysis and (2) a potential sample size increase up to 50% (only for Class III/IV +/-V LN) based on conditional power (ie, if the conditional power is ≥40% and <80%). The proportion of patients achieving CRR at Week 37, the primary endpoint, and additional efficacy data including PRR, mean percentage change from Baseline in UPCR at Week 37 and other key efficacy data will be evaluated. Summary statistics including point estimates and 95% CIs for the treatment differences in pairwise comparisons will be generated.

Given that the IA may result in sample size increase (ie, conditional power ≥40% and <80%), as indicated in the following 2 references(Mehta and Pocock, 2011; Broberg, 2013), the type I error rate remains intact or will not be inflated.

Operating characteristics (i.e., the probabilities of determining futility across various combinations of underlying truths for the true underlying response probabilities for each of the treatment arms) of any proposed futility determination rules and the probability of sample size increase will be characterized in the SAP.

An IDMC Charter will be finalized prior to the committee's first review of the data. The planned IA will be detailed in the SAP.

10.9.1. Potential Sample Size Increase Based on Interim Analysis

The potential increase in sample size (only for patients with Class III/IV +/-V LN) based on IA conditional power will be up to 50%. The (Mehta and Pocock, 2011)method will be used for adaptation of sample size re-estimate. Simulations (10,000) were performed for illustration purposes for a treatment difference of Δ=20% in CRR at Week 37. It is worth noting that, at the current planned sample size (83 per treatment group or 166 in a 2-treatment comparison), Δ=20% corresponds to 80% power, while power for a smaller Δ will be lower (ie, power for Δ=15% is around 51%). The simulation results are summarized in Table 7.

Table 7: Simulation Results for Sample Size Adjustment Based on Interim Analysis Data

Effect Size in CRR at Week 37	Conditional Power	Simulation Results (10,000 Simulations)	Sample Size Increase (only for patients with Class III/IV +/-V LN)
Δ=20% (40% versus 20%)	<40%	23.3%	No
	40% to <80%[a]	20.6%	Yes
	≥80%	56.1%	No

[a] For simulation purposes, a lower bound of 40% conditional power was chosen to consider for sample size increase. The simulations were performed using [redacted] (Chen et al., 2004)
CRR=complete renal response.

10.9.2. Specified Analyses for Independent Data Monitoring Committee Review

Safety monitoring will also be performed by an external IDMC. The IDMC will review unblinded data to evaluate efficacy and safety during the study. The IDMC will be convened regularly, at least twice a year, and ad hoc as needed. The IDMC scope, conduct, processes, and accountabilities are specified in an IDMC Charter.

10.9.3. Protocol Changes Based on Interim Analysis

Potential changes to the protocol may be applied after the planned IA is conducted. In general, no changes other than a potential sample size increase as suggested by the conditional power analysis (see Section 10.9.1) will be applied to the current study.

11. ETHICAL AND ADMINISTRATIVE CONSIDERATIONS

11.1. 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, ICH guidelines for current Good Clinical Practice (GCP), 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/regional/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.

11.2. Institutional Review Board or Independent Ethics Committee

Prior to initiation of the study at each study center, the protocol, informed consent form (ICF), other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate IRB/IEC. Written approval of the study and all relevant study information must be obtained before the study center can be initiated and before zetomipzomib or placebo can be released to the Investigator. Any necessary extensions or renewals of IRB/IEC approval must be obtained for changes to the study (ie, amendments to the protocol, the ICF, or other study documentation). The written approval of the IRB/IEC, together with the approved ICF, must be documented in the study files.

The Investigator will promptly report any new information that may adversely affect the safety of the patients or the conduct of the study to the IRB/IEC. The Investigator will submit written summaries of the study status to the IRB/IEC as required and will inform them when the study has ended.

11.3. 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 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.

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 IRB(s)/IEC(s) (and regulatory authorities, if required). The study patients will be informed about this new information and consent will be reobtained.

11.4. Direct Access to Source Data, Source Documents, and Study Reports

The Sponsor or its representatives may periodically check a sample of patient data recorded against source documents at the site. The study may be audited by the Sponsor, designee, IRB/IEC, 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 may 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.

The Sponsor or its designee is responsible for preparing a clinical study report. Study results will be provided to the Investigator.

11.5. 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 EDC 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 or designee.

Remaining biological sample material will be stored off-site at [redacted] and will be accessible to only the Sponsor for up to 2 years after the completion of the study, or until the sample material is entirely used up.

11.6. Confidentiality

Monitors, auditors, other authorized agents of the Sponsor and/or its designee, the IRB(s)/IEC(s) approving this study, the US FDA, and any other applicable agency(ies) will be granted direct access to the 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.

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 (HIPAA) and national, regional, and/or local laws and regulations on personal data protection (e.g., General Data Protection Regulation).

11.7. Financing and Insurance

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

11.8. Audit and Inspection

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

11.9. Monitoring

Data collection must be completed for each patient who signs an ICF. The Monitor will carry out source document verification in accordance with current GCP and ICH guidelines and applicable regulatory regulations at regular intervals to ensure that the data collected are accurate and reliable.

The Investigator must permit the Monitor, the IRB/IEC, 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.

Details for monitoring will be provided in a Clinical Monitoring Plan.

11.10. Quality Control and Quality Assurance

All aspects of the study will be carefully monitored by the Sponsor or its authorized representative(s) for compliance with applicable government regulation with respect to current GCP and Standard Operating Procedures (SOPs).

11.11. Data Management and Coding

The Sponsor or designee 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 designee. Quality control will be applied to each stage of data handling to ensure all data are reliable and managed correctly.

Study centers will enter data into the EDC system by completing the eCRF via a secure internet connection. Data transcribed 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 (eSource concept). Any changes to the data entered into the EDC system will be recorded in the audit trail and will be compliant with FDA CFR 21 Part 11.

An essential element of the eSource concept is that the clinical assessment data and other source data is entered during the clinical visit in an eSource EDC system. When designing the system, there are some fundamental aspects to be respected as follows:

- The ability of the physician to record clinical information in the patient medical record should not be limited or constrained.
- Information should be recorded in line with the current practice at the site.
- The integrity of the medical records should not be compromised.

- The Sponsor should have access only to pseudonymized information mandated by the protocol.

This guidance does not include direct data input from tablets, mobile phones, or other electronic devices.

Medical coding will use MedDRA for concomitant diseases and AEs and will use the WHO Drug classifications for medications.

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

11.12. Recording 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 (EOS is defined as the date of the visit of the last patient, 4 weeks following the last dose of zetomipzomib or placebo), 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 after the discontinuation of clinical development of zetomipzomib. It is the Sponsor's responsibility 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.

Kezar follows local regulatory requirements related to clinical trial registration and results disclosure. Within the United States, Kezar complies with the requirements of the Food and Drug Administration Amendments Act of 2007 to register and post results of applicable clinical trials in a timely manner.

Kezar is committed to submit for publication in peer-reviewed scientific literature, the results of registered clinical trials involving Kezar products. Kezar reserves the right to determine if the results of a registered trial will be submitted for publication and may post the results for registered trials on a clinical trials websites such as www.clinicaltrials.gov or www.clinicaltrialsregister.eu/ as a substitute for a peer-reviewed publication.

Kezar often works with clinical trial investigators to produce high-quality manuscripts for publication in various formats including but not limited to abstracts, posters, or presentations. The final clinical study report is intended to form the basis for a manuscript intended for publication in a peer-reviewed scientific journal. The authorship, timetable, and any arrangements for review by the participating investigators will be coordinated by Kezar Life Sciences, Inc. No partial subset of data from individual investigational sites can be presented or published until after the primary manuscript for the entire study has been accepted for publication in a peer-reviewed scientific journal.

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13. APPENDICES

APPENDIX 1. INTERNATIONAL SOCIETY OF NEPHROLOGY/RENAL PATHOLOGY SOCIETY (ISN/RPS) 2003 AND 2018 CLASSIFICATIONS OF LUPUS NEPHRITIS

Full text of the ISN/RPS article (Markowitz and D'agati, 2007) is available from Elsevier here: http://www.kidney-international.com/article/S0085-2538(15)52418-6/pdf

Full text of the ISN/RPS 2018 revision (Bajema et al., 2018) is available here: https://www.kidney-international.org/article/S0085-2538(17)30859-1/fulltext

APPENDIX 2. PROHIBITED MEDICATIONS

The use of any investigational agents or devices is prohibited. Besides the medications listed below, live-attenuated vaccines are also excluded. Topical and inhaled agents are permitted.

Treatment	**Washout Period Prior to Screening (unless otherwise specified)**
IA therapies, such as corticosteroids or hyaluronic acid preparations	4 weeks
IV immunoglobulin	4 weeks
Other nonbiologic immunosuppressive agents, such as cyclophosphamide cyclosporine, tacrolimus, voclosporin, kinase inhibitors, such as JAK inhibitors, and ACTH, except for oral MPA or mycophenolate in any oral formulation (which is permitted)	4 weeks
Methotrexate	8 weeks
Belimumab, anifrolumab, abatacept, or atacicept	12 weeks (4 weeks, if for extra-renal SLE and with Medical Monitor approval)
Cytokine antagonists, including, but not limited to, IL-1, IL-6, IL-17, IL-12/23, IL-23, IFN, integrin, and TNF-α antagonists	12 weeks
Leflunomide	12 weeks (4 weeks, if active powdered charcoal or cholestyramine was used)
B-cell depleting therapies (eg, rituximab)	12 weeks with levels of circulating CD19+ B cells within normal limits, or 48 weeks
Other immunosuppressive or immunomodulating biologics or investigational drugs (except for denosumab, insulin, and other approved non-immunosuppressive or modulating biologics, which are permitted)	8 weeks or 5 half-lives, whichever is longer
Transfusion with blood, packed WBC, or platelets or treatment with plasmapheresis or plasma exchange	6 weeks
AZA or 6-mercaptopurine	4 weeks prior to Baseline (Day 1)
Cholestyramine or other drugs that may interfere with enterohepatic recirculation of MMF	4 weeks prior to Baseline (Day 1)

ACTH=adrenocorticotropic hormone; AZA=azathioprine; CD19+=cluster of differentiation 19+; IA=intraarticular; IFN=interferon; IL=interleukin; IV=intravenous; JAK=Janus Kinase; MMF=mycophenolate mofetil; MPA=mycophenolic acid; TNF=tumor necrosis factor; WBC=white blood cells.

APPENDIX 3. SCHEDULE OF ASSESSMENTS

Site Visit Week	Sc	1	2	5	9	13	17	21	25	29	33	37	41	45	49	53 EOT	56 EOS[a]	ETV
Assessment Window (days)	**-35 to -1**	**NA**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**NA**
Informed consent	X																	
Medical history, including prior medications	X																	
Infectious disease blood tests[b]	X																	
Serum pregnancy test	X																	
Hepatitis B DNA[c]		X				X			X			X				X	X	X
Chest x-ray[d]	X																	
EULAR/ACR criteria for SLE	X																	
Physical examination[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG with QTcF interval[f]	X								X							X		X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical lupus disease assessments[h]	X	X				X			X			X				X	X	X
EQ-5D-5L		X				X			X			X				X	X	X
GTI assessment (including labs[i])		X							X							X		X
Estimated GFR	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[j]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-dsDNA and complements (C3 and C4)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C1q autoantibody and quantitative IgM, IgG, IgA		X				X			X			X				X	X	X
Urine pregnancy test[k]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
24-hour urine test	X					X			X			X				X	X	X
First morning void urine test	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IV methylprednisolone[l]		X																
Background medications[l]	←																	→

Site Visit Week	Sc	1	2	5	9	13	17	21	25	29	33	37	41	45	49	53 EOT	56 EOS[a]	ETV
Zetomipzomib or placebo administration[m]		← zetomipzomib or placebo administration from Week 1 to Week 52 →																
Renal histopathology and immunohistopathology[n]	X															X		X
Urine biomarker measurements	X					X			X			X				X	X	X
Blood biomarker measurements[o]		X				X			X			X				X	X	X
Sparse PK assessment[p]									X			X						
Optional PK assessment[p]				X														
AEs and concomitant medications[q]	← AEs and concomitant medications collected from Week 1 to Week 52, Week 53, Week 56, and ETV →																	

ACR=American College of Rheumatology; AEs=adverse events; anti-dsDNA=anti-double stranded DNA; CBC=complete blood count; DNA=deoxyribonucleic acid; ECG=electrocardiogram; eCRF=electronic case report form; EOS=End of Study; EOT=End of Treatment; EQ-5D-5L=EuroQol 5-Dimension 5-Level; ETV=Early Termination Visit; EULAR=European Alliance of Associations for Rheumatology; GFR=glomerular filtration rate; GTI=Glucocorticoid Toxicity Index; HbA1c=hemoglobin A1c; HBcAb=hepatitis B core antigen antibody; HBsAb=hepatitis B virus surface antibody; HBsAg=hepatitis B virus surface antigen; HIV=human immunodeficiency virus; Ig=immunoglobulin; IgA=immunoglobulin A; IgG=immunoglobulin G; IgM=immunoglobulin M; MMF=mycophenolate mofetil; MPA=mycophenolic acid; NA=not applicable; PGA=physician global assessment of disease activity; QTc=QT interval corrected; SLE=systemic lupus erythematosus (includes lupus nephritis); SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; TB=tuberculosis; WOCBP=women of child bearing potential.

[a] The end of study/safety follow-up visit will occur 4 weeks after the last dose of zetomipzomib or placebo.

[b] HBsAg, HBcAb, hepatitis C antibody, and HIV; QuantiFERON®-TB Gold/Gold Plus or T-SPOT® TB test. Positive screens may require additional testing. At Screening, HBcAb-positive patients will have additional tests of HBsAb titer, and hepatitis B DNA to determine eligibility.

[c] For those HBcAb-positive patients permitted to enter the study (HBcAb positive, HBsAg negative, HBsAb titer ≥100 IU/mL, and negative hepatitis B DNA), additional assessments for hepatitis B DNA should be performed at the indicated visits.

[d] A chest x-ray will be obtained during the Screening period if not available from within 90 days prior to signing informed consent form.

[e] A full physical examination is conducted at Screening visit only. A symptom-directed brief physical examination will be completed at all other visits. Height will be measured at the Screening visit only, and body weight will be collected throughout the study. If visit is being conducted as a telehealth visit, weight will not be collected.

[f] A 12-lead ECG with QTcF interval should be completed prior to vital signs, following 10 minutes of supine rest at indicated visits. The ECG at Week 25 should also be completed between 30 minutes to 4 hours postdose.

[g] Vital sign measurements consist of systolic and diastolic blood pressure, pulse rate, and body temperature. Blood pressure and pulse rate should be collected after the patient has had at least 10 minutes of rest in the supine position. When the time of vital sign measurement coincides with a blood sample collection, the vital signs will be measured before blood sample collection or zetomipzomib or placebo administration. A second set of vital signs must be obtained on the Day 1 (Week 1) visit 30 minutes (±15 minutes) after zetomipzomib or placebo has been administered.

[h] Clinical lupus disease assessments consist of SLEDAI-2K, SLE Flare Index, 28-Joint Count, and PGA; these assessments should also be performed to document any new or worsening manifestation(s) of SLE.

[i] Including the following assessments: HbA1c, total cholesterol, LDL cholesterol and triglycerides (non-fasting)

[j] Clinical laboratory tests consist of hematology, serum chemistry (non-fasting), urinalysis, and coagulation. When scheduled simultaneously with a dosing visit, samples for clinical laboratory tests should be collected prior to administration of zetomipzomib or placebo. A CBC must be performed locally at approximately Weeks 2, 3, and 4 and as per local practice thereafter in patients who were not already taking MMF or equivalent at Screening and thus started MMF after randomization. After dose increases of MMF or equivalent, CBC must be monitored as per local practice.

[k] A urine pregnancy test in WOCBP must be done prior to dose administration.

[l] IV methylprednisolone on Day 1 ± 7 days; for information on required and permitted background therapies and medications see Section 6.2.1 and Section 6.2.2.

[m] Once-weekly zetomipzomib or placebo injections are required from Weeks 1 to 52.

[n] Renal histopathology will be performed during the Screening period if it was not performed 12 months prior the study. Optional renal histopathology and immunohistopathology may be performed at Week 53.
[o] Blood biomarker measurements consist of cytokine activity, circulating leukocytes, and gene expression/pharmacogenomics and must be done prior to dose administration.
[p] Sparse PK samples will be drawn in all patients at Week 25 at 2 (±15 minutes) hours post dose and at Week 37 at 0.5 (±10 minutes) hours post dose. Optional PK samples will be drawn in a subset of ~30 patients at pre dose and 0.5 (±10) hours, 1 hour (±10 minutes), 2 hours (±15 minutes), and 4 hours (±15 minutes) post dose.
[q] All AEs must be recorded on the patient's eCRF, starting at the time of informed consent and continuing through 4 weeks post-last dose.

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